7 Candidate recommendations for use of HPV vaccines in national immunization programmes, for consideration by the WHO Immunization Strategic Advisory Group of Experts

The recommendations concern the two prophylactic HPV 16/18\(^1\) vaccines (i.e. bivalent and quadrivalent) that are licensed and marketed in several regions. The bivalent vaccine, Cervarix\(^\circ\), is indicated for prevention of precancers and cancer of the cervix caused by HPV 16 and 18. The quadrivalent vaccine, Gardasil\(^\circ\) or Silgard\(^\circ\), is indicated for prevention of precancers and cancer of the cervix caused by HPV 16 and 18, and anogenital warts caused by HPV 6 and 11. Hereafter, the phrases “HPV 16/18 vaccines” and “HPV 16/18 vaccination” indicate vaccination with either vaccine because both vaccines contain antigens for HPV 16 and HPV 18.

7.1 Overall recommendation

Routine HPV 16/18 vaccination should be included in immunization programmes of all countries where prevention of cervical cancer and other HPV-related diseases is a public health priority, vaccine introduction is programmatically feasible and sustainable financing can be secured. If cost-effective analyses may guide a country’s health decisions, countries should consider the cost-effectiveness of possible vaccination strategies in their country or region, when feasible.

7.2 Detailed recommendations

7.2.1 Target populations (Rationale: Sec 1.2, 1.3, 1.4, 3.1, 4.2, 5.2, Annex 2)

The primary target population should be young adolescent girls. Because vaccination is most efficacious in girls who have not become sexually active and are naive to HPV 16/18, programmes should determine the primary target age group based on data on the age of sexual initiation and/or the feasibility of reaching young adolescent girls through schools or health-care facilities, or through community-based methods. In most countries, this group would include girls within the age range of 10–13 years.

Catch-up strategies for older adolescent females and young women are recommended to supplement routine vaccination of young adolescent females. However, such programmes are only recommended if they are feasible, affordable and cost-effective, and do not divert resources from vaccination of the primary target population or from existing cervical cancer screening programmes that have been demonstrated to be effective in reducing cervical cancer incidence or mortality at a population level.

\(^1\) The phrases “HPV 16/18 vaccination” and “HPV 16/18 vaccines” refer to either the bivalent vaccine or the quadrivalent vaccine, because both contain antigens for HPV 16 and HPV 18.
Vaccinating males is not recommended because data on the efficacy against persistent HPV 16/18 infections, HPV 16/18-related precancers or cancers, or anogenital warts are not yet available for either vaccine. Most models also indicate that vaccinating males is not cost effective, except when coverage among young adolescent females is low.

7.2.2 Special populations (Rationale: Sections 3.1, 3.2 and Annex 2)

HPV 16/18 vaccines are not recommended for pregnant females. HPV 16/18 vaccines have not been causally associated with adverse pregnancy, fetal, or neonatal outcomes, but data on safety among females who were inadvertently vaccinated during pregnancy are limited. Selecting target ages for HPV vaccination that precede the onset of sexual activity will reduce the risk of inadvertently vaccinating pregnant females.

The quadrivalent HPV vaccine may be administered to lactating females, because there are data demonstrating safety in lactating females. The bivalent vaccine is not recommended for lactating females because safety data in lactating females are currently not available.

Data on the safety and immunogenicity of HPV vaccines in individuals who are immunocompromised due to medications or diseases (e.g. HIV infection) are currently very limited. However, more data will be available after completion of ongoing studies of safety and efficacy of both vaccines in immunocompromised HIV-infected adolescents and adults in several continents. Selecting target ages for HPV vaccination that precede the onset of sexual activity minimizes the risk of administering HPV vaccines to human immunodeficiency virus (HIV)-infected individuals. HPV vaccination of young adolescent females with unknown HIV infection status who have not initiated sexual activity is expected to be beneficial; it should not be deferred because of concerns about potential adverse events, because the potential benefits of vaccination outweigh the potential risks. However, vaccine immunogenicity and efficacy in HIV-infected individuals may be less than that in HIV-uninfected individuals. HIV testing before routine HPV vaccination is not advised because it lacks clear benefit and would be resource intensive.

**Alternative wording of above paragraph**

Data on the safety and immunogenicity of HPV vaccines in individuals who are immunocompromised due to medications or diseases (e.g. HIV infection) are currently very limited. However, more data will be available after completion of ongoing studies of safety and efficacy of both vaccines in immunocompromised HIV-infected adolescents and adults in several continents. The introduction of HPV immunization to girls with unknown HIV serostatus who have not begun sexual activity is expected to be beneficial; it should not be deferred because of concerns about potential adverse events, because the potential benefits of vaccination outweigh the potential risks. However, vaccine immunogenicity and efficacy in HIV-infected individuals may be less than that in HIV-uninfected individuals. HIV testing before routine HPV vaccination is not advised because it lacks clear benefit and would be resource intensive.
7.2.3 Vaccine administration

Both vaccines should be administered according to manufacturer specifications, schedules and advice on interrupted schedules; that is, three doses over 6 months (0, 2 and 6 months for the quadrivalent vaccine; and at 0, 1, and 6 months for the bivalent vaccine).

Clinical efficacy trials for both vaccines demonstrate that protection lasts for at least 5 years. The need for a booster vaccination has not been established.

Vaccinees should receive all three doses with the same product, because the two products have different characteristics, components and indications. Also, data are lacking on the safety, immunogenicity or efficacy of the two vaccines when used interchangeably.

Studies show that the following combinations of co-administration are safe and do not appreciably impair the immune response to any antigen: the quadrivalent vaccine with a recombinant hepatitis B vaccine; the quadrivalent vaccine with a diphtheria/tetanus/pertussis/poliomyelitis vaccine, and the bivalent vaccine with a diphtheria/tetanus/pertussis/inactivated poliomyelitis vaccine. Both HPV vaccines are non-infectious and can be co-administered with other non-live vaccines. Administering all vaccines together at a single visit increases the likelihood that vaccines will be received on schedule. Guidance should be updated as results of ongoing co-administration studies become available.

**Alternative wording of above paragraph**

Both HPV vaccines are non-infectious. Studies show that the following combinations of co-administration are safe and do not appreciably impair the immune response to any antigen: the quadrivalent vaccine with a recombinant hepatitis B vaccine; the quadrivalent vaccine with a diphtheria/tetanus/pertussis/poliomyelitis vaccine; and the bivalent vaccine with a diphtheria/tetanus/pertussis/inactivated poliomyelitis vaccine. HPV vaccines should only be administered with other vaccines at the same visit if studies have shown that co-administration is safe and does not appreciably impair the immune response to antigens of either vaccine. Administering all vaccines together at a single visit increases the likelihood that vaccines will be received on schedule. Guidance should be updated as results of ongoing co-administration studies become available.

7.2.4 Vaccine product choice (Rationale: Sections 1, 2, 3, 4.2, 5.5, Annex 2)

All manufacturers of HPV vaccines that supply United Nations (UN) procurement agencies and are subject to WHO prequalification should comply with WHO requirements for production, quality control and tender specification.

In settings where both vaccines are approved and marketed, decisions about use of specific and sometimes unique vaccine products should consider:

- approved indications for disease prevention (i.e. HPV 16/18-related cervical precancers and cancer, and HPV 6/11-related anogenital warts) and target populations (e.g. young adolescent girls, older adolescent girls, women and males)
- the extent and quality of data that is available to decision makers concerning vaccine safety, immunogenicity, efficacy, reactogenicity and safety in special populations that may be eligible for vaccination (e.g. females of reproductive age, lactating females and HIV-infected females), duration of HPV 16/18 antibody and clinical protection, and efficacy against cervical disease due to HPV types closely related to HPV 16/18. The extent and quality of data in the public domain on the two vaccines differs.
• unique product characteristics (e.g. price, supply characteristics and cold-chain requirements related to package volume).

7.2.5 Vaccine delivery strategies (Rationale: Section 5.2 and Annex 2)

Several vaccine delivery strategies are possible, including school-based programmes, pulsed delivery through child health days, vaccination days, periodic campaigns, routine provision through health facilities, or combination strategies. Countries should use delivery methods that are compatible with delivery infrastructure and cold-chain capacity; are affordable, cost-effective and sustainable; and achieve the highest coverage. Priority should be given to delivery strategies that ensure inclusion of females at highest risk of cervical cancer (i.e. those who later in life may have limited access to screening).

7.2.6 Integration of vaccination with other interventions (Rationale: Sec 5.1, 5.2 Annex2)

Whenever possible, HPV 16/18 vaccines should be introduced as part of a coordinated strategy to prevent cervical cancer and other HPV-related diseases. Such a strategy should include education about how to reduce behaviours that increase risk of these diseases, cervical cancer screening, and diagnosis and treatment of precancerous lesions and cancer. HPV vaccine introduction should not undermine or divert funding from existing programmes that have been proven to reduce HPV-related disease at a population level.

HPV vaccination is a primary prevention tool; it does not eliminate the need for screening, which (if available) is a secondary prevention tool. Whenever possible, vaccinated females should be screened later in life to prevent cancer caused by HPV types other than 16 and 18, as these other types may cause up to 30% of cervical cancer cases.

7.2.7 Monitoring HPV vaccination programmes (Rationale: Section 5.6, Annex 2)

After large-scale introduction of HPV vaccine, all countries should measure coverage by age and district, preferably through routine immunization monitoring systems. As with the introduction of any new vaccine, countries should conduct surveillance to identify possible, rare unexpected adverse events through existing passive reporting systems or new sentinel studies, or should track the experience of other countries using these methods. Whenever possible, countries should monitor the impact of HPV vaccination on the prevalence of vaccine-related HPV types, the incidence of cervical abnormalities and high-grade precancerous lesions, and the incidence and mortality of invasive cancer. Programmes using the quadrivalent vaccine should also monitor the impact of vaccination on anogenital wart incidence, where feasible.

7.2.8 Patient, parent and community education (Rationale: Sections 5.2, 5.4. Annex 2)

It is recommended to use educational messages and, if necessary, informed consent methods, that are tailored to the local cultural context and information needs of different audiences — vaccination candidates, parents or guardians of vaccination candidates, educators, community leaders and health-care providers.

Educational messages should stress that HPV vaccines are intended to prevent cancer; they are not therapeutic or curative; are most effective when given before onset of sexual activity; require three doses for full protection; are not intended for pregnant females; and will not prevent HIV, other sexually transmitted infections or pregnancy. Messages should also stress that vaccinees should seek cervical cancer screening later in life, if it is available. Programmes using the quadrivalent vaccine may note benefits related to wart prevention.