SAGE evidence to recommendations framework[i]

Question: In 9 to 15-year old females, is 9-valent human papillomavirus vaccine (HPV) vaccine superior to 4-valent or 2-valent HPV vaccines?

Population: 9 to 15-year old females
Intervention: 9-valent HPV vaccine
Comparison(s): 4-valent or 2-valent HPV vaccines
Outcome: Cases of cervial cancer

Background: HPV is the most common viral infection of the reproductive tract and causes a range of conditions in females and males, including precancerous lesions that may progress to cancer.

With the licensure and data on immunogenicity and protection for clinical endpoints now being available for significant periods of follow-up, the Strategic Advisory Group of Experts (SAGE) on Immunization asked for a review of the available evidence on the potential superiority of 9-valent HPV (affords protection against HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58) versus the 4- (affords protection against HPV types 6, 11, 16 and 18) or the 2-valent (affords protection against HPV types 16 and 18) vaccines.

Globally, HPV 16/18 (the two high-risk types against which all three available HPV vaccines afford direct protection) are associated with 71% of the cervical cancer cases. HPV 31/33/45 (three high-risk types against which the bi- and quadrivalent vaccines may afford cross-protection) are associated with 13% of the cases. Lastly, HPV 31/33/45/52/58 (five high-risk types against which only the 9-valent vaccine affords direct protection) are associated with 18% of the cases.

The review by the Strategic Advisory Group of Experts (SAGE) on Immunization, conducted in October 2016[1] , is based on a systematic reviews prepared by Cochrane Response, London, UK.[2]

[1] see Meeting of the Strategic Advisory Group of Experts on immunization, October 2016 – conclusions and recommendations, http://apps.who.int/iris/bitstream/10665/251810/1/WER9148.pdf?ua=1 , accessed Dec 2016

[2] (see Randomized controlled trials of human papillomavirus vaccines: Systematic reviews, http://www.who.int/immunization/sage/meetings/2016/october/04_Clinical_trials_of_HPV_vaccines.pdf?ua=1, accessed Dec 2016)

	CRITERIA	JUDGEMENTS				RESEARCH EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem a public health priority?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies by setting* ☐	Although it is preventable, according to the most recent data available (IARC GLOBOCAN 2012), cervical cancer is the fourth most common cancer among women worldwide. It is estimated that each year there are approximately 528,000 new cases and more than 266,000 deaths from cervical cancer. More than 85% of all new cases and deaths occur in less developed countries, partly because routine cervical cancer screening and treatment are not widely available.	
BENEFITS & HARMS OF THE OPTIONS	<u>Benefits of the intervention</u> Are the desirable anticipated effects large?	*No* ☐	*Uncertain* ☐	*Yes* ☒	*Varies* ☐	The review focused on the comparison of the 9-valent vs the 4-valent vaccine. It was demonstrated earlier, that both the quadrivalent and the biavalent HPV vaccine yielded high efficacy and very high antibody titres as compared to natural infection. In 9 to 15-year old females, 9-valent vaccine was non-inferior to 4-valent vaccine for GMTs for HPV 6, 11, 16, and 18 at 7 months. The 9-valent HPV vaccine resulted in substantially higher GMTs for HPV 31, 33, 45, 52, and 58 than the 4-	

			valent HPV vaccine. In 9 to 15-year old females, the ratios of seroconversion to HPV 6, 11, 16, and 18 at 7 months were the same in both the 9-valent and 4-valent HPV vaccine groups (100% seroconversion).	
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	The undesirable anticipated effects of the HPV vaccine are small. One randomized, double-blind, phase III study of the immunogenicity and safety of a 9-valent HPV versus a 4-valent HPV vaccine in 9-15-year-old girls showed comparable safety profiles, although the incidence of injection-site swelling was higher in the 9-valent HPV vaccine group (Vesikari T, et al. Pediatr Infect Dis J. 2015 Sep;34(9):992-8). This is supported by another trial assessing the safety of 9-valent vaccines vs meningococcal and Tdap Vaccines in 11- to 15-year-old boys and girls. No serious adverse events were reported. (Schilling A, et al. Pediatrics. 2015 Sep;136(3):e563-72)	The Global Advisory Committee on Vaccine Safety (GACVS) undertook to monitor HPV vaccine safety, and has met on 6 occasions to discuss safety data, of which 3 took place in the early years following licensure. Thereafter, concerns related to anaphylaxis, syncope, an episode of mass psychogenic illness, autoimmune diseases including multiple sclerosis and Guillain-Barré syndrome (GBS) and venous thromboembolism were noted. Each of these signals was investigated with robust epidemiologic methods and each was confirmed as not related to vaccination. Notably, a large study in France using administrative data from over 2 million girls found no association between HPV vaccination and autoimmune disease, including multiple

				sclerosis. A small increased risk of GBS was noted, but this finding contrasted with those of other large studies which did not find a similar association. (Global Advisory Committee on Vaccine Safety, Weekly epidemiological record. 2–3 December 2015. No 3, 2016, 91, 21–32)[3]
	Balance between benefits and harms	*Favours intervention* ☐ *Favours comparison* ☐ *Favours both* ☒ *Favours neither* ☐ *Unclear* ☐	Evidence suggests that the 3 registered vaccines (2, 4 and 9-valent) offer similar immunogenicity and protection against selected cervical endpoints (HPV cervical infection and Cervical intraepithelial neoplasia grade 1 or more.	
	What is the overall quality of this evidence for the critical outcomes?	Effectiveness of the intervention *No included studies* ☐ *Very low* ☐ *Low* ☐ *Moderate* ☒ *High* ☐ Safety of the intervention *No included studies* ☒ *Very low* ☐ *Low* ☐ *Moderate* ☐ *High* ☐	Moderate-quality evidence (see Randomized controlled trials of human papillomavirus vaccines: Systematic reviews prepared by Cochrane Response) No systematic review of literature on the safety of 9-valent HPV vaccines has been conducted. Though a rapid review of literature indicated that 9-valent HPV vaccine had a good safety	

[3] See http://www.who.int/vaccine_safety/committee/reports/wer9103.pdf, accessed Dec 2016

			profile. For rating on the quality of evidence in regard to the safety of 2 or 4-valent HPV vaccines, see http://www.who.int/immunization/position_papers/hpv_grad_safety.pdf?ua=1, accessed Dec 2016)	

VALUES & PREFERENCES	Values and preferences of the target population: Are the desirable effects large relative to undesirable effects?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☒ Yes ☐ Varies ☐	In general, limited global data are available on the values and preferences of the target population in regard to HPV vaccine. To our knowledge, no data are available on the values and preferences of the target population on 9-valent vs 4- or 2-valent HPV vaccines. Oteng et al 2011 assessed public preferences for HPV vaccines and smear test screening. Respondents preferred a vaccine that gave lifelong immunity, a vaccination programme that targeted boys and girls and a vaccine that gave protection from genital warts and cervical cancer. Harper et al 2014 assessed the decisional satisfaction associated with HPV vaccination. Regardless of the decision to accept or reject HPV vaccination, the decisional satisfaction was very high.	

RESOURCE USE	Are the resources required small?	*No* ☐ *Uncertain* ☐ *Yes* ☐ *Varies* ☒	Resources will be required for commodity procurement and for the health system. If countries have not introduced HPV vaccine yet, resources will be required for adding new vaccination visits.	
	Cost-effectiveness	*No* ☐ *Uncertain* ☒ *Yes* ☐ *Varies* ☐	Studies that compared the cost-effectiveness of switching from bi- or quadrivalent vaccine to 9-valent vaccine in adolescent females were scarce. The 9-valent vaccine price per dose and the cross-protection provided by HPV vaccine types highly influence the cost-effectiveness analyses. As the price for 9-valent vaccine remain unknown especially in low and middle income countries, the cost-effectiveness of immunization with 9-valent HPV vaccine is still uncertain and more economic evaluations are still needed to understand the true value for money of 9-valent HPV immunization.	
EQUITY	What would be the impact on health inequities?	*Increased* ☐ *Uncertain* ☐ *Reduced* ☐ Varies ☒	No data were available though it is presumed that there will not be any impact on health inequities using the 9-valent vs the 4- or 2-valent vaccine.	

ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Intervention* ☐ *Comparison* ☐ *Both* ☒ *Neither* ☐ *Unclear* ☐	Either option is presumed to be acceptable to key stakeholder, though likely the price for the vaccine will be important to consider.	
	Which option is acceptable to target group?	*Intervention* ☐ *Comparison* ☐ *Both* ☒ *Neither* ☐ *Unclear* ☐	Either option is presumed to be acceptable to the target group.	
FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ *Varies* ☒	Both the intervention as well as the alternative may be equally challenging to implement. While a growing number countries globally have already introduced HPV vaccine, in particular middle income countries which don't benefit from donor support may struggle with implementing and sustaining the vaccine financially.	

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)	Current evidence suggests that the 3 registered vaccines (2, 4 and 9-valent) offer relatively similar effectiveness for the prevention of cervical cancer. This has to do with the fact that HPV 16/18 (against which all 3 available vaccines afford specific protection) are associated with 71% of the cases. HPV31/33/45 (3 types against which the 2-valent and 4-valent vaccines are reported to give cross protection) are associated with a further 13% of cases and HPV 31/33/45/52/58 altogether (against which the 9-valent vaccine affords specific protection) are associated with 18% of the cases i.e. a further 5% compared with HPV 31/33/45. SAGE recommends that the priority of HPV immunization should remain the prevention of cervical cancer which is shown to be best achieved through the immunization of girls, prior to sexual debut. SAGE recommends that, in case they have not done so already, all countries globally now proceed with nationwide introduction of HPV vaccines. Phased introductions should only be an alternative for countries where financial or operational constraints prevent an immediate country-wide immunization programme.				

Implementation considerations	SAGE recommends that HPV vaccine be promptly introduced for young girls as part of a coordinated and comprehensive strategy to prevent cervical cancer and other diseases caused by HPV. The immunization of multiple cohorts of girls aged 9–14 years is recommended when the vaccine is first introduced. If resources are available, the age range could be expanded up to 18 years. HPV vaccine introductions based on single or multiple age cohorts will require adequate operational and financial planning. Countries considering HPV introduction can turn to the World Health Organization's (WHO) 2016 guide for Introducing HPV Vaccine Into National Immunization Programmes as well as the WHO Scaling-up HPV vaccine introduction.
Monitoring and evaluation	
Research priorities	

[i] 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/