SAGE evidence to recommendations framework[i]

Question: What is the public health impact on cervical cancer of administering HPV vaccine to 9 to 15-year old females and males versus to 9 to 15-year old females?

Population: 9 to 15-year old females and males
Intervention: HPV vaccine administered to 9 to 15-year old females and males
Comparison(s): HPV vaccine administered to 9 to 15-year old females
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.

In October 2016[1] , the Strategic Advisory Group of Experts (SAGE) on Immunization was presented with updated evidence on the burden related to HPV, HPV vaccines, impact of HPV immunization programmes, and modelling of the impact of HPV immunization schedules and strategies.

SAGE deliberations on the potential of gender-neutral immunization programmes were informed by a review of literature from 2015[2] and a recent update of this review.[3]

[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.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
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 gender-neutral immunization 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.	In countries with ≥50% vaccination coverage of girls, significant decreases between the pre- and post-vaccination periods were observed among girls aged 15–19 years old in rates for HPV 16/18 infections (RR=0.32 [95% CI 0.19–0.52]), CIN2+ lesions (RR=0.69 [95% CI 0.66–0.73]), and anogenital warts (RR=0.39 [95% CI 0.22–0.71]). Significant reductions were also observed for HPV 31/33/45 infections (RR=0.72 [95% CI 0.54–0.96]). Among

				boys aged 15–19 years (who would be for the vast majority unvaccinated), anogenital warts also decreased significantly (RR=0.66 [95% CI 0.47–0.91]). In this group, recent data from Australia show important but not statistically significant decreases in HPV-16/18 (RR=0.37 [95% CI 0.12–1.10]) and recently published data from England show 30.6% and 25.4% decreases in anogenital warts among 15 to 19-year-old women and men aged, respectively, since the introduction of the bivalent vaccine. Among women aged 20–39 years old (an age groups with lower or absent direct protection from HPV vaccination), significant decreases were observed in anogenital warts (RR=0.68 [95% CI 0.51–0.89]). Among older men, anogenital warts also decreased significantly (RR=0.82 [95% CI 0.72–0.92]). More data for CIN2+ endpoints are becoming available and significant decreases are observed in CIN2+ for girls aged

				15–19 years.
	Harms of the intervention 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.	Selected studies demonstrating excellent safety profile of HPV vaccination including boys and men: • Block SL, et al. Clinical trial and post-licensure safety profile of a prophylactic human papillomavirus (types 6, 11, 16, and 18) l1 virus-like particle vaccine. Pediatr Infect Dis J. 2010 Feb;29(2):95-101 • Castellsagué X, Immunogenicity and safety of the 9-valent HPV vaccine in men. Vaccine. 2015 Nov 27;33(48):6892-90 • Lehtinen M, et al. Safety of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in adolescents aged 12-15 years: Interim analysis of a large community-randomized controlled trial. Hum Vaccin Immunother. 2016 Nov

				14:0. [Epub ahead of print]
	Balance between benefits and harms	*Favours intervention* ☐ *Favours comparison* ☐ *Favours both* ☒ *Favours neither* ☐ *Unclear* ☐	Balancing benefits and harms of the intervention and the comparison, clearly favours both.	
	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* ☐	The systematic review of literature identified 3 studies from Australia, Canada and USA on the population-level impact of gender-neutral HPV immunization. It was noted that gender-neutral programmes were implemented recently and the follow-up after the switch from girls-only immunization is limited to 1–2 years. Consequently, it was noted to be still too early to measure the additional impact of gender-neutral vaccination at the population-level.	

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* ☐	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. Dahlström et al 10 assessed the attitudes to HPV vaccination among parents of children aged 12-15 years. Among studied parents, 76% were willing to vaccinate their child if the vaccine was for free and 63% were willing to vaccinate even if the vaccine comes with a cost.	

RESOURCE USE	Are the resources required small?	No ☒ Uncertain ☐ Yes ☐ Varies ☐	Additional resources will be required for commodity procurement and for the health system. If countries have not introduced HPV vaccine yet (for girls only or for girls and boys), resources will be required for adding new vaccination visits.	
	Cost-effectiveness	No ☐ Uncertain ☒ Yes ☐ Varies ☐	The literature was systematically searched for cost-effectiveness estimates of various HPV immunization strategies[4]. 14 studies conducted the cost-effectiveness analyses of gender-neutral HPV immunization versus female-only immunization. Almost half of the studies showed that gender-neutral immunization was cost-effective. Vaccine coverage and price played a crucial role in influencing the cost-effectiveness analyses especially in low and middle income countries (LMIC). If female vaccine coverage was greater than approximately 70–80%, the incremental effectiveness was diminished and gender-neutral	

[4] Chaiyakunapruk N, Ng S. Human papilloma virus (HPV) vaccination: an updated systematic review of cost-effectiveness analyses. Selangor, Malaysia: Monash University Malaysia; 2016. p. 9. http://www.who.int/immunization/sage/meetings/2016/october/06_Cost-effectiveness_analyses_of_HPV_immunization_programmes.pdf?ua=1, accessed Dec 2016.

			immunization that includes adolescent boys become less cost-effective than routine vaccination of adolescent girls only. Several existing economic studies failed to account for the broader benefits of HPV vaccination especially among male population such as penile and anal cancers, genital warts and oropharyngeal cancer. Exclusion of these HPV-related male benefits could results in underestimation of the real value of gender-neutral immunization. As such, more cost-effectiveness evidence for gender-neutral immunization is still needed to understand its monetary benefits especially in LMIC.	
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 related disease boys and men.	

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 target of HPV vaccine introduction will be the reduction of cervical cancer. Therefore it is presumed that key stakeholders in most countries will likely consider or have already implemented and will remain with the comparison only.	
	Which option is acceptable to target group?	*Intervention* ☐ *Comparison* ☐ *Both* ☒ *Neither* ☐ *Unclear* ☐	No data could be retrieved though several points need to be highlighted: 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 boys (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 boys (and their caregivers) to receive the vaccine.	

FEASIBILITY	Is the intervention feasible to implement?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ *Varies* ☒		Both the intervention as well as the comparison may be equally 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 and sustaining the vaccine financially. Expanding the immunization programme to be gender-neural will add to the financial burden of countries and may therefore be difficult to implement.		
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 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. Nonetheless, SAGE also recognized that gender-neutral immunization could be considered based on elements such as disease burden, sexual behaviour in a country, equity, programmatic implications, cost-effectiveness, and affordability. 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
Implementation considerations	Reaching high vaccination coverage in girls also results in herd protection for boys, which illustrates the importance of prioritizing high HPV vaccination coverage in adolescent girls. When the coverage in girls is ≥80%, gender-neutral vaccination including adolescent boys is less cost-effective than when targeting only girls and women aged 9–18 years. At lower levels of coverage, vaccination targeting only girls and women aged 9–18 years is still likely to be more cost-effective than gender-neutral vaccination.
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/