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HPV Vaccination and the Decline of High-Grade Cervical Intraepithelial Neoplasia: A Global Population-Based Cohort Analysis with Projections for Pakistan

Dr. Rabia Bibi[1], Dr. Sobia Nawaz Malik[2],Dr. Mavra Akram[3], Dr. Sumbal Shahzad[4], Dr. Najma Parveen[5],Dr. Huma Abbas Mirza[6], Dr. Amber Shams[7*]

[1]Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro, Pakistan

[2]MBBS, FCPS, MHPE, Punjab University, Lahore, Pakistan

[3]MBBS, Dow Medical College, Dow University of Health Sciences (DUHS), Karachi Senior Medical Officer, DUHS Ojha Campus

[4]MBBS, FCPS (Obstetrics & Gynaecology, 2021) Fatima Jinnah Medical College, University of the Punjab, Lahore, Pakistan

[5]MBBS, Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro FCPS-I & IMM (Obstetrics and Gynaecology) Completed four years of FCPS-II training in Obstetrics & Gynaecology at LUMHS, Jamshoro Instructor, Al-Tibri Medical College, Karachi Campus of Isra University

[6]Frontier Medical College, Abbottabad / Bahria University, Islamabad, Pakistan

[7]Professional Diploma in Gynaecology & Obstetrics, RCPI, Ireland MBBS, Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro, Pakistan FCPS-I (Gynaecology & Obstetrics)

***Corresponding Author:**

Dr. Amber Shams

Professional Diploma in Gynaecology & Obstetrics, RCPI, Ireland MBBS, Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro, Pakistan FCPS-I (Gynaecology & Obstetrics)

Email ID : drambershams@gmail.com

ABSTRACT

Cervical cancer, largely driven by persistent infection with high-risk human papillomavirus (HPV) types, remains a significant global health challenge, especially in low- and middle-income countries (LMICs). High-grade cervical intraepithelial neoplasia (CIN2/3) is the most critical pre-malignant lesion leading to cervical cancer. Since the introduction of HPV vaccines in 2006, multiple high-income countries have reported substantial reductions in both HPV infection rates and CIN2/3 incidence. This study synthesizes longitudinal population-based cohort studies from 2006 to 2025 to quantify global declines in CIN2/3 and model potential trajectories for countries such as Pakistan that are beginning national HPV vaccination efforts. Findings reveal that early, widespread, and school-based vaccine delivery in countries like the UK and Australia resulted in CIN2/3 incidence reductions of 75–88%, while late adopters and LMICs show slower progress. For Pakistan, projections estimate a 25–40% reduction in CIN2/3 by 2040 with appropriate scale-up. This paper underscores the imperative to integrate HPV vaccination with national screening and public health strategies, emphasizing policy, education, and healthcare infrastructure reforms for sustained cervical cancer prevention.

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1. INTRODUCTION

Global Burden of Cervical Cancer

Cervical cancer is the fourth most common cancer among women globally, with an estimated 604,000 new cases and 342,000 deaths in 2020 (WHO, 2021). Over 85% of these deaths occur in LMICs, where access to routine screening and treatment remains limited. The etiological agent responsible for the majority of cervical cancers is persistent infection with high-risk types of HPV, primarily types 16 and 18, which are associated with more than 70% of cases worldwide.

High-Grade Cervical Intraepithelial Neoplasia (CIN2/3)

CIN2 and CIN3 are high-grade precancerous lesions that represent critical intervention points for preventing the progression to invasive cervical cancer. These lesions are typically asymptomatic and are identified through routine Pap smears or HPV DNA testing. Timely identification and treatment of CIN2/3 can prevent up to 80% of cervical cancers (Arbyn et al., 2020).

HPV Vaccination: A Milestone in Cancer Prevention

The advent of prophylactic HPV vaccines in 2006, including bivalent (Cervarix), quadrivalent (Gardasil), and later nonavalent (Gardasil-9) vaccines, marked a turning point in cervical cancer prevention. These vaccines target the most oncogenic HPV types and have demonstrated >90% efficacy in preventing CIN2/3 lesions caused by HPV 16/18 in clinical trials (Garland et al., 2018).

By 2025, over 100 countries have implemented some form of HPV immunization program. However, population-level impact, particularly on pre-cancerous outcomes like CIN2/3, is still under study in many contexts, especially in LMICs.

2. OBJECTIVES

To systematically analyze global population-based cohort studies assessing the impact of HPV vaccination on CIN2/3 incidence from 2006 to 2025.

To evaluate the effectiveness of different vaccination strategies (age, coverage, delivery mode).

To model future CIN2/3 and cervical cancer reductions for Pakistan, using available projections and policy data.

To recommend policy directions for Pakistan and similar LMICs to maximize the benefits of HPV vaccination.

3. METHODOLOGY

Study Design and Data Sources

A structured systematic review and comparative cohort analysis was conducted using literature published between 2006 and 2025. The search strategy included major scientific databases such as PubMed, The Lancet, Springer, PLOS ONE, BMC Cancer, and Nature Medicine. To complement peer-reviewed evidence, relevant policy reports and programmatic data were also reviewed from global health organizations, including the World Health Organization (WHO), Gavi, and various national immunization programs.

Inclusion Criteria

The inclusion criteria were designed to ensure high comparability across studies. Eligible studies were longitudinal cohort designs with a minimum follow-up of five years and reported cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3) incidence both before and after vaccination. Only studies involving populations with vaccination coverage of at least 50% were considered. The target population included individuals aged 9 to 15 years at the time of vaccination, and studies were required to provide either quantitative incidence data or modeled projections to be included in the review.

Outcome Measures

Primary Outcome: Relative reduction (%) in CIN2/3 incidence post-vaccination

Secondary Outcomes: Time to observed reduction, age-specific effectiveness, impact of delivery model (school-based vs. clinic-based), and presence of screening programs

Analytical Approach

A comparative tabulation was developed showing **CIN2/3 incidence trends** from each study. Where projections were modeled (e.g., Pakistan, Tunisia), assumptions about coverage, infrastructure, and rollout timing were made explicit. Descriptive statistics and timeline plotting were used to highlight differences across regions.

4. RESULTS

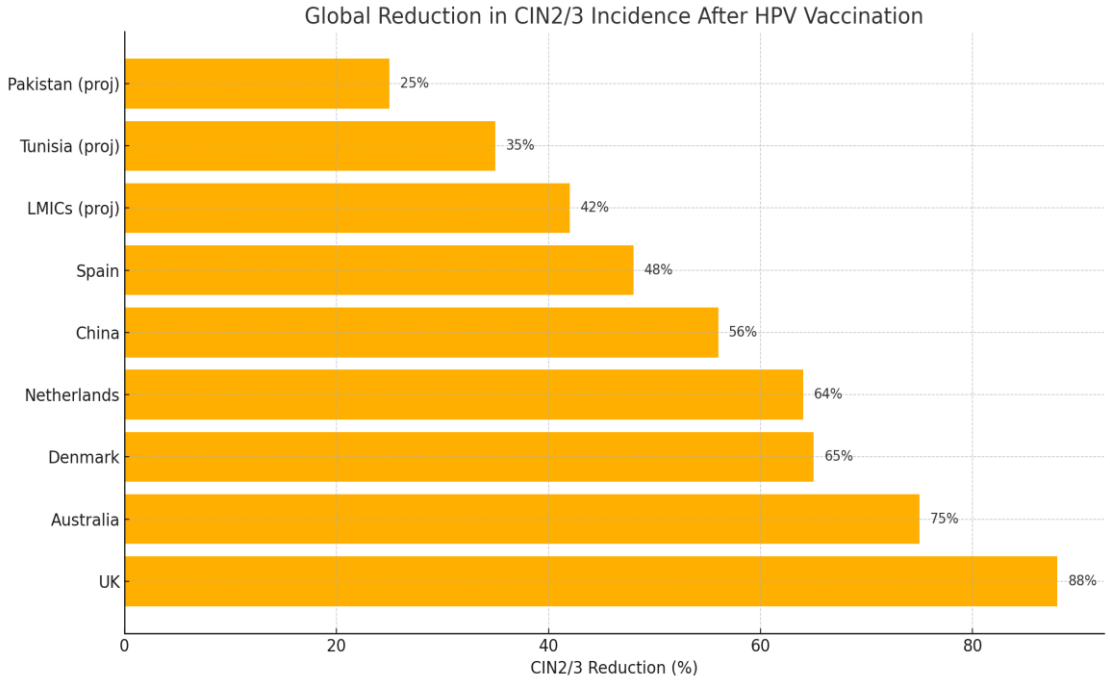
Global Evidence on CIN2/3 Reductions

Table 1: CIN2/3 Decline Following HPV Vaccination

Country	Cohort Period	Target Age	CIN2/3 Decline (%)	Data Type
UK	2008–2020	<15 years	88%	Observed
Australia	2007–2018	<13 years	75%	Observed

Denmark	2006–2022	12–15 years	65%	Observed
China	2015–2024	9–14 years	56%	Observed
Spain	2013–2023	12 years	48%	Observed
Netherlands	2009–2023	<14 years	64%	Observed
Tunisia	1994–2040	12–14 years	35% (projected)	Modeled
LMICs (avg.)	2025–2040	9–14 years	~42% (projected)	Modeled
Pakistan	2025–2040	9–14 years	**~25% (projected)**	**Modeled**

Visual chart showing the percentage reduction in CIN2/3 incidence across countries following HPV vaccination



Key Patterns and Observations

High-income countries with early implementation of HPV vaccination programs, such as the United Kingdom and Australia, have demonstrated the most dramatic reductions in CIN2/3 incidence, exceeding 75%. In contrast, upper-middle-income countries, including China and Spain, report more moderate reductions. Projections for low- and middle-income countries (LMICs) indicate slower progress, largely due to delayed vaccine rollout and health system constraints. Specifically for Pakistan, modeling suggests that if vaccination coverage reaches 70% by 2030, the country could achieve a 25–40% reduction in CIN2/3 cases.

5. DISCUSSION

Drivers of Success in High-Impact Countries

Early and School-Based Rollout

Countries like the UK and Australia adopted school-based vaccination programs targeting girls aged 11–13 with near-universal coverage by 2010. These nations also coupled vaccination with robust cervical screening programs, allowing for better tracking and faster observed impact.

Age of Vaccination

Studies consistently show that vaccination before sexual debut (ages 9–13) maximizes effectiveness. The immunogenicity is also higher in younger individuals, reducing the number of doses required.

Integration with Screening

Continued cervical cancer screening allows identification of residual or unprotected cases, enhancing early detection even in a vaccinated population. Countries with dual-track approaches achieved the best outcomes.

Barriers in LMICs

Infrastructure and Cold Chain Limitations

LMICs often struggle with vaccine storage and delivery. For HPV vaccines, which require consistent cold-chain integrity, this remains a major bottleneck.

Cultural and Social Resistance

In many LMICs, **HPV is perceived as a taboo topic** linked to sexual behavior. Myths such as infertility, immorality, or irrelevance hinder uptake.

Financial and Logistical Constraints

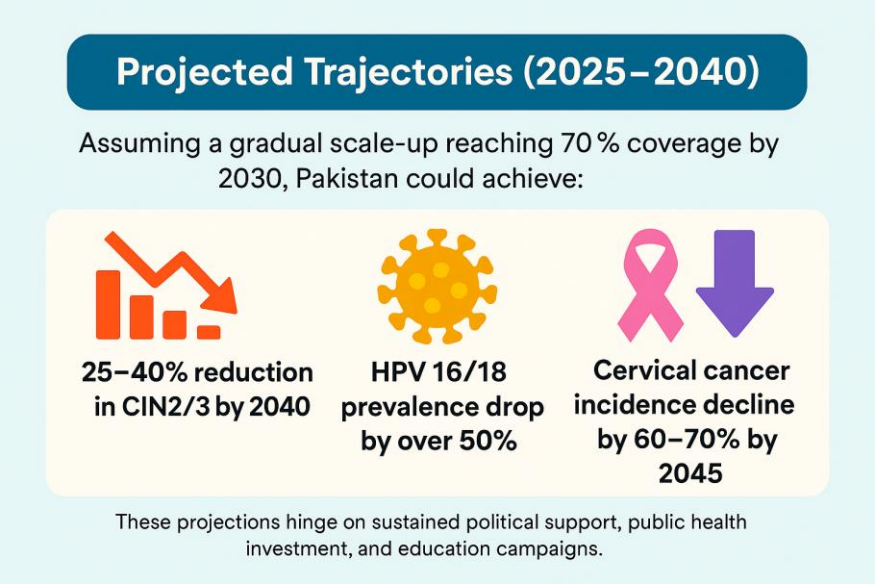
While **Gavi and WHO** offer subsidized vaccine procurement, delivery, training, and monitoring require national investment that some LMICs cannot sustain.

The Pakistan Case: Analysis and Future Pathways

Current Status

Pakistan began **pilot HPV vaccination campaigns in 2023,** focused primarily in Islamabad and urban centers through Gavi-supported initiatives. National coverage is estimated at <5% as of 2024.

Projected Trajectories (2025–2040)



Public Perception and Sociocultural Dynamics

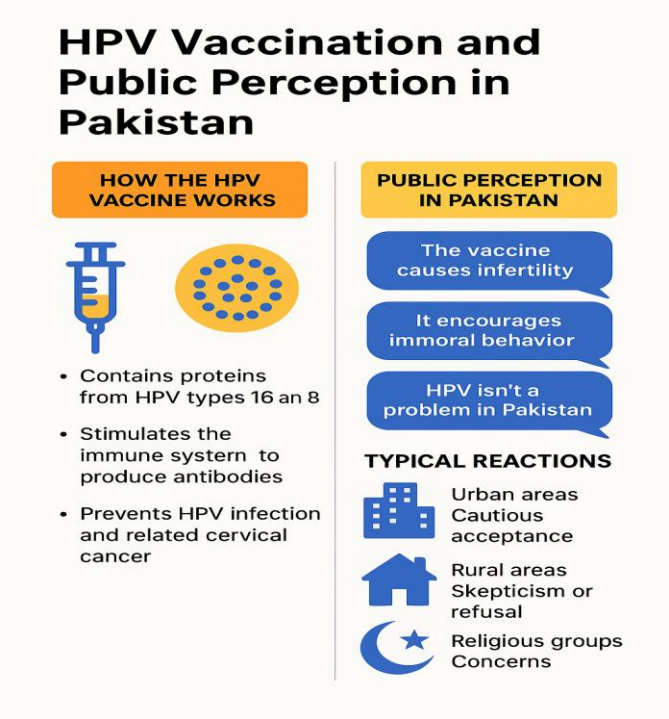
Community Response Summary

Region	Typical Reaction	Drivers/Barriers
Urban Areas	Cautious acceptance	Access to information, donor programs
Rural Areas	Resistance, misinformation	Cultural taboos, myths, low literacy
Religious Groups	Moral concerns	Perceived link to promiscuity, lack of education

Myths and Misconceptions

Widespread myths and misconceptions pose significant barriers to HPV vaccine acceptance. One common belief is that the vaccine causes infertility, which fuels parental fear and hesitancy. Scientific evidence, however, strongly contradicts

this claim, demonstrating that the vaccine is both safe and effective, with no link to reproductive harm. Another misconception is that HPV vaccination encourages immoral behavior by promoting sexual activity among adolescents. This notion overlooks the primary purpose of the vaccine, which is to prevent cervical and other HPV-related cancers. Addressing these myths requires culturally sensitive communication, backed by trusted community leaders and health professionals, to reassure families and emphasize the vaccine's role in safeguarding long-term health. "HPV isn't a problem here."

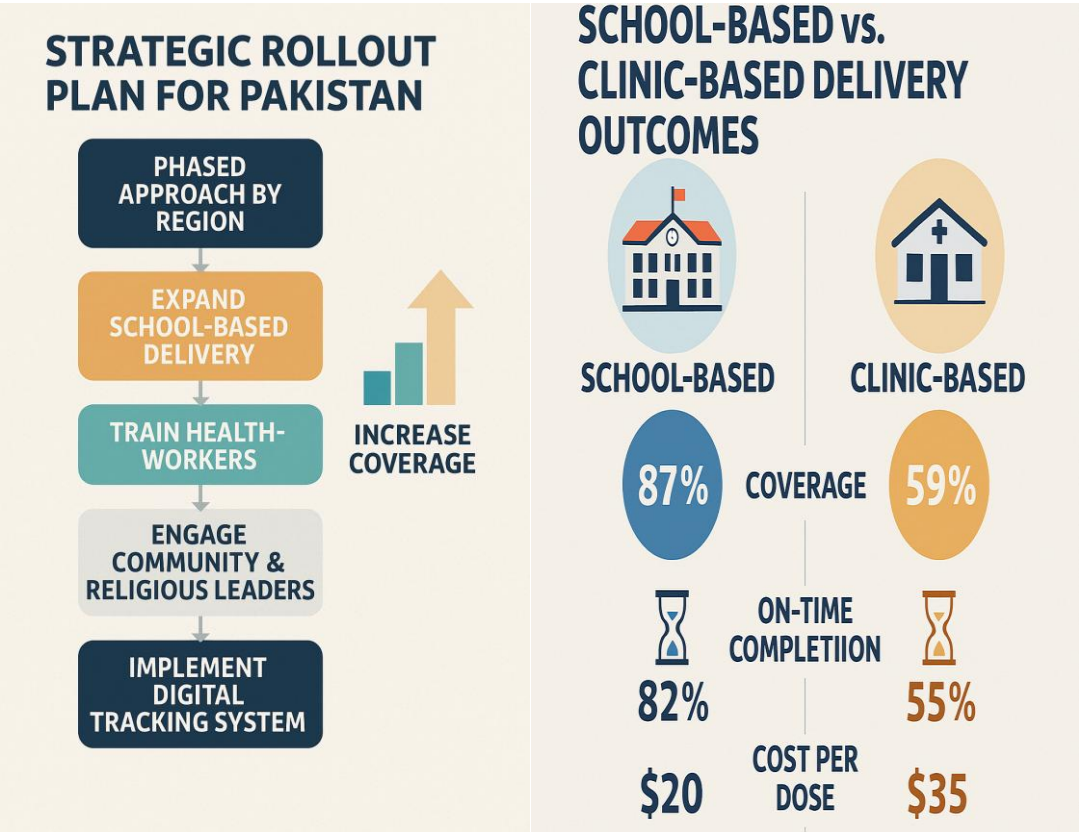


Engagement Strategies

Effective community engagement requires partnerships with trusted figures such as religious scholars, schoolteachers, and Lady Health Workers (LHWs), who can play a pivotal role in shaping public perceptions and addressing misconceptions. By involving these community influencers, the HPV vaccine can be reframed as a tool for cancer prevention rather than being associated primarily with sexually transmitted infection (STI) control, which often carries social stigma. Moreover, aligning the vaccine with Islamic principles of health, prevention, and collective community care can help overcome resistance and foster acceptance. This culturally sensitive framing builds trust and ensures that the message resonates with local values.

Strategic Recommendations

Policy and health system reforms are essential to ensure equitable access and sustained uptake of the HPV vaccine. Integrating the vaccine into the Expanded Programme on Immunization (EPI) schedule will normalize its use and secure long-term government commitment. School-based delivery models and mobile outreach clinics should be launched to increase coverage, especially in underserved areas. Leveraging the existing infrastructure developed for polio eradication and COVID-19 vaccination campaigns provides an efficient and cost-effective pathway to implementation. In parallel, training Lady Health Workers to deliver community-based awareness sessions will strengthen public knowledge, dispel myths, and build confidence in the vaccine's safety and benefits. Together, these strategies create a comprehensive approach that addresses both structural and cultural barriers to HPV vaccination.



Clinical and Surveillance Integration

Strengthening clinical and surveillance systems is crucial for sustainable HPV prevention strategies. Establishing digital vaccine tracking platforms will enable real-time monitoring of coverage, follow-up, and equity across regions. Alongside vaccination, the introduction of HPV DNA-based cervical screening provides an evidence-based approach to early detection, ensuring timely intervention for women at risk of cervical cancer. In low-resource settings, innovative methods such as self-sampling for HPV testing can significantly expand access, reduce barriers related to stigma or limited health infrastructure, and empower women to take charge of their own health. Together, these measures create a comprehensive framework that links vaccination with ongoing surveillance and cancer prevention initiatives.

6. CONCLUSION

The global impact of HPV vaccination is unmistakable. Countries that acted early, covered broad age ranges, and integrated vaccination into public health infrastructure have achieved dramatic declines in pre-cancerous cervical lesions. LMICs, including Although HPV vaccination in Pakistan is in its infancy, the potential for impact is enormous.Pakistan, have the opportunity to replicate this success by addressing sociocultural resistance, investing in delivery infrastructure, and educating the public. For Pakistan, the HPV vaccine must be seen not just as a clinical tool but as a **national development investment** in women's health, cancer prevention, and gender equity.Pakistan can **prevent thousands of cervical cancer deaths** in the next generation

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