

Human papilpma virus

دکتر امیر بهاری
فوق تخصص بیماری های عفونی کودکان
عضو هیات علمی دانشگاه



The **HPV vaccine** is recommended for all girls to prevent cervical cancer later in life.

It can be given in

**1 OR 2
DOSES**

for younger
age groups
(9-14 years)

**2 OR 3
DOSES**

for immunocompromised
individuals, such as
people living with
HIV/AIDS



**GET INFORMED.
GET SCREENED.
GET VACCINATED.**



World Health
Organization

CLINICAL MANIFESTATIONS

- Most human papillomavirus (HPV) infections are subclinical, and 90% spontaneously become undetectable within 2 years.
- persistent HPV infection can cause benign epithelial proliferation (warts) of the skin and mucous membranes as well as cancers of the lower anogenital tract and the oropharynx.
- HPV types can be grouped into cutaneous and mucosal types.
- The cutaneous types cause common skin warts, plantar warts, flat warts, and thread-like (filiform) warts.
- These cutaneous warts are benign.
- Certain mucosal types (referred to as low risk) are associated with warts or papillomas of mucous membranes, including the upper respiratory tract and anogenital, oral, nasal, and conjunctival areas.
- Other mucosal types (referred to as high risk) can cause precancers and cancers, including cervical, anogenital, and oropharyngeal cancers.

- Warts are common **benign lesions**, although they may be associated with significant **clinical problems**.
- Common skin warts are **dome-shaped** with conical projections that give the surface a **rough appearance**.
- Skin warts usually are **painless** and multiple, occurring commonly on the hands and around or under the nails.
- When small dermal vessels become thrombosed, black dots appear in the warts





- Plantar warts on the foot often are larger than warts at other sites and may not project through much of the skin surface.
- They can be painful when walking and are characterized by marked hyperkeratosis, sometimes with black dots.
- Flat warts commonly are found on the face and extremities of children and adolescents.
- Flat warts usually are small, multiple, and flat topped, seldom exhibit papillomatosis, and rarely cause pain.
- Filiform warts occur on the face and neck.

Plantar warts



- Anogenital warts, also called **condylomata acuminata**, are **skin-colored warts** with a **papular, flat, or cauliflower-like** surface that range in size from a few millimeters to several centimeters.
- These warts often occur in groups, and may be found on the penis, urethra, scrotum, vulva, anal or perianal areas and, less commonly, in the vagina or on the cervix.
- Warts usually are **painless**, although they may cause itching, burning, local pain, or bleeding and may have significant psychological impact.

Anogenital warts



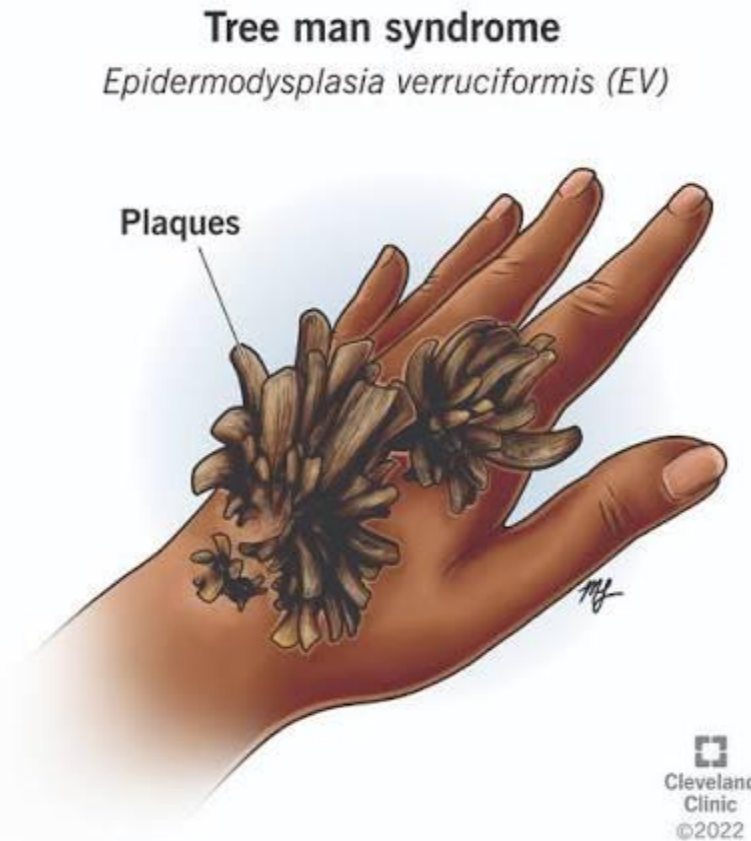
- Invasive cancers attributable to HPV include those of the cervix, vagina, vulva, penis, anus, and oropharynx (back of throat, base of tongue, and tonsils).
- **Cervical cancer** is the most common **HPV-attributable cancer** in the **female** population.
- **Oropharyngeal** cancer is the most common HPV-attributable cancer in the **male** population and the most common HPV-related cancer overall in the United States.
- Anogenital low-grade squamous intraepithelial lesions (LSILs) can result from infection with **low-risk** or **high-risk** HPV types, whereas high-grade squamous intraepithelial lesions (HSILs) result mostly from persistent infection with **high-risk HPV types**.
- In the cervix, HSILs include cervical intraepithelial neoplasia (CIN) grades 2 or 3, and adenocarcinoma in situ (AIS), which are precancerous lesions.
- LSIL and HSIL are lesions detected through routine screening with cytologic testing (**Papanicolaou [Pap]** test); **tissue biopsy** is required to make the diagnosis of **CIN**.

- Recurrent respiratory papillomatosis (RRP) is a rare condition characterized by recurring papillomas in the larynx or other areas of the upper or lower respiratory tract.
- Onset can occur in childhood or adulthood.
- The disease is referred to as juvenile-onset RRP (JORRP) when it occurs **before 12 years** of age and as **adult-onset RRP (AORRP)** when it occurs at an older age.
- JORRP is believed to result most frequently from vertical transmission of HPV at the time of **delivery**.
- JORRP is diagnosed most commonly in children between **2 and 5 years** of age, with manifestations of voice change (eg, hoarseness or abnormal cry), stridor, chronic cough, or respiratory distress.

- Respiratory papillomas can cause respiratory tract obstruction in young children, and repeated surgeries often are needed.
- Most cases of JORRP are caused by HPV 6 or 11.
- AORRP most frequently occurs between 20 and 40 years of age, with causal HPV infections most likely acquired through sexual behavior.
- Most cases of JORRP and AORRP are caused by HPV 6 or 11
- Prevalence of HPV type 6 in JORRP (50%– 70%) and AORRP (~60%) is generally higher than that of HPV 11 (6%–29%).

- **Epidermodysplasia verruciformis** is a rare, inherited disorder believed to be a consequence of a deficiency of **cell-mediated immunity**, resulting in an abnormal susceptibility to certain HPV types and manifesting as **chronic cutaneous lesions** and **skin cancers**.
- Lesions may resemble flat warts or pigmented plaques covering the torso and upper extremities.
- Most appear during the **first decade of life**, but malignant transformation, which occurs in 30% to 60% of affected people, usually is delayed until adulthood.

epidermodysplasia verruciformis



ETIOLOGY:

- HPVs are small, nonenveloped, double-stranded DNA viruses of the Papillomaviridae family, which are grouped into genera, species, and types based on DNA sequence variation.
- More than 200 types are recognized, but specific tissue tropism and disease associations are limited to date to less than 40 types.
- Types 6 and 11 cause anogenital warts (condylomata acuminata), recurrent respiratory papillomatosis, and conjunctival papillomas but rarely are found in cancer.
- High-risk HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) can be detected in almost all cervical precancers and invasive cervical cancers.
- Approximately 50% of cervical cancers worldwide are attributable to HPV type 16;
- 70% are attributable to either type 16 or 18.
- The majority of other HPV-related cancers—anogenital cancers (vulvar, vaginal, penile, anal) and oropharyngeal cancers—also are attributable to HPV type 16.
- Infection with a high-risk HPV type is considered necessary but not sufficient to cause cancer.
- The vast majority of people with an HPV infection will not develop cancer.
- Risk of developing cancer precursors or cancers is greater in people with certain immunocompromising conditions, such as human immunodeficiency virus (HIV) infection, cellular immune deficiencies, organ transplantation, and autoimmune diseases

EPIDEMIOLOGY:

- Virtually all adults will be infected with some type of HPV during their lives.
- Although HPV is common in the general population, specific risk factors include higher lifetime **number of sex partners**, **earlier age at first sex**, and **immunocompromising conditions**, including HIV infection.
- Groups that are **disproportionately affected include transgender women** and **gay**, bisexual, and other men who have sex with men.
- Nongenital hand and foot warts occur commonly among school-aged children.
- Acquisition can occur through casual contact and is facilitated by minor skin trauma.
- **Genital** HPV infections are transmitted by **intimate** contact through sexual intercourse or other close genital contact

- In female individuals, the highest prevalence of infection is in 20- to 24-year-olds.
- Most infections are subclinical and clear spontaneously within 1 or 2 years.
- Cancer is an uncommon outcome of infection that generally requires decades of persistent infection with high-risk HPV types.

- Rarely, HPV infection is **perinatally** transmitted to a child during passage through an infected birth canal at delivery, or postnatally transmitted from nongenital sites.
- When anogenital warts are diagnosed in a child, the possibility of **sexual abuse** must be considered while noting the possibility of vertical transmission to neonates

- the incubation period for symptoms of warts is estimated to range from 3 to 6 months.
- The period from infection to LSIL is likely similar.
- The period from infection to neoplastic changes is usually years to decades

DIAGNOSTIC TESTS

- Most cutaneous and anogenital warts can be diagnosed through clinical inspection.
- Serologic testing for HPV antibodies does not inform clinical decisions and is not commercially available.
- HPV-associated cervical lesions are detected through screening methods .
- Anal, vulvar, vaginal, and penile lesions may be identified using visual inspection, sometimes using magnification;
- in some cases, cytologic screening is used and suspicious lesions are biopsied,
- but to date there is no routine screening recommended for cancers at these sites.
- Many dentists screen for oral cancer but there is no widely implemented screening program

- Identifying the presence of HPV requires detection of **viral nucleic acid (DNA or RNA)** in a cellular sample from the lesion.
- Because high-risk HPV is a **sensitive** biomarker for cervical disease, primary screening with nucleic acid amplification tests (NAATs) for high-risk HPV types is increasingly favored for female individuals starting at age **25 years**.
- The increased **sensitivity** of HPV testing allows longer screening intervals for people with negative test results.
-

TREATMENT:

- There is no FDA-approved treatment for HPV infection.
- Treatment may be directed toward lesions caused by HPV.
- Regression of nongenital and genital warts occurs in approximately **30% of cases within 6 months** and **90% within several years**, even without treatment
- Most methods of treatment of cutaneous warts use **chemical or physical** destruction of the infected epithelium, including **cryotherapy** with liquid nitrogen, **laser or surgical removal of warts**, application of **salicylic** acid products, or application of topical immune-modulating agents.
- Many agents used for treatment of warts have not been tested for safety and efficacy in children, and some are contraindicated in pregnancy.

- Daily treatment with **tretinoin** has been useful for widespread flat warts in children.
- Systemic treatments, including cimetidine, have been used for refractory warts with variable success.
- Treatments for genital warts are characterized as patient-applied or provider administered.
- **Oral warts can be removed through cryotherapy**, electrocautery, or surgical excision.
- Although most forms of therapy are successful for initial removal of warts, treatment may not eradicate HPV infection from the **surrounding** tissue and **recurrences** are common

Cancer precursor lesions that are identified in the cervix (eg, AIS, CIN 2, CIN 3) or elsewhere in the genital tract may require excision or destruction.

Treatment of cervical lesions can cause substantial economic, emotional, and reproductive adverse effects, including higher risk of **preterm birth** and **perinatal mortality**.

- Respiratory papillomatosis is difficult to treat and is best managed by an experienced otolaryngologist.
- Local recurrence is common, and **repeated surgical debulking** procedures are often necessary to relieve airway obstruction, especially in young children because of their **small airway diameter**.
- Extension or dissemination of respiratory papillomas from the larynx into the trachea, bronchi, or lung parenchyma happens rarely but results in increased morbidity and mortality;
- malignant transformation occurs rarely.
- Intralesional interferon, oral indole-3-carbinole, systemic or intralesional bevacizumab, intralesional cidofovir, and HPV vaccination have been used as investigational treatments;
- however, efficacy with any of these is unproven

CONTROL MEASURES AND CARE OF EXPOSED PEOPLE:

- **Sexual abuse** should be considered if anogenital warts are found in a child. When anogenital warts are found in a child who is **prepubertal**,
- Most cancer-causing HPV infections can be prevented by **vaccination**, Delaying **sexual debut** and minimizing the lifetime **number of sex partners** are other modes of reducing risk of HPV infection.
- Consistent and correct use of **latex condom** may reduce the risk of anogenital HPV infection when infected areas are covered or protected by the condom.

The degree and duration of contagiousness in patients with a history of genital HPV infection is unknown

- People with genital warts should **refrain from sex** with **new partners** while warts are present and should inform their **current sex partners**, who also may benefit from a clinical evaluation for anogenital warts or other sexually transmitted infections.

- Although JORRP is believed to be caused by perinatal transmission of HPV types 6 and 11 during passage through the birth canal, this condition has occurred in infants born by cesarean delivery.
- Because the **preventive value of cesarean delivery** is unknown, it should not be performed solely to prevent transmission of HPV to the newborn infant

Cervical Cancer Screening

- Female individuals who have received HPV vaccine should continue to have regular cervical cancer screening.
- HPV vaccines do not provide protection against **all** HPV types associated with development of cervical cancer and do not alter the course of infections existing before vaccination.
- all organizations, recommend that cervical cytologic testing begin **at 21 years** of age for all healthy female individuals, regardless of sexual history (**the American Cancer Society recom-**
- **mends testing begin at 25 years of age**).
- **HIV-infected female** adolescents who have initiated sexual intercourse should have cervical cytologic screening (liquid-based or Pap smear) performed **twice at 6-month** intervals during the first year after diagnosis of HIV infection, and if the results are normal, annually thereafter.
- Sexually active female adolescents who have had an organ transplant or are receiving long-term corticosteroid therapy also should undergo similar cervical cytologic screening.

HPV Vaccines

- Three HPV vaccines have been licensed by the FDA for use in the United States, but only one, Gardasil 9, a 9-valent vaccine (types 6, 11, 16, 18, 31, 33, 45, 52, and 58), licensed in 2014, is currently on the US market.
- A quadrivalent vaccine (4vHPV [types 6, 11, 16, and 18], Gardasil) was licensed in 2006,
- and a bivalent vaccine (2vHPV [types 16 and 18], Cervarix) was licensed in 2009

immunogenicity

- More than 97% of healthy vaccine recipients develop antibodies to HPV vaccine types after vaccination.
- **Antibody titers** are higher in adolescents aged **9 through 15** years compared with those **16 through 26** years of age.
- Antibody titers for all HPV vaccines decrease over time but plateau by 18 to 24 months after vaccination.
- Follow-up studies through 8 and 10 years after 4vHPV and 2vHPV vaccination, respectively, have shown no waning of protection.
- Studies of 9vHPV vaccine have found that antibody titers after 2 doses administered 6 to 12 months apart to 9- through 14-year-olds are similar to 3 doses administered to women 16 through 26 years of age, the age group in which efficacy was demonstrated in clinical trials.

Efficacy

- 4vHPV and 2vHPV have been shown to be highly effective in preventing cervical precancers related to HPV types 16 and 18 in clinical trials among females 15 through 26 years of age.
- 4vHPV has been shown to be highly effective in preventing genital warts related to HPV types 6 and 11 in clinical trials among female and male individuals 16 through 26 years of age
- 4vHPV also has been shown to be highly effective in preventing anal precancers in male individuals 16 through 26 years of age.
- 9vHPV has been shown in a clinical trial among female individuals 16 through 26 years of age to provide 97% protection against the additional 5 HPV types in the 9-valent product (31, 33, 45, 52, and 58) and to produce noninferior immunogenicity for the 4 HPV types in the quadrivalent product (6, 11, 16, and 18).
- Clinical trials of 2vHPV and 4vHPV have been conducted in female individuals older than 26 years; in those without evidence of prior HPV vaccine type infection, efficacy has been demonstrated for a combined endpoint of vaccine type infection and cervical precancers.
- HPV vaccines have not been proven to have a therapeutic effect on existing HPV infection or disease and do not offer protection against progression of infection to disease from HPV acquired before immunization.
- Therefore, HPV vaccines are most effective when administered before exposure to any of the HPV types included in the vaccine.

- Assessment of the full impact of HPV vaccination on **anogenital and oropharyngeal cancers** will take decades, given the natural history of HPV-driven oncogenesis.
- However, studies have already demonstrated significant reductions in HPV-related outcomes since the vaccines were introduced,
 - including declines in vaccine-type HPV prevalence,
 - anogenital warts, JORPP, cervical precancers, and cervical cancers.
- Long-term follow-up studies are being conducted to determine the duration of protection for all HPV vaccines.

Vaccine Recommendations.

- The American Academy of Pediatrics (AAP) and the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention recommend routine HPV vaccination for all adolescents.
- The AAP recommends starting the series between the ages of **9 and 12 years**, at an age the pediatric health care professional deems optimal for acceptance and completion of the vaccination series.
- The ACIP recommends starting the series at age **11 or 12** years and states that vaccination can be administered starting at age 9 years.
-

- Pediatric health care professionals are encouraged to recommend HPV vaccination as they do other routine childhood and adolescent vaccines.
- Research has demonstrated that parents are influenced by effectively delivered **recommendations** and personal testimonials from their child's pediatrician.
- Opportunities to prevent cancers **and deaths are being missed by clinicians who describe HPV vaccine as a sexually transmitted infection vaccine rather than a cancer prevention vaccine** or who fail to inform patients and their parents or guardians that HPV vaccination is routinely recommended.

- Catch-up HPV vaccination is recommended for all people through age 26 years who are not adequately vaccinated.
- Catch-up HPV vaccination is not recommended for all adults 27 years or older.
- Instead, **shared clinical decision-making** regarding HPV vaccination is recommended for some adults 27 through 45 years of age who are not adequately vaccinated

Dosage and Administration

- HPV vaccine is administered in either 2 or 3 doses of 0.5 mL, intramuscularly, preferably in a deltoid muscle.
- For people initiating vaccination before **their 15th birthday**, the recommended schedule is 2 doses of HPV vaccine, with the second dose administered **6 to 12 months after the first dose** (minimum interval 5 months).

(Human Papillomavirus) HPV Vaccine schedule

PACE
HOSPITALS



Age	Doses
9-14 years	2 doses schedule (0 & 6 months)
15-45 years and Immunocompromised individuals of any age	3 doses schedule: • Either 0, 1, 6 months (if bivalent) • Or 0, 2, 6 months (if quadrivalent & nonavalent)

HPV vaccination could only prevent the incoming of any new HPV infections but does nothing in the treatment of any existing HPV infections or HPV related diseases.

- For people initiating vaccination on or after their 15th birthday, the recommended schedule is 3 doses of HPV vaccine.
- In a 3-dose schedule, the second dose should be administered at least 1 to 2 months after the first dose (minimum interval 4 weeks), and the third dose should be administered 6 months after the first dose (minimum interval 5 months after first dose, and 12 weeks after second dose).

People considered adequately vaccinated are those:

- Who initiated vaccination before their 15th birthday and received 2 doses of **any** HPV vaccine (9vHPV, 4vHPV, or 2vHPV) at the recommended dosing schedule
- (0, 6–12 months), or 3 doses of any HPV vaccine at the recommended dosing schedule (0, 1–2, 6 months).
- if the vaccine schedule is interrupted, the vaccine series can be continued with the next recommended dose and does not need to be restarted

- 9vHPV may be used to complete a series started with 4vHPV or 2vHPV
- there is no recommendation regarding additional vaccination with 9vHPV for people who previously completed a 4vHPV or 2vHPV vaccination series.
- Evidence of past HPV exposure or current HPV infection or disease, such as abnormal cytologic test results, cervical lesions, anogenital warts, or a positive HPV DNA test result, are not contraindications to HPV immunization.
- People in the recommended age ranges still should receive HPV vaccine to protect against any HPV types not already acquired.
- HPV vaccines can be co-administered with any live or non-live vaccine indicated at the same visit

Recommendations for Special Populations

- HPV vaccines are not live vaccines.
- For people ages **9 through 26** years with immunocompromising conditions (including primary or secondary immunocompromising conditions that might reduce cell-mediated or humoral immunity, such as B-lymphocyte antibody deficiencies, T-lymphocyte complete or partial defects, HIV infection, malignant neoplasms, transplantation, autoimmune disease, or immunosuppressive therapy), **a 3-dose** schedule of HPV vaccine is recommended regardless of age at initiation.
- Immune response and vaccine efficacy in immunocompromised people might be less than that in immunocompetent people.
- For children with a history of sexual abuse or assault, the HPV vaccination series should be started at **9 years** of age, because they may be at higher risk of repeat abuse or assault.

Vaccine Adverse Events, Precautions, and Contraindications:

- Studies have shown no serious safety concerns.
- In addition, more than 135 million doses of HPV vaccines have been distributed in the United States without evidence for **serious safety concerns**.
- **Injection site discomfort** or **pain, redness**, and **swelling** are the most commonly reported local adverse events.
- Systemic symptoms after HPV vaccine include headache, fever, nausea, dizziness, and fatigue/malaise.
- **Syncope** (fainting) has been reported in adolescents after receipt of **any** vaccination, including HPV vaccine.
- Despite common misinformation disseminated mainly on the internet and through social media, **HPV vaccine has not been associated with ovarian damage, infertility**, or postural orthostatic tachycardia syndrome (POTS).

- HPV vaccines can be administered to people with minor acute illnesses
- **Other considerations include:**
 - Immunization of people with moderate or severe acute illnesses should be deferred until after their condition improves.
 - HPV vaccines are produced in **yeast** and are contraindicated in people with a history of immediate hypersensitivity to any vaccine component, including yeast.
 - HPV vaccines are not recommended for use during **pregnancy** because of limited information about safety.
 - The health care professional should inquire about pregnancy in patients who are known to be sexually active, **but a pregnancy test is not required** before starting the HPV vaccination series.
 - If a vaccine recipient becomes pregnant, subsequent doses should be postponed until the **person is no longer** pregnant.
 - If a dose has been administered inadvertently during pregnancy, no intervention is needed.
 - Data to date show no evidence of adverse effect of any HPV vaccine on outcomes of pregnancy.

- HPV vaccines can be administered to lactating people.
- Vaccine providers, particularly when vaccinating adolescents, should observe patients (with patients seated or lying down) for 15 minutes after vaccination to decrease the risk for injury should they faint and as is recommended for all vaccines.
- If syncope develops, patients should be observed until symptoms resolve

- The goal of HPV vaccination is not simply prevention of HPV infection; it is prevention of **HPV-related cancer**.

- آیا فرد می‌تواند دوباره به همان تیپ HPV مبتلا شود؟

- بله، امکان پذیر است.
- برخلاف برخی ویروس ها (مانند سرخک)، عفونت طبیعی HPV معمولاً ایمنی قوی و پایدار ایجاد نمی کند. بنابراین:
- ممکن است همان تیپ ویروس پس از پاک شدن مجدداً از شریک جنسی آلوده دریافت شود)

Reinfection

- یا ویروس به صورت نهفته (Latent) در بدن باقی بماند و سال ها بعد دوباره فعال شود (Reactivation)،
- به ویژه در افراد دچار نقص ایمنی یا با افزایش سن.
 - بنابراین، ابتلای قبلی تضمین کننده محافظت کامل در برابر همان تیپ نیست.

آیا ابتلا به یک تیپ، در برابر سایر تیپ‌ها ایمنی ایجاد می‌کند؟

- خیر.

- HPV بیش از ۲۰۰ تیپ دارد و پاسخ ایمنی ایجادشده علیه یک تیپ معمولاً اختصاصی همان تیپ است.

- مثلاً:

- ابتلا به HPV-16 فرد را در برابر HPV-18 یا HPV-31 محافظت نمی‌کند. ابتلا به HPV-6 نیز در برابر HPV-11 یا HPV-16 ایمنی ایجاد نمی‌کند.

- به همین دلیل، فرد ممکن است همزمان یا در طول زندگی به چندین تیپ مختلف HPV مبتلا شود

چرا حتی پس از ابتلا، واکسن توصیه می‌شود؟

- این یکی از سوالات شایع بیماران است.
- زیرا:
- واکسن عفونت موجود را درمان نمی‌کند. اما از ابتلا به سایر تیپ‌های موجود در واکسن پیشگیری می‌کند. حتی اگر فرد قبلاً به یک یا دو تیپ آلوده شده باشد، ممکن است هنوز در برابر سایر تیپ‌های پرخطر یا کمخطر محافظت نداشته باشد.
- برای مثال، فردی که قبلاً به HPV-16 مبتلا شده است، با دریافت واکسن ۹ ظرفیتی همچنان می‌تواند در برابر تیپ‌های 18، 31، 33، 45، 52، 58 و همچنین 6 و 11 محافظت شود.

از توجه شما متکرم

