Strategic Advisory Group of Experts (SAGE) on Immunization Evidence to recommendations framework[1]

Question: Should an *off-label*[2], *permissive* one-dose HPV vaccine schedule for use in routine and/or multi-age cohort (MAC) catch up strategies be recommended?

Population: Main population is pre-adolescent and adolescent girls (9-14 years old), but boys and older adults are also included.
Intervention: Single dose vaccination; bivalent (Cervarix and Cecolin), quadrivalent (Gardasil), and nonavalent vaccines (Gardasil 9).
Comparison(s): No vaccination
Outcome:
Clinical outcomes: including, but not limited to invasive cervical, vaginal, vulval, anal, penile or head and neck cancer; cervical intraepithelial neoplasia (CIN) grade 3+; CIN2+; histological and cytological abnormalities; anogenital warts; high risk HPV infection (genotype-specific prevalence, incidence and/or persistence)
Immunological outcome; seroconversion or seropositivity; geometric mean titers (GMT) of HPV antibodies

Background: As of March 2022, 117 countries introduced HPV vaccine in their national immunization schedules, but these countries represent only a third of the global population of girls and 40% of the global burden of cervical cancer.

In October 2019, SAGE reviewed the evidence on a single dose of HPV vaccines to protect 9-14-year-old girls, the primary target population, against cervical cancer. SAGE concluded the quality and amount of evidence was insufficient for this policy decision and that the evidence from the purposefully designed single dose randomized control trials (RCTs) was required to inform policy decisions. Several of the RCTs and effectiveness studies designed to assess single dose schedules have generated interim results during 2021.

[1] This Evidence to Recommendation table is based on the DECIDE Work Package 5: Strategies for communicating evidence to inform decisions about health system and public health interventions. Evidence to a recommendation (for use by a guideline panel). http://www.decide-collaboration.eu/WP5/Strategies/Framework

[2] *The recommendations contained in this publication are based on the advice of independent experts, who have considered the best available evidence, a risk–benefit analysis and other factors, as appropriate. This publication may include recommendations on the use of medicinal products for an indication, in a dosage form, dose regimen, population or other use parameters that are not included in the approved labelling. Relevant stakeholders should familiarize themselves with applicable national legal and ethical requirements. WHO does not accept any liability for the procurement, distribution and/or administration of any product for any use.*

In November 2020, the World Health Assembly adopted the Global Strategy towards the elimination of cervical cancer. The strategy calls on each country to introduce HPV vaccination by 2030 and set a target of 90% of girls fully vaccinated with HPV vaccine by age of 15. HPV vaccine coverages are below the target of 90% in the majority of countries and the observed high drop out between the first and the second dose indicate programmatic challenges.

Programmatic challenges to introducing the vaccine include high cost and supply constraints. The latter have affected in particular Low-and Middle-income countries since 2018 and led to delayed introductions and delayed or canceled multi age cohort catch up strategies in GAVI eligible countries.

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No*	*Un-certain*	*Yes*	*Varies by setting*	HPV infection with oncogenic HPV types causes an estimated 604,000 cases of cervical cancer worldwide (Globocan, 2020). HPV infection also causes a proportion of cancers of the anus, the oropharynx, the vulva and vagina, and of the penis. Of HPV-associated cancers, HPV types 16 and 18 are associated with 85% of HPV-related head and neck cancers and 87% of anal cancers – the second and third most frequent HPV-related cancers with, respectively, 38 000 and 35 000 estimated cases per year. Martel et al., Int. J. Cancer: 141, 664–670 (2017) VC 2017 Anogenital HPV infection can result in benign skin and mucosal tumors, including anogenital warts in men and women The estimated median annual incidence of new anogenital warts was 137 per 100 000 men and 121 per 100 000 women. (Patel H et al. Systematic review of the incidence and prevalence of genital warts. BMC Infectious Diseases, 2013;13:39)	
		☐	☐	☒	☐		

BENEFITS & HARMS OF THE OPTIONS	Benefits of the intervention Are the desirable anticipated effects large?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Recent data shows that single dose HPV vaccine is effective for both clinical and immunological outcomes. See the summary table of Systematic Review by Cochrane Group. (see the Cochrane Systematic Review). In particular, there is one high quality RCT study which shows high Vaccine Efficacy (>95%) of single dose HPV vaccine in adolescent girls/ young women 15 to 20 years old. Modeling suggests that under an elimination scenario (all countries introduce by 2030 and all countries include a first year multi age cohort catch up for 10-14-year-old girls), this can avert at least 1.2 million additional cases of cervical cancer compared to only vaccinating a routine cohort of girls (Prem& Jitt, 2021)	
	Harms of the intervention Are the undesirable anticipated effects small?	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Since licensure in 2006, over 500 million doses of HPV vaccines have been distributed. The risk of anaphylaxis has been characterized as approximately 1.7 cases per million doses. No other serious adverse reactions have been identified and HPV vaccines have an excellent safety profile (GACVS 2017).	
	Balance between benefits and harms	***Favours intervention*** ☒	***Favours comparison*** ☐	***Favours both*** ☐	***Favours neither*** ☐	**Unclear** ▱	The benefits of protection against any HPV related diseases, cervical but also other forms of cancers and genital warts, overweigh any adverse effect of vaccination (e.g., pain during vaccination, AEFIs)	
	What is the overall quality of this	Effectiveness of the intervention ***No included studies*** ☐	***Very low*** ☐	***Low*** ☐	***Moderate*** ☒	***High*** ☒	See related GRADE tables in the Cochrane review.	Two boxes have been ticked: The high quality refers to a RCT that provided shorter term efficacy data. The moderate quality refers

	evidence for the critical outcomes?	Safety of the intervention *No included studies* ☐ | *Very low* ☐ | *Low* ☐ | *Mod-erate* ☐ | *High* ☒	The safety of HPV vaccine has been confirmed by GACVS and informed by data from large, high quality datasets from post surveillance systems (see the GACVS Report). https://www.who.int/groups/global-advisory-committee-on-vaccine-safety/topics/human-papillomavirus-vaccines/safety	to a post RCT follow up study on long term efficacy.
VALUES & PREFERENCES	How certain is the relative importance of the desirable and undesirable outcomes?	*Important uncertainty or variability* ☐ | *Possibly important uncertainty or variability* ☐ | *Probably no important uncertainty or variability* ☒ | *No important uncertainty or variability* ☐ | *No known undesirable outcomes* ☐	While global representative data are missing, there is no important uncertainty around the relative weight that the target population attributes to the desirable outcomes (i.e., protection conferred by the vaccine) and the undesirable outcomes (i.e., the currently reported AEFIs). There is no uncertainty about the value placed on prevention of cervical cancer and high acceptance of the vaccines indicated by high coverage (>80%) achieved in many programs attest to that (Bruni et al, 2021)	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐ | *Probably No* ☐ | *Uncertain* ☐ | *Probably Yes* ☐ | *Yes* ☒ | *Varies* ☐	The target population assigns more weight to the desirable effects than to the undesirable effects. Large benefits can be obtained relatively to potential undesirable effects. Effectiveness data have shown that taking the vaccine can reduce the chance to get cervical cancer by 88% (Lei J et al. NEJM 2020). Minor AEFIs (e.g. pain) are reported; the risk of serious events like anaphylaxis is very rare; no other serious adverse events have been identified.	

RESOURCE USE	Are the resources required small?	*No* ☒	*Un-certain* ☐	*Yes* ☐	*Varies* ☐	HPV vaccine is relatively more costly than other childhood vaccines. In addition, vaccine delivery costs have been demonstrated to be high for HPV vaccines (Jit. M, 2021 https://doi.org/10.1016/j.jval.2020.07.012.) From the immunization programme perspective, additional resources are needed, including financial costs and human resources, to introduce HPV vaccine to the primary target adolescent girls.	
	Cost-effectiveness	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Previous studies have shown that HPV vaccine is a cost-effective intervention in various country settings. (Abbas et al. 2020 https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30022-X/fulltext) While no CEA for LMICs was done for single dose schedules, similar gains will be obtained with lower costs, and therefore single dose schedule HPV vaccination will be a more cost effectiveness intervention (than with 2 doses).	
EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐	*Un-certain* ☐	*Re-duced* ☒	*Varies* ☐	It is important to protect girls against HPV infection, especially in low- and middle-income countries where approximately 90% of cervical cancer cases occur and secondary prevention through screening is often inaccessible and of low quality. In addition, currently around two third of the global cohort of eligible girls lack access to HPV vaccination. Therefore, this intervention is likely to improve access to HPV vaccine and reduce health inequities.	

ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Inter-vention* ☒ / *Comparison* ☐ / *Both* ☐ / *Neither* ☐ / *Unclear* ☐	Most stakeholders accept HPV vaccine introduction in national immunization programmes.	
	Which option is acceptable to target group?	*Inter-vention* ☒ / *Comparison* ☐ / *Both* ☐ / *Neither* ☐ / *Unclear* ☐	HPV vaccine is generally well accepted among target groups and their parents, However, in some geographies, vaccine hesitancy and rumours on the effect of the vaccine like infertility or other alleged AEFIs have affected vaccine uptake. Data from a study from Tanzania among participants (Mitchell et al 2021 10.1016/j.tvr.2021.200217) indicated that most participants entrusted decisions about the number of HPV vaccine doses to experts. Random allocation to the different dose groups did not feature highly in the decision to participate in the trial. Given a hypothetical choice, girls generally said they would prefer fewer doses in order to avoid the pain of injections. Parental views were mixed, with most wanting whichever dose was most efficacious. Nonetheless, a few parents equated a higher number of doses with greater protection.	

FEASIBILITY	Is the intervention feasible to implement?	*No*	*Probably No*	*Uncertain*	*Probably Yes*	*Yes*	*Varies*	As of March 2022, 117 countries have introduced HPV vaccine in the national immunization schedule. Many countries have also successfully implemented multi age cohort catch up strategies during the introduction years. Coverage varies by region and country and many countries, both higher- and lower income, have been able to achieve good coverage, at least with the first dose. (Bruniet al., 2021)
		☐	☐	☐	☐	☒	☐	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	☒

Type of recommendation	We recommend the intervention	We suggest considering recommendation of the intervention	We recommend the comparison	We recommend against the intervention and the comparison
	☒	☐ Only in the context of rigorous research ☐ Only with targeted monitoring and evaluation ☐ Only in specific contexts or specific (sub)populations	☐	☐

Recommendation (text)	Please see the WHO HPV Position Paper, published 16 December 2022
Implementation considerations	Please see the WHO HPV Position Paper, published 16 December 2022
Monitoring and evaluation	Please see the WHO HPV Position Paper, published 16 December 2022
Research priorities	Please see the WHO HPV Position Paper, published 16 December 2022

Annex 1: Table 1.4. GRADE evidence profile for single dose HPV vaccine compared with no vaccine for HPV infection, seroconversion, and antibody titers (Source: Systematic review Cochrane Response, 2022)

Certainty assessment						Nº of patients		Effect		Certainty	Comments
Nº of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Single dose bivalent HPV infection	no vaccine	Relative (95% CI)	Absolute (95% CI)		
Persistent HPV 16/18 infections: short term follow-up, 18 months											
1 RCT	not serious[1]	not serious	not serious	not serious[2]	none	2/985 (0.2%)	36/473 (7.6%)	**RR 0.03** (0.01 to 0.11)	74 fewer per 1000 (from 75 fewer to 68 fewer)	⊕⊕⊕⊕ High	Kenya1 (KEN-SHE), bivalent (Cervarix) and nonavalent (Gardasil 9), 15-20 years old at vaccination
Persistent HPV 16/18 infections: long term follow-up, 4-10 years											
2 post-hoc analyses of RCTs	serious[3]	not serious	not serious	not serious[2]	none	2/3369 (0.1%)	56/2282 (2.5%)	**RR 0.03** (0.01 to 0.10)	24 fewer per 1000 (from 24 fewer to 22 fewer)	⊕⊕⊕◯ Moderate	CVT/PATRICIA, bivalent (Cervarix), 15-25 years old at vaccination India1, quadrivalent (Gardasil), 10-18 years old at vaccination
Seroconversion to HPV 16: follow-up 6 months to 11 years											
2 RCTs, 1 post-hoc analysis of RCT, 3 observational studies	not serious	not serious	not serious	not serious	none	Seroconversion following one dose ranged from 89.8% to 100% at up to 11 years follow-up.				⊕⊕⊕⊕ High	Kenya1, China1, Costa Rica1, Fiji1, Mongolia1, USA16
Seroconversion to HPV 18: follow-up 6 months to 11 years											
2 RCTs, 1 post-hoc analysis of RCT, 3 observational studies	not serious	not serious	not serious	not serious	none	Seroconversion following one dose ranged from 56.7% to 100% at up to 11 years follow-up.				⊕⊕⊕⊕ High	Kenya1, China1, Costa Rica1, Fiji1, Mongolia1, USA16
Geometric mean titres (GMT) for HPV 16: follow-up 4-6 years											
1 post-hoc analysis of RCT, 3 observational studies	not serious	not serious	not serious	not serious	none	Ratio of GMTs following one dose ranged from 5.73 to 320.43.				⊕⊕⊕⊕ High	Costa Rica1, Netherlands1 Fiji1, Mongolia1
Geometric mean titres (GMT) for HPV 18: follow-up 4-6 years											
1 post-hoc analysis of RCT, 3 observational studies	not serious	not serious	not serious	not serious	none	Ratio of GMT following one dose ranged from 4.79 to 81.92.				⊕⊕⊕⊕ High	Costa Rica1, Netherlands1 Fiji1, Mongolia1

CI: confidence interval; **HPV:** human papillomavirus; **RCT:** randomized controlled trial; **RR:** risk ratio

1. Not downgraded despite some concerns with missing outcome data, estimates from unpublished data of modified intention-to-treat analysis of participants HPV naive at baseline.
2. Not downgraded for imprecision due to large effect estimates, despite few events.
3. Downgraded one level due to some concerns with bias due to confounding and selection of the reported result.