

Non-sexual HPV transmission and role of vaccination for a better future (Review)

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Abstract. Human papilloma viruses (HPVs) belong to the Papillomaviridae family and are epitheliotropic infecting squamous epithelia (skin and mucosae). HPV is estimated to be the cause of 99% of cervical cancers (there is no evidence of significant genetic predisposition for cervical cancer), 90% of anal cancer, 65% vaginal cancers, 50% vulvar cancers, and 45-90% oropharyngeal cancers. The route of HPV transmission is primarily through skin-to-skin or skin-to-mucosa contact. Sexual transmission is the most documented, but there have been studies suggesting non-sexual courses. The horizontal transfer of HPV includes fomites, fingers, and mouth, skin contact (other than sexual). Self-inoculation is described in studies as a potential HPV transmission route, as it was certified in female virgins, and in children with genital warts (low-risk HPV) without a personal history of sexual abuse. Vertical transmission from mother to child is another HPV transfer course. Several studies have emphasized the possibility of infection through the amniotic fluid, or the placenta, or via contact with maternal genital mucosa during natural birth. Waterborne transmission of HPV has never been demonstrated; however, HPV DNA has been detected in water environments. Routine hygiene measures are proven to be inefficient in preventing HPV transmission, as the studies which have evaluated samples of HPV on contaminated medical equipment (after standard disinfection) have found them to be still positive. Annual costs associated with the morbidity and mortality of HPV-related diseases are estimated at approximately \$4 billion. Once the HPV vaccine program in Australia was launched, many studies reported the

initial effects: A decrease in the incidence of high-grade cervical abnormalities, no new genital warts cases in females under 21 years. Promoting greater understanding in the general public about the evident benefits of vaccination can create positive vaccine attitudes and scatter the myths of spurious side effects.

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1. Introduction

Human papilloma viruses (HPVs) belong to the Papillomaviridae family and are nonenveloped double-stranded DNA viruses with over 200 types identified (1). All HPV types are epitheliotropic, infect squamous epithelia (skin and mucosae). HPV infection is widespread, in the US, the incidence is 1% in sexually active adults, and 3% in sexually active adolescents (2). Annually, 14 million persons are infected and 79 million persons have a ubiquitous infection (3).

In 2016 the estimated global prevalence of cervical HPV was 11.7% in women with non-cancerous cytology. The most frequent types worldwide are 16 (3.2%), 18 (1.4%), 31 (0.8%) and 58 (0.7%), all oncogenic papillomaviruses (4). Cervical cancer is the 4th cause of female cancer worldwide. HPV type 16 is responsible for 50% of cervical cancer cases, and together with type 18, account for 70% of cases (4).

HPV is estimated to be the cause of 99% of cervical cancers [there is no evidence of significant genetic predisposition for cervical cancer (5)], 90% of anal cancer, 65% vaginal cancers, 50% vulvar cancers, and 45-90% oropharyngeal cancers (6-8).

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The microabrasions of epithelia permit the HPV particles to penetrate the basal layer of cells (the early phase probably promotes HPV-related disease) (1). The virus can remain latent or inactive for months or years (the mechanism may be immunological). Hormones are presumed to participate in the carcinogenic mechanism (5); thus, the malignancy prospect in the case of new or recurrent HPV infections in menopausal women is uncertain.

The HPV-related disease is divided into malignant and benign tumors. The virus invades its host through the anogenital and/or oropharyngeal mucosae. The effects range from warts (low-risk types) to intraepithelial dysplastic lesions, which can advance to invasive carcinoma (high-risk types). HPV spread is the source for skin, flat, or plantar warts.

The Center for Disease Control affirms that ~80% of women and 90% of sexually active men, at a particular time of their life, will be infected with at least one HPV type (4,9).

An anogenital verruca is the most common sexually transmitted disease in the United States: in 1% of sexually active adults and 3% of sexually active teenagers. It affects both genders, 67% of patients being women (2). Infection with HPV types 6 and 11 predispose the appearance of anogenital warts in a person. A study states that the clinical presentation of symptoms is approximately 11-12 months among males and 5-6 months among females (4).

Most HPV infections are asymptomatic and/or they resolve spontaneously. The clearance time is ~6-24 months: Cervical HPV in 9.4 months and genital HPV in men 7.5 months (oncogenic and non-oncogenic types). Warts develop in ~6-10 months after initial infection (3).

The process of cancer development from HPV infection takes ~5-10 years minimum and 20-25 years on average (10).

2. Risk factors for HPV infection

Multiple sexual partners; Beginning of sexual activity in the adolescence (4); Cigarette smoking: HPV infection is a decisive component for cervical malignancy, but cigarette smoking is a co-factor (local and systemic immunosuppressive effects); Oral HPV type 16 has a higher prevalence (2%) in tobacco users (11); Sexually transmitted disease, lack or delayed treatment (12).

The International Agency for Research on Cancer (IARC) listed 7 viruses as 'carcinogenic to humans': Human T-lymphoto-trophic virus 1 (HTLV-1), Epstein Barr virus (EBV), human herpes virus 8 (HHV-8), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus 1 (HIV-1) and HPV (types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) (4). It is estimated that 15-20% of cancers are attributed to viruses (9), but only a small percentage of viral infections progress to cancer with a long evolution (years or decades). Over 30 HPV genotypes spread among the anogenital mucosa, 15 of those are liable for cervix malignancies (13).

Cervical carcinogenesis is represented by 4 causal stages (5): HPV acquisition; HPV persistence (vs. clearance); Progression to precancerous lesions; Invasive cancer.

3. Routes for HPV transmission

The route of HPV transmission is primarily through skin-to-skin or skin-to-mucosa contact. Sexual transmission is

the most documented, but there have been studies suggesting non-sexual ways.

Horizontal transmission of HPV. The horizontal transmission of HPV includes fomites, fingers, and mouth, skin contact (other than sexual). These possible routes have been largely discussed in various studies. Contaminated equipment in gynecological examination rooms has been an interesting topic of evaluation in HPV infection routes.

We know about HPVs that they are very steady viruses, repellent to heat, and drying [they show 30% infectivity after seven days of dehydration (14)]. The viruses are apt to live for days on surfaces, clothing, frequently used gynecological equipment, and fomites. Many studies have collected HPV DNA samples to assess these concerns.

A study evaluating this particular HPV transmission pattern has detected HPV DNA in 32 out of 179 (17.9%) samples collected from gynecological equipment; 11.8% were positive in hospital compared with 27.5% in private offices, which highlights a contamination rate 2.7 times higher in private practices than a hospital. A study has also revealed that ~9.4% of gloves were contaminated, and colposcopy rooms have a higher risk of being infected with HPV than outpatient offices (6).

Transvaginal ultrasound probes are protected with condoms, which act as a physical barrier to contamination (the risk of condom rupture is ~0.9-5%). Samples (21%), after ultrasound examination (with proper disinfection), were positive for HPV DNA (15). Another study revealed, by collecting high-risk HPV DNA samples from transvaginal ultrasound, after low-level disinfection and probe cover, that a considerable number of probes were contaminated: Probes (3%) tested positive in post-examination samples and 1.9% in pre-examination samples (14). Some studies looked even further at the samples collected from ultrasound probes and discovered not only HPV DNA but also free virions (1).

Most individuals are not aware they are infected because they are asymptomatic. Two different studies, one held in a university and one in a hospital, have revealed an abundance of HPV DNA on the fingers of infected persons, highlighting inadequate or non-existing hand hygiene (1). Studies demonstrated DNA HPV under fingernails of individuals with genital warts, as well as in their underwear (6).

Self-inoculation. Self-inoculation is described in studies as a potential HPV transmission route. It has been detailed in studies of HPV in female virgins (16), in children with genital warts (low-risk HPV) without a history of sexual abuse (17). A study on female virgins found 51.1% HPV positive, compared with 69.1% of sexually active females. Nevertheless, a survey showed that high-risk HPV is sexually transmitted, following 100 virgin females pre- and post-sexual contact (1,4).

Vertical transmission. Vertical transmission from mother to newborn is another HPV transmittal route. Several studies have emphasized the possibility of infection through the amniotic fluid, or the placenta, or via contact with maternal genital mucosa during natural birth.

The possibility of vertical HPV infection was discussed as early as 1950, in a study on infantile anogenital warts,

Table I. Wart treatment (2).

Topical treatment	Systemic treatment
Podophyllotoxin and podophyllin (recurrence rate 38%) - induces wart necrosis	Interferon
Imiquimod (immunomodulator)	Isotretinoin
Polyphenol E (green tea extract)	
Intralesional immunotherapy (injection with candida, mumps or trichophyton skin test antigens)	
Cidofovir (induces apoptosis) - not FDA approved	
5-Fluorouracil - not FDA approved	
Trichloroacetic acid - chemical burns, cauterizes and erodes skin and mucosa	
Cryotherapy	
Potassium hydroxide - dissolves keratin and penetrates the skin	
Surgical excision	
Photodynamic therapy	
Carbon dioxide laser	

Table II. HPV vaccine coverage in 2015 in Australia (24).

Age (years)	Sex	1st dose (%)	2nd dose (%)	3rd dose (%)
14	Girls	87	85	79
	Boys	82	79	74
15	Girls	86	83	78
	Boys	78	75	67

Coverage for the third dose increased by 10 percentage points. HPV, human papilloma virus.

Table III. Moderately high coverage with HPV vaccine; in Australia in school and beyond school age (26).

Age (years)	One-dose coverage (%)	Three-dose coverage (%)
12-13	83	73
14-15	84	72
16-17	81	66
18-19	64	38
20-26	52	32

HPV, human papilloma virus.

congenital conjunctival papilloma, and juvenile laryngeal papillomatosis (18).

Another study has revealed that HPV infection prevalence among pregnant women is low (13.4%). Among HPV types, the most frequent were type 16 (29.6%), 18 (14.7%) and 58 (14.2%). Evaluated by pairs, mother-new born, the concordance in HPV DNA was 23.6%. A higher prevalence of HPV DNA in female newborns (17.7%) over males (11.6%) was observed, without delivery-type relevance (18). This study has concluded that HPV type 16 is the most prevalent in pregnant women, and also in newborns, regardless of the nature of birth, as infection can occur during pregnancy, through the transplacental route.

Data show there is a correlation between the HPV DNA load of the mother and the ability to transfer it to newborns (1). A population-based study conducted over 20 years in Denmark found women with warts to have a 200-fold risk of their children developing juvenile laryngeal papillomatosis (1).

Waterborne transmittal. Waterborne transmittal of HPV has never been proven; still, HPV DNA has been identified in water habitats. In 2008, a study in United States concerning the variety of viruses in raw sewage uncovered for the first time 2/12 HPVs in sewage samples, but not in treated wastewater. Bibby and Peccia (19) identified in 2013 HPV in sewage sludge. They also discovered oncogenic papillomavirus: 16,18,53,

suggesting a waterborne route of infection, as was first proposed 40 years ago (13).

Epitheliotropic viruses, as demonstrated by these studies, can be found in sewage. It might be the result of scrubbing the skin and mucous membranes, but it can also be due to urine or feces pollution (4,13). Therefore, the viruses can attain water collecting sewage flow.

In Italy, Iaconelli *et al*, in 2015 (20) examined HPVs in two rivers and identified 56% of the samples as positive. Another study by Di Bonito *et al*, in 2015 (21) identified 50% of the samples from swimming water as positive for HPV (4).

The basis for the waterborne transmission hypothesis dates from 2011 (22) when it was reported that HPV type 16 remains infectious for seven days on wet surfaces (4).

4. Everyday hygiene measures

Hygiene measures are proven to be inefficient in preventing HPV transmission, as the studies which have evaluated samples of HPV on contaminated medical equipment (after conventional disinfection) have found them to still be positive, especially for type 16. Only one study has been published on HPV type 16 resistance and susceptibility to common disinfectants. HPV 16 was found resistant to alcohol-based disinfection (ethanol and isopropanol), but sensitive to hypochlorite and

high concentrations of peracetic acid-silver-based disinfectant (1,4). According to this study, we can argue for the self-inoculation and horizontal transmission of HPV. New disinfection protocols for healthcare equipment are necessary.

5. Wart treatment

Wart treatment involves local treatment (lesion destruction) and selective immunologic modification (Table I). No therapy has been proven to be superior in clinical clearance or recurrence.

6. Prophylactic treatment of HPV-related disease

In the United States, each year, 4,000 deaths occur due to cervical cancer, and more than 12,000 new cases are diagnosed. Annual costs associated with the morbidity and mortality of HPV-related diseases are estimated at ~\$4 billion (23).

Australia initiated the first HPV vaccination program in 2007, and it lasted two years. The first prophylactic vaccine for HPV was released in 2006, covering 4 types of HPV (16,18 and 6,11, which cause 90% of genital warts); in 2007, a bivalent vaccine was released, which targeted only types 16 and 18 (4). More recently, an additional vaccine has been developed, which adds 5 other types to the existing quadrivalent one: 31,33,45,52,58; GARDASIL 9 aims to prevent ~90% of HPV related disease (4).

The campaign initiated with three-dose schedule quadrivalent HPV vaccination for females aged 12-16, and lasted until the end of 2009, and routine school vaccination for 12-13-year-olds afterward. In 2013, routine vaccination began for boys up to the age of 15 (Table II) (24).

The issue of whether 2 or 3 doses are sufficient is largely studied and mostly influenced by the age of vaccine initiation (Table III).

Immunogenicity studies discovered that (5): Vaccination at young vs. old age: Higher initial, as well as subsequent antibody titers in younger people; antibody titers are higher in men than women; the difference between 2 and 3 doses is not as pronounced as the difference between 1 and 2 doses.

The World Health Organisation recommends a two-dose HPV vaccination if the first dose is initiated under 15 years of age to increase compliance and reduce the cost of vaccination [three-dose HPV vaccination is 360\$ at the time of data assembly (23)]. Several countries have already adopted this strategy. Coadministration of HPV vaccine with other adolescent vaccines does not decrease HPV immune responses (5). Many states cover the vaccination scheme of teenagers in one school year, as they can receive more than one vaccine a day (25).

In Australia, in 2014, there were no new genital warts cases in females under 21 years, due to the vaccine implementation (26,27). There has been a decrease in genital warts in age-matched heterosexual men also, ~82%, suggesting herd protection (5).

The early effects after the HPV vaccine program in Australia are: Decrease in the incidence of high-grade cervical abnormalities (associated with type 16 and 18), but no significant decrease in low-grade cervical abnormalities (mostly related to other types of HPV, or with inflammation) (28,29). Recent data suggest a real and measurable effect of Gardasil vaccination on non-targeted HPV types.

Another benefit of vaccination could occur in people already infected with targeted types of HPV (30). There is little information on this topic, but the possibility that the antibodies could break the cycle of reinfection exists, thus reducing the residence time of infection, and also reducing the risk of transmission. Vaccinating the medical staff could have a real impact, as two laser gynecological surgeons with HPV-16 positive oropharyngeal squamous cell carcinoma were reported (31).

A study on the immunogenicity of HPV vaccines in HIV-infected females is ongoing.

The duration of protection after vaccination is not entirely known, but some trials have suggested 8-9 years at the minimum. Seropositive persons produce higher antibodies in response to the HPV vaccine, so subsequent exposure after vaccination could serve as a booster to prolong the protection (9).

Adverse reactions of HPV vaccine, non-serious (5). Syncope, dizziness, nausea, headache, fever, hives.

A study in Melbourne on 26 out of 720 girls who, after receiving HPV vaccine in school, presented with dizziness, syncope and/or neurological symptoms, concluded these symptoms are a psychogenic response to mass vaccination in the school environment (25).

7. Campaigns for raising awareness of HPV

Two population-based surveys on HPV knowledge among women in Australia (before the mass media campaign on HPV vaccination) revealed modest awareness on its determinant role in cervical cancer. Only 51% of women have heard of HPV (half of whom have identified a link between HPV and cervical cancer) (25).

National surveys on HPV perception among Australians have shown that women in the middle adult years have the highest knowledge of HPV, followed by men, while the lowest awareness is among teenagers (25).

Facts revealed by the Australian studies are the 'unknown' link between HPV infection and genital warts, the fact that HPV is sexually transmitted, and that men can also be infected (25). Media campaigns presented the HPV vaccine primarily as a way to prevent cervical cancer, referring to its effects on sexually transmitted diseases (anogenital warts) as a side-note. A notable mention is the minority of parents who were reluctant to vaccinate, arguing that it can promote sexual behavior in teenagers, lacking knowledge on the subject, or being embarrassed to talk about sexually transmitted diseases with their offspring.

Promoting greater understanding in the general public about vaccination can create positive vaccine attitudes and scatter the myths of spurious side effects. By separating the health and education sectors regarding immunization, people miss the opportunity to get informed, ask questions, and understand the limitations of vaccination. Health education must be implemented in young adults, designed in such a way as to be appealing and accessible.

8. Conclusions

An HPV vaccination program is a long-term healthcare initiative with a high return on investment. Vaccinating all early adolescents of both genders against HPV has proven to

be efficient and safe, and to reduce the rate of HPV related cancers and other diseases.

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AP, RCP and MCD designed the review. AB, MEZ and FS performed the literature research and drafted the manuscript. AP, RCP and MCD substantially contributed to the conception of the study, revised and edited the final manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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