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HPV Vaccination: Broader Implementation and Development of Next-Generation Vaccines Reduce the Incidence of Cervical Cancer

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Abstract

Cervical cancer has been an important health issue of global concern which has almost universally been fuelled by the persistent infection of high-risk Human Papillomavirus (HPV). The most effective way of primary prevention is prophylactic HPV vaccination. The extensive real-world evidence obtained through national immunization programs throughout the world has given unambiguous evidence of the effect of the vaccine as a decline in the incidence of high-grade cervical pre-cancers and more importantly a reduction of risk of invasive cervical cancer (ICC) in cohorts vaccinated at a young age of adolescence. To achieve the elimination goals identified by World Health Organization (WHO) global efforts are progressively focusing on highly effective simplified strategies especially the introduction of a single-dose schedule, which is supported by long-term follow-up studies. The advent of the cheap locally produced vaccines and concomitant governmental promises in high-burden situations is a watershed turning point to overcome the historical obstacles of price and availability. The future research is aimed at next generation vaccines, such as broad spectrum L2 based vaccines and therapeutic platforms, which are likely to increase coverage and shorten logistics in distributing the vaccine, thus hastening the global initiative to end cervical cancer. This venture will only succeed with the help of the political will that is going to be maintained, the fair access, as well as the implementation of both primary and secondary preventive measures.

Keywords: Cervical cancer, global health, HPV vaccination, human papillomavirus, next-generation vaccines

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INTRODUCTION

Cervical cancer is one of the serious health issues in the world, with women being severely affected in the developing economies of low- and middle-income (LMICs). It is the fourth most common malignancy that occurs in women worldwide and it is estimated that about 90% of deaths are caused by resource-limited conditions in which screening and therapeutic options are critically restricted [1]. The invaluable causal agent of practically all cases of cervical cancer is persistent infection with high-risk human papillomavirus (HPV) genotypes, particularly HPV-16 and HPV-18, thus making vaccination a key primary preventive intervention in this regard a highly effective public-health intervention [2]. With the licensure of the first prophylactic HPV vaccine in 2006, significant gains have been reported on its safety profile, immunogenicity, and protective efficacy against persistent HPV infection, genital warts, cervical intraepithelial neoplasia (CIN) and finally invasive

cervical cancer [3, 4]. Modern vaccines, bivalent (HPV-16/18), quadrivalent (HPV-6/11/16/18) and nonvalent (HPV-6/11/16/18/31/33/45/52/58) are developed using the platform of VLPs of the major capsid protein L_1 and they have an excellent safety history [5].

The World Health Organization (WHO) has proposed bold targets to eradicate cervical cancer across the world with the 90–70-90 premise targeting 2030 to vaccinate 90% of the girls 15 years old and screen 70% of all women to identify the high-grade lesions and provision of treatment to 90% of the eligible cases [5, 6]. To meet this elimination goal it is required to have a twofold goals focus: on the one hand, to overcome the challenges of implementation and increase the scale of application of already proven high-efficacy vaccines in geographic locations with the highest disease burden; on the other hand, to develop next-generation vaccine technologies that increase coverage, simplify delivery, and become more accessible [6].

Global Context: Efficacy and Broader Implementation

The introduction of prophylactic HPV vaccines into national immunization programs (NIPs) has had a strong real-world evaluation of their massive impact on the public-health. The first evidence supported by extensive randomized controlled trials (RCTs) using the quadrivalent vaccine, high-grade cervical disease (CIN2/3) vaccine-type protection in HPV-naive women was exceptionally high over 90% (or high-grade protection) [7]. A follow-up longitudinal study of these cohorts has proven a continuum of protection of at least 10–14 years, which means that in this case, booster immunizations are not essential [8].

Real-World Impact and Herd Immunity

After implementation of NIP in Australia, in the United Kingdom, and Sweden, reductions of a factor of 2–3 in the prevalence of vaccine type HPV infections, and genital warts in addition to high grade cervical lesions have been noted [9]. A Swedish population-based linkage study, the first of its kind by Lei et al. (2020) found a statistically significant reduction in invasive cervical cancer, particularly in females who were vaccinated before the age of 17 and the risk reduction was 63% compared to that of unvaccinated individuals [10]. This protective effect was increased further in vaccinated persons who had been immunized prior to 17 years with a reduced risk of 88% highlighting the essential role of immunization policies amongst adolescents [10, 11]. Equally, surveillance data on UK surveillance showed by Palmer et al. (2019) depicted the almost complete elimination of cervical cancer and precancerous lesions among women who had immunization during the age of 12 and 13 [11, 12].

In addition to personal protection, statistics prove that the herd immunity is obtained in those populations that attain a high level of coverage. The synthesis of Australian and United States studies by Drolet et al. (2015) indicates that HPV prevalence and genital warts are significantly reduced in unvaccinated older women and males, which makes it clear that gender-neutral, high-coverage programs have a beneficial impact on people in the age group [12].

Streamlined Dosing Schedules

One of the most important changes that help the global scale-up is the simplification of dosing schedule. The original WHO guideline of a three-dosage regimen created significant logistical burdens within the low- and middle-income contexts. Trial outcomes on immunogenicity and efficacy, most recently the IARC India trial, have led WHO to change its guidance to recommend a one- or two-dose schedule in the primary target population of girls aged 9–14 years [13, 14].

Long-term follow up studies confirm the efficacy of a single dose of a vaccine. As an example, the Joshi et al. (2023) trial in India showed that the quadrivalent vaccine can offer the same amount of long-term protection against persistent HPV-16/18 infection with a single dose as two to three doses of the vaccine over a 10-year span [14–16]. Switch to single-dose regimen saves a significant amount of money, simplifies supply-chain and enables monitoring and delivery, which is an important facilitator towards enhancing coverage in high-burden jurisdictions [15, 17]. The coverage of the world is still not homogenous, although there is an overwhelming number of evidence about efficacy and safety.

By the end of 2024 at least 144 countries had added the HPV vaccine to their NIPs, but coverage rate of the first dose in girls aged 9–14 years has an estimated value of 27% as of 2023 and this is a very large gap, especially in LMICs [16].

Indian Context: Burden, Barriers, and Breakthroughs

India has one of the largest rates of bearing cervical cancer in the world, with the country bearing one-fifth of the global burden with roughly 125,000 new cases and 75,000 deaths every year [17]. According to Sankaranarayanan et al. (2012), HPV 16 and 18 are the ones that cause approximately 80% of cervical cancers in India thus highlighting the relevance of the available bivalent and quadrivalent vaccines to the Epidemiological profile of the country [18].

The Implementation Is Also a Problem That Is Difficult to Handle

In India, the HPV vaccine has been facing major challenges in the past where its implementation is concerned [19].

- *Cost and Accessibility:* In the recent past, the reliance on imported vaccines has made the vaccination prohibitively expensive to most people limiting its use to the private market [20].
- *Controversy and Hesitancy:* Initially a pilot demonstration project done in 2 states in 2009 was suspended due to controversies and several girls who died untimely, subsequently, scientific investigations showed that these deaths had nothing to do with the vaccine [21]. However, this event led to vaccine hesitancy and suspicion among the general population, which Gupta et al. (2019) reported, finding that misinformation and fear of adverse effects were identified as key challenges to take up [22].
- *Awareness and Stigma:* Knowledge, attitudes, and practices (KAP) studies including the study by Arora et al. (2025) showed that there was low knowledge regarding the relationship between HPV, vaccination, and cervical cancer in adult women [23]. In addition, the association of the vaccine with an STD creates a social and religious stigma, making it hard to be accepted by the community and consent with parents, especially in school-based programs [24].
- *Lack of National Programme:* Unlike in most of the high-income nations, India has not developed a universal and publicly funded National Immunization Program (NIP) to guarantee HPV vaccination, limiting large-scale coverage gravely [25].

Indigenous Vaccine and NIP Rollout: The Breakthrough

The landscape is currently experiencing the changing landscape. Most recently, in another historic milestone in the history of public health, in 2023, the Serum Institute of India (SII) developed and commercialized CERVAVAC, the first indigenously made quadrivalent HPV vaccine in the country [26].

- *Immunogenicity and Affordability:* The recent results of the Phase II/III clinical trial of CERVAVAC, as reported by Jain et al. (2022), indicated immunologic similarity between CERVAVAC and the reference quadrivalent vaccine Gardasil in young adults and adolescents and provided a safe and effective local vaccine [27]. Notably, the indigenous production is likely to yield a significant decrease in the cost and will respond to the main financial obstacle [28].
- *Government Action:* The inclusion of HPV vaccine in the NIP by the Union Government to cover girls between the ages of 9–14 years is a tactical move into cervical cancer eradication [29]. This gradual implementation, which mainly occurs via schools, and which is based on the concept of a single-dose timetable due to logistical and cost-saving considerations (which are also backed up by Joshi et al. (2023) data), has the potential to catapult the nation to high levels of cervical cancer coverage in a very short time and significantly reduce the national burden of the disease [14, 30].

Next-Generation HPV Vaccines: L1 VLPs Alternatives

Despite the high efficiency of the existing L1 virus-like particle (VLP)-based vaccines, research, and development efforts are directed towards the next-generation vaccines that will eliminate the drawbacks of the current products, namely the extended coverage and reduced production and delivery complexity [31].

- *Facilitating HPV Type Vaccination:* The nonvalent vaccine Gardasil 9 already covers 9 types of HPV (6, 11, 16, 18, 31, 33, 45, 52, and 58) covering about 90% of cervical infections in the globe [32]. However, the rest 10% of cancers can be caused by other high-risk types.

- *L2-Based Vaccines:* The next generation approach that has the potential of use is L2-based vaccines that will target the minor capsid protein, L2. In contrast to a much type-specific L1 protein, there is a region of L2 that is conserved in a large range of HPV types [33]. The goal of L2-based vaccines, which is to provide the protection against all oncogenic types of HPVs combined within a single vaccine, thus comprises a true pan-HPV vaccine [34]. A study by Schellenbacher et al. (2017) has shown that constructs of L2 are capable of inducing broadly neutralizing antibodies in preclinical models, which will see clinical trials of a simpler, broader-coverage vaccine [35].
- *Fusion and Chimeric VLPs:* Featuring chimeric or fusion VLPs can also be used to target non-vaccine types of cross-protection, such as the combination of antigens in many high-risk types or conserved moieties, as investigated in different preclinical studies [36].

Simplifying the Production and Delivery of Vaccines

The recent vaccines based on VLPs are not only difficult to produce but also to make them, cell-culture-based systems (e.g., yeast or insect cells) are needed to express proteins and assemble themselves, which makes them expensive to develop [37].

- *Other Expression Systems:* The development of less expensive and more scalable expression systems is under consideration. As an example, some bivalent vaccines use *E. coli* or *Pichia pastoris* expression, as observed in the formulation of some Chinese-made vaccines, which is economical in cost and time [38].
- *Thermostable and Non-Refrigerated Vaccines:* One of the important logistical challenges in the low- and middle-income countries is the cold-chain. The next-generation vaccines are under development that are thermostable and they may use dry-powder delivery or patch delivery method which will eliminate the use of refrigeration, and this will significantly enhance the distribution in the rural and remote areas [39].
- *Nucleic Acid Based Vaccines:* Once revolutionary in mRNA and DNA-based systems, the COVID-19 pandemic is being studied in HPV [40]. These technologies can be easily produced than VLP-based vaccines and might be easily modified to suit emerging HPV types [41]. The mRNA technology has a very appealing rapid scalability, and although prophylaxis use is still at an initial phase, there is considerable potential in its general applicability when it comes to a universal implementation [42].

Therapeutic HPV Vaccines

Oncolytic vaccines are a type of vaccination that is the next generation, as it is aimed at the elimination of established infections as well as the detection of precancerous or cancerous lesions [43]. Therapeutic vaccines are constitutively expressed oncoproteins E6 and E7 that are critical to maintaining the malignant phenotype and are targeted by these vaccines [44].

- *Immune Stimulation:* Therapeutic vaccines, typically peptide, protein, or nucleic acid, based are designed to induce a strong specific cytotoxic T-lymphocyte (CTL) response of E6/E7-expressing tumor cells [45]. Preclinical studies, which were analyzed by Kaufman et al. (2020), have shown that some E6/E7 targeting vaccines can trigger specific T-cell immunity and produce clinical responses in patients with high-grade precancerous lesions (CIN 2/3) or invasive cancer [46].
- *Combination Therapeutics:* The most promising future direction of the therapeutic vaccines will become their combination with the classical oncological modalities or immune checkpoint inhibitors to enhance the anti-tumor immunological response [47].

REVIEW OF LITERATURE

Protective efficacy of prophylactic HPV vaccination has been confirmed beyond doubt by means of rigorous randomized controlled trials (RCTs) and the extensive and longitudinal observational studies that have followed national immunization programs (NIPs). The research studies provide a solid evidence base that cannot be disputed by the community on the value of the vaccine to health.

Global Effect on Cervical Cancer and Pre-Cancers

Initial results in massive RCTs, in particular, the FUTURE trials, validated a great deal of effectiveness in the treatment of vaccine-type high-grade cervical disease (CIN2/3) in HPV-naive ladies [48]. Nevertheless, due to the long-time latency of cervical carcinoma, conclusive proof of invasive cancer required a long period of registry follow up.

Another significant study in Sweden by Lei et al. (2020) was a nationwide linkage study, which found a statistically significant decrease in the number of invasive cervical cancer (ICC). The cohort included 1.67 millennium of girls and women between the age of 10 and 30 years, and it was found that the quadrivalent HPV vaccination was linked to the reduced risk of ICC significantly. Importantly, a reduction of the risk was 88% among women that were vaccinated at the age of less than 17, in comparison with the unvaccinated women, which provided strong evidence of a direct effect on cancer incidence [49].

As Kemp et al. (2020) describe long-term follow-up of the FUTURE II trial cohort in Nordic countries encompassed the females as long as 14 years after the vaccination. The trial found 100% vaccinate effectiveness (VE) against high-grade cervical dysplasia caused by HPV-16/18 (CIN 2/3 and AIS) in the per-protocol cohort with long-term protection (14 years) following vaccination and no incidence of the primary endpoint, which was the protection against high-grade dysplasia induced by the quadrivalent vaccine [50].

The fact that the vaccine has a huge effect on the population health was also highlighted in observational, population-level data published in the United Kingdom and analyzed by Falcaro et al. (2021). In England, the national HPV vaccination program was associated with the 87% reduction in cervical cancer in women vaccinated at ages between 12–13, and a strong decrease in the number of lesions with high grade (CIN 3+), which confirmed the ability of the vaccine to almost eliminate the disease in the first vaccinated groups [51].

This body of evidence was summarized two recent Cochrane reviews (2025), which confirmed that all HPV vaccines have high-certainty evidence on their effectiveness in preventing infection and pre-cancerous changes. The reports indicated that girls who had been vaccinated above the age of 16–19 years were 80% less likely to develop cervical cancer in the real-life contexts. The safety issues were explicitly mentioned, and the results placed no increase in the serious adverse events in relation to the vaccines [52].

Indian Test Results on Single-Dose Effect

An evidence-based, seminal research in the Indian setting provided important data on the universal adoption of a one-dose schedule, which is a strategy that must be employed by high-burden low-and middle-income nations (LMICs). Joshi et al. (2023) evaluated long-term protection in girls between the ages of 10 and 18 years at 10 years of follow-up of the IARC-India Study Cohort that included single-, two-, and three-dose regimens of the HPV vaccine of the quadrivalent. The results showed that one dose affords equivalent protection to two or three doses against long-term HPV-16/18 infection, after 10 years [53] thus, giving solid ground to support the new recommendation by the World Health Organization, which is to give one- or two-doses, in the primary target population to simplify the logistics of vaccination in resource-limited settings such as India.

Significant Reduction in Cervical Cancer Incidence

- *General Decrease:* The evidence of real-life research is always spearheaded by significant risk reduction of invasive cervical cancer among those vaccinated cohorts. An integrated summary of an array of cohort studies revealed that there was a 63% reduction in risk of cervical cancer in vaccinated women as compared to unvaccinated women in the long term.
- *Protection of Younger Cohorts:* This vaccine should be most effective at protecting those girls vaccinated before becoming sexually active (i.e., before sexual debut). Girls who had been vaccinated against cervical cancer at ages 16 or younger were reported to have an approximate of 80 to 88% reduced risk of developing invasive cervical cancer compared to unvaccinated girls. A Swedish national trial recorded 88% reduction in the risk of cervical cancer in girls who were vaccinated before their 17th birthday.

- *Almost Eradicated in Well Vaccinated Populations:* Nationwide coverage of teenage vaccination has reported near-elimination of cervical cancer in the first full vaccinated groups. As an example, in Scotland, it was found that there were no cases of cervical cancer in women who were vaccinated against the vaccine at the age of 12 or 13 [54–57].

Reduction of Pre-Cancerous Lesions with Drama

Seeing that cervical cancer takes ten years to manifest, precancerous lesions should be decreased during early phases, and this becomes a better indicator of the effectiveness of vaccines.

- *High-Grade Lesions (CIN3+):* The incidence of high grade of cervical intraepithelial neoplasia (CIN 3+) which are the immediate antecedent of invasive cancer is substantially reduced in a continuous study [58]. Among women inoculated between the ages of 12 and 13 the rates of CIN3+ have decreased more than 90% in some countries.
- *Type-Specific Reduction:* The vaccines have an increased response to high-risk HPV types contained within them (primarily HPV-16 and 18, which cause up to 70 and 90% of global cervical cancers, respectively, and up to 90% with the nonvalent vaccine) [59]. The pre-cancerous changes caused by these particular types are found to be near 99% effective.

Herd Immunity

In well-vaccinated populations (both girls and, in increasing numbers, boys) researchers have demonstrated herd immunity in the form of a lower infection rate of HPV and HPV related disease is even in non-vaccinated individuals (including older women and men). The effect of this phenomenon is the acceleration of the general cancer rate reductions [60, 61].

To conclude, HPV vaccine is by all means an effective tool of cancer prevention as it can practically eradicate the cervical cancer especially when it is applied universally to all teenagers.

CHALLENGES AND FUTURE DIRECTIONS

Although the scientific achievements have been recorded the goal of eliminating cervical cancer will only be achieved after overcoming persistent implementation strains especially in some parts of the world like in India.

- *Sustainable Political Will and Investment:* starting with the initial expenditure of a universal National Immunization Program (NIP) is a formidable hurdle to low- and middle-income countries (LMICs) [62]. The endeavor of India to have an NIP with an indigenous, affordable vaccine is a favorable case; nevertheless, the government needs to be intensely funded and adopt a holistic approach to procurement to access the millions of eligible adolescent girls yearly [63].
- *Viable Delivery Systems:* According to Chaurasia et al. (2021), the school-based strategy is the most effective and fair delivery method of the human papillomavirus (HPV) vaccine, especially in a situation where the target population has high volumes and includes girls out of school [64]. There is a strong need to have a close partnership between education and health sector.
- *Avoiding Misinformation:* Preventive healthcare campaigns targeting the transmission of misinformation and social stigma surrounding the vaccine, and including healthcare providers, community leaders, and religious leaders, should be implemented on a long-term basis to promote the vaccine as a tool of cancer-prevention, rather than as a cure against the sexually-transmitted infection (STI) [65].
- *Single-Dose Optimization:* The adoption of a single-dose schedule has been emphasized to have significant logistical and economic benefits [14] with some of the studies like Joshi et al. (2023) highlighting its effectiveness. Further evaluations of the long-term effectiveness of single dose regimen in all approved vaccines should be done to maximize such approach on an international basis [66].
- *Integrating Prevention Pillars:* To be the most effective, HPV vaccination should be combined with other two pillars of the World Health Organization (WHO) elimination strategy screening (70% coverage with high-performance testing) and treatment (90% treatment coverage) [67].

- *Switch to Next-Generation Vaccines:* With the successful development of L2-based pan-HPV vaccines, or simplified and thermostable products, elimination processes will be further accelerated by simplifying logistics and enhancing coverage of a broader range of oncogenic types [68]. These new vaccines, however, must demonstrate effective and sustained efficacy and be offered at low-cost, tiered prices by the LMICs [69].

DISCUSSION

The available evidence clearly indicates a great influence of the HPV vaccination on the population and the health state of the individuals, thus confirming its leading role as the most efficient preventive measure against cervical cancer. The findings of long-term follow-up in Nordic countries, provided by both the Cochrane reviews (2025) and Lei et al. (2020) change the discussion on the possible efficacy to the proven effectiveness in invasive cervical cancer reduction among vaccine-based cohorts [8, 11]. The close dose response curve with vaccination age at a younger age significantly associated with reduced risks would demand a primary focus on adolescent school-based programs across the world.

The key inflection point of the elimination efforts is bridging the gap of implementation, especially in high-burden areas. The data on single-dose schedule, best illustrated by the study of the Indian cohort by Joshi et al. (2023) provides the key strategic change [12]. This streamlines the dosing process is a public-health imperative, which directly discusses the fiscal and logistical obstacles that traditionally hindered mass vaccination in the LMICs. This is further supported by Basu et al. (2022) who model the single-dose effect in India where the elimination target of the WHO is achievable [29].

The issue of the CERVAVAC introduction, which is indigenous to the Indian context along with the governmental NIP pledge is a breakthrough. It is a development that directly addresses the main historical impediments of the cost and supply, as pointed out by Gupta et al. (2019) and other authors [21]. However, according to the findings of Arora et al. (2025), the sustained success requires the strong public-communication strategies to eliminate the remained vaccine hesitancy and stigma [22]. It should focus on positioning the vaccine as a preventive measure of cancer, independent of it having any relation to an STI, and thus, achieve the desired high coverage rates.

The next-generation vaccine pipeline, in particular the broadly-protective L2-based vaccines and the production benefits of nucleic-acid-based systems, has a potential to make it even easier to worldwide deliver vaccines and to nearly universally protect against all HPV-oncolytic types. These innovations although desirable should be accompanied by a determination to give fair access and price discrimination to LMICs so that technology development will translate into health equity in the world. A combination of high-coverage vaccination with good screening and treatment of precancers has been the key triple-pillar solution to the WHO 2030 cervical cancer elimination targets.

CONCLUSION

The prophylaxis HPV vaccine constitutes a breakthrough in preventive medicine, and there is solid confirmation that it has a tremendous effective rate in terms of lowering the incidence of invasive cervical cancer and pre-cancer. Single-dose schedule is an evidence-based and vital approach to overcome both logistical and financial obstacles in high-burden environments on an international level. The obligation towards the production of indigenous vaccines also helps to alleviate the issues of cost and supply at the core. Next-generation vaccines would offer a wider coverage and allow delivery in a simpler form, but achievement of the goals of elimination stated by WHO depends on the persistent political determination, equalization of access and the combination of high-coverage vaccination with effective screening programs technologies. Education of the population to overcome the lack of will and the fair nature of the implementation of the current and future vaccination technologies are the key factors that determine success in the process of minimizing the incidence of cervical cancer and its absence in the world.

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