



**Primary Prevention of Cervical Cancer:
American Society of Clinical Oncology
Resource-Stratified Guideline**

Introduction

- Approximately 85% of incident cervical cancers occur in less developed regions, often overlapping with low- and middle-income countries (LMICs) around the world, and represent 12% of cancers among women in those regions.
- HPV causes virtually all cervical cancer and its immediate precursors everywhere in the world. The HPV 16 and HPV 18 subtypes are most associated with cervical cancer.
- The purpose of this guideline is to provide expert guidance on primary prevention, the reduction in human papillomavirus (HPV) infection by HPV vaccine administration, of cervical cancer to clinicians, public health leaders, and policymakers in all resource settings.

ASCO Guideline Development Methodology

The ASCO Clinical Practice Guidelines Committee guideline process includes:

- a systematic literature review by ASCO guidelines staff
- an expert panel provides critical review and evidence interpretation to inform guideline recommendations
- final guideline approval by ASCO CPGC

The full ASCO Guideline methodology supplement can be found at:

www.asco.org/rs-cervical-cancer-primary-prev-guideline

Clinical Questions

This clinical practice guideline addresses the overarching clinical question, What is the optimal method for primary prevention of cervical cancer in each resource stratum?

- For which cohorts is routine vaccination recommended?
- What number of doses and intervals are recommended?
- Should catch-up to subjects outside the priority age groups for vaccination be offered for the prevention of HPV infection?
- Should HPV vaccination of boys be recommended to reduce HPV infection?
- What vaccination strategy is recommended for special populations?

Target Population and Audience

Target Population

General population

Target Audience

Public health authorities, cancer control professionals, policymakers, obstetricians/gynecologists, pediatricians and other primary care providers, lay public

Summary of Recommendations

In Maximal and Enhanced Resource Settings:

- For which cohorts is routine vaccination recommended?
 - *Recommendation A1a.* Public health authorities, ministries of health, and primary care providers should routinely vaccinate girls with the target age range being as early as possible starting at 9 years through 14 years of age (*Type of recommendation: evidence-based; Evidence quality: high; Strength of recommendation: strong*).
 - *Recommendation A1b.* Public health authorities may set the upper end of the target population higher than 14 years of age, depending on local policies and resources (*Type of recommendation: evidence-based; Evidence quality: low; Strength of recommendation: moderate*).

Summary of Recommendations

- What number of doses and intervals are recommended?
 - *Recommendation A2a.* For girls 9 to 14 years of age who are immune competent, a two-dose regimen is recommended (*Type of recommendation: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate*).
 - *Recommendation A2b.* The interval between two doses should be at least 6 months and may be up to 12 to 15 months (*6 months: Type of recommendation: evidence-based; Evidence quality: high; Strength of recommendation: strong. 12 to 15 months: Type of recommendation: evidence-based; Evidence quality: low; Strength of recommendation: weak*).
 - *Recommendation A2c.* Girls 15 years of age or older at the time of the first dose/initiation (outside of target population) who receive vaccine should receive three doses (*Type: informal consensus-based; Evidence quality: intermediate; Strength of recommendation: moderate*).

Summary of Recommendations

- Should catch-up to subjects outside the priority age groups for vaccination be offered for prevention of HPV infection?
 - *Recommendation A3.* For females who have received one dose and are more than 14 years of age, public health authorities may provide additional doses/complete the series up to 26 years of age (*Type of recommendation: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate*).
- Should HPV vaccination of boys be recommended to reduce HPV infection?*
- *Recommendation A4.* For prevention of cervical cancer, if there is low vaccine coverage of the priority female target population (< 50%) in maximal or enhanced resource settings, then vaccination may be extended to boys (*Type of recommendation: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate*).
- For prevention of cervical cancer in maximal or enhanced resource settings where vaccine coverage of girls is $\geq 50\%$, there are insufficient data to recommend for or against vaccination of boys (*Type of recommendation: evidence-based; Evidence quality: insufficient; Strength of recommendation: weak*).

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Summary of Recommendations

In Limited Resource Settings:

- For which cohorts is routine vaccination recommended in limited resource settings?
 - *Recommendation B1a.* Public health authorities, ministries of health, and primary care providers should vaccinate girls as early as possible, starting at 9 years through 14 years of age (*Type of recommendation: evidence-based; Evidence quality: high; Strength of recommendation: strong*).
- What number of doses and intervals are recommended in limited resource settings?
 - *Recommendation B2a.* For girls starting at 9 years of age who are immune competent, a two dose regimen is recommended (*Type of recommendation: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate*).
 - *Recommendation B2b.* The interval between the doses should be at least 6 months and may be up to 12 to 15 months (*6 months: Type of recommendation: evidence-based; Evidence for quality: high; Strength of recommendation: strong. 12 to 15 months: Type of recommendation: evidence-based; Evidence quality: low; Strength of recommendation: moderate*).

Summary of Recommendations

- Should catch-up to subjects outside the priority age groups for vaccination be offered for prevention of HPV infection in limited resource settings?
 - *Recommendation B3.* If there are sufficient resources remaining after vaccinating high-priority populations with an adequate target (minimum recommended coverage is $\geq 50\%$ with two doses, with a target of 80%),¹ for females who have received one dose and are more than 14 years of age, public health authorities may provide additional doses/complete the series up to 26 years of age (*Type of recommendation: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate*).
- Should HPV vaccination of boys be recommended to reduce HPV infection in limited resource settings?*
- *Recommendation B4.* For prevention of cervical cancer in limited resource settings where vaccine coverage of girls is $\geq 50\%$, vaccination of boys is not recommended.
- For prevention of cervical cancer, if there is low vaccine coverage of the priority female target population ($< 50\%$) in limited resource settings, then vaccination may be extended to boys (*Type of recommendation: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate*).

Summary of Recommendations

*Qualifying Statement for A4 and B4

Extending vaccination to boys to prevent cervical cancer is not cost-effective, unless there is low vaccine coverage of the priority female target population (< 50%). Vaccination may be extended to boys for other reasons, such as to prevent other noncervical HPV-related cancers and diseases (eg, genital warts) and/or to reduce more rapidly circulating HPVs.

Summary of Recommendations

In Basic Resource Settings:

- For which cohorts is routine vaccination recommended in basic resource settings?
 - *Recommendation C1.* Public health authorities, ministries of health, and primary care providers should vaccinate girls in the priority target age group starting as early as possible through 14 years of age (*Type of recommendation: evidence-based; Evidence quality: high. Strength of recommendation: strong*).
- What number of doses and intervals are recommended in basic resource settings?
 - *Recommendation C2a.* For girls starting at 9 years of age who are immune competent, a two-dose regimen is recommended (*Type of recommendation: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate*).
 - *Recommendation C2b.* The interval between the doses should be at least 6 months and may be up to 12 to 15 (*6 months: Type of recommendation: evidence-based; Evidence quality: high; Strength of recommendation: strong. 12 to 15 months: Type of recommendation: evidence-based; Evidence quality: low; Strength of recommendation: moderate*).

Summary of Recommendations

- Should catch-up to subjects outside the priority age groups for vaccination be offered for prevention of HPV infection in basic resource settings?
 - *Recommendation C3.* High coverage of priority populations should be emphasized. Where coverage of the primary targeted group of females is high ($\geq 50\%$) and resources allow, the age group may be expanded upward in catch-up efforts (*Type of recommendation: evidence-based; Evidence quality: high; Strength of recommendation: strong*).
- Should HPV vaccination of boys be recommended to reduce HPV infection in basic resource settings? **
 - *Recommendation C4.* For prevention of cervical cancer in basic resource settings where vaccine coverage of girls is $\geq 50\%$, vaccination of boys is not recommended.
 - For prevention of cervical cancer, if there is low vaccine coverage of the priority female target population ($< 50\%$) in basic resource settings, then vaccination may be extended to boys (*Type of recommendation: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate*).

Summary of Recommendations

****Qualifying Statement (C4)**

Extending vaccination to boys to prevent cervical cancer is not cost-effective, unless there is low vaccine coverage of the priority female target population (<50%). However, if resources allow for efforts to reduce noncervical cancers and diseases and/or reduce more rapidly circulating HPVs, then vaccination may be extended to boys.

Summary of Recommendations

In All Resource Settings:

- What vaccination strategy is recommended for women who are HIV positive or women who are immunosuppressed for other reasons (all resource settings)?
 - *Recommendation D.* Females who are HIV positive or immunosuppressed for other reasons should follow the same age recommendations, but should receive three doses (*Type of recommendation: evidence-based; Evidence quality: insufficient; Strength of recommendation: weak*).
- What vaccination strategy is recommended for women who are pregnant (all resource settings)?
 - *Recommendation E.* HPV vaccination is not recommended for pregnant women (*Type of recommendation: evidence-based; Evidence quality: insufficient; Strength of recommendation: weak*).
- What vaccination strategy is recommended for women receiving treatment for cervical cancer precursor lesions (CIN2+; eg, conization, loop electrosurgical excision process, cryotherapy) (all resource settings)?
 - *Recommendation F.* No recommendation (*insufficient data*).

Summary of Recommendations

Additional Qualifying Statements

If boys are vaccinated, use the same age-related recommendations as for girls, according to resource settings. Recommendations regarding boys do not apply to men who have sex with men (MSM) and readers are referred to US CDC, Australian and other guidelines.

Special Commentary

In vaccinated cohorts, what is recommended for secondary prevention in terms of cost-effectiveness ratios for the combined strategies?

- Vaccination does not replace screening.
- Until further data are gathered, vaccinated cohorts will need to be screened.
- Screening after vaccination is discussed in detail in the ASCO Screening Resource Stratified Guideline (www.asco.org/rs-cervical-cancer-secondary-prev-guideline)

Special Commentary

Is there a need to have a registration system (i.e., enrollment, refusal, surveillance of potential adverse effects) to evaluate the impact and coverage of the strategies?

- There is a need for monitoring the implementation of vaccines in terms of coverage and outcomes detected by screening and cancer registries.
- Strengthened systems for monitoring immunization adverse events are essential for tracking potential adverse effects, especially rare or late-occurring events.
- The rationale for screening and cancer registries is the need for data over time in order to track longer-term outcomes, especially cervical cancer outcomes, and the duration of immunity/protection.

Special Commentary

Safety

- The safety profile of HPV vaccines has been assessed extensively in RCTs and by robust pharmacovigilance in the postlicensure setting using both passive and active vaccine surveillance.
- As with all serious vaccine adverse events, it is important that appropriate investigations be carried out promptly to determine whether the event is caused by the vaccine and whether any remedial action is needed.
- The key challenge faced in pharmacovigilance is to distinguish real adverse events from background conditions that would occur regardless of vaccination.
- Population-based data on incidence of potential adverse events prior to vaccination allow analysis of observed/expected rates in vaccinated populations.^{2,3}

Special Commentary

- International Papillomavirus Society assessed reviews by WHO, FDA, CDC, EMA, International Federation of Gynecology and Obstetrics, UK Medicines & Healthcare Products Regulatory Agency, TGA, and other publications and concluded that there is no evidence that neurologic disease, autoimmune diseases, or deaths are vaccine-attributable and emphasized there have been no deaths associated with HPV vaccines.⁴
- This guideline agrees with the International Papillomavirus Society policy statement on the safety of HPV vaccines.

Special Commentary

Children and Adolescents with a History of Sexual Abuse

- Offering HPV vaccine in an age-appropriate manner to children and adolescents with a history of sexual abuse is recommended by the CDC, and this population may receive vaccines according to the age- and resource-stratified recommendations.
- There has been a special concern about vaccinating children and adolescents with a history of sexual abuse, given that they may be at higher risk for HPV infection due to the cervical, vaginal, or anal trauma associated with forced penetration.
- With regard to vaccinating boys with a history of sexual abuse, the evidence is less clear but is consistent with the overall recommendations that if resources allow, boys with a history of sexual abuse should be vaccinated as young as 9 years.

Uptake

- Primary care providers and pediatricians are in a unique position to promote HPV vaccination given their longstanding relationship with their child and adolescent patients and their parents.
- Once informed and educated about the importance of HPV vaccination by a trusted source (usually their children's health care provider) parents are more likely to vaccinate their children.
- Therefore, at all levels (basic through maximal), education of primary care physicians and pediatricians about the cancer-preventive properties of HPV vaccination and its safety could provide the highest return on investment in cervical cancer primary prevention.

Cost Implications

- In low-resource settings, cost remains the primary barrier to HPV vaccination.
- Vaccination is usually second in line of cost effectiveness after routine screening, but this needs high coverage of the female population.
- Cost-effectiveness analyses support this guideline's recommendations for, at minimum, vaccination of girls ages 9 to 14. In the near future, screening will have to accompany vaccination.

Limitations of the Research and Future Directions

There were limitations on the evidence to inform some of the recommendations. Some of this is due to the relatively recent introduction of the vaccine. There were limited published data on:

- The impact on invasive cervical cancer outcomes
- The upper age range for the priority target population of girls starting at 9 years of age
- The optimal upper end of the interval (which starts at 6 months)
- Two versus three doses of 9vHPV
- CEA of vaccinating boys in limited and basic settings
- Pregnant women
- Women who have or are receiving treatment for \geq CIN2
- Vaccination for women older than 26 years
- Effectiveness studies on two doses for women who are HIV positive and immunosuppressed

Additional Resources

More information, including a Data Supplement, a Methodology Supplement, slide sets, and clinical tools and resources, is available at

www.asco.org/rs-cervical-cancer-primary-prev-guideline

Patient information is available at www.cancer.net

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