Review

Short version of the German evidence-based Guidelines for prophylactic vaccination against HPV-associated neoplasia


A B S T R A C T

Persistent infection with HPV 16 and 18 has been causally associated with the development of cervical cancer and its precursor lesions as well as with other carcinomas and their precursors, e.g. some vulvar and vaginal cancers. Furthermore HPV 6 and 11 are responsible for anogenital condylomata acuminata in more than 90% of cases. With the recently developed prophylactic bivalent (HPV 16 and 18) and quadrivalent (HPV 6, 11, 16 and 18) vaccines, it is possible to prevent infection of the cervical epithelium and other squamous epithelia, the development of premalignant lesions and, in the case of the quadrivalent vaccine, the development of condylomata acuminata. The following paper represents a summary of the full-text version of the German evidence-based Guidelines, including all evidence-based recommendations regarding the safety as well as the efficacy of the vaccines in preventing CIN, VIN/VaIN, genital warts and other HPV-associated lesions.

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Abbreviations: AIN, anal intraepithelial neoplasia; AkdÄ, Drug Commission of the German Medical Association (Arzneimittelkommission der deutschen Ärzteschaft); ATP, according to protocol; ASMA, 3-deacetylated monophosphoryl lipid A and aluminium hydroxide; AWFM, Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.); CIN, cervical intraepithelial neoplasia; dEBM, Division of Evidence Based Medicine; EMEA, European Medicines Agency; HC2 test, Hybrid Capture 2 test; HPV, human papillomavirus; ICC, invasive cervical carcinoma; ITT, intention-to-treat; Pap smear, papanicolaou test; PCR, polymerase chain reaction; PIN, penile intraepithelial neoplasia; STD, sexually transmitted disease; STIKO, Standing Committee on Vaccination at the Robert Koch Institute (Ständige Impfkommission am Robert Koch-Institut); VaIN, vaginal intraepithelial neoplasia; VIN, vulvar intraepithelial neoplasia; VLP, virus-like particle.

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1. Introduction

1.1. Preliminary remarks

The following represents a summary of the full-text version of the German evidence-based (S3) Guidelines for the prophylactic vaccination against HPV-associated neoplasia, which was published in Chemotherapie Journal, Heft 4, 2008, Zeitschrift der Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. The full version contains the individual chapters in unabridged form, additional chapters on the epidemiology and pathogenesis of the different HPV-associated lesions, sections on the impact of vaccination on secondary prevention measures, and a list of questions frequently asked by patients.

1.2. Needs analysis

Each year 494,000 women worldwide, including 6500 in Germany, develop cervical carcinoma. According to German Federal Statistical Office figures, 1660 deaths resulting from cervical carcinoma were registered in Germany in 2004. Annually, 15,000 deaths in Europe, and approximately 275,000 worldwide, can be attributed to this malignant tumour. Persistent infection with HPV 16 and 18 or any of at least 11 other high-risk HPV types has been causally associated with the development of cervical cancer and its precursor lesions (i.e. dysplasia or cervical intraepithelial neoplasia – CIN). A causal relationship has also been demonstrated for other carcinomas and their precursors, including some vulvar, vaginal, penile, and anal cancers, as well as tonsillar and laryngeal cancers, and certain types of skin cancer.

Low-risk HPV types, such as HPV 6 and 11, are responsible for anogenital condylomata acuminata (anogenital warts) in more than 90% of cases. Condylomata acuminata is the most common sexually transmitted viral disease (STD) worldwide. It has been estimated that approximately 1% of the population between the ages of 15 and 49 in Germany, and in Europe as a whole, is affected by these benign, yet extremely bothersome lesions. Studies conducted over the past several years have indicated that the incidence of these tumours continues to rise.

With the recently developed prophylactic bivalent (HPV 16 and 18) and quadrivalent (HPV 6, 11, 16 and 18) vaccines, it is now possible to prevent (a) infection of the cervical epithelium and other squamous epithelia; (b) the development of premalignant lesions; and, in the case of the quadrivalent vaccine (HPV 6, 11, 16 and 18) and (c) the development of condylomata acuminata. Therefore, the aim of prophylactic HPV vaccination in Germany is to reduce morbidity and mortality, but also to lower the high costs associated with cytologic screening, diagnostic procedures, and treatment.

1.3. Methods

A detailed description of the methodology and approach used in developing the Guidelines can be found in the Methods Report on the Guidelines, which can be provided by the Division of Evidence Based Medicine (dEBM).

1.3.1. Main questions of the Guidelines

The main questions of the Guidelines were focusing on the efficacy and safety of prophylactic vaccines against HPV-associated neoplasias such as CIN, VIN, VaIN, genital warts and others.

1.3.1.1. Data sources. To complete the evidence-based sections of the Guidelines (i.e. on the effectiveness and safety of vaccination), a systematic search of the literature published before 31 July 2007 was conducted on MEDLINE, EMBASE, and the Cochrane Library (for details, e.g. the search strategy please see full-text of the Guidelines and the method report). 1101 publications were found. However, only a total of 10 studies met the inclusion criteria for the Guidelines (Fig. 1).

1.3.1.2. Evidence assessment. Efficacy and safety were assessed using evidence-based criteria. The methodological quality of
As part of the formal consensus method, each included study was rated using the following evidence grades:

A1 Meta-analysis that includes at least one randomized study with grade A2 evidence (see below). The results of the different studies included in the meta-analysis must be consistent with one another.

A2 A randomized, double-blind, comparative clinical study of high quality (e.g. sample-size calculation, flow chart, ITT analysis, sufficient size).

B Randomized clinical study of lesser quality or other comparative study (e.g. non-randomized cohort or case-control study).

C Non-comparative study.

D Expert opinion.

In addition, the following evidence levels provide an overall rating of the available efficacy and safety data:

1 Studies with grade A1 evidence or studies with grade A2 evidence whose results are predominantly consistent with one another.

2 Studies with grade A2 evidence or studies with grade B evidence whose results are predominantly consistent with one another.

3 Studies with grade B evidence or studies with grade C evidence whose results are predominantly consistent with one another.

4 Little or no systematic empirical evidence.

1.3.1.3. Non-evidence-based sections. The references section in this abridged version of the Guidelines lists the studies that provide the data evaluated in the evidence-based chapters. Chapter B (‘Adverse Events and Safety’) contains a section on safety aspects related to the vaccine that are not dealt with in these studies. The section is based on the expertise of the authors and the literature cited in the full-text version of the Guidelines.

1.3.1.4. Consensus method. As part of the formal consensus method, evidence-based and non-evidence-based passages were formulated using a nominal group process. The passages requiring consensus were chosen unanimously by the Guidelines Group; these included the vaccination recommendations and some of the patient questions contained in the full-text version of the Guidelines.

1.3.1.5. Vaccination recommendations. All vaccination recommendations were formulated during consensus conferences that followed an evidence-based approach (i.e. systematic literature search; nominal group process). The strength of each recommendation takes into account aspects related to efficacy (including the quality of efficacy data), safety, practicability, cost-benefit ratio, etc. Vaccine recommendations appear in grey boxes.

1.3.2. Funding of the Guidelines

The Guidelines project was funded by the Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. There was no influence regarding the content of the Guidelines. Furthermore all authors provided a declaration of independence as well a conflict of interest form. These can be provided by the dEBM (see full-text version of the Guidelines).

2. Methods for detecting HPV

The current standard for identifying human papillomavirus in clinical samples is molecular detection of viral DNA. The standardized methods of HPV DNA detection are polymerase chain reaction (PCR) and the Hybrid Capture 2 (HC2) test. The HC2 test is the only method currently approved by the US FDA for routine use (i.e. in primary screening, triage, and following treatment of CIN).

First results of studies on the two currently available prophylactic HPV vaccines indicate that they have no impact on existing HPV infections. This observation would seem to imply that vaccination should always be preceded by an HPV test. However, this cannot be recommended at the present time for the following reasons:

1. The majority of persistent HPV infections are single infections (i.e. involving only one HPV type); as a result, vaccination will still confer protection against the remaining vaccine HPV types in most cases.

2. Even if a DNA test is negative, this does not rule out the possibility that a woman was previously infected with one or more types of HPV, cleared the infection, and has acquired immunity to the type or types in question.

3. Currently, there is no reasonably priced, validated HPV test that can identify whether a woman is infected with the specific HPV types that are relevant for vaccination.

4. Universal HPV testing in women aged 18 years or older would identify a large number of transient infections that have no clinical relevance and would cause considerable worry for the women and physicians involved. This is why all experts recommend waiting until women are 30 or older before including HPV tests in primary screening. When doing so, the HC2 test should be used whenever possible due to its relatively high cut-off values and correspondingly high specificity.

5. There is currently no system for measuring specific immune response to the different vaccine HPV types. The related analyses conducted within the vaccine studies used assays that were developed by the manufacturers themselves and are not commercially available.

However, testing for HPV as an adjunct to cervical cytology in primary screening is considered reasonable in women aged 30 years or more. This also applies to younger women with abnormal cytologic or colposcopic findings, or with other evidence of increased risk in their medical history. HPV testing is also indicated after treatment of CIN (please also refer to the S2-Guidelines of the German...
Society for Gynaecology and Obstetrics [Deutsche Gesellschaft für Gynäkologie und Geburtshilfe]).

Testing for pre-existing HPV infection to determine whether a vaccine should be administered is currently not recommended due to the unavailability of appropriate assays and a lack of practical advantages.

3. Vaccines/vaccine manufacturers

To date, two prophylactic vaccines against HPV infection have been developed and tested in clinical studies. Both are based on virus-like particles (VLPs), empty capsids that do not contain any viral DNA. As such, they cannot cause disease, but are able to stimulate the immune system to produce specific antibodies.

The vaccine Gardasil® was developed by Merck and is distributed in Germany by Sanofi Pasteur-MSD. Gardasil® contains VLPs of HPV types 6, 11, 16, and 18 at 20–40 μg per dose formulation and uses an aluminium hydroxide adjuvant. The VLPs are produced in yeast. Gardasil® was approved in September 2006 by the EMEA for all member states of the European Union and has been available in Germany since October 2006.

The bivalent vaccine Cervarix® was developed by GlaxoSmithKline. It contains VLPs of HPV types 16 and 18 at 10–20 μg per dose formulation and uses a proprietary adjuvant AS04, which is composed of aluminium salt and 3-deacylated monophosphoryl lipid A, a cell membrane component derived from the bacterium Salmonella minnesota. Although this induces higher antibody titers than have been observed with Gardasil®, it is still unclear whether these afford greater protection. Cervarix® was approved by the EMEA in September 2007 for all member states of the European Union.

Both vaccines are administered intramuscularly (preferably in the deltoid muscle) as a 0.5 mL dose, which should be injected in its entirety. The amount of antigen in both preparations is similar. Administering higher doses does not lead to any fundamental improvement in immune response. Both vaccines are administered in a three-dose schedule. According to current recommendations, the second dose should be given one month (Cervarix®) or two months (Gardasil®) after the first dose; the third dose should be administered six months after the first dose. At the very least, the second dose should be given within two and six months of the first dose, and the third dose within one year of the first dose.

4. Primary prevention of CIN/primary prevention of vulvar dysplasia

4.1. Efficacy in preventing CIN

A total of nine studies met the inclusion criteria for the Guidelines. Of these, seven were randomized, controlled clinical trials and two were follow-up studies. All nine studies were of high methodological quality and were thus assigned an evidence grade of A2, resulting in an evidence level of 1.

Two studies investigated a monovalent HPV 16 vaccine [1,2] in women between 16 and 23 years of age. The vaccine demonstrated 100% efficacy in preventing HPV 16-associated CIN 1–3 compared to placebo.

Three studies investigated the bivalent vaccine [3–5] in women between 15 and 25 years of age. In one of these studies [3] and its follow-up [4], the vaccine demonstrated 100% efficacy compared to placebo in preventing CIN 1–3 associated with HPV 16 or 18. In the remaining study [5], one case of CIN 2 and one case of CIN 3 were found in the vaccine group. Efficacy in preventing severe CIN associated with the vaccine HPV types was thus initially calculated to be 90.4%. A post hoc analysis demonstrated, however, that it was highly unlikely that the two lesions in the vaccine group had been caused by one of the vaccine HPV types (HPV 16), because during the follow-up of both women, HPV 16 was detected in only one clinical sample, as opposed to HPV 58, which was detected in all other samples. As a result, the infection with HPV 16 was considered to be transient and causally unrelated to the two lesions. If this finding is taken into account, the vaccine in this study also demonstrated 100% efficacy.

Four studies investigated the tetravalent vaccine [6–9] in women between 15 and 26 years of age. In three of these studies, the vaccine demonstrated 100% efficacy compared to placebo (ATP) in preventing severe CIN associated with HPV 16. In the fourth study (Future II), one woman in the vaccine group was diagnosed with CIN 3. As in the study of the bivalent vaccine described above, it is also highly unlikely that this lesion was associated with the vaccine HPV types. If we take this consideration into account, the tetravalent vaccine demonstrated an efficacy of 100% in preventing severe CIN.

4.2. Efficacy in preventing vulvar dysplasia

Two studies met the inclusion criteria for the Guidelines [6,10]. Both investigated the efficacy of the tetravalent vaccine in women aged 16–26 years, and were assigned an evidence grade of A2. However, it should be noted that one [10] of these studies was a combined analysis of three multicentre, randomized controlled trials and included the other study [6], resulting in an evidence level of 2. In both studies, the vaccine demonstrated 100% efficacy compared to placebo (ATP) in preventing severe VIN and ValN associated with the vaccine HPV types.

5. Impact on cancer screening (secondary prevention)

Initially, vaccination will have little impact on cancer screening programmes, because it will be offered to girls and young women at an age before regular screening is initiated. In addition, early detection programmes currently target women who, for the most part, have not been vaccinated because of their age. However, in several years there will be an effect, which will continue to increase as the age cohorts being vaccinated become old enough for cancer screening.

The preventive effect of vaccination is incomplete, because it affords protection against only two oncogenic HPV types associated with approximately 70% of all cervical cancer cases in Germany. Because of this limited protection, it will become important in several years to convince women who have been vaccinated that they still need to undergo regular screening.

6. Primary prevention of genital warts

6.1. Efficacy in preventing genital warts

A total of three studies on the tetravalent vaccine fulfilled the inclusion criteria for the Guidelines [6,8,9]. One of these was a follow-up study [9] that included part of the population from the main study that preceded it [8]. All three studies were assigned an evidence grade of A2, resulting in an evidence level of 1. Compared to placebo (ATP), the vaccine demonstrated 100% efficacy in preventing the development of genital warts associated with the vaccine HPV types in women aged 16–24.

In one study [8] and its follow-up [9], the incidence of genital warts was evaluated together with the incidence of all external genital lesions, including VIN and ValN. In addition, because the
CIN
- The efficacy of vaccination in preventing CIN precursor lesions positive for HPV 16/18 has been demonstrated convincingly in HPV 16/18-negative women (evidence level 1). Data on efficacy and tolerability are from studies of women between the ages of 15 and 25. However, vaccination should take place earlier – i.e. in girls and young women aged 9–17 years. Ideally, the entire course of three injections should be completed before the onset of sexual activity.

Points in favour of early vaccination:
- Lower risk of previous HPV exposure through sexual activity.
- Greater immunogenicity in younger women; no evidence of reduced tolerability.
- Easier access to target group (i.e. can be easily incorporated into routine immunization schedule).
- Girls/women aged 17 and above
  For girls/women older than 17, the benefits, risks, and costs should be discussed with a specialist before taking any decision. The likelihood of HPV infection increases with a woman's age and number of lifetime sexual partners, thus reducing the expected benefits of vaccination. The sexual behaviour of a woman's partners is also associated with the likelihood of HPV infection. Therefore a clear general recommendation cannot be made for this group.
- Women with CIN or cervical carcinoma
  Vaccination is not effective in treating existing CIN or ICC.
- Boys and young men
  If herd immunity can be established through high levels of vaccination coverage among female adolescents, there will be no need to vaccinate young men to prevent CIN.

VIN/VaIN
- Analogous to the results seen for CIN, vaccination also affords protection against vaccine HPV type-associated VIN/VaIN. The recommendations made for HPV vaccination in the setting of CIN also apply to the prevention of VIN and VaIN.

Because vaccination cannot prevent cervical carcinoma in approximately 30% of cases, both vaccinated and unvaccinated women should continue to undergo routine cervical cancer screening.

Genital warts
- The efficacy of the vaccine in preventing genital warts, the vast majority of which contain HPV 6/11, has been convincingly demonstrated in women negative for HPV 6/11 (evidence level 1). Data on efficacy and tolerability are from studies of women aged 15–25. However, the vaccine containing HPV 6 and 11 VLPs should be administered earlier – i.e. to girls and young women aged 9–17 years. Ideally, the complete course of three injections should be completed before a girl becomes sexually active.

Points in favour of early vaccination:
- Lower risk of previous HPV exposure through sexual activity.
- Greater immunogenicity in younger women; no evidence of reduced tolerability.
- Easier access to target group (i.e. can be easily incorporated into routine immunization schedule).
- Girls/women aged 17 and above
  For girls/women older than 17, the benefits, risks, and costs should be discussed with a specialist before taking any decision. The likelihood of HPV infection increases with a woman's age and number of lifetime sexual partners, thus reducing the expected benefits of vaccination. The sexual behaviour of a woman's partners is also associated with the likelihood of HPV infection. Therefore a clear general recommendation cannot be made for this group.
- Boys and young men
  Efficacy data from clinical studies are still lacking. Proof of efficacy is required before recommendations can be made for boys and young men.

Other HPV-associated lesions
- To date there is no evidence of efficacy against the following HPV-associated lesions: genital warts in men (see ‘Genital warts’ section above), laryngeal papillomatosis, head and neck tumours, PIN and penile cancer, AIN and anal cancer, perianal intraepithelial neoplasia and carcinoma, or periungual carcinoma.
- Presumably, the vaccines have the potential to prevent these other HPV-associated lesions, insofar as the latter are caused by the vaccine HPV types. However, it will take many years after vaccination is introduced to prove this effect. To do so, the proper instruments (e.g. a vaccine registry) must be put into place today.
- AIN and anal carcinoma are a particular clinical problem in HIV-positive men who have sex with men. Considering the incidence of AIN 2–3 in these patients, the efficacy of the prophylactic HPV vaccines should be evaluated in appropriately designed clinical studies.

7. Other HPV-associated lesions

At the time the Guidelines were published, no studies investigating other HPV-associated lesions were available.

8. Adverse events and safety

8.1. Adverse events (non-evidence-based section)

Adverse events are one of the most important criteria in the regulatory approval of pharmaceuticals and, in particular, of prophylactic vaccines, which are generally administered to healthy, young individuals. For this reason, the various study centres and national and international regulatory agencies have placed special emphasis on adverse events and their evaluation. There is consensus among the authorities and institutions responsible for approving and recommending HPV vaccination that the vaccines have an excellent safety profile and a low rate of adverse events. It was determined that the methods and evaluation used in safety analysis were appropriate and followed recognized procedures.

8.1.1. Local adverse events

Local adverse events such as pain, redness, swelling, and itching were observed more frequently and were more severe in vaccine recipients than in those who received placebo. This can be attributed to a specific reaction to the antigen. For any
vaccine, antigen-specific reactions may be stronger following subsequent doses in a multiple-dose schedule, or following booster doses.

8.1.2. Systemic adverse events/serious adverse events

Systemic adverse events were fever, headache, and nausea, as well as increased body temperature. The rate at which these events occurred did not differ significantly between the vaccine and placebo groups.

Individual cases (<0.1/1000) of severe, potentially vaccine-related adverse events were reported and included bronchospasm, gastroenteritis, headache/hypertension, and vaginal haemorrhage. Due to the small number of such events, no statements can be made here as to whether there is an increase in their incidence following vaccination. Only with large, Phase IV postlicensure studies will it be possible to demonstrate whether there is any association between vaccination and adverse events like these.

The longest follow-up to date is five years. During this period, no increases were observed in the incidence of new-onset autoimmune disease in any of the study arms of the various Phase II and III trials. No statistically significant differences were observed between the various arms of the studies. The somewhat higher absolute number of potential autoimmune diseases (e.g. arthritis) among vaccine recipients falls within the natural range of variation for this number of cases.

Between June 2006 and October 2007, almost 3500 potential adverse events after Gardasil® vaccination were reported to the internet-based Vaccine Adverse Event Reporting System (VAERS) in the United States. Of these events, 347 were defined as serious. VAERS received three reports of death after Gardasil® vaccination. None of these, however, appear to have been caused by the vaccine and, in each case other likely causes were identified (i.e. 2× thromboembolism in patients taking oral contraceptives, and 1× myocarditis). Of the analyses conducted by the US Center for Disease Control (CDC) and Federal Drug Association (FDA) to date, none have shown any increase in the incidence of specific diseases or complications. This HPV vaccine can therefore continue to be regarded as very safe and tolerable.

Since the introduction of HPV vaccination in Europe, a total of two deaths after Gardasil® have been reported in Germany and Austria. In both cases, it was impossible to clearly determine the cause of death. The German authorities (Paul-Ehrlich-Institut), the Immunization Advisory Board of the Austrian Society of Paediatrics and Child Health (Österreichische Gesellschaft für Kinder- und Jugendheilkunde), and the EMEA were unable to identify any causal relationship between vaccination and the deaths of the two young women. According to mortality figures published by the German Federal Statistical Office, the annual rate of unexplained deaths among women aged 15–20 years is one case per 100 000 population. In Germany, this translates to 22 cases per 2.3 million young women in 2006, or one unexplained death every two weeks. Considering that 40% of these young women were vaccinated with Gardasil®, it appears that the number of reported deaths is within the range that could be expected to occur by chance alone after the vaccination.

Based on the available evidence, there is no indication thus far of an elevated health risk associated with HPV vaccination. This finding is based on the sale of approximately 2.2 million vaccine doses of Gardasil® in Germany and Austria to date, and is consistent with data from the US and other countries that have introduced the vaccine. Autoimmune diseases, such as multiple sclerosis (MS) and Guillain-Barré Syndrome, are a recurring issue in the discussion about vaccines. There have been media reports of individual cases of polyneuropathy and complications of unclear aetiology (e.g. strabismus) occurring after HPV vaccination. In the Phase III studies investigating the vaccines, however, there was no indication of an increased incidence of such complications compared to placebo.

Surveillance and tracking of potential adverse events are important. However, the HPV Management Forum currently recommends HPV vaccination without restrictions and, in doing so, is in full agreement with the EMEA, Paul-Ehrlich-Institut, and the CDC. Due to the high vaccination rates that have been achieved, a temporal (but not causal) association between the vaccine and individual cases of unexplained death and autoimmune disease is to be expected statistically. Alarmism in this context is counterproductive. Vaccination series that have been started should be completed according to the specified immunization schedules, and HPV vaccination should continue to play an important role in preventing cervical cancer.

8.1.3. Vaccination during pregnancy and breastfeeding

HPV vaccination is offered primarily to young women, who because of their age are more likely to become pregnant than their older counterparts. Although there are no theoretical concerns or experimental data that would indicate any danger to mother or child, whether before or after birth, the outcomes of births that occurred spontaneously in the studies were analysed. There was no evidence that vaccination was unsafe in pregnant women. Ranging from 3% to 4%, the rate of births with a congenital abnormality was low and similar to that seen in surveillance registries. The number of spontaneous abortions, premature births, and Caesarean sections was comparable among vaccine and placebo recipients. In a bridging study investigating the comparative immunogenicity and reactogenicity of the tetravalent vaccine, adverse events in adolescents were compared to those observed in young adult women. A total of 11 participants became pregnant during the course of the study, and the outcomes of eight pregnancies were known (six live births of a normal infant, one spontaneous abortion, and one elective abortion). However, it should be noted that the studies conducted to date have not been designed specifically to evaluate the two currently available HPV vaccines in pregnant women. Thus, until proof of safety is demonstrated in Phase IV studies, neither vaccine can be recommended in Germany for use during pregnancy.

HPV vaccination has not led to any serious vaccine-related adverse events in mother or child during lactation. Thus, the vaccine can be administered to mothers who are breastfeeding.

8.1.4. Overdose and interrupted vaccine schedules

The adverse event profile did not differ considerably between persons who received a normal dose and those who received a dose that was higher or lower than recommended. Similarly, deviating from the recommended vaccine schedule by increasing the length of time between doses had no impact on the spectrum of adverse events observed.

8.2. Adverse events (evidence-based section)

Seven studies evaluating the rate of adverse events following HPV vaccination fulfilled the inclusion criteria for the Guidelines. Of these, one was a follow-up study. All of the studies were assigned an evidence grade of A2, resulting in an evidence level of 1.

8.2.1. Study with a monovalent vaccine (early Gardasil® basic research study with investigational monovalent vaccine)

In a study by Koutsy et al., a total of 2392 women aged 16–23 years were followed up over a median period of 23.4 months. The incidence of adverse event was comparable in both groups (vaccine and placebo) [1].
Local adverse events Injection-site pain was the most common vaccine-associated adverse event (vaccine: 86%/placebo: 82%).

Systemic adverse events Increased body temperature was the most common vaccine-associated systemic adverse event (vaccine: 42%/placebo: 44%).

Serious adverse events A total of seven women experienced an unspecified serious adverse event during the study (vaccine: four women/placebo: three women). None of these events were considered to be related to the injection. A total of three women in the vaccine group and four women in the placebo group (i.e. 0.3% of the women in each group) discontinued participation in the study due to a serious adverse event.

8.2.2. Studies with a bivalent vaccine (Cervarix®)

In a study by Harper et al., a total of 1113 women were followed up over a period of 27 months to identify adverse events [3].

Local adverse events Local injection-site reactions were the most common adverse event (vaccine: 94%, placebo: 88%). The following reactions, all of which were described as mild, occurred within one week of vaccination: injection-site pain (93%/87%), swelling (34%/21%), and redness (36%/24%).

Systemic adverse events The incidence of systemic adverse events was comparable in both groups (86% in each). Headache was the most common of these events (vaccine: 62%/placebo: 61%), followed by fatigue (58%/54%), gastrointestinal symptoms (34%/32%), itching (25%/20%), increased body temperature defined as >37.5 °C and measured orally (17%/14%); all patients had temperatures less than 39 °C, and unspecified rash (11%/10%).

Serious adverse events A total of 41 serious adverse events were reported (vaccine: 22/placebo: 19). None of these, however, were considered vaccine related. Four participants discontinued participation in the study due to a serious adverse event, including one woman in the vaccine group who experienced a spontaneous abortion. However, this was not judged to be related to the vaccination. The other three participants, who left the study for unspecified reasons, had all been in the placebo group.

In an extension-phase study, a total of 776 women were followed up for 53 months [4]. More women in the placebo group (22%) than in the vaccine group (14%) reported adverse events. This finding, however, was not explained in any detail. A particular focus of this study was the new onset of chronic diseases (i.e. disorders of the immune, endocrine, or musculoskeletal systems; respiratory and unspecified thoracic disorders). Overall, 5% of women in the placebo group and 3% of women in the vaccine group reported such adverse events. The number of serious adverse events was similar in both groups (vaccine: 4%; placebo: 5%). None of these events were considered to be vaccine related, or even potentially vaccine related.

As part of an interim analysis, a different study evaluated adverse events among 18,644 women aged 15–25 after an average of 14.8 months [5].

Local adverse events Local adverse events were more common in the vaccine group than in the placebo group and included injection-site pain (vaccine: 90%/placebo: 78%), redness (44%/28%), and swelling (42%/20%).

Systemic adverse events The number of vaccine-associated systemic adverse events was also only slightly higher in the HPV vaccine group than among controls. The most frequent systemic adverse event was fatigue (vaccine: 58%/placebo: 54%), followed by headache (54%/51%), muscular pain (52%/45%), gastrointestinal complaints (28%/27%), joint pain (21%/18%), fever (12%/11%), unspecified rash (10%/8%), and urticaria (10%/8%). The number of women in this study in whom a new-onset chronic disease (1.5%/1.7%) or an autoimmune disease (0.3%/0.3%) was detected was similar in both the vaccine and control groups.

8.2.3. Studies with a tetravalent vaccine (Gardasil®)

In a study with a tetravalent vaccine, 552 women aged 16–23 years were observed over an average of 30 months to identify adverse events [8]. A total of 89% of the women in the vaccine group and 82% of the women in the placebo group reported experiencing adverse events that were judged to be associated with the vaccine. The vast majority of adverse events (94%) were described as being of mild or moderate intensity.

Local adverse events The majority of adverse events were local in nature (vaccine and placebo: 77%). Injection-site pain was the most frequently reported local adverse event.

Systemic adverse events In total, 38% of women in the vaccine group and 33% of women in the placebo group experienced a vaccine-associated systemic adverse event. The most frequently reported systemic adverse event was headache.

Serious adverse events The number of serious adverse events was similarly low in both groups (1%) and considered unrelated to the vaccination.

In a different study, a total of 5455 women aged 16 to 24 years were followed up for an average of 36 months to identify adverse events [6].

Local adverse events In total, 87% of the women in the vaccine group and 77% of the women in the placebo group reported experiencing local adverse events that were judged to be associated with the vaccine. The most frequently reported local adverse event was injection-site pain (vaccine: 85%/placebo: 75%), followed by injection-site swelling (26%/15%), redness (25%/17%), and itching (4%/3%).

Systemic adverse events Systemic adverse events judged to be associated with the vaccine were similarly frequent in both groups (vaccine: 65%/placebo: 64%). The most common systemic adverse event was increased body temperature or fever.

Serious adverse events One woman in the vaccine group reported experiencing a serious adverse event (bronchospasmus) that was judged to be vaccine related. No serious adverse events were observed in the placebo group. None of the participants in either group discontinued participation in the study due to a serious adverse event.

In another study, adverse events in 12,167 women who had received the tetravalent vaccine were evaluated over an average of 36 months [7].

Local adverse events More women in the vaccine group reported experiencing at least one local adverse event compared to placebo (vaccine: 84%/placebo: 78%). Injection-site pain was by far the most common of these events (83%/76%).

Serious adverse events Three women in the vaccine group and two women in the placebo group experienced serious adverse events that were judged to be related to the vaccination. In the vaccine group, the serious adverse events were gastroenteritis, headache, hypertension, injection-site pain, and a decrease in joint movement at the injection site. In the placebo group, the serious adverse events were hypersensitivity to the injection, chills, headache, and fever. The one woman who discontinued participation in the study due to a serious adverse event was in the placebo group.

As part of administering the vaccine, it is important to monitor for adverse events and report them to the manufacturer and/or competent authorities (e.g. STIKO, AkdÄ) so that even rare adverse events can be registered.
### Contributors

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<th>Project title</th>
<th>Prophylactic vaccination against HPV-associated neoplasia</th>
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The authors would like to thank Matthew Gaskins, medical translator for Charité – Universitätsmedizin Berlin, for his valuable assistance in translating this article.

### References

Glossary

According to protocol (ATP): analysis including only those women who (a) received the complete vaccination series (i.e. 3 doses) within 12 months; (b) were seronegative and HPV–DNA-negative (PCR) for the vaccine HPV types from the beginning of the study until at least one month after the last dose; and (c) had no major protocol deviations.

Cervical intraepithelial neoplasia (CIN): unregulated, abnormal growth of potentially precancerous cells on the surface of the cervix.

Nominal group process: a decision-making method as part of a consensus process. A suggestion made by a core group of experts is discussed by the entire group in a structured manner. The person directing the group process can steer the discussion, but is not permitted to take active part in it.

Primary prevention: a distinction must be drawn between primary and secondary prevention. Secondary prevention aims at early disease detection, including the detection of precursor disease without symptoms (e.g. CIN) and manifest disease in its early stages (e.g. invasive cervical carcinoma), allowing for diagnosis at a point in time when the chances of cure are still good. Tertiary prevention describes activities aimed to prevent the worsening of established disease or disability, as well as the emergence of secondary disease. The goal of primary prevention is to help people reach old age and, at the same time, remain healthy. In addition, the various healthcare and social insurance payers (including statutory health insurance funds, pension insurance, and long-term care insurance), anticipate that well-designed primary prevention measures will lead to a reduction in health expenditures and the costs of long-term care.

Secondary prevention: see “Primary prevention”.