SCHEDULES AND STRATEGIES FOR HUMAN PAPILLOMAVIRUS (HPV) IMMUNIZATION

1 | POLICY QUESTIONS AND OVERALL CONCLUSIONS

1. What is the incremental effectiveness and cost-effectiveness for cervical cancer prevention of different HPV vaccines based on girls-only immunization?

- Current evidence suggests that the three registered vaccines have similar effectiveness for the prevention of cervical cancer associated to HPV types 16/18.
- As per current WHO recommendations, the priority of HPV immunization should remain the prevention of cervical cancer through the immunization of girls, prior to becoming sexually active. The priority age range should be harmonized to that of the extended 2-dose immunization schedule, i.e. 9–14 years. Achieving high coverage among adolescent girls is the priority.
- Introduction of HPV vaccines in national programmes should be *strongly* recommended, while maintaining the current qualifiers.
- At national level, the goal should be to introduce the HPV vaccine country-wide. Phased introductions toward that eventual goal should only be an alternative for those countries that cannot afford or implement operationally an immediate country-wide vaccination programme.

2. What is the incremental effectiveness and cost-effectiveness for prevention of HPV-related diseases of adolescent gender-neutral HPV immunization compared to girls-only HPV immunization?

- Vaccination coverage reached in females influences the incremental effectiveness of a gender-neutral immunization. If the vaccination coverage in girls is greater than approximately 70–80%, a gender-neutral immunization that includes adolescent boys becomes less cost-effective than immunization targeting only girls and women aged ≤18 years.
- Nonetheless, 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 men who have sex with men.

☑ **THIS SUMMARY INCLUDES**

☒ **THIS SUMMARY DOES NOT INCLUDE**

Detailed information on operational issues

- Gender-neutral immunization could be considered based on elements, such as competing health priorities, disease burden, equity, programmatic implications, cost-effectiveness, and affordability.

3. What is the incremental effectiveness and cost-effectiveness for cervical cancer prevention of immunization of multiple female cohorts (multiple age cohorts within a defined age range) compared to single age cohort immunization of only girls aged 9–13 years or of both girls and boys aged 9–13 years?

- Due to wider direct protection and stronger herd effects, immunization targeting multiple age cohorts would result in faster 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 unintended interruptions in vaccine delivery.
- Immunization of multiple cohorts of girls is cost-effective in the age range of 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 proportionally more girls and women would have already become sexually active.
- Immunization of multiple cohorts of girls aged 9–14 years should be recommended. As with single age cohort immunization, HPV vaccine introductions based on multiple age cohorts will require adequate operational and financial planning.

2 | KEY FINDINGS

Burden of cervical cancer and HPV-related cancers

Estimates are that 630,000 new HPV-related cancer cases occurred in 2012 (**Table 1**). Of those, 570,000 (90%) cases were in women and 61,000 (10%) in men. The 530,000 (84%) 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 2012, 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)	530,000	530,000	100.0%	530,000	0
Vulva (C51)	34,000	8,500	24.9%	8,500	0
Vagina (C52)	15,000	12,000	78.0%	12,000	0
Anus (C21)	40,000	35,000	88.0%	18,000	17,000
Penis (C60)	26,000	13,000	51.0%	0	13,000
Oropharynx (C01, C09–10)	96,000	29,000	30.8%	5,500	24,000
Oral Cavity (C02–06)	200,000	4,900	2.5%	1,700	3,200
Larynx (C32)	160,000	3,800	2.4%	450	3,300
Other Pharynx (C12-C14)	78,000	0	0.0%	-	-
Total	**1,200,000**	**630,000**	**54.0**	**570,000**	**61,000**

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

Asia accounts for the majority of the 530,000 cervical cancer cases, in particular because of the burden in India and China. However, the highest incidence rates are in Sub-Saharan Africa. Low- and lower-middle income countries account for 291,300 (55%) 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 in countries that have and have not introduced HPV vaccine (1, 3, 4)

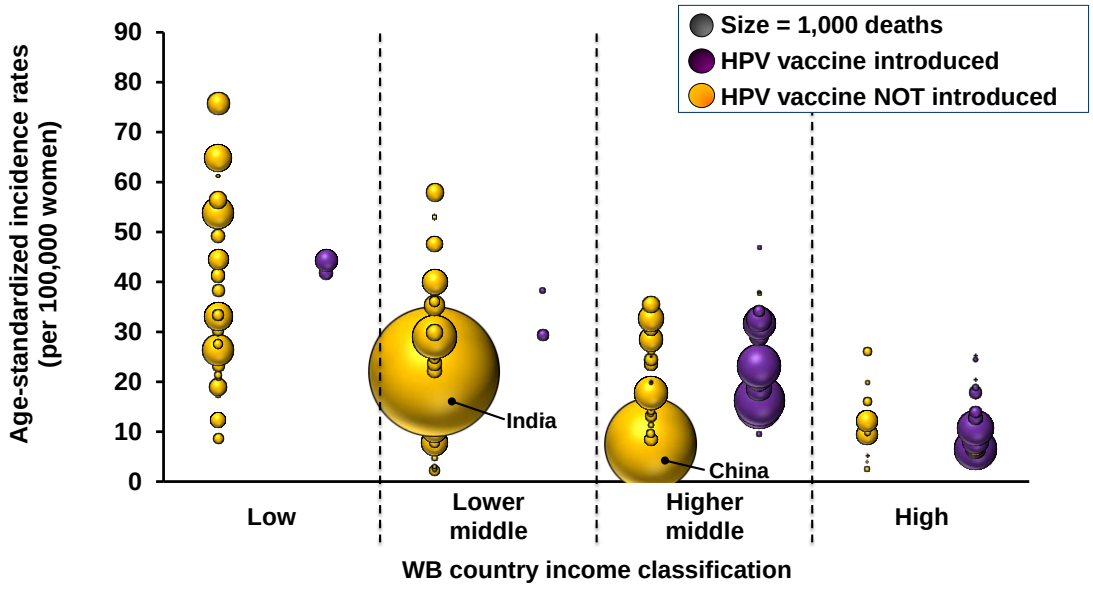


Table 2 provides the 2012 estimated number of cervical cancer cases by country income level and eligibility for GAVI support. For India (a low-middle income and GAVI-eligible country) and China (an upper-middle income and not GAVI-eligible country), 122,844 and 61,691 cervical cases were estimated, respectively.

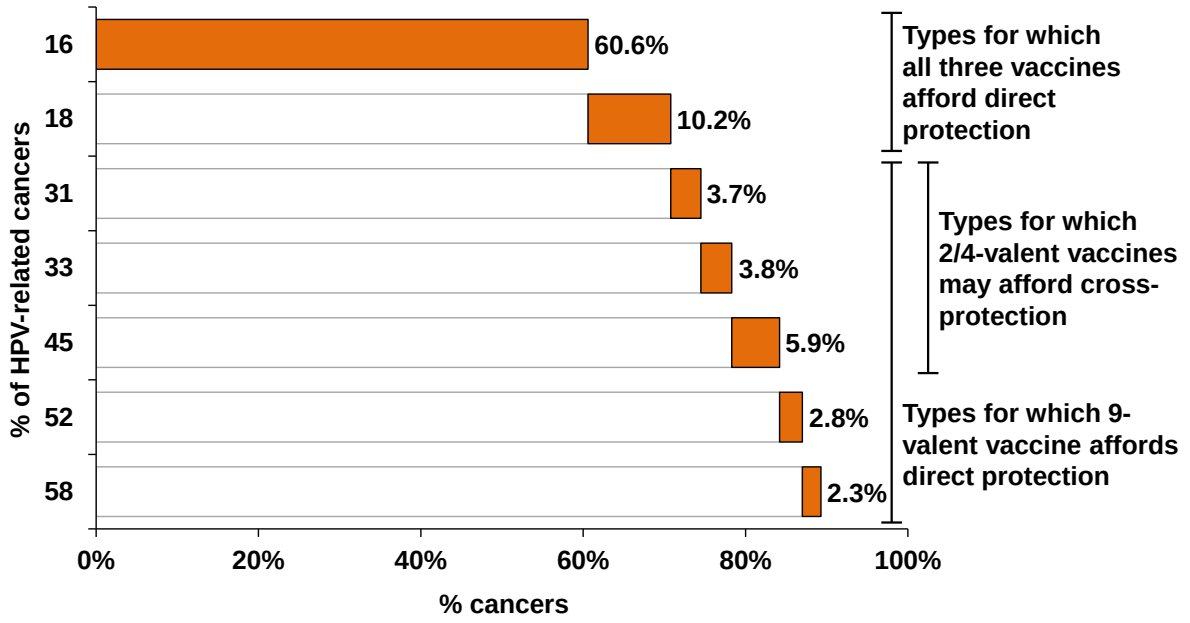
Table 2. Cervical cancer cases estimated for 2012 by country income classification by the World Bank, eligibility for GAVI support, and HPV vaccine introduction (1, 3-5)

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 71% 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 13% of the cases. Lastly, HPV 31/33/45/52/58 (five high-risk types against which only the 9-valent vaccine affords direct protection) are associated with 18% of the cases.

Figure 2. Relative contribution of different viral types to cervical cancer—World, 2012 (6)



Non-cervical HPV-related cancers are more frequently associated to HPV 16/18 than cervical cancer (80% versus 71% 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]	HPV 16/18/31/33/45/52/58 [B]	Difference [B-A]
Cervix uteri	530,000 (100%)	370,000 (71%)	470,000 (90%)	100,000 (19%)
All other sites	110,000 (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 (7-11)

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

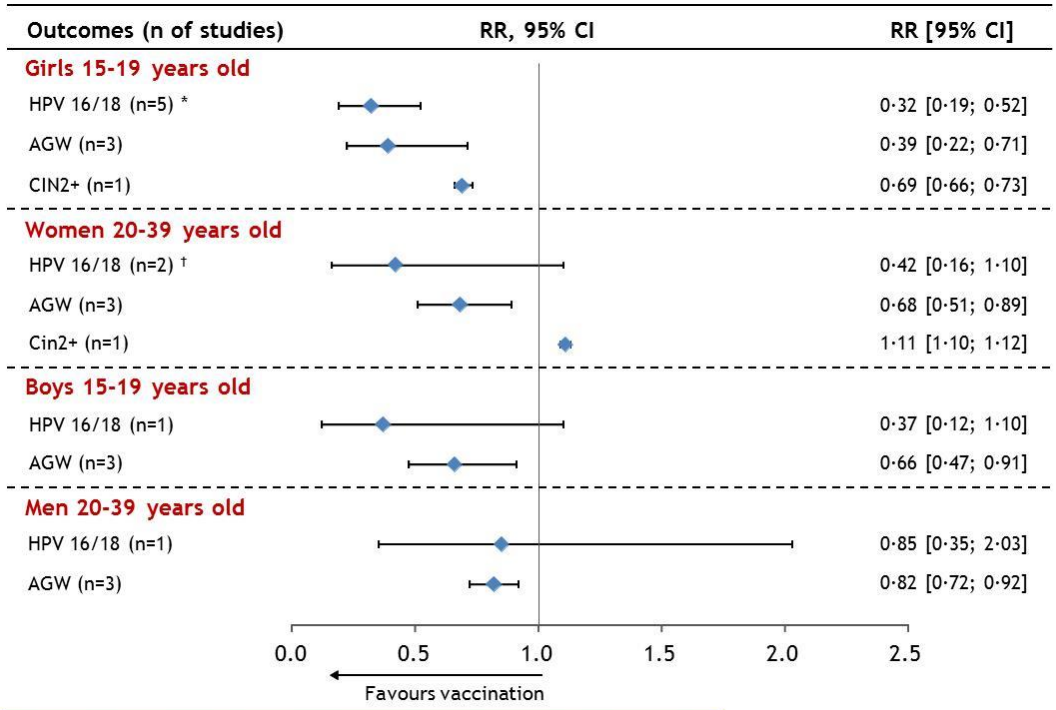
Based on evidence from both randomized clinical trials and post-introduction impact evaluations, the bi- and quadrivalent HPV vaccines provide some level of cross-protection against high-risk oncogenic HPV types other than 16/18, in particular for types 31/33/45. Available follow-up periods are 9.4 and 4.0 years for the clinical trials of the bi- and quadrivalent vaccines, respectively, while they reflect the time from vaccine introduction for impact evaluations (i.e., most data available from year 2009/2010 onwards). (7, 8, 12, 13) 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.

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% (14)



RR = prevalence ratio (post-vaccination prevalence / pre-vaccination prevalence)

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 either a gender-neutral immunization at 40% vaccination coverage or a girls-only immunization at 80% vaccination coverage.

In particular, **Figure 4** shows a greater reduction in HPV infection prevalence 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.

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. 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 4. Estimated effectiveness of girls-only and gender-neutral HPV immunization depending on vaccination coverage (15)

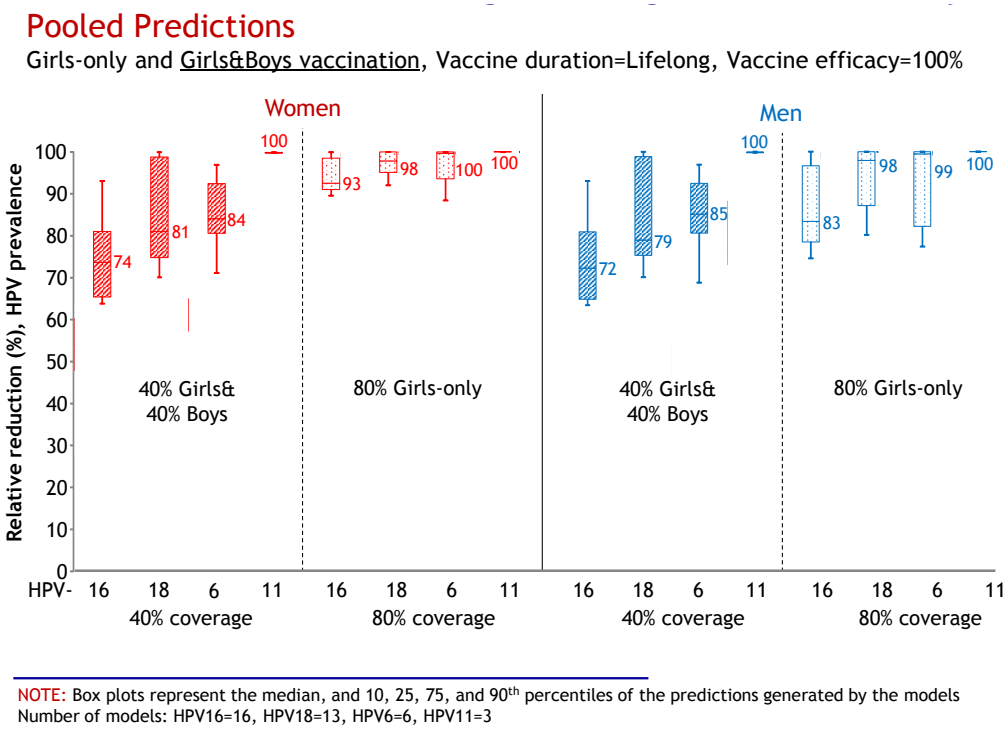
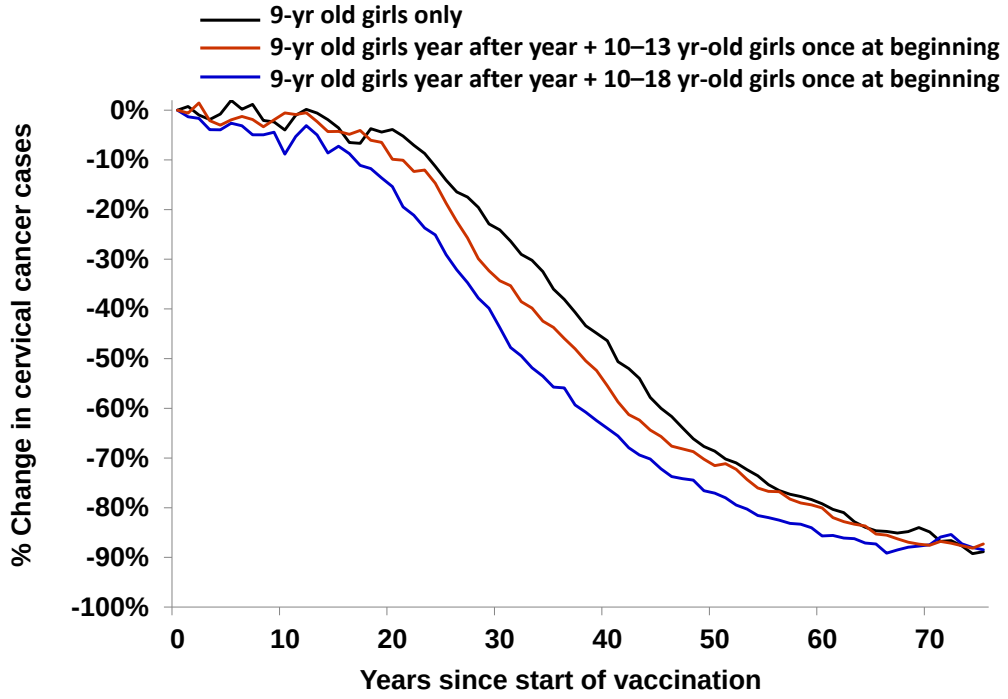


Figure 5. Estimated effectiveness of immunization targeting single and multiple age cohorts (16)



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

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). (17-19) 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.

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). (1) 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) described in detail the methods for AF calculation. (2) AFs for each cancer site are in 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. (6, 20, 21) Although HPV 6/11 are not oncogenic in cervical cancer, (18) they were not excluded from the present estimates because of possible involvement in some anogenital carcinomas, notably in the penis. (20) 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 different parts of the world, including HIV-positive women. (22, 23) The distribution of HPV types differs however by histology: the contribution of HPV 16 and HPV18 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. (24) On account of a greater predominance of HPV16 compared to cervical cancer, HPV 16

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

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 (1, 2)

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, 6, 20, 21)

Anatomical cancer site (ICD-10 code)	Total incident cases attributable to HPV	Cases attributable to (%)		
		HPV 16/18	HPV 6/11/16/18/31/ 33/45/52/58	Difference
		[A]	[B]	[B-A]
Cervix uteri (C53)	530,000	370,000 (71%)	470,000 (90%)	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. (21, 25) 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. (26) 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. (27) Inclusion criteria for the updated search were widened: studies were included whether or not they included ages 20–40 and HIV-positive men and women were included as a special interest population. Overall, 44 studies were identified in the search for studies reporting incidence, prevalence and self-reported history and added to the 37 reported in the previous review. Results are summarized by sex, age and HIV-infection status in **Table 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.

Table 7. Burden of anogenital warts (27)

	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

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). (28, 29)

In March 2014, a systematic review and meta-analysis of randomized controlled trials of HPV vaccines was submitted for consideration to SAGE. (30) 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. (31) **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. (32) Identical methods were used to update that review with studies published between February 2014 and July 2016. (14)

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 12 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

[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.

document changes over time were identified several countries, such as Bangladesh, Bhutan, China, and Rwanda.

Table 9. Endpoints of the studies systematically reviewed to evaluate the population level impact and herd effects of human papillomavirus (HPV) immunization programmes (14, 32)

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 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]) (**Figure 1**). 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.

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. It is thus difficult at present time to isolate in observational post-introduction impact evaluations the additional population-level impact of vaccinating multiple age cohorts versus that of vaccinating single age cohort.

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. (33) 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 HPV31 (prevalence ratio=0.73 [95% CI 0.58–0.92]) but little evidence of cross-protection for HPV33 and HPV45 (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. Twenty-eight studies were included in this systematic review, among which two studies analysed the cost-effectiveness of 9-valent vaccine versus bi- or quadrivalent vaccine, 14 studies conducted the cost-effectiveness analyses of gender-neutral HPV immunization versus female-only immunization, and 15 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 finding are reported here and the full summary is available online. (34) This systematic review extends a previous work by Fesenfeld et al (2013). (26)

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 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 understand the true value for money of 9-valent HPV immunization.

Cost-effectiveness of gender-neutral HPV immunization. Almost half of the studies showed that gender-neutral immunization was cost-effective. Vaccine coverage and price play a crucial role in influencing the cost-effectiveness analyses especially in LMIC. If female vaccine coverage is greater than approximately 70–80%, the incremental effectiveness is diminished and gender-neutral immunization that includes adolescent boys become less cost-effective than routine vaccination of adolescent girls only. Several existing economic studies fail 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.

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

[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.

herd effects. However, the extend 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. 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.

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. (35) 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. (36) **Table 10** shows the percent of people aged 20–24 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**). (37)

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 (36)

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 6. Percentage of adolescents aged 15–19 years who have had sexual intercourse by age 15 years (35)

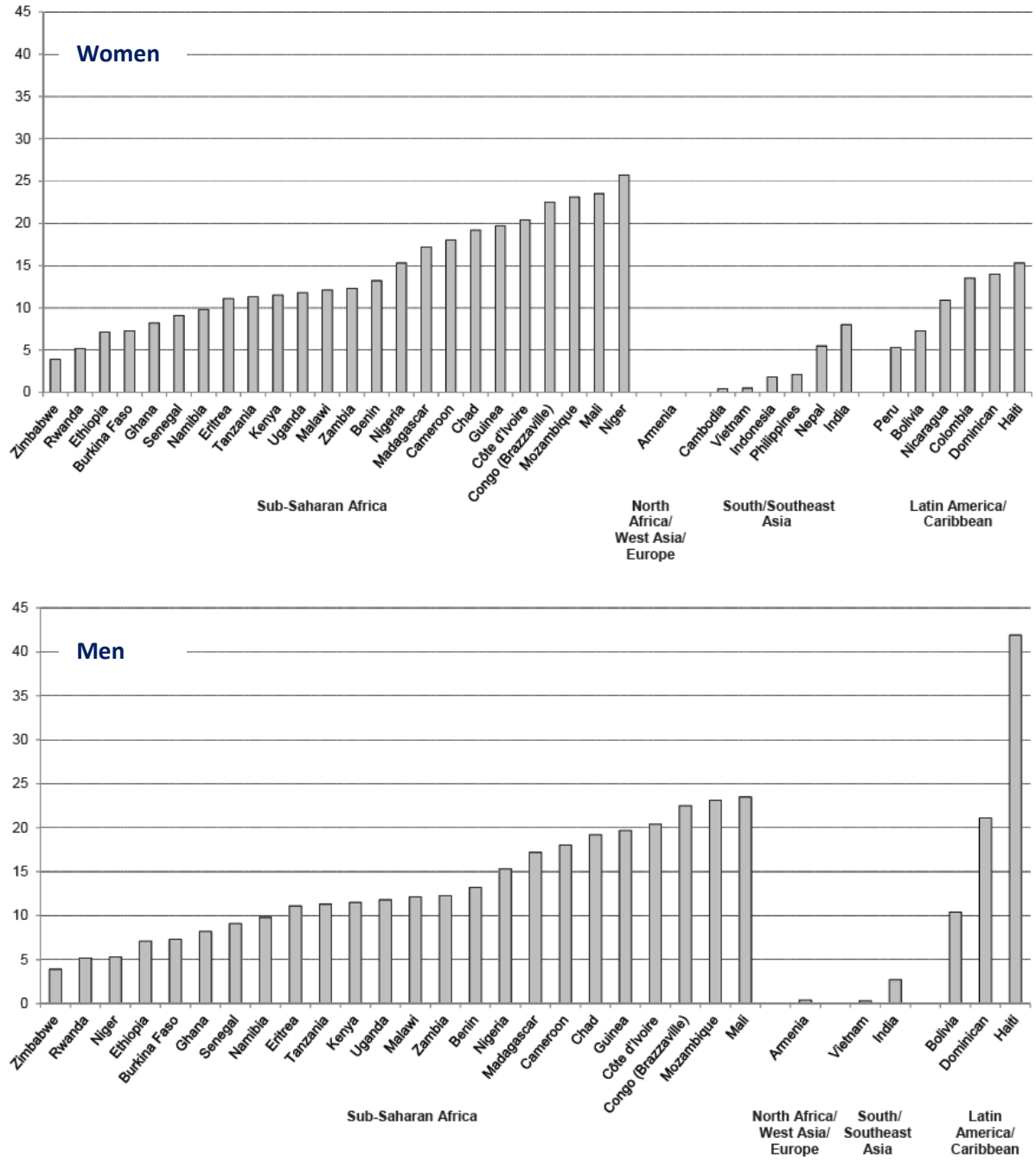
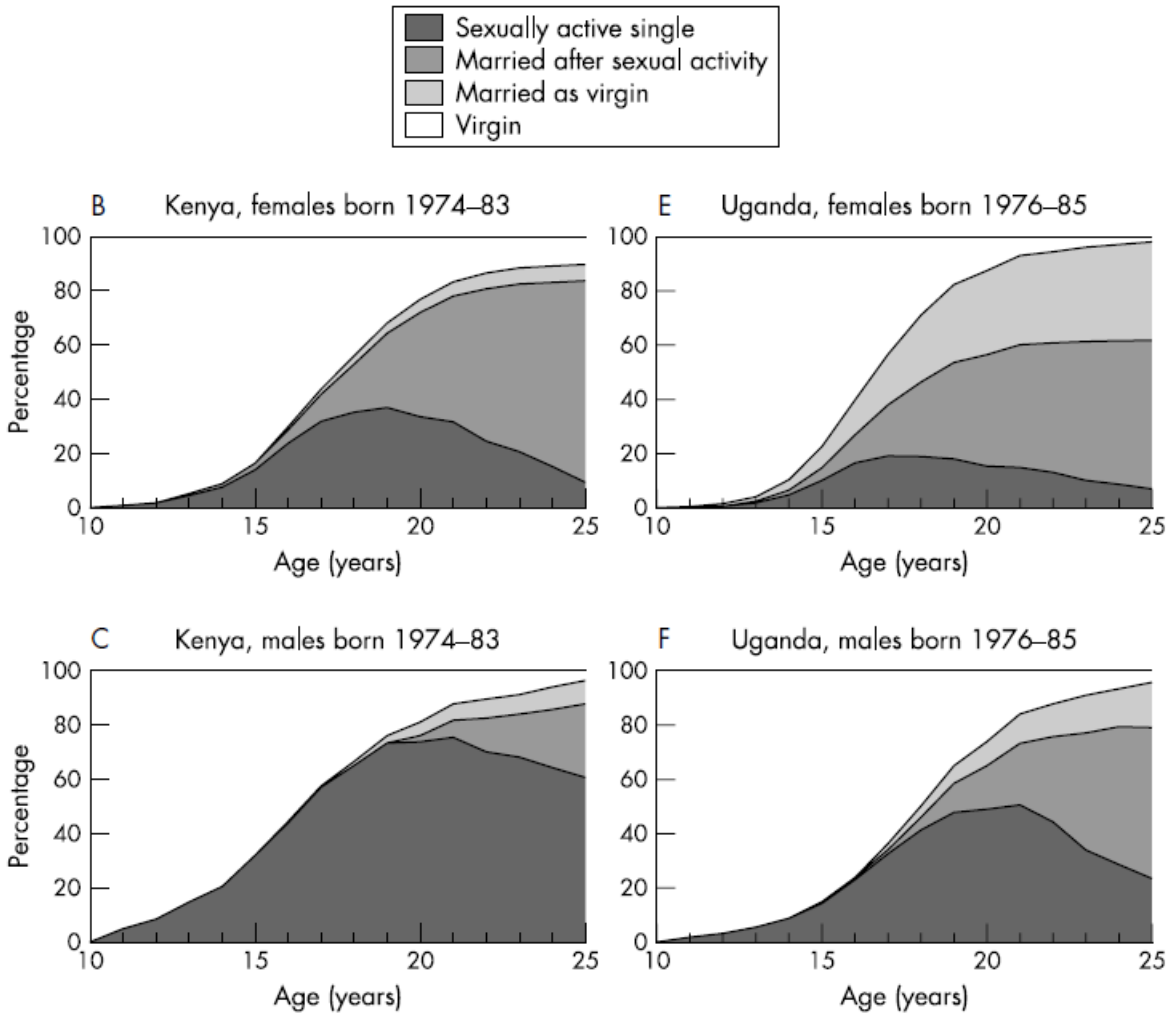


Figure 7. Percentage of females and males aged 10–25 years of Kenya and Uganda who were sexually active, by marital status (37)



4 | LIST OF SUPPORTING DOCUMENTS AVAILABLE ONLINE

- Global burden of cancers attributable to infections in 2012: a synthetic analysis, 8 pages (2)
- Systematic review of the burden of anogenital warts, 18 pages (27)
- Systematic review of clinical trials of HPV vaccines, 119 pages (31)
- Systematic review of population-level impact and herd effects of HPV immunization programmes, 9 pages (14)
- Systematic review of cost-effectiveness analyses of HPV immunization programmes, 9 pages (34)
- Modelling methods and estimated effectiveness of various HPV immunization strategies
- Statements by WHO GACVS on the safety of HPV vaccines, 2013–2016, 14 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	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					in males 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
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 22non-infected women]	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
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