Vaccination against cervical cancer

Gezondheidsraad **President**
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport

Subject : Presentation of advisory report *Vaccination against cervical cancer*
Your reference : PG/ZP-2.746.254
Our reference : I-191/AK/KG/cn/831-E
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Dear Minister,

I am pleased to be able to present you with my Council's advisory report *Vaccination Against Cervical Cancer.* The report sets out the advice of a specially convened Health Council committee with regard to the possible inclusion of vaccination against human papilloma virus (HPV), the virus that causes cervical cancer, in the National Immunisation Programme (NIP).

When considering the desirability of including this new form of vaccination in the NIP, the committee applied the seven criteria developed by the council in the context of its report on the future of the programme, published in 2007. The efficiency of vaccination against HPV was assessed using two cost-effect analysis models. One of these models was developed for your ministry by researchers at the VU University, Amsterdam, in collaboration with the RIVM, the other by the Erasmus Medical Centre, Rotterdam.

The Committee's recommendation is that vaccination against HPV should be provided through the NIP for girls at the age of twelve. In addition, the Committee believes that a catch-up programme should be organised for girls aged between thirteen and sixteen at the time of the vaccination's introduction. The Committee also suggests that the Health Care Insurance Board should consider whether the vaccination of girls and women aged seventeen or older can be funded through the Reimbursement System for Pharmaceutical Products (Geneesmiddelenvergoedingssysteem). Because much has still to be learned about HPV vaccination, and because it will be a long time before its precise impact is apparent, the Committee considers it essential that, when the vaccination is introduced, a monitoring programme is also set up. The aim of such a programme should be to gather information about the effectiveness of the vaccination, the duration of protection afforded, any side-effects, acceptance and relevant behavioural factors. I fully endorse the recommendations of the committee contained in the advisory report.

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The attached report is to be followed by a second report, which will focus on certain questions contained in your request for advice, which have yet to be addressed. These questions concern possible improvements to the established cervical cancer screening programme.

Yours sincerely,

Prof. J.A. Knottnerus

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No. 2008/08E, The Hague, March 31, 2008

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues...” (Section 22, Health Act).

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Executive summary

New vaccine can help to prevent cervical cancer

The Netherlands has had a successful cervical cancer screening programme for several decades. Women between the ages of thirty and sixty are checked for the disease or its precursors, with a view to providing treatment as early as possible in appropriate cases. Recently, however, vaccines have come onto the market, which can be used to prevent cervical cancer – one of the more common forms of cancer in women.

It has been known for some time that persistent infection by human papilloma virus (HPV) is responsible for cervical cancer. HPV is transmitted by sexual contact; most women acquire HPV infections, most of them without any untoward consequences. However, a small percentage of women who become infected go on to develop pre-cancerous conditions and in a small proportion of these women, the pre-cancerous conditions lead to cervical cancer. The vaccines now available prevent the development of the precursors of cervical cancer, and thus are likely to prevent the cancer itself. The use of such vaccines would therefore enable primary prevention, to complement the existing early detection and early treatment activities.

Vaccines require careful assessment before they can be included in the National Immunisation Programme

Now that vaccination against HPV is possible, it is necessary to consider whether such vaccination should be included in the National Immunisation Programme (NIP). The NIP is the vehicle for the provision of large-scale public vaccination in the Netherlands. If inclusion in the programme is considered appropriate, it is also necessary to decide which population groups should undergo vaccination. The Minister of Health, Welfare and Sport accordingly asked the Health Council to address these questions.

New forms of vaccination are not included lightly in the National Immunisation Programme. Inclusion in the NIP implies administration to large numbers of healthy people, which is justifiable only where there is convincing scientific evidence that the vaccination is both effective and safe. Various other criteria must also be met before a vaccination can be added to the NIP list. However, it is important to recognise that absolute satisfaction of any individual criterion is not possible: almost no vaccine is totally effective or entirely without adverse events.

It is not possible to say definitively whether a new form of vaccination should or should not be included in the NIP until it has been carefully assessed against the relevant criteria. Such assessment is required for HPV vaccination just as for any other form of vaccination. Indeed, assessment is all the more important where a new vaccine, such as HPV vaccine, is concerned, since relatively little experience of its use has been gained and little long-term research has been conducted.

The currently available data on efficacy and safety is favourable

The first criterion for admission to the NIP is that the condition addressed by the vaccine must be a serious public health problem. This is self-evidently the case where HPV vaccination is concerned: cervical cancer is a relatively common form of cancer in women between thirty and sixty years old. Despite the existence of an effective screening programme, there are roughly six hundred cases of the disease a year in the Netherlands, leading to the death of between 200 and 250 women.

Whether HPV vaccination satisfies the second criterion – that the vaccination should be an effective means of preventing the relevant disease – is harder to say. The vaccines have been developed only recently and, because the interval between HPV infection and the development of cervical cancer averages about twenty years, there are as yet no data to show whether vaccination leads to a fall

in the incidence of cervical cancer. At present, the only information available relates to the vaccine's effectiveness as a means of preventing HPV infection and the precursors of cervical cancer. Nevertheless, it is reasonable to assume that a lower infection rate and a lower incidence of pre-cancerous conditions – phenomena which *are* demonstrably associated with vaccination – will lead to less cervical cancer. The basis for this assumption is the proven correlation between prolonged HPV infection and the development of cancer of the cervix.

Certainty regarding the effectiveness of vaccination as a means of preventing cervical cancer can be obtained only through clinical use of the vaccine and by following up vaccinated girls and women over an extended period. Further research and conscientious monitoring are therefore essential.

Research has shown that vaccination is useful only if a woman has yet to be infected by HPV. It would therefore seem rational to make the vaccine available to girls at an age when most have yet to become sexually active. The Committee regards twelve years old as appropriate in this regard. The question arises, however: if girls are vaccinated at that age, does the vaccine provide lifelong protection against HPV infection? Unfortunately, this question cannot yet be answered with confidence. Here again, long-term research is required to establish whether booster vaccinations are needed in order to provide proper protection.

It is also worth noting that, even if vaccination were fully efficacious, it could not prevent more than 70 per cent of cervical cancer cases in the Netherlands. The reason being that the available vaccines are designed to protect against two particular cancer-triggering HPV types, which together account for 70 per cent of cases of the disease.

With regard to safety, the third assessment criterion, there is currently no reason to suppose that the vaccine has any adverse events that might preclude its inclusion in the NIP. Nevertheless, the possibility cannot be excluded that, if it were administered to large numbers of people, relatively uncommon adverse events might come to light in due course. This underlines the importance of careful monitoring following the introduction of this form of vaccination.

The cost is relatively high

The fourth and fifth assessment criteria relate to the acceptability of the vaccination in its own right and as an element of the vaccination programme as a whole. The Committee sees no problem on either count: if vaccination against HPV were included in the NIP, it would not represent a disproportionate burden on the target group. Nevertheless, the particular nature of this vaccination does warrant consideration. Given that what is at issue is the vaccination of twelve-year-old

girls against a sexually transmitted infection that can lead to cancer, proper education is very important.

Assessment of HPV vaccination against the sixth criterion – that the vaccination should be an efficient means of preventing the target disease – is more difficult. Because the Netherlands already has a successful cervical cancer screening programme, the benefit attainable by HPV vaccination is less than it would be in a country without such a well organized programme. Consequently, the cost-benefit ratio is less favourable in the Netherlands than in most countries. It should be recognised that the inclusion of HPV vaccination in the NIP would not do away with the need for screening, partly because vaccination does not provide universal protection and partly because unvaccinated women would still need screening.

Given that screening will continue to be necessary even if HPV vaccination is provided through the NIP, the cost of operating the combined programme will be quite high, relative to the attainable health benefit. This is apparent from modelling undertaken specifically to support this report. Furthermore, uncertainty exists regarding a number of factors relevant for modelling, such as the long-term efficacy of the vaccine, the possible need for booster vaccinations, and the price of the vaccine. It is only by monitoring prolonged use that the relationship between the cost of vaccination and the benefits will become clear.

Nevertheless, the Committee believes the capital cost apparent at the present time to be justified by the attainable benefits. It is reasonable to suppose that the provision of HPV vaccination to twelve-year-old girls, in combination with screening, will in due time prevent several hundred more cases of cervical cancer a year, and about a hundred deaths.

Hence, the introduction of this vaccination may be regarded as urgently needed – the seventh and final assessment criterion. No other form of vaccination currently under consideration for inclusion in the NIP is capable of having such a marked effect on mortality. Equally urgent is a catch-up programme of vaccination for girls aged thirteen to sixteen at the time that HPV vaccination is introduced. Considerable health benefit could be obtained by vaccinating females in this age range, since most of them will not yet have been infected by the virus.

Where older girls and women are concerned, consideration should be given to funding vaccination through the Reimbursement System for Pharmaceutical Products (Geneesmiddelenvergoedingssysteem). This would imply communally-funded vaccination outside the context of the NIP.

Inclusion in the NIP requires flanking policy

Assessment against the seven criteria suggests that the admission of HPV vaccination to the NIP would be justified. A particularly attractive feature of such a move is that a certain amount of cervical cancer could be prevented altogether, rather than merely caught early and treated. The Committee accordingly recommends the introduction of HPV vaccination for twelve-year-old girls through the NIP. The Committee further recommends that girls aged thirteen to sixteen at the time that HPV vaccination is introduced be vaccinated in the context of a catch-up programme. Finally, it is also recommended that consideration should be given to asking the Health Care Insurance Board to look at the possibility of funding the vaccination of girls and women aged seventeen or older through the Reimbursement System for Pharmaceutical Products.

The Committee qualifies its recommendations by emphasising that the introduction of HPV vaccination to the NIP should be accompanied by establishment of an ongoing programme for studying and monitoring the effectiveness and safety of this form of vaccination and the longevity of the protection afforded. Other relevant factors, such as public acceptance and the effectiveness of the accompanying education activities (which are very important in this case), require careful evaluation as well. Such steps are necessary in order to obtain the knowledge that is currently lacking, and to ensure that the vaccination programme remains effective and safe.

Following the introduction of HPV vaccination, participation in the cervical cancer screening programme will continue to be very important, even for vaccinated women. It is vital that this message is effectively communicated to the public.

Chapter 1

Introduction

1.1 Background to the request for advice

New vaccine can prevent cervical cancer

Vaccines have recently become available that can prevent infection by human papilloma virus (HPV). This represents an important medical development, because HPV infection can lead to cervical cancer in women. It is therefore now possible to immunise people against a cause of cancer. Hence, the question arises: should programmatic vaccination against HPV be introduced.

The Netherlands has a vehicle specifically for the provision of large-scale public vaccination: the National Immunisation Programme (NIP). In the context of the NIP, the advantages and disadvantages of a given form of vaccination are carefully assessed on the basis of the best available scientific knowledge. This approach ensures the effective and safe provision of vaccines and results in the prevention of much morbidity and mortality.

In the past, the NIP has focused primarily on preventing childhood illness. In recent years, however, its scope has been broadened to include vaccines for older children and adults. In principle, therefore, general vaccination against HPV could be provided through the NIP. Nevertheless, certain conditions must be met before any new form of vaccination is deemed suitable for inclusion in the programme.

Reasons for considering general vaccination against HPV

Those conditions were set out in a recent Health Council report over the future of the NIP.[1] In that report, the Council defined an assessment framework and seven criteria for the inclusion of vaccinations in public programmes. The report also made a provisional assessment of the merit of adding HPV vaccination to the NIP. In view of the potential health benefit, the Council described the emergence of vaccines against HPV-induced cancer as a major development. However, uncertainty regarding the vaccination's effectiveness and safety, an appropriate vaccination strategy and the implications for the existing screening programme meant that it was not possible to make any firm recommendations at that time.

1.2 Methodology and scope

Request from the Minister of Health, Welfare and Sport

On 20 March 2007, the Minister of Health, Welfare and Sport (VWS) asked the Health Council to advise specifically on the prevention of cervical cancer by vaccination against HPV. The text of the minister's request for advice is reproduced in Annex A. On 10 July 2007, the President of the Council accordingly set up the Committee on the Prevention of Cervical Cancer. The members of this committee are listed in Annex B. The Committee's draft report was reviewed by three standing expert committees within the Health Council: the Medical Standing Committee, the Infection and Immunity Standing Committee and the Standing Committee on Medical Ethics and Medical Law; the report was also submitted for comment to the National Immunisation Programme Committee.

The minister asked the Health Council to advise on, amongst other things, the effectiveness, safety and efficiency of general vaccination against HPV and – if such vaccination was considered advisable – on the most suitable target group. He also asked the Council to comment on the desirability of trying to provide protection to people outside the target group at the time of introduction. The relationship between any new vaccination programme and the cervical cancer screening programme was also identified as having important policy ramifications. The Netherlands' cervical cancer screening programme has been running since 1976[2] and has proven to be effective.[3-6] Consequently, in a report published in January 2008, the European Centre for Disease Prevention and Control placed the Netherlands amongst the countries where vaccination against HPV was likely to yield comparatively modest health benefits.[7] Careful assessment of the interaction between vaccination and screening is therefore important. The long-term

consequences of any general HPV vaccination programme for the screening of vaccinated women for cervical cancer need to be established, since screening will have to continue in some form or other.

Demarcation in the interests of prompt reporting

The approach taken by the Committee was designed to expedite the reporting process, while ensuring that the efficiency of vaccination was properly assessed in comparison with the existing effective screening programme.

However, it has not proved possible to answer all the minister's questions on the basis of the scientific data presently available. So, for example, it has not been possible to draw conclusions regarding the value of vaccinating boys. To do so, the Committee would require additional information about the HPV-related disease burden and about the effectiveness of vaccination as a means of reducing that burden. Sophisticated dynamic modelling of the spread of HPV infection and the effects of vaccination could also be helpful in the latter context. However, data from modelling of the situation in the Netherlands are not expected until sometime in the course of 2008. Given the urgency of the minister's request, the Committee was not minded to wait for such data before publishing its report.

Nor has it been possible in the available time to consider possible changes to the screening programme that are unrelated to the inclusion of HPV vaccination in the NIP, such as the use of an HPV test in screening for cervical cancer. Such issues will be given proper attention in the second advisory report that the Committee will prepare in response to the minister's request for advice.

The Health Care Insurance Board (CVZ) has previously advised against the inclusion of Gardasil, one of the two vaccines now available, in the list of medicines covered by the national health insurance system.[8] That advice was based partly on an assessment of the therapeutic value and efficiency of vaccination in the context of individual use. The Committee has taken account of the relevant elements of the CVZ report when preparing its advice.

Focus on cervical cancer and preventive vaccines

In this advisory report, the Committee considers only vaccination against HPV as a means of preventing cervical cancer. The latter disease is the most serious health problem associated with HPV infection and it is the condition regarding which most data are available. By focusing exclusively on cervical cancer, the Committee has disregarded other conditions related to HPV, such as anal cancer

and genital warts. Nor is consideration given to the question of therapeutic vaccination. Researchers are currently investigating the possibility of vaccinating women who already have cervical cancer, with a view to slowing or even halting the progress of the disease. However, therapeutic vaccines are at a much earlier stage of development than the preventive vaccines discussed in this report.

1.3 Seven criteria

The Committee assessed the possible inclusion of vaccination against HPV-induced cancer in the NIP on the basis of the seven criteria defined in an earlier advisory report, which have since been adopted by the Minister of VWS.[1] Assessment against the criteria entails examination of all the issues relevant to the formulation of balanced advice reflecting the best available scientific knowledge.

1.4 Structure of this report

The structure of this report is based upon the seven criteria. In chapter 2, the Committee outlines the assessment framework and the criteria used in the context of that framework. In the subsequent chapters, the Committee assesses HPV vaccination against those criteria. Thus, chapter 3 deals with the seriousness and extent of the disease burden associated with HPV. In chapter 4, data on the anticipated effectiveness of vaccination are examined. Chapter 5 considers the issue of safety, and the acceptability of vaccination, in isolation and in the context of the vaccination programme as a whole, is addressed in chapter 6. One particularly important question is how vaccination compares with the existing cervical cancer screening programme (‘smear testing’) in terms of efficiency. That question is dealt with in chapter 7, where the Committee also presents its views on the value of a catch-up programme for girls who are outside the primary target group if and when programmatic vaccination is introduced. In chapter 8, the Committee considers the urgency of introducing general HPV vaccination. The Committee’s final conclusion is presented in chapter 9, along with a summary of the considerations upon which it is based and of possible alternatives to the introduction of HPV vaccination to the NIP. Finally, in chapter 10, various implementation issues are examined. The need for public information – about which the minister specifically enquired – is also discussed.

Chapter 2

Criteria for inclusion in the NIP

2.1 Assessment framework for vaccinations

With a view to ensuring that policy in this field is consistent and reasonable, it is desirable to formulate criteria for the inclusion of vaccinations in the NIP. Such an assessment framework, which can serve a similar function to that which the Wilson and Jungner criteria have in relation to screening, was recently published by the Health Council, in its advisory report on the future of the NIP.[1]

The Council based its proposals on two ethical principles: (1) that the best possible protection should be afforded to the population as a whole and (2) that benefit should be fairly distributed across population groups, with protection provided on the basis of need.

Seven criteria were put forward, designed for assessing the desirability of making a particular form of vaccination available to a particular target group through a public vaccination programme, such as the NIP. In his response to the advisory report, the Minister of VWS indicated that when new vaccinations were considered for inclusion in public programmes, they would in future be assessed against the Council's criteria.

2.2 The seven criteria

The seven criteria provide a framework for the systematic examination of arguments for and against the inclusion of particular vaccinations within the NIP.

Each criterion is formulated on the assumption that the previous criterion has been satisfied. There is nothing to be gained, for example, from considering the effectiveness of a vaccine if the disease that it protects against is either rare or not very serious. And cost-effectiveness need be assessed only if it is clear that the vaccine will be effective and safe when given to the relevant target group.

The criteria should not, however, be regarded as a sort of checklist for generating instant answers to NIP inclusion questions. To arrive at a conclusion, it is necessary to carefully assess the available scientific information in order to decide whether each criterion is satisfied. Furthermore, judgements on the desirability of inclusion are always qualified: almost no vaccine is 100 per cent effective or entirely without side-effects. The situation will be even more complex whenever several options are under consideration, each with its own pros and cons.

Assessment should be performed by an independent body, such as the Health Council, which has no interest in the outcome and is not involved in vaccination programme implementation. The seven criteria are summarised in table 1 and are discussed in the following chapters.

Table 1 Criteria for providing vaccination to a particular group through a public programme.[1]

Seriousness and extent of the disease burden
1 The infectious disease causes considerable disease burden within the population: • The infectious disease is serious for individuals, and • The infectious disease affects or has the potential to affect a large number of people.
Effectiveness of the vaccination
2 Vaccination may be expected to considerably reduce the disease burden within the population: • The vaccine is effective for the prevention of disease or the reduction of symptoms. • The necessary vaccination rate is attainable (if eradication or the creation of herd immunity is sought).
3 Any adverse reactions associated with vaccination are not sufficient to substantially diminish the public health benefit.
Acceptability of the vaccination
4 The inconvenience or discomfort that an individual may be expected to experience in connection with his/her personal vaccination is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole.
5 The inconvenience or discomfort that an individual may be expected to experience in connection with the vaccination programme as a whole is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole.
Efficiency of the vaccination
6 The ratio between the cost of vaccination and the associated health benefit compares favourably to the cost-benefit ratio associated with other means of reducing the relevant disease burden.
Priority of the vaccination
7 The provision of vaccination may be expected to serve an urgent or potentially urgent public health need.

Chapter 3

Seriousness and extent of the disease burden

The first step in the assessment of HPV vaccination for inclusion in the NIP is to establish the levels of morbidity and mortality associated with the conditions that HPV infection can cause. The principal condition caused by HPV infection – and the disease on which this report concentrates – is cervical cancer. However, HPV is linked to other conditions as well.

In the context of cervical cancer, it is important to distinguish between two tissue types: (the more common) squamous cell carcinoma and (the less common) adenocarcinoma. Where reference is made in this advisory report to cervical cancer, both types are referred to, unless distinction is explicitly made.

3.1 Virus and infection

3.1.1 Proven correlation between virus and disease

HPV infection is a prerequisite for the development of cervical cancer. It was in the 1970s that Zur Hausen *et al.* first detected HPV in association with cervical cancer and speculated that the virus played a role in the development of the disease.[9,10] In 1996, HPV was formally classified as a carcinogen by the World Health Organization (WHO). Various studies demonstrated a very strong correlation between the occurrence of cervical cancer and HPV infection.[11,12] It is now generally assumed that HPV infection is the trigger for all cases of cervical can-

cer.[13] The correlation between HPV and cervical cancer is one of the strongest known correlations between an environmental factor and cancer in humans.

It is worth noting that not all types of the virus cause cervical cancer. More than a hundred types of HPV are known; of these, more than forty can lead to genital infections, and at least thirteen are carcinogenic in humans. The types concerned are HPV-16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66. Globally, HPV-16 and 18 are together responsible for roughly 70 per cent of cervical cancer cases; each of the other types causes a (much) smaller percentage.[14,15] The proportion of adenocarcinoma cases accounted for by HPV-16 and 18 is at least as great as the proportion of squamous cell carcinoma cases.[15-17] The relative significance of the other HPV types in the causation of cervical cancer varies around the world. The HPV types that can cause cancer are known as high-risk HPV types (hrHPV).

Only a small proportion of women who contract an HPV infection ultimately develop cervical cancer. Other factors must therefore play a role. Research has indentified various cofactors, including smoking and the number of sexual partners.[5,18-20] These cofactors play a relatively minor role, however, relative to HPV.[21,22]

3.1.2 Communication of the virus

HPV is communicated by sexual contact. Infection by HPV is a very common sexually transmitted infection (STI) in young women. Woodman *et al.* undertook a study of more than a thousand fifteen-to-nineteen-year-old girls who visited an oral contraception advice centre in Birmingham (UK). Over a period of three years, 44 per cent of the girls contracted one or more types of HPV infection. Most common were HPV-16 and 18 infections, found in 10.5 and 6.6 per cent of the subjects, respectively.[23,24] Ho *et al.* monitored six hundred slightly older female students (average age: twenty) in New Jersey (USA) and observed that, within three years of the study starting, 43 per cent of them had been infected by one or more types of HPV.[25]

If a person is infected with HPV, the risk of that person passing the infection on to any sexual partner is very high: at least 40 per cent and possibly 80 per cent or more.[26,27] Consequently, the number of changes of partner needed to maintain an epidemic is low. Few data are available that shed light on the risk of a woman contracting an hrHPV infection at some time in her life. However, the data that are available suggest that most women will be infected by one or more types of hrHPV at some point.[27,28]

Condom use reduces the likelihood of transmission, but does not exclude the possibility. Women whose male sexual partners consistently use condoms are 70 per cent less likely to acquire infections than women whose partners rarely use condoms.[29] Consistent condom use is also associated with lower rates of abnormality in the cervical epithelium among women with persistent HPV infections.[30,31] The same study found that, in men, condom use led to better rates of recovery from HPV-associated penile lesions.

3.1.3 *Natural history of the infection*

HPV infections normally become established in the transitional zone between the squamous epithelium of the cervix and the cylindrical epithelium of the cervical canal. The position of this transitional zone varies. Before puberty and after the menopause, it is in the cervical canal but, during a woman's fertile years, and especially during pregnancy, the transitional zone extends to the perimeter of the cervix. It may be that, because the average age of first sexual contact is now lower than it was in previous generations, the vulnerable transitional zone is exposed from a relatively early age.[27]

The natural history of HPV infection may be summarised as follows.[23,25,27,28,32-38] Most women contract hrHPV infections at one time or another, most of which are asymptomatic. It is not possible to define risk groups for HPV infection. Although infections may persist for months, most disappear without intervention and cause no abnormalities in the cells of the cervical epithelium. In a small minority of cases, however, infection becomes chronic and does lead to changes in the epithelial cells and pre-malign abnormalities of the cervix (cervical intraepithelial neoplasms, or CINs). Three precancerous states are recognised, characterised by minor, moderate and serious lesions (CIN1, CIN2 and CIN3, respectively) and increasing degrees of abnormality. However, chronic (persistent) infections and even CINs are spontaneously rectified more often than not. It is likely that a variety of factors relating to the virus and the host collectively dictate the course of infection, but what those factors are and how they interact is largely unknown. Consequently, it is not possible to identify any particular groups as being at risk of progression. Without intervention, roughly 2 per cent of all hrHPV infections ultimately lead to cervical cancer.

3.1.4 *Immune response to infection*

HrHPV is extremely well adapted to the epithelial cells of the skin and mucous membranes of the external sex organs and cervix. In the relatively sheltered envi-

ronment of the epithelial cells, the virus rarely comes into contact with the immune system's antigen-presenting cells. Initially, HPV multiplies at a fairly modest rate.[39] In the basal cell layer of the epithelium, where HPV first takes hold, only intracellular HPV proteins are expressed, so it is unlikely that humoral mechanisms (antibodies) play a role during the early stages of infection. Innate immunity is more likely to be significant in this phase.[40,41] Later, most women develop an effective immune response, enabling the immune system to destroy the virus. This response is predominantly cellular, mediated by HPV-specific T-cells, and immunological memory is acquired.[42,43] Antibodies may also be produced, which probably play an important role in fighting off any subsequent re-infection by the same HPV type. Such acquired immunity is likely to afford little protection, however, against other HPV types.[44] If the immune system is not able to deal with the virus, a persistent infection may develop.[22] Viral persistency is a precondition for the ultimate development of cervical cancer.[36]

3.2 Morbidity and mortality associated with cervical cancer

Globally, cervical cancer is the second most common form of cancer in women, after breast cancer.[45] Roughly 80 per cent of new cervical cancer cases occur in developing countries.[45] In the Netherlands, six to seven hundred women a year are diagnosed with cervical cancer. The national screening programme ensures that the condition is detected early in many cases. As a result, effective treatment in the form of excision of the transitional zone is usually possible. Nevertheless, between 200 and 250 Dutch women a year die as a result of this condition. Approximately half of the fatal cases involve women who had not participated in the screening programme. If cancer is not detected early, more radical surgery, chemotherapy or radiotherapy is required. Even if such treatment is successful, it is liable to have permanent implications, such as lymphoedema of the legs, urinary and defecation problems, and sexual difficulties. Without treatment, cervical cancer is always fatal.

Partly because of the screening programme, cervical cancer-related morbidity and mortality are lower in the Netherlands than in its neighbouring countries. This is apparent from the data for 2004 presented in table 2.[46] Furthermore, the incidence (frequency of new cases) is falling in the Netherlands: in 1989, it stood at 9.1 per 100,000 women, but by 2003 it had fallen to 6.2 per 100,000 (European Standardised Rate).[47] The decline was attributable entirely to fewer cases of squamous cell carcinoma; the incidence of adenocarcinoma remained unchanged.[48] The reason for this is that the abnormalities that precede adenocar-

cinoma (adenocarcinoma in-situ, AIS) are not easy to observe by means of a conventional smear test, because they occur inside the cervical canal.5 In the same period, mortality due to cervical cancer fell from 3.3 to 2.0 per 100,000 women per year.[47] The figures for the Netherlands presented in table 2 are higher than those cited in this paragraph, because they were calculated by a different method.[46]

Efforts continue to bring about further reductions, partly on the basis of improved screening. It is hoped that better detection rates can be achieved by testing for the genetic material of HPV and by home testing (self-sampling) for women who are averse to participation in the screening programme.

Table 2 Cervical cancer in 2004, disease burden and mortality in the 25 EU countries, Iceland, Norway and Switzerland.

	Age-standardised incidence per 100,000 woman-years	Age-standardised mortality per 100,000 woman-years
Estonia	20.3	8.9
Slovakia	20.3	7.4
Czech Republic	20.2	7.4
Lithuania	20.1	12.4
Slovenia	19.6	5.1
Poland	19.2	9.6
Hungary	18.0	8.9
Portugal	17.2	5.6
Denmark	15.2	5.0
Luxemburg	13.2	4.1
Cyprus	13.1	6.2
Norway	12.9	3.8
Germany	12.3	4.4
Belgium	12.0	4.9
France	11.7	3.8
Latvia	11.5	10.0
Austria	10.9	4.4
Switzerland	10.1	2.0
UK	9.8	3.6
Sweden	9.7	3.6
Italy	9.5	2.6
Spain	9.5	3.0
Iceland	9.2	2.7
Ireland	8.6	3.7
Greece	8.0	2.7
Netherlands	***8.0***	***3.0***
Malta	6.0	3.4
Finland	4.9	1.6

3.3 Morbidity and mortality due to other HPV-related conditions

Other forms of cancer

Various other forms of cancer are associated with HPV, albeit to a lesser extent than cervical cancer.[45] Infection by HPV-16 or 18 is responsible for the vast majority of cases of anal cancer, distributed equally between men and women. Cancer of the vulva and vagina and cancer of the penis is attributable to HPV in 40 per cent of cases. Finally, HPV is responsible for roughly 10 per cent of cancers of the pharynx and 3 per cent of mouth cancer cases.[45] The Committee was unable to find a great deal of attribution data relating specifically to the Netherlands,[49] but it is considered unlikely that the percentages given above are not reflected in the Netherlands.

Some HPV types that are not involved in genital infections, such as HPV-5 and 8, may also be carcinogenic. In combination with exposure to UV radiation, these forms of HPV may play a role in the development of skin cancer.[21]

Genital warts

Two other humane papilloma viruses, HPV types 6 and 11, are responsible for nearly all cases of genital warts; 20 to 50 per cent of the warts are simultaneously infected with one or more hrHPVs.[50] A Dutch study of people consulting their GPs in connection with sexually transmitted infections found that the national prevalence of genital warts was 64 cases per 100,000 people.[51] Genital warts are therefore a common sexually transmitted viral condition in the Netherlands.

3.4 Conclusions

The disease burden associated with cervical cancer is considerable

In an earlier report, the Health Council described cervical cancer as a disease that is serious for individual sufferers and affects a large number of people.[1] Further evidence in support of this conclusion has been presented in the report now before you. The disease burden associated with cervical cancer is considerable, even though the Netherlands has an effective screening programme, leading to the early diagnosis and treatment of many women. The Committee recognises that the disease burden in the Netherlands is considerably less than that in most other countries, where there is no such effective screening. This means that the

health benefit potentially attainable through vaccination is not as great in the Netherlands as in many other countries.

It is very likely that HPV is responsible for other conditions as well

As well as causing cervical cancer, HPV is responsible for considerable disease burden in the form of other conditions, including other forms of cancer and genital warts. However, the data available on these other conditions are insufficient to support an assessment of the benefit attainable through public vaccination. This means, for example, that it is not presently possible to make any definitive statement about the importance of vaccinating boys. Further research into the disease burden associated with other HPV-induced cancers is desirable.

If vaccination is introduced, twelve-year-old girls are the most appropriate target group

The Committee sees the prevention of cervical cancer as the primary aim of the proposed provision of HPV vaccination through the NIP. In view of the strong correlation between HPV infection and the development of cervical cancer, this aim can best be achieved by preventing such infection, which implies vaccinating girls at an age when the vast majority have yet to become sexually active. Hence, the Committee believes that the target group for any public vaccination programme should be girls no more than twelve years old. In a large-scale study of sexual behaviour in the Netherlands, 3 per cent of girls reported having had sexual relations at that age.[52]

Chapter 4

The effectiveness of vaccination

As indicated in the previous chapter, even though the Netherlands has a successful screening programme, considerable health benefit could be obtained by reducing morbidity and mortality associated with cervical cancer, one of the possible consequences of HPV infection. The next step in the assessment process is to establish whether vaccination could bring about such a reduction. That is the question addressed in this chapter, which begins with certain background information about the vaccines that are now available.

4.1 Data on the vaccines

Development of the vaccine

The discovery that cervical cancer was caused by HPV infection opened the way for the development of preventive vaccines. HPV consists of a circular DNA chain with 8,000 base pairs enclosed in a mantle of L1 and L2 structural proteins. HPV vaccines consist of so-called virus-like particles (VLPs) of L1 protein produced using recombinant DNA technology. Thus synthesised, this protein spontaneously takes on the form of a virus particle[53] and can therefore be used to stimulate the production of antibodies capable of neutralising the virus itself. An important feature of such a vaccine is that it contains no viral DNA, which might be carcinogenic.

The original research into the efficacy of the vaccines against papilloma viruses was carried out on laboratory animals. Injecting the animals with VLPs appeared to protect them against infection and against related conditions. Similarly high levels of antibody production were subsequently induced in humans.

Two pharmaceuticals companies, Merck and GlaxoSmithKline, were then awarded licences to use the VLP production technique.

Two vaccines now available

Two vaccines against HPV are now available. The first, Gardasil, produced by Merck and marketed in Europe by Sanofi Pasteur MSD, was approved and registered in 2006; the second, the GlaxoSmithKline product Cervarix, became available in the autumn of 2007.[54,55] The Health Council generally prefers not to refer to pharmaceutical products by their brand names in its reports. However, the Committee felt such specific reference was necessary in this context, in the interest of clarity.

Both vaccines are designed to provide immunity against HPV-16 and 18: the two types of the virus responsible for about 70 per cent of cervical cancer cases. Gardasil also provides protection against HPV-6 and 11, which together cause nearly all genital warts. Broader-spectrum vaccines capable of protecting against hrHPVs other than HPV-16 and 18 may become available in due course.

The vaccines differ from one another in terms of the adjuvants (vaccine-aiding agents) they utilise. Gardasil uses the well-established adjuvant aluminium hydroxyphosphate sulphate, while Cervarix uses the equally widely employed aluminium hydroxide, but in combination with monophosphoryl lipid A, a chemically modified lipopolysaccharide, that influences the innate immune system. The latter complex is known as ASO4. Cervarix stimulates higher levels of antibody production, but the significance of this phenomenon for its protective effect is not known.

In Europe, Gardasil is licensed for administration to people aged between nine and twenty-six; it is indicated for the prevention of CIN2 or CIN3 (CIN2/3), cervical cancer, the precursors of vulva cancer (serious intra-epithelial neoplasms of the vulva, VIN2/3) in girls and women, as well as the prevention of genital warts in boys and men.[54]

The terms of the licence are based on data on the vaccine's efficacy and safety for girls and women aged sixteen to twenty-six, and on data on the serological response to vaccination in and the safety for girls and boys aged nine to fifteen. The European Medicines Agency (EMEA) highlights the fact that there

are no data regarding the protection afforded to boys and men.[54] In the USA, the vaccine is not licensed for administration to boys or men.

Cervarix is licensed in Europe for administration to girls and women aged ten to twenty-five; it is indicated for the prevention of CIN2/3 and cervical cancer.[55] The terms of the licence are based on data on the vaccine's efficacy and safety for girls and women aged fifteen to twenty-five, and on data on the serological response to vaccination in and the safety for girls and women aged ten to twenty-five.

Effect of vaccination compared with the effect of natural infection

Once a person has recovered from a natural infection, he or she is normally protected against re-infection by the same micro-organism. Vaccination seeks to induce similar protection (immunity) without any symptoms of the natural disease. Vaccination against childhood illnesses is a classic example of this. However, while vaccination can lead to immunity in much the same way as a natural infection, it sometimes uses a different mechanism. That is the case with HPV.

Natural immunity following infection by the virus is based mainly on T-cell-mediated cellular immunity (see 3.1.4). Vaccination induces immunity by a somewhat different mechanism. Intramuscular administration of the vaccine triggers a systemic immune response involving antibody production on a scale that far exceeds that associated with natural infection. The antibodies produced have a powerful neutralising capacity: they have been shown to be very effective at tackling the primary infection. It has also been demonstrated that vaccination induces immunological memory.[56] The extent to which cellular mechanisms also contribute to the immunity acquired following vaccination is not known.

With both Gardasil and Cervarix, three doses are required to provide protection. The vaccination scheme for Gardasil is zero, two and six months, while that for Cervarix is zero, one and six months.

4.2 Data on effectiveness

4.2.1 How efficacy is best measured

It is important to consider the effectiveness of any proposed vaccination, i.e. its ability to reduce morbidity and mortality and thus to serve its primary purpose of providing health benefit. HPV vaccination is difficult to assess in this way, however. There is a considerable interval between the contraction of an HPV infection and the development of cervical cancer (usually at least fifteen years[57-59]), but

the follow-up programmes to gather information about the efficacy of the vaccines have so far been running only for about six years. As a result, it is not yet possible to draw definitive conclusions regarding the effectiveness of vaccination as a means of preventing cervical cancer.

It is nevertheless possible to gauge effectiveness in other ways. As long ago as 2003, the WHO brought together a group of experts, including representatives of government and industry, to discuss an assessment framework for HPV vaccines.[60] This group decided that the efficacy of such vaccines could reasonably be assessed by reference to data not only on cervical cancer, but also on moderate or serious pre-malign abnormalities (CIN2/3 and AIS). This view took account of both pragmatic and moral considerations.

The principal moral consideration was that the development of such pre-malign abnormalities is a precondition for the development of cervical cancer. This principle already underpins the success of the existing screening programme: pre-malign lesions are detected and treated, thus reducing the incidence of cervical cancer. On the pragmatic side, if vaccine efficacy were deemed demonstrable only by data on cervical cancer, it would be many years before a conclusion could be reached and much greater study populations would be needed, possibly making trials impractical and unviable. Such an approach would also raise ethical objections, because any woman in whom CIN3 is detected requires treatment.[60]

The group additionally indicated that persistent hrHPV infection rates could be regarded as a measurable outcome of vaccination. Such infections are considered to be a necessary precondition for the development of (the precursors of) cervical cancer, and their prevention may therefore be viewed as a measure of a vaccine's protective effect.[60]

The Committee decided to adopt this assessment framework, subject to the qualification that it would have been scientifically preferable to use the CIN3 rate as the sole indicator of effect. CIN3 is significantly more likely to develop into cervical cancer than CIN2 (the respective rates of risk in women under the age of thirty-five being at least 12 per cent and 5 per cent).[32,61,62] Furthermore, the diagnosis of CIN3 is more reliable than that of CIN2.[63] Unfortunately, however, the published data on the efficacy of the vaccines (considered below) relate to both CIN2 and CIN3, making separate analysis impossible.

4.2.2 The available research results

The efficacy of the vaccines in the prevention of CIN2/3 has been studied in accordance with the WHO assessment framework. In addition, the effect of vac-

cination on persistent hrHPV infections has been monitored. A significant body of published trial data is now available.[64-70] The work done with the two vaccines differed in terms of study design and analytical methodology. One difference concerned the inclusion/exclusion criteria: the Gardasil analysis was confined to women that were free of hrHPV infection both before the first inoculation and after the third, whereas the criterion for inclusion in the Cervarix analysis was the absence of infection at the outset only.

The efficacy of Gardasil against CIN2/3 and against AIS was calculated to be 99 per cent (95% confidence interval [95%RI] 93-100 per cent) after an average follow-up of three years.[65] It was also found that Gardasil vaccination afforded protection against the precursors of cancer of the vagina (VaIN2/3) and the vulva (VIN2/3). With these conditions, the efficacy was 100 per cent (95%CI 72-100 per cent). Vaccination also proved effective against genital warts (100 per cent, 95%CI 92-100 per cent).[67,68] Research into the effect of vaccination on the persistency of HPV infections was carried out in the context of earlier (phase II) trials,[71] through the combined analysis of persistent infections involving one or more of the four HPV types addressed by the vaccine. The efficacy against such combined infections was found to be 90 per cent (95%CI 71-97 per cent). It is not clear what this implies in terms of the vaccine's efficacy against infection by HPV-16 or HPV-18 on its own.

The efficacy of Cervarix against CIN2/3 was found to be 90 per cent (95%CI 53-99 per cent), given an average follow-up of fifteen months.[69] At the end of the study, some CINs proved to contain several hrHPVs. The authors concluded that three of these lesions (including two from the vaccine group) were not caused by HPV-16 or 18.[69] If the figures are corrected accordingly, the efficacy rises to 98 per cent (95%CI 74-100 per cent).

The efficacy of Cervarix has been investigated against both histological abnormalities and persistent HPV infection.[69,70] In one study, a relatively small group of women (less than a thousand) was followed up over a relatively long period (an average of 4.5 years). Persistent infections involving the vaccine-related hrHPVs were much less common in vaccinated women than in women in the control group.[70] After both six and twelve months, the efficacy was found to be 94 per cent (95%CI 78-99 per cent after six months and 61-100 per cent after twelve months). Another study, involving a larger group of women (nearly 16,000), but a shorter follow-up (an average of 15 months) yielded similar results: the efficacy after six and twelve months being 80 per cent (95%CI 70-87 per cent) and 76 per cent (95%CI 48-90 per cent), respectively.[69]

In the Committee's view, these findings indicate that, in the relatively short term, both vaccines are efficacious against the development of the precursors of cervical cancer. There is also published evidence that Cervarix in particular protects against persistent infection by vaccine-related HPV types. It will be many years, however, before the efficacy of the vaccines in the prevention of cervical cancer, the actual target disease, can be quantified.

4.2.3 *Protection against non-target HPV types*

The existing vaccines consist of VLPs of the structural L1 proteins in HPV types 16 and 18. The antibodies produced in response to vaccination are effective against the corresponding virus types. However, there are immunological similarities between various hrHPVs. HPV-16 and HPV-31, for example, have similar epitopes (protein components against which antibodies develop), as do HPV-18 and HPV-45. Antibodies to HPV-16 therefore respond to HPV-31 as well, and antibodies to HPV-18 respond to HPV-45. This may lead to cross-immunity, with antibodies to HPV-16 (or HPV-18) also protecting against HPV-31 (or HPV-45). This is of theoretical significance, because it may be that the vaccines afford at least partial protection against hrHPVs other than those for which they have been designed. It is not clear from the study data whether this happens in practice, because the antibodies seem to have responded less strongly to the other hrHPVs referred to than to the target virus types.[44]

The question of cross-immunisation was addressed by the aforementioned studies into the effectiveness of Cervarix vaccination in the prevention of HPV infection.69,70 In the small group/long follow-up study, the researchers monitored HPV-31 and HPV-45 infections, but not persistency.70 There was a reduction in such infections, but the level of protection against non-target hrHPVs was found to be lower than the level of protection against the target types; the efficacy was 54 per cent against HPV-31 (95%CI 12-78 per cent) and 94 per cent against HPV-45 (95%CI 63-100 per cent). In the large group/short follow-up study, protection against persistent infections – a more clinically relevant outcome indicator – was also investigated. Vaccination was found to reduce the frequency of HPV-31 and HPV-45 infections that persisted for six months, but it was not as effective against these types as against HPV-16 and HPV-18: its efficacy was 36 per cent against HPV-31 (95%CI 0.5-60 per cent) and 60 per cent against HPV-45 (95%CI 3-85 per cent).[69] The relatively short duration of this study means that the data support no conclusions regarding the level of cross-immunity after twelve months.

The first data on the cross-protection afforded by Gardasil were presented at a congress in the USA in the summer of 2007.[72] The reported study looked at the effect of vaccination on the development of CINs attributable to non-target hrHPVs. The results indicated that Gardasil affords 38 per cent protection (95%CI 6-60 per cent) against ten hrHPVs other than HPV-16 and HPV-18, which are together responsible for 16 per cent of cervical cancer cases in Europe. The data were not broken down by particular hrHPV type and have yet to be reported in any peer-reviewed scientific journal.

On the basis of the available data, the Committee concludes that there is reason to believe that vaccination with either of the two vaccines now available may protect against non-target hrHPVs. However, the Committee does not consider the data sufficiently firm to inform its decision-making at the present time.

4.3 Qualification of the research results

4.3.1 Age and gender of the study groups

The data on the efficacy of HPV vaccines referred to above were obtained from studies whose subjects were girls and women older than the ultimate target group. The Gardasil research, for example, involved girls and women aged sixteen to twenty-six.[65] To support the licence application, additional research was conducted into the serological response to vaccination in girls and boys aged nine to fifteen.[54] In this research, the subjects exhibited higher levels of antibody production than older girls and women. The product has been licensed for administration to younger girls and boys on the basis of this 'bridging research'. The Cervarix research involved girls and women aged fifteen to twenty-five.[69] Again, the vaccine's efficacy in younger girls was investigated by means of serological research.[55,73] No data have been published on the efficacy of Cervarix in boys or men.

The Committee concludes that it may be assumed on the basis of research with older girls and women that the vaccines are effective against the precursors of cervical cancer when administered to girls aged nine to fifteen. Research into the efficacy of the vaccines in younger girls is not practicable in the Committee's view: cervical cancer and its precursors are almost never found in this age group, so it is almost impossible to determine the vaccine's effect on these clinical outcomes. Such research would also necessitate subjecting large groups of young girls to regular internal examinations, which the Committee considers undesirable.

The Committee takes the view that the indirect nature of the evidence necessitates further research into the efficacy of the vaccines against persistent HPV infection and the precursors of cervical cancer in vaccinated girls and young women. It is also concluded that there are no data available regarding the efficacy of vaccination in the prevention of disease in boys or men. It is anticipated that the first such data will be published towards the end of 2008.

4.3.2 *Duration of protection*

The studies of the HPV vaccines revealed antibody levels much higher than those associated with natural infection. Antibody levels were still high in subjects about five years after vaccination (the longest anyone has been followed up in the studies reported so far). The Committee therefore considers it likely that immunity continues for at least twice that period following vaccination, i.e. for at least ten years. That hypothesis is supported by Olsson *et al.*'s recent observation that vaccination creates immunological memory.[56] The team found that a single booster jab five years after the original series of three injections was sufficient to restore antibody levels within a week; a month after the booster, they were even higher than they had been following the original vaccination.

According to the Committee, the research data currently available show that the vaccines provide at least five years of protection. The high antibody levels observed after that time and the existence of immunological memory indicate that the duration of protection is probably longer. Nevertheless, the possibility cannot be excluded that one or more booster vaccinations will be required to ensure lifelong protection. Nor is it known whether, if protection diminishes over time, hrHPV infections will occur and, if so, whether they will follow a similar course to that seen in unvaccinated women.[22]

4.3.3 *Virus-related factors*

HPV-16 and 18 are together responsible for roughly 70 per cent of all cervical cancer cases. In theory, therefore, vaccination has the potential to bring about a 70 per cent reduction in the incidence of cervical cancer.

However, it is conceivable that vaccination will lead to an increase in the frequency of infections involving non-target hrHPVs, as a result of the phenomenon of type replacement: other virus types taking the place of their suppressed rival types. Another possibility is a phenomenon known as unmasking, whereby an hrHPV that was previously a hidden participant in combined infections with HPV-16 or 18 continues to cause infections on its own once the more prominent

type has been suppressed. In a commentary on one of the vaccines efficacy research reports, Sawaya and Smith-McCune do not exclude the possibility of type replacement.[74] Finally, there is a possibility of 'hypermutation' in the target vaccine types in response to the selective pressure of the vaccine-induced antibodies. The Committee regards hypermutation as a less likely scenario, because HPV is a very stable virus, unlike for example HIV.

Whether the above-mentioned phenomena actually occur, and whether the decline in the incidence of cervical cancer is consequently less than the theoretical maximum, can be determined only in practice. The Committee considers it important that monitoring is geared to the early detection of phenomena such as type replacement if they should occur.

4.3.4 Effectiveness in practice

The vaccine efficacy data described above were obtained under experimental, ideal circumstances. Under such circumstances, the efficacy of the vaccines in preventing the precursors of cervical cancer and persistent infections associated with HPV types 16 and 18 is reported to be 90 to 99 per cent or even higher.

The Committee estimates the efficacy of the vaccines against cervical cancer, the ultimate target disease, to be 90 per cent. Up to 30 per cent of cervical cancer cases are caused by hrHPVs other than the target types; hence, the vaccine's coverage is roughly 70 per cent. Even in the event of programmatic vaccination through, for example, the NIP, not all girls will be vaccinated; the Committee regards a vaccination rate of 85 per cent to be attainable. Given efficacy of 90 per cent, coverage of 70 per cent and a vaccination rate of 85 per cent, the maximum achievable reduction in cervical cancer is 54 per cent.

The above figures are based on the data currently available. Data on the vaccines' effectiveness in day-to-day practice have yet to be collected.

4.4 Conclusions

Vaccination protects against persistent infection and the precursors of cervical cancer

The initial effect of vaccination is favourable: vaccination leads to the formation of antibodies against the target hrHPVs and thus to protection against infection by those hrHPVs. This in turn brings about a major short-term reduction in the incidence of the precursors of cervical cancer. It is known that the development of such precursors is a prerequisite for the subsequent development of the cancer

itself. However, whether vaccination does in fact protect against cervical cancer will not be known for many years to come.

It is not yet clear whether booster vaccinations will be needed

The duration of the protection afforded by vaccination has yet to be determined. It is known, however, that high antibody levels persist for at least five years and that immunological memory is created. Protection is required, however, for several decades. The possibility that re-vaccination will be needed in order to provide such prolonged protection cannot be excluded at the present time.

Vaccination can theoretically prevent up to 70 per cent of cervical cancer cases

Even if the vaccines were fully effective, cervical cancer would not be eradicated, because the hrHPVs targeted by the vaccines now available are responsible for 'only' 70 per cent of cases. There are indications that the vaccines may provide a degree of cross-protection against other hrHPVs related to the primary target types, but the ultimate clinical significance of the observations remains unclear.

Follow-up research can provide proof of efficacy

The Committee concludes that there is evidence that the vaccines are efficacious against cervical cancer (the primary target disease) when administered to girls (the primary target group). Their efficacy against the necessary precursors of cervical cancer is proven, but no proof of their efficacy against the disease itself is currently available or likely to be available for many years to come. In the Committee's view, the indirect nature of the evidence for the efficacy of HPV vaccination is such that, if HPV vaccination is introduced to the NIP, it necessitates follow-up research into the efficacy of the vaccination as a means of preventing infection and the development of cervical cancer and its precursors.

Monitoring is required

The Committee has qualified the available data in various respects. In view of the uncertainties that remain, the Committee believes that, if HPV vaccination is introduced to the NIP, it should be carefully monitored. Monitoring should focus

particularly on the efficacy of vaccination, on the duration of the protection provided and on safety (see chapter 5).

Little is known about the effect of vaccination on other conditions

The Committee believes that there are currently insufficient data to support any firm conclusions regarding the effects of vaccination on conditions other than cervical cancer in women and on HPV-induced conditions in boys and men. Nevertheless, it is felt that there are grounds for cautious optimism: the data that are available suggest that the vaccines are effective against such conditions, and the role played by the target hrHPVs in the development of other conditions makes an effect plausible.

Chapter 5

Safety

Although the available data provide an incomplete picture of the effectiveness of HPV vaccination, they are sufficient to support the expectation of significant health benefit: vaccination leads to fewer infections and thus to a reduced incidence of the precursors of cervical cancer. We may therefore move on to the next criterion. Thus, this chapter of the report considers whether vaccination might have any adverse effects that offset the attainable health benefit.

5.1 The importance of safety management in public programmes

A public vaccination programme involves the provision of vaccination for preventive ends, usually to healthy people. If the programme is successful and the vaccination effective, the risk of manifestation of the target disease is minimal. Furthermore, the phenomenon of herd immunity means that a degree of protection is often afforded to unvaccinated people as well. When a vaccination programme is successful, the health benefits can be taken for granted and public attention tends to focus on any adverse effects that may occur.

In its report on the future of the National Immunisation Programme, the Health Council devoted considerable attention to the management of safety. The topics addressed in that context included the methodology of research into side-effects and the associated pitfalls, the existing data registration systems, the seriousness-classification of adverse effects and the regulatory framework.[1]

Although the trials so far conducted have involved the administration of HPV vaccine to thousands of women (nearly 12,000 have been given Gardasil and more than 16,000 Cervarix), the numbers are small compared with those that would be involved in general vaccination. If vaccination were made available to all twelve-year-old girls in the Netherlands, that would mean treating roughly 100,000 young people a year. Certainty regarding the vaccine's safety and insight into any rare side-effects that it might have are therefore very important.

5.2 Data from the European licensing process

In the HPV vaccine trials, both the efficacy and the safety of the products have been carefully studied. When a vaccine is considered for licensing, data from scientific research into its possible adverse effects are assessed very carefully. Both vaccines have been licensed (registered) for sale on the European market by the European Medicines Agency (EMEA), and each of them is the subject of a European Public Assessment Report (EPAR).[54,55]

5.2.1 Data on the adverse effects of Gardasil

General data

In the trials, Gardasil was administered to a total of 11,813 people, predominantly women aged sixteen to twenty-six.[54] These people reported adverse effects more often than the recipients of a placebo. The effects in question were mainly phenomena local to the injection site, such as pain, inflammation and swelling. A small proportion of subjects (0.1 per cent of the vaccine groups) withdrew from the trial on account of such reactions.

No serious adverse effects were reported, either in the vaccine group or in the placebo group. Short-lived immunological phenomena were very rare and no evidence was found for a correlation between such phenomena and HPV vaccination. A slightly larger number of vaccine recipients reported problems that could have been indicative of immunologically mediated conditions (nine out of 11,813 people in the vaccine group and three out of 9,701 in the placebo group). The occurrence of such conditions is currently the subject of further research. The Committee would make the point that relatively little is generally known about the occurrence of immunologically mediated conditions in the target group for vaccination, girls of about twelve years old.

Data on use of the vaccine during pregnancy and when breastfeeding

During the trials, 1,115 women who had received the vaccine became pregnant. The data on the course of these women's pregnancies gave no cause for concern. Furthermore, no adverse effects on pregnancy, foetal development, birthing or postnatal development were noted during the animal experiments that preceded the trials. It was observed, however, that antibodies against all four relevant HPV types passed through the placenta. The EMEA accordingly recommends that pregnant women should delay vaccination until they have given birth[54] and Gardasil is not licensed for use during pregnancy.

Some 995 of the trial participants were breastfeeding during the trials; 500 of them had received the vaccine, 495 a placebo. The babies of these mothers went on to develop serious medical conditions in, respectively, seventeen and nine cases (3.4 and 1.8 per cent). However, the EMEA concluded that these conditions were not related to the vaccination. The vaccine *is* licensed for use during lactation.[54]

Data on interaction with other pharmaceutical products

The Gardasil trials included a study of the vaccine's effect when administered concomitantly with hepatitis B vaccine. The administration of this second vaccine had no demonstrable influence on the subjects' immune response to the HPV vaccine, or on the monitored safety indicators. Conversely, the administration of Gardasil had no influence on the effect of the hepatitis B vaccine.

Nearly 60 per cent of the Gardasil trial subjects were using oral contraceptives. No evidence was found to suggest that these products interfered with the immune response to HPV vaccination.[54]

5.2.2 Data on the adverse effects of Cervarix

General data

In the trials, Cervarix was administered to a total of 16,142 people, mainly in the fifteen-to-twenty-five age band.[55] Phenomena local to the injection site were more common in the vaccine group than in the control group (which received a hepatitis A vaccine). However, the phenomena concerned were generally mild and short-lived. Fatigue, headache and muscle pain were also more common in the vaccine group. The higher incidence of local and general phenomena in the vaccine group did not lead to a higher dropout rate in the HPV vaccine group

than in the control group. Furthermore, no differences were found between the groups in terms of the incidence of chronic or auto-immune conditions following vaccination. Data on the safety of Cervarix from relatively long-term follow-up research have been reported by Harper *et al.*.[70,75]

Data on use of the vaccine during pregnancy and when breastfeeding

During the vaccine trials, 870 of the HPV vaccine recipients reported becoming pregnant. The data on the course of these women's pregnancies gave no cause for concern. A subanalysis of pregnancies that began at about the time of vaccination found that spontaneous abortion was more common in the HPV vaccine recipients than in the hepatitis A vaccine recipients.[55] No such difference was detected, however, between the HPV vaccine recipients and the members of a second control group, who had received a placebo. Like Gardasil, Cervarix is not licensed for use during pregnancy.

The Committee is not aware of any data regarding the possible effects of vaccination in breastfeeding mothers.

Data on interaction with other pharmaceutical products

No data have been published concerning the possibility of an interaction between Cervarix and other pharmaceutical products, such as vaccines.

The ASO4 adjuvant

Cervarix makes use of a recently developed adjuvant, ASO4 (see 4.1). The EMEA considers it possible that the previously reported local phenomena following vaccination are partly attributable to this adjuvant.[55] The EMEA's final – positive – assessment of the vaccine makes no separate reference to ASO4.

5.3 Qualification of the available data

Age and gender of the study groups

The subjects of the vaccine trials were girls and women aged fifteen to twenty-six. Hence, the data on the adverse effects of the vaccines relate largely to girls and women in this age group. Far fewer data are available concerning girls of the age of the likely programmatic vaccination target group, or concerning males. Where Gardasil is concerned, there are data on only about 930 girls aged

between nine and seventeen, and on 1,056 boys aged between nine and fifteen.[54] Where Cervarix is concerned, a separate study has been conducted, comparing 458 women aged fifteen to twenty-five and 158 girls aged ten to fourteen.[73] No evidence was found to suggest that the younger recipients exhibited a different adverse effect profile.[54,55,73]

At the Committee's request, representatives of the vaccine manufacturers met the Committee to present the available data on possible adverse effects in the primary target group. Some of the data concerned are in the public domain.[73] The information presented to the Committee reinforced the belief that there is no reason to expect the likely target group to respond differently from the trial subject group (made up of a comparatively large number of older women).

Duration of adverse effect monitoring period

As previously indicated, relatively little is known about the safety of either vaccine in the context of a large-scale administration programme. Rare adverse effects might come to light only when the vaccine is given to a large number of people. Furthermore, recipients have so far been monitored for adverse effects only for a few years – a relatively short period for the detection of possible side-effects such as selective influences on the immune system (previously identified by the Health Council as a possible consequence of the increasing use of very pure vaccines[1]). The Committee stresses, however, that there is currently no reason to suspect that the HPV vaccines may have any such selective effect.

Immunologically mediated conditions

If general cervical cancer vaccination is introduced, the Committee wishes to see more research into immunologically mediated conditions and their possible correlation with HPV vaccination. The reason being that such conditions, which include certain forms of diabetes, tend to manifest themselves at exactly the age when the vaccine is likely to be administered. If such conditions develop after vaccination, suspicions of a causal relationship are liable to arise, and it will be difficult to determine whether these suspicions are well founded or not. In the past, for example, there have been suspicions of a link between MMR vaccination and autism.[76] In 2007, the Health Council concluded that there was no reason to believe that a causal relationship existed in that instance.[77]

Another complication where HPV vaccination is concerned is the paucity of precise data on the frequency of auto-immune conditions in the likely target age group for vaccination. Although data from a study of a cohort of girls and young

women in the USA have recently been published,[78] the authors warn that the data cannot be extrapolated to other countries. Since no comparable data from the Netherlands are yet available, the Committee recommends research into this topic.

5.4 Conclusions

Adverse effect profiles give no cause for concern

The Committee attaches great importance to the monitoring of safety in public vaccination programmes. The adverse effect profiles of the two HPV vaccines give no cause for concern. There is no reason to believe that HPV vaccination may have adverse health effects that would offset its public health benefit. Nevertheless, in view of the envisaged scale of the public administration programme, it is desirable to have more data. There is a relative paucity of data on the primary target group for vaccination, young girls, and no data on the long-term effects of vaccination.

If vaccination is introduced, post-marketing surveillance and monitoring will be required

If HPV vaccination is introduced to the NIP, the Committee believes that it is very important that data on vaccine use and possible adverse effects are gathered by means of post-marketing surveillance, continuing for an extended period. Collection and assessment of the necessary data should be based on a monitoring system capable of detecting possible long-term immunological side effects. This implies the ability to link individual data from the vaccination registry to data from disease registries.

Chapter 6

The acceptability of vaccination

A vaccine must be effective and safe in order to be deemed suitable for general administration. However, it is also important that the vaccination in question is acceptable. In this chapter, the Committee assesses HPV vaccination against the fourth and fifth of the seven criteria. In an earlier report, the Health Council indicated that acceptability was a product of the inconvenience and discomfort experienced by recipients and the fairness of the burden distribution across different population groups.[1] For children and their parents, the most obvious effects of vaccination are often the transient forms of discomfort associated with injection. Such discomforts are in themselves minor and cannot generally be considered serious harm. Nevertheless, the fact that they are likely to be experienced by a large number of people means that they do warrant proper examination. The object must be to minimise the discomfort associated with vaccination as far as possible. The justification for vaccination could be questioned if one population group had to bear the discomfort and inconvenience, while another received the benefits.

In view of the particular nature of HPV vaccination, the Committee has considered a further dimension of acceptability, namely the appropriateness of providing vaccination through the NIP against a sexually transmitted infection that can lead to cancer.*

* Infection with the hepatitis B virus can also lead to cancer, but in the Netherlands this does not constitute the primary reason for vaccination. Moreover, vaccination against hepatitis B in the Netherlands currently is targeted towards specific risk populations.

6.1 Acceptability of an individual vaccination

Both vaccines are administered in three doses, by means of intramuscular injection. With Gardasil, the second and third injections are given one and six months after the first; with Cervarix they are given two and six months after the first. The fourth criterion is that the discomfort or inconvenience experienced by a vaccine recipient should be reasonable in relation to the health benefit for the recipient personally and for the wider population.

It is not yet possible to say simply that this criterion is or is not met by HPV vaccination. There is evidence to suggest that the vaccines are efficacious as a means of preventing cervical cancer, but definite proof is still awaited. Furthermore, uncertainty remains regarding the duration of the protection provided; booster injections may be required. It is probable, however, that vaccinated women will at least subsequently be less prone to cytological abnormalities and CINs[79] – a worthwhile benefit in itself. If provided in the context of a combined vaccination-screening programme, vaccination can reduce the number of false positive screening results and thus reduce the stress associated with 'false alarms'. There are as yet no empirical data on these benefits, however.

On the basis of what is presently known, the Committee believes that the inconvenience and discomfort associated with vaccination by means of three intramuscular injections is certainly justified by the likely health benefits. However, data from follow-up research into the efficacy and safety of HPV vaccination are required before conclusions may be drawn regarding the long-term position.

6.2 Acceptability of the vaccination programme as a whole

The fifth criterion is that the inconvenience and discomfort associated with the public vaccination programme as a whole, including HPV vaccination, should be justified by the health benefit to the individual vaccine recipient and the population as a whole.

For the satisfaction of this criterion, the Health Council has previously indicated that, under normal circumstances, a child should receive no more than two injections per session.[1] Such a limit is felt to be necessary not only in the interest of individual vaccine recipients and their parents, but also in order to maintain the highest possible rate of participation in the NIP, in the wider public interest. The Committee does not believe that the addition of HPV vaccination to the NIP would compromise satisfaction of this criterion, since the vaccine would be

administered at an age when no other vaccination takes place in the context of the programme.

However, the merits of general vaccination against hepatitis B are currently being debated; the Health Council anticipates reporting on this issue in the second quarter of 2008. One of the options is the general vaccination of adolescents, at roughly the same age as proposed for HPV vaccination. If general vaccination against hepatitis B at that age is introduced, it will be necessary to consider whether a combination vaccine against HPV and hepatitis B would be possible, with a view to minimising the inconvenience and discomfort to recipients. The benefit of a combination vaccine would for the time being be felt only by girls; just how much benefit would be derived from combined vaccination would depend partly on how many injections were involved in hepatitis B vaccination.

6.3 General acceptability

HPV vaccination differs from the existing NIP vaccinations

HPV vaccination differs in various respects from the 'classic' vaccination of infants against childhood diseases. The differences that exist could lead to a lower vaccination rate.

One key difference is that HPV vaccination would be the first NIP vaccination against an infection that can lead to cancer or against a condition transmitted by sexual contact. Furthermore, vaccination would probably be provided at an age when most girls are not yet sexually active and when many parents are likely to hope that their children are not yet considering becoming sexually active. Vaccination could be interpreted as a tacit sign of approval or even encouragement for (premature) sexual activity. The Committee therefore anticipates that HPV vaccination may meet moral objections from some parents. However, research has found no evidence that HPV vaccination is likely to lead to increased or earlier sexual activity.[80] Furthermore, the results of studies carried out in the Netherlands and elsewhere indicate that the vast majority of parents are prepared to have their daughters vaccinated.[80-82] Whether willingness expressed in a survey translates into practice when vaccination is actually available has yet to be seen. The Committee takes the view that good public information is vital, preferably with separate material targeted at girls and their parents.

The need for communication with the vaccine recipients themselves also distinguishes HPV vaccination from the classic NIP vaccinations; information concerning the latter is necessarily aimed primarily at parents.

Another difference between HPV vaccination and the established forms of vaccination is that the former is likely to be restricted to one sex, at least for the time being. The reason being that, in the Committee's view, there are currently insufficient data on the efficacy of HPV vaccination in boys and men to justify its provision to males. The Committee imagines that this could be interpreted as an unbalanced response to a health problem perpetuated by males and females alike. The Committee considers it important that information material regarding HPV vaccination respects people's sensibilities in this regard.

Effect on levels of participation in the screening programme

It is possible that the availability of an HPV vaccine could lead to fewer women participating in the cervical cancer screening programme. Similar concerns have been expressed in other countries.[83] The Committee regards this possibility as a potentially serious matter, since vaccination does not provide complete protection against cervical cancer or its precursors. Public information material, particularly that aimed at girls and women invited for vaccination in the context of any catch-up programme, must emphasise the partial nature of the protection afforded by vaccination.

6.4 Conclusions

Introduction of HPV vaccination would not cause unreasonable inconvenience or discomfort

There is no cause to question the acceptability of HPV vaccination, either in isolation (criterion 4) or in the wider context of a public vaccination programme (criterion 5), provided that the limited data currently available regarding the effectiveness and safety of vaccination are confirmed by the necessary follow-up research.

Particular characteristics of HPV vaccination require attention

HPV vaccination differs from the 'classic' forms of vaccination provided through the NIP in various respects. While the Committee does not believe that these differences diminish the acceptability of HPV vaccination, it is considered important that the particular characteristics of this form of vaccination are taken into account, especially in the context of public information.

One point of concern is the possibility that the general provision of HPV vaccination might lead to reduced levels of participation in cervical cancer screening.

Chapter 7

The efficiency of vaccination

Is the introduction of HPV vaccination an efficient way of reducing cervical cancer? When resources are limited, choices have to be made regarding the way the available funds are used. Cost-effectiveness analysis is a means of quantifying the health benefit (increased life expectancy or quality of life) gained, as well as the associated costs and savings. In this instance, one needs to look beyond the vaccination itself. The Netherlands already has a successful screening programme, so a comparative assessment is in order. However, it is also instructive to calculate the collective costs and benefits of the two programmes, since – if vaccination is introduced – it will be provided alongside screening.

7.1 Comparison of vaccination and the existing screening programme

When assessing a possible new preventive programme, the normal procedure is to compare it against the existing situation in order to establish whether the additional costs are justified by the additional health benefits. Where possible, a new preventive programme will normally replace all or part of any existing programme.

To date, the prevention of cervical cancer in the Netherlands has been based on cytological screening. All women aged between thirty and sixty are invited to take a so-called ‘smear test’ every five years. This procedure involves examining material taken from the cervix for the presence of abnormal cells.

The vaccination option therefore needs to be compared with the established screening programme. That comparison is complicated, however, by a number of factors, which are discussed below.

Different forms of prevention

The aim of screening is the early detection of cervical cancer and its precursors. In other words, screening is a form of secondary prevention. Vaccination, by contrast, involves primary prevention: HPV infection is prevented, so that cervical cancer cannot subsequently develop.

Prevention is better than cure. If no other considerations applied, the Committee would endorse this saying. However, it is important to assess the effects of both approaches. What burden does each place on the subject? What negative effects of each can be anticipated?

Different age groups have different interests

Because of the considerable time interval between HPV infection and the development of cervical cancer (roughly twenty years, on average), the relative significance of each prevention option (vaccination and screening) differs substantially from one age group to another.

For girls of about twelve years old, vaccination has considerable significance, while screening will not become relevant for nearly twenty years. It is not without reason that the Committee has previously identified them as the primary target group for vaccination. For women aged twenty-five or older, screening is of more immediate relevance, and there is little to be gained from vaccination because a high percentage of them will already be or have been infected by HPV. Furthermore, the vaccines are licensed only for administration to women up to the age of twenty-seven. For girls and women aged twelve to twenty-five, the two forms of prevention differ less in their significance, although the percentage of women who are or have been infected by HPV will increase with age, thus reducing the value of vaccination to older age groups.

Despite these differences, the ultimate effect of vaccination cannot be considered in isolation from screening, even where young girls are concerned, because screening will remain necessary for both vaccinated and unvaccinated women.

New test methods mean changes in the screening programme

The question of whether vaccination should be introduced to the NIP arises at a time when major changes to the screening programme are under consideration.

The proportion of women undergoing screening at some point in the five-year cycle was 77 per cent in 2003 and 79 per cent in 2006.[6] The participation level, particularly among women in high-risk groups, was suboptimal.[84] Efforts are being made to increase participation among women in these groups by sending them self-sampling packs through the post. The initial results of this initiative have been encouraging.[85] Another development is the introduction of HPV tests: instead of the traditional microscopic examination of cellular material for abnormalities, a DNA test is performed to check for the presence of genetic material from hrHPVs. With regard to the detection of CIN3 and cervical cancer, HPV tests are much more sensitive than conventional smear tests, but they are also less specific.[5,86-88] Debate as to how HPV testing can best be integrated within the Dutch screening programme is currently ongoing.

The developments outlined above may increase the effectiveness of the screening programme. However, it is not yet possible to comment on the course of change in the screening programme; the Committee is to return to this subject in a future report. The assessment of the merits of vaccination and screening presented here is therefore based on the current situation.

Interaction between vaccination and screening

If general HPV vaccination is introduced, HPV-16 and HPV-18 infections – and therefore CINs and cervical cancer associated with these virus types – will very probably become less common. As a result, the number of cases of cervical cancer and its precursors detected through the screening programme is likely to decline.

Other forms of interaction between vaccination and screening are also possible. As previously indicated, girls and women may wrongly assume that, having been vaccinated, they are not at risk of contracting cervical cancer, and this may lead to lower rates of participation in the screening programme.

7.2 Modelling

7.2.1 Models, data and assumptions

The Committee had access to output from various cost-effect analysis models. The Ministry of VWS has asked the National Institute of Public Health and the Environment (RIVM) to develop models for assessing the cost-effectiveness of HPV vaccination in comparison with screening. To this end, the RIVM teamed up with the VU University, Amsterdam (Professor C.J.L.M. Meijer, Adviser to the Committee, and Dr. J. Berkhof). The Committee has also been able to take account of data from the modelling and cost-effect analysis of HPV vaccination in comparison with screening undertaken by the Erasmus University Medical Centre in Rotterdam (Dr. M. van Ballegooijen, Adviser to the Committee). VUmc and Erasmus MC both have considerable experience with the modelling of cervical cancer in the Dutch population.[12,62,89-92]

In the advisory report *The Future of the National Immunisation Programme: Towards a Programme for All Age Groups*, published in March 2007, the Health Council indicated that the cost-benefit assessment of a particular form of vaccination should always be based upon analytical data produced by impartial expert investigators.[1] The Committee believes that the data provided by VUmc and Erasmus MC conform to this description.*

The Committee was additionally able to peruse the findings of cost-effect analyses performed by GlaxoSmithKline and Sanofi Pasteur MSD. Furthermore, analytical data from other countries were available to the Committee for comparison.[93-97]

In consultation with the Committee, the researchers at VUmc and Erasmus MC defined a common set of vaccination modelling parameters. The object of vaccination was defined as the prevention of cervical cancer and the basic analysis was performed assuming the general vaccination of girls at the age of twelve.[52] Neither the possible efficacy of vaccination against other HPV-induced cancers and genital warts, nor the vaccination of boys was taken into account.

The effects and cost of vaccination were compared with those of the existing screening practices. However, in order that the effectiveness of vaccination could be properly assessed, a hypothetical situation characterised by the absence of

* As part of their ongoing research programmes VUmc and Erasmus MC also received grants from GlaxoSmithKline, the producer of Cervarix. These were unrestricted grants. GSK had no role in the design, the analysis or the reporting of the study.

screening was also modelled. In this way, it was possible to assess whether vaccination could form an alternative to the Netherlands' existing screening programme.

It was assumed that the efficacy of a complete series of three injections was 90 per cent. The spectrum of the vaccines (the proportion of cervical cancer cases caused by the target hrHPVs) was taken to be 70 per cent. It was further assumed that the protection afforded by vaccination was lifelong and that no cross-immunity against other hrHPVs was provided. Almost everywhere in the Netherlands, the take-up of vaccinations currently made available to infants and young children through the NIP is at least 95 per cent of the target group.[1] However, the Committee considers it unlikely that such a high take-up rate can be achieved for HPV vaccination; the models therefore assume a take-up of 85 per cent. In this context, the Committee makes the assumption that willingness to submit to vaccination is not dependent on the risk of cervical cancer. This is contrary to what data from the screening programme suggest; in practice it appears that take-up in high-risk groups is lower than in other groups.

The cost of the programme was discounted at annual rates of zero and 4 per cent; health effects were discounted at annual rates of zero and 1.5 per cent.

In the sensitivity analyses, the influences of declining immunity (efficacy) necessitating booster vaccinations at the age of thirty were modelled.

Since it is not known what the vaccines would cost if in widespread use, calculations were made first assuming a pharmacy price of 125 euros per dose, and then assuming lower prices. One of the manufacturers has indicated that, if HPV vaccination were introduced to the NIP, the price would be no more than 90 euros per dose.

The cost-effectiveness of one-off catch-up programmes for the vaccination of girls aged thirteen and above was also analysed.

The main findings of the modelling process are summarised below. More detailed information is available through our website (www.healthcouncil.nl) in reports for the Health Council by VUmc (in Dutch) and Erasmus MC (in English).

7.2.2 *Health effects*

Both research groups' findings suggest that the provision of vaccination alongside the existing screening programme would result in major reductions in morbidity and mortality (table 3).

In both models, the number of deaths prevented by combined vaccination and screening (column D) works out at roughly 100 per 100,000 women more than

the number prevented by screening alone (column B). The Rotterdam model puts the increase in the number of disease cases prevented at roughly 220 per 100,000 women; the corresponding figure produced by the Amsterdam model is 360 per 100,000 women. The output from both models suggests reductions in disease incidence and mortality of roughly 50 per cent compared with the present situation.

The two models indicate that between 275 and 450 girls need to be vaccinated to prevent one case of cervical cancer; roughly a thousand girls need to be vaccinated to prevent one death. These findings are broadly consistent with similar calculations made for Canada, where the epidemiological situation is reasonably similar.[98] Interestingly, the Canadian investigators found that the number of girls that needed to be vaccinated to achieve a given benefit increased if it was assumed that the protective effect of vaccination gradually diminished over time. The administration of booster vaccinations could largely negate that effect, but would of course increase the cost.

The VUmc and Erasmus MC researchers also estimated morbidity and mortality avoidable by screening and by vaccination, relative to a hypothetical situation involving no preventive intervention. The estimates produced by the Amsterdam model were significantly higher, partly because it was assumed that the *a priori* risk of cervical cancer was the same for women that did not participate in the screening programme as for women that did. By contrast, the Rotterdam researchers assumed, on the basis of historical data, that the *a priori* risk for the 10 per cent of women that took no part in the screening programme was three times as high.

The modelling of morbidity and mortality in the no-intervention scenario makes it possible to directly compare the estimated impact of screening and with that of vaccination. The output of both models indicated that less morbidity and mortality was preventable by vaccination than by the existing screening programme (table 3).

7.2.3 *Cost-effectiveness*

When cost and health effects were discounted according to existing guidelines, the cost-effectiveness of providing vaccination alongside the existing screening programme was put at nearly 21,000 euros per QALY by the VUmc researchers, but at more than 30,000 euros per QALY by the Erasmus MC team.

The difference between the two estimates is due to various factors. The Erasmus MC researchers estimated that nearly 80 per cent of target-group women would undergo cytological testing at least once every five years, whereas the

VUmc team worked on the basis of 73 per cent. In addition, the Rotterdam team used a higher cost figure for screening. Another difference arose from the way that the VUmc researchers modelled the natural history of HPV infection, which made the vaccine appear more effective than it did in the Rotterdam model. Finally, in the Amsterdam model, the levels of morbidity and mortality due to cervical cancer in women aged thirty to forty are estimated to be relatively high and those in women over sixty to be relatively low. This too makes the impact of vaccination greater in the Amsterdam model than in the Rotterdam model.

Both groups of researchers calculate that vaccination would be less cost-effective in comparison to the no-intervention scenario than screening is. The Rotterdam researchers calculate that the price of vaccine would need to fall from 125 euros per dose to 31 euros before vaccination became as cost-effective as screening. If booster vaccination is required at the age of thirty, the price of the vaccine would need to come down to 27 euros per dose in order to achieve parity.

Table 3 Modelling of cervical cancer prevention strategies in the Netherlands: number of cases of disease, mortality, lost life-years, lost QALYs, cost and cost-effectiveness in a cohort of 100,000 women followed from birth to death. (Sources: VUmc and Erasmus MC).

	VUmc				Erasmus MC			
	a. No intervention	b. Screening only[a]	c. Vaccination only[a]	d. Vaccination and screening[b]	a. No intervention	b. Screening only[a]	c. Vaccination only[a]	d. Vaccination and screening[b]
Health effects								
Number of cases of cervical cancer	1,851	634	731	275	986	408	451	191
Mortality	699	184	277	79	394	170	183	77
Lost life-years	19,070	5,280	7,320	1,960	10,095	4,132	4,708	1,880
Lost QALY's	20,030	5,710	7,690	2,160	10,804	5,040	5,063	2,604
Cost								
Smear testing	0	22,500,000	0	22,500,000	0	28,743,622	0	28,704,746
Treatment of precursors	0	6,900,000	0	4,100,000	0	4,308,518	0	3,157,103
Treatment cervical cancer	41,000,000	12,100,000	16,100,000	4,600,000	20,236,932	9,192,209	9,426,339	4,219,757
Vaccination	0	0	35,700,000	35,700,000	0	0	34,993,992	34,993,992
Total cost	41,000,000	41,500,000	51,700,000	66,900,000	20,236,932	42,244,349	44,420,331	71,075,597
Cost-effectiveness								
Euros/life-year gained Discount 0%/0%	n.v.t.	34	907[c]	8,370	n.v.t.	3,691	4,489	12,799
Euros/life-year gained Discount 1,5%/4,0%	n.v.t.	584	5,752[c]	22,900	n.v.t.	3,219	13,708	32,959
Euros/QALY Discount 0%/0%	n.v.t.	33	864[c]	7,818	n.v.t.	3,818	4,213	11,832
Euros/QALY Discount 1,5%/4,0%	n.v.t.	561	5,429[c]	20,862	n.v.t.	3,433	12,700	30,045

[a] Compared with no-intervention scenario.
[b] Compared with screening only.
[c] Assuming 95 per cent vaccine efficacy.

7.3 Assessment

The models suggest that the health benefit attainable by providing vaccination alongside the existing screening programme is considerable.

It is more difficult, however, to draw conclusions regarding efficiency. For the purpose of assessing the efficiency of preventive measures, a cost-effectiveness ceiling of 20,000 euros per QALY is sometimes applied in the Netherlands. The estimates made using both models are above this figure: the VUmc estimate is a little higher, and the Erasmus MC estimate is significantly higher. Nevertheless, if the price of vaccine can be negotiated down, the cost-effectiveness of vaccination can be brought within the range that is generally deemed to be acceptable.

However, the money needed to introduce vaccination could be used to improve the screening programme. In the models described here, vaccination was compared with the existing screening programme. Yet the screening programme is likely to undergo significant changes in the near future, such as the introduction of HPV testing alongside or instead of smear testing and the use of HPV self-sampling for women who do not take up the invitation to attend a clinic for screening (see 7.1). Because these possible changes are still being assessed, they could not be included in the cost-effect analyses within the available time window.

Certain other options for making the screening programme more effective are available for immediate implementation, however. These include increasing take-up by a GP appointment system and the targeting of groups in which the take-up is relatively low (women aged thirty to thirty-four, women from non-Western backgrounds and women of low socio-economic status).[6,84,99,100] Such measures could be implemented within the applicable cost-effectiveness parameters. Nevertheless, the Committee felt that the comparison of vaccination with an improved screening programme was outside the remit of this report. It is also worth noting that the efficiency of the existing screening programme was optimised as recently as 1996, in line with the criterion of 20,000 euros per QALY. The cost-effectiveness figures produced by the analyses reported here are much more favourable, mainly because the discount rate for health effects has since been reduced from 4 to 1.5 per cent.

Comparison of the cost and effects of vaccination against those of an improved screening programme would require formal cost-effect analyses, which were not possible within the time available for preparation of the present advisory report. However, it is unlikely that the availability of additional data

from such analyses would lead the Committee to a different conclusion regarding the efficiency or potential significance of vaccination. This holds true both in relation to the changes expected in the longer term (the introduction of HPV testing and self-sampling), and the take-up enhancing changes that could be made immediately.

7.4 Cost and benefits of a catch-up vaccination programme

The VUmc researcher team additionally investigated the possible effects of a catch-up vaccination programme for girls over the age of twelve. In order to assess such effects, it is first necessary to ascertain whether the vaccines would be effective when administered to older girls, who are more likely than their younger counterparts to have already contracted hrHPV infections.

Most of the subjects involved in the research into the efficacy of the two HPV vaccines were women who at the outset had not been infected by hrHPV. The limited data available regarding women who had already been infected by hrHPV prior to vaccination do not indicate that the recipients benefited from the vaccine.[54,55,101] It seems likely, therefore, that vaccination is beneficial only for girls and women who have yet to be infected by the target hrHPVs; vaccination may be expected to protect a woman who has been infected by one of the two target hrHPVs against subsequent infection by the other.

As indicated in 3.1.3, hrHPV infections are common in young, sexually active women around the age of twenty. Prevalence studies indicate that hrHPV infections peak in the twenty-to-twenty-four age group.[79,102-104] Calculation of the effect of a catch-up programme is complicated by the fact that little is known about the prevalence of hrHPV infections in girls under the age of twenty, in the Netherlands or other countries.

In the absence of exact data on the prevalence of hrHPV infection in girls aged twelve to about twenty, it is necessary to make assumptions, in the context of which information about sexual activity is useful. The Rutgers Nisso Group research mentioned earlier found that, at the age of twelve, 3 per cent of girls reported having had sexual intercourse.[52] Between the ages of thirteen and eighteen, the figure rose to 4, 8, 29, 37, 63 and 77 per cent, respectively. The research also showed that, in this age range, reported experience of intercourse varied considerably between ethnic groups: 39 per cent in girls of Antillean origin, 28 per cent in girls of indigenous origin, 23 per cent in girls of Surinamese origin, 11 per cent in girls of Turkish origin and 6 per cent in girls of Moroccan origin. The available data allowed no further distinction of age-related differences by ethnicity.

Using the Rutgers Nisso Group data and the limited data available on the frequency of HPV infection in young people, the VUmc researchers modelled various early hrHPV infection curves. These curves were then used to perform cost-effect analyses of a catch-up vaccination programme for girls and women aged thirteen to eighteen.

These tentative analyses suggest that vaccinating girls aged thirteen to sixteen is about as cost-effective as vaccinating twelve-year-old girls. From the age of seventeen, the cost-effectiveness of vaccination gradually declines. The rate of decline in the cost-effectiveness of vaccination depends mainly on the age-related incidence of hrHPV infection, about which (as previously indicated) considerable uncertainty exists. The Committee consequently takes the view that the scope of any catch-up programme should for the time being be dictated by efficiency as well as practical factors. It is therefore concluded that, provided that the price of the vaccine can be reduced, a catch-up programme would be appropriate for girls aged thirteen to sixteen.

7.5 Comparison with other modelling studies

7.5.1 Pharmaceutical companies' own research

GlaxoSmithKline and Sanofi Pasteur MSD commissioned their own cost-effect analyses. All the models used were based on approximations of the (natural) history of HPV infection and cervical cancer and the influence of vaccination. Some of the models sought to simulate the effects of vaccination not only on cervical cancer, but also on other HPV-induced conditions, such as genital warts and head and neck cancers. The main differences with the modelling work by the VUmc and Erasmus MC concern the assumed efficacy of the vaccine, the likely vaccination take-up rate and the cost of treatment and vaccination.

On behalf of GSK, Innovus refined a model developed by Goldie *et al.* and adapted it to the Dutch situation.[105,106] A number of key assumptions underpinning this model are more optimistic than those made by the Committee: the efficacy of the vaccine is put at 95 per cent and the vaccination take-up rate at 100 per cent. The cost-effectiveness of vaccinating twelve-year-old girls, in combination with the present screening programme, works out at 15,543 euros per QALY. The corresponding figure for the catch-up vaccination of girls aged up to sixteen is 18,736 euros (J.J. Tamminga and D.E.M. Zandbergen-van den Boogaardt, written communication 2007).

Sanofi Pasteur MSD also commissioned a cost-effect analysis of vaccination in the Netherlands, carried out by Mapi Values Netherlands.[107] This analysis

assumed that the efficacy of the vaccine was 100 per cent and that the take-up was 90 per cent, leading to a cost-effectiveness figure for vaccination in combination with the existing screening programme of 13,698 euros. The figure for the catch-up vaccination of girls aged thirteen to eighteen was put at 14,209 euros.

The Committee concludes that the pharmaceutical companies' own models are based on optimistic assumptions regarding certain key parameters. The optimistic nature of these assumptions probably explains, at least in part, why the output from these models differs from the analyses conducted by VUmc and Erasmus MC.

Dynamic models

The models described so far, including those developed by the VUmc and Erasmus MC, take no account of the possible indirect effects of vaccination, which may be considerable. So-called dynamic models do take account of such effects. However, such models are more difficult to construct and require more detailed data, as a consequence of which they are often not available. Using a dynamic model, it would be possible to simulate the effects of vaccination on circulation of the virus, for example. Indirect effects are often favourable; reduced virus circulation can be advantageous to unvaccinated girls and women, for instance. Dynamic modelling would also enable study of the circumstances under which the vaccination of boys and men should be considered for the protection of girls and women. Dynamic models have been used to assess the effects of HPV vaccination in other countries, [27,108,109] but development has not yet reached the point where they can be used to assess the value of HPV vaccination in the Netherlands. The Committee considers it important that work on the development of such models is promoted in order to enhance understanding of the effects of vaccination on the transmission of HPV, and thus on the prevalence of cervical cancer.

7.6 Conclusions

The greatest health benefit is attainable by providing both vaccination and screening

The Committee concludes that providing both vaccination and screening would bring more health benefit than providing either on its own. The models developed for the Committee consistently predict that the introduction of vaccination

alongside the existing screening programme would roughly halve the number of cases of cervical cancer and the number of associated deaths.

The cost would be relatively high

Even assuming that the vaccine provides lifelong protection, the cost per QALY of a combined programme is relatively high compared with the cost-effectiveness ceiling of 20,000 euros. The main uncertainties attached to the calculated figures concern the ultimate efficacy of the vaccine, the duration of protection and the health benefits attainable through modifications to the screening programme. The price of the vaccine would need to be brought down considerably before the cost-effectiveness of vaccination matched that of enhancing the screening programme.

The pharmaceutical companies' own models are based on optimistic assumptions regarding certain key parameters. The optimistic nature of these assumptions probably explains, at least in part, why the output from these models differs from the analyses conducted by VUmc and Erasmus MC.

A catch-up programme for girls aged thirteen to sixteen is desirable

Because of the uncertainty surrounding the numbers of new hrHPV infections, the Committee takes the view that the scope of any catch-up programme should for the time being be dictated by efficiency and practical factors. It is therefore concluded that, provided that the price of the vaccine can be reduced, a catch-up programme would be appropriate for girls aged thirteen to sixteen.

Chapter 8

The urgency of the vaccination

8.1 Points of departure

The priority criterion, the last of the seven, relates to the vaccination's relative importance, compared with other vaccinations that might be used. Assessment against this criterion is necessary because both the financial resources and the practical scope for incorporating new forms of vaccination within the programme are limited.

To be deemed suitable for introduction to the programme, a vaccination must address a (potentially) urgent public health problem. As a consequence, priority may, for example, be given to the provision of protection against a disease against which individuals cannot easily protect themselves. As with the first criterion, the word 'potentially' warrants clarification. A potentially urgent public health is a problem that may not exist or may not be serious, but is liable to arise or become serious without preventive intervention.

8.2 Significance for public health

In the previous chapters of this report, the Committee has indicated vaccinating girls against cervical cancer is important for public health. It is anticipated that vaccination will ultimately prevent several hundred cases of cervical cancer and about a hundred deaths a year – about half the number that now occur. If the price of vaccine can be negotiated down, the cost-effectiveness of vaccination

can be brought within the range that is generally deemed to be acceptable. Considerable health benefit can also be secured at a reasonable cost, by the catch-up vaccination of girls aged thirteen to sixteen – again, provided that the price of vaccine comes down.

Women cannot realistically be expected to protect themselves against cervical cancer by means other than vaccination: safe sex and condom use offer only limited protection against HPV infection.

The advisory report *The Future of the National Immunisation Programme: Towards a Programme for All Age Groups* lists twenty-three vaccinations that might be considered for inclusion in the NIP.[1] In due course, the Health Council is to follow up the present report by advising on vaccination against hepatitis B, rota virus-induced diarrhoea, shingles and chicken pox. It is not anticipated that any of these candidate vaccinations will be capable of reducing morbidity and, crucially, mortality to an extent comparable with that achievable through HPV vaccination.

8.3 The vaccination of girls and women outside the NIP target group

In chapter 7, the Committee indicated that it did not favour the general vaccination of girls and women aged seventeen or older through a public programme such as the NIP. Nevertheless, individual girls and women of seventeen or older may well stand to benefit from vaccination. The Committee therefore believes that consideration should be given to asking the Health Care Insurance Board to look at the possibility of funding the vaccination of girls and women aged seventeen or older through the Reimbursement System for Pharmaceutical Products (Geneesmiddelenvergoedingssysteem).

8.4 Conclusion

The vaccination of girls against HPV would serve an urgent public health need

The Committee concludes that the vaccination of young girls against cervical cancer through the NIP would serve an urgent public health need. So too would the catch-up vaccination of girls aged thirteen to sixteen. It is also recommended that consideration should be given to asking the Health Care Insurance Board to look at the possibility of funding the vaccination of girls and women aged seventeen or older through the Reimbursement System for Pharmaceutical Products.

Chapter 9

Considerations and recommendations

In the preceding chapters, the Committee has examined the merits of introducing HPV vaccination to the NIP, by reference to seven assessment criteria. The Committee has found it difficult to reach a conclusion as to whether this form of vaccination should be provided through the NIP. However, it was not the case that the satisfaction of any one criterion was in doubt. Rather, while there were valid arguments to be made for the introduction of HPV vaccination, considerable uncertainty existed in relation to various points. These uncertainties have previously been highlighted elsewhere.[22,110,111] Therefore, before presenting its recommendations on the merit of general HPV vaccination, the Committee wishes to set out the pertinent considerations and list the alternatives to inclusion in the NIP that have been considered.

9.1 Summary of pertinent considerations

Arguments in favour of general vaccination:

- In the Netherlands, between the 200 and 250 women die from cervical cancer each year. Vaccination could ultimately cut that number by roughly half.
- Unlike screening, vaccination is a means of primary prevention.
- Vaccination has been shown to protect girls and women of fifteen to twenty-six against persistent infections involving the vaccine's target hrHPVs and against the precursors of cervical cancer associated with those hrHPVs. Such

precursors are a precondition for the development of cervical cancer. The vaccination of girls at the age of the likely target group results in the strong production of antibodies against the target hrHPVs.
- One of the two types of cervical cancer, adenocarcinoma, cannot easily be detected early using the existing (cytological) screening methods. Vaccination, however, is expected to protect equally against adenocarcinoma and squamous cell carcinoma.
- The adverse effect profile of the vaccines available from the relatively short-term monitoring possible to date gives no cause for concern.

The uncertainties:

- It is not yet certain that the vaccines are effective in the prevention of cervical cancer, the ultimate target disease. However, a variety of practical and moral considerations make it impracticable to determine the vaccines' effectiveness prior to introduction.
- No research has been conducted into the effect of vaccinating girls of the age of the likely target group on the persistency of the virus or on the incidence of the precursors of cervical cancer. Again, however, there are practical and moral reasons why such research cannot reasonably be undertaken. The evidence for the efficacy of the vaccination when administered to the target group is therefore indirect.
- The vaccines are currently known to provide protection for at least six year. However, the possibility that lifelong protection may necessitate re-vaccination cannot yet be excluded.
- If the protection afforded by vaccination proves to diminish over time and no booster vaccination is received, it is unclear whether an hrHPV infection would take a different course to that which would be expected in an unvaccinated woman.
- It is unclear whether vaccination type replacement by, or the unmasking of, other hrHPVs is likely, and what the clinical consequences of such phenomena might be. Nevertheless, since the vaccines are aimed at the most oncogenic hrHPVs, it is less likely that the disease burden will 'bounce back' significantly, even if type replacement or unmasking does occur.
- As with any new pharmaceutical product, the possibility cannot be excluded that certain rare, delayed or target group-specific adverse effects will become apparent only after large-scale introduction.
- It is not clear what the take-up rate will be among girls and women to whom vaccination is made available.

- Because HPV vaccination is intended to provide protection against a sexually transmitted infection, it might possibly be seen by some people as legitimising unsafe sex.
- Little is known about the effect of vaccination on other HPV-related conditions, but the data that are available are encouraging.

Arguments against general vaccination:

- At the current vaccine prices, the cost per QALY of a combined vaccination and screening programme would be relatively high compared with the cost-effectiveness ceiling of 20,000 euros. The price of the vaccine would need to be reduced considerably before the cost-effectiveness of vaccination came within the range that is generally deemed to be acceptable.

9.2 Recommendation regarding introduction to the NIP

The Committee recommends the introduction of HPV vaccination for twelve-year-old girls to the NIP. The Committee further recommends a catch-up programme for the vaccination of girls aged thirteen to sixteen at the time that HPV vaccination is introduced. Finally, it is also recommended that consideration should be given to asking the Health Care Insurance Board to look at the possibility of funding the vaccination of girls and women aged seventeen or older through the Reimbursement System for Pharmaceutical Products.

Since much remains to be learned about the vaccination, and some issues will take a long time to clarify, the Committee emphasises that the introduction of HPV vaccination to the NIP should be accompanied by the establishment of a targeted monitoring programme. The programme should be geared to gathering information about the effectiveness of the vaccination, the duration of protection, adverse effects, acceptance and relevant behavioural factors. The Committee regards the creation of such a programme as a condition for the introduction of HPV vaccination.

The introduction of HPV vaccination to the NIP will be expensive. The Committee cannot currently say whether it would be possible to secure more health benefit by investing a similar amount of money in improvement of the cervical cancer screening programme. The Committee's inability to reach a conclusion on that point is due partly to the uncertainties surrounding the cost-effectiveness of vaccination – regarding the ultimate price of the vaccine, for example – and partly to the fact that the effects of proposed improvements to the screening programme cannot yet be estimated. What is certain, however, is that vaccination

would be beneficial to public health. The Committee considers it unlikely that the availability of additional cost-effect data will lead to a significant reassessment of the efficiency or importance of vaccination.

In a later report, the Committee will look more closely at possible ways of improving the screening programme and will seek to assess the implications of such changes for the cost and cost-effectiveness of preventing cervical cancer.

One point of concern for the Committee is that HPV vaccination might lead to lower levels of participation in the screening programme if vaccinated girls and women mistakenly believe that they are no longer at risk. The Committee considers it very important that such misconceptions are addressed through appropriate communications channels.

9.3 Alternatives to provision through the NIP

The Committee considered various ways of making HPV vaccination available, other than provision through the NIP. The Committee's assessment of these alternatives is based on the assumptions that there will be two vaccines on the market and that it will be a long time before various uncertainties relating to vaccination are resolved; it is also assumed that an effective monitoring programme will be established.

Individual vaccination outside the NIP

The vaccines are already available from GPs, enabling girls and women to independently opt for vaccination. The Committee sees three drawbacks to continuation of this situation. First, it is unlikely that the vaccine will be widely used because of its high over-the-counter cost. Second, partly because of the first drawback, social inequalities are likely to arise. The latter drawback might justify a fresh request to the CVZ to allow vaccination to be funded through the Reimbursement System for Pharmaceutical Products. Third, the monitoring system viewed as essential by the Committee could not easily be set up in the context of the present system.

Pilot introduction

In theory, one possible way of gathering data with a view to removing the uncertainties surrounding HPV vaccination would be controlled introduction in a research setting. However, the Committee sees such an idea as flawed in various ways. First, the pilot project would need to be very large – perhaps including all

girls in the Netherlands – and to run for many years. Second, a large group of girls would not be given the vaccine, or would only be given it later. If, for example, the study ran for ten years and was nationwide, that might imply that ten half-year cohorts of girls (about 500,000 individuals) were not vaccinated, or at least not until much later. Furthermore, some of those girls might choose to be vaccinated privately, with significant implications for the study outcome and data interpretation.

Chapter 10

Implementation

Although the Committee considers implementation to be outside its advisory remit, certain implementation-related issues do warrant consideration here. After all, what is proposed is the first addition to the NIP of a vaccination against a sexually transmitted infection that can lead to cancer, to be administered at an age when vaccination has not previously been provided through the programme. Such a move raises various implementation questions, which potentially have a major bearing on success. In the following paragraphs, the Committee briefly outlines the points that require particular attention.

10.1 Age of vaccination

The introduction of HPV vaccination has organisational implications. Both vaccines have to be administered by three separate injections, at intervals of between one and five months. The proposed age of vaccination does not coincide with any of the standard consultations that take place in the context of the present Youth Health Care Programme. There is presently a consultation at the age of thirteen (in the second year of secondary education),[1] but it does not involve the administration of any vaccines. The Committee advocates HPV vaccination at the age of twelve and therefore regards the latter consultation as too late.

10.2 Monitoring of effectiveness and safety

As previously indicated, the Committee regards the creation of a programme to monitor the effectiveness of the vaccination, the duration of protection, adverse effects, acceptance and relevant behavioural factors as a precondition for the introduction of HPV vaccination to the NIP. In the context of such a programme, clear demarcation of the duties and responsibilities of, on the one hand, the vaccine manufacturers and, on the other, the Dutch government is essential.

10.3 Public information

In its report *The Future of the National Immunisation Programme: Towards a programme for All Age Groups*, the Health Council made various general points regarding the provision of public information about the NIP.[1] Vaccination against cervical cancer introduces a number of specific public information issues, some of which are identified in the chapter of this report that deals with acceptability. In the Committee's view, at least the following points need to be taken into account:

First, there is the question of which target condition should be highlighted. HPV vaccination is intended to prevent a sexually transmitted infection that can lead to cancer. Should public information material relating to the vaccination emphasise the prevention of a sexually transmitted infection or the prevention of cervical cancer? The concept of vaccination against cancer may encounter less resistance than the idea of vaccinating young girls against an infection contracted through sexual activity.

Public information about HPV vaccination needs to address various groups. The Committee therefore believes it would be advantageous to have differentiated material, aimed at girls and at their parents. It may also be desirable to tailor material to distinct cultural, ethnic or religious groups.

Third, there is the matter of the recommendation that girls should be vaccinated, but boys should not. Scientifically speaking, the Committee believes that such an approach is entirely justified, but it may be hard for the public to understand, given the role that boys play in the transmission of HPV.

If a catch-up programme for girls aged up to sixteen is established, allowance needs to be made for the fact that some of these girls will have become sexually active before they are vaccinated. Public information material needs to explain why the vaccination of this group is nevertheless important.

Finally, there is the question of vaccination for girls and women aged seventeen or older. Individual girls and women in this age group may well derive health benefit from vaccination. If the funding of vaccinations for this age group is made possible, the public information needs to be adapted accordingly. For example, should a decision as to whether or not to vaccinate be preceded by a discussion about sexual activity?

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Annexes

Annex **A**

Request for advice

On 20 March 2007, the President of the Health Council was asked by the Minister of Health, Welfare and Sport to prepare an advisory report on the prevention of cervical cancer. The text of the Minister's letter (reference PG/ZP-2.746.254) is reproduced below.

I hereby request your Council's advice on the prevention of cervical cancer, in the light of new techniques and developments. These include not only new screening techniques, such as thin-layer cytology and testing for high-risk types of the human papilloma virus (hrHPV), but also the availability of preventive vaccines against this virus. The latter development is the immediate trigger for this request for advice. HPV is a sexually transmissible virus, which people can carry without being aware of it. Infection with certain types of this virus can sometimes lead to the development of cervical cancer.

In the Netherlands, roughly six hundred women a year are diagnosed with cervical cancer. A national cervical cancer screening ('smear testing') programme was started in the 1990s, for women aged between thirty and sixty. The programme has substantially reduced cervical cancer-related mortality in the Netherlands. Nevertheless, 200 to 250 women die from this disease every year. Research suggests that the effectiveness of screening depends primarily on reaching the target group; overall, the programme currently reaches 77 per cent of the target group once every five year. My ministry's policy is aimed at further increasing the screening take-up rate.

The new screening techniques that are relevant in this context were discussed in general terms in your Annual Report on Screening for Disease 2006. A trial is currently in progress, in which the

effectiveness of a programme that incorporates hrHPV testing is being compared with conventional screening. The results of this trial are expected in the course of 2007.

In November 2006, an HPV vaccine came onto the market. The manufacturer claims that the vaccine protects against the precursors of cervical cancer and against genital warts. The vaccine is licensed for the Dutch market and is indicated for males and females aged nine and above.

In view of the results of HPV vaccination and the developments outlined above, I shall be grateful if you will advise me, on the basis of the latest scientific knowledge, as to the desirability of introducing HPV vaccination to the National Immunisation Programme, or providing it through another national vaccination programme, as part of an integrated and optimised strategy on the prevention of cervical cancer in the Netherlands.

More specifically, I shall be grateful if you will advise me regarding the following points:

- The relationship between a possible vaccination programme and a modified cervical cancer screening programme, with regard to efficiency, effectiveness and cost-effectiveness, in both the short term and the long term
- The effectiveness and safety of HPV vaccines
- The preferred target group for vaccination, and the desirability of vaccination for males and females in various age groups
- The importance of a catch-up programme for the vaccination of people who are not in the target group if and when general vaccination is introduced
- The cost-effectiveness of HPV vaccination, with reference to the results of the cost-effect study of HPV vaccination undertaken by the RIVM
- The cost-effectiveness of vaccination for the distinct purposes of preventing cervical cancer and preventing genital warts
- Relevant public information issues, given that the proposal is to introduce vaccination against a sexually transmitted infection

Naturally, I wish you to also take account of international developments in the field of cervical cancer prevention. Please submit your report by the end of 2007.

Yours sincerely,
[signed]
Dr. A. Klink
Minister of Health, Welfare and Sport

Annex **B**

The committee and experts consulted

- Prof. J. van der Noordaa, *chairman*
  Emeritus Professor of Virology, University of Amsterdam
- Dr. A. Ansink
  gynaecologist/oncologist, Erasmus University Medical Centre, Rotterdam
- Dr. M. van Ballegooijen, *advisor*
  physician-epidemiologist, Erasmus University Medical Centre, Rotterdam
- Prof. I.D. de Beaufort
  Professor of Health Ethics, Erasmus University Medical Centre, Rotterdam
- Prof. P.J.E. Bindels
  Professor of General Practice, Academic Medical Centre, University of Amsterdam
- Prof. J.T. van Dissel
  Professor of Internal Medicine/Infectious Disease, Leiden University Medical Centre
- Dr. P.G.H. Janssen, *advisor*
  GP, Netherlands Association of General Practitioners, Utrecht
- Prof. G.G. Kenter
  Professor of Oncological Gynaecology, Leiden University Medical Centre
- Prof. M.E.E. Kretzschmar, *advisor*
  theoretical epidemiologist, RIVM, University Utrecht
- Prof. C.J.L.M. Meijer, *advisor*
  Professor of Pathology, VU University Medical Centre, Amsterdam

- Prof. C. Melief
  Professor of Immune-Haematology, Leiden University Medical Centre
- Dr. H.E. de Melker
  epidemiologist, Centre for Infectious Disease Control, Bilthoven
- Dr. W.G.V. Quint, *advisor*
  molecular biologist, DDL Diagnostic Laboratory, Voorburg
- A. Rendering LL.M, *advisor*
  Screening and Population Research Cluster, Public Health Directorate, Ministry of Health, Welfare and Sport, The Hague
- Dr. T.G.J. van Rossum, *advisor*
  physician, Medicines Evaluation Board, The Hague
- Prof. E.A.M. Sanders
  Professor of Immunology and Infections, University of Utrecht
- W.A. van Veen, physician, *advisor*
  Health Council, The Hague
- Dr. H.J.C. de Vries
  dermatologist, Academic Medical Centre, University of Amsterdam
- Dr. K. Groeneveld, *scientific secretary*
  medical immunologist, Health Council, The Hague
- Dr. H. Houweling, *scientific secretary*
  physician-epidemiologist, Health Council, The Hague

The Committee consulted the following people and bodies:

- Dr. T. Aguado, World Health Organization, Geneva
- Dr. M. Arbyn, Scientific Institute or Public Health, Brussels
- Dr. J Berkhof, VU University Medical Centre, Amsterdam
- Dr. P. Claeys, International Center for Reproductive Health, Gent
- Dr. V. Coupé, VU University Medical Centre, Amsterdam
- Dr. M.A.E. Conyn-van Spaendonck, National Institute of Public Health and the Environment, Bilthoven
- Dr. G. Garnett, Imperial College, London
- GlaxoSmithKline, Rixensart: Dr. P. Monteyne, Dr. C.G. van Schagen, Dr. H. Tamminga and Dr. M. Wettendorff
- Dr. K. Irwin, World Health Organization, Geneva
- Dr. D. Kennedy, Joint Committee on Vaccination and Immunisation, London
- I.M.C.M. de Kok MSc, Erasmus University Medical Centre, Rotterdam
- Dr. N. Malila, Finnish Cancer Registry, Helsinki

- Dutch Association for the Critical Use of Injections (Nederlandse Vereniging Kritisch Prikken, Roosendaal: C. Buis, M. de Munck and H. Visser
- Dr. S. Poulsen, National Board of Health, Copenhagen
- Sanofi Pasteur MSD, Hoofddorp: Dr. G. Demol, C.A. Kievid and R. Tensen, physician
- Olive Foundation (Stichting Olijf) for women with gynaecological cancer, Amsterdam: J. van Leeuwen
- Dr. C.A. Siegrist, University of Geneva
- Dr. A. Tegnell, National Board of Health and Welfare, Stockholm
- Dr. M. Zappa, CSPO Center for Study and Prevention of Cancer, Florence

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.