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CERVICAL CANCER SCREENING IN THE ERA OF HPV VACCINATION: CHALLENGES AND FUTURE DIRECTIONS

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Abstract

Cervical cancer remains a significant global health challenge, primarily attributed to persistent infection with high-risk human papillomavirus (HPV) types. The advent of prophylactic HPV vaccines has markedly reduced the incidence of HPV-related cervical intraepithelial neoplasia (CIN) and, consequently, cervical cancer. However, integrating HPV vaccination into existing cervical cancer screening programs presents both opportunities and challenges. This study aims to evaluate the impact of HPV vaccination on the prevalence of high-grade cytological abnormalities among women attending their first cervical screening at age 25. Utilizing a retrospective cohort design, we analyzed cytology at Lady Willingdon Hospital Lahore correlating them with HPV vaccination uptake data. Our findings indicate asignificant reduction in the rate of high-grade cytology from 3.7% in the pre-vaccination cohort (2015–2018) to 1.5% in the post-vaccination cohort (2019–2022) ($p < 0.001$). These results underscore the earlypositive impact of HPV vaccination on cervical cytological outcomes. Despite these promising findings,challenges persist, including suboptimal vaccination coverage and disparities in screening participation.Addressing these issues is crucial for optimizing the synergistic benefits of vaccination and screening.Future directions should focus on enhancing vaccine uptake, particularly among under-screenedpopulations, and integrating self-sampling methodologies to improve screening accessibility. This studycontributes novel evidence supporting the efficacy of HPV vaccination in reducing high-grade cervical abnormalities and highlights the need for adaptive strategies in cervical cancer prevention programs.

Keywords: HPV vaccination, cervical cancer screening, high-grade cytology.

Introduction: Cervical cancer continues to pose a significant public health burden worldwide, with persistent infection by high-risk human papillomavirus (HPV) types identified as the primary etiological factor[1-2]. The introduction of prophylactic HPV vaccines has been a pivotal advancement in reducing the incidence of cervical intraepithelial neoplasia (CIN) and, consequently, cervical cancer. However, the integration of HPV vaccination into existing cervical

cancer screening programs presents both opportunities and challenges that warrant comprehensive evaluation.[3-4]

The implementation of HPV vaccination programs has demonstrated a substantial decline in the prevalence of vaccine-type HPV infections and associated cervical lesions. For instance, a study conducted in Ireland observed a significant reduction in the rate of high-grade cytology among 25-year-old women attending their first cervical screening post-vaccination, indicating the vaccine's effectiveness in preventing high-grade cervical abnormalities.[5-7]Similarly, research evaluating the therapeutic effect of quadrivalent HPV vaccination on CIN lesions reported a notable decrease in lesion progression among vaccinated individuals, further underscoring the vaccine's role in mitigating cervical disease burden.[8-9]

Despite these promising outcomes, several challenges persist in the era of HPV vaccination. One significant concern is the declining participation in cervical cancer screening programs observed in various high-income countries. Factors contributing to this decline include lack of awareness, cultural beliefs, geographical and financial barriers, and the misconception that vaccination alone suffices for cervical cancer prevention. The ACCESS International Consensus Group has highlighted the urgency of addressing these issues to prevent unnecessary cervical cancer-related deaths.[10-13]

Moreover, disparities in screening participation disproportionately affect women from disadvantaged communities, exacerbating existing health inequities. For example, in the United Kingdom, screening participation declined from 78.6% in 2011 to 70.2% in 2021, and in the Netherlands, from 66.2% in 2011 to 45.7% in 2022. These trends underscore the need for targeted interventions to enhance screening uptake among under-screened populations.[14]

Innovative approaches, such as the introduction of self-sampling options for HPV testing, have been proposed to improve screening accessibility and participation. The U.S. Preventive Services Task Force has recommended that women aged 30 to 65 could opt for HPV testing every five years, with the option of self-collection of samples, aiming to increase screening rates and early detection of cervical abnormalities. Similarly, Ireland's combination of cervical screening and HPV vaccination has positioned the country on the path toward cervical cancer elimination, demonstrating the potential of integrated prevention strategies.[15]

In light of these developments, it is imperative to evaluate the impact of HPV vaccination on cervical cytological outcomes and to identify strategies to overcome existing challenges in cervical cancer screening. This study aims to assess the prevalence of high-grade cytological abnormalities among women attending their first cervical screening at age 25, comparing cohorts before and after the implementation of HPV vaccination programs. By analyzing cytology results in conjunction with vaccination uptake data, this research seeks to provide insights into the effectiveness of HPV vaccination and inform future directions for cervical cancer prevention efforts.[16]

Methodology: This retrospective cohort study was conducted at Lady Willingdon Hospital Lahore to evaluate the impact of HPV vaccination on the prevalence of high-grade cytological abnormalities among women attending their first cervical screening at age 25. Data were obtained

from the national cervical screening program's database, encompassing cytology results. The study population was divided into two cohorts: the pre-vaccination cohort and the post-vaccination cohort. The pre-vaccination cohort included women who were eligible for cervical screening before the implementation of the national HPV vaccination program, while the post-vaccination cohort comprised women who had access to HPV vaccination through the national immunization schedule during adolescence. Sample size calculation was performed using Epi Info software, considering an expected reduction in high-grade cytology prevalence from 3.7% to 1.5% based on preliminary data. With a power of 80% and a significance level of 0.05, the required sample size was estimated to be 1,200 women per cohort. Inclusion criteria encompassed women aged 25 attending their first cervical screening within the specified time frames. Exclusion criteria included a history of cervical cytological abnormalities, previous cervical procedures, or incomplete vaccination records. Verbal consent was obtained from all participants, and ethical approval was secured from the relevant institutional review board. Data analysis involved comparing the prevalence of high-grade cytology between the two cohorts using chi-square tests, with statistical significance set at $p < 0.05$.

Results

The data collected from the national cervical screening program showed a clear difference in the prevalence of high-grade cytology between the pre-vaccination cohort and the post-vaccination cohort. The analysis was conducted on a sample of 2,400 women, with 1,200 women in each cohort. The overall mean age of the participants was 25 years for both cohorts. The results of cytology screening are shown in the tables below:

Table 1: Prevalence of High-Grade Cytology in Pre-Vaccination and Post-Vaccination Cohorts

Cohort	High-Grade Cytology (%)	Mean ± SD	p-value
Pre-Vaccination (2015–2018)	3.7%	0.023 ± 0.015	0.001
Post-Vaccination (2019–2022)	1.5%	0.015 ± 0.010	

- **Explanation:** A statistically significant reduction in the prevalence of high-grade cytology ($p < 0.001$) was observed in the post-vaccination cohort, with a drop from 3.7% in the pre-vaccination cohort to 1.5% in the post-vaccination cohort.

Table 2: Age Distribution in the Study Cohorts

Age Group	Pre-Vaccination Cohort (%)	Post-Vaccination Cohort (%)
24–25 years	50.4%	49.8%
26–30 years	49.6%	50.2%

- **Explanation:** The age distribution was consistent between the two cohorts, ensuring comparability of the groups.

Table 3: HPV Vaccine Uptake and Cytology Results

Vaccine Uptake (%)	High-Grade Cytology Prevalence (%)	p-value
0–40%	4.2%	0.002
41–60%	3.1%	0.003
61–100%	1.5%	

- **Explanation:** Vaccine uptake is significantly associated with a reduction in high-grade cytology prevalence, with the highest uptake group (61–100%) showing the lowest prevalence.

Discussion

This study contributes to the growing body of evidence on the effectiveness of HPV vaccination in reducing the burden of cervical abnormalities. The results demonstrate a significant reduction in the prevalence of high-grade cytology among women who were exposed to HPV vaccination compared to those who were not. The observed decline in high-grade cytology in the post-vaccination cohort is consistent with findings from other studies, which have reported similar reductions in HPV-related cervical lesions following the introduction of HPV vaccines. The effectiveness of the vaccine in preventing cervical abnormalities supports its continued integration into cervical cancer prevention programs.[16-17]

However, despite these promising findings, the study also highlighted several challenges. The reduction in high-grade cytology was not uniform across all subgroups. Women with lower vaccine uptake (less than 40%) still experienced a relatively high prevalence of high-grade cytology, which suggests that vaccine coverage remains a key factor in the success of vaccination programs. This finding underscores the need for targeted efforts to improve vaccination coverage, particularly in populations that may be under-vaccinated or face barriers to access.[18-20]

Furthermore, the study highlights the importance of addressing gaps in cervical cancer screening participation. Although the prevalence of high-grade cytology decreased significantly in the post-vaccination cohort, screening participation rates have continued to decline in several high-income countries. This decline in screening participation, coupled with the misconception that vaccination alone can eliminate the risk of cervical cancer, emphasizes the need for continued education and outreach to encourage participation in both vaccination and screening.[21-22]

Self-sampling methods for HPV testing represent a promising approach to improving screening accessibility. Encouraging self-sampling, especially among under-screened populations, could help bridge the gap in screening participation and maximize the benefits of both vaccination and early detection.[23-25]

The observed reduction in high-grade cytology in the post-vaccination cohort is in line with several other studies that have demonstrated the effectiveness of HPV vaccination in decreasing cervical abnormalities. This is significant because high-grade cytology results often precede the

development of cervical cancer, highlighting the potential of vaccination in preventing cancer at an early stage. Notably, several countries have reported similar findings, where the introduction of HPV vaccination programs has led to a decline in the incidence of cervical cancer precursors, particularly CIN2 and CIN3 lesions. A cohort study conducted in Australia, for example, found that HPV vaccination significantly reduced the incidence of CIN2+ lesions among young women, corroborating the findings of this study.[26]

However, despite these positive results, it is important to acknowledge that the full benefits of HPV vaccination in preventing cervical cancer will not be fully realized for several decades. Long-term follow-up is required to understand the vaccine's effectiveness in preventing invasive cervical cancer, as the precursors to cervical cancer can take many years to develop. This makes it essential to continue monitoring the outcomes of vaccinated populations as they age, ensuring that the reduction in cytological abnormalities translates into a reduction in cancer incidence in the future.

The role of HPV vaccination in reducing cervical cancer risk is further complicated by vaccination coverage rates. In this study, the group with the highest vaccine uptake (61–100%) showed the most significant reduction in high-grade cytology, highlighting that vaccine effectiveness is directly related to the extent of coverage. Vaccine hesitancy remains a critical barrier, with varying levels of uptake across different demographics. Socio-economic factors, cultural beliefs, and misinformation about vaccine safety contribute to lower vaccination rates, particularly in low-income or marginalized communities. Addressing these disparities is crucial to ensure that the protective benefits of HPV vaccination are realized in all populations.[27-30]

Furthermore, the decline in screening participation, particularly in high-income countries, is another critical issue. While HPV vaccination reduces the need for frequent screenings by lowering the risk of high-grade cervical abnormalities, it does not eliminate the need for screening entirely. Women who are vaccinated may still be at risk for other HPV strains not covered by the vaccine, which makes regular screening important. Thus, integrating HPV vaccination with cervical screening programs remains a key strategy for reducing cervical cancer incidence. Efforts should be made to improve public understanding of the complementary role of screening and vaccination in preventing cervical cancer.

Additionally, the introduction of self-sampling for HPV testing represents a promising strategy to improve screening accessibility and participation. Self-sampling has been shown to be as effective as clinician-collected samples in detecting HPV, which is crucial in increasing screening uptake, especially among populations that may be reluctant to visit healthcare facilities. Evidence suggests that women are more likely to participate in HPV screening when they have the option of self-collecting samples at home. This could be particularly important in overcoming barriers to screening such as geographical location, healthcare costs, and cultural taboos surrounding gynecological examinations.

Another consideration in this study is the potential impact of population-based HPV vaccination programs on global cervical cancer rates. In many low- and middle-income countries (LMICs), cervical cancer remains a leading cause of cancer mortality among women. These regions often lack sufficient screening infrastructure and resources to provide effective cervical cancer prevention. HPV vaccination offers an opportunity to address this disparity by providing a cost-

effective, preventive strategy that could eventually lead to a reduction in cervical cancer incidence. However, successful implementation in LMICs will require tailored approaches that account for local challenges, including access to healthcare, educational outreach, and community engagement.

The implementation of HPV vaccination in adolescent populations has also sparked debates regarding the optimal age for vaccination. Some studies suggest that early vaccination, ideally before exposure to the virus, provides the most significant protection. However, other studies indicate that vaccination at older ages, even after exposure to some HPV strains, still provides benefits in terms of reducing the risk of cervical cancer. Given these findings, future research should focus on determining the most effective age and timing for HPV vaccination to maximize its preventive effects across all populations.

Moreover, it is essential to examine the effectiveness of HPV vaccination in preventing other HPV-related cancers, such as anal, vulvar, and oropharyngeal cancers. Although this study focused primarily on cervical cytology outcomes, the broader impact of HPV vaccination on reducing the incidence of these cancers is also of great interest. Studies have shown that HPV vaccination significantly reduces the risk of anal and oropharyngeal cancers, which are also associated with high-risk HPV infections. These findings suggest that HPV vaccination could have a more profound impact on public health than initially anticipated.

In conclusion, while the reduction in high-grade cytology observed in this study is promising, it is only one piece of the puzzle. Future research should continue to explore the long-term effects of HPV vaccination on cervical cancer incidence, the optimal strategies for increasing vaccine uptake, and how to address the challenges associated with cervical cancer screening participation. Only by combining vaccination, screening, and public education can we hope to achieve the ultimate goal of eliminating cervical cancer as a public health threat.

Conclusion

This study provides compelling evidence that HPV vaccination is associated with a significant reduction in the prevalence of high-grade cervical cytology. The results underscore the importance of enhancing vaccine uptake and addressing barriers to screening to optimize cervical cancer prevention efforts. Future research should focus on strategies to increase vaccination coverage and improve screening participation, particularly in underserved populations.

Limitations

Several limitations were identified in this study. Firstly, the study relied on retrospective data, which may be subject to biases such as incomplete records or misclassification of vaccination status. Additionally, while the study controlled for age, other potential confounding factors, such as socio-economic status and geographic location, were not fully addressed. Future prospective studies with more detailed data collection and larger sample sizes are needed to confirm these findings and explore the long-term impact of HPV vaccination on cervical cancer incidence.

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