

The Impact of HPV Vaccination on Cervical Cancer in adolescent females: A narrative review

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ABSTRACT

To effectively prevent cervical cancer, a leading cause of global morbidity and mortality among women, widespread adoption of the HPV vaccine has a well-established link to human papillomavirus (HPV) infection. HPV vaccine must be the vaccine's effectiveness in reducing HPV infections, and subsequent cervical lesions have been extensively demonstrated, marking a pivotal milestone in public health. Important research highlights the vaccine's safety profile, allaying worries and promoting trust in its application. By targeting HPV strains responsible for a majority of cervical cancer cases, vaccination emerges as a strategic intervention to curb the burden of this malignancy. The strategy is used to search PubMed and Google Scholar, with only free full-text and English language study included. However, addressing existing misconceptions and ensuring equitable vaccine access remains imperative. Informed decision making is pivotal, necessitating comprehensive public health initiatives that educate communities about the vaccine's benefits. Encouragingly, successful vaccination programs in various regions have demonstrated tangible reductions in HPV prevalence and cervical cancer incidence. This review concludes by emphasizing the urgent need for global collaboration to integrate HPV vaccination into routine immunization schedules, thereby fortifying the collective effort to mitigate cervical cancer's impact. As a cost-effective, evidence-based strategy, widespread HPV vaccination stands as a linchpin in the ongoing battle against cervical cancer, promising a healthier future for women worldwide.

Keywords: Cervical cancer, HPV, human papillomavirus, prevention, screening

Introduction and Background

Cervical cancer, primarily caused by genital HPV infections, has seen significant advancements in prevention and early detection. Routine gynecological examinations and the treatment of malignant lesions have proven highly effective in preventing squamous cervical cancer, the most common variant.^[1] However, their impact on adenocarcinoma is somewhat limited.

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Unfortunately, cervical cancer ranks second among cancers leading to death in women, with an estimated 280,000 deaths reported among the approximately 500,000 new cases in recent years.^[2]

The American Cancer Society (ACS) took a significant step in 2002 by recommending DNA testing, liquid-based cytology, and human papillomavirus (HPV) testing for the early detection and treatment of cervical cancer.^[3] This marked the first time the inclusion of HPV testing in cervical cancer screening guidelines.^[3] The accumulation of evidence strongly suggests that cervical cancer necessitates vaginal infection with 1 of the 15 human papillomavirus (HPV) strains.^[4] This imperative connection has driven the development of preventive vaccinations aimed at curbing the incidence of cervical cancer. Notably, despite some

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indications of cross-reactivity between specific HPV types, it remains crucial to emphasize that HPV infections, particularly with a subset of strains, play a pivotal role in the development of cervical cancer. Over the past two decades, a growing body of evidence has substantiated this theory, presenting an exceptional opportunity to leverage vaccination as a proactive strategy for preventing cancer.^[5] The recognition of the pivotal role of HPV infections in cervical cancer underscores the significance of ongoing efforts to advance vaccination initiatives and enhance public awareness for effective cancer prevention.

John Schiller's involvement in developing the HPV vaccine has been made possible through collaborations with other scientists, spanning over 30 years. This productive partnership has significantly contributed to the progress achieved in the field.^[6] Early detection of subtle epithelial modifications, facilitated by virological and cytological screening methods, allows for timely intervention in HPV infections. Cytological inspection of cervical smears identifies low- or high-grade intraepithelial lesions (S.I.L.) and abnormal growths of squamous cells, collectively referred to as cervical intraepithelial neoplasia (C.I.N.).^[1] C.I.N. grading, ranging from 1 to 3, signifies the percentage of abnormal cells in the cervical epithelium observed in histological sections.^[1] In the context of global health, there is a promising initiative to vaccinate against HPV in cancer risk countries until 2030. This represents a strategic effort to combat the prevalence of HPV infections and reduce the burden of cervical cancer on a global scale. As of 2020, human papillomavirus (HPV) vaccinations were available in only 114 nations, with the majority being economically affluent.^[7] Surprisingly, these vaccines formed part of national immunization programs in less than 25% of low-income countries.^[7] The glaring gaps in vaccination introduction and coverage were particularly pronounced in regions of Asia and Africa, where the risk of cervical cancer is high.^[7]

There are two widely used preventive HPV vaccines: the quadrivalent (4vHPV; Gardasil/Silgard, Merck and Co Kenilworth, New Jersey) and bivalent (2vHPV; Cervarix, GSK, Rixensart, Belgium) vaccines. The nonvalent 9vHPV vaccine (Merck, Gardasil 9) is authorized for use in very few countries. The 4vHPV vaccine targets HPV 16/18 and HPV 6/11, covering five oncogenic varieties (31/33/45/52/58).^[7,8] The National Immunization Program incorporated HPV vaccination for girls aged 10–12 years, marking a pivotal focus in 2010.^[9] This age range was identified as the most critical target group. A significant stride was made in January 2012 with the initiation of free school-based delivery specifically tailored for this primary target demographic.^[9] Complementing this, girls born between 1993 and 1998 are entitled to free catch-up vaccination, extending its availability until 2014.^[9]

The program's effectiveness is systematically evaluated by contrasting the incidence rates between vaccinated and unvaccinated individuals within comparable populations.^[8] Numerous national and international immunization protocols

prioritize human papillomavirus vaccination as a primary preventive measure against genital warts and other malignancies associated with human papillomavirus, notably cervical cancer vaccinations.^[7] In commemoration of the 10th anniversary of the widely adopted 4vHPV vaccine, our ongoing study delves into its efficacy and impact. As the predominant HPV vaccine in numerous nations globally, the 4vHPV vaccine is under thorough scrutiny to assess its purported influence on HPV infection, anogenital warts, and cervical cytological and histological abnormalities.^[9] Our systematic review synthesizes real-world evidence, offering comprehensive insights into the vaccine's performance.

Aligning with these efforts, the Ministry of Health has published "Cervical Cancer National Screening Standards".^[10] These guidelines advocate for at least one screening for women aged 35–40 years as a secondary protective measure, recommending smears every five years.^[10] Additionally, the guidelines suggest discontinuation of screening for women whose last two tests yield negative results.^[10] In contrast, rates for women above 30 years who remain unvaccinated have exhibited no significant change during the same period. These findings underscore the tangible impact of vaccination programs in curbing the prevalence of HPV-related conditions, reinforcing the ongoing importance of systematic screening and vaccination initiatives. Encouragingly, recent data highlight substantial reductions in the incidence of genital warts among women under 21 years who have received vaccinations, with rates plummeting by over 90% in the last five years.^[11]

Review

Methodology

A papillomavirus (HPV) vaccination is a primary safeguard against cervical cancer. We conducted searches through the Medical Research Examination and Retrieve System (MEDLINE) for relevant, original, and peer-reviewed publications utilizing the Google Scholar and PubMed databases. The customized search strategy employed for each database involved specific terms: (HPV vaccination (Title/Abstract) AND Cervical cancer (Title/Abstract) or cervical cancer pant OR (Title/Abstract) screening HPV (Title/Abstract). Some additional data are used by the governmental portal like the World Health Organization (WHO), the Ministry of Health and Family Welfare (MOHFW), and National Government of India Cancer Registry Program (NCRP).

Figure 1 depicts the study inclusion and exclusion criteria for this article.

Knowledge and attitudes

In the survey, 90% of participants indicated no personal or familial connections with cervical cancer. Awareness regarding risks, symptoms, and screening techniques was gauged, with results summarized in Table 1. Notably, sexually transmitted

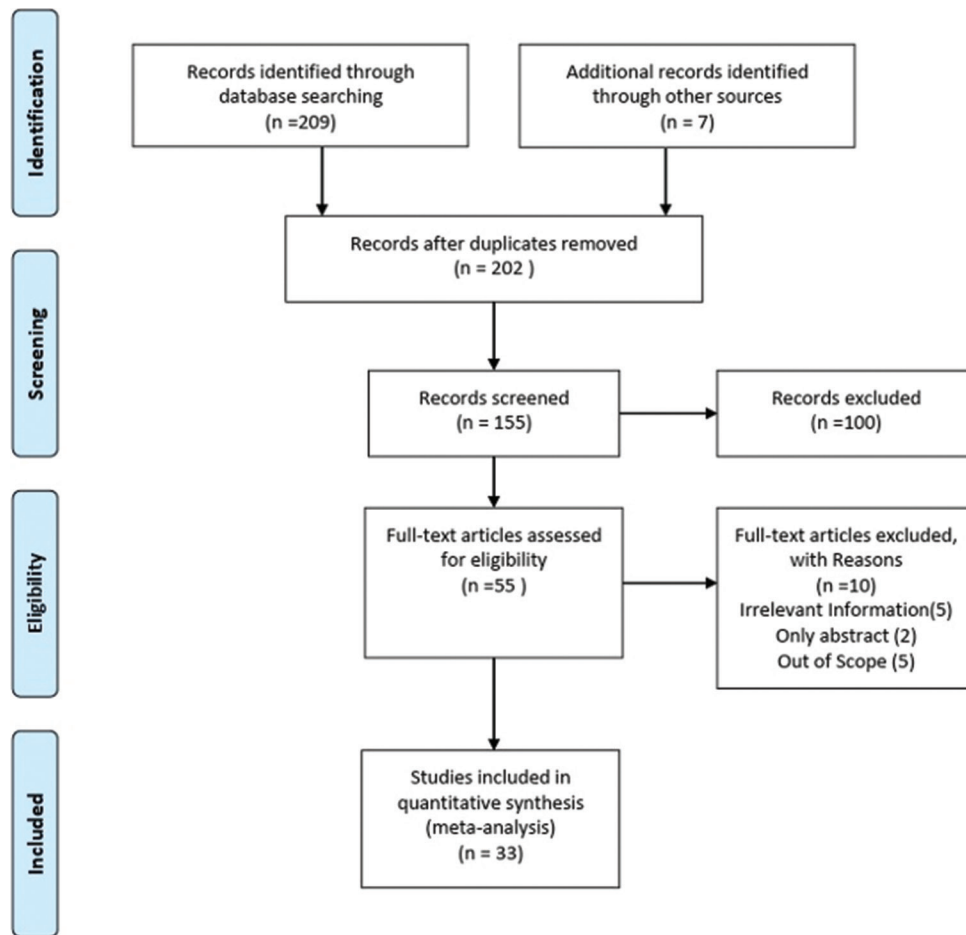


Figure 1: Inclusion and exclusion criteria

diseases (STDs) were frequently mentioned (69%), whereas obesity (28%) and cigarettes (30%) were less commonly cited as risk factors. This underscores a prevailing lack of direct experience with cervical cancer within the surveyed group. In terms of risk factor awareness, STDs emerged as the most prominent concern, surpassing obesity, and smoking. These findings shed light on the need for targeted education campaigns to enhance understanding and recognition of various risk factors associated with cervical cancer.

Discussion

The relationship between cervical cancer and HPV infection

HPV infections, commonly associated with cervical cancer, are often transient, resolving within 12 to 24 months for most individuals. However, for some women, the persistence of HPV infections poses a significant risk of developing precancerous conditions.^[18] The body's immune system plays a crucial role in eliminating HPV infections containing carcinogenic types. Failure to completely clear such infections may lead to the progression from aberrant cells to the development of malignant cells. A notable concern arises as ten percent of women with HPV infections on their cervix experience recurring infections,

elevating the potential risk of cervical cancer.^[19] Precancerous changes occur when the vulva, genitals, penis, or anus becomes infected with high-risk HPV, and if not promptly detected and removed, these changes have the potential to evolve into cancer.^[19] It is important to note that such malignancies occur significantly less frequently than cervical cancer itself.

HPV latency, unlike herpes simplex virus, is likely mediated by immune control. However, the percentage of HPV infections that become latent remains unknown. The carcinogenic process is believed to be influenced by low or absent hormones. Consequently, the cancer risk associated with new or recurrent HPV infections in women remains uncertain. This complex interplay between HPV infection and the development of cervical cancer highlights the multifaceted nature of the disease and underscores the need for ongoing research to unravel its intricacies.^[20,21]

Fundamental issues in HPV vaccination

Currently, critical questions surround the complete understanding of the effectiveness of HPV vaccinations. Two primary unresolved issues are the duration of vaccine safety and the necessity, if any, for additional doses. The exact lifetime of protection provided by current vaccinations remains unknown.

Table 1: Summary of some important articles selected on vaccine effects and implementation prevention and study findings

Author	Title	Types of study	Key findings
Abraham Degarege, MSc. Kristopher Fennie, PhD ^[12]	Urban–rural inequities in the parental attitudes and beliefs towards Human papillomavirus infection, cervical cancer, and HPV vaccine in Mysore, India	A cross-sectional	Parents’ opinions on the HPV vaccine’s safety as well as its capacity to prevent cervical cancer were similar in both urban and rural areas. Moreover, parents in rural and urban regions believed the same things about their daughters’ vulnerability to HPV-related infections and cervical cancer.
Charles JN. Lacey ^[13]	Unresolved issues in the management of human papillomavirus-associated mucosal high-grade pre-cancers	Review article	High-grade oropharyngeal pre-cancer: More investigation is needed, including studies involving the evaluation by specialists of high-definition upper airway imaging in high-risk individuals (>50 years old, HPV16-E6 seropositive). HPV therapeutics: vaccines and anti-HPV medications remain largely unmet needs in the field. It is essential to support research in these fields.
Amy Leval, ^[14]	Quadrivalent Human Papillomavirus Vaccine Effectiveness: A Swedish National Cohort Study	The open cohort study	GW rates fell among adults over 20 who had not had an HPV vaccination, suggesting that women who were more likely to get GW were the ones who favored using the vaccine. The vaccination’s performance was 76% (95% CI=73% to 79%) among individuals who had three doses, the first of which was administered before the age of twenty-one. The best efficiency (93%, 95% CI: 73% to 98%) was observed in girls who had immunizations before reaching 14 years old.
Lisa Rambout, BScPhm ^[15]	Prophylactic vaccination against human papillomavirus infection and disease in women.	a systematic review of randomized controlled trials	The meta-analysis found that, when compared to control groups, prophylactic HPV vaccination was associated with a lower incidence of high-grade cervical lesions caused by vaccine-type HPV strains. In combined per-protocol studies, the Peto odds ratio was 0.14 (95% CI 0.09-0.21), whereas in modified intention-to-treat analysis, it was 0.52 (95% CI 0.43-0.63) Furthermore, vaccination is quite successful in avoiding low-grade lesions, persistent HPV infection, genital warts, and other illnesses and side effects related to HPV.
Jiangrong Wang ^[9]	Mode of HPV vaccination delivery and equity in vaccine uptake	A nationwide cohort study	In three delivery modes, there was a slight difference in the dose completion between girls whose mothers were not Swedish-born and their family income and educational attainment. The differences ranged from 1.4% to 8.2. When comparing catch-up vaccination to school-based and subsidized delivery, the lower dose completion linked to low education and foreign-born individuals tended to be more pronounced; however, the differences between delivery modes were not statistically significant.
Gulay Yilmazel ^[10]	Knowledge, Attitudes, and Beliefs about Cervical Cancer and Human Papilloma Virus Vaccination with Related Factors in Turkish University Students	The study was cross-sectional and descriptive	Female students were found to have negative attitudes regarding getting an HPV vaccination, contemplating getting one and thinking about immunizing their daughters against the virus. Training, education, and counseling should be directed toward students who are unsure or do not consider getting an HPV vaccination, as this group of students is thought to be at higher risk of developing cervical cancer. While some people disagree that all students should receive free and mandatory HPV vaccinations, a considerable number of female students expressed concerns about the vaccine’s potential side effects and cost.
Pui Woo Angela Yam, Pak Lun Lam ^[16]	A Cross-Sectional Study on Knowledge, Attitude, and Practice related to Human Papillomavirus Vaccination for Cervical Cancer Prevention between Medical and Non-Medical Students	This was a cross-sectional observational study	Compared to non-medical students, medical learners in Hong Kong, particularly those in their senior year, demonstrated a more thorough understanding and favorable attitudes regarding HPV vaccination. On the other hand, both medical and non-medical learners received the same HPV vaccination regimen.

Contd...

Table 1: Contd...

Author	Title	Types of study	Key findings
Ivan Branković ^[17]	Applying a gender lens on human papillomavirus infection: cervical cancer screening, HPV DNA testing, and HPV vaccination	Review article	Research indicates that there are complex differences in the cervical screening follow-up procedures for various subgroups of women. Pap smears are less common among women who have lower educational attainment, are older, are homeless, uninsured, have had intimate relationships with other women, are obese, and have homelessness. Choosing to get vaccinated against HPV might be difficult for various reasons.

Table 2: Types of vaccine according to age^[23,24]

Types of vaccine	Founder of vaccine	Year of invention HPV vaccine	Dose of vaccine	Ages	Type of HPV infection
Gardasil.	Merck & Co.	2006	Gardasil is given in three doses over six months.	aged 9–26.	Types of HPV 6, 11, 16, and 18
Gardasil 9	Merck & Co.	2014	Gardasil is given in three doses over six months.	aged 9–26	31, 33, 45, 52, and 58)
Cervarix	GlaxoSmithKline	2007	Cervarix is given in three doses over six months.	Aged 9-25 in females	Types 16 and 18

However, existing data indicate that the monovalent HPV-16 vaccine offers protection for more than 9 years, the bivalent vaccine for over 8.4 years, and the quadrivalent vaccine for more than 5 years [Table 2].^[22]

It is noteworthy that the monovalent vaccine proved ineffective compared to the quadrivalent HPV-16 immunization. Despite these uncertainties, vaccination stands as the most effective primary preventive intervention against cervical cancer, as most HPV genotypes in the target group contribute to its development. Vaccination remains unparalleled in its capacity to replace other preventive measures. The current HPV vaccines offer protection against specific carcinogenic strains, particularly the nine types covered by the 9vHPV vaccine (31, 33, 45, 52, and 58).^[13] In experimental settings, this vaccine has demonstrated a remarkable success rate, reducing the prevalence of these HPV types and precursors in the cervical and genital areas by at least 96%.^[13]

While progress has been made, ongoing research is crucial to resolving lingering uncertainties and optimizing the long-term efficacy of HPV vaccination strategies.

Preventive role of screening

Despite the introduction of the Papanicolaou test (Pap test) half a century ago, cervical cancer remains a significant threat to women, causing considerable morbidity and mortality, particularly in developing countries like Iran.^[2,25] In industrialized nations, where screening using cytology has decreased, the death rate has seen a decline. However, in countries with limited resources and access to healthcare, severe cases of cervical cancer persist.^[2,25]

The Pap test, a widely adopted screening method, exhibits limitations with a sensitivity ranging from 30 to 87% and specificity from 68 to 100%.^[2,26] Factors such as tiny lesions, sample preparation errors, or contamination can affect its

accuracy.^[2,27] Due to the Pap test's inadequate sensitivity, some screening programs have transitioned to liquid-based cellular analysis (LBC).^[2,27] While LBC enhances the detection of high-grade lesions, it struggles to effectively differentiate between them. Studies suggest an increased incidence of atypical squamous cell types of unknown significance (ASCUS) with liquid-based cytology.^[2,27] High-grade Squamous Intraepithelial Lesions (S.I.L.) detected through cytological screening can be promptly addressed through ablation or conization, often leading to successful treatment.^[2,27] However, a significant challenge arises from the lack of access to screening, particularly in wealthy nations with underprivileged minorities, cultures where screening is not practiced, remote areas, or countries with insufficient funding for screening initiatives. Consequently, cervical cancer has a disproportionate impact in these scenarios, with 80% of the 473,000 new cases and 274,000 deaths reported in 2002^[2,27] occurring in developing countries. Addressing these disparities in access to screening is crucial for effective cervical cancer prevention on a global scale.

High need for HPV vaccines

The global distribution of HPV types exhibits heterogeneity, and variants cross-neutralize differently in various geographic locations. This diversity underscores the potential value of a multivalent vaccine suitable for a worldwide population. To address this need, collaboration among governments, and nongovernmental organizations, including the World Health Organization (WHO) and the Global Alliance for Vaccinations (GAVI), pharmaceutical sectors, and nonprofit organizations is imperative.^[27]

The recommended age for HPV vaccination is 11 to 12 years, with immunization starting as early as age 9 years.^[23] All preteens must receive the HPV vaccine to protect against HPV infections

that may lead to cancer in the future. Additionally, teenagers and young adults up to 26 years who have not initiated or completed the HPV vaccination series should undergo vaccination.^[23] The CDC recommends a two-dose schedule, administered 6 to 12 months apart, for children aged 11 to 12 years, with the first dose typically given at ages 11 to 12 years.^[23] If the first dose is administered before age 15 years, only two doses are required. However, young adults and adolescents aged 15 to 26 years initiating the series later should receive three doses.^[23] For children aged 9 to 14 years who have received two doses in the previous 5 months, a third dose is advised. Individuals with compromised immune systems, aged 9 to 26 years, are recommended to take three doses.^[23] Adults aged 27 to 45 years, who have never received the vaccination, may opt for vaccination after consulting with their doctor to assess the benefits and likelihood of HPV exposure.^[23] While the effectiveness in this age group may be reduced due to prior HPV exposure, vaccination remains a preventive option for those at risk.

HPV vaccine against cervical cancer

The HPV vaccine is a groundbreaking preventive measure designed to target specific types of the HPV known to cause oropharyngeal, vulvae, vaginal, and anal cancers, with cervical cancer being the most prevalent.^[23,28] It also protects the majority of HPV types responsible for causing genital warts.^[23,28] By focusing on these specific HPV strains, the vaccine effectively mitigates the associated health risks.

For optimal effectiveness, the HPV vaccine is recommended before multiple exposures to HPV. Individuals with prior exposure to certain strains may experience a reduced protective effect. The primary objective is to administer the vaccine before any contact with HPV, as there is currently no treatment available for diseases or infections associated with this virus.

The impact of HPV vaccinations since their recommendation in 2006 has been substantial. There has been an 88% decrease in the incidence of teenage girls contracting HPV strains linked to most HPV-related cancers and an 81% reduction in those contracting strains associated with genital warts.^[23,28] This decline extends beyond genital warts, illustrating the broader positive impact of HPV vaccination on overall HPV-related health issues in younger populations.

Notably, the introduction of HPV vaccination has led to a decrease in the occurrence of cervical cancer among young women. The vaccine provides long-lasting protection, as individuals who received the HPV vaccine have been monitored for a minimum of 12 years, with no evidence indicating a weakening of immunity over time.^[23,28] This underscores the enduring benefits of HPV vaccination in preventing not only cervical cancer but also other HPV-related diseases, highlighting its crucial role in public health initiatives.^[23,28] The collaborative efforts of governments, organizations, and healthcare professionals are essential to ensuring widespread access to

and awareness of the HPV vaccine, contributing to the global reduction of HPV-related diseases.^[23,28]

Effectiveness of HPV vaccines

Clinical trials have unequivocally demonstrated the remarkable efficacy of HPV vaccinations, particularly in preventing cervical infections caused by the targeted HPV strains.^[29,30] These vaccines prove most effective when administered before an individual's initial contact with the virus, ideally before the onset of sexual activity.^[29,30] The preventive impact extends beyond the cervix, with evidence indicating reduced infections in other HPV-affected tissues, such as the anus.

Noteworthy among the HPV vaccines are Gardasil, Cervarix, and Gardasil 9, each designed to protect against specific HPV strains. Extensive clinical studies have affirmed that these vaccines offer a decade or more of robust protection against infections linked to their intended HPV types. Gardasil, for instance, targets HPV 18, Cervarix focuses on HPV 17, and Gardasil 9 encompasses protection against HPV 19, among others.^[29,30]

Ongoing long-term studies are currently underway to comprehensively assess the extended success rate and durability of these vaccines. Researchers are actively delving into the sustained effectiveness of HPV vaccinations beyond the initial 10-year period.^[29,30] These extensive studies aim to deepen our understanding of the prolonged protection afforded by these vaccines, offering insights into their continued efficacy and potential for longer-term immunization strategies.

As these investigations progress, scientists anticipate gaining a more nuanced understanding of the duration of protection, contributing to informed vaccination strategies, and reinforcing the pivotal role of HPV vaccines in the prevention of HPV-related diseases.^[29,30] These ongoing efforts underscore the commitment to refining and advancing public health measures through thorough research and evidence-based practices.

The negative effects of the HPV vaccine

While HPV vaccinations have proven highly effective, it is essential to acknowledge potential adverse effects, although they are generally mild and transient. Among the most common side effects reported are pain, swelling, or redness at the injection site. Occasionally, individuals may experience fainting or dizziness after receiving the vaccine, emphasizing the importance of remaining seated for fifteen minutes following the injection to mitigate this risk.^[31,32]

In addition to injection site reactions, some individuals may encounter weakness, exhaustion, nausea, headaches, or vomiting. It is crucial to note that these side effects are typically short-lived and not experienced by everyone. The overall safety profile of HPV vaccinations is continuously monitored by regulatory bodies, such as the FDA and the CDC, to promptly identify and address any unexpected or serious issues.^[31,32]

It is important for individuals receiving the HPV vaccine and healthcare providers alike to be aware of these potential side effects, promoting informed decision making and proactive management of any adverse reactions. The monitoring and reporting systems in place contribute to the ongoing safety assessment of HPV vaccinations, ensuring that their benefits in preventing HPV-related diseases are weighed against potential risks.^[31,32] As research and surveillance continue, efforts are directed toward refining vaccine safety and further enhancing public confidence in the overall health impact of HPV vaccinations.^[31-33]

Conclusions

Safeguarding against cervical cancer with the HPV vaccine

Extensive research attests to the invaluable role of the HPV vaccine in preventing cervical cancer, a grave health concern linked to HPV infections. The HPV vaccine emerges as a dependable and safe strategy for steering clear of cervical cancer, particularly when administered to girls before the age of 15 years, optimizing its protective efficacy. The proactive approach of early vaccination not only reduces the incidence of cervical cancer but also serves as a life-saving intervention. HPV infections, particularly types 16 and 18, are primary contributors to HPV-related cancers. All three HPV vaccinations offer robust protection against these causative strains, establishing cervical cancer as one of the most preventable malignancies.

Moreover, the HPV vaccine's preventive impact extends beyond mere avoidance of HPV infections that can lead to cancer; it virtually eliminates numerous HPV infections and precancerous lesions. This dual benefit makes cervical cancer exceptionally preventable, with screenings playing a crucial role in detecting precancerous lesions before they progress into cancerous stages. The human papillomavirus vaccine not only shields against the threat of cervical cancer but also facilitates the adoption of comprehensive prevention measures. By integrating vaccination and screening strategies, we have a powerful toolkit to combat cervical cancer effectively. The ongoing commitment to HPV vaccination initiatives, coupled with regular screenings, holds the promise of further reducing the burden of cervical cancer and advancing global public health efforts in the prevention of this highly preventable malignancy.

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Conflicts of interest

There are no conflicts of interest.

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