World Health Organization

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 the 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): 2 doses of HPV vaccination
Outcome:
Clinical outcome: 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 started to generate 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 show that single dose HPV vaccine is highly efficacious (VE > 95%) in a RCT among 15 to 20 year old population (Kenshe RCT, Barnabas et al. 2021), and showed similar efficacy compared to 2 or 3 doses of HPV vaccine in 10-18 year old girls in a post RCT follow up study (IARC India, 2021, Basu et al. 2021). See the summary table of Systematic Review by Cochrane Group. (see the Cochrane Systematic Review) Modeling suggests that under an elimination scenario (all countries introduce by 2030 and 90% of girls vaccinated with 2 doses of HPV vaccine by age 15) vaccination can prevent more than 61 million cases of cervical cancer over the next century (Brisson 2020). If future evidence from RCTs comparing 1 vs 2 doses do not confirm non-inferiority and 1 dose would have marginally lower protection at individual level, higher one dose coverage and any resulting herd protection would likely result in a larger public health impact (Prem, Brisson 2021).	
		☐	☒	☐	☐		

					Future improvements in quality and coverage of cervical cancer screening and treatment programmes may mitigate any lower protection from a single dose. There is no immune correlate of protection. Direct evidence on the duration of protection exists for the time vaccines have been licensed (2006). There is evidence that the immune response is stable for a period up to 11 years for a single dose (Costa Rica, CVT data. Kreimer et al., 2020). Similar to other schedules (2 or 3 dose), it is unknown whether a booster dose is beneficial.	
	<u>Harms of the intervention</u> 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). 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 Furthermore, by reducing the number of doses to a single dose the existing risk will be diminished.	

Balance between benefits and harms	*Favours inter-vention*: ☐ *Favours com-parison*: ☐ *Favours both*: ☒ *Favours neither*: ☐ Unclear: ▱	The benefits of protection against all HPV related diseases, cervical but also other forms of cancers and genital warts, outweigh any harm that may arise from vaccination (e.g., pain during immunization, AEFIs)		
What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies*: ☐ *Very low*: ☐ *Low*: ☒ *Mod-erate*: ☐ *High*: ☐ Safety of the intervention *No included studies*: ☒ *Very low*: ☐ *Low*: ☐ *Mod-erate*: ☐ *High*: ☒	As per the Grade table (attached) The quality of evidence on non-inferiority (1 vs 2 doses (IARC India post RCT follow up, Basu et al., 2021 and CVT; Kreimer et al 2020) is low. However, VE outcomes are comparable to high quality 0 vs 1 dose RCT data (Kenshe RCT, Barnabas et al.2021). A growing number of lower quality observation studies confirm the findings from intervention studies. Studies that apply buffer periods in the analysis (excluding participants that did not have sufficient time between vaccination date and outcome measurement date) and studies which adjusted for the most confounding (i.e., studies at the least risk of bias) were more likely to report smaller differences in effect between one and two doses. The very high and comparable efficacy (97.5%) from high quality single dose 0 vs 1 RCT lend further weight.		

							(see the Cochrane Response Systematic Review) High quality safety data based on large, high quality datasets from post-marketing surveillance systems https://www.who.int/groups/global-advisory-committee-on-vaccine-safety/topics/human-papillomavirus-vaccines/safety	
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* ☐	There is no uncertainty about the value placed on prevention of cervical cancer and high acceptance of the vaccination as indicated by high coverage achieved in many programs (Bruni et al., 2021) There is uncertainty about the duration of protection because no direct evidence on the duration of protection beyond 16 years (for several decades) exists for HPV vaccines and there is no immune correlate of protection. There is evidence that the immune response is stable for a period up to 11 years for a single dose (Costa Rica, CVT RCT. Kreimer et al 2020). Similar to other schedules (2 or 3 dose), it is unknown whether a booster dose is beneficial. In some geographies vaccine hesitancy and fear of infertility or other alleged AEFIs affects vaccine uptake. While the risk of infertility, or observed rare conditions such as CRPS or POTS, are not uncertain (*there is no increased risk or*	

							causal link to HPV vaccination according to GACVS), it has proven to strongly affect vaccine uptake and acceptance of some programmes. The existence of - or the potential development of - high performing cervical cancer screening and treatment programmes using high quality tests, may mitigate any residual risk or lower protection after a single dose	
	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	*No* ☐	*Probably No* ☐	*Uncertain* ☐	*Probably Yes* ☒	*Yes* ☐	*Varies* ☐	Large benefits can be obtained relative to the potential undesirable effects. Reducing the number of required doses to a single dose while obtaining a similarly large benefits in terms of cancer cases averted is preferred by vaccinees as well as by immunization programmes. It leads to reduction in individual and programme level costs while further reducing the risk of pain and AEFIs.	
RESOURCE USE	Are the resources required small?	*No* ☐		*Un-certain* ☐	*Yes* ☒		*Varies* ☐	HPV vaccine is relatively costly compared to traditional vaccines. In addition, vaccine delivery cost has been demonstrated to be high for HPV vaccines. (Jit. M, 2021.https://doi.org/10.1016/j.jval.2020.07.012) A reduction from two doses to a single dose per eligible girl will lead to considerable programme savings. Supply constraints have affected programme options (WHO Global HPV market study Nov 2020)	.

						From an immunization programme perspective, the intervention will not require additional costs and lead to cost reductions in vaccines, human resource time and complexity (registration, tracking). From the perspective of the beneficiaries, adolescent girls and parents, a single dose will reduce any financial costs due to transportation and other opportunity costs.	
	Cost-effectiveness	*No* ☐	*Un-certain* ☐	*Yes* ☒	*Varies* ☐	Cost effectiveness studies have shown that HPV vaccine is cost-effective intervention in various country settings (Abbas et al., 2020.) . These cost effectiveness data are not only based on older vaccine prices (average HPV dose price is going down) but also based on the need for 2 doses. Cost effectiveness of a single dose schedule is therefore higher.	
EQUITY	What would be the impact on health inequities?	*Increa-sed* ☐	*Un-certain* ☐	*Re-duced* ☒	*Varies* ☐	Currently, two thirds of the global cohort of eligible girls lack access to HPV vaccines. They live in low- and middle-income countries that represent 60% of cervical cancer disease burden. A single dose can lead to earlier access to HPV vaccines (more girls can be reached with the current limited supply of vaccines in the short run) as it would reduce supply constraints. By making HPV introduction more affordable for low-income countries, immunization programmes may decide to advance introductions and protect more girls earlier, thereby reducing health inequities.	

ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)? *Inter-vention* ☒ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Un-clear* ☐		A small-scale informal survey among EPI programmes from low and middle income setting with current and planned HPV programmes (survey carried out between July and October 2021 for WHO SAGE) indicated that a majority would consider adoption of a one dose recommendation for MAC on programmatic grounds. This survey did not ask specifically about a scenario to lower the routine cohort to 1 dose. SAGE & WHO policy endorsement was mentioned as an important criterion for NITAG decisions.	.
	Which option is acceptable to target group? *Inter-vention* ☐ *Comparison* ☐ *Both* ☒ *Neither* ☐ *Un-clear* ☐		A study from Tanzania among participants in a 1 vs 2 dose trial (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 dosing was most efficacious. Nonetheless, some parents equated a higher number of doses with greater protection.	
FEASIBILIT	Is the intervention *No* *Probably* *Uncer* *Probably* *Yes* *Varies*		As per March 2022, 117 countries have introduced HPV vaccine in the national immunization programme at 2- or 3 doses	

	feasible to implement?	*No* □ *tai n* □ *Yes* □ □ ☒ □	schedules successfully. Single dose vaccine programmes would be easier and more efficient. In the informal survey among EPI programmes from low and middle income setting with current and planned HPV programmes carried out between July and October 2021 for WHO SAGE, a majority considered 1 dose vaccination feasible. Experience with reduction in the HPV vaccine schedule exists. Following a policy change in 2014 (WHO HPV position paper, 2014) nearly all countries in the world switched successfully from 3 to 2 dose routine schedules, most within 3 years.	

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

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Annex 1 Grade Table 1 vs 2 doses (source: Systematic Review, Cochrane Response 2022)

Single dose HPV vaccine systematic review

Evidence profile 2: Effectiveness and immunogenicity of one dose of HPV vaccine compared with two doses

Table 2.7. GRADE evidence profile for single dose HPV vaccine compared with two doses for HPV infection, seroconversion, and antibody titres

Certainty assessment						№ of patients		Effect		Certainty	Comments
№ 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: long term follow-up, 4-10 years											
2 post-hoc analyses of RCTs	serious[1]	not serious	not serious	serious[4]	none	2/3369 (0.06%)	8/4199 (0.19%)	**RR 0.32** (0.07 to 1.48)	1 fewer per 1000 (from 2 fewer to 1 more)	⊕⊕◯◯ Low	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, 2 observational studies	not serious	not serious	not serious	not serious	none	Seroconversion following one dose ranged from 89.8% to 100% and following two doses 97% to 100% at up to 11 years follow-up.				⊕⊕⊕⊕ High	Tanzania1, China1, Costa Rica1, Fiji1, USA16
Seroconversion to HPV 18: follow-up 6 months to 11 years											
2 RCTs, 1 post-hoc analysis of RCT, 2 observational studies	not serious	not serious	not serious	not serious	none	Seroconversion following one dose ranged from 56.7% to 100% and following two doses 81.1% to 100% at up to 11 years follow-up.				⊕⊕⊕⊕ High	Tanzania1, China1, Costa Rica1, Fiji1, USA16
Geometric mean titres (GMT) for HPV 16: follow-up 6 months to 11 years											
2 RCTs, 1 post-hoc analysis of RCT, 1 observational study	not serious	not serious	not serious	not serious	none	Ratio of GMTs comparing one with two doses ranged from 0.11 to 0.67 at up to 11 years follow-up.				⊕⊕⊕⊕ High	Tanzania1, China1, Costa Rica1, Fiji1
Geometric mean titres (GMT) for HPV 18: follow-up 6 to 11 years											
2 RCTs, 1 post-hoc analysis of RCT, 1 observational study	not serious	not serious	not serious	not serious	none	Ratio of GMTs comparing one with two doses ranged from 0.17 to 1.07 at up to 11 years follow-up.				⊕⊕⊕⊕ High	Tanzania1, China1, Costa Rica1, Fiji1

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

1. Downgraded one level due to some concerns with bias due to confounding and selection of the reported result.
2. Downgraded one level due to imprecision, few events and a 95% confidence interval that encompasses a benefit, no effect, and a harm.