SAGE evidence to recommendations framework[i]

Question: What is the incremental effectiveness and cost-effectiveness of vaccinating multiple age cohorts versus a single age cohort in high income countries (HIC) and low and middle income countries (LMIC)?

Population: Girls and young women.
Intervention: HPV vaccine administered to single age cohort immunization of girls aged 9–13 years
Comparison(s): HPV vaccine administered to multiple female cohorts (multiple age cohorts within a defined age range)
Outcome: Cervical 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.

The population-level effect of HPV vaccination is expected to vary considerably between these countries, depending on 1) the vaccine used, 2) vaccination strategies and population targeted for vaccination, and 3) vaccination coverage achieved.

In October 2016[1] , the Strategic Advisory Group of Experts (SAGE) on Immunization was presented with updated evidence on the impact of HPV immunization programmes, and modelling of the impact of HPV immunization schedules and strategies. Aim was to inform SAGE on the population-level effects of HPV vaccination for of single versus multiple age cohort immunization.

SAGE deliberations on the effect of vaccinating multiple cohorts were informed by a systematic review of literature [2,3] as well as by modelling and cost-effectiveness analysis.[4,5]

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION

[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] Drolet M, Benard E, Boily MC, Ali H, Baandrup L, Bauer H, et al. Population-level impact and herd effects following human papillomavirus vaccination programmes: a systematic review and meta-analysis. Lancet Infect Dis. 2015;15(5):565-80.

[3] Drolet M, Bénard É, Brisson M. Population-level impact and herd effects following papillomavirus immunization programmes: a systematic review and meta-analysis. Québec, Canada: Université Laval; 2016. p. 9. http://www.who.int/immunization/sage/meetings/2016/october/05_Population-level_impact_and_herd_effects_of_HPV_immunization_programmes.pdf?ua=1, accessed March 2017.

[4] http://www.who.int/immunization/sage/meetings/2016/october/06_Cost-effectiveness_analyses_of_HPV_immunization_programmes.pdf?ua=1, accessed March 2017.

[5] Modelling estimates of the incremental effectiveness & cost effectiveness of HPV vaccination. http://www.who.int/immunization/sage/meetings/2016/october/07_Modelling_HPV_immunization_strategies.pdf?ua=1, accessed March 2017

PROBLEM	Is the problem a public health priority?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies by setting* ☐	Estimates are that 630,000 new HPV-related cancer cases occurred in 2012. Of those, 570,000 (90%) cases were in women and 61,000 (10%) in men. It is estimated that each year there are approximately 528,000 new cases and more than 266,000 deaths from cervical cancer making it the fourth most common cancer among women worldwide. 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* ☐	Tangible benefits of vaccinating multiple cohorts include, but are not limited to, more rapid population level impact (herd effects), indirect protection of unvaccinated women, and direct protection of boys and men, including men who have sex with men. Based on modelling data, in HIC and LMIC, vaccinating multiple age cohorts is predicted to result in a substantially shorter time in achieving the impact of the vaccination than vaccination of	Many countries included catch-up vaccination in their HPV vaccination programs (Australia, Canada, Denmark, Greece, New-Zealand, Norway, Sweden, the UK and the USA). Most countries with high routine vaccination coverage also included a catch-up program (or campaign).

			single age cohorts. However, the impact of multiple age cohort vaccination could be reduced in countries with early age at HPV infection. Most studies reported that immunization targeting multiple age cohorts were cost-effective due to wider primary protection and more rapid herd effects. The systematic review of literature concluded that there are too few countries with high routine vaccination coverage without catch-up vaccination to isolate the additional population-level impact of vaccinating multiple age cohorts (vs a single cohort).	
	<u>Harms of the intervention</u> Are the undesirable anticipated effects small?	*No* ☐ *Uncertain* ☐ *Yes* ☒ *Varies* ☐	HPV vaccine has been demonstrated to have excellent safety profiles, in both men and women. No population level deleterious effects are presumed when implementing the proposed intervention.	
	Balance between benefits and harms	*Favours intervention* ☒ *Favours comparison* ☐ *Favours both* ☐ *Favours neither* ☐ *Unclear* ☐	Balancing benefits and harms of the intervention and the comparison, favours the intervention.	

	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*	No assessment of the quality of the evidence has been undertaken.	

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* ☐	Although evidence on the values and preferences of the target population in regard to vaccinating multiple cohorts versus only girls could not be retrieved, it is presumed that the desirable effects (substantially shorter time in achieving the impact of the vaccination) are large compared to the undesirable effects of the vaccination within multiple age-cohorts.	

RESOURCE USE	Are the resources required small?	*No* ☒ *Uncertain* ☐ *Yes* ☐ *Varies* ☐	Additional resources will be required for commodity procurement and for the health system.	
	Cost-effectiveness	*No* ☐ *Uncertain* *Yes* ☒ *Varies* ☐	Most studies reported that immunization targeting multiple age cohorts were cost-effective due to wider primary protection and more rapid herd effects. However, the extend of immunization age needs to be interpreted cautiously as several studies analyzed the cost-effectiveness of HPV immunization in a single age range only and did not compare in the next age range gradually. The incremental cost-effectiveness for each additional age cohort of girls and women aged ≥15 years is expected to decline gradually as more girls and women would have already become sexually active. Above age 15 years, the upper age limit at which HPV immunization stop being cost-effective depends on the country context. Duration of vaccine protection and vaccine price influences the cost-effectiveness of targeting multiple age cohort immunization. If duration of vaccine protection is reduced to a minimum	

			of 10 years, the cost-effectiveness ratio increases and is only cost-effective in the broader age range of immunization, 12-24 years old. Hence, further economic evidences on immunization based on multiple age cohorts are still required especially in LMIC and also in determining the most cost-effective age limit of HPV vaccination.	
EQUITY	What would be the impact on health inequities?	*Increased* ☐ *Uncertain* ☐ *Reduced* ☒ Varies	No data were available though it is presumed that there will be impact on health inequities in decreasing the burden of HPV in a broader range of female and male cohorts.	
ACCEPTABILITY	Which option is acceptable to key stakeholders (Ministries of Health, Immunization Managers)?	*Intervention* ☐ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☒	In most countries, in particular in LMIC with limited financial resources, the vaccination of multiple age-cohorts, although cost-effective, may be difficult to finance. Nevertheless, to rapidly reduced the burden of cervical cancer, the intervention is likely to be acceptable to key stakeholders.	

	Which option is acceptable to target group?	*Intervention* ☐ *Comparison* ☐ *Both* ☐ *Neither* ☐ *Unclear* ☒	No data could be retrieved though several points need to be highlighted: Although evidence on the acceptability of the intervention to the target population could not be retrieved, it is presumed that the target population would be in favor of the intervention, as more age-cohorts may benefit from the more rapidly induced direct and indirect effects of the intervention. Nevertheless, HPV vaccination has triggered episodes of vaccine hesitancy in various settings globally. Fear of injection or fear of adverse events may drive the willingness of girls and young women (and their caregivers) to receive the vaccine. Short- and long term effectiveness of HPV vaccination against HPV related disease may drive the willingness of girls and young women (and their caregivers) to receive the vaccine.	

FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ *Varies* ☒		The intervention may be challenging to implement. While a growing number countries globally have already introduced HPV vaccine, in particular LMICs which don't benefit from donor support may struggle with implementing of vaccination alone. Additional financial burden will be added by vaccinating multiple cohorts 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)	SAGE noted that, due to estimated larger direct protection and stronger herd effects, immunization targeting multiple age cohorts between 9 and 18 years would result in faster and larger population impact than immunization of single age cohorts. It should also offer opportunities for economies of scale in delivery and could make programmes more resilient to any interruptions in vaccine delivery. Immunization of multiple cohorts of girls is cost-effective in the age range 9–14 years, in particular when the recommended extended 2-dose schedule is used. The incremental cost-effectiveness for each additional age cohort of girls and women aged ≥15 years depends on country context because immunization requires a 3-dose schedule and the proportion of sexually active females is larger in this older age cohort.
Implementation considerations	
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/