Human papillomavirus vaccines: WHO position paper

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Background

- HPV is the most common viral infection of the reproductive tract

- In women, persistent infection with specific HPV types (most frequently HPV-16 and HPV-18) may lead to precancerous lesions which, if untreated, may progress to cervical cancer.

- Associated with oropharyngeal and anogenital cancers

Epidemiology of HPV infection

HPV prevalence in cervical specimens from women:

- The HPV prevalence worldwide among women is estimated to be 11.7% .

- The highest prevalence was in sub-Saharan Africa (24%), Latin America and the Caribbean (16.1%), eastern Europe (14.2%), and south-eastern Asia (14%).

Epidemiology of HPV infection

- Age-specific HPV prevalence peaked at younger ages (<25 years) with a prevalence of 24.0%, with lower prevalence at middle-ages.

- In some low-income countries in Asia and Africa, HPV prevalence is very similar in women in all age groups.

- HPV types 16 and 18 were the most frequent types worldwide, with HPV-16 the most common type in all regions.

Epidemiology of HPV infection

HPV prevalence in men:

- A systematic review of genital HPV prevalence in men aged >18 years concluded that prevalence peaked at slightly older ages than in women and remained constant or decreased slightly with increasing age.

Epidemiology of HPV infection

HPV prevalence:

- varied from 1% to 84% among low-risk men,
- and from 2% to 93% among high-risk men (sexually transmitted infection [STI] clinic attendees, HIV-positive men, and male partners of women with HPV infection or abnormal cytology).

Epidemiology of HPV infection

- HIV-positive men who have sex with men showed the highest prevalence.

- Anal HPV infections are very common in men who have sex with men.

Epidemiology of HPV infection

A clinical trial:

The prevalence of any HPV type:

- 18.7% at the penis
- 13.1% at the scrotum
- 7.9% at the perineal/perianal region
- and 21.0% at any site

Epidemiology of HPV infection

HPV-associated cervical cancer in women:

- It was estimated that 630 000 new HPV-related cancers occurred in women in 2012, of which 530 000 (84%) were cervical cancer.

- 266 000 deaths worldwide, accounting for 8% of all female cancer deaths that year.

- HPV-16 and HPV-18 together are responsible globally for 71% of cases of cervical cancer. (60.6%: HPV-16 and 10.2%: HPV-18)

Epidemiology of HPV infection

Mortality rates:

- Ranging from <2 per 100 000 women in industrialized countries
- 28 per 100 000 in some developing countries

Epidemiology of HPV infection

- While infection with a high-risk HPV type is the underlying cause of cervical cancer, most women infected with high-risk HPV do not develop cancer.

- Infection persists in only a small percentage of women and only a small percentage of chronic infections progress to pre-cancer, of which even fewer will progress to invasive cancer.

Epidemiology of HPV infection

Other HPV-associated disease in men and women:

- Anogenital HPV infection can result in malignant cancers or benign skin and mucosal tumors, including anogenital warts in men and women. (Types 6 and 11 account for up to 90% of all cases)

- The median time between infection and the development of anogenital warts is 11–12 months in men and 5–6 months in young women.

- HPV is also the cause of a proportion of cancers of the anus, the oropharynx, the vulva and vagina, and of the penis.

Pathogen

- Human papillomaviruses belong to the family *Papillomaviridae*
- Double-stranded DNA genome is enclosed by major and minor structural proteins, L1 and L2 respectively
- Highly tissue-specific and infect both cutaneous and mucosal epithelium.
- 12 high-risk HPV types: (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59)

Disease

- HPV viruses are spread through contact with infected genital skin, mucous membranes, or bodily fluids, and can be transmitted through sexual intercourse including

- Most (70–90%) of HPV infections are asymptomatic and resolve spontaneously within 1–2 years.

- Persistent HPV infection is a necessary cause of cervical cancer.

- Persistent HPV infection is defined by the presence of HPV DNA on repeated clinical biological samples over a period of time, usually 6 months.

- About 5–10% of all infected women develop persistent infection

- Persistent infections may progress towards premalignant lesions, classified histopathologically as cervical intra-epithelial neoplasia (CIN), and to cancer.

- CIN is further classified as: CIN 1: mild dysplasia; CIN 2: moderate to marked dysplasia; and CIN 3: severe dysplasia to carcinoma in situ.

- Most CIN lesions regress spontaneously

- The interval between the acquisition of HPV infection and progression to invasive carcinoma is usually 20 years or longer.

- Predisposing conditions and risk factors:
- HPV type
- immune status
- co-infection with other STIs
- parity and young age at first pregnancy
- tobacco smoking

Disease

- HPV-6 and HPV-11 can also cause a rare condition known as recurrent respiratory papillomatosis (RRP)

- warts form on the larynx or other parts of the respiratory tract with the risk of airway obstruction.

- RRP occurs in 2 forms:

1- Juvenile

2- Adult

Immune response after HPV infection

- The median time from HPV infection to seroconversion is approximately 8–12 months

- HPV infections are restricted to the epithelial layer of the mucosa and do not induce a vigorous immune response.

Immune response after HPV infection

The available data on whether natural infection with HPV induces protection against reinfection are equivocal.

There appears to be a reduced risk of reinfection with the same HPV type but infection does not seem to provide group-specifc or general immune protection from reinfection with other HPV types.

Diagnosis of cervical HPV infection/disease

- Identification test of HPV DNA performed on cervical or vaginal swabs.

- HPV-induced changes in the cervical epithelium can be detected by microscopic examination of exfoliated cells, known as the Papanicolaou (Pap) test.

Treatment

- Although there is no virus-specific treatment for HPV infection, screening and treatment for pre-invasive disease of the cervix is highly successful in preventing progression to cervical cancer.

- Cryotherapy
- Surgical removal of abnormal tissue : loop electrosurgical excision procedure (LEEP), cone biopsy

Vaccines

- Three prophylactic HPV vaccines:

1. The quadrivalent vaccine was first licensed in 2006
2. The bivalent vaccine in 2007
3. The nonavalent vaccine in 2014

- Using recombinant DNA technology, all 3 vaccines are prepared from the purified L1 structural protein
- None of the vaccines contains live biological products or viral DNA

Bivalent HPV vaccine:

- HPV types 16 and 18
- Intramuscular injection
- Available in 1-dose or 2-dose vials or prefilled syringes
- From the age of 9 years
- Prevention of premalignant anogenital lesions affecting the cervix, vulva, vagina and anus, and cervical and anal cancers causally related to specifc HPV types

Bivalent HPV vaccine:

- Age 9–14 years, a 2-dose schedule (0.5 mL at 0 and 5–13 months) is recommended.
- Age ≥15 years, 3 doses (0.5 mL at 0, 1, 6 months)
- The second dose can be given between 1 and 2.5 months after first dose
- And the third dose between 5 and 12 months after the first dose.

- If, at any age, the second vaccine dose is administered before the fifth month after the first dose, the third dose should always be administered.

Quadrivalent HPV vaccine:

- HPV types 6, 11, 16 and 18
- Intramuscular injection
- Available in 1-dose vials or prefilled syringes
- From the age of 9 years
- Prevention of premalignant lesions and cancers affecting the cervix, vulva, vagina and anus caused by high-risk HPV types, and anogenital warts causally related to specific HPV types

Quadrivalent HPV vaccine:

- Age 9–13 years, a 2-dose schedule (0.5 mL at 0 and 6 months).

- If the second vaccine dose is administered earlier than 6 months after the first dose, a third dose should be administered.

Quadrivalent HPV vaccine:

- Alternatively, the vaccine can be administered according to a 3-dose (0.5 mL at 0, 2, 6 months) schedule.

- The second dose should be administered at least 1 month after the first dose and the third dose should be administered at least 3 months after the second dose

Quadrivalent HPV vaccine:

- Age ≥14 years, 3-dose schedule (0.5 mL at 0, 2, 6 months)
- The second dose should be administered at least 1 month after the first dose
- And the third dose should be administered at least 3 months after the second dose.

Nonavalent HPV vaccine:

- HPV types (6, 11, 16, 18, 31, 33, 45, 52 and 58)
- Intramuscular injection
- Available in 1-dose vials or prefilled syringes
- From the age of 9 years
- Prevention of premalignant lesions and cancers affecting the cervix, vulva, vagina and anus caused by high-risk HPV types, and anogenital warts causally related to specifc HPV types

Nonavalent HPV vaccine:

- Aged 9–14 years, a 2-dose schedule (0.5 mL at 0 and 5-13 months)

- If the second vaccine dose is administered earlier than 5 months after the first dose, a third dose should always be administered

Nonavalent HPV vaccine:

- The vaccine can be administered according to a 3-dose schedule (0.5 mL at 0, 2, 6 months).
- The second dose should be administered at least 1 month after the first dose
- and the third dose should be administered at leas 3 months after the second dose.

Nonavalent HPV vaccine:

- For individuals 15 years of age and older: a 3-dose schedule (0.5 mL at 0, 2, 6 months).

Cross_protection:

the bivalent and quadrivalent HPV vaccines provide some level of cross-protection against high-risk HPV types other than16 and18,in particular for types31,33 and 45.

The extent of any cross-protection against non-vaccine HPV types conferred by the nonavalent vaccine is not yet known

Duration of protection

For the quadrivalent vaccine using a 3-dose schedule, no breakthrough cases of cervical/genital disease related to HPV types 6, 11, 16, and 18 were observed among vaccinated during 10 years of follow-up.

For the bivalent vaccine, immunogenicity and efficacy of a 3-dose schedule against infection and cervical lesions associated with HPV-16 and HPV-18 have been demonstrated up to 8.4 and 9.4 years respectively

For the nonavalent vaccine, efficacy of a 3-dose schedule against infection and cervical/vulvar/vaginal lesions has been demonstrated up to 5.6 years post vaccination.

Vaccine safety

Local reactions:

Pain is more commonly reported at the time of injection than in the hours and days following Vaccination.

>1000 women aged 18–45,local reactions included pain,redness and swelling occurred more frequently with bivalent than quadrivalent vaccine.

Systemic reactions:

Adverse events following HPV vaccination are generally non-serious and of short duration.

Mild systemic adverse events possibly related to vaccination included headache, dizziness, myalgia,arthralgia, and gastrointestinal symptoms (nausea, vomiting, abdominal pain).

Although case reports have identified a range of new onset chronic conditions occurring post-vaccination, including autoimmune diseases,a well-conducted population-based study showed no association between HPV vaccine and such conditions.

- The vaccines can be used in persons who are immunocompromised or HIV-infected.

- The safety of the HPV vaccines in children younger than 9 years has not been established.

- In the absence of well-controlled studies in pregnant women,as a precautionary measure vaccination with HPV vaccine is not recommended in pregnancy.

- Breastfeeding is not a contraindication for HPV vaccination.

Cost- effectiveness

Vaccination of multiple cohorts of girls in the age range 9-14 is cost-effective ,even when including only the rate of cervical cancer as an outcome.

WHO position:

WHO recommended that HPV vaccines should be included in national immunization programmes.

Prevention of cervical cancer is best achieved through the immunization of girls, prior to sexual debut.

Primary target groups

the WHO-recommended primary target population for HPV vaccination is girls aged 9–14 years, prior to becoming sexually active.

Achieving high vaccination coverage in girls (>80%) reduces the risk of HPV infection for boys

secondary target groups

Vaccination of secondary target populations, females aged ≥15 years or males,is recommended only if this is feasible, cost-effective, and does not divert resources from vaccination of the primary target population or from effective cervical cancer screening programmes.

Vaccination schedule:

The current evidence supports the recommendation for a 2-dose schedule with

an interval no greater than 12–15 months between the first and second dose in aged 9–14.

This schedule also has cost saving and programmatic advantages that may facilitate high coverage

A 3-dose schedule (0, 1–2, 6 months) should be used for all vaccinations initiated ≥15 years of age, including in those younger than 15 years known to be immunocompromised and/or HIV-infected .

Travellers and health-care workers:

This group are not at special risk of contracting HPV infection and they should follow the vaccine recommendations for the general population.

Research priorities

Further research is needed to generate data on the longer-term clinical effectiveness and the duration of protection, particularly for the nonavalent HPV vaccine, after 2-dose and 3-dose schedules.

Multicentre studies in low-income countries among healthy young women and among special populations (HIV-infected ,malnourished,those exposed to endemic malaria infection) would provide additional evidence of the impact of the vaccine in those populations.

Further evidence is required on the effectiveness and cost-effectiveness of a 1-dose schedule, and on the immunogenicity and safety of administering HPV vaccine to children less than 9 years of age.

Thanks for your attention.