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INVITED ARTICLE

The AOFOG recommendations on human papillomavirus vaccination in the Asia-Pacific region

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Abstract

Cervical cancer remains a disease burden in Asia. The Asia and Oceania Federation of Obstetrics and Gynecology envisages a need to produce a set of recommendations on the implementation of human papilloma virus vaccination program for both lower-middle-income countries (LMICs) and high-income countries (HICs), with an attempt to harmonize the practices yet allow flexibility to cater for different cultures, religions, needs and background of individual countries/cities. International guidelines and literature were sought, and recommendations were made in seven selected areas, including (i) the target groups for vaccination, (ii) the doses of vaccination including the use of single-dose vaccination, (iii) the types of vaccines, (iv) suggestions for special populations including those with previous HPV infection, human immunodeficiency virus carriers, and lesbian, gay, bisexual, transgender, questioning/queer group, (v) interchangeability and the need of revaccination/booster, (vi) novel technologies and vaccines, and (vii) public education.

KEYWORDS
cancer of the cervix, HPV vaccine, single-dose

INTRODUCTION

Cervical cancer was the fourth most common female cancer in the world.[1] A total of 662 301 new patients were diagnosed in 2022, among which 60% were in Asia.[1] It still ranked the top in some Asian countries like Myanmar and Nepal. HPV vaccination is a primary preventive tool against cervical cancer. Robust data had already shown that HPV vaccines had 90–100% efficacy against HPV-16/18-related cervical, vaginal, and vulval high-grade squamous intraepithelial lesion (HSIL), and adenocarcinoma *in situ*.[2–7] The Asia and Oceania Federation of Obstetrics and Gynecology (AOFOG) previously conducted a survey study involving 10 different countries/areas from lower-middle-income countries (LMICs) to high-income countries (HICs), and it demonstrated a vast heterogeneity in the implementation of HPV prevention programs.[8] For example, HPV vaccines were not funded by governments in certain LMICs like Nepal and China. Even in countries with national HPV vaccination programs, the types of vaccines, the target groups, and the coverage rates varied. In a recent report on cervical cancer indicators in 21 Asian National Cancer Centers Alliance member countries, 11 (52%) countries had introduced HPV vaccination as part of their national vaccination program or school health program.[9] There were only three (14%) countries, including Bhutan, Brunei, and Singapore, had reported first-dose national vaccination coverage of above 90% for girls by 15 years of age.

The World Health Organization (WHO) initiated a global coalition to eliminate cervical cancer in May 2018, aiming to reduce the incidence of cervical cancer to below four per 100, 000 women by the 90–70–90 strategy, that is, to vaccinate 90% of girls by 15-years-old, to screen 70% of women by a high-performance test by 35-years-old and again by 45-years-old, and to treat and manage 90% of women with pre-cancerous and cancerous lesions, respectively, by 2030.[10] Following the WHO global campaign, the AOFOG Manila Declaration was issued on November 19, 2019.[11] Furthermore, the AOFOG Cervical Cancer Elimination Working Group was formed in 2022, with the aim of advancing education and facilitating the exchange of knowledge regarding cervical cancer prevention through webinars and practical workshops.

Asia-Pacific Region is a continent full of diversity with different ethnic groups, different languages, different cultures and religions. Among the 51 countries, there are about 15 HICs, at least 24 LMICs, and 2 lower-income countries. Currently, there is no guideline on HPV vaccination that can cover the needs of the whole Asia-Pacific Region universally. However, the AOFOG envisages that there is still a need to establish some standards to help the harmonization in the care related to HPV vaccination in this region.

METHODS

Guidelines from international organizations, such as the WHO and the US Centers for Disease Control and Prevention (CDC), as well as different national guidelines in Asia-Pacific Region, where available in the literature, were reviewed. Some key areas were identified, and two sets of recommendations were developed, one as a minimum standard for less-resourced areas, and another one as a preferred standard to better-resourced areas. The principles of these recommendations are as follows:

(1) These should be simple yet clear.

(2) These should be evidence-based yet some flexibility should be allowed.

(3) The recommendations should cater for the needs and economics of different countries.

(4) Different cultures and regions should be respected.

The recommendations were developed by representative members of the Council, the Oncology Committee, and the Cervical Cancer Elimination Working Group of the AOFOG, with at least three from LMICs, upper-middle-income countries and HICs, respectively, classified according to the World Bank Group database.[12]

RECOMMENDATIONS

Target group

a. *Minimum standard*: *Girls aged 9–14 years*

In the WHO Cervical Cancer Elimination Initiative, at least 90% of girls aged 9–14 years should be vaccinated.[10] Therefore, the minimum standard that each country should adopt is to vaccinate this group of young girls.

b. *Preferred standard*: *Females and males aged 9–26 years and considering vaccination up to 45 years*

Multiple studies showed that HPV vaccines were effective against high-grade cervical, vulvar, or vaginal HPV-related diseases in young women at 16–26 years.[6,13–15] For example, the efficacy of the nonavalent vaccine against diseases related to the vaccine HPV types was 100% (95% confidence interval (CI), 70.4–100%) in women aged 16–26.[6] In addition, the efficacy of HPV vaccines against HPV-6/11/16/18 was close to 90% in patients aged 26–45 years who were naïve to these HPV subtypes.[16,17] The US Advisory Committee on Immunization Practices acknowledged that individuals between 27 and 45 years who are not sufficiently vaccinated may face a risk of new HPV infection so they may still benefit from vaccination.[18] Hence, if resources are allowed, the AOFOG advises that catch-up vaccination should be provided to women aged 15–26 years, and

women below 45 years should also be considered for HPV vaccination.

HPV infection was associated with more than 90% of anal cancers, 70% of oropharyngeal cancers, and 50% of anal cancers.[19–22] Besides, the prevalence of HPV-positive oropharyngeal cancers rose by 225% (95% CI, 208%–242%) at the population level between 1988 and 2004, from 0.8 per 100 000 to 2.6 per 100 000 individuals.[23] There are also no effective screening tests and treatments for pre-invasive lesions in HPV-related diseases in men. The efficacy of HPV vaccines against HPV-6/11/16/18 lesions was 90.4% (95% CI, 69.2–98.1) in the per-protocol group and 91.8% (95% CI, 69.4–98.6) after long-term follow-up. Based on these data, the AOFOG recommends HPV vaccination for males at 9–26 years if resources allow.

Schedules of vaccination

a. *Minimum standard*: *One dose for adolescents aged 9–20 years, and two doses for women older than 21*

There were studies showing that two-dose schedule had similar immunogenicity and efficacy to the conventional three-dose regimen in young females.[24–26] Hence, in 2014, the WHO recommended the two-dose schedule with an at least 6-month interval for girls younger than 15-years-old.[27] Subsequently, posthoc analysis of the Costa Rica HPV Vaccine Trial showed that the vaccine efficacy (VE) against HPV 16 or 18 was similar among women aged 18–25 years receiving three-dose (80.2%; 95% CI, 70.7%–87.0%), two-dose (83.8%; 95% CI, 19.5%–99.2%), and single-dose (82.1%; 95% CI, 40.2%–97.0%).[28] Similarly, there was no decline in the HPV 16 or 18 antibody titers between years 4 and 11 among women with different doses of vaccines. Basu et al. subsequently demonstrated that girls aged 10–18 years receiving one dose of quadrivalent vaccine (95.4%; 95% CI, 85.0%–99.9%) had similar VE compared to those receiving two doses (93.1%; 95% CI, 77.3%–99.8%) and three doses (93.3%; 95% CI, 77.5%–99.7%) in a prospective cohort study from a suspended randomized trial.[29] And the protective effect could last for at least 10 years. In a modeling study in India, it was estimated that single-dose vaccination could prevent at least 21% more cancer cases per dose compared to two-dose vaccination because single-dose regimen can free up resources and provide catch-up vaccination for females aged 11–20 years.[30]

The cost of the vaccine is a major obstacle to the uptake of the vaccines.[8] Single-dose vaccination could potentially improve the cost-effectiveness and compliance rate. Together with the above evidence of vaccination, the WHO Strategic Advisory Group of Experts on Immunization recommended in April 2022 that one-dose or two-dose for the primary target group, that is, girls aged 9–14 years, as well as other females aged 15–20 years, while those at 21 years or above should have two-dose regimen with a 6-month interval.[31]

b. *Preferred standard*: *One or two doses for adolescents aged 9–20 years, and two doses for women older than 21*

Although the Costa Rica HPV Vaccine Trial showed no difference in the VE and antibody levels against HPV-16/18 regardless of the number of doses of HPV vaccine, the antibody level of those receiving one dose was significantly lower when compared to those receiving the two and three doses.[28] Besides, one systematic review found moderate to severe bias among 35 studies that evaluated the number of doses of HPV vaccines.[32] Although it appeared that the estimated effectiveness was highest with three doses, those studies with serious bias tended to show lower effectiveness with fewer doses. While the Australian Government is implementing single-dose vaccination for immunocompetent people at 9–25 years,[33] the US Centers for CDC and the ACIP did not support the routine use of single-dose HPV vaccination at the moment.[34] The European Society of Gynecological Oncology (ESGO) stated that single-dose vaccination was better than no vaccination.[35] Similar to the ESGO, the AOFOG agrees that caution should be taken when interpreting the current data regarding single-dose vaccination, and the decision on a single-dose regimen should depend on the resources and infrastructure of individual countries.

Currently, there are several prospective trials evaluating the efficacy of single-dose HPV vaccination (Table 1). Preliminary results of the KEN SHE trial showed that females at 15–20 years had adequate protection against HPV infection after a single dose of bivalent or nonvalent vaccine at 18-month follow-up.[36] The DoRIS also demonstrated similar HPV-16/18 seroconversion rates between single dose and 2–3 doses of bivalent and nonavalent vaccines at 24 months in girls of 9–14 years.[37]

Type of vaccines

a. *Minimum standard*: *Bivalent or quadrivalent HPV vaccines*

Recently, there were a few new vaccines (Table 2).[38] One of them was a quadrivalent vaccine, Cervavac®, produced by the Serum Institute of India and the Indian Government. It was approved for females and males aged 9–26 years in Sep 2022 at price of only five euro each dose.[39] Another was a bivalent vaccine, Cecolin®, produced in China (Xiamen Innovax Biotech Co, Ltd, Xiamen, China).[40] The GAVI has supported the introduction of HPV vaccine into national immunization programs in 38 countries by end of 2023, with either bivalent (Ceravix® or Cecolin®) or quadrivalent (Gardasil®).[41]

TABLE 1 Current studies comparing different doses of HPV vaccines.

Study titles	Clinical trial numbers	Study designs	Vaccines	Comparison arms	Sample sizes	Ages	Primary outcomes	Countries
ESCUDDO	NCT03180034	Randomized double-blind	Cervarix and Gardasil9	1 versus 2 cycles	28 000	12–21	Incidence of persistent HPV 6 and/or HPV-18 cervical infections	Costa Rica
DoRIS[37]	NCT02834637	Randomized open-label	Cervarix and Gardasil9	1 versus 2 versus 3 cycles	930	9–14	Proportion with HPV 16/18-specific seropositivity	Tanzania
HANDS	NCT03832049	Randomized, open-label	Gardasil9	1 versus 2 versus 3 cycles	1720	4–26	Antibody levels and incidence of adverse events	Gambia
KEN SHE[38]	NCT03675256	Randomized double-blind	Cervarix and Gardasil9	1 versus 2 versus 3 cycles	2275	15–20	Incidence of persistent HPV 16/18/21/33/45/52/58 and duration of response	Kenya
PRIMAVERA	NCT03728881	Non-randomized, open-label	Cervarix × 1 cycle versus Gardasil × 3 cycles		1240	9–14/18–25	HPV 16/18 antibody levels	Costa Rica
PRISMA	NCT05237947	Randomized double-blind	Cervarix and Gardasil9	1 cycle	5000	18–30	Incidence of persistent HPV infection	Costa Rica

TABLE 2 Different approved HPV vaccines.

Vaccine brand names	Targeted HPV types	Manufacturers	License dates
Gardasil®	HPV-6, HPV-11, HPV-16, HPV-18	Merck & Co.	2006
Cervarix®	HPV-16, HPV-18	GlaxoSmithKline	2007
Gardasil 9®	HPV-6, HPV-11, HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52, HPV-58	Merck & Co.	2014
Cecolin®	HPV-16, HPV-18	Xiamen Innovax Biotechnology	2020
Walvax recombinant HPV vaccine	HPV-16, HPV-18	Shanghai Zerun Biotechnology	2022
CERVAVAC®	HPV-6, HPV-11, HPV-16, HPV-18	Serum Institute of India	2022

The AOFOG recommends the use of bivalent or quadrivalent vaccines, including those new vaccines that have been adequately evaluated in clinical trials, in countries where nonavalent vaccine is not available.

b. *Preferred standard*: *Nonavalent HPV vaccine*

There has been robust evidence proving the efficacy of nonavalent HPV vaccines against HPV-6, 11, 16, and 18 infection and HPV-16/18-related high-grade cervical, vulvar, or vaginal diseases in females at 16–26 years.[6] Compared to quadrivalent vaccines, the VE of nonavalent vaccine against high-grade cervical, vulvar, or vaginal diseases related to HPV-31, 33, 45, 52 and 58 in the pre-specified per-protocol population was 96.7% (95% CI, 80.9%–99.8%), and VE against persistent infection related to these HPV subtypes lasting for 6 months or more was 96.0% (95% CI 94.4%–97.2%).[6] The antibody response In girls and boys aged 9–15 was not inferior to that in young women aged 16–25.[42,43] With the widened protection against other high-risk HPV subtypes beyond HPV-16 and 18, and no additional serious adverse events when comparing the bivalent and quadrivalent vaccines, the AOFOG suggests the use of nonavalent vaccines where resources are available.

Special populations

i. *Women with previous HPV-related diseases with/without treatment*

a. *Minimum standard*: *Bivalent or quadrivalent HPV vaccines*

It had been shown women who were seropositive for one or more types of HPV-6/11/16/18 had reduced risk of reinfection or reactivation of diseases with these HPV

types after receiving quadrivalent vaccine compared to those without vaccination.[44] And for those who have previous excision surgery for cervical HSIL, quadrivalent vaccine could reduce 46% of HPV-related diseases and 65% of cervical HSIL.[45] In a recent systematic review that compared women with and without HPV vaccination who had local surgery for genital preinvasive lesions, HPV vaccination could reduce the risk of recurrence of CIN2+ (risk ratio (RR) 0.43; 95% CI, 0.30–0.60%; $I^2 = 58$), in particular to HPV-16/18 (RR 0.26; 95% CI 0.16–0.43; $I^2 = 0\%$), as well as the risk of recurrence of CIN3 (RR 0.28; 95% CI, 0.01%–6.37%; $I^2 = 71\%$).[46] However, the studies were heterogeneous and the results could be biased. The benefits against the recurrence of persistent HPV infection, genital wart, vulvar/vaginal/anal intraepithelial neoplasia were not certain.

b. *Preferred standard*: *Could be considered for HPV vaccines after counseling*

Due to the inadequacy of the current evidence, there is no strong guideline or recommendation on vaccinating women with previous HPV infection with/without treatment. But if these women request to receive HPV vaccination and resources allow, the AOFOG advises the physicians to consider it after thorough counseling.

ii. *Human immunodeficiency virus (HIV) carriers*

a. *Minimum standard*: *Two doses of HPV vaccines*

Immunocompromised condition like HIV infection is a well-known factor for HPV infection and its related cancer. At the same time, there was also a certain about the immunogenicity of HPV vaccination due to a potentially weakened immune system. The WHO recommended that immunocompromised women should have at least two doses of HPV vaccines if three doses are not feasible.[47]

b. *Preferred standard*: *Three doses of HPV vaccines*

The Australian Government recommended three doses of HPV vaccines for immunocompromised people except those with hyposplenia or asplenia.[33] A meta-analysis of 18 studies showed that by 28 weeks after three doses of bivalent, quadrivalent, and nonavalent vaccines in patients living with HIV, the pooled proportion of seropositivity was 0.94–1.00 for either HPV-16 or HPV-18, and the seropositivity lasted for at least 2–4 years despite a decline over time and the benefit appeared to be less robust for HPV-18.[48] However, there was a lack of data on the clinical benefit and efficacy against HPV infection and its related disease. However, as this group of patients is prone to develop HPV-related preinvasive and invasive diseases, the AOFOG recommended three doses of HPV vaccines if there is no restriction on resources.

iii. *Lesbian, gay, bisexual, transgender, questioning/queer (LGBTQ)*

a. *Minimum standard*: *Two doses of HPV vaccines*
b. *Preferred standard*: *Three doses of HPV vaccines*

It had been estimated that more than 50% of HIV-negative gay and bisexual men (GBM) had anogenital HPV infection, and GBM and men who have sex with men (MSM) might have a 17-time higher risk of developing anal cancer compared to heterosexual men.[49] In a study in the United States, the vaccination rates were low among LGBTQ, ranging from 9.8% in cisgender men to 39.8% in bisexual individuals.[50] There was also a mistaken belief that HPV infection was low in lesbians and the HPV vaccination rate was low.[51,52]

Indeed, the importance of HPV vaccination has been overlooked to a certain extent in this group of individuals. In the United Kingdom, HPV vaccination program for MSM aged 15 years or above was just launched on April 18, where eligible MSM is given three doses of the quadrivalent vaccine (Gardasil®) within 1 year.[53] In Canada, males aged 9–26 and GBM older than 27 years were recommended to receive HPV vaccination.[54] There is no solid guideline on the application of HPV vaccination in LGBTQ. But since most of these individuals are 15-years-old or above, and substantial work is still required in public education, the AOFOG recommends at least two doses of HPV vaccines, and preferably three doses of at least quadrivalent vaccine if resources are available, for this group of individuals.

Inter-changeability and revaccination

a. *Minimum and preferred standards: It is allowed to complete the vaccination with nonavalent HPV vaccine if it is initiated with bivalent or quadrivalent vaccine, but routine booster and/or revaccination after completion of vaccination is not necessary*.

The American College of Obstetricians and Gynecologists (ACOG) suggested that those who have commenced bivalent or quadrivalent HPV vaccines could complete the vaccination with the recommended doses and appropriate minimum interval using nonavalent vaccine.[55] However, for those who have completed bivalent or quadrivalent vaccine, booster and/or routine revaccination with nonavalent vaccine is not necessary, as there is no obvious extra benefit. The Australian Government holds a similar suggestion, though there is no restriction if anyone who wishes to have protection against the additional HPV subtypes.[33]

TABLE 3 AOFOG recommendations on HPV vaccination in Asia-Pacific Region.

Areas to be addressed	Standard (minimum)	Standard (preferred)
1. Target group	Girls aged 9–14 years	Females and males 9–26 years, and considering vaccination up to 45 years
2. Doses of vaccines	9–14: 1 dose 15–20: 1 dose > = 21: 2 doses Not routine after 26 years old	9–14: 1 or 2 dose(s) 15–20: 1 or 2 dose(s) > = 21: 2 doses
3. Types of vaccines	Bivalent/ quadrivalent (must undergo Phase 3 trials)	Nonavalent
4. Special populations		
i. Those with previous HPV-related diseases with/without treatment	Not mandatory for vaccination	Allowed for vaccination upon thorough counseling
ii. HIV patients	2 doses	3 doses
iii. LGBTA	2 doses	3 doses
5. Inter-changeability and revaccination / booster	Cross-over from 2vHPV or 4vHPV to 9vHPV is allowed to complete the recommended doses of vaccine. Routine booster and/or revaccination after completion of vaccination with 2vHPV or 4vHPV is not necessary	
6. Novel technologies/vaccines	Need further research; involve LMIC countries	
7. Public education	Need public education including information on cervical screening and life-style modification	

Novel technologies/vaccines

a. *Minimum and preferred standards: All novel HPV vaccines should be evaluated appropriately by clinical research, and it is recommended to include LMIC as much as possible*.

Skin has been identified as an immune-responsive organ due to its enriched reservoir of antigen-presenting cells, skin resident T cells, and other immune cells involved in innate and adaptive immune responses.[56,57] Hence, there has been interest in skin vaccination, including HPV vaccine microarray patches.[58] Several new HPV vaccines are also under development.[41] The AOFOG holds the stance that all these emerging technologies/vaccines should be fully evaluated by well-designed clinical trials. The AOFOG also advocates for including the LMICs in these trials, as these regions have the highest disease burden yet the people there are underrepresented.

Public education

Although HPV vaccination has been implemented for almost two decades, there is still a lot of misunderstanding and myths about HPV and the vaccines.[59] For example, one questionnaire study in North Korea revealed that only 30% of the healthcare workers were aware of the causal relationship between HPV and cervical cancer.[60] Several barriers to HPV uptake had also been identified. Infrastructural factors included shortage and/or uneven distribution of vaccines, and a lack of affordability and/or government subsidy.[9] Factors related to the recipients included concerns about vaccine safety, limited understanding or awareness of HPV vaccination, time limitations, and suboptimal health-seeking behavior.[61] The COVID-19 pandemic further disrupted the services of HPV vaccination.

The AOFOG encourages individual countries/cities to promote public education through a variety of methods such as campaigns, informational materials, public talks, videos, and social media, aiming to reduce some misconceptions and increase the cervical cancer screening and HPV vaccination uptake rate.[8] The need for continuing cervical cancer screening after HPV vaccination should also be emphasized.

The above recommendations are summarized in Table 3.

CONCLUSION

Cervical cancer is potentially preventable, but it remains a major health problem in the Asia-Pacific region. Due to the variety of cultures, religions, infrastructure, and economic status among different countries/cities, it is challenging to have one mutual guideline that can standardize the practice related to HPV vaccination for all countries/cities. Since the establishment of the AOFOG Manila Declaration, there were multiple webinars, talks, and workshops in different countries, allowing experts from different countries to share their experience on cervical cancer elimination and HPV vaccination. We hope that this recommendation can take further step by setting a benchmark for both low- and high-resource countries/cities, outlining the minimum and preferred standards. By doing so, individual countries/cities can use these recommendations as a point of reference to design their HPV vaccination program or to audit their practices.

CONFLICT OF INTEREST STATEMENT

The authors disclosed no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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