German evidence and consensus-based (S3) guideline: Vaccination recommendations for the prevention of HPV-associated lesions

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Summary

Anogenital and oropharyngeal infections with human papilloma viruses (HPV) are common. Clinically manifest disease may significantly impact quality of life; the treatment of HPV-associated lesions is associated with a high rate of recurrence and invasive neoplasms, such as cervical, anal, vulvar, penile, and oropharyngeal cancers, which are characterized by significant morbidity and mortality. Vaccination against HPV is an effective and safe measure for the primary prevention of HPV-associated lesions, but immunization rates are still low in Germany. The present publication is an abridged version of the German evidence and consensus-based guideline “Vaccination recommendations for the prevention of HPV-associated lesions”, which is available on the website of the German Association of the Scientific Medical Societies (AWMF). On the basis of a systematic review with meta-analyses, a representative panel developed and agreed upon recommendations for the vaccination of different populations against HPV. In addition, consensus-based recommendations were developed for specific issues relevant to everyday practice. Based on current evidence and a representative expert consensus, these recommendations are intended to provide guidance in a field in which there is often uncertainty and in which both patients and health care providers are sometimes confronted with controversial and emotionally charged points of view.
Information about the present guideline

Instructions on using the guideline

The present publication is a shortened version of the long version of the S3 guideline, which is available on the website of the German Association of the Scientific Medical Societies (AWMF). This is an updated version – some text segments have been adopted from the previous version of the guideline from 2013 [1]. A comprehensive presentation of the methods of guideline development, the composition of the guideline committee, and the management of conflicts of interest can be found in the separately available guideline development report. A detailed description of the guideline questions, methods, and the results of the systematic assessment of the evidence can be found in the evidence report. In addition, a short version of the guideline is available. All guideline documents specified above are freely available on the AWMF website at https://www.awmf.org/leitlinien/detail/ll/082-002.html.

Guidelines are systematically developed resources for clinically relevant consultation and decision situations. Only a limited selection of standardized clinical situations can be considered during compilation of a guideline. Prior to implementation of the recommendations, specialist information of manufacturers need to be reviewed with respect to the specific situation (for example, indication, incompatibilities, comorbidities, contraindications). Recommendations of clinical guidelines are not legally binding; in certain situations, physicians may or even must deviate from the given recommendations.

If vaccination is not performed according to the recommendations of the Standing Committee on Vaccination (STIKO) [2, 3] at the Robert Koch Institute (RKI) and the currently valid vaccination recommendations of the federal states, respectively, health insurances may refuse reimbursement of costs associated with the vaccination. Patients have to be informed, if the vaccination is performed in deviation from the currently valid vaccination recommendations of the STIKO or the federal states and the official approval of the vaccines. In some federal states, recommendations may deviate from the nation-wide vaccination calendar, for example in Saxony, where HPV vaccination for all people (women and men) is recommended up to the age of 26 [4]. In individual cases, some health insurances may reimburse the costs of HPV vaccination in populations and age groups not covered by STIKO recommendations; therefore, a relevant inquiry may be useful.

Level of recommendation, evidence classification, and consensus strength

All recommendations of this guideline that were formally consented are presented in marked boxes. Wording and symbols used for the standardized presentation of strength and direction of the recommendations (grade of recommendation) are shown in Table 1. The recommendation strength considers various aspects for practical implementation that are also included in Table 1.

Evidence-based recommendations include information on the quality of the evidence according to the GRADE system [7]. As specified in the GRADE methods, the assessment of confidence in the (pooled) effect estimates [8] was outcome-based, according to the evaluation of various factors (risk of bias [9], precision [10], consistency [11], directness [12], publication bias [13]). The consensus strength was classified according to the categories specified by the AWMF policy [6].

Epidemiology of diseases preventable by HPV vaccination

Anogenital infections with human papilloma viruses (HPV) belong to the most common sexually transmitted infections [14–20]. In sexually active young people, infections with numerous types of HPV are detectable relatively soon after commencing sexual life, and 85 % to more than 90 % of sexually active people acquire HPV infection during their lifetime. These are usually transient infections that are no longer detectable by HPV DNA testing after six to 18 months [21–30]. Persistent infections with high-risk (HR) types of HPV, such as HPV16 or HPV18, may, however, cause precancerous lesions (intraepithelial neoplasms, IEN) after several months to years, which may progress to invasive cancers after several years [25, 29, 31]. In 2013, more than 7,500 cases of cancer in Germany were attributable to chronic HPV infections [32].

Cervical cancer is the most common HPV-associated cancer. More than 99 % of all cervical cancers are HPV-related. Approximately 70 % of all cervical cancers are caused by HPV16 and HPV18, the remaining 30 % by other types of HR HPV [25, 33, 34]. With approximately 570,000 new cases per year (and 230,000 deaths), cervical cancer is the second-most common cancerous disease in women [24, 35]. In Germany, there are currently an estimated 4,400 new cases of cervical cancer and 1,600 deaths per year, although cancer screening has been offered since the 1970s. These numbers did not significantly change in recent years. With a crude
incidence rate of 10.5 new cases per 100,000/year, Germany ranks average among European countries [36].

Nearly all anal cancers (89–100 %) are caused by HR HPV, predominantly by HPV16 [28]. The incidence of anal cancer in the general population is 1–2 per 100,000/year. In Western countries, including Germany, a continuous increase in the incidence of anal cancer has been observed in both women and men for several years [36–38]. In Germany, the number of newly diagnosed cases of anal cancers is currently estimated at approximately 2,500 per year (1,500 in women, 980 in men) [36]. Compared to the general population, three populations or patient groups are at a markedly increased risk of developing anal cancer: (1) men having sex with other men (MSM), (2) women with a history of HPV-related genital dysplasia/cancer, and (3) immunosuppressed individuals, such as organ transplant recipients or persons living with HIV (PLWH) [39–44]. The incidence of anal cancer in HIV-positive MSM is 60–100 per 100,000/year [42, 44].

25–40 % of vulvar cancers and 70–80 % of vaginal cancers are HPV-related [35, 45, 46]. Especially for vulvar cancers, an increase in incidence rates has been observed in recent years. This applies also to Germany [36, 38]. The majority (78–87 %) of precancerous stages of penile cancers and up to half (33–51 %) of all penile cancers are caused by HPV. Again, HPV16 is the most frequently identified type of HPV [47, 48]. In Germany, the number of newly diagnosed cases of penile cancer is estimated at approximately 250 per year [49].

HPV infections are also a causative factor in the development of oropharyngeal cancer (OPC). More than 50 % of tongue root and tonsil cancers are positive for HR HPV [50, 51]. In Western countries, including Germany, a continuous increase in HPV-related OPCs has been observed in recent years, with men much more frequently affected than women. This increase applies to both the proportion of HPV-related OPCs in relation to all OPCs and the incidence rates of OPCs.
Objectives of the guideline

The present evidence and consensus-based guideline is intended to evaluate the efficacy of the three HPV vaccines for different patient populations from an evidence-based perspective. On the basis of a systematic review with meta-analyses, a representative panel developed and agreed upon recommendations. The main objective of the guideline is to protect individuals against HPV infections and their consequences; in other words, to reduce the population-related disease burden of HPV-associated lesions – from benign to malignant, invasive tumors. An additional objective is the clarification of specific issues relevant to everyday practice by providing consensus-based recommendations. Based on current evidence and a representative expert consensus, these recommendations are intended to provide orientation in a field where there is often uncertainty and in which both patients and health care providers are sometimes confronted with controversial and emotionally charged points of view.

A further objective of this guideline was the development of recommendations for organizational measures to improve the currently inadequate implementation of HPV vaccination in Germany [75]. These recommendations are only available in the long version of the guideline, and are not included in the current publication.

Primary prevention

General recommendations for vaccination between the ages of 9 and 14 years

**Recommendation 01: evidence-based recommendation**

| Grade of recommendation: ⬆⬆ | Agreement: strong consensus* |
|---------------------------|----------------------------|
| GRADE: low ⊕⊕⊕◯ to moderate ⊕⊕⊕◯ | We recommend to vaccinate all children aged 9 to 14 years against HPV, irrespective of their gender and as early as possible. |

*Agreement: 100 %.

**Evidence (recommendation 01):**

Girls aged 9 to 14 years: indirect evidence from twelve randomized, placebo-controlled trials [76–88] reporting data on older participants negative for various relevant types of HPV at the time of enrollment. See evidence report for detailed information.

Boys aged 9 to 14 years: indirect evidence from two randomized, placebo-controlled trials [89–91] providing data on older participants negative for various relevant types of HPV at the time of enrollment. See evidence report for detailed information.

Evidence report (summary): girls aged 9 to 14 years

None of the identified RCTs included girls aged 14 years or younger. However, the included publications provided data on adolescent or older women that were, at the time of enrollment, seronegative and DNA-negative for the types of HPV included in the vaccines and, in some cases, also additional types. In terms of vaccination efficacy, this population may be considered as representative for girls prior to their first sexual contact. In this respect, the data on the reported endpoints provide indirect evidence for the issue addressed here.

For the comparison of the bivalent (2v-) HPV vaccine with placebo in girls prior to their first sexual contact, eight publications [76–83] on six RCTs were included. Seven publications [76–79, 81–83] reported data on the occurrence of cervical intraepithelial neoplasia (CIN), but only four [77–79, 81] of these publications reported data related to the occurrence of CIN irrespective of the HPV type. Concerning CIN1+, CIN2+, and CIN3+, a significant advantage was observed for the participants in the vaccine group (CIN1+: 3 RCTs, RR: 0.50,
95% CI: 0.42–0.59, GRADE: moderate; CIN2+: 4 RCTs, RR: 0.33, 95% CI: 0.25–0.43, GRADE: moderate; CIN3+: 2 RCTs, RR: 0.08, 95% CI: 0.03–0.23, GRADE: moderate).

With respect to severe adverse events (SAEs) and mortality, no significant differences were observed between vaccine and placebo groups (SAEs: 6 RCTs, RR: 1.00, 95% CI: 0.93–1.09, GRADE: moderate; mortality: 6 RCTs, RR: 1.17, 95% CI: 0.59–2.31, GRADE: low). Regarding mortality, it should be noted that the follow-up period varied between individual studies and ranged from one to six years (median).

For the comparison of the quadrivalent (4v-) HPV vaccine with placebo in girls prior to their first sexual contact, five publications [84–88] on six RCTs were included. Four [84, 86–88] of the five publications reported data on participants that received at least one dose; the other publication [85] reported exclusively on participants that received a complete vaccination series. Two publications [86, 87] on three RCTs collected data on genital warts. However, in the present systematic review, we only considered data from one publication [86] on two of these RCTs that reported the endpoint of genital warts irrespective of the triggering or associated HPV type. Participants vaccinated against HPV were at a significantly reduced risk of developing genital warts (2 RCTs, RR: 0.17, 95% CI: 0.12–0.26, GRADE: moderate). Concerning CIN, four publications [84, 86–88] on five RCTs were included. However, only one of these publications [86] reported data on two RCTs on the occurrence of CIN irrespective of the triggering or associated HPV type. Vaccinated participants had a significantly lower relative risk of developing CIN of different severity (CIN1+: 2 RCTs, RR: 0.71, 95% CI: 0.61–0.82, GRADE: low; CIN2+: 2 RCTs, RR: 0.57, 95% CI: 0.44–0.76, GRADE: moderate; CIN3+: 2 RCTs, RR: 0.54, 95% CI: 0.36–0.82, GRADE: low). Moreover, the same publication [86] reported a significantly reduced risk of developing vulvar and vaginal intraepithelial neoplasia (VIN and VaIN) by 4v-HPV vaccination (VIN/VaIN1: 2 RCTs, RR: 0.45, 95% CI: 0.28–0.72, GRADE: moderate; VIN/VaIN2–3: 2 RCTs, RR: 0.23, 95% CI: 0.10–0.52; GRADE: moderate). No significant differences between the groups were observed with respect to AIN1 and AIN2+ (2 RCTs, RR: 1.69, 95% CI: 0.18–21.97, GRADE: low). With regard to the occurrence of PIN3, with mixed samples of heterosexual men and MSM) (2 RCTs, RR: 0.56, 95% CI: 0.12–2.69, GRADE: low) and PIN2 (1 RCT, RR: 1.69, 95% CI: 0.18–21.97, GRADE: low).

No significant differences were observed with respect to SAEs (6 RCTs, RR: 0.83, 95% CI: 0.68–1.01, GRADE: low) and mortality (6 RCTs, RR: 1.65, 95% CI: 0.79–3.46, GRADE: low). Regarding mortality, it should be noted that the majority of the included studies reported a follow-up period of less than five years.

For the comparison of the nonavalent (9v-) HPV vaccine with placebo, no randomized controlled trials reporting on clinical endpoints could be included.

For the comparison of the 9v-HPV vaccine with the 4v-HPV vaccine, data from a current Cochrane review [92] were used: there were no differences with respect to the occurrence of high-grade CIN or invasive cervical cancer (OR: 1.00, 95% CI: 0.85–1.16, GRADE: high) and the combined endpoint of high-grade CIN, VIN, and VaIN (OR: 0.99, 95% CI: 0.85–1.15, GRADE: high). These data refer to girls/women aged 9 to 26 years. In addition, data on adverse events were analyzed, but this also contained data on one RCT that included boys/men. With 9v-HPV vaccination, local adverse events occurred slightly more often than with the 4v-HPV vaccine (RR: 1.07, 95% CI: 1.05–1.08, GRADE: high). No significant differences were observed with respect to SAEs (RR: 0.60; 95% CI: 0.14–2.61, GRADE: low) and mortality (RR: 1.20, 95% CI: 0.37–3.94, GRADE: low).

Evidence report (summary): boys aged 9 to 14 years

None of the identified RCTs included boys aged 14 years or younger. However, the included publications reported data on adolescent or older men that were, at the time of enrollment, seronegative and DNA-negative for types of HPV included in the vaccines and, in some cases, also additional types. Regarding vaccination efficacy, this population may be considered as representative for boys prior to their first sexual contact. In this respect, the data on the reported endpoints provide indirect evidence regarding the addressed issue.

Three publications [89–91] on two RCTs met the inclusion criteria and reported data on the occurrence of anal and genital warts as well as penile and anal intraepithelial neoplasia (PIN and AIN). All of the included placebo-controlled trials on this issue analyzed the efficacy of the 4v-HPV vaccine. None of the publications reported data referring to relevant endpoints irrespective of the HPV types associated with the lesions. In the following section, therefore, data on clinical endpoints are reported that refer exclusively to lesions associated with the HPV types included in the vaccine. For anal and genital warts, three publications [89–91] on two RCTs were included. Two of these publications [89, 91] reported data on the same RCT. One of these [91], however, reported exclusively data of the 602 MSM aged 16 to 26 years participating in the RCT. In this publication, no significant difference was found for the occurrence of anal warts (1 RCT, RR: 0.08, 95% CI: 0.00–1.45; GRADE: very low). Concerning the occurrence of genital warts, however, the risk for vaccinated participants was significantly reduced in the meta-analysis of the data from both RCTs (each with mixed samples of heterosexual men and MSM) (2 RCTs, RR: 0.21, 95% CI: 0.11–0.41, GRADE: moderate). Two publications [89, 90] showed no significant differences for PIN1 (2 RCTs, RR: 0.56, 95% CI: 0.12–2.69, GRADE: low) and PIN2 (1 RCT, RR: 1.69, 95% CI: 0.18–21.97, GRADE: low).

Until the end of the follow-up period, none of the participants presented with PIN3. With regard to the occurrence of AIN, one publication [91] reported data of 402 MSM aged 16 to 26 years that had received a complete vaccination series (that is, all three doses). The risk of AIN1 and AIN2 was significantly reduced in vaccinated participants (AIN1: 1 RCT, RR: 0.27, 95% CI: 0.09–0.79, GRADE: moderate; AIN2+: 1 RCT, RR: 0.25, 95% CI: 0.07–0.86, GRADE: low). No statistically
significant difference was found for AIN3+ (1 RCT, RR: 0.36, 95 % CI: 0.07–1.75, GRADE: low). With respect to SAEs and mortality, two publications [89, 90] on two RCTs were included that revealed no statistically significant differences (SAEs: 2 RCTs, RR: 0.69, 95 % CI: 0.29–1.65, GRADE: low; mortality: 2 RCTs, RR: 0.31, 95 % CI: 0.09–1.01, GRADE: low).

With regard to the evaluation of mortality, it should be noted that the analyzed data are derived from studies with a median follow-up period of less than four years.

For the comparison of the 9v-HPV vaccine with the 4v-HPV vaccine, data from a current Cochrane review [92] were used: For this comparison, no data on the clinical efficacy (for example, AIN, PIN, invasive cancers) were identified. While data on adverse events were analyzed in the mentioned review, these contain also data of two RCTs that included girls/women (see summary above).

### General recommendations for vaccination at the age of 15 years or older

**Recommendations 02-04: evidence-based recommendations**

| Grade of recommendation: | Agreement: strongest consensus* |
|--------------------------|---------------------------------|
| GRADE: low               | We recommend to vaccinate HPV vaccine-naive adolescents aged 15 to 17 years against HPV, irrespective of their gender and as early as possible. |

| Grade of recommendation: | Agreement: strongest consensus* |
|--------------------------|---------------------------------|
| GRADE: moderate          | We suggest to vaccinate HPV vaccine-naive adolescents aged 18 to 26 years against HPV, irrespective of their gender. |

| Grade of recommendation: | Agreement: majority agreement – consensus** |
|--------------------------|-----------------------------------------------|
| GRADE: low               | We suggest against recommending the HPV vaccination to HPV vaccine-naive adults aged 27 years or older, irrespective of their gender. |

### Evidence (recommendations 02-04):

- **GRADE: low**
  - ⊗⊗⊗⊗ to high
  - Girls and women aged 15 years or older: evidence from eight randomized placebo-controlled trials [78, 79, 83, 84, 86, 88, 93, 94]. See evidence report for detailed information
  
- **GRADE: low**
  - ⊗⊗⊙⊙ to high
  - Boys and men aged 15 years or older: evidence from three randomized placebo-controlled trials [89–91, 95]. See evidence report for detailed information

*Agreement: 100 %, **this recommendation was approved with majority agreement for women (72.7 %) and with consensus for men (81.8 %).

For the comparison of the 2v-HPV vaccine with placebo in girls/women after their first sexual contact, five publications [78, 79, 83, 93, 94] on four RCTs were included. Four publications [78, 79, 83, 94] on three RCTs reported data on the occurrence of CIN, but only three of these publications [78, 79, 83] reported data related to the occurrence of CIN irrespective of HPV types. Vaccinated participants were at a significantly reduced risk of CIN1+ (3 RCTs, RR: 0.69, 95 % CI: 0.57–0.83, GRADE: low), CIN2+ (3 RCTs, RR: 0.71, 95 % CI: 0.51–0.97, GRADE: low), and CIN3+ (2 RCTs, RR: 0.55, 95 % CI: 0.43–0.71, GRADE: high).

Concerning CIN2+, analysis of subgroups stratified by age provided an explanation for the statistical heterogeneity (I² = 75 %): in younger women (15–25 years), the risk of CIN2+ was significantly reduced after vaccination (2 RCTs, RR: 0.61, 95 % CI: 0.44–0.84; GRADE: moderate), whereas no significant difference was found in older women (> 26 years) (1 RCT, RR: 0.95, 95 % CI: 0.73–1.24; GRADE: moderate). No significant differences were observed with respect to SAEs (6 RCTs, RR: 1.00, 95 % CI: 0.93–1.09, GRADE: high) and mortality (6 RCTs, RR: 1.17, 95 % CI: 0.59–2.31; GRADE: moderate). The follow-up period varied between the individual studies and ranged from one to six years (median).

For the comparison of the 4v-HPV vaccine with placebo in girls/women after their first sexual contact, three publications [84, 86, 88] on four RCTs were included. One publication [86] on two RCTs reported a significantly lower risk of genital warts in the group of women vaccinated against HPV (2 RCT, RR: 0.38, 95 % CI: 0.31–0.47, GRADE: high). Three publications [84, 86, 88] on four RCTs reported data on CIN: the risk of CIN1+ and CIN3+ was significantly reduced in vaccinated participants (CIN1+: 2 RCTs, RR: 0.82, 95 % CI: 0.75–0.88, GRADE: moderate; CIN3+: 2 RCTs, RR: 0.81, 95 % CI: 0.69–0.96, GRADE: moderate); no significant differences were found for CIN2+ (3 RCTs, RR: 0.96, 95 % CI: 0.65–1.41, GRADE: low). Concerning CIN2+, analysis of subgroups stratified by age revealed that the risk of CIN2+ in younger women (16–26 years) vaccinated against HPV was reduced compared to non-vaccinated women (2 RCTs, RR: 0.81, 95 % CI: 0.72–0.92, GRADE: moderate). In contrast, no significant differences between the groups were found in the RCT that included older women (1 RCT, RR: 1.21, 95 % CI: 0.84–1.75; GRADE: moderate). One publication [86] on two RCTs found a significant advantage for women vaccinated against HPV with respect to VIN/VaIN1 (2 RCTs, RR: 0.70, 95 % CI: 0.54–0.92, GRADE: moderate) and VIN/VaIN2 (2 RCTs, RR: 0.49, 95 % CI: 0.32–0.76, GRADE: high). No significant differences between the groups were observed with respect to SAEs.
Evidence report (summary): boys/men aged 15 years or older

Four publications [89–91, 95] on three RCTs met the inclusion criteria and reported data on a comparison of the 4v-HPV vaccine and placebo in boys and men aged 16 years or older. Only one [89] of the four studies reported data referring to one of the relevant endpoints irrespective of the HPV types associated with the lesions (genital warts). With exception of this endpoint, only data on clinical endpoints that refer exclusively to lesions associated with the HPV type included in the vaccine are reported in the following section. Two publications [89, 91] on one RCT reported data on the occurrence of anal and genital warts. In a subgroup analysis that evaluated data of the MSM participating in the RCT (age: 16 to 26 years), the occurrence of anal warts was significantly reduced in vaccinated participants (1 RCT, RR: 0.42, 95 % CI: 0.23–0.79, GRADE: moderate). Similarly, in the total sample consisting of heterosexual men and MSM, occurrence of genital warts was significantly reduced in vaccinated men (1 RCT, RR: 0.38, 95 % CI: 0.26–0.58, GRADE: high). One publication [89] on one RCT reported no significant differences between vaccinated and non-vaccinated participants for PIN1 (1 RCT, RR: 0.75, 95 % CI: 0.17–3.34, GRADE: moderate) and PIN2 (1 RCT, RR: 1.50, 95 % CI: 0.25–8.94, GRADE: moderate). No PIN3 lesions occurred during the observation period. One publication [91] on one RCT reported data on AIN in 551 MSM. For participants vaccinated against HPV, a significantly reduced risk was found for AIN1 (1 RCT, RR: 0.50, 95 % CI: 0.34–0.75, GRADE: moderate) and AIN2 (1 RCT, RR: 0.46, 95 % CI: 0.27–0.79, GRADE: moderate). No significant difference between the groups was found for AIN3 (1 RCT, RR: 0.53, 95 % CI: 0.25–1.12; GRADE: low). With respect to SAEs and mortality in men after their first sexual contact, three publications [89, 90, 95] on three RCTs could be included, which documented for both endpoints a statistically significant advantage of questionable clinical significance and low confidence in the effect estimate concerning the group of vaccinated participants (SAEs: 3 RCTs, RR: 0.38, 95 % CI: 0.15–0.93; GRADE: low).

Additional effects of HPV vaccination: non-systematically researched data

While RCTs in medical and clinical research are, for example, suitable to detect causal effects of interventions, population-based epidemiological studies are useful to assess the efficacy of health policy measures. In a systematic review with meta-analyses by Drolet et al. (2019) [96], population-based data from 14 industrialized nations before and after HPV vaccination were compared. Irrespective of the implementation of measures taken and the real extent of realization of HPV vaccination, a significant reduction of various relevant endpoints were shown in different age groups within a period between five and eight years after introduction of vaccination: There was, for example, a reduction in the prevalence of genital infections with HPV16 and HPV18 by 83 % in the group of girls aged 13–19 years (RR: 0.17; 95 % CI: 0.11–0.25) and by 66 % in women aged 20–24 years (RR: 0.34; 95 % CI: 0.23–0.49). The incidence of anogenital warts was reduced by 67 % in the group of girls aged 15–19 years (RR: 0.33; 95 % CI: 0.24–0.46), by 54 % in women aged 20–24 years (RR: 0.46; 95 % CI: 0.36–0.60), and by 31 % in men aged 25–29 years (RR: 0.69; 95 % CI: 0.53–0.89).

A significant reduction of anogenital warts was also found in boys and men: it was 48 % in boys aged 15–19 years (RR: 0.52; 95 % CI: 0.37–0.75) and 32 % in men aged 20–24 years (RR: 0.68; 95 % CI: 0.47–0.98). In addition, there was a significant reduction in the incidence of histologically confirmed CIN2+ by 51 % in girls aged 15–19 years (RR: 0.49; 95 % CI: 0.42–0.58) and by 31 % in women aged 20–24 years (RR: 0.69; 95 % CI: 0.57–0.84) within a period of five to nine years after implementation of HPV vaccination. An analysis stratified by existing vaccination recommendations and extent of implementation showed, for countries with general vaccination recommendations for various age
cohorts (for example, 9–26 years) with implementation of the recommendations at 50 % or more, a significantly faster and more pronounced decline in the incidence of anogenital warts and CIN2+ compared to countries with vaccination recommendations for only one age cohort (for example, 9–14 years) and/or implementation in less than 50 % of those for whom vaccination is recommended.

Association with HPV infections, especially infections with HPV16, has been verified for various oropharyngeal cancers [97–100]. Accordingly, a preventive effect of HPV vaccination is also assumed for the development of oropharyngeal cancers [101]. This assumption is supported by the experimental detection of neutralizing antibodies in the oral mucosa after vaccination [102]. In a randomized controlled trial [103] with 7,466 women aged 18–25 years that received either 2v-HPV vaccine (vaccine group) or hepatitis A vaccination (control group), the prevalence of oropharyngeal HPV16/18 infections was reduced by 93 % in the vaccine group (93.3 %; 95 % CI: 63–100 %) compared to the placebo group four years after vaccination. In a cross-sectional study, the prevalence of oropharyngeal HPV16/18/6/11 infection was also reduced to a similar extent, when HPV-vaccinated and non-vaccinated participants were compared [104]. These data are supported by another cross-sectional study with 3,040 participants [105]. Moreover, after implementation of HPV vaccination in Australia, the incidence of recurrent juvenile laryngeal papillomatosis decreased from initially 0.16 per 100,000 to 0.02 per 100,000 within a period of four years after implementation of HPV vaccination [106].

HPV testing before vaccination

**Recommendation 05: consensus-based recommendation**

Grade of recommendation: ↓↓  We recommend against HPV testing for decision-making before vaccination.

*Agreement: 62.5 %.

Ideally, HPV vaccination shall be performed before the first sexual contact. In practice, however, there is often the question of vaccination at a later time; in this context, the question of HPV testing before vaccination regularly arises.

Currently, detailed HPV typing during daily routine seems to be associated with more disadvantages than benefits [107]. Given that persistent HPV infections are often single infections, protection against additional vaccine types may still be provided in a substantial proportion of cases. Given that cross-protection will provide coverage of additional HPV types, complete ineffectiveness of vaccination due to persistent infections is even less likely. In addition, comprehensive HPV testing in the age group of 18 years and older would identify numerous transient infections without any clinical relevance. This would result in considerable insecurity of affected individuals and attending physicians. According to the guideline of the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) for organized cancer screening programs (oKFE-RL), for example, HPV testing in primary screening is only performed from the age of 35 as a supplement to cytology tests [108, 109]. In case of conspicuous findings regarding cytology, colposcopy, or history, the S3 guideline on prevention of cervical cancer recommends HPV testing also for younger women [110].

For the recommendation specified above, only a majority agreement was reached within the guideline group. Members of the guideline committee that did not agree were in favor of a weak rather than a strong recommendation against HPV testing before vaccination, given that, in their opinion, HPV testing may be useful in a few situations. However, the recommendation in the form specified above achieved the highest level of agreement.

**Booster vaccinations**

**Recommendation 06: consensus-based recommendation**

Grade of recommendation: ↓↓  We recommend against performing booster vaccinations after a complete vaccination series.

*Agreement: 100 %.

Given that no definite data on the duration of protection provided by vaccination are available, no final recommendation can be provided at this moment – current data, however, argue against the requirement of a booster vaccination after a complete vaccination series. There is increasing evidence for a long-lasting effective protection against infections with the HPV types included in the vaccine. During a 12-year follow-up of women immunized with the 4v-HPV vaccine, for example, no vaccination breaches in the form of HPV16/18-positive CIN2+ were observed; the data permit the conclusion that the corresponding efficacy of vaccination is still higher than 90 % even ten years after the vaccination [111]. In a subgroup of women that had received the 2v-HPV vaccine in the context of a phase IIb trial and were followed over a period of 9.4 years, there were also no vaccination breaches, while 21 cases of infections persisting for six months occurred in the placebo group [112]. This correlates with a constant average antibody titer in vaccinated women over this period that was several times higher than the immune response acquired naturally [112]. Similar results...
were obtained in comparable long-term follow-up studies of vaccinated women [113–115]. Based on a mathematic model calculation, two studies extrapolate a duration of protection of at least 50 years [113] and 21 years [114], respectively.

Individuals after primary oncologic disease and corresponding (chemo-)therapy, especially after autologous stem cell transplantation, may present an exception of the recommendation given above. These populations might benefit from an HPV booster vaccination even after a complete vaccination series – currently, however, no data from clinical trials verifying the clinical benefit of a booster vaccination in this population are available. In a statement established on initiative of the STIKO, administration of one additional single dose of the HPV vaccine is recommended after antineoplastic therapy (in case of completed basic immunization against HPV prior to therapy). After autologous stem cell transplantation, a new, basic immunization against HPV is recommended in children and adolescents aged nine years and older [116].

**Interchangeability of vaccines**

| Recommendation 07: consensus-based recommendation |
|---------------------------------------------------|
| **Grade of recommendation:** 0                    |
| **Agreement:** strong consensus*                  |
| Continuation of a vaccination series started with the 4-valent HPV vaccine with the 9-valent HPV vaccine may be considered. |

*100 % agreement.

Similar to other vaccinations, an initiated HPV vaccination series should, in general, be completed with the same HPV vaccine. Only few data from clinical trials on the interchangeability of vaccines are available. A randomized study comparing the immunogenicity after a complete vaccination series with the 9v-HPV vaccine with a mixed vaccination series (one vaccination with the 2v-HPV and one vaccination with the 9v-HPV vaccine) showed that protective antibody titers against the nine HPV types included in the 9v-HPV vaccine were present in both study groups after the intervention (the group with mixed HPV vaccination had higher antibody titers against HPV16 and 18; the group with the complete 9v-HPV vaccination series had higher antibody titers against the other seven HPV types) [117]. Irrespective of the chosen HPV vaccine, vaccines approved in Germany will probably be less effective. Therefore, the decision to vaccinate individuals who have already received a complete vaccination series with the 2v-HPV or 4v-HPV vaccine, with the 9v-HPV vaccine to achieve protection against additional types of HPV will remain a decision made on a case-by-case basis. For the recommendation specified above, only a majority agreement was reached within the guideline group, given that the available evidence mentioned above refers only to supplementation of a complete vaccination series performed with the 4v-HPV vaccine and not on supplementation of a complete vaccination series with the 2v-HPV vaccine. However, the recommendation in the form specified above achieved the highest level of agreement within the guideline committee.

**Additional vaccination after completed vaccination**

| Recommendation 08: consensus-based recommendation |
|---------------------------------------------------|
| **Grade of recommendation:** 0                    |
| **Agreement:** majority agreement*                |
| For individuals that have already received a complete vaccination series with the 2-valent or 4-valent HPV vaccine, vaccination with the 9-valent HPV vaccine may be considered to achieve protection against additional types of HPV. |

*75 % agreement.

If a complete HPV vaccination series has been performed already, another HPV vaccination to maintain protection against those HPV types covered by the used vaccine is not required. In this situation, another HPV vaccination is only relevant, if it is intended to provide protection against the additional HPV types included in the 9v-HPV vaccine. In a randomized trial, women aged 12 to 26 years that had already received the 4-valent HPV vaccine, received three doses of the 9v-HPV vaccine or placebo. There were no relevant differences between the study groups with respect to safety, while protective antibody titers against the additional five HPV types were found [119]. There are, however, no data on clinical endpoints demonstrating that additional vaccination with the 9v-HPV vaccine provides benefits for the concerned patients. It should be noted that the 2v-HPV and 4v-HPV vaccines will already induce a certain cross-protection against other HPV types (for example, HPV types 31, 33, 35, 45, 52) [120, 121], while vaccination at a later time (after onset of sexuality) will probably be less effective. Therefore, the decision to vaccinate individuals who have already received a complete vaccination series with the 2v-HPV or 4v-HPV vaccine, with the 9v-HPV vaccine provides benefits for the concerned patients.
Secondary prevention

Vaccination in case of existing HPV-associated lesions

| Recommendations 09-10: consensus-based recommendations |
|------------------------------------------------------|
| **Grade of recommendation:** ↓                     |
| **Agreement:** strong consensus*                    |
| We suggest against HPV vaccination with the aim of a therapeutic effect during treatment of existing HPV-associated lesions. |

| **Grade of recommendation:** 0                     |
| **Agreement:** consensus**                         |
| For HPV vaccine-naive women with cervical intraepithelial neoplasia (CIN), HPV vaccination before or after treatment of CIN with the aim of reducing the recurrence rate may be considered. |

*Agreement: 100 %, **agreement: 81.8 %.

So far, RCTs with immunocompetent and HIV-positive participants have provided no evidence for therapeutic efficacy of the currently approved HPV vaccines regarding either persistence of HPV or elimination of existing benign or pre-malignant neoplasms [122–124]. Given that the prophylactic HPV vaccines presumably only prevent the initial steps of infection, effects of HPV vaccination on the clinical course of already existing HPV-associated lesions are unlikely, even on the basis of theoretical considerations [125].

Although therapeutic efficacy of HPV vaccination is unlikely, results of individual studies indicate that HPV vaccination may provide protection against reinfection and the resulting recurrence after successful therapy of existing HPV-associated lesions. However, the study results on this issue are heterogeneous, and most studies suggesting secondary prophylactic efficacy of vaccination are characterized by a retrospective study design and a relatively small study size.

The first publication on this topic included the highest number of cases so far, with 587 and 229 vaccinated patients with cervical and vulvar lesions, respectively [126]. This was a retrospective analysis of a subgroup of patients from two RCTs on the efficacy of the 4v-HPV vaccine, where the patients were diagnosed with cervical, vulvar or vaginal HPV-associated lesions after they had received the first dose of the vaccine and were treated accordingly. Regarding cervical as well as vulvar and vaginal lesions, a significant effect of HPV vaccination on the incidence of new lesions was observed after treatment: Compared to the group of non-vaccinated women, 65 % fewer CIN2+ and 35 % fewer vulvar and vaginal dysplasias or genital warts occurred in the group of vaccinated women. In a comparable retrospective evaluation of a subpopulation of an RCT on 2v-HPV vaccination, the incidence of CIN2+ after surgical intervention was reduced by 88 % in vaccinated women compared to non-vaccinated women [127].

The mentioned data are remarkable, because the effect was observed although the patients had been vaccinated prior to surgical therapy. On the other hand, two non-randomized controlled trials on the effect of postinterventional vaccination also showed reduced recurrence rates in vaccinated women [128, 129]. The same result was obtained in an RCT on women free of recurrence or HPV who were either vaccinated against HPV or received exclusively follow-up controls three months after treatment of an HPV-associated disease [130].

For men with anogenital HPV-associated lesions, the results of the few available studies are more heterogeneous. This is also due to the heterogeneity of the examined study populations (in part, HIV-positive participants). A retrospective comparative cohort study showed a reduction of newly occurring anal condylomas after vaccination of men aged 26 years or older that had sex with other men and no manifest HPV lesions at least twelve months prior to vaccination [131]. In contrast, an RCT found no benefit for vaccination of men with genital warts in addition to local treatment with respect to the recurrence rate [122]. In an RCT with HIV-positive patients with persistent HPV infections, supplementary therapy with the 4v-HPV vaccine had no additional effect on the persistent anal HPV infection or high-grade AIN [95]. Smaller case series also found no evidence for an effect of HPV vaccination on the post-therapeutic recurrence rate of anogenital condylomas [132].

Given the heterogeneity of the available data, no definite recommendation for HPV vaccination before or after treatment of HPV-associated lesions with the aim of reducing reinfection or recurrence rate can be provided. While various studies on adjuvant HPV vaccination showed a statistically significant reduction of the recurrence rate in women after treatment of cervical, vulvar and vaginal HPV-associated lesions, especially for men with HPV-associated anogenital lesions no significant effect of vaccination was obtained in RCTs. One limiting factor is, however, that some of these studies included HIV-positive men. The available data suggest that early emergence of new lesions due to new infections may be prevented by vaccination. As already mentioned in the section above, vaccination is not effective against recurrence induced by persistence of the same HPV type or against persistent disease. It is, therefore, the view of the guideline group that the decision has to be made on a case-by-case basis.
Screening

The effectiveness of cervical cancer screening with respect to a reduction in the incidence of cervical cancer and to some extent also mortality has been verified in randomized and non-randomized trials [133, 134]. Accordingly, two effective instruments are available for prevention of cervical cancer: primary prevention by HPV vaccination and secondary prevention by early recognition of non-invasive precursor lesions (CIN). Efficacy and cost effectiveness of prevention of cervical cancer will depend on developing, in the medium term, an integrated concept for the interaction of both approaches [135–138].

The strategy of the screening program is to determine the individual risk of participants for the development of CIN3 or cervical cancer (CIN3+) based on screening findings (cytology and/or HPV testing). However, positive and negative predictive values of the test procedure depend to a considerable degree on the prevalence of the evaluated population, and the current risk calculations are based on the analysis of non-vaccinated screening participants. If vaccinated women, irrespective of age, present with abnormal findings during screening, a highly differentiated interpretation is essential.

To monitor the impact of the new screening strategy in Germany, it is expected that in the first quarter of 2020 the G-BA will assign the task of systematically monitoring the screening program and evaluating it with respect to various aspects to the German Institute for Quality Assurance and Transparency in Healthcare (IQTIG) [139, 140]. This will allow for differentiated statements on screening in Germany and optimization of cancer screening in a targeted manner. The evaluation will include data on the rate of false-positive findings, is increasingly called into question [137, 141, 142]. However, the question whether a specific screening strategy should be recommended for vaccinated women cannot be answered based on individual parameters alone, but only within the overall view of the results available from the evaluation, which also include factors such as the program utilization in different populations [140]. Given that the results of an evaluation in the German context are not yet available, no specific recommendations for the execution of cervical cancer screening can be provided for HPV-vaccinated women at this time. Cervical cancer screening should be offered irrespective of HPV status in accordance with the recommendations of the S3 guideline prevention of cervical cancer [110] and the requirements of the directives for organized cancer screening programs [108, 109].

**Recommendation 11: consensus-based recommendation**

| Grade of recommendation: † |
|---------------------------|
| Agreement: strong consensus:* |

We suggest to offer cervical cancer screening in accordance with the recommendations of the S3 guideline on prevention of cervical cancer [110] and the requirements of the directives for organized cancer screening programs [108, 109], irrespective of the HPV vaccination status.

*Agreement: 100 %.

**Special populations**

**Immunocompromised individuals**

| Recommendations 12-14: consensus-based recommendations |
|--------------------------------------------------------|
| Grade of recommendation: †                             |
| Agreement: strong consensus:*                          |

We recommend to vaccinate immunosuppressed or immunocompromised children and adolescents aged 9 to 17 years against HPV, if this has not yet been done.

| Grade of recommendation: †                             |
| Agreement: strong consensus:*                          |

We suggest to vaccinate immunosuppressed or immunocompromised individuals aged 18 years or older against HPV, if this has not yet been done, especially until the age of 26 years.

| Grade of recommendation: †                             |
| Agreement: strong consensus:*                          |

We suggest to use the vaccination regimens with three doses to vaccinate immunosuppressed or immunocompromised individuals of all age groups against HPV.

*Agreement: 100 %.

Compared to the general population, immunosuppressed individuals, such as organ transplant recipients or patients with systemic diseases treated with immunosuppressants, for example systemic lupus erythematosus (SLE) or chronic inflammatory bowel diseases (IBD), are at a higher risk of developing HPV-related diseases [143–153]. An enhanced risk of HPV-associated lesions may also exist after oncological diseases with corresponding (chemo-)therapy [154, 155].
Given that the prophylactic HPV vaccines are inactivated vaccines, immunosuppression does not per se represent a contraindication for vaccination.

Concerning the 4v-HPV vaccine, smaller studies on immunogenicity and safety are available for iatrogenically immunosuppressed female patients with chronic inflammatory bowel disease (9–26 years of age, 3-dose regimen [156]), organ transplant recipients [157–159], and female SLE patients [160–164].

For female SLE patients, the 4v-HPV vaccine (3-dose regimen) is immunogenic (seroconversion rates of 76–100 %), well tolerated, safe, and did not result in increased disease activity. However, the number of patients included in the studies was low (case control study with 50 patients and 50 healthy controls aged 18–35 years [163]; open, prospective study with 27 patients aged 12–26 years [162]; phase I study with 34 women aged 19–50 years with mild to moderate SLE [160]). Although a study on long-term immunity after 4v-HPV vaccination (3 doses) on women with SLE (18–35 years of age) showed that most patients still had antibodies against the four vaccine types five years after vaccination (84–94 % for the four different types of HPV), the antibody titers were significantly lower than in healthy controls. 21 % of the patients presented with seroreversion for at least one of the vaccine types. This applied in particular to women with higher cumulative doses of immunosuppressants [164]. Population-based studies have shown that 4v-HPV vaccination in girls and women with pre-existing autoimmune disease is not associated with an increased incidence of new cases of autoimmune diseases [165, 166].

Three studies on girls/young women with autoimmune or rheumatic disease, each with low case numbers, are available for the 2v-HPV vaccine. The three studies demonstrate the safety and immunogenicity of the 2v-HPV vaccine (3 doses) in the studied patient groups, although the observed vaccination titers were lower than in healthy controls [167–169]. In a systematic review on immunogenicity and safety of HPV vaccination in patients with autoimmune disease, both the 2v-HPV and the 4v-HPV vaccine were assessed as effective and safe for these patients, with the limitation that only a few studies with low patient numbers were available [170].

Several national guidelines and the WHO recommend HPV vaccination of organ transplant recipients, usually at the age of 9 to 26 years [144, 151, 171, 172]. There are, however, no studies on clinical efficacy of HPV vaccination in organ transplant recipients, but only small uncontrolled studies on safety and immunogenicity of the 4v-HPV vaccine (3-dose regimen), each with less than 50 participants aged 11–35 years [144, 157–159]. Although two of these studies found lower seropositivity rates and lower antibody titers against the HPV vaccine types in organ transplant recipients compared to healthy controls, the clinical significance of these findings remains unclear [144, 157, 158, 171].

### Persons living with HIV (PLWH)

| Recommendations 15-18: consensus-based recommendations |
|------------------------------------------------------|
| **Grade of recommendation:** ↑                       |
| **Agreement:** strong consensus*                     |
| **Grade of recommendation:** 0                       |
| **Agreement:** strong consensus*                     |
| **Grade of recommendation:** ↓                       |
| **Agreement:** strong consensus**                    |
| **Grade of recommendation:** ↑                       |
| **Agreement:** strong consensus*                     |

*Agreement: 100 %, **agreement: 91.7 %.

Anogenital HPV infections are very common in PLWH [173, 174]. Anal HPV infections are found in more than 90 % of HIV-positive MSM. Infections with HR HPV types are present in 70–80 %, and infections with multiple types of HPV are present in more than 70 % [173, 175, 176]. In HIV-positive women, both cervical and anal HPV infections are very common, as well [177]. In a recently published meta-analysis, the prevalence of anal HPV was 59 % and 76 % in HIV-positive women and men, respectively. In both genders, HPV16 was the most common type of HR HPV. However, the predominance of HPV16 was less pronounced than in HIV-negative individuals, and other HR HPV types occurred more often [28]. PLWH often present with persistent HPV infections [178]. Accordingly, PLWH are, in part, at a significantly enhanced risk of developing HPV-related condylomas, dysplasias, and cancers compared to the general population [149, 153, 174, 176, 179–184]. The incidence rates of anal cancer in HIV-positive MSM are up to 100 times higher than those of the general population and reach values of 60 to 100 per 100,000 person years [183, 184].

All approved HPV vaccines can be given to HIV-positive individuals [185]. Several studies have shown that HPV vaccination is also safe and immunogenic in HIV-positive children, women and men and does not affect the number
Persons using HIV pre-exposure prophylaxis (PrEP)

| Recommendations 19-20: consensus-based recommendations |
|---------------------------------------------------------|
| **Grade of recommendation:** ↑↑ |
| **Agreement:** strong consensus* |
| **Recommendation:** We recommend to vaccinate HPV vaccine-naive adolescents starting the use of HIV pre-exposure prophylaxis (PrEP) against HPV. |
| **Grade of recommendation:** ↓ |
| **Agreement:** consensus** |
| **Recommendation:** We suggest against vaccinating HPV vaccine-naive adults starting the use of HIV pre-exposure prophylaxis (PrEP) against HPV. |

*Agreement: 100 %, agreement: 90.9 %.

High incidence rates of HPV are observed in adolescent, HIV-negative MSM aged 16 to 20 years [193]. In a relatively small cross-sectional study with HIV-negative MSM using PrEP, anal HPV infections were found in all age groups in more than 85 % of men and even in 95 % of younger MSM aged 19 to 29 years [194]. Another recently published study on HIV-negative MSM demonstrated that users of PrEP are at a similarly high risk of HPV infections as HIV-positive MSM. In users of PrEP, multiple HPV infections were common, and HPV types included in the 9v-HPV vaccine were found in 77 % (anal), 22 % (penile), and 6 % (oral) of the samples [195].

As discussed above, HPV vaccination is no longer useful in cases of previous or current infections with the vaccine types, given that no effect on existing HPV infections or clinically manifest lesions can be expected: several controlled trials have demonstrated the lack of efficacy of HPV vaccination on already existing infections with the vaccine types in both women and men [95, 123, 196, 197]. In view of the high anogenital HPV prevalence in users of PrEP, HPV vaccination in this population is controversial, although vaccination of MSM has been suggested based on results of model calculations [198, 199].

The high anogenital HPV prevalence in adult users of PrEP as an argument against vaccination of this population is countered by the relatively high HPV-associated disease load and incidence of new HPV infections as arguments in favor of vaccination of this population: in the study of Cotte et al. [195] mentioned above, the incidence of HR HPV infections during intake of PrEP was 72.3 per 1000 person months. Whereas in anal PCR swabs the prevalence of one HR HPV type included in the 9v-HPV vaccine was 64 %, only 24 % of the PrEP users had a prevalence of more than one of the HR HPV types included in the 9v-HPV vaccine. These data indicate that the 9v-HPV vaccine might be useful for the prevention of anogenital HPV-associated lesions in this population, although the benefit is certainly significantly reduced compared to individuals before first sexual contact.
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