

New insights into the potential of prophylactic and therapeutic intradermal vaccination against Human Papilloma Virus (HPV)

Arya Mehta | Momen Rbeihat | Danielle Pasmans | Daniele Scalco Vasconcelos | Koen Beyers | Vanessa Vankerckhoven

Idevax BV, Belgium May 2026

HPV & cancer

Human Papilloma Virus (HPV) infection is the most frequent Sexually Transmitted Disease Infection (STI) and the second most common cause of cancer attributable to an infectious agent globally [1].

HPV is **not limited** to females only: while HPV is well-known to be the key cause of cervical cancer in women, it causes various cancers in men as well [2,3]. Indeed, HPV is responsible for a substantial fraction of other anogenital- and oropharyngeal cancers resulting in 570.000 HPV related cancer cases per year in women and 60.000 cases per year in men (Figure 1&2) [4].

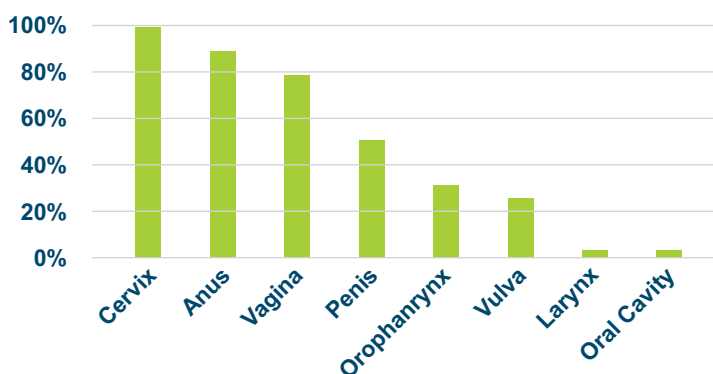
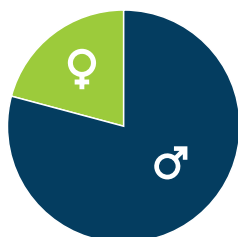


Figure 1: Frequency (%) of anogenital- and oropharyngeal cancers caused by HPV infection. Adapted from [4].

Oral and oropharyngeal cancers



Anogenital Cancer

Anus, Vulva, Penis & Vagina

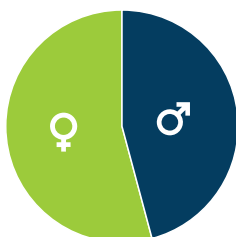


Figure 2: World cancer cases accountable to HPV. Adapted from [4].

A call for elimination of cervical cancer was issued by the World Health Organization (WHO) in May 2018, followed by the American Cancer Society in June 2018. In September 2019, the European Cancer Organization raised the bar even higher by passing a resolution for the elimination of all HPV-associated cancers [1].

HPV virology & epidemiology

The science of virology classifies HPV as non-enveloped, double-stranded, and a circular DNA virus [5]. The HPV genome encodes seven early proteins (E1, 2, 4, 5, 6, 7, 8) and two late proteins (L1 and L2) (Figure 3). E1 and E2 proteins are essential for HPV replication within host cells and are expressed early in the virus life cycle. L1 and L2 viral capsid proteins are necessary for the initial infection of the basal layer of the epithelium [6]. In many HPV-associated lesions that progress into cancers, the HPV viral DNA

genome integrates into the host's genome. This process often leads to the deletion of many early (E1, E2, E4, and E5) and late (L1 and L2) genes. The deletion of E2 during integration leads to elevated expression of E6 and E7 who together drive malignant transformation and uncontrolled tumour growth [8].

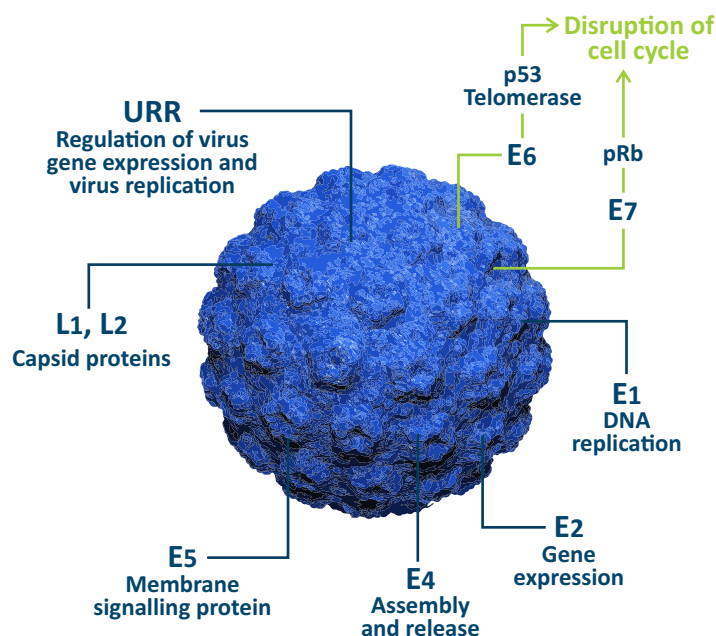


Figure 3: The HPV genome

More than 200 HPV genotypes have been fully characterized and are classified into low- and high-risk types according to their carcinogenic potential [8]. HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 are carcinogenic while HPV68 is probably carcinogenic. These types are referred to as high-risk types [8]. HPV 16 and 18 together are responsible globally for 70% of cervical cancers. HPV16 is detected in about 90% of HPV-related anal, vaginal, vulvar, penile and oropharyngeal cancers [8]. Low-risk group HPV types 6 and 11 cause 90% of external anogenital warts (as well as low-grade changes in cervical cells) [9].

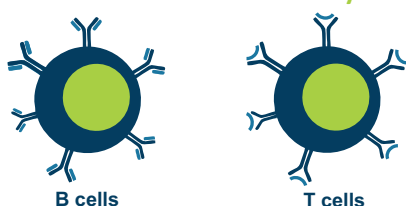
The main route of infection is any vaginal, anal, or oral sexual contact encounters with someone who is infected with HPV; however, any skin-to-skin contact may transmit the virus and cause infection [10]. Indeed, HPV infection is very common but in the majority of cases, the host immune system will clear the infection. 80% of cases clear within 24 months and 90% of cases within 48 months. A persistent HPV infection of the cervix however might progress to cervical intra-epithelial neoplasia (CIN) and if left untreated to cancer.

The Centres for Disease Control and Prevention (CDC) declared that HPV is the most common Sexually Transmitted Disease (STI) in the United States [10]. Lewis et al. concluded that HPV causes a high burden of infection in the United States [11]. Their statistics showed that 42 million people were infected with disease-associated HPV in 2018, and new infections were estimated in 13 million people [11].

HPV vaccination

Using protection methods such as condoms and adopting a monogamous sexual partnership lessen the chances of acquiring HPV infection. Nonetheless, HPV vaccines are key to prevent HPV related infections [10]. While the prophylactic vaccines work on forming neutralizing antibodies, the mechanism of action for HPV therapeutic vaccines aims at generating cell-mediated immunity [12].

Prophylactic HPV vaccines work on inducing neutralizing **antibodies**.
Therapeutic HPV vaccines aim at generating **cell-mediated immunity**



HPV prophylactic vaccines

Since 2006, three types of prophylactic HPV vaccines based on virus-like particles (VLP's) assembled from recombinant HPV capsid proteins (bivalent, tetravalent, and 9-valent), have been approved. All these vaccines have proven their effectiveness in the prevention of HPV-related cancers and benign conditions [13]. Data from recent surveillance systems and studies demonstrate that these vaccines are effective in preventing infection and diseases (vaccine efficacy 93% to 100%) [8].

Currently there are six licensed HPV vaccines: three bivalent, two quadrivalent, and one nonavalent vaccine. All of these are effective in preventing infection against HPV16 and HPV18 [14].

Initially, HPV vaccination was introduced only for young girls aged 11 to 13, but more and more countries have been adopting pan-gender vaccination programs for HPV, including supplying free HPV vaccines to men who have sex with men [2,15,16]. CDC recommends HPV vaccines for all pre-teens regardless of gender between the ages of 11 and 12, or up to the age of 26. However, adults between 27 and 45 years old may also get the vaccine after consulting with their healthcare provider [10]. The WHO recommends a one or two-dose schedule for girls aged 9-14 and for girls and women aged 15-20 [17].

Additionally, one of the key goals in the Europe's Beating Cancer Plan is to vaccinate young people against HPV to help eliminate several types of cancer. Specifically, the Plan aims to at least vaccinate 90% of the EU's target population of girls as well as increase HPV vaccination uptake in boys [18].

A recent study published in The Lancet Oncology, showed that no cases of cervical cancer have been detected in Scotland in anyone who received the HPV vaccine when they were 12 or 13 years [19].

HPV vaccination distribution

At the end of 2019, 88% of high-income countries introduced HPV vaccination in women and girls compared to less than 40% of LMICs. Additionally, 44% of high-income countries also started

vaccinating boys, compared to only 5% of LMICs [20].

According to View-Hub, which presents recent vaccine data, maintained and updated by International Vaccine Access Center (IVAC), more and more countries are introducing the HPV vaccine. In July 2024, 137 countries have introduced HPV vaccines in their national immunization program, of these 26, countries are part of Gavi – The Vaccine Alliance. On the other hand, 27 countries are planning to introduce the HPV vaccine (14 are Gavi members), a total of 7 countries (of which 2 Gavi countries) have introduced the HPV vaccine subnationally, and 23 countries have not (yet) introduced the HPV vaccines in their national immunization programs yet (12 are Gavi members) (Figure 4) [21].

HPV Vaccine	BIVALENT	QUADRIVALENT	NONAVALENT
HPV Types	16 18	6 11 16 18	6 11 16 18 31

A recent study published in **The Lancet** showed that **no cases of cervical cancer** have been detected in Scotland in anyone who received the **HPV vaccine** when they were 12 or 13 years.

Reasons for the lower uptake of HPV vaccination in LMICs, which has been exacerbated by the COVID-19 pandemic, include financial and human resource constraints and worldwide shortage of HPV vaccine supply [20].

According to PATH, "a single-dose HPV vaccination schedule could alleviate the financial and logistical barriers in LMIC countries face and accelerate HPV vaccine introduction into national immunization schedules" [22].

As a single-dose schedule has the potential to reach the WHO goal of having 90 per cent of girls vaccinated by the age of 15 by 2030, SAGE (the WHO Strategic Advisory Group of Experts on Immunization) reviewed all evidence and concluded that a single dose of HPV vaccine delivers solid protection, comparable to 2-dose schedules, against HPV [23].

The one-dose regimen is considered very convenient for LMIC: (1) to resolve supply constraints; (2) to resolve tracing issues for vaccinees that do not return for their second dose. Re-adoption of the two-dose regimen can only be done provided cheaper vaccines and/or alternative delivery methods such as intradermal vaccination that allow for dose-saving can be introduced [23, 24].

Because there is limited evidence regarding the efficacy of a single dose in immunocompromised individuals, including those with HIV, they should receive three doses if feasible, and if not at least two doses [23].

HPV therapeutic vaccines

Despite the availability of prophylactic HPV vaccines there is still a great HPV-associated disease burden worldwide. As such, there is an urgent need to develop therapeutic vaccines to eradicate existing HPV infections and associated diseases. The main aim of therapeutic vaccines is to eliminate the precancerous lesions and the persistent infection caused by HPV.

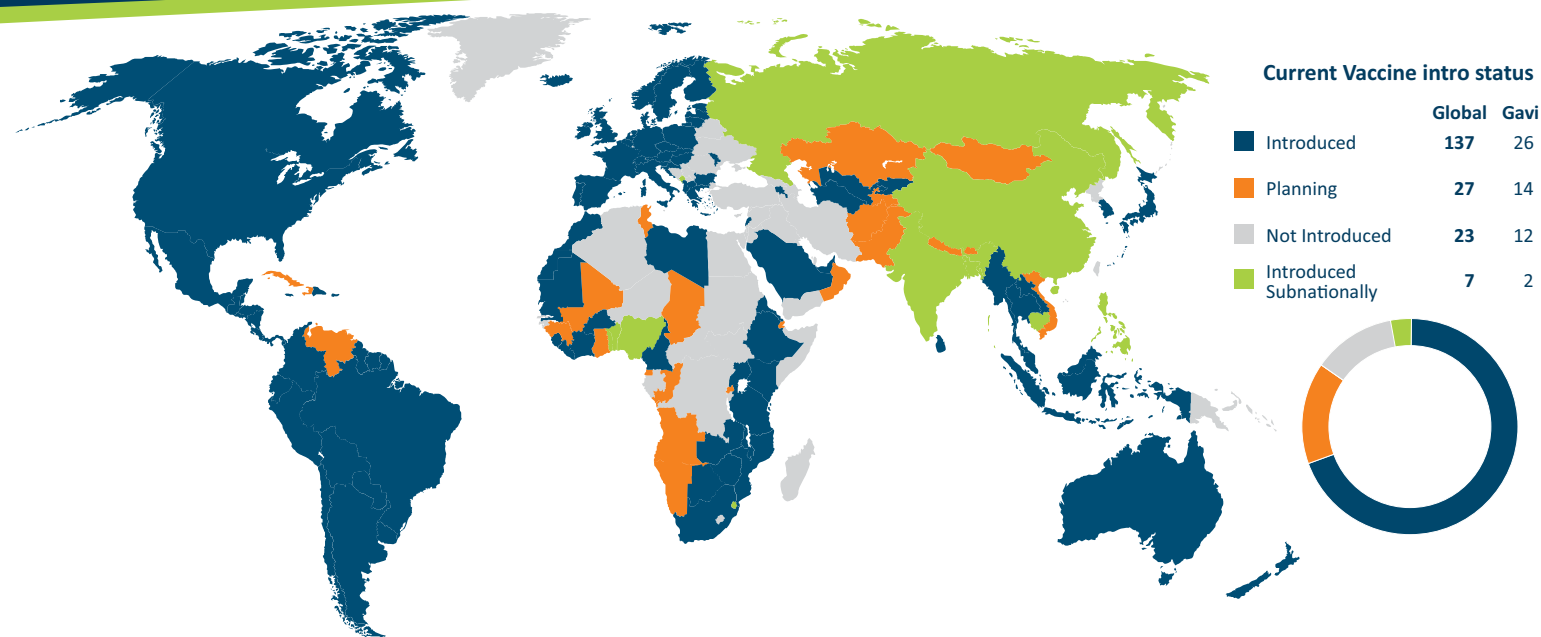


Figure 4: World map for HPV vaccines introduction into national immunization program. Adapted from [17].

Therapeutic vaccines are targeting already established HPV infection by inducing virus specific T-cell response [12]. To the date, almost all therapeutic vaccines for HPV include the oncoproteins E6 and E7, which are expressed from one of the functional genomes of the HPV virus [12].

Immunotherapy for cervical cancer is targeting E6 and E7, as these proteins play a major role in the initiation and progression of the malignancy, and are fundamentally expressed in premalignant and invasive lesions, whereas being non expressed in healthy cells [12,25]. Promising results have been observed with clinical trials involving therapeutic HPV vaccines to treat established cervical cancer [26].

Intradermal HPV vaccination as a possible future route of administration?

The immune network in the dermis layer of skin is a rich network of various immune cells [23]. The abundance of antigen-presenting cells in the dermis makes it an alluring target for multiple vaccines.

As a result, delivery of vaccine to the skin, compared to the muscle and subcutaneous tissue, offers dose-sparing properties which lowers the cost, allows for easier storage and distribution of vaccines and improves vaccine availability, particularly in LMIC [28].

An important study on the dose-sparing and cost-saving potential of ID vaccination against HPV was conducted by Nelson et al. [29] who performed a pilot randomized study to assess the safety, immunogenicity, reactogenicity and tolerability for ID administration of HPV vaccines (using two vaccines Cervarix® and Gardasil®) in comparison to the IM route. Immunogenicity showed seroconversions for all subjects by day 95. The ID administration presented more reactogenicity compared to IM administration, but it was reported as being tolerable and no safety concerns were raised [29].

An ongoing randomized Phase IV trial including men and women

(27 – 45 years old), is comparing the bivalent HPV vaccine to the nonvalent HPV vaccine using a fractional dose (one fifth, 0.1ml) administrated intradermally. The study results are expected to be concluded by the end of 2024 [30].

A recent first in human phase I trial showed that HPV-16 E6 synthetic peptides conjugated to an optimized Toll-like receptor 2 ligand can safely be used as an intradermal therapeutic vaccine to induce robust HPV16-specific T-cell immunity in patients previously treated for HPV16 positive (pre-) malignancies [31].

As the SAGEs of the WHO is trying to solve the dose issue of the HPV vaccine, the ID route can be a potential solution. It offers dose-sparing possibilities as administering 15-20% of the recommended IM dose of the HPV vaccine, ID can elicit comparable efficacy.

IDEVAX's VAX-ID® which is suited for standardized, accurate and reliable intradermal drug delivery, could offer a safe and user-friendly approach for prevention and treatment of HPV related cancers.



Figure 5: IDEVAX's VAX-ID® device for intradermal drug delivery

References

- Colzani E et al. Human papillomavirus vaccination in the European Union/European Economic Area and globally: a moral dilemma. *Euro Surveill.* 2021. PMID: 34915976
- Cheng L et al. Human Papillomavirus Vaccines: An Updated Review. *Vaccines (Basel).* 2020 PMID: 32708759.
- Näsman A et al. A global epidemic increase of an HPV-induced tonsil and tongue base cancer - potential benefit from a pan-gender use of HPV vaccine. *J Intern Med.* 2020. PMID: 31733108.
- de Martel C et al. Worldwide burden of cancer attributable to HPV by site, country and HPV type. *Int J Cancer.* 2017. PMID: 28369882
- Luria L et al. Human Papillomavirus. [Updated 2022 Jan 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK448132/>
- Hancock G et al. Therapeutic HPV vaccines. *Best Pract Res Clin Obstet Gynaecol.* 2018. PMID: 29108943.
- Yang A et al. Perspectives for therapeutic HPV vaccine development. *J Biomed Sci.* PMID: 27809842.
- Fappani C et al. HPV Type-Specific Prevalence a Decade after the Implementation of the Vaccination Program: Results from a Pilot Study. *Vaccines (Basel).* 2021. PMID: 33916132.
- Brianti P et al. Review of HPV-related diseases and cancers. *New Microbiol.* 2017. PMID: 28368072.
- Centers for Disease Control and Prevention. (2022, April 12). Std Facts - Human papillomavirus (HPV). Centers for Disease Control and Prevention. Retrieved July 2024, from <https://www.cdc.gov/std/hpv/stdfact-hpv.htm>
- Lewis RM et al. Estimated Prevalence and Incidence of Disease-Associated Human Papillomavirus Types Among 15- to 59-Year-Olds in the United States. *Sex Transm Dis.* 2021 PMID: 33492097.
- Garbuglia AR et al. The Use of Both Therapeutic and Prophylactic Vaccines in the Therapy of Papillomavirus Disease. *Front Immunol.* 2020. PMID: 32133000.
- Aimagambetova G et al. Human Papillomavirus Vaccination: Past, Present and Future. *Vaccines (Basel).* 2022 PMID: 36146476.
- WHO - Human papillomavirus vaccines (HPV) - Retrieved July 2024, from [Immunization, Vaccines and Biologicals \(who.int\)](https://www.who.int/immunization/vaccines/biologicals)
- Prue G et al. It is time for universal HPV vaccination. *Lancet.* 2018. PMID: 30238882.
- Kirby T. MSM in England to be offered free HPV vaccination. *Lancet Oncol.* 2018. PMID: 29456089.
- WHO - WHO updates recommendations on HPV vaccination schedule – Retrieved July 2024 from [WHO updates recommendations on HPV vaccination schedule](https://www.who.int/news/item/11-04-2022-one-dose-human-papillomavirus-(hpv)-vaccine-offers-solid-protection-against-cervical-cancer)
- European Commission - Human papilloma virus (HPV) – Retrieved July 2024 from [HPV - European Commission \(europa.eu\)](https://ec.europa.eu/health/hpv-vaccine/)
- Burki T. HPV vaccination programme success in Scotland. *Lancet Oncol.* 2024. PMID: 38310913.
- Drolet M et al. Optimal human papillomavirus vaccination strategies to prevent cervical cancer in low-income and middle-income countries in the context of limited resources: a mathematical modelling analysis. *Lancet Infect Dis.* 2021. PMID: 34245682.
- Hub by Ivac. VIEW. (n.d.). Retrieved July 2024 from [Human Papillomavirus Vaccine | ViewHub \(view-hub.org\)](https://www.humanpapillomavirusvaccine.com/viewhub/)
- Kuter BJ et al. Current and future vaccine clinical research with the licensed 2-, 4-, and 9-valent VLP HPV vaccines: What's ongoing, what's needed? *Prev Med.* 2021. PMID: 33678229.
- WHO. One-dose human papillomavirus (HPV) vaccine offers solid protection against cervical cancer. Retrieved July 2024 from [https://www.who.int/news/item/11-04-2022-one-dose-human-papillomavirus-\(hpv\)-vaccine-offers-solid-protection-against-cervical-cancer](https://www.who.int/news/item/11-04-2022-one-dose-human-papillomavirus-(hpv)-vaccine-offers-solid-protection-against-cervical-cancer)
- Single-dose HPV vaccination: Challenges and Opportunities Webinar. Nov 21, 2022. Webinar ID 831 1850 2459. IPVS. (2022, October 12). Retrieved November 28, 2022, from <https://ipvsoc.org/>
- Chabeda A et al. Therapeutic vaccines for high-risk HPV-associated diseases. *Papillomavirus Res.* 2018 PMID: 29277575.
- Small W Jr et al. Cervical cancer: A global health crisis. *Cancer.* 2017. PMID: 28464289.
- Tong PL et al. The skin immune atlas: three-dimensional analysis of cutaneous leukocyte subsets by multiphoton microscopy. *J Invest Dermatol.* 2015. PMID: 25007044.
- Hickling JK et al. Intradermal delivery of vaccines: potential benefits and current challenges. *Bull World Health Organ.* PMID: 21379418.
- Nelson EA et al. A pilot randomized study to assess immunogenicity, reactogenicity, safety and tolerability of two human papillomavirus vaccines administered intramuscularly and intradermally to females aged 18–26 years. *Vaccine.* 2013. PMID: 23770335.
- Intradermal, fractional dose of HPV vaccines: - full text view. Full Text View - ClinicalTrials.gov. (n.d.). Retrieved July 2024 from [Study Details | Intradermal, Fractional Dose of HPV Vaccines: | ClinicalTrials.gov](https://www.clinicaltrials.gov/study/NCT01401401)
- Speetjens FM et al. Intradermal vaccination of HPV-16 E6 synthetic peptides conjugated to an optimized Toll-like receptor 2 ligand shows safety and potent T cell immunogenicity in patients with HPV-16 positive (pre-)malignant lesions. *J Immunother Cancer.* 2022 PMID: 36261215.

VAX-ID Instruction for Use

