SCHEDULES AND STRATEGIES FOR HUMAN PAPILLOMAVIRUS (HPV) IMMUNIZATION

1 | POLICY QUESTIONS AND OVERALL CONCLUSIONS FROM THE SAGE WG

The SAGE Working Group on HPV immunization held its first meeting on 27-28 September, in Menthon-Saint-Bernard, France.

The objectives of the meeting were:

• To examine the evidence and assess the potential contribution of HPV vaccination to the achievement of the proposed cervical cancer elimination goals under various scenarios.

• To discuss preliminary outcomes of systematic reviews and meta-analyses on burden of HPV-related cancers and anogenital warts, immunogenicity and efficacy of HPV vaccines in clinical trials, and effectiveness of HPV immunization programmes.

• To review preliminary modelling estimates on incremental effectiveness and cost-effectiveness of different HPV immunization strategies.

QUESTIONS CONSIDERED BY THE WORKING GROUP

1. What are the potential effects and cost-effectiveness of various vaccination strategies towards the achievement of cervical cancer elimination?
2. What is the potential contribution of HPV vaccination towards cervical cancer elimination?
3. What are the interim goals that can be achieved through immunization as part of the efforts towards cancer elimination?
4. What indicators can be proposed to monitor the accomplishment of these interim goals?
5. What is the additional research related to vaccines and immunization needed to attain these goals? And outline potential innovations that may help enhance the achievement of these goals.

The conclusions and recommendations from the Working Group meeting can be found in the Working Group report.

☑ **THIS SUMMARY INCLUDES**

☒ **THIS SUMMARY DOES NOT INCLUDE**

Detailed information on operational issues

2 | KEY FINDINGS

Burden of cervical cancer and HPV-related cancers

Estimates are that 700,000 new HPV-related cancer cases occurred in 2018 (**Table 1**). Of those, 630,000 (90%) cases were in women and 71,000 (10%) in men. The 570,000 (82%) cervical cancer cases drive these figures. Accurate HPV prevalence data and cancer incidence rates are lacking for many countries and are a source of uncertainty in particular for the burden of non-cervical cancers and for the burden in men.

Table 1. Cancer cases attributable to human papillomavirus (HPV) estimated for 2018, by cancer site (1;2)

Anatomical cancer sites (ICD-10 code)	Total incident cases	Total incident cases attributable to HPV	AF	Incident cases attributable to HPV by gender	
				Females	Males
Cervix uteri (C53)	570,000	570,000	100.0%	570,000	0
Vulva (C51)	44,000	11,000	24.9%	11,000	0
Vagina (C52)	18,000	14,000	78.0%	14,000	0
Anus (C21)	49,000	43,000	88.0%	22,000	21,000
Penis (C60)	34,000	18,000	51.0%	0	18,000
Oropharynx (C09–10)	93,000	29,000	30.8%	5,400	24,000
Oral Cavity (C00–06)	350,000	8,900	4.3%	3,100	5,800
Larynx (C32)	180,000	4,300	4.6%	500	3,700
Hypopharynx (C12-13)	81,000	0	0.0%	-	-
Total	**1,400,000**	**700,000**	**49.0**	**630,000**	**71,000**

Notes: Numbers over 100 are rounded to the closest two-digit number; ICD, international classification of diseases; AF, attributable fraction.

The vast majority of cervical cancer are in Sub-Saharan Africa and South-Eastern Asia. (1) The highest regional incidence and mortality rates are seen in Africa, with rates elevated in Southern Africa, Eastern Africa and Western Africa. Low- and lower-middle income countries account for more than half of cervical cancer cases, a burden that is in sharp contrast with the limited access to HPV vaccine by adolescent girls (**Figure 1**).

Figure 1. Comparison of cervical cancer incidence and % countries that have introduced HPV vaccine (3-5)

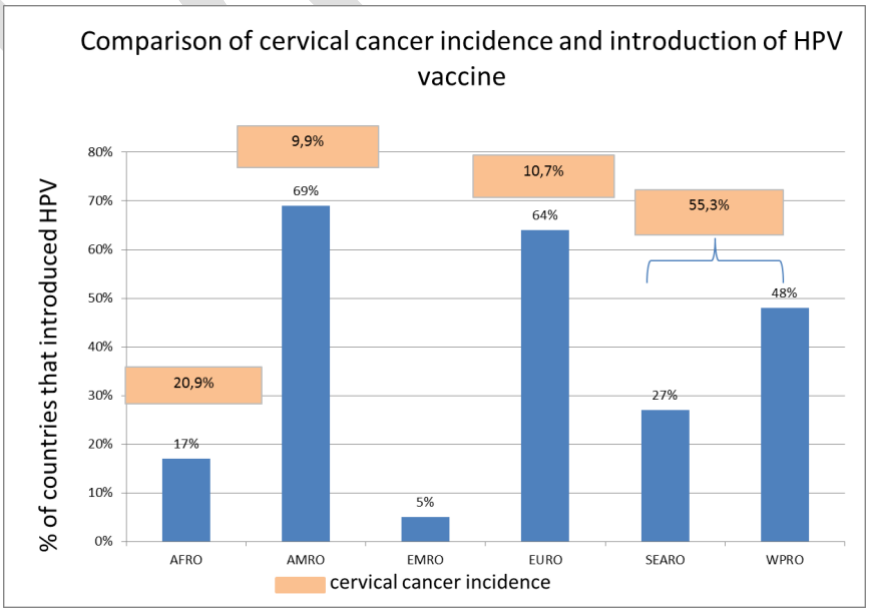


Table 2 provides the 2012 estimated number of cervical cancer cases by country income level and eligibility for GAVI support. For India (a low-middle income and GAVI-eligible country) and China (an upper-middle income and not GAVI-eligible country), 122,844 and 61,691 cervical cases were estimated, respectively.

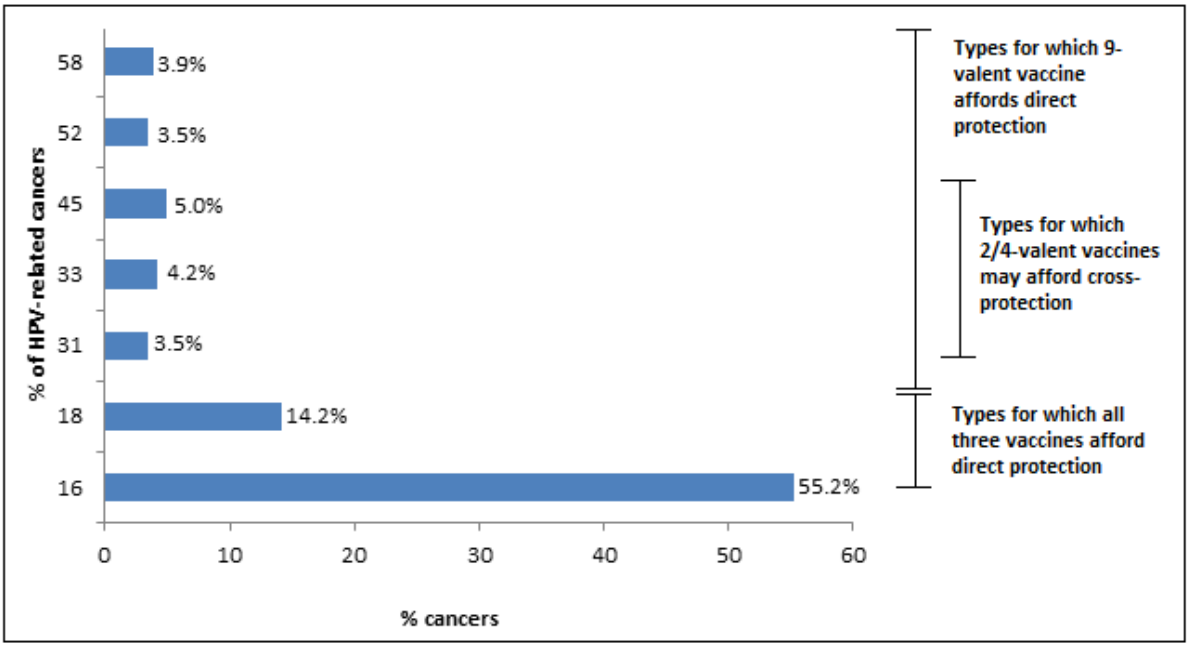
Table 2. Cervical cancer cases estimated for 2012 by country income classification by the World Bank, eligibility for GAVI support, and HPV vaccine introduction (3-6)

Country classification	**Cervical cancer cases (% of all cases)**		
	Total	**In countries that have introduced the HPV vaccine**	**In countries that have NOT introduced the HPV vaccine**
- Country income classification			
-- Low	59,804 (11.4%)	5,281 (1.0%)	54,523 (10.4%)
-- Lower middle	231,462 (44.1%)	1,340 (0.3%)	230,122 (43.8%)
-- Upper middle	169,448 (32.2%)	74,329 (14.1%)	95,119 (18.1%)
-- High	59,698 (11.3%)	50,683 (9.6%)	9,015 (1.7%)
-- Not categorized	4,956 (0.9%)	4,956 (0.9%)	0 (0.0%)
- GAVI support			
-- Eligible	239,158 (45.6%)	5,593 (1.1%)	233,565 (44.5%)
-- Not eligible	286,210 (54.4%)	130,996 (24.9%)	155,214 (29.5%)
Total	**525,368 (100.0%)**	**136,589 (26.0%)**	**388,779 (74.0%)**

Relative contribution of different viral types to HPV-related cancers

HPV is a necessary cause of **cervical cancer**. Globally, HPV 16/18 (the two high-risk types against which all three available HPV vaccines afford direct protection) are associated with 69.4% of the cases (**Figure 2**). HPV 31/33/45 (three high-risk types against which the bi- and quadrivalent vaccines may afford cross-protection) are associated with 12.7% 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 20.1% of the cases.

Figure 2. Relative contribution of different viral types to cervical cancer—World, 2012 (7)



Non-cervical HPV-related cancers are more frequently associated to HPV 16/18 than cervical cancer (80% versus 69.4% of HPV-related cancers, **Table 3**). HPV 16/18 are associated with 85% of head-and-neck cancers and 87% of anal cancers—the second and third more frequent HPV-related cancers with 38,000 and 35,000 estimated cases per year (**Table 6**). On the other hand, non-cervical HPV-related cancers are less frequently associated with HPV 31/33/45/25/58 than cervical cancer (10% versus 19%, **Table 3**).

Table 3. Relative contribution of selected high-risk HPV types to cervical and non-cervical HPV-related cancers

Anatomical cancer site	**Cancers attributable to HPV**	**Estimated number of cancers attributable to (% [by row])**		
		HPV 16/18 [A]	**Top ten most common HPV strains [B]**	**Difference [B-A]**
Cervix uteri	530,000 (100%)	370,000 (71%)	470,000 (90%)	100,000 (19%)
All other sites	110,00 (100%)	84,800 (80%)	95,300 (90%)	10,500 (10%)
Total	**640,000 (100%)**	**454,800 (71%)**	**565,300 (90%)**	**110,500 (17%)**

Note: adapted from **Table 6**.

Efficacy and immunogenicity of HPV vaccines

All three HPV vaccines afford strong protection at least against HPV 16/18 infections. Consequently, vaccination with any one of the vaccines is expected to provide substantial public health benefits in terms of prevention of cervical cancer and other HPV-associated cancers.

Data on immunogenicity and protection for clinical endpoints are now available for significant periods of follow-up. Available minimum follow-up periods for the different HPV vaccines are summarized in **Table 4**. Detailed data from a systematic review of randomized controlled trials of HPV vaccine is available in **Appendix 1**.

Table 4. Available minimum follow-up period for immunogenicity and selected cervical endpoints of HPV vaccine clinical trials among young women (8-12)

Endpoints	Available minimum follow-up period		
	2vHPV vaccine	4vHPV vaccine	9vHPV vaccine
Immunogenicity	9.4 years	9.9 years	≥3.5 years
Incident HPV cervical infection	9.4 years	9.9 years	5.5 years
Cervical intraepithelial neoplasia grade 1 or more	9.4 years	9.9 years	5.5 years

Based on evidence from both randomized clinical trials and post-introduction impact evaluations, the bi- and quadrivalent HPV vaccines provide some level of cross-protection against high-risk oncogenic HPV types other than 16/18, in particular for types 31/33/45. Available follow-up periods are 9.4 and 4.0 years for the clinical trials of the bi- /quadrivalent and 9-valent vaccines, respectively, while they reflect the time from vaccine introduction for impact evaluations (i.e., most data available from year 2009/2010 onwards). (8;9;13;14) Post-introduction impact evaluations are expected to provide in the near future additional long-term data on this cross-protection, including for endpoints such as cervical intraepithelial neoplasia (CIN) of grade 3.

Effectiveness and immunogenicity of one dose of HPV vaccine compared with two or three doses

A systematic review on the effectiveness of one dose of HPV vaccine was presented at the meeting of the SAGE working group on human papillomavirus immunisation, on 27-28 September 2018. (15) The review did not identify any randomised comparisons from randomised controlled trials (RCTs). The report included 18 cohort studies in females, of which two were post-hoc analyses of RCTs, and 2 case-control studies that contained data on clinical or immunogenicity outcomes.

The risk of bias for all studies and all outcomes was assessed and deemed to be high. Risk of bias assessments varied depending on the outcome being assessed, however many questions were judged at unclear risk of bias due to a lack of reporting, which did not allow for judgement. For many outcomes there was insufficient evidence, due to a small number of participants in the studies receiving only one dose of HPV vaccine, and few events of interest occurring in this group.

For the outcome of genital warts, seven studies were pooled, and the overall estimate showed that two doses (or three doses) of HPV vaccine results in significantly fewer cases of genital warts than one dose. In addition to the high risk of bias, there was high heterogeneity between these studies, so

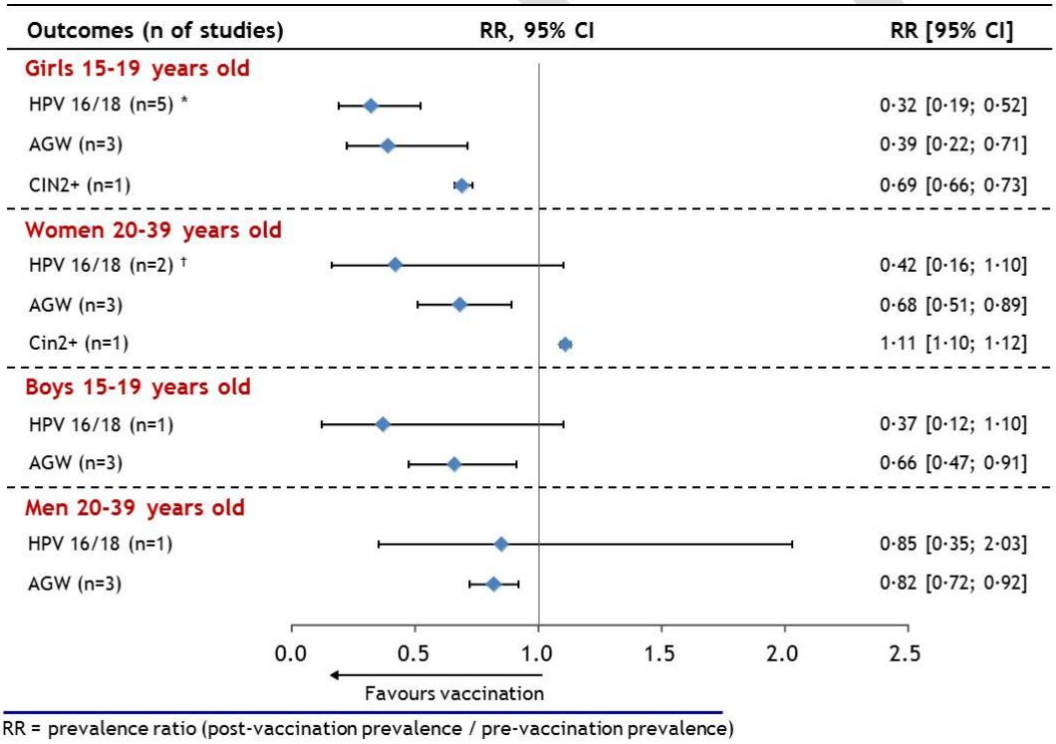
these results must be interpreted with caution. Only three studies reported adjusted formal analyses of one dose compared to three or two doses for genital warts, all showed a significant difference in favour of three doses or two doses.

As of October 2018, there are at least two (NCT02834637, NCT03180034) ongoing RCTs evaluating the efficacy of one dose of HPV vaccine. These RCTs will help clarify non-inferiority of one dose of HPV vaccine compared to two doses, in terms of immunogenicity and persistent HPV infection. The estimates from RCTs will provide a higher level of certainty. (the full report is available on the SAGE workspace)

Impact of HPV immunization programmes and herd effects

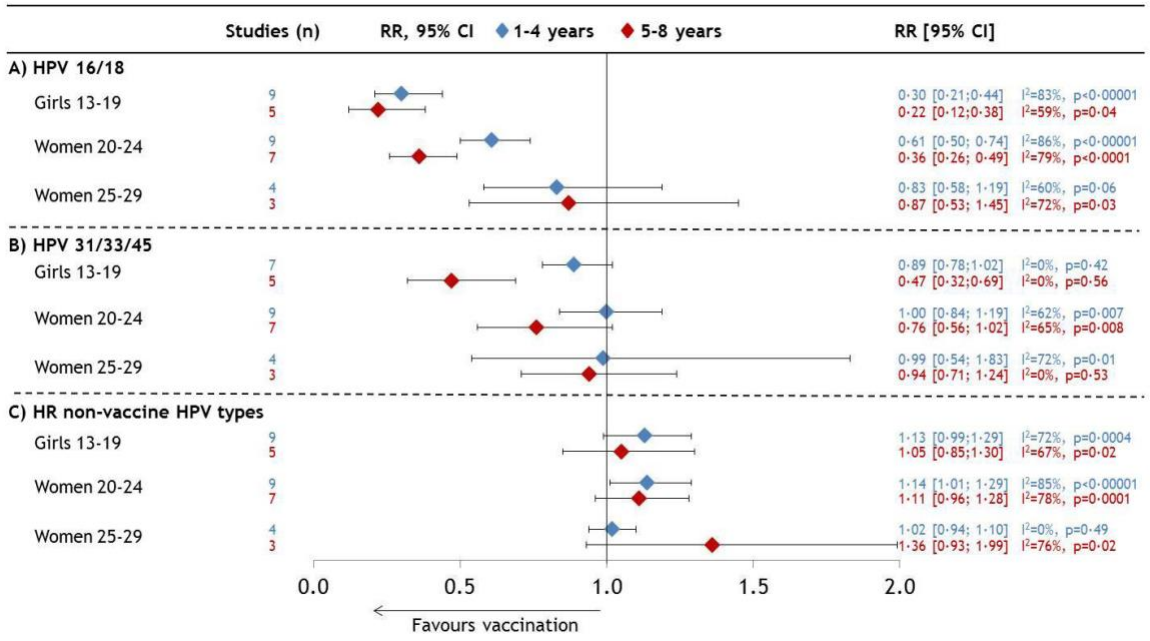
High population-level impact and the presence of herd effects were observed in high-income countries after both bi- and quadrivalent HPV vaccination when coverage was ≥50% (**Figure 3**). Post-introduction impact data for the 9-valent HPV vaccine are not available yet.

Figure 3. Observed population-level impact and herd effects of girls-only HPV vaccination in high-income countries with coverage ≥50% (16)

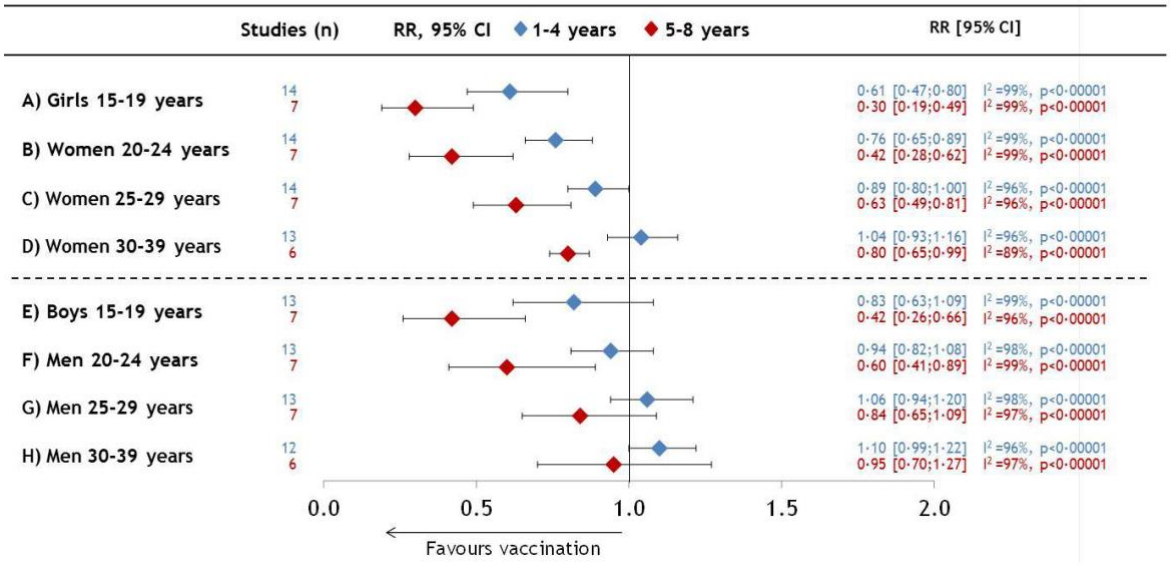


Updated figure

Changes in the prevalence of HPV infections between the pre-vaccination and post-vaccination periods (1-4, 5-8 years) (17)



Changes in anogenital wart diagnoses between the pre-vaccination and post-vaccination periods (1-4, 5-8 years) in countries using the quadrivalent vaccine (17)



Effectiveness and cost-effectiveness of HPV immunization strategies

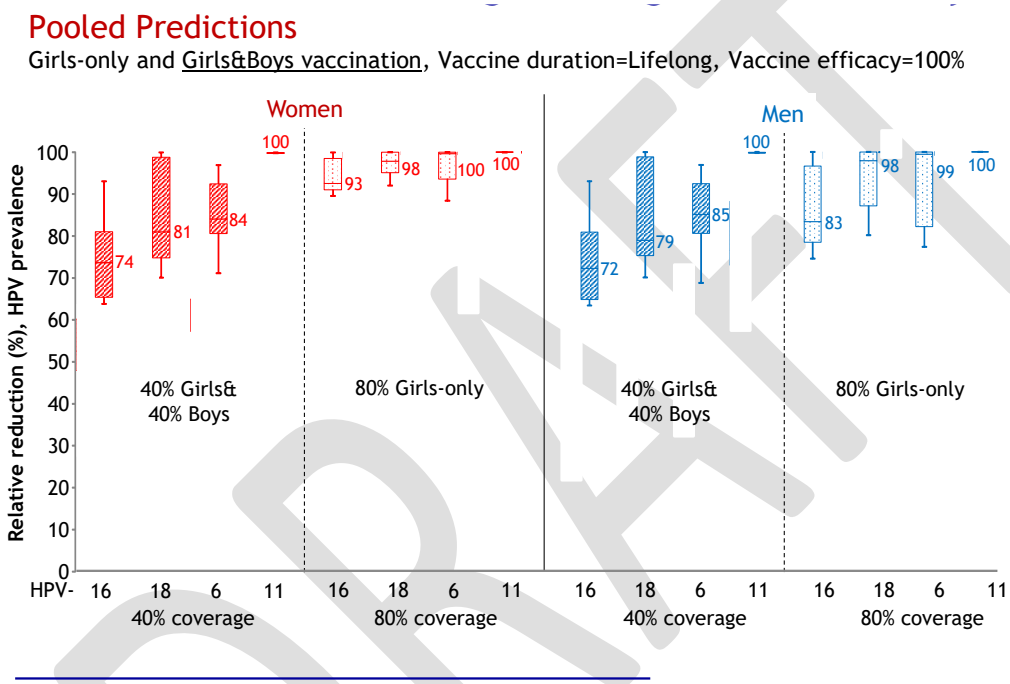
Modelling provides insight into the trade-offs of different HPV immunization strategies. **Figure 4** graphs the modelling estimates of the reduction in prevalence of HPV 6/11/16/18 in infections in women and men for vs girls-only immunization at 40% or 80% vaccination coverage.

In particular, **Figure 4a** shows a greater reduction in HPV infection prevalence, in HIC, for both women and men with a girls-only immunization at 80% vaccination coverage than a gender-neutral

immunization at 40% vaccination coverage. High coverage for girls only is thus more effective than offering the vaccine to boys. Nonetheless, there may be other tangible benefits to gender-neutral HPV immunization. Furthermore, **Figure 4b** supports the same conclusion in LMICs.

Similarly, **Figure 5** graphs the long-term reduction in cervical cancer cases for three different combinations of immunization targeting single or multiple age cohorts and with different age ranges in HICs and LMICs. Compared to the immunization targeting a single age cohort, immunization targeting multiple age cohorts would result in faster effectiveness due to wider direct protection and more rapid herd effects. As with single age cohort immunization, HPV vaccine introductions based on multiple age cohorts will require adequate operational and financial planning.

Figure 4a. Estimated effectiveness of girls-only and gender-neutral HPV immunization depending on vaccination coverage (18)



NOTE: Box plots represent the median, and 10, 25, 75, and 90th percentiles of the predictions generated by the models
Number of models: HPV16=16, HPV18=13, HPV6=6, HPV11=3

Figure 4b. Estimated effectiveness of girls-only and gender-neutral HPV immunization depending on vaccination coverage in HIC(a) and LMIC (b)

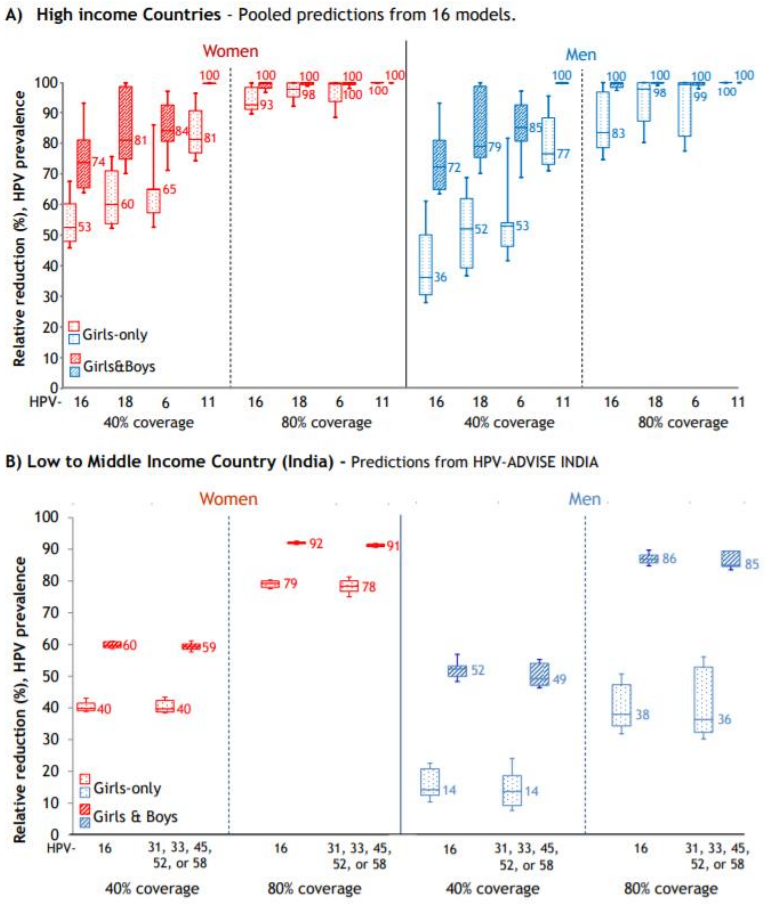
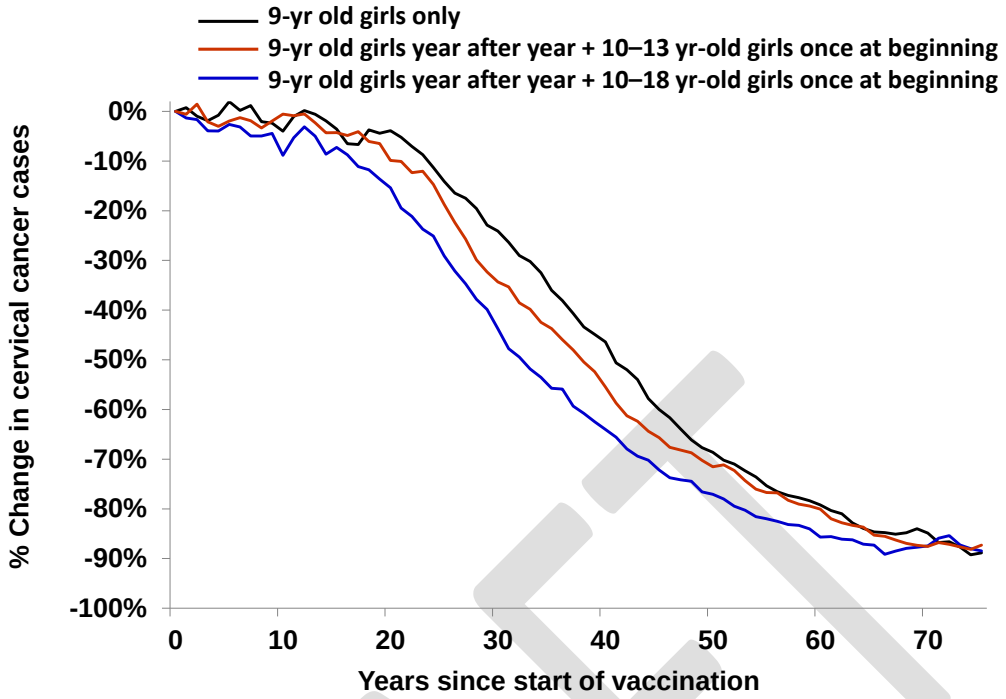
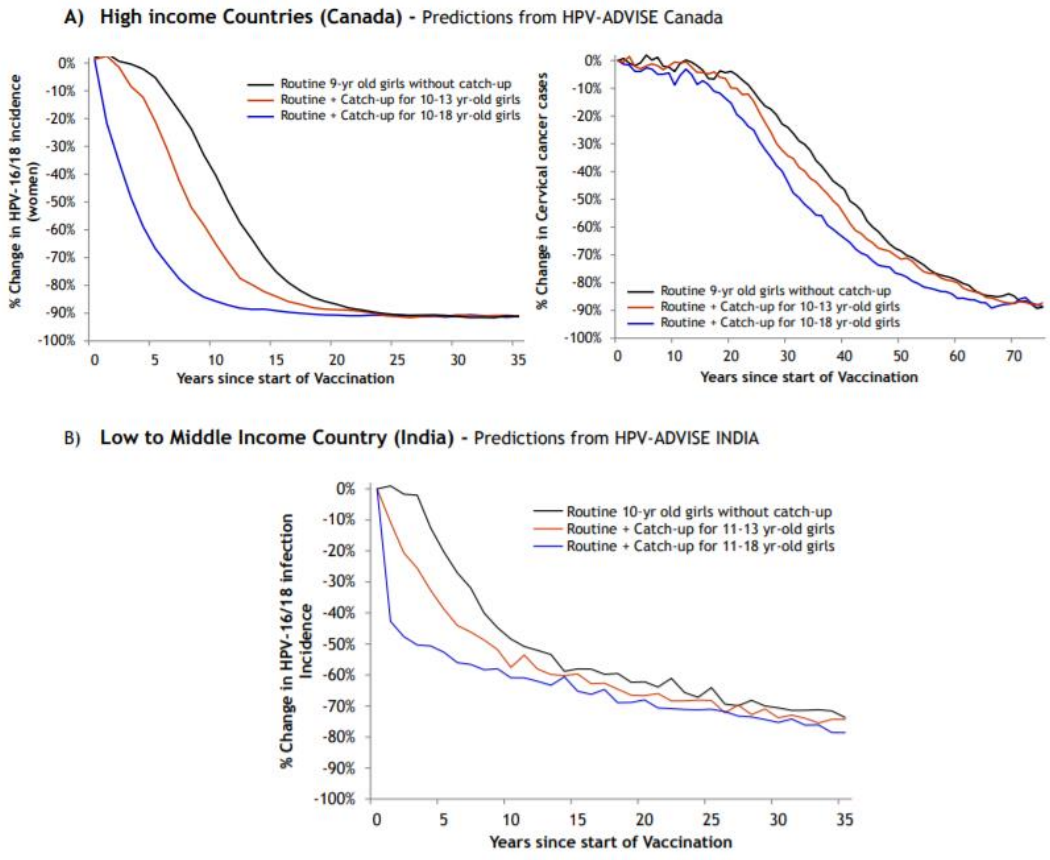


Figure 5a. Estimated effectiveness of immunization targeting single and multiple age cohorts (19)



Assumptions: 9-valent vaccine, coverage=80%, protection duration=lifelong, vaccine efficacy=95%, country=Canada

Figure 5b. Estimated effectiveness of immunization targeting single and multiple age cohorts in HIC and LMIC



3 | SUMMARIES OF EVIDENCE

Burden of HPV-attributable cancers by anatomical sites, sex, countries and HPV types[1]

Introduction. HPV were repeatedly assessed by the International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans (Monographs N°64, 90, and 100B). (20-22) After thoroughly reviewing epidemiological studies and mechanistic studies, the IARC working group classified HPV alpha types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 as carcinogenic to humans (Group 1), and HPV alpha type 68 as probably carcinogenic (Group 2A). These thirteen types are commonly referred to as high-risk or oncogenic types. Cancer sites for which the evidence of HPV involvement is considered sufficient are cervix uteri, vulva, vagina, penis, anus, oral cavity, and oropharynx. The IARC working group also observed that there were positive associations for larynx. Further evidence for larynx has since accumulated and we include it in our list of cancer sites for HPV in our attributable risk estimates.

Most cervical cancers result from HPV16/18 types (73%) and HPV6/11/16/18/31/33/45/52/58 types (90%) of infections and therefore are preventable through screening and vaccination. (23) 4.5% of new cancer cases, including cancers of the cervix, anogenital tract and head and neck, are associated with HPV infection. Cervical cancer alone accounts for 83% of those cases, most of which affect women in less-developed countries. The findings emphasize the importance of HPV screening and vaccination and the need for less-costly vaccines.

Methods. Estimates of the number of new cancer cases in 2012 were obtained from GLOBOCAN 2012 version 1.0 and high-quality cancer registries (for rarer cancer types and sub-types). (3) The number of cases due to HPV was calculated by country and then aggregated into eight geographical regions based on the United Nations classification and into WHO regions. The population attributable fraction (AF) for HPV is the proportion of new cancer cases that would have been prevented in a population if all HPV infections had been avoided or successfully treated before they caused cancer. Plummer et al. (2016) (2) described in detail the methods for AF calculation. AFs for each cancer site are summarized in **Table 1**. The relative contribution of HPV 16/18 and HPV 6/11/16/18/31/33/45/52/58 to HPV-associated cancer burden was derived from published meta-analyses. (7;24;25) Although HPV 6/11 are not oncogenic in cervical cancer, (21) they were not excluded from the present estimates because of possible involvement in some anogenital carcinomas, notably in the penis. (24) On account of substantial differences in incidence, sex- and country-specific distribution, and methods for causal attribution, the HPV-associated cancers will be assessed separately for: 1) the cervix, 2) other anogenital tract; and 3) head and neck and finally summarized.

Cervical cancer. Cervical cancer accounts for 530,000 cases every year or over 80% of HPV-attributable cancer cases worldwide (**Table 1**). The majority of cervical cancer occurs in the WHO Regions of South-east Asia, Western Pacific, and Africa (in **Table 5** SEARO, WPRO, and AFRO, respectively). HPV 16/18 are the most virulent types and together are responsible globally for 71% of cervical cancer cases. This percentage rises to 90% for HPV 6/11/16/18/31/33/45/52/58 (**Table 6**). The distribution of HPV 16/18 or the nine seven types is similar in women with cervical cancer in

[1] Prepared by Silvia Franceschi and Martyn Plummer, WHO/IARC, Lyon, France.

different parts of the world, including HIV-positive women. (26;27) The distribution of HPV types differs however by histology: the contribution of HPV 16 and HPV 18 is similar in adenocarcinoma.

Other anogenital cancers. Globally, 8,500 cases of vulvar carcinoma, 12,000 of vaginal cancer, 35,000 of anal cancer (of whom half in men), and 13,000 of penile cancer were attributable to HPV (**Table 1**). As for cervical cancer, the burden of HPV-associated anogenital cancers varies by WHO region but is not larger in less developed regions (**Table 5**). Anal cancer is a relatively rare malignancy but it is one of the most commonly occurring cancers in HIV-positive men who have sex with men. (28) On account of a greater predominance of HPV 16 compared to cervical cancer, HPV 16 and 18 are globally responsible for 87% of anal cancer (**Table 6**). The relative contribution of HPV 6/11/16/18/31/33/45/52/58 is 96%. Vulvar cancers and penile cancers are also relatively rare in all countries and were shown to have different aetiology, with or without active involvement of HPV infection, depending on histological sub-type, age group, and region. (2)The warty-basaloid sub-type and younger patients showed the highest HPV AF. Vaginal cancer is rarer than cancer of the vulva but HPV AF is higher. The relative contribution of HPV 16/18 (approximately 70%) and HPV 6/11/16/18/31/33/45/52/58 (approximately 85%) are similar in vulvar, vaginal, and penile cancer.

Table 5. Cancer cases attributable to human papillomavirus (HPV) estimated for 2012, by anatomical cancer site and WHO region or country development level (2;3)

WHO region	Total incident cases of all cancers	Total incident cancer cases attributable to HPV	AF	Anatomical cancer site						
				Cervix uteri	Vulva & vagina	Penis	Anus		Head & neck	
				Females	Females	Males	Males	Females	Males	Females
AFRO	660,000	100,000	15.2%	94,000	2,100	1,000	1,100	1,300	390	170
EURO	3,700,000	97,000	2.6%	67,000	5,400	2,800	3,000	4,500	12,000	2,800
EMRO	550,000	16,000	2.9%	14,000	720	74	480	390	400	210
PAHO	2,900,000	110,000	3.8%	83,000	5,800	3,200	2,800,	4,600	8,000	2,200
SEARO	1,800,000	200,000	10.9%	180,000	3,600	4,000	3,100	2,400	7,000	1,400
WPRO	4,400,000	110,000	2.5%	93,000	2,500	2,100	6,800	4,500	3,100	840
Total	**14,000,000**	**630,000**	**4.5%**	**530,000**	**20,000**	**13,000**	**17,000**	**18,000**	**31,000**	**7,700**

Notes: Numbers over 100 are rounded to the closest two-digit number; AF, attributable fraction.

Table 6. Cancer cases attributable to human papillomavirus (HPV) estimated for 2012, by anatomical cancer site and attributable HPV types (2;7;24;25)

Anatomical cancer site (ICD-10 code)	Total incident cases attributable to HPV	Cases attributable to (%)		
		HPV 16/18	Most common HPV strains	Difference
		[A]	[B]	[B-A]
Cervix uteri (C53)	530,000	370,000 (71%)	470,000 (94%)	100,000 (19%)
Vulva (C51)	8,500	6,200 (73%)	7,400 (87%)	1,200 (14%)
Vagina (C52)	12,000	7,400 (64%)	9,900 (85%)	2,500 (21%)
Penis (C60)	13,000	9,200 (70%)	11,000 (84%)	1,800 (14%)
Anus (C21)	35,000	30,000 (87%)	33,000 (96%)	3,000 (9%)
Head & neck (C01-06, 09–10,32)	38,000	32,000 (85%)	34,000 (90%)	2,000 (5%)
Total	**630,000**	**460,000 (73%)**	**570,000 (90%)**	**110,000 (17%)**

Notes: Numbers over 100 are rounded to the closest two-digit number; ICD, international classification of diseases.

Head and neck cancers. Head and neck cancers represent a large and heterogeneous group of malignancies, for which tobacco and alcohol consumption have long been recognized as the predominant causes worldwide. However, a fraction of these cancers, especially in the oropharynx, are caused by HPV (29,000 cases per year of whom 24,000 men) (**Table 1**). The fraction of oropharyngeal cancers attributable to HPV varies greatly being highest in more developed countries (up to 70% in the most recent studies in the USA and some North European countries), but much lower (<20%) and still uncertain in many countries. For cancers of the oral cavity (4,900 cases per year attributed to HPV of whom 3,200 men) and larynx (3,800, of whom 3,200 men), the prevalence of HPV was evaluated only in a few case series. (25;29) Most of the studies were conducted in Europe and North America, and yielded an average prevalence of approximately 4% at both sites. HPV AF in cancers of the oral cavity and larynx is lower (1–2%) in the rest of the world in which tobacco smoking and chewing are still very common. On account of a greater predominance of HPV16 compared to cervical cancer, HPV 16 and 18 are globally responsible for 85% of cancer of the head and neck while the relative contribution of HPV 6/11/16/18/31/33/45/52/58 is 90% (**Table 6**).

Limitations. AF for HPV is relatively accurate compared to AF for other infectious agents and, by and large, for lifestyle factors on account of the predominant weight of cervical cancer for which HPV is considered a necessary cause. Substantial limitations of the AFs presented in this report include, however, lack of HPV prevalence data and accurate cancer incidence rates for many countries. In addition, an accurate classification of the site/subsite of cancer origin in the head and neck and the

anogenital tract (other than the cervix) is difficult when cancer diagnosis is made in advanced stages and hence the burden of these disease is likely to be underestimated in less developed regions. The relative contribution of the nine HPV types in cervical cancer and other anogenital cancers may be overestimated because of the high frequency of multiple infections especially if newer very sensitive HPV assays are used.

Conclusions. Overall, 640,000 cancer cases are attributable to HPV every year. Wide geographical variation in the fraction of cancers attributable to HPV exists by region, sex, and age group. HPV-attributable cancers account for 8.6% and 0.8% of all cancers in women and men, respectively. HPV AF of all cancers in women ranges from <3% in Australia/New Zealand and the US to 26% in Sub-Saharan Africa. Globally, the relative contribution of HPV 16/18 and of HPV 6/11/16/18/31/33/45/52/58 types is 73% and 90%, respectively (**Table 6**). The population AFs that are shown in this report represent a useful base for prediction models and a potential incentive to act. However, AF should not be confused with the number of preventable cancers, i.e. fraction of cases that can be prevented by specific intervention(s) in a specific time frame.

Burden of anogenital warts[2]

A systematic review updated and expanded upon a previously published review on the burden of anogenital warts (AGW). The previous review by Fesenfeld et al. (2013) included studies that reported incidence, prevalence and self-reported history of AGW in the general adult population, published from January 2001 to January 2012. (30) Abstracts from relevant conferences 2009–2011 were also included. Studies were excluded if the adult population considered did not include at least ages 20 through to 40 years of age or if they focused on immuno-compromised or high-risk populations or children less than 15 years of age. The current review extended the search for publications from January 2012 to June 2016. (31) This update further extends the search period from June 2016 to December 2017. Inclusion criteria for the updated search were widened: studies were included on all age groups and HIV-positive men and women were included as a special interest population. High risk groups such as sex workers and men who have sex with men (MSM) were excluded. Overall, 44 studies were identified in the search for studies reporting incidence, prevalence and self-reported history and added to the 93 reported in the previous review. Results are summarized by sex, age and HIV-infection status in **Table 7**.

Table 7. Burden of anogenital warts (31)

	All ages		
	Both sexes	**Men**	**Women**
Incidence (per 100,000 persons)			
- HIV-negative persons of all ages	85–790	77–560	76–1,030
- HIV-negative persons aged ≤30 years	230–790	130–560	320–1,030
- HIV-positive persons	1,389	N/A	N/A
Prevalence (%)			
- All settings	0.019–17.0	0.014–13.7	0.023–10.0
- High detection and prevalence settings omitted	0.019–1.1	0.014–1.3	0.023–0.9
- HIV-positive persons	1.6–17.0	7.3–31	2.8–3.7

[2] Edited from a contribution prepared by Brian Buckley, Nicholas Henschke, Nicola Maayan, Rachel Marshall, Vittoria Lutje, and Karla Soares-Weiser, Cochrane Response, London, UK. The original contribution is available online at the SAGE workspace.

For AGW ***incidence***, data come from 33 studies, of which only one reported an estimate of incidence in HIV-positive persons. Incidence estimates were higher for studies that included data from settings where AGW detection is more likely (e.g. settings where genital examinations are routine) and/or attending population at greater risk (e.g. sexually transmitted infection clinics). The certainty of the evidence was judged as very low.

For ***prevalence***, data come from 27 studies. The certainty of the evidence was judged as very low or low; the most common risks of bias related to case definition, the validity of outcome measurement, and the representativeness of populations and sampling frames.

Finally, 14 studies compared ***health-related quality of life***, health status and health utilities amongst people with AGW and amongst people with other HPV-related diseases, healthy controls or population norms. The identified studies suggest that AGW have a significant impact on overall health related quality of life, in particular in terms of anxiety and depression. The factors contributing to the overall decrement in health status measures appear to be primarily associated with anxiety and depression, and to a lesser degree discomfort and pain. The certainty of the evidence was judged as very low or low.

Efficacy and immunogenicity data from randomized controlled trials of HPV vaccines

Three HPV vaccines are licensed and their characteristics are summarized in **Table 8**.

Table 8. Characteristics of licensed human papillomavirus vaccines

Characteristic	Bivalent (2v) vaccine	Quadrivalent (4v) vaccine	9-valent (9v) vaccine
Trade name and manufacturer	Cervarix™, GSK	Gardasil™, Merck	Gardasil9™, Merck
Virus-like particle types (VLP)	16/18	6/11/16/18	6/11/16/18/ 31/33/45/52/58
L1 protein dose	20/20 µg	20/40/40/20 µg	30/40/60/40/ 20/20/20/20/20 µg
System for VLP L1 expression	*Trichoplusia ni* (Hi-5) insect cell line infected with L1 recombinant baculovirus	*Saccharomyces cerevisiae* (bread yeast) expressing L1	Same as 4v vaccine
Adjuvant	ASO4 (500 µg aluminum hydroxide, 50 µg 3-O-deacylated-4'-monophosphoryl lipid A)	225 µg AAHS (amorphous aluminum hydroxyphosphate sulfate)	500 µg AAHS

Note: Adapted from Herrero et al. (2015) and Stanley (2016). (32;33)

In March 2014, a systematic review and meta-analysis of randomized controlled trials of HPV vaccines was submitted for consideration to SAGE. (34) As a result, a 2-dose HPV immunization schedule with a minimum interval of 6 months between doses was recommended for adolescents aged 9–14 years who are not HIV-positive or immunocompromised.

That work was now extended to include trials with female participants that have been published in the meantime as well as, without limitations in time, all trials with male participants regardless of their sexual orientation or whether living with a HIV infection. (35) **Appendix 1** lists the characteristics and findings of the included studies. Nine different comparisons were formally carried out as follows:

- Two doses of HPV vaccine versus three doses of HPV vaccine in younger females (9 to 15 years)
- Longer interval (0, 12 months) versus shorter interval (0, 6 months) of 2-valent HPV vaccine in females

- Two doses of HPV vaccine in younger females (9 to 15 years) versus three doses of HPV vaccine
- 9-valent HPV vaccine versus 4-valent HPV vaccine in females
- HPV vaccines versus placebo (or control vaccine) in males
- HPV vaccines in males versus HPV vaccines in females
- 9-valent HPV vaccine versus 4-valent HPV vaccine in males
- HPV vaccines in men who have sex with men (MSM)
- HPV vaccines in HIV-infected males and females

These formal comparisons, included an evaluation of the quality of evidence based on GRADE, is assembled into a document available online.

Observed impact and herd effects of HPV immunization programmes[3]

A systematic review updated and expanded upon a previously published review on the population-level impact and herd effects of HPV immunization programmes. The previous review by Drolet et al. (2015) included studies published between January 2007 and February 2014. (36) Identical methods were used to update that review with studies published between February 2014 and July 2016. (16) A further update of the systematic review that includes studies until June 15, 2017 is under review by a peer review journal. (17)

Studies were eligible if they reported changes, between the pre- and post-vaccination periods, in the incidence or prevalence of at least one HPV-related endpoint: HPV infection, anogenital warts, or CIN grade 2 or higher. Heterogeneity was assessed across studies and trends analysis was performed to examine dose-response association between each study effect measure and HPV vaccination coverage. All analyses were stratified by age and sex and random-effects models were used to derive pooled relative risk (RR) estimates. The pooled estimates presented in the updated review are based temporarily on data collected in the initial systematic review and on descriptive statistics for the newly identified articles.

Table 9 shows the studies included in the original and updated systematic review. Overall, studies were conducted in 13 high-income countries. Although no study examined the impact of HPV vaccination in LMIC, baseline data and/or description of the surveillance system they will be used to document changes over time were identified several countries, such as Bangladesh, Bhutan, China, and Rwanda.

[3] Edited from a contribution prepared by Mélanie Drolet, Élodie Bénard and Marc Brisson, Université Laval, Québec, Canada. The original contribution is available online at the SAGE workspace.

Table 9. Endpoints of the studies systematically reviewed to evaluate the population level impact and herd effects of human papillomavirus (HPV) immunization programmes (16;17;36)

Endpoints	Studies identified for the original systematic review (1/2007–1/2014)	Studies identified for the updated systematic review (published 2/2014–7/2016)
HPV infection	7	15 (11 new studies/ 4 updates of previously identified studies)
CIN2+	2	7 (6/1)
AGW	11	8 (5/3)
Total	**20**	**29 (21/8)**

Notes: CIN2+, cervical intraepithelial neoplasia grade 2 or higher; AGW, anogenital warts; a study published in the 2 years reports both HPV infection and CIN2+ endpoints.

Additional evidence is emerging on the population-level impact of **girls-only** HPV immunization. In particular, the direct and herd effects of HPV vaccination from the initial review are confirmed in the updated review. All data only refers to bi-and quadrivalent HPV vaccines. In the first four years following the introduction of HPV vaccination, HPV-16/18 prevalence decreased significantly among girls aged 13-19 years and women aged 20-24 years compared to the pre-vaccination period. After 5-8 years of vaccination, HPV-16/18 prevalence decreased significantly by 78% (RR 0·22 [95% CI 0·12–0·38]) and 64% (RR 0·36 [95% CI 0·26–0·49]) among girls aged 13-19 years and women aged 20-24 years, respectively, compared to the pre-vaccination period. No significant changes in HPV 16/18 prevalence were observed among women aged 25-29 years (mostly unvaccinated) during the 0-4 and 5-8 years follow-up periods. (**Figure 1**). For HPV 31/33/45, there were substantial but non-significant decreases in prevalence during the first 4 years of vaccination among girls aged 13-19 years. However, after 5-8 years of vaccination, HPV 31/33/45 prevalence decreased significantly by 53% (RR 0·47 [95% CI 0·32–0·69]) among girls aged 13-19 years and non-significantly by 24% (RR 0·76 [95% CI 0·56–1·02]) among women aged 20-24 years. No significant changes in HPV 31/33/45 prevalence were observed among women aged 25-29 years during the 0-4 and 5-8 years follow-up periods. Finally, although mostly non-significant, slight increases in the prevalence of high-risk types not included in the vaccine were observed for all age groups. Furthermore, a study in Australia among boys aged 15-19, and men aged 20-29 and 30-39, demonstrated a lower seroprevalence of the vaccine-specific HPV types 6, 11, 16, and 18 in males in all 3 age groups compared with results from the previous pre-vaccination 2005 HPV serosurvey (37).

In the first four years following the implementation of quadrivalent HPV vaccination, anogenital wart diagnoses decreased significantly among girls/women aged 15-19 and 20-24 years. In addition, non-significant but substantial decreases were observed among mostly unvaccinated older women and boys aged 15-19 years. After 5-8 years of HPV vaccination, declines in anogenital wart diagnoses were significant for girls/women in all age groups examined and for boys/young men. Anogenital wart diagnoses decreased significantly by 70% (RR 0·30 [95% CI 0·19–0·49]) and 20% (RR 0·80 [95% CI 0·65–0·99]) among the youngest and oldest groups of girls/women, respectively, and by 58% (RR 0·42 [95% CI 0·26–0·66]) and 40% (RR 0·60 [95% CI 0·41–0·89]) among boys aged 15-19 years and young men aged 20-24 years, respectively. Studies on the population-level impact of **gender-neutral** HPV immunization were done for Australia, Canada and USA. However, 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 is still too early to measure the additional impact of gender-neutral vaccination at the population-level.

Many countries or territories (Australia, British Columbia in Canada, Denmark, Greece, New Zealand, Norway, Sweden, the UK and the USA) included **catch-up** vaccination in their HPV immunization programmes. However, most of these countries also achieved high coverage in the primary age target of adolescent girls. One Study in Australia found that vaccinating multiple age cohorts produced markedly faster direct/herd effects, and it added benefits that last for 20–70 years. Furthermore, the number needed to vaccinate to prevent 1 anogenital warts (AGW) case or cervical cancer (CC) was similar for routine + catch-up (AGW = 9.9, CC = 678) and routine-only vaccination (AGW = 9.9, CC = 677), thus providing similar levels of efficiency per person vaccinated (17).

The systematic review of studies evaluating the impact of HPV immunization programmes shows that HPV immunization is highly effective amongst vaccinated individuals and provides herd effects in settings with high vaccination coverage. This observation reinforces the need for high vaccination coverage to maximize the population-level impact and herd effects of HPV immunization programmes.

A systematic review and meta-analysis published in October 2016 evaluated changes between pre- and post-vaccination periods in infection rates of high-risk HPV types other than types 16/18. (38) The study included 9 studies with data for 13,886 girls and women aged ≤19 years and 23,340 women aged 20–24 years. Among the younger age group, evidence of cross-protection was found for HPV 31 (prevalence ratio=0.73 [95% CI 0.58–0.92]) but little evidence of cross-protection for HPV 33 and HPV 45 (prevalence ratio=1.04 [95% CI 0.78–1.38] and 0.96 [95% CI 0.75–1.23]).The authors concluded that continued monitoring for either decreases or increases in infections rates of non-vaccine high-risk HPV types is important.

Cost-effectiveness of HPV immunization programmes[4]

Literature was systematically searched for cost-effectiveness estimates of various HPV immunization strategies. Thirty-four studies were included in this systematic review, most conducted in high-income countries. (39) There is no evidence from low-middle income countries. Six studies analysed the cost-effectiveness of 9-valent vaccine versus bi- or quadrivalent vaccine, 8 studies conducted the cost-effectiveness analyses of gender-neutral HPV immunization versus female-only immunization, and 17 studies evaluated the cost-effectiveness of single age cohort vaccination of 12-year-old girls combined with multiple age-cohort immunization. Three studies analysed both the cost-effectiveness of gender-neutral immunization and multiple age-cohort immunization. Key findings are reported here and the full summary is available online. This systematic review extends a previous work by Fesenfeld et al. (2013) (30)

Cost-effectiveness of different HPV vaccines in girls-only immunization.

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

[4] Edited from a contribution prepared by Nathorn Chaiyakunapruk and Siokshen Ng, Monash University Malaysia. The original contribution is available online at the SAGE workspace.

price for 9-valent vaccine remain unknown especially in LMIC, the cost-effectiveness of immunization with 9-valent HPV vaccine is still uncertain and more economic evaluations are still needed to determine more accurate the value for money of 9-valent HPV immunization.

Three studies concluded that vaccination with 9-valent vaccine was likely to be cost-effective compared to current vaccines, at least within the price range explored. In HICs (e.g. Canada and Austria), vaccination with 9-valent vaccine was cost-effective if the additional cost of 9-valent vaccine compared to quadrivalent vaccine is less than US$23-US$47 while in LMICs (e.g. Kenya and Uganda), the additional cost of 9-valent vaccine must not exceed US$8.40-US$9.80. Two studies concluded that switching to a 9-valent gender-neutral HPV vaccination was cost-saving regardless of the assumptions on cross-protection. However, one study reported that providing additional 9-valent vaccination to females aged 13–18 years who had previously completed a series of HPV vaccine was not cost-effective because additional 9-valent vaccination incurred an extra cost of a full price 9-valent vaccine for each vaccinated person. In contrast, when a primary quadrivalent HPV program was completely switched to a primary 9-valent program instead, the additional cost incurred was the differences in cost between the 9-valent and quadrivalent vaccines only. (39)

Cost-effectiveness of gender-neutral HPV immunization.

Eight studies reported that vaccinating adolescent boys in addition to girls was cost-effective. However, two studies further specified that this vaccination strategy was no longer cost-effective when vaccine coverage for female is above 75%. Majority of the cost-effective studies comprehensively captured all HPV-related diseases including male-associated cancers such as penile and oropharyngeal cancer. Hence, the assumption of lower female vaccine coverage and the inclusion of male-associated HPV diseases would result in a more favourable conclusion for the gender-neutral HPV vaccination strategy.

Cost-effectiveness of vaccinating multiple age cohorts.

Most studies reported that immunization targeting multiple age cohorts were cost-effective due to wider primary protection and more rapid herd effects. Specifically, the multiple age-cohort female vaccination strategy was cost-effective in the age range of 9–14 years old. However, the cut-off range where HPV vaccination was no longer cost-effective varied among studies and was more important in differentiating between studies than their overall conclusions. (39) Nine studies concluded that HPV vaccination was cost-effective until the age of 24, three studies up to the age of 25 and one study till the age of 26. However, it is important to address that two of these cost-effectiveness studies compared multiple age-cohort vaccination to no vaccination strategy instead of routine vaccination of female aged 12. However, the extension of immunization age needs to be interpreted cautiously as several studies analysed the cost-effectiveness of HPV immunization in a single age range only and did not compare in the next age range gradually. When HPV vaccination was compared in the next age range gradually, it was cost-effective till the age of 18 years only in two studies and 15 years in one study. (39) However, above the age of 15 years, the upper age limit at which HPV immunization stop being cost-effective depends on the country context. A study in United Kingdom concluded that HPV vaccination up to the age of 18 years was only cost-effective in the presence of protection to non-naïve women, demonstrating that the exclusion of vaccine protection among non-naïve women may underestimate the cost-effectiveness of vaccinating additional older age women. (40) A Canadian study found that HPV vaccination till the age of

18 years was cost-effective irrespective of the delivery method, with school-based delivery had a lower ICER compared to clinic-based delivery. (41) Among the seventeen studies, only one study reported that multiple age-cohort vaccination (17–25 years) was not cost-effective unless vaccine price in Netherlands was reduced by 52%. (39) 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.

Vaccine price has also emerged as an important parameter in the cost-effectiveness analyses. The assumed vaccine prices ranged widely across studies, from below US$5.60 per dose in LMIC to US$360 per dose in HIC. A Brazilian study demonstrated that when vaccine price increased from US$12 to US$135 per dose, vaccinating adolescent boys in addition to girls was no longer cost-effective even when vaccine coverage for female was minimized to 25%. (39)

Effectiveness and cost-effectiveness modelling of HPV immunization strategies

Modelling methods and estimated effectiveness are available online under the supplemental material for the SAGE meeting.

Age of sexual initiation

Several resources are available on age at sexual initiation specifically for LMIC.

An analysis of demographic health surveys published in September 2012 compared national trends in adolescent reproductive and sexual. (42) This analysis included also the percentage of people who had had sexual intercourse by age 15 years in 37 LMIC (**Figure 6**). For most countries, ≤15% of adolescents would have had sexual intercourse by age 15 years. The analysis also reports data on age-mixing in sexual relationships (e.g., adolescent women who had sex with partners who were ≥6 years older).

Chandra-Mouli et al. (2014) also reported that sexual activity of adolescents varies markedly for boys and versus girls and by region. (43) **Table 10** shows the percent of people aged 20–49 years in 12 LMIC who reported having had sexual intercourse by ages 15 and 18 years.

Actual distribution of adolescents who are sexually active by a specific age can also be found. For instance, Zaba et al. (2004) reported data for Kenya and Uganda (**Figure 7**). (44)

Finally, UNAIDS launched in July 2016 a website that reports information on men who have sex with men. The data include estimates of population size and HIV prevalence. The site is accessible at www.aidsinfoonline.org.

Table 10. Report of sexual intercourse by ages 15 and 18 years reported by people aged 20–24 years in 12 LMIC (43)

Region/country, year of survey	% respondents reporting having had sexual intercourse by age 15 years		18 years	
	Male	Female	Male	Female
Sub-Saharan Africa				
- Ghana, 2008	5	7	27	41
- Mali, 2006	4	26	27	73
- Tanzania, 2010	6	15	40	58
- Zimbabwe, 2010-11	4	4	23	38
Asia/Central Asia				
- Azerbaijan, 2006	1	1	22	12
- Bangladesh 2011	1	28	6	64
- Cambodia, 2010	0	1	4	15
- India, 2005-06	-	13	-	43
Latin America/Caribbean				
- Brazil, 1996	33	10	75	43
- Dominican Republic, 2007	27	16	72	51
- Haiti, 2012	35	13	77	51
- Peru, 2012	-	7	-	43

Figure 6a. Percentage of adolescents aged 15–19 years who have had sexual intercourse by age 15 years (42)

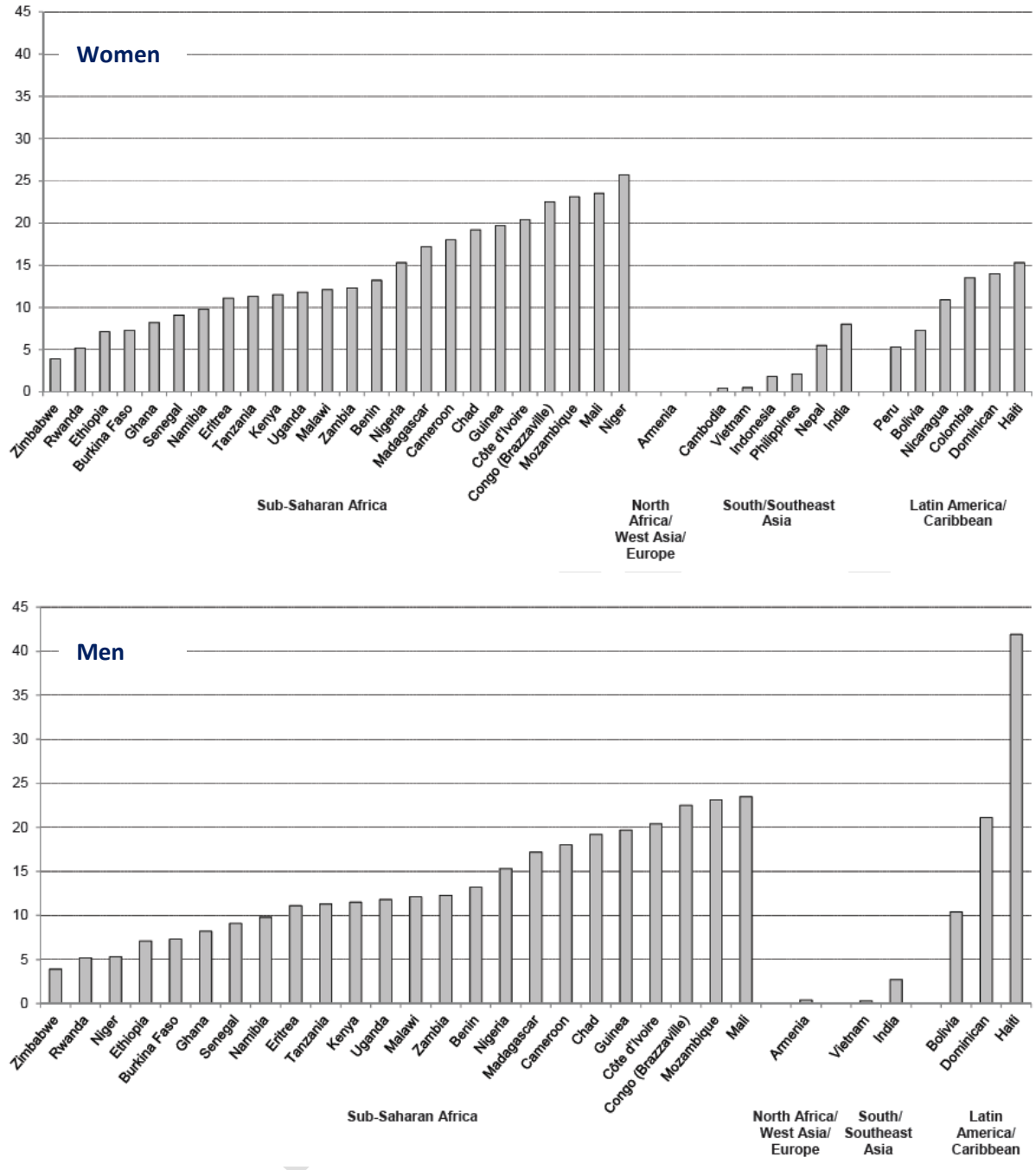


Figure 6b. Percentage of 15-year old girls who report sexual intercourse (Data up to date as of 16 Mar 2017)

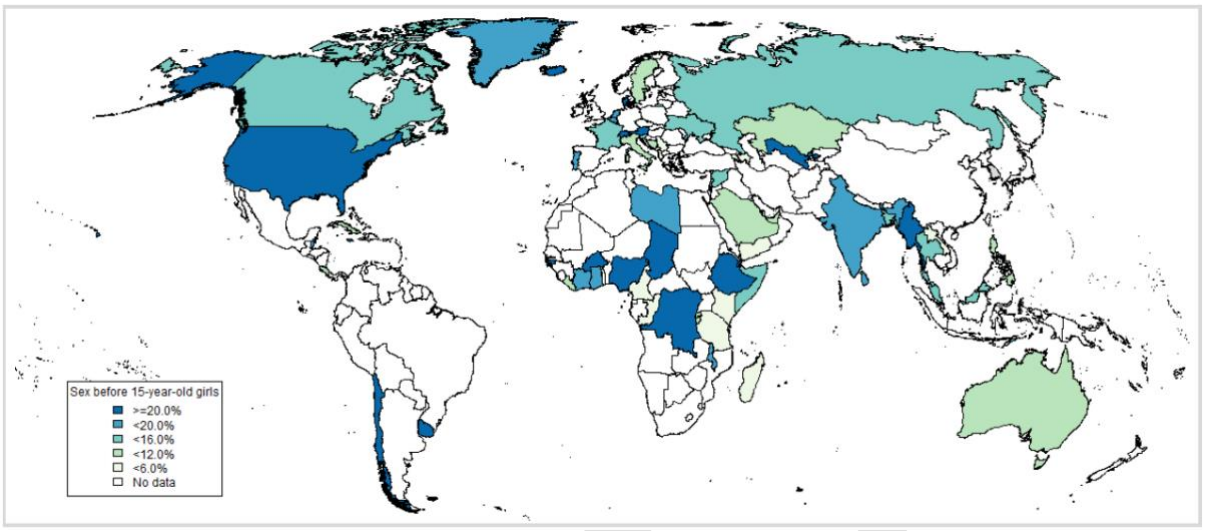


Figure 6c. Percentage of adults aged 20-49 years who have had sexual intercourse by age 15 years

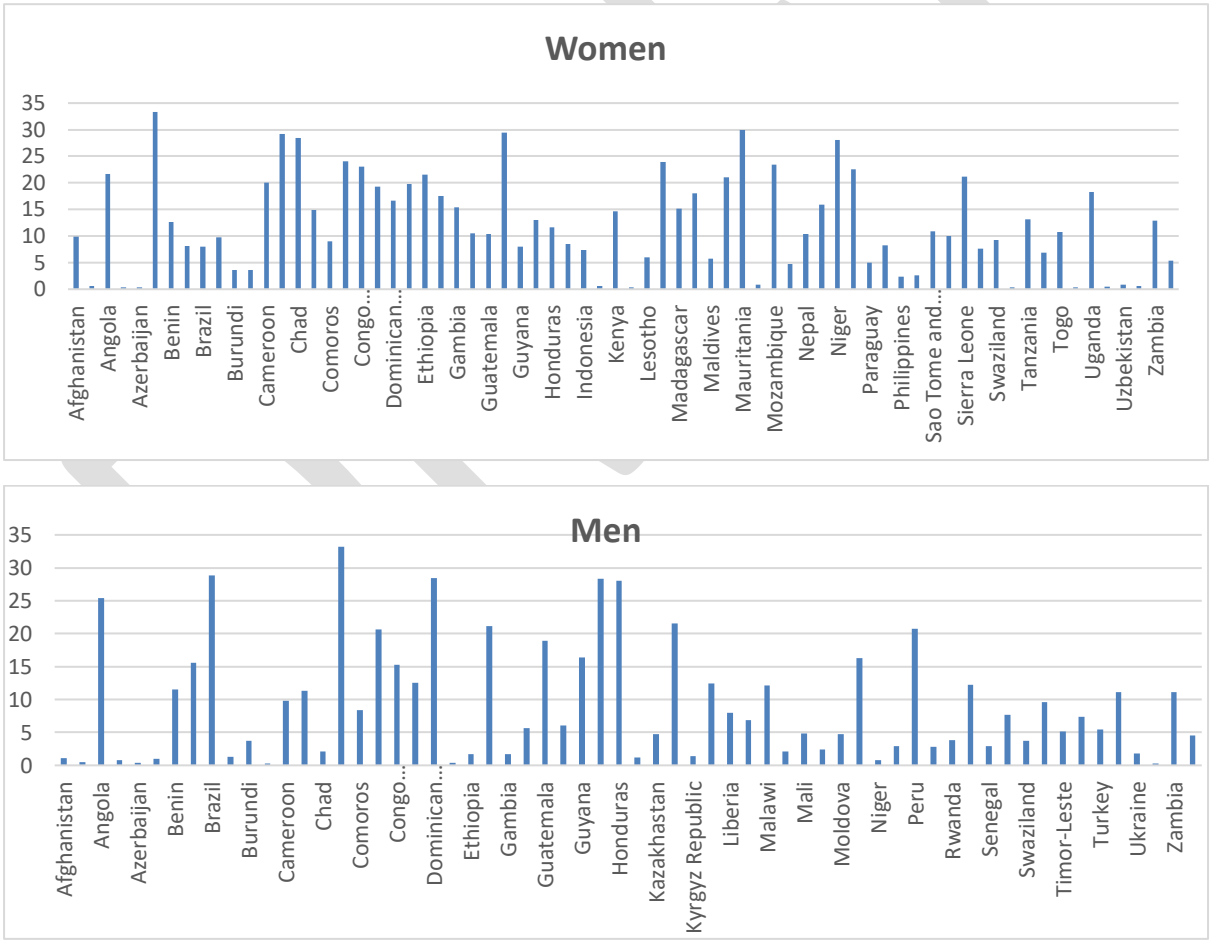
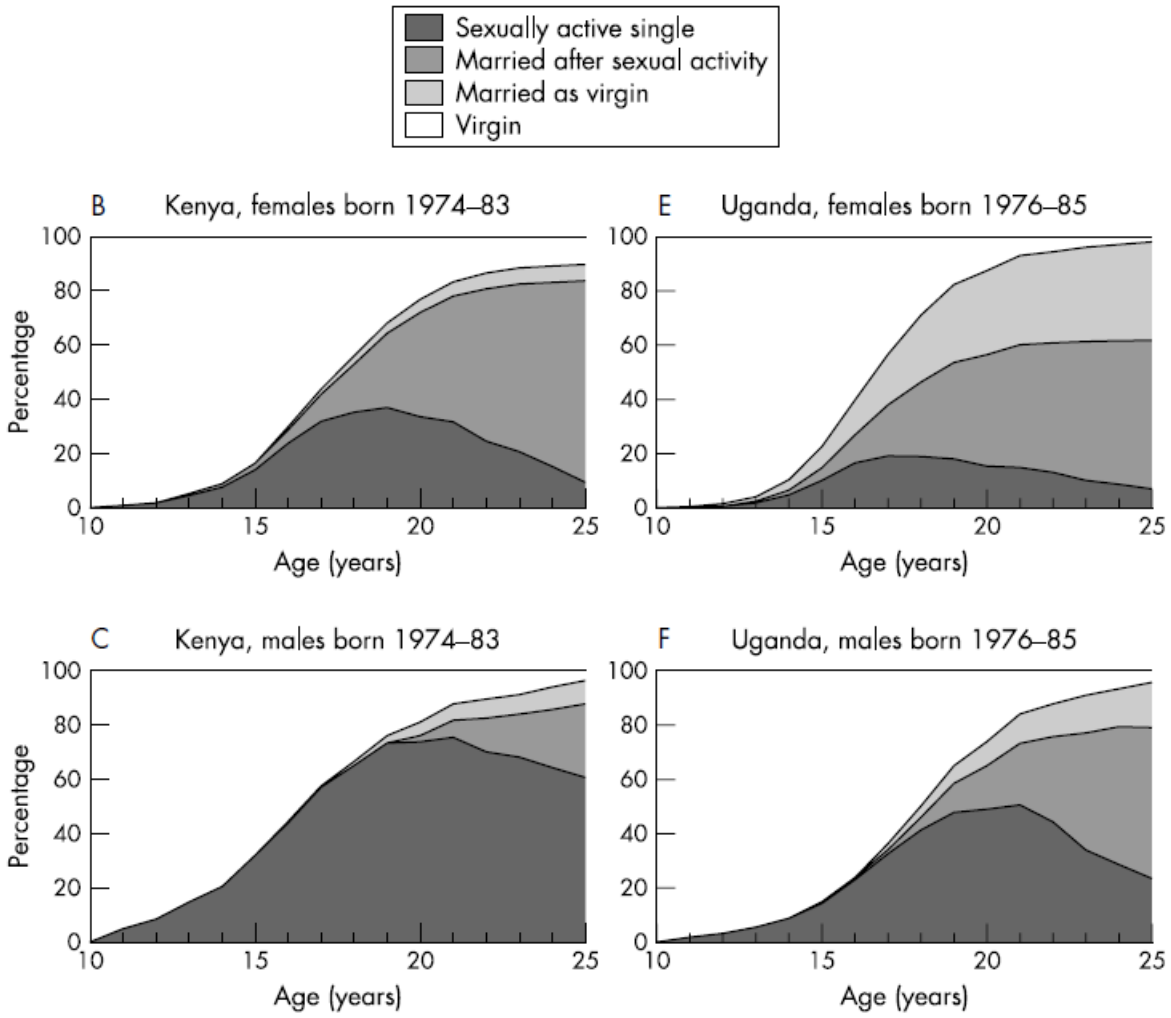


Figure 7. Percentage of females and males aged 10–25 years of Kenya and Uganda who were sexually active, by marital status (44)



Vaccine Acceptability

A systematic review was published in 2014 of peer-reviewed studies on the knowledge and awareness of cervical cancer, HPV and HPV vaccine, and willingness and acceptability to vaccinate. (45) A total of 124 relevant articles were selected and reviewed and 29 articles based on 27 studies in 13 different SSA countries including 6 countries which implemented HPV vaccination pilot programs (Cameroon, Lesotho, Rwanda, South Africa, Tanzania and Uganda). Twelve studies examined acceptability levels of HPV vaccine and one study examined acceptability. All studies reported high levels of acceptability of HPV vaccine.

The main conclusion was there is an urgent need for more education to inform the public about HPV, HPV vaccine, and cervical cancer. The vaccine has in general high level of acceptability, but still need to successfully be introduced in the vaccination programmes. There is a lack of preparedness to introduce the vaccine in in most of sub-Saharan African countries

The Wits Reproductive Health and HIV Institute (Wits RHI), is working to prepare a proposal to assess key factors responsible for sub-optimal uptake of HPV vaccination in the national public sector programme in South Africa, with a particular focus on second-dose uptake. The main objective will be to identify areas to improve vaccination coverage addressing vaccine hesitancy.

Vaccine Supply

Twelve years after the first HPV vaccine registration, less than half of WHO Member States have introduced HPV vaccine into the routine national immunization schedule. Introductions are lowest in Gavi 73 countries and non-Gavi, non-PAHO middle-income countries (MICs)

HPV Supply is currently insufficient to meet demand and some countries have or will have to postpone introductions. WHO issued a call for action towards global cervical cancer elimination in May 2018 which, through national introductions in all countries and increased coverage, is estimated to increase total demand for HPV vaccines by at least 100M doses over the next 10 years.

Due to the cervical cancer elimination initiative, sizeable increases in supply will be required, therefore supply constraints are expected until at least 2024. This timing may change depending on selected vaccination strategies and investment decisions of current manufacturers, as well as on the timing of the three programs in advanced stage of clinical development.

Meeting the projected demand volumes required for multi-age cohort (MAC) introductions (9–14 years of age), as per WHO recommendation, will remain especially problematic in large countries, as well as meeting additional demand generated by implementing gender-neutral HPV vaccination.

Affordability of HPV vaccines in non-Gavi MICs is a barrier which needs to be addressed to encourage introduction.

4 | LIST OF SUPPORTING DOCUMENTS AVAILABLE ONLINE

- Systematic review and meta-analysis of HPV vaccine clinical trials: 1 final report and 12 individual studies, 351 pages in total
- Systematic review of burden of anogenital warts, 83 pages
- Summary of scenarios for cervical cancer elimination, 1 page
- Articles of HPV introduction and costing, three articles with 17, 13 and 8 pages
- Systematic review and meta-analysis of HPV vaccination impacts, 10 pages
- Single-dose HPV vaccination: general summary, technical synthesis, white paper and systematic review, 159 pages in total
- Article of potency of HPV prophylactic vaccines, 6 pages
- HPV Vaccine – Global Market Study, 30 pages
- Systematic review of cost-effectiveness of HPV vaccination, 16 pages

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APPENDIX

Appendix 1. Summary of evidence from randomized controlled trials of human papillomavirus virus identified in the update and extension of the systematic review done by D'Addario et al. (2014)

Topic	Reference	HPV vaccine	Setting	Population	Intervention	Outcome	Summary of finding	Evidence certainty
2 doses in younger females vs. 3 doses in older females	Romanowski et al, 2011, 2014 & 2016	2v	Canada & Germany	9 to 25-year old females [124 participants]	2 doses (0,6m) in females aged 9–14 years vs. 3 doses (0,1,6m) in females aged 15–25 years	Immunogenicity	Similar GMTs for HPV 16/18 at 60-month follow-up	VERY LOW
2 doses in younger females vs. 3 doses in older females	Lazcano Ponce et al, 2014	2v	Mexico	9 to 25-year old females [1,526 participants]	2 doses (0,6m) in females aged 9–10 years vs. 3 doses (0,1,6m) in females aged 18–24 years	Immunogenicity	• Higher GMTs for HPV 16/18 up to 21-month follow-up • Similar seropositivity for HPV 16/18 one month after last dose (at 7-month follow-up)	LOW (GMTs) MODERATE (seropositivity)
2 doses in younger females vs. 3 doses in older females	Puthanakit et al, 2016	2v	Canada, Germany, Italy, Taiwan, and Thailand	9 to 25-year old females [1,032 participants]	2 doses (0,6m) in females aged 9–14 years vs. 3 doses (0,1,6m) in females aged 15–25 years	Immunogenicity	• Similar or higher GMTs for HPV 16 and 18, respectively, one month after last dose (at 7-month follow-up) • Similar seropositivity for HPV 16/18 at 12-month follow-up	LOW (GMTs) MODERATE (seropositivity)
2 doses in younger females vs. 3 doses in older females	Hernández-Ávila et al, 2016	4v	Mexico	9 to 26-year old females [300 participants]	2 doses (0,6m) in females aged 9–10 years vs. 3 doses (0,2,6m) in females aged 18–24 years	Immunogenicity	Non-inferior GMTs for HPV 6/11/16/18 at 21-month follow-up	LOW (HPV 6) MODERATE (HPV 11/16/18)
2 doses in younger females vs. 3 doses in older females	Dobson et al, 2013	4v	Canada	9 to 26-year old females [569 participants]	2 doses (0,6m) in females aged 9–13 years vs. 3 doses (0,2,6m) in females aged 16–26 years	Immunogenicity	• Higher GMTs for HPV 11/16 and similar for HPV 6/18 at 36-month follow-up • Similar seropositivity for HPV 6/11/16/18 at 36-month follow-up	VERY LOW (LOW/MODERATE at earlier follow-ups)
2 doses in younger females	Data from vaccine manufacturer presented at a	9v	14 countries	9 to 26-year old females [600 participants]	2 doses (0, 6m) in females aged 9–14 years vs. 3	Immunogenicity	Higher GMTs and similar seropositivity for HPV 6/11/16/18/ 31/33/45/52/58 one month after last	MODERATE

Topic	Reference	HPV vaccine	Setting	Population	Intervention	Outcome	Summary of finding	Evidence certainty
vs. 3 doses in older females	national NITAG				doses (0,2,6m) in females aged 16–26 years		dose (at 7-month follow-up)	
2 vs. 3 doses in younger females	Leung et al, 2015	2v & 4v	France, Hong Kong, Singapore, Sweden	9 to 14-year old females [1,074 participants]	2 doses (0,6m) of 2v vaccine vs. 2 (0.6m) or 3 doses (0,2,6m) of 4v vaccine in girls of same age	Immunogenicity	Higher GMTs for 2 doses of 2-valent vaccine and similar seropositivity for HPV 16/18 at 12-month follow-up	LOW (GMTs HPV 16) MODERATE (GMTs HPV 18) HIGH (seropositivity)
2 vs. 3 doses in younger females	Sankaranarayanan et al, 2016	4v	India	10 to 18-year old females [17,729 participants]	3 doses (0,2,6m), 2 doses (0,6m), 2 doses (0,2m), and single dose	Immunogenicity & efficacy for incident and persistent cervical infection	• Cluster-randomised trial that lost randomization due to events unrelated to study; data were analysed as an observational study • Antibody titres of 3-dose and 2-dose (0,6m) groups show similar decay kinetics and were similar up to 48-month follow-up • Frequency of incident HPV 6/11/16/18 infections was similar irrespective of the number of vaccine doses received	N/A
Interval between doses	Puthanakit et al, 2016	2v	Canada, Germany, Italy, Taiwan, and Thailand	9 to 14-year old females (seronegative at baseline) [965 participants]	12- vs. 6-month interval in 2-dose schedule	Immunogenicity	Higher GMT for HPV 16/18 with longer interval between doses, but similar seroconversion rates for HPV 16/18 one month after last dose	MODERATE
9- vs. 4-valent in females	Vesikari et al, 2015	9v	Belgium, Denmark, Finland, Italy, Spain, Sweden	9 to 15-year old females [600 participants]	3 doses (0,2,6m) of 9- vs. 4-valent vaccine in younger girls	Immunogenicity	• Similar GMTs for HPV 6/11/16/18 and higher for HPV 31/33/45/52/58 at one month after last dose (at 7 month follow-up) • Similar seropositivity for HPV 6/11/16/18, but reference did not report in full seropositivity rates for4-valent vaccine control group for HPV 31/33/45/52/58 at one	MODERATE (GMTs and seropositivity for HPV 6/11/16/18) LOW (for seroconversion for HPV 31/33/45/52/58)

Topic	Reference	HPV vaccine	Setting	Population	Intervention	Outcome	Summary of finding	Evidence certainty
							month after last dose (at 7 month follow-up)	
9- vs. 4-valent in females	Joura et al, 2015	9v	17 countries	16 to 26-year old females [14,215 participants]	3 doses (0,2,6m) of 9- vs. 4-valent vaccine in younger girls	Immunogenicity and efficacy for persistent infection, CIN, VIN and VaIN	• Similar GMTs for HPV 6/16, lower for HPV 11, and higher for HPV 18/31/33/45/52/58 at 24-month follow-up • Similar seropositivity for HPV 6/11/16 and higher for HPV 18/31/33/45/52/58 at 24-month follow up • No differences in efficacy for HPV 6/11/16/18 and condyloma, higher efficacy for persistent infection, CIN2/3 or worse, VIN/VaIN 1-2/3 or worse at 24-month follow-up	HPV 6/11/16/18: MODERATE LOW (CIN2/3 and worse, condyloma) HPV 31/33/45/52/58: MODERATE LOW (VIN1/VaIN1 and worse)
Vaccines vs. placebo in males	Petaja et al, 2009	2v		10 to 18-year old males [270 participants]	3 doses (0,1,6m) of 2-valent vaccine vs. control vaccine	Immunogenicity	No data about effects of 2-valent vaccine on GMTs or seropositivity because no placebo data were reported for this outcome	VERY LOW
Vaccines vs. placebo in males	Giuliano et al, 2011 Hillman et al, 2012	4v	18 countries	16 to 26-year old males [4,065 participants]	3 doses (0,2,6m) of 4-valent vaccine vs. placebo	Immunogenicity and efficacy for external genital lesions, condyloma acuminatum, persistent HPV 6/11/16/18 infections, and PIN	• Lower rates of external genital lesions (any or by HPV 6/11/16/18, condyloma acuminatum, persistent HPV 6/11/16/18 infections) in vaccine group and similar rates for PIN at 2.9-year median follow-up • Higher GMTs and seropositivity for HPV 6/11/16/18 at 36-month follow-up • No comparison on seropositivity/ seroconversion possible because no placebo data reported for this outcome	MODERATE LOW (PIN, seropositivity)
Vaccines in males vs. in	Lehtinen et al, 2015	2v	Finland	12 to 15-year old males [1,695 participants]	3 doses (0,1,6m) of 2-valent vaccine in males	Immunogenicity	Similar GMTs and seropositivity for HPV 16/18 at 3.5-year follow-up	LOW

Topic	Reference	HPV vaccine	Setting	Population	Intervention	Outcome	Summary of finding	Evidence certainty
females					vs. in females			
Vaccines in males vs. in females	Reisinger et al, 2007 Ferris et al, 2014	4v	10 countries	9 to 15-year old males [1,167 participants]	3 doses (0,2,6m) of 4-valent vaccine in males vs. in females	Immunogenicity and efficacy for persistent infection	• Similar persistent infection rates for HPV 6/11/16/18 at 8-year follow-up • GMTs for HPV 6/11/16/18 initially similar or higher for males than females, but with increasing follow-up time similar or higher for females • Similar seropositivity for HPV 6/11/16/18 at 18-month follow-up	VERY LOW (persistent infection) LOW (GMTs) MODERATE (seropositivity)
Vaccines in males vs. in females	Van Damme et, 2015	9v	24 countries	9 to 15-year old males [3,066 participants]	3 doses (0,2,6m) of 4-valent vaccine in males vs. in females	Immunogenicity and efficacy for persistent infection	• Similar GMTs for HPV 6/11/16/31/52 and higher GMTs for HPV 18/33/45/58 at 3-year follow-up • Similar seropositivity rates for all 9 HPV types at 3-year follow-up	LOW
Vaccines in males vs. in females	Data from vaccine manufacturer presented at a national NITAG	9v	14 countries	9 to 26-year old females [600 participants]	2 doses (0, 6m) in males aged 9–14 years vs. 3 doses (0,2,6m) in females aged 16–26 years	Immunogenicity	Similar seropositivity for HPV 6/11/16/18/ 31/33/45/52/58 one month after last dose (at 7-month follow-up)	MODERATE
Vaccines in males vs. in females	Castellsagué et al., 2015	9v	17 countries	16 to 26-year old males and females [2,200 participants	3 doses (0,1,6m) in males vs. in females	Immunogenicity	Higher GMTs and similar seropositivity rates for HPV6/11/16/ 18/31/33/45/ 52/58 one month after last dose (at 7-month follow)	MODERATE
9- vs. 4-valent vaccines in males	Van Damme et, 2016	4v & 9v	Belgium	16 to 26-year old males (seronegative at baseline) [454 participants]	3 doses (0,1,6m) of 9- vs. 4-valent vaccines	Immunogenicity	• Higher GMTs for HPV 6/31/33/ 45/52/58, but similar GMTs for HPV11/16/18 one month after last dose (at 7-month follow-up) • Higher seroconversion rates for HPV6/31/33/45/52/58, but similar seroconversion rates for HPV 6/ 11/16/18 one month after last dose (at 7-month follow-up)	HIGH

Topic	Reference	HPV vaccine	Setting	Population	Intervention	Outcome	Summary of finding	Evidence certainty
Women and girls living with HIV	McClymont, et al, 2018	4v	Canada	9 years or older, not pregnant, had to have a cervix, living with HIV	3 doses (0,2,6m) vs non-HIV infected women (/or unvaccinated women living with HIV from historical data)	Immunogenicity	• Vaccinated women living with HIV may be at higher risk for vaccine failure than vaccinated women without HIV. • Overall rates of vaccine failure were low and rates of persistent qHPV were lower than in unvaccinated women living with HIV	Not provided
Men who have sex with men (MSM)	Palefsky et al, 2011	4v	Australia, Brazil, Canada, Croatia, Germany, Spain, USA	16 to 26 year-old MSM (seronegative at baseline) [602 participants]	3 doses (0,2,6m) vs. placebo	Efficacy for persistent anal infection, anal intraepithelial neoplasia (AIN), and genital warts	• Reduced incidence of persistent infection by HPV6/11/16/18 and of AIN2/3 at 2.9-year follow-up • Similar incidence of AGW over 2.9-year follow-up	MODERATE LOW (persistent hpv11 infection and genital warts)
Men who have sex with men (MSM)	Castellsagué et al., 2015	9v	17 countries	16 to 26-year old MSM, men who have sex with women (MSW) and females (seronegative at baseline) [313 MSM, 1,106 MSW, 1,101 women]	3 doses (0,1,6m) in MSM vs. females or MSW	Immunogenicity	• Compared to females, lower GMTs for HPV6/11/16/31/33/45/52/58, but similar GMTs for HPV18 one after last dose (at 7-month follow) • Compared to MSW, lower GMTs for all 9 HPV types • Compared to females and MSW, similar rates of seropositivity for all 9 HPV types	MODERATE
Men and women living with HIV	Levin et al, 2010 Weinberg et al, 2012	4v	USA, Puerto Rico	7 to 11-year old males and females (seronegative at baseline) [90 and 27 persons in vaccine and control groups, respectively]	3 doses (0,2,6m) vs. placebo	Immunogenicity	Higher GMTs and seroconversion rates for HPV 6/11/16/18 with 4-valent vaccine at 24–month follow-up and one month after last dose, respectively	MODERATE
Men and women living with HIV	Denny et al, 2013	2v	South Africa	18 to 25-year old females (mixed sero-status at baseline) [42 HIV-infected and	3 doses (0,1,6m) in HIV-infected vs. non-infected women	Immunogenicity	• Lower GMTs for HPV 16/18 in HIV-infected women one month after last dose (at 7-month follow) • Similar seroconversion rates for HPV 16/18 at 12-month follow-up	LOW

Topic	Reference	HPV vaccine	Setting	Population	Intervention	Outcome	Summary of finding	Evidence certainty
				22non-infected women]				
Men and women living with HIV	Toft et al, 2014 Faust et al, 2016	2v & 4v	Denmark	18+ year old HIV-infected males and females (seronegative at baseline) [92 participants]	3 doses 80,1/2,6m) of 4- vs. 2-valent vaccines	Immunogenicity	• Similar GMTs for HPV16/18 at 12-month follow-up • Similar seroconversion rates for HPV 16; seroconversion rates for HPV 18 lower with 4-valent vaccine at 12-month follow-up	MODERATE

Appendix 2. Summary of evidence from "Two-dose schedules for human papillomavirus vaccine: Systematic review and meta-analysis". (2017)

D'Addario M, Redmond S, Scott P, Egli-Gany D, Riveros-Balta AX, Henao Restrepo AM, et al. Two-dose schedules for human papillomavirus vaccine: Systematic review and meta-analysis. Vaccine. 2017;35(22):2892-901.

Topic	Reference	HPV vaccine	Setting	Population	Intervention	Outcome	Summary of finding	Evidence certainty
2 vs 3 dose	Sow 2013	2v	Senegal and Tanzania	2 dose (10-14) vs 3 dose (15 to 25)	2 dose (0,1 months) vs 3 dose (0,1,6 months)	Immunogenicity	• 100% of initially seronegative participants in the vaccine group were seropositive for both anti–HPV-16 and anti–HPV-18 antibodies (n = 130 and n = 128 for 10–14-year-olds, respectively; n = 190 and n = 212 for 15–25-year-olds). • GMTs for HPV-16 and HPV-18 were higher in 10–14-year-olds (18 423 [95% confidence interval, 16 185–20 970] than in 15–25-year-olds (10 683 [9567–11 930]. • Seropositivity was maintained at month 12.	the power to demonstrate a lower limit of the 95% confidence interval (CI) >90% if the true seroconversion rate was 98%, was 94% for participants aged 10–14 years and 99% for participants aged 15–25 years

Appendix 3. Summary of evidence from "Human papillomavirus vaccine effectiveness by number of doses: Systematic review of data from national immunization programs". (2018)

Markowitz LE, Drolet M, Perez N, Jit M, Brisson M. Human papillomavirus vaccine effectiveness by number of doses: Systematic review of data from national immunization programs. Vaccine. 2018.

Topic	Reference	HPV vaccine	Setting	Population	Intervention	Outcome	Summary of finding	
Cross-protection	Kavanagh et. al. (2014)	2v	Scotland	15-17 year old females	1 dose vs 2 vs 3	Immunogenicity	HPV Prevalence • Three doses of bivalent vaccine are associated with a significant reduction in prevalence of HPV 16 and 18 from 29.8% (95% confidence interval 28.3, 31.3%) to 13.6% (95% confidence interval 11.7, 15.8%). • Cross-protection against HPV 31, 33 and 45. • HPV 51 and 56 emerged as the most prevalent (10.5% and 9.6%, respectively) non-vaccine high-risk types in those vaccinated, but at lower rates than HPV 16 (25.9%) in those unvaccinated	
1 vs 2 vs 3 doses	Cuschieri et al (2016)	2v	Scotland	15-17 yr old femalea	1 dose vs 2 vs 3	Immunogenicity	HPV Prevalence • VE for prevalent HPV 16/18 infection associated with 1, 2 and 3 doses was 48.2% (95% CI 16.8, 68.9), 54.8% (95% CI 30.7, 70.8) and 72.8% (95% CI 62.8, 80.3). • Equivalent VE for prevalent HPV 31/33/45 infection was -1.62% (95% CI -85.1, 45.3), 48.3% (95% CI 7.6, 71.8) and 55.2% (95% CI 32.6, 70.2).	

1 vs 2 vs 3 doses	Herweijer et al. (2014)	4v	Sweden	10-19 year old females	1 dose vs 2 vs 3	Immunogenicity	Anogential warts • Statistically significant effectiveness for 3, 2 and 1 doses compared to 0 • Significantly higher effectiveness of 3 compared to 2 and 1 doses • With buffer periods > 4 months, no significant difference between 3 and 2 doses • Similar results for age groups 10–16 and 17–19, except effectiveness for 1 dose without buffer period statistically significant for 10–16 year-olds	
1 dose vs 2 vs 3	Blomberg et al (2015)	4v	Denmark	12-27	1 dose vs 2 vs 3	Immunogenicity	Anogential warts • Statistically significant effectiveness for 1 compared to 0 dose • Effectiveness not reported for 3 and 2 doses compared to 0 • Effectiveness significantly increased with each dose • With dose interval > 4 months, no significant difference between 3 and 2 doses • Similar results when stratified by age at vaccination	
1 dose vs 2 vs 3	Dominiak-Felden et al. (2015)	4v	Belgium	10-23	1 dose vs 2 vs 3	Immunogenicity	Anogential warts • Statistically significant effectiveness for 3 and 2 doses, but not 1 compared to 0 • Effectiveness CI overlap for 3 and 2 doses; no overlap for 3 and 1 doses	

1 dose vs 2 vs 3	Perkins et al. (2017)	4v	United States	9-25	1 dose vs 2 vs 3	Immunogenicity	Anogential warts • Statistically significant effectiveness for 3 doses compared to 0 • Effectiveness not reported for 2 and 1 doses compared to 0 · • Higher effectiveness for 3 compared with 1 doses, but no significant difference between 3 and 2 doses • With buffer period of 1 year, no change in findings (data not shown) • Similar results with dose interval > 5 months for 2 doses	
1 dose vs 2 vs 3	Navarro-Illana et al. (2017)	4v	Spain	14-19	1 dose vs 2 vs 3	Immunogenicity	Anogential warts • Statistically significant effectiveness for 3, 2, and 1 doses compared to 0 • Effectiveness CI overlap for 3, 2 and 1 doses	
1 dose vs 2 vs 3	Lamb et. al. (2017)	4v	Sweden	10-19	1 dose vs 2 vs 3	Immunogenicity	Anogential warts • Effectiveness not reported for 3, 2 and 1 doses compared to 0 • Higher effectiveness of 3 doses compared to 2 doses, when 2 doses administered either0–3 months or 8 months apart • No significant difference between 3 and 2doses when the 2 doses administered within 4–7 months • Similar results when stratified by age at vaccination	
1 dose vs 2 vs 3	Gertig et al. (2013)	4v	Australia	12-19	1 dose vs 2 vs 3	Immunogenicity	CIN3/AIS • Statistically significant effectiveness for 3, but not 2 and 1 doses compared to 0 • Effectiveness CI overlap for 3, 2 and 1 dose	

1 dose vs 2 vs 3	Crowe et al. (2014)	4v	Australia	12-26	1 dose vs 2 vs 3	Immunogenicity	High grade histological lesion • Statistically significant effectiveness for 3 and 2 doses, but not 1 compared to 0 • Effectiveness CI overlap for 3 and 2 doses, no overlap for 3 and 1 doses • Buffer periods from 1 to 12 months - no consistent impact on 3, 2 and 1 dose effective-ness estimates • Similar results when stratified by age at vaccination	
1 dose vs 2 vs 3	Brotherton et al. (2015)	4v	Australia	12-26	1 dose vs 2 vs 3	Immunogenicity	CIN3/AIS • Statistically significant effectiveness for 3, but not 2 and 1 doses compared to 0 • Effectiveness CI for 3, 2 and 1 doses do not overlap • With increasing buffer periods, some effectiveness for 2 and 1 doses in several age groups • No difference in effectiveness by interval between 2 doses • Similar results when stratified by age at vaccination	
1 dose vs 2 vs 3	Hofstetter et al. (2016)	4v	United States	11-20	1 dose vs 2 vs 3	Immunogenicity	Any abnormal cytology • Statistically significant effectiveness for 3 and 2, but not 1 dose compared to 0 • Effectiveness CI overlap for 3, 2 and 1 doses • Similar results when stratified by age at vaccination, although effectiveness of 2 doses compared to 0 not always significant	

1 dose vs 2 vs 3	Kim et al. (2016)	4v	Canada	10-15	1 dose vs 2 vs 3	Immunogenicity	High grade cytology • Statistically significant effectiveness for 3, but not 2 and 1 doses compared to 0 • Effectiveness CI overlap for 3, 2 and 1 doses	
1 dose vs 2 vs 3	Pollock et al. (2014)	2v	Scotland	15-17	1 dose vs 2 vs 3	Immunogenicity	CIN3 · • Statistically significant effectiveness for 3, but not 2 and 1 doses compared to 0 • Effectiveness CI overlap for 3 and 2 doses, no overlap for 3 and 1 doses	