ECDC SCIENTIFIC ADVICE

Public consultation on draft guidance for introduction of HPV vaccines in EU countries: focus on 9-valent HPV vaccine and vaccination of boys and people living with HIV

The content of this guidance was developed by the European Centre for Disease Prevention and Control (ECDC) based on a technical report including grading of the quality of the evidence performed by the Catalan Institute of Oncology (Laia Bruni Coccoz, Beatriz Serrano Carro, Mireia Diaz Sanchis, Claudia Robles, Maria Brotons Agullo, Laia Alemany, Xavier Bosch) and three systematic reviews prepared by ECDC (Edoardo Colzani and Kate Olsson) the Robert Koch Institute (Bernhard Ultsch, Thomas Harder and Ole Wichmann) and Santé publique France (Daniel Levy-Bruhl), and the Universities of Parma and of Pisa (Michele Antonelli, Diego Bernini, Alice Canale, Paola Cella, Elisa Filippetti, Pierluigi Lopalco, Anna Odone, Filippo Quattrone, Carlo Signorelli, Marcello Tirani and Alberto Tulipani).

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In line with ECDC's commitment to openness and transparency, and in order to receive comments from the scientific community and stakeholders, ECDC is launching a public consultation on the preliminary guidance 'Varicella vaccine in the European Union'.

How to submit contributions:

- Use the dedicated email address exclusively and refer to the respective line and page numbers.
- Consult the guidelines for submission of contributions and note that only contributions following ECDC guidelines will be considered.
- For more information on the processing of your personal data in the context of this consultation, read the specific privacy statement.
- Deadline: 29 April 2019.

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Abbreviations and glossary

AE	Adverse event
AEFI	Adverse event following immunisation
AIN	Anal intraepithelial neoplasia
2vHPV	Bivalent HPV vaccine
CIN	Cervical intraepithelial neoplasia
CRPS	Complex regional pain syndrome
CI	Confidence interval
CEA	Cost-effectiveness analysis
Cost-effectiveness	The extent to which an intervention or prevention programme is effective in relation to its costs, i.e. euro/life years gained
Determinant	Factor increasing the probability of occurrence of an event
Direct evidence	Evidence on relative effects of HPV vaccination derived entirely from direct comparisons
EMA	European Medicines Agency
EP	Evidence profile
4vHPV	Four-valent HPV vaccine
GUM	Genito-urinary medicine
GMT	Geometric mean titre
GSK	GlaxoSmithKline
GAVCS	Global Advisory Committee on Vaccine Safety
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	Health technology assessment
HPV	Human papilloma virus
ICER	Incremental cost-effectiveness ratio
ICO	Istituto Catala' d'Oncologia
Impact of vaccination programme	Impact on overall population level effect of a vaccination program. It depends on many factors such as vaccine coverage, herd protection/immunity, effectiveness and efficacy of the vaccine.
Indirect evidence	Evidence of HPV vaccine effectiveness derived entirely from indirect comparisons
Precancerous lesion	Lesion involving abnormal cells associated with an increased risk of developing into cancer
LY	Life years
MSM	Men who have sex with men
MSD	Merck Sharp & Dohme
NICE	National Institute for Health and Care Excellence
NZ$	New Zealand dollar
9vHPV	Nine-valent HPV vaccine
PeIN	Penile intraepithelial neoplasia
PICO	Population Intervention Comparison Outcome
POTS	Postural orthostatic tachycardia syndrome
QALY	Quality-adjusted life years
6MPI	Six-month persistent infection
SoF	Summary of findings
Vaccine effectiveness	Real-world reduction of disease in population due to vaccine with evidence coming from observational studies
Vaccine efficacy	Percentage reduction of disease in vaccinated group of people compared to an unvaccinated group, using the most favorable conditions, e.g. experimental setting
Vaccine hesitancy	Delay in acceptance or refusal of vaccines despite availability of vaccination services
VE	Vaccine efficacy/effectiveness
Viroprevalence	Prevalence of virus in population
VPD	Vaccine-preventable disease
VaIN	Vaginal intraepithelial neoplasia
VLP	Virus-like particle
VIN	Vulvar intraepithelial neoplasia

Executive summary

Scope

ECDC has previously produced two guidance documents on human papilloma virus (HPV) vaccination published in 2008 and 2012 that addressed questions related to the introduction of HPV immunisation in EU/EEA Member States.

This guidance covers the following areas in relation to HPV vaccination: efficacy of the nine-valent HPV vaccine, HPV vaccination in people living with HIV and HPV vaccination in males and the cost-effectiveness of extending the HPV vaccination programme to include males.

The document summarises evidence from studies included in the licensing file of HPV vaccines together with post-licensure, peer-reviewed data and analysis where available. This guidance does not address the safety of HPV vaccines observed during the pre- and post-licensing period.

Guidance development

A comprehensive review and appraisal of the evidence concerning the areas mentioned above were conducted using the GRADE methodology whenever applicable. Four systematic reviews were used to collect the available evidence on each topic. An ad hoc expert panel reviewed the appraised body of evidence, provided information on additional evidence and identified evidence gaps for future research. The panel formulated the conclusions listed below based on the evidence provided.

Key conclusions

- The nine-valent HPV vaccine is efficacious in preventing persistent HPV infection and cervical high-grade or worse lesions caused by the additional HPV types 31, 33, 45, 52 and 58 covered by the vaccine (evidence quality: high) and HPV types 6, 11, 16 and 18 (evidence quality: moderate due to indirectness) in females 16–26 years.
  The nine-valent HPV vaccine is also efficacious in preventing persistent HPV infections, genital warts and high-grade anal intraepithelial lesions caused by HPV types 6, 11, 16 and 18 (evidence quality: moderate due to indirectness) among males 16–26 years.
  Immunogenicity data suggest:
  - non-inferiority of the nine-valent HPV vaccine compared to the quadrivalent HPV vaccine against HPV types 6, 11, 16 and 18;
  - stronger immune response against the additional serotypes 31, 33, 45, 52 and 58 contained in the nine-valent HPV vaccine compared to the quadrivalent HPV vaccine; and
  - stronger immunogenicity of the nine-valent HPV vaccine against vaccine serotypes in males and females 9–15-years compared to females 16–26 years.
- The quadrivalent HPV vaccine reduces the risk of persistent HPV infections, genital warts and high-grade anal intraepithelial lesions in males 16–26 years (including men who have sex with men) evidence quality: high), while data on the efficacy of the bivalent HPV vaccine against HPV infection and HPV-related disease in males were not found.
  mmunogenicity data suggest:
  - non-inferiority of quadrivalent and bivalent HPV vaccines administered to males compared to females; and
  - higher immunogenicity of quadrivalent and bivalent HPV vaccines administered to males 9–15 years compared to females aged 16–26 years for specific HPV types contained in each vaccine.
- There was no direct evidence on the efficacy of HPV vaccination on HPV-related clinical outcomes in people living with HIV for the period covered by the systematic review, although low quality of evidence of efficacy of the quadrivalent HPV vaccine on oral HPV infection became available in 2018.
- Cost-effectiveness analysis is sensitive to context and context-specific studies should optimally be done to inform decision-making in this area. According to the cost-effectiveness models reviewed, if the priority is the prevention of cervical disease in women, adding males to current female-only HPV vaccination programmes becomes increasingly cost-effective with:
  - persistently lower vaccination coverage among females; and
  - lower vaccine cost.

  However, increasing vaccination coverage among girls may still be a more cost-effective primary objective.

If vaccination uptake is lower in specific population subgroups (in terms of geographical region, ethnicity, socio-economic status and religion), it may be preferable to channel resources to increasing uptake among the unvaccinated. If the objective of the HPV vaccination programme is to prevent all HPV-related disease, a universal HPV vaccination may become a more cost-effective option.

Possible public health implications

For individual protection, since HPV vaccination is more efficacious when given to subjects naïve to the HPV types contained in the vaccine and the immunogenic response has been observed to be stronger in preadolescents than adults, greater benefit is expected from the vaccine by immunising preadolescent individuals. Subjects at higher risk of HPV infection and illness, such as people living with HIV and men who have sex with men, may particularly benefit from the vaccination despite possibly experiencing lower vaccine efficacy due to increased risk of exposure to HPV types included in the vaccines or lower immune response.

As for vaccination programmes, a universal (i.e. gender-neutral) vaccination strategy is more resource-demanding, but will likely provide more resilient herd protection at lower levels of vaccine uptake. It may also favour a more pronounced decrease of HPV viroprevalence and circulation and could more effectively protect all risk groups.

A female-only HPV vaccination of preadolescent girls is probably more cost-effective at current vaccine cost, but does not sufficiently protect men who have sex with men. It is less equitable and probably less resilient to sudden drops in vaccine uptake.

Different sexual mixing patterns in each population may leave some minority groups excluded from the benefits of the intervention (i.e. when sexual partners are mainly chosen from the same population subgroup). Targeting any such group is an option to consider to ensure equity of access and to improve the effectiveness of the HPV vaccination programme.

Ongoing studies will provide evidence on certain identified research gaps concerning HPV vaccination and allow for additions and updates to this guidance.

1 Introduction

1.1 Scope and objectives of guidance

In 2008, following the first introduction of HPV vaccines in 2006, ECDC produced an HPV vaccination document providing guidance on how to identify target populations for HPV vaccination, support the identification of strategy options for HPV vaccine delivery in EU countries, model costs and outcomes of HPV vaccination and monitor and evaluate the impact of HPV vaccination [1]. In 2012, ECDC published an updated guidance addressing among other aspects the efficacy and impact of vaccination in males, cost-effectiveness of adding males to the current HPV vaccination programmes and specific aspects related to HPV vaccine hesitancy [2]. The current document aims to systematically look at further updated evidence on HPV vaccination of males and the cost-effectiveness of adding males to the routine HPV vaccination programmes and if possible provide more solid conclusions based on additional research that has been performed in the last six years. It also aims to provide guidance concerning the recently licensed nine-valent HPV vaccine (9vHPV) and on the efficacy of HPV vaccines in people living with HIV.

Information on safety of HPV vaccines concerning the topics covered in this guidance has been collected and appraised (see tables in annexes), but will not be discussed in the document as no additional evidence on safety has emerged. Safety of HPV vaccines, and effectiveness and impact of HPV vaccination in women, have been recently assessed by a number of reviews and studies and will not be discussed in this public health guidance. A brief summary of the most recent and comprehensive assessments can be found in 2.4 and 2.5.

1.2 Target audience

The target audiences for this document are public authorities, national policymakers, entities responsible for the planning of healthcare and social support systems, national vaccination programmes and professional society organisations with an interest in HPV and/or immunisation programmes.

2 Background

HPV is one of the most widespread and common sexually transmitted infections worldwide and is acquired soon after onset of sexual activity. The recognition of the central role of HPV in the etiology of virtually all cervical cancers has radically changed the perspective of diagnosis and prevention of this disease. As other less common genital and non-genital cancers have been shown to be attributable to HPV, not only females, but also males may actually suffer from severe consequences of this viral infection. Moreover, virtually all genital warts are due to HPV, contributing to the large burden of HPV-related disease in both sexes.

Few pathologies other than cervical cancer offer such a wide range of prevention tools and strategies: cervical cytology for screening, HPV vaccines for primary prevention and more recently HPV detection tests for screening. However, no high-quality screening programs are currently available to prevent HPV-related disease other than cervical cancer in women. Moreover, despite the unequivocal success of organised population-based cervical screening programs, cervical cancer is still an important cause of morbidity and death among European women. Therefore, vaccination against HPV is expected to provide a significant added benefit for the prevention of all HPV-attributable diseases. Evidence on efficacy and effectiveness of HPV vaccines thus needs to be continuously monitored in order to guide public health actions.

2.1 Burden of HPV and HPV-related diseases in European countries

Although most sexually active women acquire a cervical HPV infection during their lifetime, most of these infections clear without any clinical significance [3]. The overall prevalence of a detectable HPV infection in European women from the general population is estimated to be 14%, although it is highly dependent on age. Most European populations show a large peak of HPV incidence in the first years after the onset of sexual activity (namely during adolescence and early 20s) decreasing and stabilising thereafter [4].

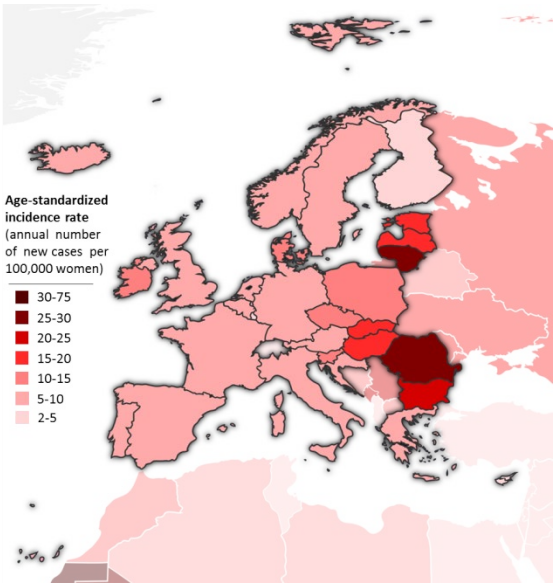
Only a small fraction of HPV infections persists and eventually progresses to cervical cancer. From the more than 200 HPV types identified, only a few are classified as carcinogenic, namely HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59 [5]. Persistent infection with carcinogenic HPV types, also known as high-risk (HR) HPV types, may lead to precancerous lesions and cancer. HR HPV types are not only responsible for virtually all cervical cancer cases, but are also causally related with a variable fraction of other anogenital cancers (vulvar, vaginal, penile and anal cancers) and a subset of head and neck cancers, particularly oropharyngeal cancers [6–8]. Among HR HPV types, HPV16 and HPV18 stand out for their highest carcinogenic capacity [9]. Low-risk (LR) HPV types 6 and 11 are associated with anogenital warts and recurrent respiratory papillomatosis [10,11]. HPV16, the most carcinogenic type, is consistently the most frequent type detected in HPV-related cancers both in Europe and worldwide [12].

In EU/EEA countries, there are 33 987 newly diagnosed cervical cancer cases and 13 239 deaths each year, with age-standardised incidence rates of 9.6 cases and mortality rates of 2.8 deaths per 100 000 women [13]. Through cervical cancer screening, between 263 227–503 010 cases of precancerous lesions (CIN2 or worse) are diagnosed annually [14]. Incidence rates of other HPV related anogenital cancers are much lower than those observed for cervical cancer. In Europe, 14 700 annual cases of anogenital cancers other than cervix are attributable to HPV, with 5 400 cases diagnosed in men (about half in the anus and half in the penis) and 9 300 cases diagnosed in women (4 200 in the anus and 5 100 in the vulva and vagina). Regarding precancerous lesions, it is estimated that between 13 997–27 773 cases for VIN2/3, between 2 596–4 751 cases for VaIN2/3, and 1 549 cases in women and 1 097 cases in men for AIN2/3 are diagnosed each year [14]. Head and neck cancers also constitute a heavy burden, particularly in men, with an estimated 13 800 cases diagnosed annually (11 000 in males and 2 800 in females). Further, increasing trends in the incidence of HPV-positive head and neck cancers have been consistently observed in the last decade in concomitance with the decline in tobacco use. This increase concerned in particular HPV-positive oropharyngeal cancers among young men in northern Europe and North America [15].

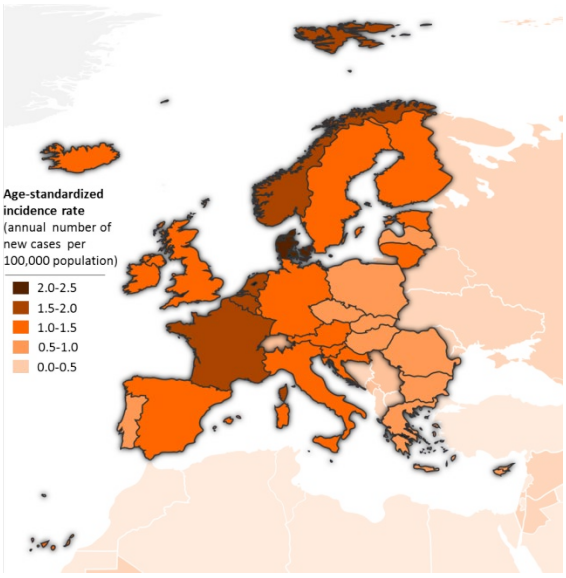
People living with HIV are a specific risk group with a high burden of HPV. In fact, while the proportion of HPV-positive among HIV-uninfected European women with normal cytologic findings is 14%, it is 33% among European women who are infected with HIV [16]. Additionally, HIV-associated immunosuppression may increase the carcinogenicity of HPV types and therefore the likelihood of developing a cancer attributable to HPV [17]. A study among men who have sex with men in Hungary identified that 97.5% of HIV-positive and 58.3% of HIV-negative men who have sex with men were positive for any type of HPV [18]. In Europe, HPV-16, followed by HPV-18 and HPV-33, is the most common serotype associated with invasive cervical cancer in women living with HIV [16]. Finally, although it is difficult to obtain reliable figures on the incidence of genital warts, an annual incidence of 0.1–0.2% in developed countries, with a peak during teenage years and young adulthood, has been estimated [10,19].

Figure 1. Age-standardised (world) incidence rates per 100 000 of cancer cases attributable to HPV in 2012

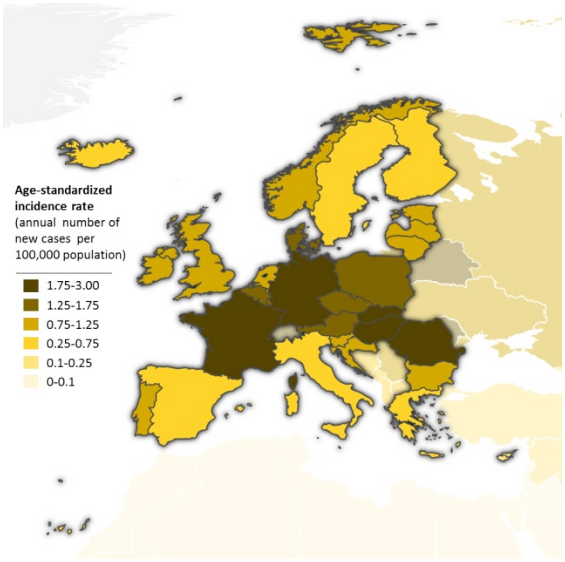
A. Cervical cancer



B. Other HPV-attributable anogenital cancers (vulvar, vaginal, anal and penile)



C. HPV-attributable head and neck cancers (oropharynx, oral cavity and larynx)



Adapted from GLOBOCAN 2012, IARC -27.6.2018
de Martel C, Int J Cancer. 2017

2.2 Human papillomavirus vaccines

There are currently three HPV vaccines licensed in Europe: the bivalent vaccine Cervarix (GlaxoSmithKline Biologicals) that contains virus-like-particles (VLPs) of HPV types 16 and 18, the quadrivalent HPV vaccine Gardasil/Silgard (Merck Sharp & Dohme – MSD) that includes VLPs of HPV types 6, 11, 16 and 18 and the nonavalent vaccine (MSD), that contains VLPs of HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58. Potentially, the bivalent and the quadrivalent vaccines could prevent 71% of all cervical cancer cases worldwide (i.e. those attributable to HPV types 16 and 18), while the nonavalent vaccine could increase the preventive potential to 89% of cervical cancer cases [12,20].

The three vaccines are licensed for the prevention of premalignant anogenital lesions (cervical, vulvar, vaginal and anal), cervical cancers and anal cancers causally related to high-risk types included in the vaccines. In addition, the quadrivalent and nonavalent vaccines are licensed for the prevention of genital warts. All vaccines are approved from the age of 9 years with a recommended schedule of two doses (0–6 months) up to the age of 14 years forthe bivalent and nonavalent vaccines and up to the age of 13 years for the quadrivalent vaccine. In individuals older

than the above indicated ages, the recommended schedule is 3 doses administered at months 0, 1 (or 2) and 6 [7,21–23].

The duration of protection from HPV-related cervical and genital disease attributable to serotypes 6, 11, 16 and 18 has been demonstrated for at least 10 years with the quadrivalent vaccine given in a 3-dose schedule to preadolescents and adolescents. A duration of 9.4 years of protection from infection and cervical lesions attributable to HPV-16 and HPV-18 has also been demonstrated with the bivalent vaccine in a 3-dose schedule. Finally, 5.6 years of protection from infection and cervical, vulvar and vaginal lesions with the nonavalent vaccine in a 3-dose schedule was shown [7].

2.3 HPV vaccine introduction in Europe

By 2018, all EU/EEA countries had introduced HPV vaccination in their national immunisation programs [24]. Fifty percent of countries introduced HPV vaccination within the first three years after the European Commisison granted a license for human use of the first HPV vaccines in 2006–2007 and the remaining EU/EEA countries have progressively introduced vaccination in the last 5 years. Table 1 shows the main characteristics of the programmes. Most current programmes target preadolescent girls within the age range of 9–14 years either through organised school-based vaccination plans or delivery through primary care services (including family doctors, nurses and gynaecologists). Many countries initially introduced vaccination as multiple age-cohort vaccination accompanied by temporary catch-up programmes for older ages to only maintain afterwards catch-up programs for already targeted cohorts that missed vaccination at the recommended ages [25]. Several countries (22%) have also expanded or will soon expand vaccination to boys of the same age in recent years, namely Austria, Croatia, the Czech Republic, Denmark [29], Germany [32], Italy, Liechtenstein, Norway [26–28], and the United Kingdom [30–31]. Other EU/EEA Member States are considering expanding the programme to include boys as well [33].

Program performance varies considerably across Europe. HPV vaccine uptake varies not only between countries, but also within countries at the regional level. Finland, Hungary, Iceland, Malta, Norway, Portugal, Spain and the UK have reported national coverage above 70%. In other countries such as France or Germany, coverage has stabilised below 50%, but other countries such as Denmark and Ireland have faced serious HPV vaccination crises resulting in dramatic drops from 80% coverage to 25%, followed by a partial recovery in the last two years thanks to successful HPV vaccination campaigns [34]. By 2015, it was estimated that 14 million European females had received the full vaccination course and 17 million at least one dose: this could potentially prevent 76 000 cervical cancer cases in these vaccinated girls [25].

198 **Table 1. Status of HPV national immunisation programmes in EU/EEA countries, 2018**

Country or territory	Year of introduction	Current age targets for vaccination in years (female, male[a])				Delivery	Reported coverage and timing of the primary target vaccination (% and year of vaccination)
		Primary (female, male)		Catch-up (female, male)			
Austria	2014	9	9	10–11 12–15 (PF)	10–11 12–15 (PF)	Sch. (4th grade) Health c. (catch-up)	60% F (2014) 40% M (2014)
The HPV vaccine has been available since February 2014 for all children living in Austria in the fourth grade (consummate 9 year of age) free of charge. Before 2014, the vaccine was recommended but not publicly funded. The children are vaccinated at school and, in some Länder, also in public vaccination centres and by established pediatricians. In addition, the HPV vaccine is offered free of charge from the age of 9–12 years in the public vaccination centers. Länder also provide catch-up vaccinations at a reduced cost price for children up to the age of 15 years.							
Belgium							
Brussels	2007	13–14	-	12–18 (PF)	-	Sch. (2nd year 2ry sch.) Health c. (catch-up)	35.7% (2012/13)
Flanders	2007	12–13	-	12–18 (PF)	-	Sch. (1st year 2ry sch.) Health c. (catch-up)	72% (2014/15)
Wallonia	2007	13–14	-	12–18 (PF)	-	Sch. (2nd year 2ry sch.) Health c. (catch-up)	29.3% (2012/13)
Flanders: For girls who do not qualify for the free vaccination or opt for a different vaccine than the free vaccine offered, a partial reimbursement is provided through health insurance.							
Bulgaria	2012	12–13				Health c.	17.7% (2014)
In 2007, an expert advisory body, including members from the Ministry of Health and National Center for Infectious and Parasitic Disease Control, issued official recommendations for the use of HPV vaccines in Bulgaria for girls aged 12–18 years before first sexual contact, with catch-up vaccinations up to the age of 26 years. In June 2009, the Ministry of Health included the HPV vaccine in the recommended vaccination list. In 2012, the National Programme for Primary Prevention of Cervical Cancer was approved by the council of ministers. Reimbursement of the cost of vaccination by the National Health Insurance Fund, for the cohort of girls aged 12 years in Bulgaria and vaccination of this cohort started in the beginning of 2013.							
Croatia	2016	13	13	-	-	Sch. (8th grade)	-
Voluntary HPV immunisation with HPV vaccine was available free of charge to all female and male persons from the age of nine years until the end of 2016.							
Cyprus	2016	12–13	-	-	-	Sch.	-
Czech Republic	2012	13-14	13–14 (since 2018)	-	-	Health c.	-
Denmark	2009	12		<18		Health c.	25% (2017) 80% before 2014
As from 1 February 2018, boys who feel attracted to boys can receive HPV vaccination free of charge if they are between 15–20 years old. The offer ended on 31 December 2018. From 1 January 2014–21 December 2015, HPV vaccination was offered to any girl or woman born between 1993–1997. Denmark is offering HPV vaccination to boys and girls as of 2019.							
Estonia	2018	12–14	-	-	-	Sch.	-
As of January 2020, all 12-year-old girls will be vaccinated within the immunisation programme.							
Finland	2013	11–12	-	-	-	Sch. (6th grade)	70.4%* (2017)
During the first two years of the programme, the vaccination was also administered to girls aged 13–15 years (7th–9th grade).							
France	2007	11–14 (PF)	-	<20 (PF)	-	Health c.	21.4% (15 years old (yo) in 2016)
Until September 2012, French guidelines recommended the 3-dose vaccine regimen to be administered routinely to all girls aged 14 years and catch-up vaccination to women aged 15–23 without sexual activity or with a sexual debut during the year before vaccination. In 2012, the recommendation expanded to girls aged 11–14 years old with a catch-up vaccination until theage of 20 years. The reimbursement rate for these vaccines is 65% of the price.							
Germany	2007	9–14	9–14	<18	<18	Health c.	30.5% (15 yo in 2014)

On 8 June 2018, the Standing Committee on Vaccination (STIKO) recommended vaccination of boys in Germany. The STIKO recommendation is the basis for the fact that statutory health insurance companies have taken over the costs of vaccination. STIKO published its recommendation in the epidemiological bulletin of the Robert Koch-Institut. Thereafter, the federal joint committee Gemeinsame Bundesausschuss decided to include the vaccination against HPV to all 9–14-year-old girls and boys in the catalog of statutory health insurance in September 2018. The decision have been submitted to the federal ministry of health for review and entry into force after publication in the federal gazette.							
Greece	2008	11–14	-	15–18 18–26 (until December2016)	-	Health c.	11.9% (11-19 yo in 2009)
Hungary	2014	12	-	-	-	Sch. (7th grade)	80% (2015)
Several local governments have decided to pursue their own earlier initiative, thus providing the vaccine to those who are not eligible to the national vaccination programme due to their age.							
Iceland	2011	12	-	-	-	Sch. (7th grade)	89% (2016)
Older girls are given the opportunity to receive the vaccine against the prescription and by paying for it.							
Ireland	2010	12–13	-	-	-	Sch. (1st year 2ry sch.)	51% (2016/2017)
In September 2011, a catch-up programme was introduced, targeting all girls of 6 years of age or equivalent from 2011–2014.							
Italy	008	11	11 (since 2015 in certain regions)	Variable by region	-	Health c.	56.3% (2015)
The HPV vaccination is actively offered free of charge to girls up to 12 years of age in all Italian regions. Some regions have extended the offer of vaccination to girls in other age groups. Some regions also offer free of charge HPV vaccination to people living with HIV, male and female. Most regions also consider a facilitated payment for ages not included in the primary target. In 2015, male vaccination started free of charge in six regions.							
Latvia	2010	12	-	-	-	Sch. and health c.	49.4% (2015)
Liechtenstein	2008	11–14	11–14 (since 2016)	15–26	15–26 (since 2016)		-
Liechtenstein follows the recommendations of Switzerland. Vaccination is free of charge for girls and womenaged 11–6 years within the framework of the cantonal vaccination programmes. This has been extended to boys and young men aged 11–26 years since 1 July 2016.							
Lithuania	2016	11	-	-	-		-
Luxembourg	2008	11–13	-	-	-	Health c.	58%* (2015/2016)
In Luxembourg, the HPV vaccination programme was introduced in 2008, targeting 12–17-year-old girls offering a choice of bivalent or quadrivalent vaccine free of charge. In 2015, the programme was changed offering the bivalent vaccine only to 11–13-year-old girls. Since January 2019, the programme has been expanded free of charge to all 9–14-year-old boys and girls.							
Malta	2012	12	-	-	-	Health c.	92.6% (2015)
One of the actions included in the national cancer plan for the Maltese islands 2017–2021 is the consolidation of the HPV vaccination programme. An evaluation of the programme will be performed at the completion of the first five years. This will include an exploration of the impact of expanding the programme to include male children of the same age cohort of the girls already being invited.							
Netherlands	2009	12–13	-	-	-	Health c.	53.4% (2016)
In 2009, a HPV vaccination catch-up campaign was organised for girls born between 1993–1996 (13–16 years of age at the time). Since 2010, 12-year-old girls are invited to receive the HPV vaccination within the National Immunisation Programme and includes girls who were born in 1997 or thereafter. All girls receive an invitation when turning 13 years of age. The vaccination is free and not mandatory.							
Norway	2009	12	12 (from 2018/2019)	≤25 (2016–2018)	-	Sch. (7th grade)	83% (2016/2017)
From 1 November 2016, and available for two years, women born in 1991 or later are offered HPV vaccination free of charge. The Government will offer HPV vaccine to all 7th-grade boys as part of the childhood immunisation programme. The offer has been introduced from the school year 2018–2019.							
Poland							
Since 2008, HPV vaccination has been recommended in the national immunisation programme for girls aged 11–12 years. The expert committee, appointed on the initiative of the Polish Pediatric Society in 2010, recommended HPV vaccines also for girls aged 13–18 years who had not been vaccinated previously. However, Poland did not introduce this vaccination into the compulsory programmes. Prophylactic vaccination against HPV is charged extra in primary healthcare centres, therefore the coverage of Polish teenagers vaccinated against HPV is estimated to be between 7.5%– 10%. Certain districts decided to introduce programmes of prophylactic HPV vaccination and finance them.							
Portugal	2008	10	-	-	-	Health c.	87% (2014)
In October 2008, the HPV vaccination was introduced in the national immunisation programme for 13-year-old girls born from 1995. From 2009–2011, a catch-up vaccination campaign was run for girls ≤17 years (born between 1992–1994). From 2014–2016, girls from 10–13 years old were covered. Since 2017, only 10-year-old girls are vaccinated.							
Romania	2013	11–14	-	-	-	Health c.	-
In 2008, the Romanian Ministry of Health rolled out a school-based immunisation campaign providing free vaccines for 10–11-year-old girls. Coverage statistics revealed that only 2.57% of the girls received vaccination and the programme was suspended. In 2009 an information campaign was launched, followed by a second vaccination programme, targeting 12–14-year-old girls. A catch-up programme was also launched, where adult women were given the opportunity to get the vaccine							

free of charge through their health provider. Despite the accessibility of the vaccine, initiation remained low and the school-based programme was discontinued at the end of 2011.The programme was launched for the third time in April 2013. HPV vaccination is included in the National Vaccination Program in the category 'Vaccination of Population at Risk' and is addressed to girls aged 11–14 years.							
Slovakia	2016	13 (PF)	-	-	-		-
The recommendation was implemented into legislation, and it says that if a doctor considers there is a need for the vaccination against infections caused by oncogenic HPV, then the vaccination should be given to girls from the target age group. The recommendation is also targeting other age groups, but these have to pay the total price of the vaccines. Neither routine HPV vaccination nor catch-up programmes have been started in Slovakia. HPV vaccines are partially reimbursed by the national healthcare system: the bivalent HPV vaccine at 11% and the quadrivalent vaccine 7.5% subsidised.							
Slovenia	2009	11–12	-	-	-	Sch. (6th grade)	46.4% (2016–2017)
Spain	2007-8	12	-	-	-	Sch. and/or health c. (depending on the region)	77.8% (2016)
Vaccination programmes vary by region. The Inter-Territorial Council of the National Health System, the coordination body for the different Health services from the autonomous communities of Spain, approved general recommendation to initiate routine HPV vaccination in Spain in 2007, with a cohort of girls to choose between 11–14 years of age, but with a preference for age 14, and a deadline for implementation until 2010. Afterwards, each autonomous community designed its own implementation programme starting in 3 of them in 2007, and the rest in 2008.							
Sweden	2012	10–12	-	<18	-	Sch. (5-6th grades)	71.7 % (13 yo in 2017)
In 2010, the HPV vaccine was included in the free-of-charge national vaccination programme targeting all girls born 1999 or later and attending the 5th or 6th grade in school. However, the vaccinations did not start until 2012 due to delays in the procurement process. At the same time, all counties additionally introduced free-of-charge catch-up vaccinations targeting girls born from 1993–1998. According to an update of the regulation of child vaccinations (HSLF-FS 2016:51), all girls should now be offered HPV vaccinations up to the age of 18.							
United Kingdom	2008-12	11–13	-	<18	-	Sch. (8-10th grades) Health c. (catch-up)	81% (UK-Scotland, 2014) 73.3% (UK-Wales, 2014) 74.6% (UK-N. Ireland, 2014) 83.1% (UK-England, 2014)
Vaccination programmes and start year of the programme vary slightly by region. Girls who missed HPV vaccination first time around, can receive a catch up HPV vaccination up to the age of 18. At the start of the programme there was a catch-up for girls born between 1991–1995. UK will offer HPV vaccination to boys and girls as of 2019.							

**: coverage for at least one dose*
a: funded vaccination programmes unless otherwise stated
PF: partially funded
Sch.: school
Health c.: health council [25,35,36].

2.4 Post-licensure safety and global monitoring of HPV vaccines

The three licensed HPV vaccines all showed an excellent safety profile in clinical trials before receiving approval from the European Medicines Agency (EMA). After licensure, the EMA, other regulatory agencies and international bodies continue to monitor the safety of HPV vaccines and accumulated data regarding the safety profile of the three HPV vaccines are reassuring so far [37–40]. The Global Advisory Committee for Vaccine Safety (GACVS) of the World Health Organization (WHO) has thoroughly reviewed the evidence on the safety of HPV vaccines on seven occasions, assessing post-licensure surveillance data from the bivalent and the quadrivalent vaccines, data from manufacturers and any safety concerns that have arisen. Since the licensure of HPV vaccines, the committee has assessed concerns on aluminium-containing adjuvants and anaphylaxis, syncope, mass psychogenic illness, autoimmune conditions (including Guillain-Barré syndrome and multiple sclerosis), venous thromboembolism, stroke, pregnancy outcomes, complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS) and premature ovarian failure. It has not found any adverse event of concern to be causally associated with the vaccine besides the risk of anaphylaxis (1.7 cases per million doses) and syncope related to anxiety or stress caused by the injection [37]. The risk of syncope is relatively common in response to any vaccination, especially among adolescents, and its associated complications are potential serious injuries. Nevertheless, complications of syncope can be prevented by following the established recommendation of 15-minute observation after administration of the HPV vaccine. The risk of syncope following vaccination with HPV vaccine is not increased compared to other adolescent vaccines, as shown in an analysis of data from the United States [38]. Similarly, reported rates of anaphylaxis after HPV vaccination are not higher than those observed for other vaccines [39]. In the last review of GAVCS in June 2017 with over 270 million doses of HPV vaccines distributed worldwide and more than a decade of follow-up, the committee considered HPV vaccines to be safe [37]. Furthermore, in 2015, EMA

reviewed the evidence regarding CRPS and POTS in young women receiving HPV vaccines, concluding that the evidence does not support a causal association between HPV vaccines and the development of these syndromes [40].

In light of these up-to-date high-quality evaluations not differring from what was found (see evidence tables on safety in the annexes), aspects related to safety of HPV vaccines are not reported in this document. For discussion on safety of HPV vaccines, refer to periodic monitoring by GACVS and Cochrane's recent systematic reviews on HPV vaccine from 2016–2017 [37,41].

2.5 Effectiveness and impact of HPV vaccines

Since the approval of the first HPV vaccine in 2006, there has been an increasing body of evidence regarding the effectiveness and population impact of HPV vaccines against HPV infection, genital warts and high-grade cervical lesions (CIN2+). In 2015, a meta-analysis including 20 studies from 9 countries showed a significant impact of HPV vaccination when comparing pre- and post-vaccination periods, with herd protection effects and cross-protection against non-vaccine HPV types demonstrated when a high vaccine coverage was achieved [42]. Regarding HPV infection, this meta-analysis documented a 68% reduction in prevalence of HPV types 16 and 18 in girls aged 13–19 years when at least 50% coverage was achieved. Additionally, a 28% reduction in prevalence of HPV types 31, 33 and 45 in same-aged girls and a cross-protective effect in women aged 20–39 years and men under 20 years of age were observed [42]. Reductions in prevalence of HPV vaccine types have been documented so far in vaccinated women in Australia, Belgium, France, Germany, Sweden and the UK, vaccinated women and men in the US and non-vaccinated men in Australia [35,42–44]. Data from the UK (Scotland) published in 2017 also recently confirmed high-level of cross-protection against HPV types 31, 33, and 45 seven years after vaccination with the bivalent vaccine [45]. The reduction of high-grade CIN observed in the meta-analysis was 31% in women aged 15–19 years [42]. In recent years, a reduction in high-grade cervical precancerous lesions has also been observed in targeted populations in several countries such as Australia, Canada, Denmark,, Sweden, the UK (Scotland) and the US [35,42,43]. Australia has now demonstrated reductions in high-grade cervical precancerous lesions in women up to 30 years of age [35]. Finally, the meta-analysis documented a genital warts decrease by 61% in women aged 15–19 years [42]. The population impact of the quadrivalent HPV vaccine on genital warts has been documented in Australia, Belgium, Canada, Denmark, Germany, Israel, Italy, New Zealand, Spain, Sweden and the US [19,35,42–44,46].

3 Guidance development

For the development of the guidance, the following steps were undertaken:

- identification of public health questions for guidance
- collection of evidence
- evidence appraisal and synthesis
- ad hoc scientific panel meeting; and
- external consultations.

3.1 Identification of public health questions for guidance

In order to update and expand on the two previous HPV vaccination guidances, ECDC prepared a short list in 2016 of proposed topics for its second update on the HPV vaccination guidance. ECDC vaccine-preventable disease (VPD) national focal points[1] were contacted for consultation on proposed topics for the new HPV vaccination guidance and the following topics were eventually selected:

- efficacy and effectiveness of 9vHPV vaccination in the prevention of HPV-related illness
- efficacy and effectiveness of HPV vaccination in males
- efficacy and effectiveness of HPV vaccination in people living with HIV; and
- cost-effectiveness of adding males to current HPV vaccination programme.

3.2 Collection of evidence

A systematic review was performed on each of the following topics: efficacy and effectiveness of 9vHPV vaccine, outsourced to the University of Parma, efficacy and effectiveness of HPV vaccination in males, performed internally at ECDC, and cost-effectiveness of adding HPV vaccination in males, performed by the Robert Koch Institut.

For investigating the efficacy of HPV vaccination in people living with HIV, information on people living with HIV was retrieved from the systematic review on efficacy and effectiveness of HPV vaccination in males and from a systematic review performed by Cochrane Response on randomised controlled trials of HPV vaccines [41].

The systematic reviews on the effect of the 9vHPV vaccine and the systematic review on the effect of HPV vaccination in males included data from the main pre-licensure efficacy and immunogenicity clinical trials. The 9vHPV systematic review collected evidence until 30 January 2017. The systematic review of HPV vaccine in males collected evidence until 12 April 2017. The systematic review on cost-effectiveness of adding males to the vaccination schedule reviewed evidence until 2016.

3.3 Evidence appraisal and synthesis

The appraisal and synthesis of the full body of evidence from the systematic reviews was outsourced to the Catalan Institute of Oncology (ICO), which performed additional data extraction, updated the systematic searches and applied the GRADE methodology to evidence collected where applicable [47].

3.3.1 Methods for evidence synthesis on efficacy and effectiveness of 9-valent HPV vaccine, HPV vaccines in men and in people living with HIV

GRADE methodology was used to evaluate the evidence of effectiveness and efficacy based on three systematic reviews on the efficacy and effectiveness of the 9vHPV vaccine, HPV vaccination in males and HPV vaccination in people living with HIV [47].

A critical appraisal was performed and additional information from the original articles was extracted where necessary. Data extraction included information on study characteristics such as design, site, period and inclusion/exclusion criteria. Additionally, for 9vHPV vaccine synthesis, data on efficacy of the 4vHPV vaccine were extracted from the main clinical trials. The rationale was that the pivotal efficacy trial for the 9vHPV vaccine compared the 9vHPV vaccine to the 4vHPV vaccine [49]. The trial provided direct evidence for the prevention of HPV 31, 33, 45, 52 and 58-related outcomes, but for HPV 6, 11, 16 and 18-related outcomes, the criteria were to determine non-inferior immunogenicity. Consequently, to infer 9vHPV vaccine efficacy for the prevention of HPV 6,

[1] Nominated representatives of the EU Member States responsible for strategic and operational collaboration on technical and scientific issues for specific diseases areas

11, 16 and 18-related outcomes, indirect data from 4vHPV vaccine trials were used. Data were extracted by one investigator. In addition, both systematic reviews were updated until January 2018. The update was performed via PUBMED using the same search strategy of the original systematic reviews, although with single extraction.

As mentioned above, two sources were used to identify the articles to be included in the evidence synthesis for people living with HIV:

- a Cochrane systematic review of randomised controlled trials of HPV vaccines [41]; and
- HIV data from the systematic review on HPV vaccine in males performed by ECDC. Data were extracted from the original articles (or the Cochrane systematic review when information was not available in the original article) by one investigator from the ICO group.

The evidence synthesis for the three topics was prepared and structured around a comprehensive subset of PICO (Population Intervention Comparison Outcome) questions on efficacy and immunogenicity (Tables Supp01,02,04,05,07). In addition, a GRADE evidence summary including the main benefits and harms was prepared for each topic.

The evidence synthesis for each PICO question included evidence profile (EP) and summary of findings (SoF) tables. PICO questions on immunogenicity included geometric mean titres (GMTs) and seroconversion outcomes for HPV vaccine types. PICO questions on efficacy included 6-month persistent infection (6MPI) and the main clinical outcomes related to HPV vaccine types. Immunogenicity and efficacy data were extracted from analyses of the per-protocol populations, if not otherwise indicated, for comparability's sake. The EP and SoF tables included quality assessment and summary of results sections (including data on absolute and relative effects). When estimations of relative effect were missing either in the systematic reviews or main articles, estimates were calculated. Calculations included GMT ratios, differences in seroconversion and relative risks.

To prepare the GRADE evidence summaries, the following outcomes were chosen for females: prevention of 6MPI, cervical intraepithelial neoplasia grade 2 or 3 or worse (CIN2/3 or worse), cervical cancer, vulvar intraepithelial neoplasia grade 2 or 3 or worse (VIN2/3 or worse), vulvar cancer, vaginal intraepithelial neoplasia grades 2 or 3 or worse (VaIN2/3 or worse), vaginal cancer and anogenital warts in females. The following outcomes were chosen for males: 6MPI, anal intraepithelial neoplasia grade 2 or 3 or worse (AIN2/3 or worse), anal cancer, penile intraepithelial neoplasia grade 2 or 3 or worse (PeIN2/3 or worse), penile cancer and anogenital warts in males. GRADE evidence summaries were stratified by age group and sex.

GRADE methodology was also applied to evaluate the quality of the evidence for each PICO question and the evidence summaries (i.e. review of the risk of bias, inconsistency, indirectness, imprecision, publication bias and other considerations). Risk of bias assessment was extracted from the systematic reviews whenever possible (ECDC and Cochrane systematic reviews). The criteria used to evaluate imprecision were as follows: downgrade one level if the number of events in the control group were ≤10 or the 95% confidence interval (95% CI) was very wide or not estimable. Indirectness was considered when surrogates were used to assess evidence for other outcomes (i.e. CIN2/3+, VIN2/3+, VaIN2/3+, PeIN2/3+, AIN2/3+ to assess evidence for cervical, vulvar, vaginal, penile or anal cancer, respectively, or immunogenicity data to assess efficacy outcomes).

3.3.2 Methods for evidence synthesis on cost-effectiveness of adding males to the current HPV vaccination protocols

Only those studies from the systematic review that evaluated the cost-effectiveness of universal vaccination were selected for evidence synthesis in this guidance. The systematic review was updated by ICO by adding relevant studies published until 31 December 2017 not included in the original report. The additional articles retrieved were the following: Bresse 2014 [50], Blakely 2014 [51], Haeussler 2015 [52], Jiménez 2015 [30], Damm 2017 [53], Qendri 2017 [54], Largeron 2017 [55] and Mennini 2017 [56].

Twenty-one studies were finally identified for assessing the cost-effectiveness of universal vaccination, of which 12 were published in the last four years [50–6970] (Tables A36–39).

The variables extracted from the articles were author, country, year of publication, year of analysis, model time horizon, cost perspective, health outcomes included in the model, vaccine type, currency used in the analysis, vaccination coverage, vaccine schedule, vaccine efficacy, duration of protection, vaccine cost (in local currency and converted to EUR using exchange rates), base strategy, comparator strategy, incremental cost-effectiveness ratios (ICER, numerator expressed in local currency and converted to EUR using exchange rates), health outcome unit and the CEA threshold used in the article. The list of multiple registries that identify the different ICERs from each article and the parameters that lead to the specific result are reported in the annex (Tables A36–39).

ICER is the most common summary measure used to define cost-effectiveness of an intervention and is defined as the cost difference in cost between two interventions (e.g. A and B) divided by the difference in health effects: ICER=Cost A–Cost B)/Effect A–Effect B), where said change in health effects is usually measured in terms of the number of life years (LYs) saved or the number of quality-adjusted life years (QALYs) gained. As such, the ICER is frequently expressed as the cost per LY saved or QALY gained. In order to draw conclusions about which strategies

are cost-effective, ICERs must be compared to a predetermined reference value or threshold below which an intervention would be considered cost-effective. This threshold serves to signpost policy-makers which of the possible interventions offer an efficient use of resources. It can also be understood as the upper limit of what society is willing to pay for an additional unit of health effect (e.g. QALY) [70]. There is no consensus as to a universal ICER threshold, with different HTA agencies defining country-specific benchmarks to aid the decision-making process. The most extensive discussion on the use of these values have been held in the UK, where NICE has defined a range of GBP 20,000–GBP 30 000/QALY gained as the threshold [71]. In the rest of Europe, the thresholds range from EUR 20 000/QALY gained in Spain to EUR 50 000/QALY gained reported in studies in Denmark and Germany [53,66,72]). In the US, interventions that cost less than USD 50 000/QALY gained or, occasionally, between USD 50 000–USD 100 000/QALY gained are considered to be good value for the resources invested [73]. A universal threshold was proposed by WHO's Commission on Macroeconomics and Health in its 2002 report on investing in health for economic development. This report recommends that an intervention can be considered highly cost-effective if the ICER is less than the country's per capita gross domestic product (GDP) and cost-effective if the ICER is less than three times the per capita GDP [74].

3.4 Ad hoc scientific panel meeting

An ad hoc panel of experts was set up to review the assessed body of evidence, provide potential additional information on recent evidence that may have been missed, advise on potential research gaps that will need to be filled to better inform HPV vaccination policy and draw conclusions on the main topics of this guidance. The following competences were prioritised in order to choose panel members: vaccine effectiveness/impact, VPD epidemiology, modelling/health economics, evidence-based public health, STI epidemiology, cancer epidemiology, STI clinical management, clinical virology, tumour virology, pathology, social sciences, vaccine hesitancy and health communication. In the selection of panel members, priority was given to ECDC internal staff in order to guarantee scientific independence. Additional external experts were included in the panel to cover areas where internal expertise was missing based on their scientific and technical excellence in the areas of HPV and STI research. Of the 16 selected members of the panel, 11 were ECDC staff and five were external experts and researchers in areas related to STI, HPV, clinical and tumour virology, pathology and impact of HPV vaccination. All panel members (internal and external) provided their declarations of interests that were assessed in accordance with ECDC's Independence Policy. In order to guarantee full independence of the current guidance, only ECDC members of the panel took part in drawing conclusions on the available evidence, while all panel members contributed to the discussion and identification of additional evidence and research gaps.

3.5 External consultations

Several rounds of consultations were performed before finalising the document. Expert panel members had a chance to review the document and contribute additional text as co-authors or with comments. After finalising the first complete draft and passing ECDC'S quality check and internal clearance, the document underwent a round of consultation with the ECDC Advisory Forum composed of appointed representatives of National Institutes of Health from each EU/EEA Member State. Finally, an open public consultation will be performed with relevant stakeholders (e.g. learned societies, universities, professional societies, patient organisations) actively contacted and invited to provide their input.

4 Conclusions

4.1 Evidence of efficacy of 9-valent HPV vaccine

4.1.1 Efficacy of 9vHPV vaccine in females 16–26 years old

Data used to evaluate efficacy on HPV 31, 33, 45, 52, and 58-related clinical outcomes came from a pivotal efficacy trial [49] that compared the 9vHPV vaccine to the 4vHPV vaccine in females 16-26 years. Additional data from trials on immunogenicity of 9vHPV vaccine against these HPV types have also been considered [75,76]. For HPV 6, 11, 16 and 18-related outcomes, data from trials with 9vHPV vaccine were used to infer non-inferiority with the 4vHPV vaccine [77–79] (Tables 2, A3–A5, supplemental documents Supp04, Supp05).

Table 2. Evidence type for benefits: 9vHPV vaccination of females 16–26 years old

Benefits	Design	Efficacy	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type (GRADE)
HPV types 6, 11, 16 and 18							
Compared to 4vHPV vaccine, 9vHPV vaccine showed non-inferior immunogenicity and efficacy for these serotypes (evidence quality for efficacy: moderate).							
HPV types 31, 33, 45, 52 and 58							
6MPI	9vHPV compared to 4vHPV (1RCT)(b)	96.0% (94.6–97.1)	Not serious	Not serious	Not serious	Not serious	High
CIN2/3, VIN2/3, VaIN2/3 or worse		97.4% (85.0–99.9)	Not serious	Not serious	Not serious	Not serious	High
CIN2/3 or worse		97.1% (83.5–99.9)	Not serious	Not serious	Not serious	Not serious	High
VIN2/3, VaIN2/3 or worse		100.0% (71.5–100.0)	Not serious	Not serious	Not serious	Very serious[β]	Low

HPV: human papillomavirus; 6MPI: 6-month persistent infection; CIN: cervical intraepithelial neoplasia; VIN: vulvar intraepithelial neoplasia; VaIN: vaginal intraepithelial neoplasia.
**: downgraded by 1 for indirectness due to use of immunobridging to 4vHPV vaccine*
a: downgraded by 1 for imprecision due to low event rate
β: downgraded by 1 for imprecision due to very wide 95% confidence interval
a: HPV types 6, 11, 16 and 18 data from protocols 007/NCT00365716 and NCT00365378, 013/NCT00092521, 015/NCT00092534 (PICO2 Supp04); supportive data from protocols 001/NCT00543543 (PICO5 and PICO6 Supp05), 002/NCT00943722 (PICO2 and PICO8 Supp05), 003/NCT01651949 (PICO11 Supp05)
b: HPV types 31, 33, 45, 52 and 58 data from protocol 001/NCT00543543 (PICO1 Supp04); supportive data from Protocols 002/NCT00943722 (PICO2 and PICO8 Supp05), 003/NCT01651949 (PICO11 Supp05) [49,75–79].

Regarding HPV types 31, 33, 45, 52, and 58 in females 16–26 years old, the 9vHPV vaccine prevented 6MPI (efficacy 96.0%; CI 95% 94.6–97.1) and high grade lesions (including CIN2/3 or worse, VIN2/3 or worse and VaIN2/3 or worse; efficacy 97.4%; 85.0–99.9) for at least six years since vaccination (evidence quality: high). The 9vHPV vaccine resulted in significant decreases in the incidence of CIN2/3 or worse compared with the 4vHPV vaccine for the additional serotypes (efficacy 97.1%; 83.5–99.9; evidence quality: high), but showed no significant decrease for VIN2/3 or worse or VaIN2/3 or worse (evidence quality: low). The modified intention to treat analysis showed that 9vHPV was efficacious in reducing the risk of persistent HPV infection due to additional vaccine types 31, 33, 45, 52 and 58 in individuals who were not HPV infected at study entry, but was not more efficacious than 4vHPV in reducing the risk of persistent HPV infection due to the additional vaccine types among individuals who were already infected with HPV at baseline. The 9vHPV vaccine resulted in considerably higher GMTs than the 4vHPV vaccine for HPV types 31, 33, 45, 52, and 58 at months 7 and 42 and seroconversion rates at month 7 in females vaccinated with the 9vHPV for these types were ≥99.6%.

Regarding HPV types 6, 11, 16 and 18, vaccine efficacy studies comparing 9vHPV to placebo were not possible due to ethical issues (the other two previously licensed vaccines protect against HPV 16 and HPV 18 that are the two most carcinogenic types), so only studies comparing the 9vHPV vaccine to 4vHPV vaccine were performed. The 9vHPV vaccine showed non-inferiority at months 7 and 43 compared to the 4vHPV vaccine. Comparable incidence of infection, disease, cytological and abnormalities related to HPV 6, 11, 16, and 18 were reported between the two vaccine groups in the pivotal trial [49]. Seroconversion rates to these HPV types were ≥ 99.8% for both vaccines. Previous vaccine trials have already shown that the 4vHPV vaccine is effective in preventing 6MPI (efficacy 89.0%; 70.0–97.0), CIN2/3 or worse (efficacy 98.2%; 93.3–99.8), VIN2/3 and VaIN2/3 or worse (efficacy 100.0%; 82.6–100.0) and anogenital warts (efficacy 98.9%; 96.1–99.9) related to HPV types 6, 11, 16 and 18

[78]. This can be considered indirect evidence of efficacy of 9vHPV against these outcomes when due to HPV 6, 11, 16 or 18 (evidence quality: moderate).

4.1.2 Efficacy of 9vHPV vaccine in females 9–15 years

In 9–15-year-old females, the 9vHPV vaccine resulted in substantially higher GMTs for HPV types 31, 33, 45, 52, and 58 at month 7 and was non-inferior to the 4vHPV vaccine for GMTs for HPV types 6, 11, 16, and 18 [80,81]. At month 7, seroconversion rates to HPV vaccine types were ≥99.6% following vaccination with the 9vHPV and the 4vHPV vaccines (no significant difference between vaccines in the rate of seroconversion for HPV types 6, 11, 16 and 18 and significantly higher seroconversion rates for HPV types 31, 33, 45, 52 and 58).

There were no significant differences in seroconversion rates between females aged 9–15 and 16–26 years following vaccination with the 9vHPV vaccine. GMTs for 9vHPV vaccine types at month 7 were higher with either two or three doses of vaccine in females 9–15 years old compared to females 16–26 years old who received three doses of vaccine. There was no significant difference in seroconversion rates between 9–15 and 16–26-year-old females following vaccination with the 9vHPV vaccine (seroconversion rates to HPV vaccine types were ≥99.5% in both groups).

4.1.3 Efficacy of 9vHPV vaccine in males

Direct evidence on efficacy of the 9vHPV vaccine against HPV-related illness due to types 31, 33, 45, 52 and 58-related outcomes could not be assessed due to lack of clinical efficacy data on the 9vHPV vaccine in males.

For HPV types 6, 11, 16 and 18-related health outcomes, since efficacy studies comparing the 9vHPV vaccine to placebo could not be performed (4.1.1), indirect evidence from a 4vHPV vaccine efficacy trial in males 16–26 years old [82–83], and efficacy and immunogenicity trials comparing 9vHPv and 4vHPV [84] was used to infer non-inferior efficacy of 9vHPV (Tables 3, A10–A17, supplemental documents Supp04, Supp05).

Table 3. Evidence type for benefits: 9vHPV vaccination of males 16–26 years old

Benefits	Design	Efficacy	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type (GRADE)
HPV types 6, 11, 16 and 18							
6MPI	4vHPV compared to placebo (1RCT)(a)	85.6% (73.4–92.9)	Not serious	Not serious	Serious*	Not serious	Moderate
AIN2/3		74.9% (8.8–95.4)	Not serious	Not serious	Serious*	Not serious	Moderate
PeIN2/3		100.0% (3 788.2–100.0)	Not serious	Not serious	Serious*	Very serious[β]	Very low
Anogenital warts		89.4% (65.5-97.9)	Not serious	Not serious	Serious*	Not serious	Moderate
HPV types 31, 33, 45, 52 and 58							
6MPI	9vHPV compared to 4vHPV (1RCT)(b)	Outcomes not assessable by GRADE methodology due to the lack of clinical efficacy data in males. Efficacy study in males would require a comparison between the investigational 9vHPV vaccine and the licensed 4vHPV vaccine (using a placebo would not be acceptable since the 4vHPV vaccine prevents anal lesions due to HPV types 16 and 18). Consequently, low incidence of HPV 6, 11, 16 and 18-related disease would be expected with both vaccines and study would require prohibitively large sample size. As alternative approach, two immunobridging studies used to infer efficacy of the 9vHPV vaccine in men 16–26 years old. Studies evaluate immunogenicity of 9vHPV vaccine in males 16–26 years old compared to either 4vHPV or 9vHPV vaccine in females 16–26 years old (population used to establish 9vHPV vaccine efficacy).					
AIN2/3							
PeIN2/3							
Anogenital warts							

HPV: human papillomavirus; 6MPI: 6-month persistent infection; AIN: anal intraepithelial neoplasia; PeIN: penile intraepithelial neoplasia
**: downgraded by 1 for indirectness due to use of immunobridging to 4vHPV vaccine*
a: downgraded by 1 for imprecision due to low event rate
β: downgraded by 1 for imprecision due to very wide 95% confidence interval
a: HPV types 6, 11, 16 and 18 data from Protocol 020/NCT00090285 (PICO1, PICO2 Supp01); supportive data from protocols 003/NCT01651949 (PICO11 Supp05), 020/NCT02114385 (PICO10 Supp05)
b: HPV types 31, 33, 45, 52 and 58 data from Protocol 001/NCT00543543 (PICO1 Supp04); supportive data from protocols 003/NCT01651949 (PICO11 Supp05), 020/NCT02114385 (PICO10 Supp05) [49,76,82–85].

Immunogenicity data on the 9vHPV vaccine administered to males 16–26 years old resulted in higher GMTs than the 4vHPV vaccine for HPV types 31, 33, 45, 52, and 58 at month 7 from the first immunisation dose, and seroconversion rates at month 7 in males vaccinated with the 9vHPV for these types were 100.0%. Regarding HPV types 6, 11, 16 and 18, the 9vHPV vaccine showed non-inferior immunogenicity compared to the 4vHPV vaccine at month 7. Seroconversion rates to these HPV types were ≥98.2% following vaccination with any of the two vaccines. The 9vHPV vaccine resulted in higher GMTs in heterosexual males than females and men who have sex with men 16–26 years old at month 7, but seroconversion rates for HPV vaccine types were ≥99.5% in all groups. The results from these immunogenicity studies support the extrapolation of 4vHPV vaccine efficacy data for HPV 6, 11, 16, 18- related health outcomes in 16–26-year-old males to same-aged heterosexual males and men who have sex with men vaccinated with the 9vHPV vaccine.

In 9–15-year-old males, GMTs for the 9vHPV vaccine types at month 7 were higher with either two or three doses of vaccine compared to females 16–26 years old who received three doses of vaccine. There was no significant difference in seroconversion rates between 9–15-year-old males and 16–26-year-old females for seropositivity to the 9vHPV types (seroconversion rates to HPV vaccine types were ≥99.5% in both groups).

4.1.4 Conclusions

- 9vHPV vaccine is efficacious for at least six years in preventing six-month persistent HPV infection and high-grade cervical lesions due to types 31, 33, 45, 52, and 58 in females 16–26 years old not infected with HPV at time of vaccination (evidence quality: high).
- There is no direct evidence of efficacy of 9vHPV vaccine against HPV-related infection and illness in males.
- Immunogenicity data show a non-inferior response of 9vHPV vaccine against the four HPV types included into the 4vHPV vaccine, which was already shown to be effective against HPV-related illness caused by serotypes 6, 11, 16 and 18. This can be considered indirect evidence that the 9vHPV vaccine is effective against HPV-related disease caused by serotypes 6, 11, 16 and 18 in females and males (evidence quality: moderate).
- The 9vHPV vaccine provides stronger immunogenicity against vaccine serotypes in 9–15-year-old males and females compared to 16–26-year-old females.
- Immunogenicity data on 16–26-year-old males and 9–15–year-old females show a stronger immune response from the 9vHPV vaccine compared to the 4vHPV vaccine against the additional 31, 33, 45, 52, and 58 serotypes contained in the 9vHPV vaccine.

4.2 Evidence on efficacy of quadrivalent and bivalent vaccines for boys/men

4.2.1 Efficacy of quadrivalent and bivalent vaccines in males 16–26-years

Evidence on efficacy of HPV vaccination against HPV-related illness was obtained from the pivotal 4vHPV vaccine efficacy trial in males [82–83,85] comparing the 4vHPV vaccine with placebo. Additional indirect evidence on efficacy was also gathered from immunogenicity studies [77,84,86] (Tables 4, A22–24, supplemental documents Supp01–02,Supp04).

Table 4. Evidence type for benefits: 4vHPV vaccination of males 16–26 years old

Benefits	Design	Efficacy	Risk of bias	Inconsistency	Indirectness*	Imprecision	Evidence type (GRADE) 4vHPV vaccine
HPV types 6, 11, 16 and 18							
6MPI	4vHPV compared to placebo (1RCT)(a)	85.6% (73.4–92.9)	Not serious	Not serious	Not serious*	Not serious	High
AIN2/3		74.9% (8.8–95.4)	Not serious	Not serious	Not serious*	Not serious	High
PeIN2/3		100.0% (-3 788.2–100.0)	Not serious	Not serious	Not serious*	Very seriousβ	Low
Anogenital warts		89.4% (65.5–97.9)	Not serious	Not serious	Not serious*	Not serious	High

HPV: human papillomavirus; 6MPI: 6-month persistent infection; AIN: anal intraepithelial neoplasia; PeIN: penile intraepithelial neoplasia
a: downgraded by 1 for imprecision due to low event rate
β: downgraded by 1 for imprecision due to very wide 95% confidence interval
a: HPV types 6, 11, 16, 18 data from protocol 020/NCT00090285 (PICO1, PICO2 Supp01); supportive data from protocols 020/NCT00090285 (PICO14,PICO15 Supp02), 020/NCT02114385 (PICO3 Supp02), 003/NCT01651949 (PICO4,PICO12,PICO13 Supp02) [76,82–86].

In the per-protocol analysis, the 4vHPV vaccine prevented 6MPI (efficacy 85.6%; 73.4–92.9), AIN2/3 (74.9%; 8.8–95.5) and anogenital warts (efficacy 89.4%; 65.5–97.9) related to HPV types 6, 11, 16 and 18 (evidence quality: high). Efficacy against PeIN2/3 was not assessable due to lack of statistical power and thus the quality of evidence was considered low because of very serious imprecision. In the intention-to-treat analysis, efficacy with respect to persistent infection with HPV-6, 11, 16, or 18 was 47.8% (95% CI, 36.0–57.6), efficacy against genital warts caused by vaccine types was 65.5% (45.8–78.6), while the rate of grade 2 or 3 anal intraepithelial neoplasia related to infection with HPV-6, 11, 16, or 18 was reduced by 54.2% (95% CI, 18.0–75.3). Differences between

per-protocol and intention-to-treat analyses are likely due to the HPV status of the respective populations at time of vaccination (i.e. per-protocol population all HPV-naïve at vaccination).

At month 7, seroconversion rates against HPV6, 11, 16 and 18 were ≥98.4% following vaccination with 4vHPV vaccine, with GMTs reaching peak values. A gradual decline in GMTs was observed after month 7, although 89.5%, 94.3%, 98.3% and 57.3% of subjects remained seropositive to the four HPV types at month 36. GMTs were generally higher in heterosexual males than men who have sex with men, but seroconversion rates for HPV types 6, 11 and 16 were ≥94.1% at month 7 and ≥89.4% at month 36 in both groups and ≥80.0% at month 7 and ≥53.3% at month 36 for HPV18 in both groups.

4.2.2 Efficacy of quadrivalent and bivalent HPV vaccination in males 9–15 years old

For this age group, only evidence from immunogenicity trials was available [75,80,82,83,87–91] (Tables A25–A27, supplemental files Supp01, Supp02, Supp04).

Following vaccination with the 4vHPV vaccine, GMTs for HPV types 6, 11, 16 and 18 at month 7 were non-inferior (or even 1.5-fold higher) than those observed in girls 9–15 years old and from 1.8–2.7-fold higher than those observed in females 16–23 years old. Seroconversion rates for these types at month 7 in males 9–15 years old vaccinated with the 9vHPV vaccine were ≥99.6%. After month 7, a gradual decline in GMTs was observed, although more than 84.8% of males remained seropositive for HPV types 6, 11 and 16 and 60.8% for HPV18 at month 96.

Following vaccination with the 2vHPV vaccine, all subjects (100.0%) seroconverted for the HPV vaccine types at month 7. After month 7, a gradual decline in GMTs for HPV types 16 and 18 was observed, although all subjects remained seropositive at month 42. GMTs were higher in males aged 10–18 years than in females aged 15–25 years.

Conclusions

- The evidence of efficacy of 4vHPV vaccine and 2vHPV vaccine in men is currently limited.
- There is direct evidence that 4vHPV vaccination is efficacious in 16–26-year-old males in preventing six months persistent infections, genital warts and anal intraepithelial neoplasia (i.e. anal cancer precursor lesion) due to HPV types 6, 11, 16 or 18.
- There is no direct evidence on the efficacy of 2vHPV vaccine against HPV-related infection and illness in males.
- 4vHPV and 2vHPV vaccines induce high seroconversion rates and non-inferior immunogenicity in 9–15-year-old males compared to 9–15-year-old females.
- 4vHPV vaccine and 2vHPV vaccine provide stronger immunogenicity in males 9–15 years old compared to females 16–26 years old.

4.3 Efficacy of HPV vaccination in people living with HIV

Direct evidence on the efficacy of HPV vaccination against HPV-related illness for people living with HIV was not found during the time period covered by the systematic review (supplemental file Supp07).

A study on the 4vHPV vaccine in HIV-infected children 7–12 years of age reported seroconversion rates against HPV types 6, 11, 16 and 18 of ≥97% at month 7, with substantially higher GMTs for HPV types 6, 11, 16 and 18 at months 7 and 24 compared to placebo (evidence quality: moderate) [92–93]. In a study of HIV infected males older than 18 years of age, the 4vHPV vaccine resulted in seroconversion rates ≥94.9% against the four vaccine types (evidence quality: very low) [94].

In a study of the 2vHPV vaccine in women aged 18–25 years, GMTs were lower among HIV-infected women compared to the GMTs observed in HIV-uninfected women at month 7. Seroconversion rates of 100.0% against HPV 16 and 18 were observed in both groups at month 7 (evidence quality: low) [95].

In another study comparing the 2vHPV and 4vHPV vaccines in HIV infected adults aged ≥18 years, GMTs for HPV16 did not differ following vaccination with the 2vHPV and 4vHPV vaccines, but they were higher for the 2vHPV vaccine against HPV18 at months 7 and 12 from first immunisation dose (evidence quality: moderate). At month 12 from the first immunisation dose, seroconversion rates following vaccination with 4vHPV and 2vHPV vaccines were 95.7% vs 100.0% respectively against HPV16 and 73.9% vs 97.8% respectively against HPV18 [96–97].

4.3.1 Recent evidence not included in systematic review

Since the closure of the systematic review, arecent study of moderate size and relatively short follow-up (2 years) published in 2018 was identified [98] reporting direct evidence on the efficacy of 4vHPV vaccination against persistent HPV infection in women living with HIV. According to this article, women living with HIV have a higher

risk of persistent HPV infection and illness due to HPV serotypes 6, 11, 16 and 18 compared to women not living with HIV despite HPV vaccination. Women living with HIV vaccinated against HPV had lower rates of persistent HPV infection compared to a historical cohort of women living with HIV not vaccinated against HPV. Additionally, after HPV vaccination, women living with HIV with a low CD4 count (<350 cells/µL) showed a higher incidence of HPV-related illness.

Another study on the efficacy of the 4vHPV vaccine against persistent anal HPV infections and lesions in people living with HIV and older than 27 years was stopped due to futility by the Data and Safety Monitoring Board [99]. This is probably due to the high baseline prevalence of infections with preventable HPV types among individuals living with HIV and over 27 years old included in the study. However, the trial did still find some evidence of the efficacy of the 4vHPV vaccine against oral HPV infection due to vaccine HPV types.

4.3.2 Conclusions

- There is no current direct evidence of clinical efficacy of HPV vaccines in people living with HIV.
- Immunogenicity data show high seroconversion rates against HPV vaccine types in people living with HIV following 4vHPV and 2vHPV vaccination, but lower antibody titres compared to people not living with HIV vaccinated against HPV.
- New upcoming evidence on the efficacy of HPV vaccination in people living with HIV is emerging from ongoing studies.

4.4 Evidence of cost-effectiveness of adding males to current national HPV vaccination programmes

The cost-effectiveness of any HPV vaccination strategy is context-specific and depends on both epidemiology and healthcare financing. However, all reviewed studies are consistent in finding the vaccination of preadolescent girls against HPV to be a cost-effective strategy for reducing the health and economic burden of HPV-related disease at the population level. Furthermore, there is evidence to suggest that where there is a high level of vaccination coverage in females, an indirect protective benefit is conferred on males (in heterosexual Australian men under the age of 22 years attending sexually transmitted infection (STI) clinics, the prevalence of HPV 16/18/6/11 has fallen by 78% since the prevaccination period [100].

In certain settings, a universal HPV vaccination programme has been introduced or proposed, with vaccination offered to both males and females of a certain age. Such a programme may address certain concerns:

- In the context of female-only vaccination, the indirect benefits of herd protection among men who have sex with men are limited [101].
- The degree of herd protection extended to males is associated with vaccination coverage in females, which has been suboptimal in many settings [25].
- On equity grounds, some consider it preferential for both males and females to have access to the direct benefits of vaccination [102].

Whether a universal HPV vaccination programme will be deemed cost-effective in any given setting depends on a number of factors, including:

- health outcomes considered in the analysis (cervical disease, anogenital warts, non-cervical cancers)
- duration of vaccine protection
- baseline coverage rates in females (where appropriate)
- choice of baseline scenario (absence of any HPV vaccination vs. female-only programme)
- costs of vaccine procurement and delivery; and
- setting-specific health economic factors (e.g. ICER threshold, discounting rate and payer perspective).

4.4.1 Evidence on marginal impact of including different health outcomes

Economic evaluations of HPV vaccination vary in the range of disease endpoints considered. In the simplest case, modelling analyses focus on the impact on cervical cancer incidence [68]. In other studies, additional outcomes are included, sometimes progressively [50,63,65]. The most comprehensive studies to date include precancerous lesions of the cervix and vagina, genital warts, recurrent respiratory papillomatosis and cancers of the vulva, vagina, anus, penis and head and neck (including oropharyngeal) [50,65,67,69]. A review of economic evaluations of HPV vaccination from 2017 concluded that across a number of studies, the ICER is on average 2.85 times more favourable for female-only vaccination and 3.89 times more favourable for universal vaccination when non-cervical HPV-related diseases are included [103]. The inclusion of genital warts as an outcome of interest appears to be a significant factor in reducing the ICER, with one study showing a marginal reduction of 41% in the case of 75% vaccination coverage [104].

Tables A36–A39 summarise by study how the ICER is affected by the inclusion of different health outcomes. Additional information is provided in Table A35, where the main characteristics of the studies are included. This table also includes the cost-effectiveness analysis (CEA) threshold used by the authors at the time of the analysis to evaluate the cost-effectiveness of that particular strategy. Of note, these thresholds may vary in time and therefore may not be currently valid.

In broad terms, the ICER decreases when incorporating the potential impact of the vaccine on additional HPV-related health outcomes. The consequence is that cost-effectiveness may be underestimated if the analysis is restricted to a subset of disease endpoints.

4.4.2 Evidence of marginal impact of duration of protection

The duration of protection offered by HPV vaccines is currently unknown and therefore cost-effectiveness studies make assumptions about the rate at which induced immunity wanes.

Duration of protection was assumed to be either lifelong, 20 years or 10 years post-booster dose in most studies. The assumption significantly affected the ICER estimated by each model. The longer the duration of protection, the lower the marginal impact of the gender-neutral vaccination approach on the ICER compared to the female-only vaccination strategy.

Among the studies included in this review, all but three considered the case where vaccine protection is lifelong.

Eight studies conducted a sensitivity analysis to judge how the ICER would be altered if the duration of protection were shorter (e.g. 10, 20, 25 or 35 years; Table A38). All agreed that findings on cost-effectiveness were sensitive to assumptions on duration of vaccine protection. Notably, five studies concluded that the ICER would increase in the case of waning vaccine-induced immunity (since individuals become susceptible again and may be re-infected) [51–52,63,105–105 and three studies concluded that it would decrease (since lifelong protection in females reduces virus circulation and means that there is less disease to be averted in males) [55,61,67].

4.4.3 Evidence on marginal impact of varying coverage

In the included studies, the ICERs of adding males generally increase with higher baseline vaccination coverage in females. The general view is that increasing female coverage is a more efficient strategy for reducing the burden of HPV-related disease in the population than extending vaccination to males, in particular when priority is given to the prevention of cervical cancer. In fact, as mentioned above, cost-effectiveness models are very sensitive to the inclusion of different health outcomes, the assumed duration of vaccine protection, female coverage rates and the cost of the vaccine. Several studies agree that vaccinating males could be cost-effective where female coverage is low or if vaccine costs were substantially reduced.

Tables A36–A39 summarise the main results grouped by study on how ICERs comparing universal vaccination with female vaccination vary by different vaccination coverage rates in females (and in males in certain cases). Certain studies include catch-up vaccination for females only or for both sexes. Additional main characteristics of the studies are included in Table A35.

4.4.4 Evidence on marginal impact of vaccine cost

As the HPV vaccine price decreases, universal vaccination becomes more cost-effective and some authors have identified the threshold price. For example, a study in New Zealand found that extending vaccination to boys based on a three-dose schedule would only be cost-effective when the price was below NZD 125 per dose (approximately EUR 71 in 2011) [60]. Another recent study from the Netherlands published in 2017 found that the vaccination of boys based on a two-dose regime would be considered cost-effective when the vaccination cost was below EUR 65 per dose, which was the actual cost in the country from 2012–2014 [54].

4.4.5 Evidence of cost-effectiveness of adding men who have sex with men to current national HPV vaccination programmes

Men who have sex with men account for a disporoportionately high burden of male HPV-related disease, but benefit less than other males from the herd protection of female-only vaccination [100]. In cases where universal vaccination is found not to be cost-effective, an alternative could be a targeted strategy, e.g. vaccinating men who have sex with men.

The potential impact and cost-effectiveness of a focused HPV vaccination programme for men who have sex with men has been modelled in Australia [106], the United Kingdom [101] and the United States [107–108]. Kim et al. [107] assessed a healthy cohort of men who have sex with men starting at the age of 12 years for lifetime risk of anal cancer and genital warts. Under different scenarios of age at vaccination, duration of vaccine protection, HPV and HIV exposure and anal cancer incidence, cost-effectiveness ratios remained lower than the aforementioned threshold of USD 100 000/QALY gained. Assuming 50% coverage and 90% vaccine efficacy, HPV vaccination of men who have sex with men at the age 12 years had a cost-effectiveness ratio of USD 15 290/QALY gained

compared to no vaccination (assuming 0% HPV exposure). The cost-effectiveness ratio was USD 19 160/QALY gained if men who have sex with men were vaccinated at age 26 years assuming 10% exposure to HPV 16, 18, 6 and 11 and USD 37 830/QALY gained when assuming 50% prior exposure to vaccine types 6, 11, 16 and 18.

Using a dynamic model, Lin et al. evaluated the impact of offering vaccination to men who have sex with men who visited genito-urinary medicine clinics (GUM) in the UK [101]. Substantial declines in anogenital warts and male HPV-related cancer incidence were estimated by offering HPV vaccination to men who have sex with men aged 16–40 years. Specifically, anogenital warts incidence was estimated to decrease by 35% within five years (15% where only HIV-positive men who have sex with men were vaccinated) and HPV-related cancer incidence was projected to drop by 55% within 100 years (40% where only HIV-positive men who have sex with men were vaccinated). The authors also indicated that HPV vaccination of this group could be cost-effective if all men who have sex with men up to age 40 years were vaccinated at a cost of GBP 48 per dose or only HIV-positive men who have sex with men were vaccinated at maximum cost of GBP 96.50 per dose. However, they acknowledged that those attending GUM clinics are a subset of the larger population of men who have sex with men. As a consequence of the findings of Lin et al., HPV vaccination has been offered to men who have sex with men aged 45 and under attending GUM clinics in England since April 2018 [109].

In contrast, a compartmental model analysis in Australia concluded that the greatest health benefits for men who have sex with men would only be achieved by targeting 9–15-year-old boys and a vaccination programme for young men who have sex with menaged 15–26 years in addition to the boys program would only be cost-effective if implemented immediately [106].

HPV vaccination as a secondary strategy for the prevention of recurrent high-grade anal intraepithelial lesions and invasive anal cancer was assessed for both HIV-negative and positive men aged 27 years and above in the United States [107,110,111]. For both, the risk of recurrence and subsequent progression to invasive anal cancer decreased by around 60% compared to no vaccination. Such an intervention was found to be cost-effective for HIV-negative men and cost-saving for HIV-positive men.

4.4.6 Conclusions

- The cost-effectiveness of adding males to female-only HPV vaccination programme depends on several factors and model assumptions that may be context-specific, including vaccine price, vaccination coverage rates in females, duration of protection, vaccine efficacy in males and assumed serotype-specific efficacy of the HPV vaccine against different health outcomes.
- Parameters used in cost-effectiveness studies in recent years include lower coverage rates for females, prices well below the original market values and a greater range of potential health benefits due to HPV vaccination.
- If the priority of the HPV vaccination programme is the prevention of cervical disease in women, then adding males to current female-only HPV vaccination programmes becomes more cost-effective with:
  - persistently lower vaccination coverage among females; and
  - lower cost of the vaccine.

  However, increasing vaccination coverage among girls may still be a more cost-effective primary objective.
- If vaccination uptake is lower in specific population subgroups (in terms of geographical region, ethnicity, socio-economic status and/or religion), it may be preferable to channel resources to increasing uptake among the unvaccinated.
- If the objective of the HPV vaccination programme is to prevent all HPV-related disease, then a universal HPV vaccination may become a more cost-effective option to consider.

5 Implications for public health practice and research

This section is based on ECDC's reflections on the potential implications for public health practice of the evidence-based conclusions reported in Section 4.

5.1 Possible implications for current national HPV immunisation programmes

Virtually all countries in the EU/EEA currently have a HPV vaccination programme targeting preadolescent girls (Table 1). A growing number of Member States are considering or have already adopted gender-neutral HPV vaccination [26,29–33]. Several considerations related to this decision are briefly discussed below.

Sufficiently high HPV vaccination coverage is not only crucial to obtain direct protection of a large number of vaccinated individuals, but also to achieve herd (indirect) protection of those who did or could not get vaccinated. Virtually all cost-effectiveness analyses identify HPV vaccination programmes for preadolescent girls to be cost-effective, even those with relatively low vaccination coverage rates. However, herd effects improve the cost-effectiveness of vaccination and are mainly observed at high vaccination coverages rates [104,112]. Routine vaccination of preadolescent girls is still the primary target of HPV vaccination as it provides the greatest health impact while cost-effectiveness analyses assessing other vaccine target groups are in fact less conclusive [104,113]. Vaccinating additional age cohorts would advance health benefits to older age groups, although cost-effectiveness becomes less favourable as age at vaccination increases.

The extension of HPV vaccination to preadolescent males can further improve the indirect protection of unvaccinated girls and women through herd immunity and can directly prevent HPV-related conditions in men, including men who have sex with men. Related to this, a Finnish randomised community trial published in 2018 recently demonstrated that gender-neutral vaccination generates significant herd effects and cross-protection against a number of non-vaccine HPV types in a low-to-moderate coverage scenario [114–115]. Including men in HPV vaccination programs may be a less efficient strategy if done at the expense of female vaccination coverage for reducing the burden of HPV in the population. However, as the HPV vaccine price decreases, the cost-effectiveness of universal vaccination can improve. Aside from the vaccine price, other previously discussed factors that influence the cost-effectiveness of adding males to HPV vaccination programs include coverage among girls, number of doses, duration of protection and number of HPV-related health outcomes considered primary objectives of the immunisation programme [113].

Evidence on duration of protection was not assessed in the current guidance, but it is an important factor in determining the overall impact of the vaccination. Cost-effectiveness models show that the longer the duration of protection, the less the marginal impact of the gender-neutral vaccination approach is compared to the female-only vaccination strategy (Annex 1). Ongoing studies suggest that currently licensed vaccines administered to preadolescent girls provide at least 10 years of protection [7]. Age at vaccination and vaccination schedule (i.e. number of doses) influence the strength of the immunogenic response to the vaccine and may possibly also affect duration of protection, though no correlate of protection for HPV vaccination has been identified yet. Certain large population-based observational studies will produce more data on some of these aspects in the future [44,116–118]).

The current evidence of HPV vaccine efficacy in males is limited and refers to the prevention of persistent HPV infections, genital warts and anal cancers precursor lesions (anal intraepithelial neoplasia) by the 4vHPV vaccine. No meaningful vaccine efficacy estimate is available for penile intraepithelial lesions and there is no direct evidence of efficacy against anal, penile and oropharyngeal cancers. Quite importantly, vaccine efficacy is significantly higher for individuals who are HPV-naïve, so vaccinating before the beginning of sexual activity (i.e. before exposure to HPV infection) is generally preferable.

The demonstrated efficacy of HPV vaccination on different HPV-related health outcomes also needs to be considered when modelling cost-effectiveness of HPV vaccination. It is biologically plausible that HPV vaccination is effective against all vaccine HPV type-attributable cancers and illnesses, even though some of these effects are not yet supported by currently available evidence.

The introduction of the 9vHPV vaccine will likely have an impact on the new additional vaccine HPV types beyond what has been observed with cross-protection from other previously licensed HPV vaccines [119]. The 9vHPV vaccine could thus be potentially more beneficial for adults already infected with some HPV type (e.g. people living with HIV, men who have sex with men and women older than 25 years), as these individuals would thus be protected against at least some of the additional HPV types contained in the 9vHPV vaccine. However, the effectiveness of the 9vHPV vaccine in preventing cancers due to HPV-16 and HPV-18, responsible for the majority

of the HPV-related cancers, should also be compared to the effectiveness of other available vaccines in order to evaluate options for an optimal immunisation strategy [105,120]. On the other hand, potential changes in the cost-effectiveness of intervention following introduction of the 9vHPV vaccine should be taken into consideration. A recent modelling study published in 2016 assuming 95% vaccine-type efficacy and life-long protection predicted that administering 9vHPV to girls could already provide the majority of the benefits achievable with a gender-neutral vaccination strategy [121].

5.1.1 Organisational aspects

The cost of the vaccine is one of the main determinants of the cost of intervention and a key driver for estimating cost-effectiveness. The choice of which type of HPV vaccine to use should be linked to the evidence of its effectiveness and impact, which may vary between countries due to different epidemiological situations, HPV type distribution and HPV vaccination programme objectives (e.g. prevention of cervical cancer and HPV-related diseases). The Centre d'expertise et de référence en santé publique in Canada recommended a mixed vaccination schedule based on some of these considerations in 2018 [122].

In virtually all studies considered, evidence shows that girls-only vaccination programme is a cost-effective strategy. However, achieving and maintaining high vaccine uptake over time may be challenging in practice. Recent experiences in certain Member States suggest that sudden drops in vaccination coverage are possible [34]. In such events, a female-only vaccination programme could also suffer from important drops in indirect protection of unvaccinated groups, possibly causing significant HPV-associated harm in the population over time. A gender-neutral vaccination programme would be more resilient against sudden drops of vaccination coverage as it would provide more robust and stronger indirect protection, as emerged from literature recently published in 2016 and 2018 [114–115,123].

However, gender-neutral vaccination requires the administration of about twice as many doses and this comes with a cost for society. Nevertheless, returns on investment can be anticipated due to increased direct and indirect (herd) protection that may prevent the cost of treating excess cases of genital warts and cancer attributable to HPV in both sexes. Among other factors, this once again will be dependent on the local epidemiology of HPV-related illnesses, their current and future trends and the HPV serotypes mainly involved and circulating. The number of doses administered to each person will affect the resources needed for intervention and this will also depend on age at HPV vaccination. Currently, WHO recommendations indicate that two doses of HPV vaccine are enough when given to preadolescents and adolescents under 15 years of age, while three doses are recommended in individuals above 15 years of age [7].

Adding groups at risk like people living with HIV and men who have sex with men to the routine girls-only vaccination policy may be considered as an alternative option in case of limited resources. In fact, despite lower vaccine efficacy due to the higher prevalence of HPV infection in these groups, the overall impact of the intervention could still be high due to the high absolute risk among these people [124].

5.1.2 Social aspects

Cervical cancer disproportionally affects women with lower socio-economic status and socio-economic differences have been observed in attendance to cervical screening [125–127]. In certain European settings, HPV vaccination has been observed to be associated with more equal access across all socio-economic strata of the population [128]. If this were not the case, special attention should be paid to reaching all socio-economic strata and groups in the population in order to increase the benefits of HPV vaccination without causing health inequalities.

Since HPV is an STI, sexual mixing patterns and HPV viral circulation may vary across countries and groups. For this reason, additional resources may be best invested in certain settings in reaching girls belonging to unvaccinated subgroups of the population rather than starting a universal HPV immunisation programme that may still not protect these under-vaccinated communities (e.g. specific ethnic, cultural, socio-economic or religious groups). A HPV vaccination strategy should ideally take into account evidence on sexual mixing patterns and on circulation of HPV viral types within the population.

5.1.3 Ethical considerations

Men who have sex with men are at increased risk of HPV infection and transmission. They have limited to no protection from a female-only vaccination strategy and thus do not directly benefit from it. Adding men who have sex with men to a female-only vaccination strategy may pose certain challenges. The best immunogenic response against HPV is achieved by vaccinating preadolescent individuals, while it may turn out unfeasible and questionable to identify men who have sex with men at such an early age. Moreover, from the evidence that was reviewed in the guidance, men who have sex with men appear to have lower immunogenic responses to HPV vaccination compared with heterosexual men from the same age group and this could be possibly due to more exposure to HPV. Gender-neutral vaccination of all preadolescents would directly (and indirectly for the unvaccinated) protect men who have sex with men without posing any of these challenges.

A universal vaccination would also be more equal by giving both sexes the opportunity to get directly protected against HPV-related disease. This is a value judgement that each country should independently consider in light of their local situation and all the previous discussions.

Additionally, achieving the highest possible indirect (herd) protection and obtaining sustained reduction of HPV circulation in the population may also positively affect people who cannot directly benefit from HPV vaccination, such as those with immunocompromised conditions.

Regardless of the HPV vaccination strategy chosen, different countries may optionally consider offering HPV vaccination to men who have sex with men who are no longer in the target (age) groups for routine HPV vaccination in order to provide them with some direct protection against HPV-related disease.

5.2 Possible implications of vaccinating people living with HIV

In the presence of limited direct evidence, immunogenicity data suggest that seroconversion is achieved following HPV vaccination by most people living with HIV and no safety signals for HPV vaccine have emerged in this group from previous literature reviews [41]. Although the studies reviewed in the guidance did not discriminate between different levels of immunosuppression of people living with HIV, it is known that the immunogenic response to a vaccine of people living with HIV may depend on their immunocompetence status (e.g. CD4 count), which also depends on whether they are on HIV treatment [129]. The general principle that earlier vaccination causes better immune response should theoretically also be valid for people living with HIV given sufficient immunity.

People living with HIV are also at increased risk of HPV infection. This may decrease the benefits of the vaccination as they may be less likely to be HPV-naïve. This once again underscores the need to vaccinate against HPV as early as possible in order to obtain greater benefits from immunisation.

5.3 Possible implications of HPV vaccine hesitancy

Despite the high number of girls successfully vaccinated in Europe every year, many still miss the opportunity to be vaccinated. Vaccine hesitancy refers to 'delay in acceptance or refusal of vaccination despite availability of vaccination services' [11], thus mainly addressing perceptions and opinions of the population that is offered or eligible for vaccination. Understanding knowledge, attitudes and decision patterns regarding HPV vaccination at all levels (decision makers, healthcare workers, parents, target populations) could be relevant for increasing and maintaining high uptake. It is important to mention the role of healthcare workers, as they are among the most trusted advisors and influencers of vaccination decisions [130] since they may administer the vaccine, inform the population on their eligibility for HPV vaccination, address concerns regarding the safety and efficacy of the vaccine and provide recommendations when requested. Healthcare workers' perceptions and opinions regarding HPV vaccination may influence their clinical behaviour and consequently patient vaccine hesitancy, as well as vaccine acceptability in general.

Identifying effective interventions and communication strategies, tailored to different target groups and adapted to the local context, is also an important aspect to consider.

5.4 Remaining knowledge gaps

No HPV vaccine impact or effectiveness data were captured by the systematic reviews on the topics covered by the guidance. The knowledge gap concerning real-life evidence on the 9vHPV vaccine and HPV vaccination in males will be filled by ongoing studies and could confirm positive findings coming from efficacy and immunogenicity studies.

After reviewing and discussing the evidence, the expert panel identified the following specific knowledge gaps and areas in need of further evidence:

- more data on efficacy and effectiveness of all available HPV vaccines in males
- additional evidence of cross-protection of all available HPV vaccines
- additional and updated evidence on strength and duration of protection of HPV vaccines
- effect of HPV vaccination according to sexual transmission patterns (e.g. number of sexual partners, subgroups of the population with different viral mixing patterns and vaccination uptake)
- efficacy of a single dose of HPV vaccine for those who do not complete the full cycle
- additional benefit of 9vHPV vaccination for women older than 25 years
- data on efficacy/effectiveness of 2vHPV vaccine in males
- data on HPV vaccine efficacy and kinetics of anti-HPV antibodies in people living with HIV
- additional evidence on HPV vaccine efficacy against genital warts and anal intraepithelial neoplasia in men who have sex with men

- age-specific prevalence of HPV infection of the oral cavity
- efficacy of HPV vaccines on oral HPV infection in males
- efficacy of HPV vaccines in immunosuppressed individuals (including people living with HIV)
- identification of immune-correlates of protection and potential use in public health surveillance
- immune/vaccine responses of different HPV serotype variants
- effectiveness of therapeutic HPV vaccination
- impact of HPV vaccination on screening uptake behaviour
- continuous vigilance on possible HPV serotype replacement
- vigilance on HPV vaccine failures and their characterisation; and
- factors affecting HPV vaccine uptake (including reasons for lower uptake in males in several settings).

6 Next steps

Research is ongoing in several of the areas covered by the guidance. Large cohort studies are being carried out and will provide data on the real-life effectiveness of the vaccine on HPV-related illness [44,116–118], while new impact assessements of current HPV vaccination programmes are being performed [46]. As more countries worldwide recommend universal HPV vaccination, it is possible that more evidence on the impact of HPV vaccination will become available in the coming years. Studies on HPV infection of the oral cavity may shed more light on the impact of HPV vaccination on oropharyngeal cancers attributable to HPV, as they have increased in certain developed countries [15,99]. Ongoing studies on the efficacy of a single dose of HPV vaccine may be informative in many respects, including kinetics of anti-HPV antibodies, duration of protection, best possible HPV vaccination schedule and cost-effectiveness [131]. More head-to-head comparisons of existing vaccines and experiences from the use of mixed HPV vaccination schedules may also produce additional insight on how to maximise effectiveness of intervention and improve efficiency [132]. Some data may be incorporated into future modelling studies to inform decision-making while taking into account possible changes in costs of intervention (including screening) and evidence about anticipated desirable effects of the vaccination.

6.1 Screening in post-vaccination era

The first routine HPV vaccination cohorts are starting to reach the age where they are invited for cervical screening for the first time. Recent research published in 2016–2017 suggests that in a (partially) vaccinated population, less intensive screening programmes, characterised by a later start age, longer time interval and less invasive primary test, may provide similar or higher benefits at lower cost (and lower harm as measured by colposcopy rate) than maintaining current screening guidelines [133–134].

However, Kim et al. [69] note that a universal screening policy aiming to target the average risk profile in a population, not taking into account vaccination status, may lead to inefficiencies and foregone health benefits. Therefore, it is essential to assess the unfolding impact of a less frequent screening programme on the unvaccinated: whether they will be at a heightened risk as they lose some of the direct benefit of screening or adequately protected by herd immunity. In a modelling study predicting cervical cancer incidence in England up to 2040, Castanon et al. emphasise that focus should be placed on increasing screening coverage among unvaccinated women [135].

Furthermore, the advent of primary HPV testing [133,136], together with the development of new technologies for triage [137], will alter the general approach to the prevention of HPV-related disease over the coming years [112].

The guidance will need to be further updated within the next five years with evidence emerging from research and implementation of the intervention.

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Annex 1. Supporting tables

Table A1. Numbers of cases and rates (per 100 000) of cancer attributable to HPV in 2012 by country

	Cervical cancer				Other anogenital	Head and neck
	Annual number new cases	Incidence ASR (W)	Annual number of deaths	Mortality ASR (W)	Incidence ASR (W)	Incidence ASR (W)
Austria	363	5.8	178	2	1.19	1.27
Belgium	639	8.6	219	1.9	1.54	1.68
Bulgaria	1 254	24.5	437	7	0.97	1.01
Croatia	325	10	140	3.2	1.14	0.84
Cyprus	31	4.1	17	1.5	0.92	0.18
Czech Republic	1 016	14.1	315	3.2	0.99	1.44
Denmark	363	10.6	97	1.9	2.16	1.48
Estonia	186	19.9	80	5.9	1.05	0.86
Finland	143	4.3	53	1	1.02	0.65
France	2 862	6.8	1167	1.9	1.76	1.88
Germany	4 995	8.2	1 566	1.7	1.27	1.79
Greece	421	5.2	208	1.8	0.82	0.27
Hungary	1 178	18	461	5.3	0.93	3.04
Iceland	14	7.9	2	0.4	1.49	0.54
Ireland	357	13.6	101	3.3	1.4	0.9
Italy	2 918	6.7	1 016	1.5	1.07	0.46
Latvia	284	17.3	135	6.3	0.99	0.92
Lithuania	615	26.1	221	7.5	1.08	1.16
Luxembourg	24	4.9	13	2.4	1.29	1.31
Malta	12	3.8	3	0.8	0.98	0.48
Netherlands	750	6.8	242	1.6	1.66	0.95
Norway	294	9.8	101	2.3	1.67	0.8
Poland	3 513	12.2	1 858	5.4	0.72	1.27
Portugal	720	9	390	3.7	0.92	1.02
Romania	4 343	28.6	1 909	10.8	0.77	2.02
Slovakia	607	16.1	232	5.2	0.94	2.08
Slovenia	139	10.5	64	3	1.2	0.84
Spain	2 511	7.8	848	2.1	1	0.65
Sweden	451	7.4	187	1.9	1.28	0.72
United Kingdom	659	7.1	979	1.8	1.35	0.99

Age-standardised (world) incidence rate (per 100 000) of cancer cases attributable to HPV in 2012 by country in Europe.
GLOBOCAN 2012, IARC -27.6.2018
de Martel C, Int J Cancer. 2017
ASR (W): age-standardised rate (women)

Efficacy of 9vHPV vaccine in females 16–26 years old

Table A2. Evidence type for benefits: 9vHPV vaccination of females 16–26-years

Outcome-related HPV type	Benefits	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type (GRADE)
HPV types 6, 11, 16 and 18	6MPI	4vHPV (3RCT) (a)	Not serious	Not serious	Serious*	Not serious	Moderate
	CIN2/3 or worse		Not serious	Not serious	Serious*	Not serious	Moderate
	Cervical cancer		Not serious	Not serious	Very serious*γ	Not serious	Low
	VIN2/3, VaIN2/3 or worse		Not serious	Not serious	Serious*	Not serious	Moderate
	Vulvar or vaginal cancer		Not serious	Not serious	Very serious*γ	Not serious	Low
	Anogenital warts		Not serious	Not serious	Serious*	Not serious	Moderate
HPV types 31, 33, 45, 52 and 58	6MPI	9vHPV (1RCT) (b)	Not serious	Not serious	Not serious	Not serious	High
	CIN2/3, VIN2/3, VaIN2/3 or worse		Not serious	Not serious	Not serious	Not serious	High
	CIN2/3 or worse		Not serious	Not serious	Not serious	Not serious	High
	Cervical cancer		Not serious	Not serious	Seriousγ	Not serious	Moderate
	VIN2/3, VaIN2/3 or worse		Not serious	Not serious	Not serious	Very seriousαβ	Low
	Vulvar or vaginal cancer		Not serious	Not serious	Seriousγ	Very seriousαβ	Very low

HPV: human papillomavirus; 6MPI: 6-month persistent infection; CIN: cervical intraepithelial neoplasia; VIN: vulvar intraepithelial neoplasia; VaIN: vaginal intraepithelial neoplasia.

**: Downgraded by 1 for indirectness due to use of immunobridging to 4vHPV vaccine.*

γ: Downgraded by 1 for indirectness due to use of ≥CIN2, ≥VIN2 or ≥VaIN2 as surrogate markers for cervical, vulvar or vaginal cancer.

α: Downgraded by 1 for imprecision due to low event rate.

β: Downgraded by 1 for imprecision due to very wide 95% confidence interval.

a: HPV types 6, 11, 16 and 18 data from protocols 007/NCT00365716 and NCT00365378, 013/NCT00092521, 015/NCT00092534 [4-6] (PICO2 Supp04); supportive data from protocols 001/NCT00543543 [1] (PICO5 and PICO6 Supp05), 002/NCT00943722 [2] (PICO2 and PICO8 Supp05), 003/NCT01651949 [3] (PICO11 Supp05)

b: HPV types 31, 33, 45, 52 and 58 data from protocol 001/NCT00543543 [1] (PICO1 Supp04); supportive data from protocols 002/NCT00943722 [2] (PICO2 and PICO8 Supp05), 003/NCT01651949 [3] (PICO11 Supp05).

Sources: 1. Huh WK, et al. Lancet. 2017;390:2143-2159; 2. Van Damme P, et al. Pediatrics. 2015;136:e28-39; 3. Castellsagué, et al. Vaccine. 2015;33:6892-901; 4. Kjær SK, et al. Cancer Prev Res. 2009;2:868-78; 5. Dillner J, et al. BMJ. 2010;341:c3493; 6. Villa LL, et al. Lancet Oncol. 2005;6:271-8.2

Table A1. Available data for females 16–26 years old from 9vHPV vaccine trials

Outcomes	HPV 6, 11, 16 and 18-related		HPV 31, 33, 45, 52 and 58-related	
	Direct	Indirect	Direct	Indirect
6MPI	No(a)	Immunogenicity(b)[1-3]	Yes [1]	Immunogenicity [1–3]
CIN2/3, VIN2/3, VaIN2/3 or worse	No(a)	Immunogenicity(b)[1-3]	Yes [1]	Immunogenicity [1–3]
CIN2/3 or worse	No(a)	Immunogenicity(b)[1-3]	Yes [1]	Immunogenicity [1–3]
Cervical cancer	No	Immunogenicity(b)[1-3]	No	≥CIN2, immunogenicity [1–3]
VIN2/3, VaIN2/3 or worse	No(a)	Immunogenicity(b)[1-3]	Yes [1]	Immunogenicity [1–3]
Anogenital warts	No(a)	Immunogenicity(b)[1-3]	--	--

HPV: human papillomavirus; 6MPI: 6-month persistent infection; CIN: cervical intraepithelial neoplasia; VIN: vulvar intraepithelial neoplasia; VaIN: vaginal intraepithelial neoplasia.
a: 9vHPV vaccine clinical used 4vHPV vacine as a comparator. This trial did not have enough power to assess vaccine efficacy for clinical endpoints related to HPV types 6, 11, 16 and 18.
b: Immunogenicity of 9vHPV compared with 4vHPV vaccine was used to infer efficacy.

Sources: 1. Huh WK, et al. Lancet. 2017;390:2143-2159; 2. Van Damme P, et al. Pediatrics. 2015;136:e28-39; 3. Castellsagué X, et al. Vaccine. 2015;33:6892-901.

Table A2. 4vHPV vaccine trials for HPV 6, 11, 16 and 18-related outcomes in females 16–26 years old

Protocol	Intervention	Comparator	Number	Outcome	Efficacy
007/NCT00365716 and NCT00365378, 013/NCT00092521, 015/NCT00092534 [4-6]	4vHPV in females 16–26 years (per protocol population)	Placebo in females 16–26 years old	551	6MPI	89.0% (70.0–97.0) – PICO2 Supp04
			15 729	CIN2/3 or worse	98.2% (93.3–99.8) – PICO2 Supp04
			15 802	VIN2/3, VaIN2/3 or worse	100.0% (82.6–100.0) – PICO2 Supp04
			15 334	Anogenital warts	98.9% (96.1–99.9) – PICO2 Supp04

HPV: human papillomavirus; 6MPI: 6-month persistent infection; CIN: cervical intraepithelial neoplasia; VIN: vulvar intraepithelial neoplasia; vVaIN: vaginal intraepithelial neoplasia.

Sources: 4. Villa LL, et al. Lancet Oncol. 2005;6:271-8; 5. Kjær SK, et al. Cancer Prev Res. 2009;2:868-78; 6 .Dillner J, et al. BMJ. 2010;341:c3493.

Table A3. 9vHPV vaccine trials for HPV 31, 33, 45, 52 and 58-related outcomes in females 16–26 years old

Protocol	Intervention	Comparator	Number	Outcome	Efficacy
001/NCT00543543 [1]	9vHPV in females 16–26 years old (per protocol population)	4vHPV in females 16–26 years old	11 896	6MPI	96.0% (94.6–97.1) – PICO1 Supp04
			12 033	CIN2/3, VIN2/3, VaIN2/3 or worse	97.4% (85.0–99.9) – PICO1 Supp04
			11 892	CIN2/3 or worse	97.1% (83.5–99.9) – PICO1 Supp04
			12 021	VIN2/3, VaIN2/3 or worse	100.0% (–71.5–100.0) – PICO1 Supp04
			14 215	Seroconversion and geometric mean titres (by HPV)	PICO5, PICO6 Supp05
002/NCT00943722 [2]	9vHPV in females and males 9–15 years old (per protocol population)	9vHPV in females 16–26 years old (immunobridging)	3 074	Seroconversion and geometric mean titres (by HPV)	PICO2, PICO8 Supp05
003/NCT01651949 [3]	9vHPV in females 16–26 years old (per protocol population)	9vHPV in males 16–26 years old (immunobridging)	2 520	Seroconversion and geometric mean titres (by HPV)	PICO11 Supp05

HPV: human papillomavirus; 6MPI: 6-month persistent infection; CIN: cervical intraepithelial neoplasia; VIN: vulvar intraepithelial neoplasia; VaIN: vaginal intraepithelial neoplasia.

Sources: 1. Huh WK, et al. Lancet. 2017;390:2143-2159; 2. Van Damme P, et al. Pediatrics. 2015;136:e28-39; 3. Castellsagué X, et al. Vaccine. 2015;33:6892-901.

Efficacy of 9vHPV vaccine in females 9–15 years old

Table A4. Evidence type for benefits: 9vHPV vaccination of females 9–15 years old

Outcome-related HPV type	Benefits	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type (GRADE)
HPV types 6, 11, 16, 18	6MPI	4vHPV (3RCT)(a)	Not serious	Not serious	Very serious*,¥	Not serious	Low
	CIN2/3 or worse		Not serious	Not serious	Very serious*,¥	Not serious	Low
	Cervical cancer		Not serious	Not serious	Very serious*,γ,¥	Not serious	Low
	VIN2/3, VaIN2/3 or worse		Not serious	Not serious	Very serious*,¥	Not serious	Low
	Vulvar or vaginal cancer		Not serious	Not serious	Very serious*,γ,¥	Not serious	Low
	Anogenital warts		Not serious	Not serious	Very serious*,¥	Not serious	Low
HPV types 31, 33, 45, 52 and 58	6MPI	9vHPV (1RCT)(b)	Not serious	Not serious	Serious¥	Not serious	Moderate
	CIN2/3, VIN2/3, VaIN2/3 or worse		Not serious	Not serious	Serious¥	Not serious	Moderate
	CIN2/3 or worse		Not serious	Not serious	Serious¥	Not serious	Moderate
	Cervical cancer		Not serious	Not serious	Very seriousγ,¥	Not serious	Low
	VIN2/3, VaIN2/3 or worse		Not serious	Not serious	Serious¥	Very seriousαβ	Very low
	Vulvar or vaginal cancer		Not serious	Not serious	Very seriousγ,¥	Very seriousαβ	Very low

HPV: human papillomavirus; 6MPI: 6-month persistent infection; CIN: cervical intraepithelial neoplasia; VIN: vulvar intraepithelial neoplasia; VaIN: vaginal intraepithelial neoplasia

**: Downgraded by 1 for indirectness due to use of immunobridging to 4vHPV vaccine.*

¥: Downgraded by 1 for indirectness due to use of immunobridging to females 16–26 years old.

γ: Downgraded by 1 for indirectness due to use of ≥CIN2, ≥VIN2 or ≥VaIN2 as surrogate markers for cervical, vulvar or vaginal cancer.

α: Downgraded by 1 for imprecision due to low event rate.

β: Downgraded by 1 for imprecision due to very wide 95% confidence interval.

a:HPV types 6, 11, 16, 18 data from protocol 007/NCT00365716 and NCT00365378, 013/NCT00092521, 015/NCT00092534 [5–7] (PICO2 Supp04); supportive data from protocols 001/NCT00543543 [1] (PICO5 and PICO6 Supp05), 002/NCT00943722 [2] (PICO2 and PICO8 Supp05), 009/NCT01304498 [3] (PICO1 Supp05), 010/NCT01984697 [4] (PICO3 Supp05)

b: HPV31, 33, 45, 52 and 58 data from protocol 001/NCT00543543 [1] (PICO1 Supp04); supportive data from protocols 002/NCT00943722 [2] (PICO2 and PICO8 Supp05), 009/NCT01304498 [3] (PICO1 Supp05), 010/NCT01984697 [4] (PICO3 Supp05).

Sources: 1. Huh WK, et al. Lancet. 2017;390:2143-2159; 2. Van Damme P, et al. Pediatrics. 2015;136:e28-39; 3. Vesikari T, et al. Pediatr Infect Dis J. 2015;34:992-8; 4. Iversen OE, et al. JAMA. 2016;316:2411-2421; 5. Kjær SK, et al. Cancer Prev Res. 2009;2:868-78; 6. Dillner J, et al. BMJ. 2010;341:c3493; 7. Villa LL, et al. Lancet Oncol. 2005;6:271-8.2.

Table A5. Available data for females 9–15 years old from 9vHPV vaccine trials

Outcomes	HPV 6, 11, 16 and 18-related		HPV 31, 33, 45, 52 and 58-related	
	Direct	Indirect	Direct	Indirect
6MPI	No	Immunogenicity(a)[2-4]	No	Immunogenicity [2-4]
CIN2/3 or worse	No	Immunogenicity(a)[2-4]	No	Immunogenicity [2-4]
Cervical cancer	No	Immunogenicity(a)[2-4]	No	≥CIN2, immunogenicity [2-4]
VIN2/3, VaIN2/3 or worse	No	Immunogenicity(a)[2-4]	No	Immunogenicity [2-4]
Anogenital warts	No	Immunogenicity(a)[2-4]	--	--

HPV: human papillomavirus; 6MPI: 6-month persistent infection; CIN: cervical intraepithelial neoplasia; VIN: vulvar intraepithelial neoplasia; VaIN: vaginal intraepithelial neoplasia.
a: Immunogenicity of two clinical trials comparing 3 doses of the 9vHPV vaccine in females aged 9–15 years old with females aged 16–26 years and comparing 3 doses 9vHPV with 4vHPV vaccine in females aged 9–15 years old was used to infer efficacy.

Sources: 2. Van Damme P, et al. Pediatrics. 2015;136:e28-39; 3. Vesikari T et al. Pediatr Infect Dis J. 2015;34:992-8; 4. Iversen OE, et al. JAMA. 2016;316:2411-2421.

Table A6. 4vHPV vaccine trials for HPV 6, 11, 16 and 18-related outcomes in females 9–15 years old

Protocol	Intervention	Comparator	Number	Outcome	Efficacy
007/NCT00365716 and NCT00365378, 013/NCT00092521, 015/NCT00092534 [5-7]	4vHPV in females 16– 26 years old (per protocol population)	Placebo in females 16–26 years old	551	6MPI	89.0% (70.0-97.0) – PICO2 Supp04
			15 729	CIN2/3 or worse	98.2% (93.3-99.8) – PICO2 Supp04
			15 802	VIN2/3, VaIN2/3 or worse	100.0% (82.6-100.0) – PICO2 Supp04
			15 334	Anogenital warts	98.9% (96.1–99.9) – PICO2 Supp04

HPV: human papillomavirus; 6MPI: 6-month persistent infection; CIN: cervical intraepithelial neoplasia; VIN: vulvar intraepithelial neoplasia; VaIN: vaginal intraepithelial neoplasia.

Sources: 5. Villa LL, et al. Lancet Oncol. 2005;6:271-8; 6 Kjær SK, et al. Cancer Prev Res 2009;2:868-78; 7 Dillner J, et al. BMJ. 2010;341:c3493.

Table A7. 9vHPV vaccine trials for HPV 31, 33, 45, 52 and 58-related outcomes in females 9–15 years old

Protocol	Intervention	Comparator	Number	Outcome	Efficacy
001/NCT00543543 [1]	9vHPV in females 16–26 years old (per protocol population)	4vHPV in females 16–26 years old	11 896	6MPI	96.0% (94.6-97.1) - PICO1 Supp04
			12 033	CIN2/3, VIN2/3, VaIN2/3 or worse	97.4% (85.0-99.9) - PICO1 Supp04
			11 892	CIN2/3 or worse	97.1% (83.5-99.9) - PICO1 Supp04
			12 021	VIN2/3, VaIN2/3 or worse	100.0% (–71.5-100.0) - PICO1 Supp04
			14 215	Seroconversion and geometric mean titres (by HPV)	PICO5, PICO6 Supp05
002/NCT00943722 [2]	9vHPV in females 9–15 years old (per protocol population)	9vHPV in females 16–26 years old (immunobridging)	2 405	Seroconversion and geometric mean titres (by HPV)	PICO2, Supp05
009/NCT01304498 [3]	9vHPV in females 9–15 years old (per protocol population)	4vHPV in females 9–15 years old (immunobridging)	600	Seroconversion and geometric mean titres (by HPV)	PICO1 Supp05
010/NCT01984697 [4]	9vHPV (2 doses) in females 9–14 years old (per protocol population)	9vHPV (3 doses) in females 16–26 years old (immunobridging)	554	Seroconversion and geometric mean titres (by HPV)	PICO3 Supp05

HPV: human papillomavirus; 6MPI: 6-month persistent infection; CIN: cervical intraepithelial neoplasia; VIN: vulvar intraepithelial neoplasia; VaIN: vaginal intraepithelial neoplasia.

Sources: 1. Huh WK, et al. Lancet. 2017;390:2143-2159; 2. Van Damme P, et al. Pediatrics. 2015;136:e28-39; 3. Vesikari T et al. Pediatr Infect Dis J. 2015;34:992-8; 4. Iversen OE, et al. JAMA. 2016;316:2411-2421.

Efficacy of 9vHPV vaccine in males 16–26 years old

Table A8. Evidence type for benefits: 9vHPV vaccination of males 16–26 years old

Outcome-related HPV type	Benefits	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type (GRADE)
HPV types 6, 11, 16 and 18	6MPI	4vHPV (1RCT) (a)	Not serious	Not serious	Serious*	Not serious	Moderate
	AIN2/3		Not serious	Not serious	Serious*	Not serious	Moderate
	Anal cancer		Not serious	Not serious	Very serious*γ	Very seriousαβ	Very low
	PeIN2/3		Not serious	Not serious	Serious*	Very seriousαβ	Very low
	Penile cancer		Not serious	Not serious	Very serious*γ	Very seriousαβ	Very low
	Anogenital warts		Not serious	Not serious	Serious*	Not serious	Moderate
HPV types 31, 33, 45, 52 and 58	6MPI	9vHPV (1RCT) (b)	These outcomes are not assessable by GRADE methodology due to the lack of clinical efficacy data in males. Efficacy study in males would require a comparison between the investigational 9vHPV vaccine and the licensed 4vHPV vaccine (using a placebo would not be acceptable since the 4vHPV vaccine prevents anal lesions due to HPV types 16 and 18). Consequently, low incidence of HPV 6, 11, 16 and 18-associated disease would be expected with both vaccines, and the study would require a prohibitively large sample size. As an alternative approach, two immunobridging studies were used to infer efficacy of 9vHPV vaccine in men 16–26 years. These studies evaluate the immunogenicity of the 9vHPV vaccine in males 16–26 years old compared to either 4vHPV or 9vHPV vaccine in females 16–26 years old (the population used to establish 9vHPV vaccine efficacy).				
	AIN2/3						
	Anal cancer						
	PeIN2/3						
	Penile cancer						

HPV: human papillomavirus; 6MPI: 6-month persistent infection; AIN: anal intraepithelial neoplasia; PeIN: penile intraepithelial neoplasia.
**: Downgraded by 1 for indirectness due to use of immunobridging to 4vHPV vaccine.*
γ: Downgraded by 1 for indirectness due to use of AIN2/3 or PeIN2/3 as surrogate markers for anal cancer or penile cancer.
α: Downgraded by 1 for imprecision due to low event rate.
β: Downgraded by 1 for imprecision due to very wide 95% confidence interval.
a: HPV types 6, 11, 16, 18 data from protocol 020/NCT00090285 [4–6] (PICO1, PICO2 Supp01); supportive data from protocols 003/NCT01651949 [2] (PICO11 Supp05), 020/NCT02114385 [3] (PICO10 Supp05)
b: HPV types 31, 33, 45, 52 and 58 data from protocol 001/NCT00543543 [1] (PICO1 Supp04); supportive data from protocols 003/NCT01651949 [2] (PICO11 Supp05), 020/NCT02114385 [3] (PICO10 Supp05).

Sources: 1. Huh WK, et al. Lancet. 2017;390:2143-2159; 2. Castellsagué, et al. Vaccine. 2015;33:6892-901; 3. Van Damme P, et al. Vaccine. 2016;34:4205-4212; 4. Palefsky J, et al. N Engl J Med 2011;365:1576-85; 5. Giuliano AR, et al. N Engl J Med. 2011;364:401-11; 6. Goldstone SE, et al. Vaccine. 2013;31:3849-55.

Table A9. Available data for males 16–26 years old from 9vHPV vaccine trials

Outcomes	HPV 6, 11, 16 and 18-related		HPV 31, 33, 45, 52 and 58-related	
	Direct	Indirect	Direct	Indirect
6MPI	No	Immunogenicity(b) [2,3]	No	Immunogenicity [2,3]
AIN2/3	No	Immunogenicity(b) [2,3]	No	Immunogenicity [2,3]
Anal cancer	No	Immunogenicity(b) [2,3]	No	Immunogenicity [2,3]
PeIN2/3	No	Immunogenicity(b) [2,3]	No	Immunogenicity [2,3]
Penile cancer	No	Immunogenicity(b) [2,3]	No	Immunogenicity [2,3]
Anogenital warts	No	Immunogenicity(b) [2,3]	--	--

HPV: human papillomavirus; 6MPI: 6-month persistent infection; AIN: anal intraepithelial neoplasia; PeIN: penile intraepithelial neoplasia.
a: Immunogenicity from the pivotal clinical trial (in females 16– 26 years old) and from two immunobridging clinical trials (comparing 3 doses of the 9vHPV vaccine in heterosexual males aged 16–26 years old with females aged 16–26 years and comparing 3 doses 9vHPV with 4vHPV vaccine in males aged 16–26 years) were used to infer efficacy.

Sources: 2. Castellsagué X, et al. Vaccine. 2015;33:6892-901; 3. Van Damme P, et al. Vaccine. 2016;34:4205-4212.

Table A10. 4vHPV vaccine trials for HPV 6, 11, 16 and 18-related outcomes in males 16–26 years old

Protocol	Intervention	Comparator	Number	Outcome	Efficacy
020/NCT00090285 [4-6]	4vHPV in males 16–26 years (per protocol population)	Placebo in males 16–26 years	2 790	6MPI	85.6% (73.4–92.9) – PICO1 Supp01
			402	AIN2/3*	74.9% (8.8–95.4) – PICO2 Supp01
			402	Anal cancer	--
			2 805	PeIN2/3	100.0% (−3788.2–100.0) – Supp01
			2 805	Penile cancer	--
			2 805	Anogenital warts	89.4% (65.5–97.9) – PICO1 Supp01

HPV: human papillomavirus; 6MPI: 6-month persistent infection; AIN: anal intraepithelial neoplasia; PeIN: penile intraepithelial neoplasia.
** population: men who have sex with men (MSM)*

Sources: 4 Palefsky J, et al. N Engl J Med 2011;365:1576-85; 5 Giuliano AR, et al. N Engl J Med. 2011;364:401-11; 6 Goldstone SE, et al. Vaccine. 2013;31:3849-55.

Table A11. 9vHPV vaccine trials for HPV 31, 33, 45, 52 and 58-related outcomes in males 16–26 years old

Protocol	Intervention	Comparator	Number	Outcome	Efficacy
001/NCT00543543 [1]	9vHPV in females 16–26 years old (per protocol population)	4vHPV in females 16–26 years old	14 215	Efficacy outcomes	PICO1 Supp04
				Seroconversion and geometric mean titres (by HPV)	PICO5, PICO6 Supp05
003/NCT01651949 [2]	9vHPV in heterosexual males 16–26 years old (per protocol population)	9vHPV in females 16–26 years old (immunobridging)	2 520	Seroconversion and geometric mean titres (by HPV)	PICO11 Supp05
020/NCT02114385 [3]	9vHPV in males 16–26 years old (per protocol population)	4vHPV in males 16–26 years old (immunobridging)	500	Seroconversion and geometric mean titres (by HPV)	PICO10 Supp05

HPV: human papillomavirus.

Sources: 1 Huh WK, et al. Lancet. 2017;390:2143-2159; 2. Castellsagué X, et al. Vaccine. 2015;33:6892-901; 3 Van Damme P, et al. Vaccine. 2016;34:4205-4212.

Efficacy of 9vHPV vaccine in males 9–15 years old

Table A12. Evidence type for benefits: 9vHPV vaccination of males 9– 15years old

Outcome -related HPV type	Benefits	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type (GRADE)
HPV6, 11, 16 and 18	4vHPV (1RCT)(a)		Not serious	Not serious	Very serious*¥	Not serious	Low
	AIN2/3		Not serious	Not serious	Very serious*¥	Not serious	Low
	Anal cancer		Not serious	Not serious	Very serious*γ¥	Very seriousαβ	Very low
	PeIN2/3		Not serious	Not serious	Very serious*¥	Very seriousαβ	Very low
	Penile cancer		Not serious	Not serious	Very serious*γ¥	Very seriousαβ	Very low
	Anogenital warts		Not serious	Not serious	Very serious*¥	Not serious	Low
HPV31, 33, 45, 52 and 58	6MPI	9vHPV (1RCT) (b)	Outcomes not assessable by GRADE methodology due to lack of clinical efficacy data in males. Efficacy study in males would require comparison between investigational 9vHPV vaccine and licensed 4vHPV vaccine (using a placebo would not be acceptable since 4vHPV vaccine prevents anal lesions due to HPV types 16 and 18). Consequently, low incidence of HPV types 6, 11, 16 and 18-associated disease would be expected with both vaccines and the study would require a prohibitively large sample size. Two immunobridging studies used to infer efficacy of 9vHPV vaccine in men 9–15 years old. Studies evaluate immunogenicity of 3 doses or 2 doses of 9vHPV vaccine compared 9vHPV vaccine in females 16–26 years old (population used to establish 9vHPV vaccine efficacy).				
	AIN2/3						
	Anal cancer						
	PeIN2/3						
	Penile cancer						

HPV: human papillomavirus; 6MPI: 6-month persistent infection; AIN: anal intraepithelial neoplasia; PeIN: penile intraepithelial neoplasia.
**: Downgraded by 1 for indirectness due to use of immunobridging to 4vHPV vaccine.*
¥: Downgraded by 1 for indirectness due to use of immunobridging to males 16–26-year old.
γ: Downgraded by 1 for indirectness due to use of AIN2/3 or PeIN2/3 as surrogate markers for anal cancer or penile cancer.
α: Downgraded by 1 for imprecision due to low event rate.
β: Downgraded by 1 for imprecision due to very wide 95% confidence interval.
a: HPV types 6, 11, 16, 18 data from protocol 020/NCT00365716 [4-6] (PICO1, PICO2 Supp01); supportive data from protocols 002//NCT00943722 [2] (PICO 8 Supp05), 010/NCT01984697 [3] (PICO9 Supp05)
b: HPV 31, 33, 45, 52 and 58 data from protocol 001/NCT00543543 [1] (PICO1 Supp04); supportive data from protocols 002//NCT00943722 (PICO 8 Supp05) [2], 010/NCT01984697 [3] (PICO9 Supp05).

Sources: 1. Huh WK, et al. Lancet. 2017;390:2143-2159; 2. Van Damme P, et al. Pediatrics. 2015;136:e28-39; 3. Iversen OE, et al. JAMA. 2016;316:2411-2421; 4. Palefsky J, et al. N Engl J Med 2011;365:1576-85; 5. Giuliano AR, et al. N Engl J Med. 2011;364:401-11; 6. Goldstone SE, et al. Vaccine. 2013;31:3849-55.

Table A13. Available data for males 9 to 15 years old from the 9vHPV vaccine trials

Outcomes	HPV 6, 11, 16 and 18-related		HPV 31, 33, 45, 52 and 58-related	
	Direct	Indirect	Direct	Indirect
6MPI	No	Immunogenicity(b)[2-3]	No	Immunogenicity [2-3]
AIN2/3	No	Immunogenicity(b)[2-3]	No	Immunogenicity [2-3]
Anal cancer	No	Immunogenicity(b)[2-3]	No	Immunogenicity [2-3]
PeIN2/3	No	Immunogenicity(b)[2-3]	No	Immunogenicity [2-3]
Penile cancer	No	Immunogenicity(b)[2-3]	No	Immunogenicity [2-3]
Anogenital warts	No	Immunogenicity(b)[2-3]	--	--

HPV: human papillomavirus; 6MPI: 6-month persistent infection; AIN: anal intraepithelial neoplasia; PeIN: penile intraepithelial neoplasia.
a: Immunogenicity from the pivotal clinical trial (in females 16–26 years old) and from two immunobridging clinical trials (comparing 3 doses of the 9vHPV vaccine in heterosexual males aged 16–26 years old with females aged 16–26 years and comparing 3 doses 9vHPV with 4vHPV vaccine in males aged 16–26 years old) were used to infer efficacy.

Sources: 2. Van Damme P, et al. Pediatrics. 2015;136:e28-39; 3. Iversen OE, et al. JAMA. 2016;316:2411-2421.

Table A14. 4vHPV vaccine trials for HPV 6, 11, 16 and 18-related outcomes in males 9–15 years old

Protocol	Intervention	Comparator	Number	Outcome	Efficacy
020/NCT00365716 [4–6]	46vHPV in males 16–26 years old (per protocol population)	Placebo in males 16–26 years old	2 790	6MPI	85.6% (73.4–92.9) – PICO1 Supp01
			402	AIN2/3*	74.9% (8.8–95.4) – PICO2 Supp01
			402	Anal cancer	--
			2 805	PeIN2/3	100.0% (-3 788.2–100.0) – PICO1 Supp01
			2 805	Penile cancer	--
			2 805	Anogenital warts	89.4% (65.5–97.9) – PICO1 Supp01

HPV: human papillomavirus; 6MPI: 6-month persistent infection; AIN: anal intraepithelial neoplasia; PeIN: penile intraepithelial neoplasia.
** population: men who have sex with men (MSM).*

Sources: 4 Palefsky J, et al. N Engl J Med 2011;365:1576-85; 5 Giuliano AR, et al. N Engl J Med. 2011;364:401-11; 6 Goldstone SE, et al. Vaccine. 2013;31:3849-55.

Table A15. 9vHPV vaccine trials for HPV 31, 33, 45, 52 and 58-related outcomes in males 9–15 years old

Protocol	Intervention	Comparator	Number	Outcome	Efficacy
001/NCT00543543 [1]	9vHPV in females 16–26 years old (per protocol population)	4vHPV in females 16–26 years old	14 215	Efficacy outcomes	PICO1 Supp04
				Seroconversion and geometric mean titres (by HPV)	PICO5, PICO6 Supp05
002/NCT00943722 [2]	9vHPV in males 9–15 years old (per protocol population)	9vHPV in females 16–26 years old (immunobridging)	2 405	Seroconversion and geometric mean titres (by HPV)	PICO8, Supp05
010/NCT01984697 [3]	9vHPV (2 doses) in males 9–14 years old (per protocol population)	9vHPV (3 doses) in females 16–26 years old	554	Seroconversion and geometric mean titres (by HPV)	PICO9 Supp05

HPV: human papillomavirus.

Sources: 1. Huh WK, et al. Lancet. 2017;390:2143-2159. 2. Van Damme P, et al. Pediatrics. 2015;136:e28-39. 3. Iversen OE, et al. JAMA. 2016;316:2411-2421.

Safety of 9vHPV vaccine in females

Table A16. Evidence type for harms: 9vHPV vaccination of females

Harms	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type (GRADE)
Any adverse events	2RCT (a)	Not serious	Not serious	Not serious	Not serious	High
Injection site events (day 1 to 15)[α]		Not serious	Not serious	Not serious	Not serious	High
Systemic adverse events (day 1 to 15)[β]		Not serious	Not serious	Not serious	Not serious	High
Serious adverse events any time[δ]		Not serious	Not serious	Not serious	Not serious	High
Discontinuation due to adverse events		Not serious	Not serious	Not serious	Not serious	High

HPV: human papillomavirus; RCT: randomised clinical trial.
Analysis in participants who received at least 1 study vaccine dose and for whom safety follow-up data were available.
Outcomes are recorded regardless of causality.
[α]: Injection site adverse events include pain, swelling, erythema and pruritus.
[β]: Systemic events are defined as all events that are not correlated to the injection site and are not serious (they include principally headache, pyrexia and dizziness).
[δ]: Serious events were defined as side effects that results in death, life-threatening, or requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity or in congenital anomaly/birth defect.
a: data from protocols 001/NCT00543543 [1] (PICO5 Supp06) and 009/NCT01304498 [2] (PICO1 Supp06); supportive data from protocols 002/NCT00943722 [3] (PICO2-Supp06), 010/NCT01984697 [4] (PICO3 Supp06) and 006/NCT01047345 [5] (PICO6 Supp06).

Sources: 1 Huh WK, et al. Lancet. 2017;390:2143-2159. 2 Van Damme P, et al. Vaccine. 2016;34:4205-4212. 3 Van Damme P, et al. Pediatrics. 2015;136:e28-39. 4 Iversen OE, et al. JAMA. 2016;316:2411-2421. 5 Garland SM, et al. Vaccine. 2015;33:6855-64.

Table A17. Available harm data for females from 9vHPV vaccine trials

Harms	Females 16–26 years old			Females 9–15 years old		
	Protocol (design)	Incidence in 9vHPV % (n/N)	Incidence in 4vHPV % (n/N)	Protocol (design)	Incidence in 9vHPV % (n/N)	Incidence in 4vHPV % (n/N)
Any adverse events	001/NCT00543543 (1RCT) (a)	6 660/7 071 (94.2%)	6 448/7 078 (91.1%)	009/NCT01304498 (1RCT)(b)	287/299 (96.0%)	281/300 (93.7%)
Injection site events (days 1–15)[α]		6 416/7 071 (90.7%)	6 012/7 078 (84.9%)		274/299 (91.6%)	265/300 (88.3%)
Systemic adverse events (days 1–15)[β]		3 948/7 071 (55.8%)	3 883/7 078 (54.9%)		142/299 (47.5%)	156/300 (52.0%)
Serious adverse events any time[δ]		233/7 071 (3.3%)	184/7 078 (2.6%)		1/299 (0.3%)	2/300 (0.7%)
Discontinuation due to adverse events		<8/7 071 (0.1%)	4/7 078 (0.1%)		1/299 (0.3%)	1/300 (0.3%)

HPV: human papillomavirus; RCT: randomised clinical trial
Analysis in participants who received at least 1 study vaccine dose and for whom safety follow-up data were available.
Outcomes are recorded regardless of causality.
[α]: Injection site adverse events include pain, swelling, erythema and pruritus.
[β]: Systemic events are defined as all events that are not correlated to the injection site and are not serious (they include principally headache, pyrexia and dizziness).
[δ]: Serious events were defined as side effects that results in death, life-threatening, or requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or in congenital anomaly/birth defect.
a: data from protocol 001/NCT00543543 [1] (PICO5 Supp06); supportive data from protocols 002/NCT00943722 [3] (PICO2-Supp06), 010/NCT01984697 [4] (PICO3 Supp06) and 006/NCT01047345 [5] (PICO6 Supp06).
b: data from protocol 009/NCT01304498 [2] (PICO1 Supp06); supportive data from protocols 002/NCT00943722 [3] (PICO2-Supp06) and 010/NCT01984697 [4] (PICO3 Supp06).

Sources: 1. Huh WK, et al. Lancet. 2017;390:2143-2159. 2. Van Damme P, et al. Vaccine. 2016;34:4205-4212. 3. Van Damme P, et al. Pediatrics. 2015;136:e28-39. 4. Iversen OE, et al. JAMA. 2016;316:2411-2421. 5. Garland SM, et al. Vaccine. 2015;33:6855-64.

Safety of 9vHPV vaccine in males

Table A18. Evidence type for harms: 9vHPV vaccination of males

Harms	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type (GRADE)
Any adverse events	1RCT (a)	Not serious	Not serious	Not serious	Not serious	High
Injection site events (days 1–15)[α]		Not serious	Not serious	Not serious	Not serious	High
Systemic adverse events (days 1–15)[β]		Not serious	Not serious	Not serious	Not serious	High
Serious adverse events any time[δ]		Not serious	Not serious	Not serious	Not serious	High
Discontinuation due to adverse events		Not serious	Not serious	Not serious	Serious[*]	Moderate

HPV: human papillomavirus; RCT: randomised clinical trial
Analysis in participants who received at least 1 study vaccine dose and for whom safety follow-up data were available.
Outcomes are recorded regardless of causality.
[α]: Injection site adverse events include pain, swelling, erythema and pruritus.
[β]: Systemic events are defined as all events that are not correlated to the injection site and are not serious (they include principally headache, pyrexia and dizziness).
[δ]: Serious events were defined as side effects that results in death, life-threatening, or requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or in congenital anomaly/birth defect.
[*]: Downgraded by 1 for imprecision due to wide 95% confidence interval
a: data from protocol 020/NCT02114385 [1] (PICO9 Supp06); supportive data from protocol 003/NCT01651949 [2] (PICO10-Supp06), 002/NCT00943722 [3] (PICO7-Supp06), 010/NCT01984697 [4] (PICO8 Supp06).

Sources: 1. Van Damme P, et al. Vaccine. 2016;34:4205-4212. 2. Castellsagué, et al. Vaccine. 2015;33:6892-901. 3. Van Damme P, et al. Pediatrics. 2015;136:e28-39. 4. Iversen OE, et al. JAMA. 2016;316:2411-2421.

Table A19. Available harm data for males from 9vHPV vaccine trials

Harms	Males 16–26 years old			Males 9–15 years old		
	Protocol (design)	Incidence in 9vHPV % (n/N)	Incidence in 4vHPV % (n/N)	Protocol (design)	Incidence in 9vHPV % (n/N)	Incidence in 4vHPV % (n/N)
Any adverse events	020/NCT02114385 (1RCT) (a)	204/248 (82.3%)	203/248 (81.9%)	002/NCT00943722 and 010/NCT01984697 (2 Not RCT) (b)	584/958 (61.0%)	--
Injection site events (days 1–15)[α]		196/248 (79.0%)	179/248 (72.2%)		506/958 (52.8%)	--
Systemic adverse events (days 1–15)[β]		101/248 (40.7%)	100/248 (40.3%		289/958 (30.2%)	--
Serious adverse events any time[δ]		0/248 (0.0%)	6/248 (2.4%)		16/958 (1.6%)	--
Discontinuation due to adverse events		0/248 (0.0%)	0/248 (0.0%)		0/958 (0.0%)	--

HPV: human papillomavirus; RCT: randomised clinical trial
Analysis in participants who received at least 1 study vaccine dose and for whom safety follow-up data were available.
Outcomes are recorded regardless of causality.
[α]: Injection site adverse events include pain, swelling, erythema and pruritus.
[β]: Systemic events are defined as all events that are not correlated to the injection site and are not serious (they include principally headache, pyrexia and dizziness).
[δ]: Serious events were defined as side effects that results in death, life-threatening, or requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or in congenital anomaly/birth defect.
a: data from protocol 020/NCT02114385 [1] (PICO9 Supp06); supportive data from protocol 003/NCT01651949 [2] (PICO10-Supp06)
b: data from protocols 002/NCT00943722 [3] (PICO7-Supp06), 010/NCT01984697 [4] (PICO8 Supp06).

Sources: 1. Van Damme P, et al. Vaccine. 2016;34:4205-4212. 2. Castellsagué, et al. Vaccine. 2015;33:6892-901. 3. Van Damme P, et al. Pediatrics. 2015;136:e28-39. 4. Iversen OE, et al. JAMA. 2016;316:2411-2421.

Efficacy of HPV vaccines in males 16–26 years old

Table A20. Evidence type for benefits: HPV vaccines in males 16–26 years old

Outcome-related HPV type	Benefits	Design	Risk of bias	Inconsistency	Indirectness*	Imprecision	Evidence type (GRADE) 4vHPV vaccine (a)	Evidence type (GRADE) 9vHPV vaccine* (b)
HPV types 6, 11, 16 and 18	6MPI	4vHPV (1RCT) (a)	Not serious	Not serious	Not serious	Not serious	High	Moderate
	AIN2/3		Not serious	Not serious	Not serious	Not serious	High	Moderate
	Anal cancer		Not serious	Not serious	Serious$^{\gamma}$	Very serious$^{\alpha\beta}$	Low	Very low
	PeIN2/3		Not serious	Not serious	Not serious	Very serious$^{\alpha\beta}$	Low	Very low
	Penile cancer		Not serious	Not serious	Serious$^{\gamma}$	Very serious$^{\alpha\beta}$	Low	Very low
	Anogenital warts		Not serious	Not serious	Not serious	Not serious	High	Moderate

HPV: human papillomavirus; 6MPI: 6-month persistent infection; AIN: anal intraepithelial neoplasia; PeIN: penile intraepithelial neoplasia.
$^{\gamma}$: Downgraded by 1 for indirectness due to use of AIN2/3 or PeIN2/3 as surrogate marker for anal cancer or penile cancer.
$^{\alpha}$: Downgraded by 1 for imprecision due to low event rate.
$^{\beta}$: Downgraded by 1 for imprecision due to very wide 95% confidence interval.
*: Evidence quality for efficacy of the 9vHPV vaccine downgraded 1 level due use of immunobridging studies to extrapolate efficacy (indirectness for the 9vHPV vaccine changes from 'Not serious' to 'Serious' and from 'Serious' to 'Very serious').
a: HPV types 6, 11, 16, 18 data from protocol 020/NCT00090285 [1-3] (PICO1, PICO2 Supp01); supportive data from protocols 020/NCT00090285 [4] (PICO14,PICO15 Supp02)
b: HPV types 6, 11, 16, 18 data from protocol 020/NCT00090285 [1-3] (PICO1, PICO2 Supp01); supportive data from protocols 020/NCT02114385 [5] (PICO3 Supp02), 003/NCT01651949 [6] (PICO4,PICO12,PICO13 Supp02), 001/NCT00543543 [7] (PICO1 Supp04).

Sources: 1. Palefsky J, et al. N Engl J Med 2011;365:1576-85. 2. Giuliano AR, et al. N Engl J Med. 2011;364:401-11. 3.Goldstone SE, et al. Vaccine. 2013;31:3849-55. 4. Hillman RJ, et al. Clin Vaccine Immunol. 2012;19:261-7. 5. Van Damme P, et al. Vaccine. 2016;34:4205-4212. 6. Castellsagué, et al. Vaccine. 2015;33:6892-901. 7. Huh WK, et al. Lancet. 2017;390:2143-2159.

Table A21. Available data for males 16–26 years old from HPV vaccine trials

Outcomes	HPV 6, 11, 16 and 18-related	
	Direct	Indirect
6MPI	Yes (a) [2–3]	Immunogenicity (b) [4–6]
AIN2/3	Yes (a) [1]	Immunogenicity (b) [4–6]
Anal cancer	No	Immunogenicity (b) [4–6]
PeIN2/3	Yes (a) [2–3]	Immunogenicity (b) [4–6]
Penile cancer	No	Immunogenicity (b) [4–6]
Anogenital warts	Yes (a) [1–3]	Immunogenicity (b) [46]

HPV: human papillomavirus; 6MPI: 6-month persistent infection; AIN: snal intraepithelial neoplasia; PeIN: penile intraepithelial neoplasia.
a: Efficacy from 4vHPV vaccine trials in males 16–26 years.
b: Immunogenicity from two immunobridging clinical trials with 9vHPV vaccine (comparing the 9vHPV vaccine in heterosexual males 16–26 years old with females 16–26 years and comparing 9vHPV vaccine with 4vHPV vaccine in malesaged 16–26 years) and from clinical trials with the 4vHPV vaccine (comparing 4vHPV in 16–26-year-old men who have sex with men with heterosexual males 16–23 years old) were used to infer efficacy.

Sources: 1. Palefsky J, et al. N Engl J Med 2011;365:1576-85. 2. Giuliano AR, et al. N Engl J Med. 2011;364:401-11. 3. Goldstone SE, et al. Vaccine. 2013;31:3849-55. 4. Hillman RJ, et al. Clin Vaccine Immunol. 2012;19:261-7. 5. Van Damme P, et al. Vaccine. 2016;34:4205-4212. 6. Castellsagué X, et al. Vaccine. 2015;33:6892-901.

Table A22. HPV vaccine trials for HPV vaccine-related outcomes in males 16–26 years old

Protocol	Intervention	Comparator	Number	Outcome	Efficacy	Comments
020/NCT00090285 [1-4]	4vHPV in males 16–26 years old (per protocol population)	Placebo in males 16–26 years old	2 790	6MPI	85.6% (73.4-92.9) – PICO1 Supp01	
			402	AIN2/3	74.9% (8.8-95.4) – PICO2 Supp01	Efficacy in MSM
			402	Anal cancer	--	
			2 805	PeIN2/3	100.0% (-3 788.2-100.0) – PICO1 Supp01	
			2 805	Penile cancer	--	
			2 805	Anogenital warts	89.4% (65.5-97.9) – PICO1 Supp01	Efficacy in subgroup 402 MSM (100.0% (8.2-100)) - PICO2 Supp01
	4vHPV in MSM heterosexual males 16–26 yearsold (per protocol population)	4-valent in heterosexual males 16–23 years old	4 065	Seroconversion and geometric mean titres (by HPV)	PICO14, PICO15 Supp02	
020/NCT02114385 [5]	9vHPV in males 16–26 years old (per protocol population)	4vHPV in males 16–26 years old (immunobridging)	500	Seroconversion and geometric mean titres (by HPV)	PICO3 Supp02	
003/NCT01651949 [6]	9vHPV in heterosexual males 16–26 years old (per protocol population)	9vHPV in females 16–26 years old (immunobridging)	2207	Seroconversion and geometric mean titres (by HPV)	PICO4 Supp02	
	9vHPV in MSM 16–26 years (per protocol population)	9vHPV in females/males 16–26 years old (immunobridging)	2520	Seroconversion and geometric mean titres (by HPV)	PICO12, PICO13 Supp02	
001/NCT00543543 [7]	9vHPV in females 16–26 years old (per protocol population)	4vHPV in females 16–26 years old	14215	Efficacy outcomes	PICO1 Supp04	

HPV: human papillomavirus; 6MPI: 6-month persistent infection; AIN: anal intraepithelial neoplasia; PeIN: penile intraepithelial neoplasia; MSM: men who have sex with men.

Sources: 1. Palefsky J, et al. N Engl J Med 2011;365:1576-85. 2. Giuliano AR, et al. N Engl J Med. 2011;364:401-11. 3. Goldstone SE, et al. Vaccine. 2013;31:3849-55. 4. Hillman RJ, et al. Clin Vaccine Immunol. 2012;19:261-7. 5. Van Damme P, et al. Vaccine. 2016;34:4205-4212. 6. Castellsagué X, et al. Vaccine. 2015;33:6892-901. 7. Huh WK, et al. Lancet. 2017;390:2143-2159.

Efficacy of HPV vaccines in males 9–15 years old

Table A23. Evidence type for benefits: HPV vaccines in males 9–15 years old

Outcome-related HPV type	Benefits	Design	Risk of bias	Inconsistency	Indirectness*	Imprecision	Evidence type (GRADE) 4vHPV vaccine (a)	Evidence type (GRADE) 9vHPV/2vHPV vaccines* (b)
HPV types 6, 11, 16 and 18	6MPI	4vHPV (1RCT)(a)	Not serious	Not serious	Serious¥	Not serious	Moderate	Low
	AIN2/3		Not serious	Not serious	Serious¥	Not serious	Moderate	Low
	Anal cancer		Not serious	Not serious	Very serious¥γ	Very seriousαβ	Very low	Very low
	PeIN2/3		Not serious	Not serious	Serious¥	Very seriousαβ	Very low	Very low
	Penile cancer		Not serious	Not serious	Very serious¥γ	Very seriousαβ	Very low	Very low
	Anogenital warts		Not serious	Not serious	Serious¥	Not serious	Moderate	Low

HPV: human papillomavirus; 6MPI: 6-month persistent infection; AIN: anal intraepithelial neoplasia; PeIN: penile intraepithelial neoplasia.
¥: Downgraded by 1 for indirectness due to use of immunobridging to males 16 to 26-year old
γ: Downgraded by 1 for indirectness due to use of AIN2/3 or PeIN2/3 as surrogate marker for anal cancer or penile cancer.
α: Downgraded by 1 for imprecision due to low event rate.
β: Downgraded by 1 for imprecision due to very wide 95% confidence interval.
**: Evidence quality for efficacy of 9vHPV and the 2vHPV vaccines downgraded 1 level due to use of immunobridging to extrapolate efficacy (indirectness for the 9vHPV vaccine changes from 'Serious' to 'Very serious').*
a: HPV types 6, 11, 16, 18 data from protocol 020/NCT00090285 [1-3] (PICO1, PICO2 Supp01); supportive data from protocols 020/NCT00090285 [4] (PICO14,PICO15 Supp02), NCT00092495 [5] (PICO5 Supp02), NCT00092547 [6,7] (PICO6, PICO7, PICO8 Supp02).
b: HPV types 6, 11, 16, 18 data from protocol 020/NCT00090285 [1-3] (PICO1, PICO2 Supp01); supportive data from protocols NCT00534638 [8] (PICO11 Supp02), NCT00309166 [9] (PICO16 Supp02), 002/NCT00943722 [10] (PICO1 Supp02), 010/NCT01984697 [11] (PICO2 Supp02), 001/NCT00543543 [12] (PICO1 Supp04).

Sources: 1. Palefsky J, et al. N Engl J Med 2011;365:1576-85. 2. Giuliano AR, et al. N Engl J Med. 2011;364:401-11. 3. Goldstone SE, et al. Vaccine. 2013;31:3849-55. 4. Hillman RJ, et al. Clin Vaccine Immunol. 2012;19:261-7. 5. Block SL, et al. Pediatrics. 2006;118:2135-45. 6. Reisinger KS, et al. Pediatr Infect Dis J. 2007;26:201-9. 7. Ferris D, et al. Pediatrics. 2014;134:e657-65. 8. http://clinicaltrials.gov/ct2/show/NCT00534638?cond=NCT00534638&rank=1 9. Petäjä T, et al. J Adolesc Health. 2009;44:33-40. 10. Van Dame P, et al. Pediatrics. 2015;136:e28-39. 11. Iversen OE, et al. JAMA. 2016;316:2411-2421. 12. Huh WK, et al. Lancet. 2017;390:2143-2159.

Table A24. Available data for males 9–15 years old from HPV vaccine trials

Outcomes	HPV types 6, 11, 16 and 18-related	
	Direct	Indirect
6MPI	No	Immunogenicity(a)[5-11]
AIN2/3	No	Immunogenicity(a)[5-11]
Anal cancer	No	Immunogenicity(a)[5-11]
PeIN2/3	No	Immunogenicity(a)[5-11]
Penile cancer	No	Immunogenicity(a)[5-11]
Anogenital warts	No	Immunogenicity(a)[5-11]

HPV: human papillomavirus; 6MPI: 6-month persistent infection; AIN: anal intraepithelial neoplasia; PeIN: penile intraepithelial neoplasia.
a: Immunogenicity from immunobridging clinical trials with the HPV vaccines in males aged 9–5 years compared to females aged 16–26 years, were used to infer efficacy.

Sources: 5. Block SL, et al. Pediatrics. 2006;118:2135-45. 6. Reisinger KS, et al. Pediatr Infect Dis J. 2007;26:201-9. 7. Ferris D, et al. Pediatrics. 2014;134:e657-65. 8. http://www.clinicaltrials.gov/ct2/show/NCT00534638?cond=NCT00534638 9. Petäjä T, et al. J Adolesc Health. 2009;44:33-40. 10. Van Dame P, et al. Pediatrics. 2015;136:e28-39. 11 Iversen OE, et al. JAMA. 2016;316:2411-2421.

Table A25. HPV vaccine trials for HPV vaccine-related outcomes in males 9–15 years old

Protocol	Intervention	Comparator	Number	Outcome	Efficacy	Comments
020/NCT00090285 [1-4]	4vHPV in males 16–26 years old (per protocol population)	Placebo in males 16–26 years old	2790	6MPI	85.6% (73.4–92.9) – PICO1 Supp01	
			402	AIN2/3	74.9% (8.8-95.4) – PICO2 Supp01	Efficacy in MSM
			402	Anal cancer	--	
			2805	PeIN2/3	100.0% (−3788.2-100.0) – PICO1 Supp01	
			2805	Penile cancer	--	
			2805	Anogenital warts	89.4% (65.5-97.9) – PICO1 Supp01	Efficacy in subgroup 402 MSM (100.0% (8.2-100)) – PICO2 Supp01
	4vHPV in MSM heterosexual males 16–26 years old (per protocol population)	4-valent in heterosexual males 16–23 years old	4065	Seroconversion and geometric mean titres (by HPV)	PICO12, PICO15 Supp02	
NCT00092495 [5]	4vHPV in males 10–15 years old (per protocol population)	4vHPV in females 16–23 years old (immunobridging)	769	Seroconversion and geometric mean titres (by HPV)	PICO5 Supp02	
018/NCT00092547 [6,7]	4vHPV in males 9–15 years old (per protocol population)	4vHPV in females 9–15 years old (immunobridging)	952	Seroconversion and geometric mean titres (by HPV)	PICO6, PICO7, PICO8 Supp02	
NCT00534638 [8]	2-valent HPV in males 12–15 years old (per protocol population)	None	536	Seroconversion and geometric mean titres (by HPV)	PICO11 Supp02	
NCT00309166 [9]	2-valent HPV in males 10–18 years old (per protocol population)	4vHPV in females 15–25 years old (immunobridging)	522	Seroconversion and geometric mean titres (by HPV)	PICO16 Supp02	
002/NCT00943722 [10]	9vHPV in males 9–15 years old	9vHPV in females 16–26 years old (immunobridging)	938	Seroconversion and geometric mean titres (by HPV)	PICO1 Supp02	
010/NCT01984697 [11]	9vHPV in males 9–14 years old (2 doses)	9vHPV in females 16–26 years old	553	Seroconversion and geometric mean titres (by HPV)	PICO2 Supp02	
001/NCT00543543 [12]	9vHPV in females 16–26 years old (per protocol population)	4vHPV in females 16–26 years old	14215	Efficacy outcomes	PICO1 Supp04	

HPV: human papillomavirus; 6MPI: 6-month persistent infection; AIN: anal intraepithelial neoplasia; PeIN: penile intraepithelial neoplasia; MSM: men who have sex with men.

Sources: 1. Palefsky J, et al. N Engl J Med 2011;365:1576-85. 2. Giuliano AR, et al. N Engl J Med. 2011;364:401-11. 3. Goldstone SE, et al. Vaccine. 2013;31:3849-55. 4. Hillman RJ, et al. Clin Vaccine Immunol. 2012;19:261-7. 5. Block SL, et al. Pediatrics. 2006;118:2135-45. 6. Reisinger KS, et al. Pediatr Infect Dis J. 2007;26:201-9. 7 .Ferris D, et al. Pediatrics. 2014;134:e657-65. 8. http://www.clinicaltrials.gov/ct2/show/NCT00534638?cond=NCT00534638 9. Petäjä T, et al. J Adolesc Health. 2009;44:33-40. 10. Van Dame P, et al. Pediatrics. 2015;136:e28-39. 11. Iversen OE, et al. JAMA. 2016;316:2411-2421. 12. Huh WK, et al. Lancet. 2017;390:2143-2159.

Safety of HPV vaccines in males

Table A26. Evidence type for harms: HPV vaccination in males

Harms	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type (GRADE)
Any adverse events	5RCT (a)	Not serious	Not serious	Not serious	Not serious	High
Injection site events (days 1–15)		Not serious	Not serious	Not serious	Not serious	High
Systemic adverse events (days 1–15)		Not serious	Not serious	Not serious	Not serious	High
Serious adverse events any time		Not serious	Not serious	Not serious	Not serious	High
Discontinuation due to adverse events		Not serious	Not serious	Not serious	Serious*	Moderate

HPV: human papillomavirus; RCT: randomised clinical trial
Analysis in participants who received at least 1 study vaccine dose and for whom safety follow-up data were available.
Outcomes are recorded regardless of causality.
**: Downgraded by 1 for imprecision due to wide 95% confidence interval.*
a: data from protocol 020/NCT00090285 [1] (PICO7 Supp03), 020/NCT02114385 [2] (PICO3 Supp03), 018/NCT00092547 [3] (PICO6 Supp03), NCT00534638 [4] (PICO9 Supp03), NCT00309166 [5] (PICO11 Supp03); supportive data from protocol 020/NCT00090285 [6] (PICO10 Supp03), 003/NCT01651949 [7] (PICO4 Supp03), NCT00092495 [8] (PICO5 Supp03), NCT00943722 [9] (PICO1 Supp03), NCT01984697 [10] (PICO2 Supp03).

Sources: 1. Moreira ED, et al. Hum Vaccin. 2011;7:768-75. 2. Van Damme P, et al. Vaccine. 2016;34:4205-4212. 3. Reisinger KS, et al. Pediatr Infect Dis J. 2007;26:201-9. 4. Lehtinen M, et al. Hum Vaccin Immunother. 2016;12:3177-3185. 5. Petäjä T, et al. J Adolesc Health. 2009;44:33-40. 6. PalefskyJ M, et al. N Engl J Med. 2011;365:1576-85. 7. Castellsagué X, et al. Vaccine. 2015;33:6892-901. 8. Block SL, et al. Pediatrics. 2006;118:2135-45. 9. Van Damme P, et al. Pediatrics. 2015;136:e28-39. 10. Iversen OE, et al. JAMA. 2016;316:2411-2421.

Table A27. Available harm data for males from HPV vaccine trials

Harms	Males 16–26 years old			Males 9–15 years old		
	Protocol (design)	Incidence in vaccinated % (n/N)	Incidence in controls (placebo group) n/N (%)[α]	Protocol (design)	Incidence in vaccinated % (n/N)	Incidence in controls (placebo group) n/N (%)[¥]
Any adverse events	020/NCT00090285 and 020/NCT02114385 (2RCT) (a)	1 446/2 193 (65.9%)	1 134/1 950 (58.2%)	018/NCT00092547, NCT00534638 and NCT00309166 (3RCT) (b)[γφ]	956/1 128 (84.8%)	812/1 050 (77.3%)
Injection site events (days 1–15)		1 365/2 193 (62.2%)	1046/1 950 (53.6%)		880/1 128 (78.0%)	690/1 050 (65.7%)
Systemic adverse events (days 1–15)		376/2 193 (17.1%)	283/1 950 (14.5%)		543/1 128 (48.1%)	526/1 050 (50.1%)
Serious adverse events any time		8/2 193 (0.4%)	11/1 950 (0.6%)		27/1 128 (2.4%)	16/1 050 (1.5%)
Discontinuation due to adverse events		0/248 (0.0%)	--		0/1 128 (0.0%)	0/1 050 (0.0%)

HPV: human papillomavirus; RCT: randomised clinical trial
Analysis in participants who received at least 1 study vaccine dose and for whom safety follow-up data were available.
Outcomes are recorded regardless of causality.
a: data from Protocol 020/NCT00090285 [1] (PICO7 Supp03), 020/NCT02114385 [2] (PICO3 Supp03); supportive data from Protocol 020/NCT00090285 [6] (PICO10 Supp03), 003/NCT01651949 [7] (PICO4 Supp03)
b: data from protocol 018/NCT00092547 [3] (PICO6 Supp03), NCT00534638 [4] (PICO9 Supp03), NCT00309166 [5] (PICO11 Supp03); supportive data from protocols NCT00092495 [8] (PICO5 Supp03), NCT00943722 [9] (PICO1 Supp03), NCT01984697 [10] (PICO2 Supp03)
[α]: only data from protocol 020/NCT00090285
[γ]: Data from protocol NCT00309166 provided for specific symptoms (pain, redness, fatigue) not included in this table.
[φ]: Data from protocol 018/NCT00092547 include males and females.
[¥]: Placebo group from protocol 018/NCT00092547 vaccinated with hepatitis B vaccine.

Sources: 1. Moreira ED, et al. Hum Vaccin. 2011;7:768-75. 2. Van Damme P, et al. Vaccine. 2016;34:4205-4212. 3. Reisinger KS, et al. Pediatr Infect Dis J. 2007;26:201-9. 4. Lehtinen M, et al. Hum Vaccin Immunother. 2016;12:3177-3185. 5. Petäjä T, et al. J Adolesc Health. 2009;44:33-40. 6. PalefskyJ M, et al. N Engl J Med. 2011;365:1576-85. 7. Castellsagué X, et al. Vaccine. 2015;33:6892-901. 8. Block SL, et al. Pediatrics. 2006;118:2135-45. 9. Van Damme P, et al. Pediatrics. 2015;136:e28-39. 10. Iversen OE, et al. JAMA. 2016;316:2411-2421.

Efficacy of HPV vaccines in females aged 25 years or above

Table A28. Evidence type for benefits: HPV vaccines in females aged 25 years or above

Outcome-related HPV type	Benefits	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type (GRADE)
HPV types 6, 11, 16 and 18¥	Combined 6MPI, CIN or external genital lesions*	2vHPV and 4vHPV (2RCT) (a)	Not serious	Not serious	Not serious	Not serious	High
	Combined 6MPI or CIN1 or worse#		Not serious	Not serious	Not serious	Not serious	High
	6MPI		Not serious	Not serious	Not serious	Not serious	High
	CIN2/3 or worse		Not serious	Not serious	Not serious	Very seriousαβ	Low
	Cervical cancer		Not serious	Not serious	Seriousγ	Very seriousαβ	Very low
	VIN2/3, VaIN2/3 or worse*		Not serious	Not serious	Not serious	Very seriousαβ	Low
	Vulvar or vaginal cancer		Not serious	Not serious	Seriousγ	Very seriousαβ	Very low
	Anogenital warts*		Not serious	Not serious	Not serious	Seriousα	Moderate
HPV types 31, 33, 45, 52 and 58	6MPI		Not evaluable with GRADE methodology. No efficacy data for 9vHPV vaccine in females aged 25-years or older.				
	CIN2/3 or worse						
	Cervical cancer						
	VIN2/3, VaIN2/3 or worse						
	Vulvar or vaginal cancer						

HPV: human papillomavirus; 6MPI: 6-month persistent infection; CIN: cervical intraepithelial neoplasia; VIN: vulvar intraepithelial neoplasia; VaIN: vaginal intraepithelial neoplasia.
¥: HPV 6, 11, 16 and 18-related outcomes for 4vHPV vaccine and HPV 16 and 18-related outcomes for 2vHPV vaccine
**: Only data from 4vHPV vaccine trial (Protocol 019/NCT00090220).*
#: Only data from 2vHPV vaccine trial (NCT00294047).
α: Downgraded by 1 for imprecision due to low event rate.
β: Downgraded by 1 for imprecision due to very wide 95% confidence interval.
γ: Downgraded by 1 for indirectness due to use of CIN2/3, VIN2/3 or VaIN2/3 or worse as surrogate marker for cervical, vulvar or vaginal cancer.
a: Efficacy data from two pivotal RCT in females (≥25-year old): 4vHPV vaccine protocol 019/NCT00090220 [1] (PICO1 Supp09) and 2vHPV vaccine NCT00294047 [2] (PICO2 Supp09); supportive immunogenicity data from protocol 019/NCT00090220 [1] (PICO1, PICO2 Supp10), NCT00294047 (PICO3, PICO4 Supp10), NCT00423046 [3,4] (PICO5,PICO6 Supp10).

Sources: 1. Castellsagué X, et al. Br J Cancer. 2011;105:28-37. 2. Wheeler CM, et al. Lancet Infect Dis. 2016;16:1154-1168. 3. Einstein MH, et al. Hum Vaccin. 2009;5:705-19. 4. Einstein MH, et al. Hum Vaccin Immunother. 2014;10:3435-45.

Table A29. Available data for females aged 25 years or above from HPV vaccine trials

Outcomes	HPV 6, 11, 16 and 18-related¥		HPV 31, 33, 45, 52 and 58-related	
	Direct	Indirect	Direct	Indirect
Combined 6MPI, CIN, or external genital lesions	Yes (a) [1]	Immunogenicity (a,b) [1-4]	No	No
Combined 6MPI or CIN1 or worse	Yes (b) [2]	Immunogenicity (a,b) [1-4]	No	No
6MPI	Yes (a,b) [1,2]	Immunogenicity (a,b) [1-4]	No	No
CIN2/3 or worse	Yes (a,b) [1,2]	Immunogenicity (a,b) [1-4]	No	No
Cervical cancer	No	Immunogenicity (a,b) [1-4]	No	No
VIN2/3, VaIN2/3 or worse	Yes (a) [1]	Immunogenicity (a,b) [1-4]	No	No
Vulvar or vaginal cancer	No	Immunogenicity (a,b) [1-4]	No	No
Anogenital warts	Yes (a) [1]	Immunogenicity (a,b) [1-4]	--	--

HPV: human papillomavirus; 6MPI: 6-month persistent infection; CIN: cervical intraepithelial neoplasia; VIN: vulvar intraepithelial neoplasia; VaIN: vaginal intraepithelial neoplasia.
¥: HPV 6, 11, 16 and 18-related outcomes for 4vHPV vaccine and HPV 16 and 18-related outcomes for 2vHPV vaccine.
a: efficacy from 4vHPV vaccine trials (in females ≥25 years old)
b: efficacy from 2vHPV vaccine trials (in females ≥25 years old).

Sources: 1. Castellsagué X, et al. Br J Cancer. 2011;105:28-37. 2. Wheeler CM, et al. Lancet Infect Dis. 2016;16:1154-1168. 3. Einstein MH, et al. Hum Vaccin. 2009;5:705-19. 4. Einstein MH, et al. Hum Vaccin Immunother. 2014;10:3435-45.

Table A30. HPV vaccine trials for HPV 6, 11, 16 and 18-related outcomes in females aged 25 years or above

Protocol	Intervention	Comparator	No.	Outcome	Efficicacy
019/NCT00090220 [1]	4vHPV in females 24–45 years old (per protocol population)	Placebo in females 24–45-years old	[a]	Combined 6MPI, CIN, or external genital lesions	87.7% (78.1-94.8) – PICO1 Supp09
			[a]	6MPI	89.6% (79.3-95.4) – PICO1 Supp09
			[a]	CIN2/3 or worse	83.3% (-37.6-99.6) – PICO1 Supp09
			[a]	Cervical cancer	--
			[a]	VIN2/3, VaIN2/3 or worse	--
			[a]	Vulvar or vaginal cancer	--
			[a]	Anogenital warts	100.0% (3.8-100.0) – PICO1 Supp09
			1 249	Seroconversion and geometric mean titres (by HPV)	PICO1, PICO2 Supp10
NCT00294047 [2]	2vHPV in females ≥25 years old (per protocol population)	Placebo in females ≥25 years old	3 670	Combined 6MPI or CIN1 or worse	90.5% (78.6-96.5) – PICO2 Supp09
			3 601	6MPI	91.4% (79.4-97.1) – PICO2 Supp09
			3 670	CIN2/3 or worse	83.7% (–46.5-99.7) – PICO2 Supp09
			3 670	Cervical cancer	--
			233	Seroconversion and geometric mean titres (by HPV)	PICO3, PICO4 Supp10
NCT00423046 [3,4]	2vHPV in females 27–45-years old (per protocol population)	4vHPV vaccine in females 27–45 years old	249	Seroconversion and geometric mean titres (by HPV)	PICO5, PICO6 Supp10

HPV: human papillomavirus; 6MPI: 6-month persistent infection; CIN: cervical intraepithelial neoplasia; VIN: vulvar intraepithelial neoplasia; VaIN: vaginal intraepithelial neoplasia.

[a]: Number of subjects included to assess especific outcome not provided in the paper.

Sources: 1. Castellsagué X, et al. Br J Cancer. 2011;105:28-37. 2. Wheeler CM, et al. Lancet Infect Dis. 2016;16:1154-1168. 3. Einstein MH, et al. Hum Vaccin. 2009;5:705-19. 4. Einstein MH, et al. Hum Vaccin Immunother. 2014;10:3435-45.

Safety of HPV vaccines in females aged 25 years or above

Table A31. Evidence type for harms: HPV vaccines in females aged 25 years or above

Harms	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Evidence type (GRADE)
Any adverse events	2RCT (a)	Not serious	Not serious	Not serious	Not serious	High
Injection site events (days 1–15)		Not serious	Not serious	Not serious	Not serious	High
Systemic adverse events (days 1–15)		Not serious	Not serious	Not serious	Not serious	High
Serious adverse events any time		Not serious	Not serious	Not serious	Seriousa	Moderate
Discontinuation due to adverse events		Not serious	Not serious	Not serious	Seriousa	Moderate

HPV: human papillomavirus; RCT: randomised clinical trial.
Analysis in participants who received at least 1 study vaccine dose and for whom safety follow-up data were available
a: data from protocol 019/NCT00090220 [1] (PICO1 Supp11) and NCT00294047 [2] (PICO2 Supp11); supportive data from NCT00423046 [3] (PICO3 Supp11).
a: Downgraded one level for imprecision: wide 95%CI.

Sources: 1. Castellsagué X, et al. Br J Cancer. 2011;105:28-37. 2. Skinner SR, et al. Lancet. 2014;384:2213-27. 3. Einstein MH, et al. Hum Vaccin Immunother. 2014;10:3435-45.

Table A32. Available harm data for females aged 25 years or above from HPV vaccine trials

Harms	Females aged 25-years or above		
	Protocol (design)	Incidence in HPV vaccine % (n/N)	Incidence in placebo % (n/N)
Any adverse events*	019/NCT00090220 and NCT00294047 (2RCT) (a)	1 645/1 890 (87.0%)	1 535/1 888 (81.3%)
Injection site events (day 1 to 15)		3 888/4 529 (85.8%)	3 445/4 739 (72.7%)
Systemic adverse events (day 1 to 15)*		1 121/1 890 (59.3%)	1 135/1 888 (60.1%)
Serious adverse events any time		285/4 740 (6.0%)	267/4 855 (5.5)
Discontinuation due to adverse events*		7/1 890 (0.4%)	2/1 888 (0.1%)

HPV: human papillomavirus; RCT: randomised clinical trial.
Analysis in participants who received at least 1 study vaccine dose and for whom safety follow-up data were available.
**: only data from 4vHPV vaccine trial (Protocol 019/NCT00090220)*
a: data from protocol 019/NCT00090220 [1] (PICO1 Supp11) and NCT00294047 [2] (PICO2 Supp11); supportive data from NCT00423046 [3] (PICO3 Supp11).

Sources: 1. Castellsagué X, et al. Br J Cancer. 2011;105:28-37. 2. Skinner SR, et al. Lancet. 2014;384:2213-27. 3. Einstein MH, et al. Hum Vaccin Immunother. 2014;10:3435-45.

1684 **Table A33. Main characteristics of 21 studies that include cost-effectiveness analysis of universal vaccination**

Author year	Publication year	Country	Currency	Analysis year	Horizon*	Perspective**	Vaccine used	Vaccine schedule	Health outcome unit***	CEA threshold defined
Taira 2004	2004	US	USD	2001	38 y	3PP	2-valent	3 doses	QALYg	50 000–100 000
Elbasha 2007	2007	US	USD	2005	100 y	3PP	4-valent	3 doses	QALYg	No
Kulasingam 2007	2007	Australia	AUD	2005	73 y	3PP	2-valent	3 doses	QALYg	No
Jit 2008	2008	UK	GBP	2006	100 y	3PP	4-valent	3 doses	QALYg	30 000
Kim 2009	2009	US	USD	2006	100 y	SP	4-valent	3 doses	QALYg	50 000
Zechmeister 2009	2009	Austria	EUR	2007	52 y (80 y)	3PP & SP	2-valent	3 doses	LYg	No
Olsen 2010	2010	Denmark	EUR	2007	62 y	3PP	4-valent	3 doses	QALYg	No
Elbasha 2010	2010	US	USD	2008	100 y	3PP	4-valent	3 doses	QALYg	50 000–100 000
Chesson 2011	2011	US	USD	2008	100 y	SP	4-valent	3 doses	QALYg	100 000
Burger 2014	2014	Norway	USD	2010	100 y	SP	4-valent	3 & 2 doses	QALYg	83 000
Laprise 2014	2014	Canada	CAD	2010	70 y	3PP	4-valent	3 & 2 doses	QALYg	40 000
Pearson 2014	2014	New Zealand	NZD	2011	98 y	3PP	4-valent	3 doses	QALYg	45 000
Bresse 2014	2014	Austria	EUR	2012	100 y	3PP	4-valent	3 doses	QALYg	No
Blakely 2014	2014	New Zealand	NZD	2011	98 y	3PP	4-valent	3 doses	QALYg	No
Haeussler 2015	2015	Italy	EUR	2015	Long-term	3PP	4-valent	3 doses	QALYg	25 000–40 000
Jiménez 2015	2015	Norway	NOK	2014	100 y	3PP & SP	4-valent & 2-valent	3 doses	QALYg	215 000
Olsen 2015	2015	Denmark	EUR	2008	62 y (40 y)	3PP	4-valent	3 & 2 doses	QALYg	No
Qendri 2017	2017	Netherlands	EUR	2011	Lifetime	3PP	2-valent	2 doses	LYsg	40 000
Damm 2017	2017	Germany	EUR	2010	100 y	3PP & SP	4-valent & 2-valent	3 & 2 doses	QALYg	50 000
Largeron 2017	2017	Germany	EUR	2014	100 y	3PP	4-valent vs 9-valent	2 doses	QALYg	40 000
Mennini 2017	2017	Italy	EUR	2014	100 y	3PP	4-valent vs 9-valent	2 doses	QALYg	25 000–40 000

1685 *y: years*
1686 *3PP: third-party payer or heath care system perspective*
1687 *SP: societal perspective*
1688 *QALYg: quality-adjusted life years gained.*

1689

1690 **Table A34. Incremental cost-effectiveness ratios (ICERs) in local currency from societal perspective and critical parameters**

Author, year	Health outcomes	Vaccination coverage*	Vaccine efficacy*	Duration of protection	Vaccine cost (local currency)**	Base strategy (sex, age)	Comparator strategy (sex, age)	ICER (local currency)
Kim 2009	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	75%	F100%/M90%	Lifelong	360	F12	FM12	114 510 (USD/QALY)
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	75%	F100%/M50%	Lifelong	360	F12	FM12	164 580 (USD/QALY)
	CIN, CC, VA, VU, ANA (W), ORPH (W)	75%	F100%/M90%	Lifelong	360	F12	FM12	208 110 (USD/QALY)
	CIN, CC, VA, VU, ANA (W), ORPH (W)	75%	F100%/M50%	Lifelong	360	F12	FM12	242 520 (USD/QALY)
	CIN, CC	75%	F100%/M90%	Lifelong	360	F12	FM12	290 290 (USD/QALY)
	CIN, CC	75%	F100%/M75%	Lifelong	360	F12	FM12	382 860 (USD/QALY)
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	75%	F100%/M90%	Lifelong	360	F12	FM12	90 870 (USD/QALY)
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	75%	F100%/M75%	Lifelong	360	F12	FM12	123 940 (USD/QALY)
	CIN, CC	50%	F100%/M85%	Lifelong	360	F12	FM12	>220 000 (USD/QALY)
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	50%	F100%/M85%	Lifelong	360	F12	FM12	62 070 (USD/QALY)
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	50%	50%	Lifelong	360	F12	FM12	92 000 (USD/QALY)
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	75%	F100%/M85%	Lifelong	261	F12	FM12	63 000 (USD/QALY)
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	75%	50%	Lifelong	261	F12	FM12	<100 000 (USD/QALY)
Zechmeister 2009	CIN, CC (time horizon 80y)	65%	90%	10 y+booster	330+110	F12 + B22F	FM12 + B22FM	25 000 (EUR/LY)
	CIN, CC	65%	90%	10 y+booster	330+110	F12 + B22F	FM12 + B22FM	299 000 (EUR/LY)
Chesson 2011	CIN, CC,VA, VU, ANA, PEN, ORPH, GW, RRP	75% @ age 12	F 95%/M 90%	Lifelong	500	F12+CU13–26F	FM12+CU13–26F	184 300 (USD/QALY)
	CIN, CC,VA, VU, ANA, PEN, ORPH, GW, RRP	20% @ age 12	F 95%/M 90%	Lifelong	500	F12+CU13–26F	FM12+CU13–26F	23 600 (USD/QALY)
	CIN, CC,VA, VU, ANA, PEN, ORPH, GW, RRP	30% @ age 12	F 95%/M 90%	Lifelong	500	F12+CU13–26F	FM12+CU13–26F	41 400 (USD/QALY)
	CIN, CC	75% @ age 12	F 95%/M 90%	Lifelong	500	F12+CU13–26F	FM12+CU13–26F	741 300 (USD/QALY)
	CIN, CC	20% @ age 12	F 95%/M 90%	Lifelong	500	F12+CU13–26F	FM12+CU13–26F	69 600 (USD/QALY)

	CIN, CC	30% @ age 12	F 95%/M 90%	Lifelong	500	F12+CU13–26F	FM12+CU13–26F	121 700 (USD/QALY)
	CIN, CC, GW	75% @ age 12	F 95%/M 90%	Lifelong	500	F12+CU13–26F	FM12+CU13–26F	436 000 (USD/QALY)
	CIN, CC, GW	20% @ age 12	F 95%/M 90%	Lifelong	500	F12+CU13–26F	FM12+CU13–26F	52 100 (US$/QALY)
	CIN, CC, GW	30% @ age 12	F 95%/M 90%	Lifelong	500	F12+CU13–26F	FM12+CU13–26F	89 100 (USD/QALY)
	CIN, CC,VA, VU, ANA, PEN, ORPH	75% @ age 12	F 95%/M 90%	Lifelong	500	F12+CU13–26F	FM12+CU13–26F	229 600 (USD/QALY)
	CIN, CC,VA, VU, ANA, PEN, ORPH	20% @ age 12	F 95%/M 90%	Lifelong	500	F12+CU13–26F	FM12+CU13–26F	29 700 (USD/QALY)
	CIN, CC,VA, VU, ANA, PEN, ORPH	30% @ age 12	F 95%/M 90%	Lifelong	500	F12+CU13–26F	FM12+CU13–26F	50 800 (USD/QALY)
	CIN, CC, VA, VU, ANA, PEN, ORPH, GW, RRP	20% @ age 12	F 95%/M 90%	Lifelong	360	F12+CU13–26F	FM12+CU13–26F	13 100 (USD/QALY)
	CIN, CC, VA, VU, ANA, PEN, ORPH, GW, RRP	20% @ age 12	F 95%/M 90%	Lifelong	600	F12+CU13–26F	FM12+CU13–26F	31 200 (USD/QALY)
	CIN, CC, VA, VU, ANA, PEN, ORPH, GW, RRP	30% @ age 12	F 95%/M 90%	Lifelong	360	F12+CU13–26F	FM12+CU13–26F	25 900 (USD/QALY)
	CIN, CC, VA, VU, ANA, PEN, ORPH, GW, RRP	30% @ age 12	F 95%/M 90%	Lifelong	600	F12+CU13–26F	FM12+CU13–26F	52 500 (USD/QALY)
	CIN, CC, VA, VU, ANA, PEN, ORPH, GW, RRP	75% @ age 12	F 95%/M 90%	Lifelong	360	F12+CU13–26F	FM12+CU13–26F	129 000 (USD/QALY)
	CIN, CC, VA, VU, ANA, PEN, ORPH, GW, RRP	75% @ age 12	F 95%/M 90%	Lifelong	600	F12+CU13–26F	FM12+CU13–26F	223 800 (USD/QALY)
	CIN, CC, VA, VU, ANA, PEN, ORPH, GW, RRP	30% @ age 12	F 95%/M 90%	Lifelong	500	F12	FM12	25 000 (USD/QALY)
	CIN, CC, VA, VU, ANA, PEN, ORPH, GW, RRP	45% F vs 30% FM	F 95%/M 90%	Lifelong	500	F12	FM12	103 500 (USD/QALY)
Burger 2014	CIN, CC	71%	F 100%/M 90%	Lifelong	225	F12	FM12	145 500 (USD/QALY)
	CIN, CC, VA, VU, ANA, ORPH (only female)	71%	F1 00%/M 90%	Lifelong	225	F12	FM12	119 300 (USD/QALY)
	CIN, CC, VA, VU, PEN, ANA, ORPH (all)	71%	F 100%/M 90%	Lifelong	225	F12	FM12	81 700 (USD/QALY)
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	71%	F100%/M 90%	Lifelong	225	F12	FM12	60 100 (USD/QALY)
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	71%	F 100%/M 90%	Lifelong	150	F12	FM12	40 400 (USD/QALY)
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	F 71%/M 60%	F 100%/M 90%	Lifelong	150	F12	FM12	44 400 (USD/QALY)
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	F 71%/M 80%	F 100%/M 90%	Lifelong	150	F12	FM12	56 100 (USD/QALY)

	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	71%	F 100%/M 90%	20 y	150	F12	FM12	38 300 (USD/QALY)
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	F 90%/M 71%	F 100%/M 90%	Lifelong	150	F12	FM12	Dom
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	79%	F 100%/M90% (2d)	Lifelong	100	F12	FM12	27 680 (USD/QALY)
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	F 71%/M 60%	F 100%/M 90%	Lifelong	225	F12	FM12	65 800 (USD/QALY)
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	F 71%/M 80%	F 100%/M 90%	Lifelong	225	F12	FM12	82 300 (USD/QALY)
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	71%	F 100%/M 90%	20 y	225	F12	FM12	57 200 (USD/QALY)
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	F 90%/M 71%	F 100%/M 90%	Lifelong	225	F12	FM12	Dom
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	79%	F 100%/M 90% (2d)	Lifelong	150	F12	FM12	42 320 (USD/QALY)
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	71%	F 100%/M 90%	Lifelong	450	F12	FM12	116 700 (USD/QALY)
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	F 71%/M 60%	F 100%/M 90%	Lifelong	450	F12	FM12	127 200 (USD/QALY)
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	F 71%/M 80%	F 100%/M 90%	Lifelong	450	F12	FM12	157 400 (USD/QALY)
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	71%	F 100%/M 90%	20 y	450	F12	FM12	111 400 (USD/QALY)
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	F 90%/M 71%	F 100%/M 90%	Lifelong	450	F12	FM12	Dom
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	79%	F 100%/M 90% (2d)	Lifelong	300	F12	FM12	84 330 (USD/QALY)
Jiménez 2015	CIN, CC, VU, GW	82%		Lifelong	3340	F12	FM12	1 626 261 (NOK/DALY)
Damm 2017	CIN, CC, GW	50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4%	20 y	450	F12	FM12	111 386 (EUR/QALY)
	CIN, CC, GW	50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4% (2d)	20 y	300	F12	FM12	68 118 (EUR/QALY)
	CIN, CC (2-valent)	50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4%	20 y	450	F12	FM12	124 453 (EUR/QALY)
	CIN, CC (2-valent)	50%	HPV16/18 F 98% HPV6/11 F 100%	20 y	300	F12	FM12	77 607 (EUR/QALY)

			HPV16/18/6/11 M 90.4% (2d)					
	CIN, CC, GW	F 20%/M 50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4%	20 y	450	F12	FM12	41 104 (EUR/QALY)
Damm 2017	CIN, CC, GW	F20%/M 50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4% (2d)	20 y	300	F12	FM12	20 617 (EUR/QALY)
	CIN, CC (2-valent)	F 20%/M 50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4%	20 y	450	F12	FM12	54 574 (EUR/QALY)
	CIN, CC (2-valent)	F 20%/M 50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4% (2d)	20 y	300	F12	FM12	30 959 (EUR/QALY)
	CIN, CC, GW	F 20%/M 80%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4%	20 y	450	F12	FM12	55 158 (EUR/QALY)
	CIN, CC, GW	F 20%/M 80%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4% (2d)	20 y	300	F12	FM12	30 164 (EUR/QALY)
	CIN, CC (2-valent)	F 20%/M 80%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4%	20 y	450	F12	FM12	68 758 (EUR/QALY)
	CIN, CC (2-valent)	F 20%/M 80%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4% (2d)	20 y	300	F12	FM12	40 440 (EUR/QALY)

**: Vaccination coverage and efficacy separated by / means two different coverages used in study referring to two separate populations. When numbers are separated by 'vs', two different coverages were compared in different scenarios.*

***: 'Vaccine cost' separated by + means cost of initial vaccination (three) doses plus cost of booster dose.*

Abbreviations

Health outcomes: Cervical cancer (CC), cervical intraepithelial neoplasia (CIN), genital warts (GW), vaginal cancer (VA), vulvar cancer (VU), anal cancer (ANA), penile cancer (PEN), oropharingeal cancer (ORPH), recurrent respiratory papillomatosis (RRP)

Sex: females (F), women (W), males (M)

Other: years (y), at (@), dose (d), catch-up (CU), booster (B), quality-adjusted life years (QALY), life years (LY), dominant (Dom).

1700 **Table A35. Incremental cost-effectiveness ratios (ICERs) converted to EUR from societal perspective and critical parameters**

Author year	Health outcomes	Vaccination coverage*	Vaccine efficacy	Duration of protection	Vaccine cost (EUR)**	Base strategy (sex, age)	Comparator strategy (sex, age)	ICER (EUR)
Kim 2009	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	75%	F 100%/M 90%	Lifelong	286	F12	FM12	90 881
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	75%	F 100%/M 50%	Lifelong	286	F12	FM12	130 619
	CIN, CC, VA, VU, ANA (W), ORPH (W)	75%	F 100%/M 90%	Lifelong	286	F12	FM12	165 167
	CIN, CC, VA, VU, ANA (W), ORPH (W)	75%	F 100%/M 50%	Lifelong	286	F12	FM12	192 476
	CIN, CC	75%	F 100%/M 90%	Lifelong	286	F12	FM12	230 389
	CIN, CC	75%	F 100%/M 75%	Lifelong	286	F12	FM12	303 857
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	75%	F100%/M90%	Lifelong	286	F12	FM12	72 119
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	75%	F 100%/M 75%	Lifelong	286	F12	FM12	98 365
	CIN, CC	50%	F 100%/M 85%	Lifelong	286	F12	FM12	>174 603
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	50%	F 100%/M 85%	Lifelong	286	F12	FM12	49 262
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	50%	50%	Lifelong	286	F12	FM12	73 016
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	75%	F 100%/M 85%	Lifelong	207	F12	FM12	50 000
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	75%	50%	Lifelong	207	F12	FM12	<79 365
Zechmeister 2009	CIN, CC (time horizon 80 y)	65%	90%	10 y+booster	330+110	F12 + B22F	FM12+B22FM	25 000
	CIN, CC	65%	90%	10 y+booster	330+110	F12 + B22F	FM12+B22FM	299 000
Chesson 2011	CIN, CC,VA, VU, ANA, PEN, ORPH, GW, RRP	75% @ age 12	F 95%/M 90%	Lifelong	340	F12+CU13–26F	FM12+CU13–26F	125 374
	CIN, CC,VA, VU, ANA, PEN, ORPH, GW, RRP	20% @ age 12	F 95%/M 90%	Lifelong	340	F12+CU13–26F	FM12+CU13–26F	16 054
	CIN, CC,VA, VU, ANA, PEN, ORPH, GW, RRP	30% @ age 12	F 95%/M 90%	Lifelong	340	F12+CU13–26F	FM12+CU13–26F	28 163
	CIN, CC	75% @ age 12	F 95%/M 90%	Lifelong	340	F12+CU13–26F	FM12+CU13–26F	504 286
	CIN, CC	20% @ age 12	F 95%/M 90%	Lifelong	340	F12+CU13–26F	FM12+CU13–26F	47 347
	CIN, CC	30% @ age 12	F 95%/M 90%	Lifelong	340	F12+CU13–26F	FM12+CU13–26F	82 789
	CIN, CC, GW	75% @ age 12	F 95%/M 90%	Lifelong	340	F12+CU13–26F	FM12+CU13–26F	296 599

	CIN, CC, GW	20% @ age 12	F 95%/M 90%	Lifelong	340	F12+CU13–26F	FM12+CU13–26F	35 442
	CIN, CC, GW	30% @ age 12	F 95%/M 90%	Lifelong	340	F12+CU13–26F	FM12+CU13–26F	60 612
	CIN, CC,VA, VU, ANA, PEN, ORPH	75% @ age 12	F 95%/M 90%	Lifelong	340	F12+CU13–26F	FM12+CU13–26F	156 190
	CIN, CC,VA, VU, ANA, PEN, ORPH	20% @ age 12	F 95%/M 90%	Lifelong	340	F12+CU13–26F	FM12+CU13–26F	20 204
	CIN, CC,VA, VU, ANA, PEN, ORPH	30% @ age 12	F 95%/M 90%	Lifelong	340	F12+CU13–26F	FM12+CU13–26F	34 558
	CIN, CC, VA, VU, ANA, PEN, ORPH, GW, RRP	20% @ age 12	F 95%/M 90%	Lifelong	245	F12+CU13–26F	FM12+CU13–26F	8 912
	CIN, CC, VA, VU, ANA, PEN, ORPH, GW, RRP	20% @ age 12	F 95%/M 90%	Lifelong	408	F12+CU13–26F	FM12+CU13–26F	21 224
	CIN, CC, VA, VU, ANA, PEN, ORPH, GW, RRP	30% @ age 12	F 95%/M 90%	Lifelong	245	F12+CU13–26F	FM12+CU13–26F	17 619
	CIN, CC, VA, VU, ANA, PEN, ORPH, GW, RRP	30% @ age 12	F 95%/M 90%	Lifelong	408	F12+CU13–26F	FM12+CU13–26F	35 714
	CIN, CC, VA, VU, ANA, PEN, ORPH, GW, RRP	75% @ age 12	F 95%/M 90%	Lifelong	245	F12+CU13–26F	FM12+CU13–26F	87 755
	CIN, CC, VA, VU, ANA, PEN, ORPH, GW, RRP	75% @ age 12	F 95%/M 90%	Lifelong	408	F12+CU13–-26F	FM12+CU13–26F	152 245
	CIN, CC, VA, VU, ANA, PEN, ORPH, GW, RRP	30% @ age 12	F 95%/M 90%	Lifelong	340	F12	FM12	17 007
	CIN, CC, VA, VU, ANA, PEN, ORPH, GW, RRP	45% F vs 30% FM	F 95%/M 90%	Lifelong	340	F12	FM12	70 408
Burger 2014	CIN, CC	71%	F 100%/M 90%	Lifelong	169	F12	FM12	109 398
	CIN, CC, VA, VU, ANA, ORPH (only female)	71%	F 100%/M 90%	Lifelong	169	F12	FM12	89 699
	CIN, CC, VA, VU, PEN, ANA, ORPH (all)	71%	F 100%/M 90%	Lifelong	169	F12	FM12	61 429
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	71%	F 100%/M 90%	Lifelong	169	F12	FM12	45 188
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	71%	F 100%/M 90%	Lifelong	113	F12	FM12	30 376
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	F 71%/M 60%	F 100%/M 90%	Lifelong	113	F12	FM12	33 383
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	F 71%/M 80%	F 100%/M 90%	Lifelong	113	F12	FM12	42 180
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	71%	F 100%/M 90%	20 y	113	F12	FM12	28 797
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	F 90%/M 71%	F 100%/M 90%	Lifelong	113	F12	FM12	
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	79%	F 100%/M 90% (2d)	Lifelong	75	F12	FM12	20 812

	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	F 71%/M 60%	F 100%/M 90%	Lifelong	169	F12	FM12	49 474
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	F 71%/M 80%	F 100%/M 90%	Lifelong	169	F12	FM12	61 880
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	71%	F 100%/M 90%	20 y	169	F12	FM12	43 008
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	F 90%/M 71%	F 100%/M 90%	Lifelong	169	F12	FM12	
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	79%	F100%/M 90% (2d)	Lifelong	113	F12	FM12	31 820
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	71%	F 100%/M 90%	Lifelong	338	F12	FM12	87 744
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	F 71%/M 60%	F 100%/M 90%	Lifelong	338	F12	FM12	95 639
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	F 71%/M 80%	F 100%/M 90%	Lifelong	338	F12	FM12	118 346
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	71%	F 100%/M 90%	20 y	338	F12	FM12	83 759
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	F 90%/M 71%	F 100%/M 90%	Lifelong	338	F12	FM12	
	CIN, CC, VA, VU, PEN, ANA, ORPH, GW, RRP	79%	F 100%/M 90% (2d)	Lifelong	226	F12	FM12	63 406
Jiménez 2015	CIN, CC, VU, GW	82%		Lifelong	400	F12	FM12	194 529
Damm 2017	CIN, CC, GW	50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4%	20 y	450	F12	FM12	111 386
	CIN, CC, GW	50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4% (2d)	20 y	300	F12	FM12	68 118
	CIN, CC (2-valent)	50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4%	20 y	450	F12	FM12	124 453
	CIN, CC (2-valent)	50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4% (2d)	20 y	300	F12	FM12	77 607
	CIN, CC, GW	F 20%/M 50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4%	20 y	450	F12	FM12	41 104
	CIN, CC, GW	F 20%/M 50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4% (2d)	20 y	300	F12	FM12	20 617

	CIN, CC (2-valent)	F 20%/M 50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4%	20 y	450	F12	FM12	54 574
Damm 2017	CIN, CC (2-valent)	F 20%/M 50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4% (2d)	20 y	300	F12	FM12	30 959
	CIN, CC, GW	F 20%/M 80%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4%	20 y	450	F12	FM12	55 158
	CIN, CC, GW	F 20%/M 80%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4% (2d)	20 y	300	F12	FM12	30 164
	CIN, CC (2-valent)	F 20%/M 80%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4%	20 y	450	F12	FM12	68 758
	CIN, CC (2-valent)	F 20%/M 80%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4% (2d)	20 y	300	F12	FM12	40 440

**: Vaccination coverages separated by / means two different coverages were used in study referring to two separate populations. When the numbers are separated by 'vs', two different coverages were compared in different scenarios.*

***: 'Vaccine cost' separated by + means cost of initial vaccination (three) doses plus cost of booster dose.*

Abbreviations

Health outcomes: cervical cancer (CC), cervical intraepithelial neoplasia (CIN), genital warts (GW), vaginal cancer (VA), vulvar cancer (VU), anal cancer (ANA), penile cancer (PEN), oropharingeal cancer (ORPH), recurrent respiratory papillomatosis (RRP)

Sex: females (F), women (W), males (M)

Other: years (y), at (@), dose (d), catch-up (CU), booster (B).

1710 **Table A36. Incremental cost-effectiveness ratios (ICERs) in local currency from third-party payer or healthcare system perspective and critical parameters**

Author, year	Health outcomes	Vaccination coverage*	Vaccine efficacy	Duration of protection	Vaccine cost (local currency)**	Base strategy (sex, age)	Comparator strategy (sex, age)	ICER (local currency)
Taira 2004	CC	70%	90%	10 y post booster	300+100	F12 + B22F	FM12 + B22FM	442 039 (USD/QALY)
	CC	30%	90%	10 y post booster	300+100	F12 + B22F	FM12 + B22FM	40 865 (USD/QALY)
	CC	70%	90%	10 y	300	F12	FM12	51 646 (USD/QALY)
	CC	70%	90%	10 y post booster	300+200	F12+2B(5/5)	FM12+2B(5/5)	388 368 (USD/QALY)
	CC	70%	90%	10y	300	F12	FM18	57 795 (USD/QALY)
	CC	Highest risk girls 30%	90%	10 y post booster	300+100	F12 + B22F	FM12 + B22FM	116 413 (USD/QALY)
Elbasha 2007	CIN, CC, GW	70%	90%	Lifelong	360	F12	FM12	Dom
	CIN, CC, GW	70% (50%CU)	90%	Lifelong	360	F12+CU1224F	FM12+CU12–24F	41 803 (USD/QALY)
	CIN, CC, GW	70% (50%CU)	90%	Lifelong	360	F18+CU18–24F	FM18+CU18–24FM	Dom
	CIN, CC, GW	70% (50%CU)	90%	Lifelong	360	F18+CU18–24F	FM15+CU15–24FM	Dom
	CIN, CC, GW	70% (50%CU)	90%	Lifelong	360	F12+CU12–24F	FM12+CU12–24FM	42 697 (USD/QALY)
	CIN, CC, GW	70% (50%CU)	90%	Lifelong	300	F12+CU12–24F	FM12+CU12–24F	33 469 (USD/QALY)
	CIN, CC, GW	70% (50%CU)	90%	Lifelong	500	F12+CU12–24F	FM12+CU12–24F	61 250 (USD/QALY)
	CIN, CC, GW	70% (50%CU)	90%	10y	360	F12+CU12–24F	FM12+CU12–24F	54 755 (USD/QALY)
	CIN, CC, GW	70% (50%CU)	100%	Lifelong	360	F12+CU12–24F	FM12+CU12–24F	Dom
	CIN, CC, GW	70% (50%CU)	74%	Lifelong	360	F12+CU12–24F	FM12+CU12–24F	39 990 (USD/QALY)
	CIN, CC, GW	50%	90%	Lifelong	360	F12+CU12–24F	FM12+CU12–24F	23 862 (USD/QALY)
	CIN, CC, GW	90%	90%	Lifelong	360	F12+CU12–24F	FM12+CU12–24F	Dom
	CIN, CC, GW	70% (50%CU)	90%	Lifelong	360	FM12+CU12–24F	FM12+CU12–24FM	45 056 (USD/QALY)
	CIN, CC, GW	70% (50%CU)	90%	Lifelong	300	FM12+CU12–24F	FM12+CU12–24FM	36 161 (USD/QALY)
	CIN, CC, GW	70% (50%CU)	90%	Lifelong	500	FM12+CU12–24F	FM12+CU12–24FM	65 810 (USD/QALY)

	CIN, CC, GW	70% (50%CU)	90%	10 y	360	FM12+CU12–24F	FM12+CU12–24FM	54 928 (USD/QALY)
	CIN, CC, GW	70% (50%CU)	100%	Lifelong	360	F12+CU12–24F	FM12+CU12–24F	Dom
	CIN, CC, GW	70% (50%CU)	100%	Lifelong	360	FM12+CU12–24F	FM12+CU12–24FM	51 436 (USD/QALY)
	CIN, CC, GW	70% (50%CU)	74%	Lifelong	360	FM12+CU12–24F	FM12+CU12–24FM	43 930 (USD/QALY)
	CIN, CC, GW	50%	90%	Lifelong	360	FM12+CU12–24F	FM12+CU12–24FM	36 235 (USD/QALY)
	CIN, CC, GW	90%	90%	Lifelong	360	FM12+CU12–24F	FM12+CU12–24FM	100 418 (USD/QALY)
Kulasingam 2007	CIN, CC	80%	100%	Lifelong	345	No vaccination	FM12	33 644 (AUD/QALY)
	CIN, CC	80%	84%	Lifelong	345	No vaccination	FM12	36 920 (AUD/QALY)
	CIN, CC	80%	100%	10 y	345	No vaccination	FM12	104 669 (AUD/QALY)
	CIN, CC	80%	84%	10 y	345	No vaccination	FM12	107 776 (AUD/QALY)
	CIN, CC	70%	100%	Lifelong	345	No vaccination	FM12	29 278 (AUD/QALY)
	CIN, CC	70%	84%	Lifelong	345	No vaccination	FM12	34 380 (AUD/QALY)
	CIN, CC	90%	100%	Lifelong	345	No vaccination	FM12	38 503 (AUD/QALY)
	CIN, CC	90%	84%	Lifelong	345	No vaccination	FM12	40 018 (AUD/QALY)
Jit 2008	CIN, CC, GW	80%	100%	Lifelong	211	F12	FM12	520 255 (GBP/QALY)
	CIN, CC, GW	80%	100%	10 y	211	F12	FM12	113 846 (GBP/QALY)
	CIN, CC, GW	80%	100%	20 y	211	F12	FM12	172 892 (GBP/QALY)
Zechmeister 2009	CIN, CC	65%	90%	10 y+booster	330+110	F12 + B22F	FM12 + B22FM	311 000 (EUR/LY)
Olsen 2010	CIN, CC, GW	70%	100%	-	415	No vaccination	FM12	18 677 (EUR/QALY)
Elbasha 2010	CIN, CC, VA, VU, GW, PEN, H&N, ANA, RRP	90% @ age 26	90%	Lifelong	400	F9-26	FM9-26	25 664 (USD/QALY)
	CIN, CC, VA, VU, GW, H&N, ANA, RRP	90% @ age 26	90%	Lifelong	400	F9-26	FM9-26	27 511 (USD/QALY)
	CIN, CC, VA, VU, GW, ANA, RRP	90% @age26	90%	Lifelong	400	F9-26	FM9-26	46 978 (USD/QALY)

	CIN, CC, VA, VU, GW, RRP	90% @age26	90%	Lifelong	400	F9-26	FM9-26	62 293 (USD/QALY)
	CIN, CC, VA, VU, GW	90% @age26	90%	Lifelong	400	F9-26	FM9-26	69 038 (USD/QALY)
	CIN, CC, VA, VU	90% @age26	90%	Lifelong	400	F9-26	FM9-26	178 908 (USD/QALY)
	CIN, CC	90% @age26	90%	Lifelong	400	F9-26	FM9-26	195 322 (USD/QALY)
Laprise 2014	CC, VU, VA, ANA, PEN, ORPH, GW	80%	95%	Lifelong	255	F9+CU14F	FM9+CU14F	167 100 (CAD/QALY)
	CC, VU, VA, ANA, PEN, ORPH, GW	50%	95%	Lifelong	255	F9+CU14F	FM9+CU14F	68 911 (CAD/QALY)
	CC, VU, VA, ANA, PEN, ORPH, GW	80%	95%	20 y	255	F9+CU14F	FM9+CU14F	119 000 (CAD/QALY)
	CC, VU, VA, ANA, PEN, ORPH, GW	80%	95%	25 y	255	F9+CU14F	FM9+CU14F	170 300 (CAD/QALY)
	CC, VU, VA, ANA, PEN, ORPH, GW	50%	95%	25 y	255	F9+CU14F	FM9+CU14F	70 941 (CAD/QALY)
	CC, VU, VA, ANA, PEN, ORPH, GW	80%	95%	35 y	255	F9+CU14F	FM9+CU14F	184 400 (CAD/QALY)
	CC, VU, VA, ANA, PEN, ORPH, GW	80%	95% (2d)	20 y	170	F9+CU14F	FM9+CU14F	86 200 (CAD/QALY)
	CC, VU, VA, ANA, PEN, ORPH, GW	50%	95% (2d)	20 y	170	F9+CU14F	FM9+CU14F	55 411 (CAD/QALY)
	CC, VU, VA, ANA, PEN, ORPH, GW	50%	95% (2d)	25 y	170	F9+CU14F	FM9+CU14F	68 017 (CAD/QALY)
	CC, VU, VA, ANA, PEN, ORPH, GW	50%	95% (2d)	30 y	170	F9+CU14F	FM9+CU14F	52 676 (CAD/QALY)
	CC, VU, VA, ANA, PEN, ORPH, GW	80%	95% (2d)	30 y	170	F9+CU14F	FM9+CU14F	135 450 (CAD/QALY)
Pearson 2014	CIN, CC, VU, ANA, ORPH, GW	56%/45%	99%	20 y	339	No vaccination	FM12	41 100 (NZD/QALY)
	CIN, CC, VU, ANA, ORPH, GW	73%	99%	20 y	339	No vaccination	FM12	54 600 (NZD/QALY)
	CIN, CC, VU, ANA, ORPH, GW	56%/45%	99%	20 y	339	F12	FM12	118 000 (NZD/QALY)
	CIN, CC, VU, ANA, ORPH, GW	56%/45% vs 73%	99%	20 y	339	F12 (56%/45%)	FM12 (73%)	148 000 (NZD/QALY)
	CIN, CC, VU, ANA, ORPH, GW	73%	99%	20 y	339	F12	FM12	247 000 (NZD/QALY)
	CIN, CC, VU, ANA, ORPH, GW	56%/45%	99%	Lifelong	339	F12	FM12	111 000 (NZD/QALY)
	CIN, CC, VU, ANA, ORPH, GW	73%	99%	Lifelong	339	F12	FM12	234 000 (NZD/QALY)

	CIN, CC, VU, ANA, ORPH, GW	56%/45%	99%	Lifelong	168	F12	FM12	81 300 (NZD/QALY)
	CIN, CC, VU, ANA, ORPH, GW	73%	99%	Lifelong	168	F12	FM12	173 000 (NZD/QALY)
	CIN, CC, VU, ANA, ORPH, GW	56%/45%	99%	Lifelong	22	F12	FM12	55 300 (NZD/QALY)
	CIN, CC, VU, ANA, ORPH, GW	73%	99%	Lifelong	22	F12	FM12	121 000 (NZD/QALY)
Bresse 2014	CIN, CC	65%	F 76-100%/M 41-96%	Lifelong	330	No vaccination	FM9	26 701 (EURQALY)
	CIN, CC, VA	65%	F 76-100%/M 41-96%	Lifelong	330	No vaccination	FM9	26 279 (EUR/QALY)
	CIN, CC, VA, VU	65%	F 76-100%/M 41-96%	Lifelong	330	No vaccination	FM9	25 567 (EUR/QALY)
	CIN, CC, VA, VU, GW	65%	F 76-100%/M 41-96%	Lifelong	330	No vaccination	FM9	15 820 (EUR/QALY)
	CIN, CC, VU, VA, GW, ANA	65%	F 76-100%/M 41-96%	Lifelong	330	No vaccination	FM9	13 850 (EUR/QALY)
	CIN, CC, VU, VA, GW, ANA, ORPH	65%	F 76-100%/M 41-96%	Lifelong	330	No vaccination	FM9	10 136 (EUR/QALY)
	CIN, CC, VU, VA, GW, ANA, ORPH, PEN	65%	F 76-100%/M 41-96%	Lifelong	330	No vaccination	FM9	10 033 (EUR/QALY)
	CIN, CC, VU, VA, GW, ANA, ORPH, PEN	65%	F 76-100%/M 41-96%	20 y	330	No vaccination	FM9	19 590 (EUR/QALY)
	CIN, CC, VU, VA, GW, ANA, ORPH, PEN	65%	F 76-100%/M 41-96%	Lifelong	281	No vaccination	FM9	8 202 (EUR/QALY)
	CIN, CC, VU, VA, GW, ANA, ORPH, PEN	65%	F 76-100%/M 41-96%	Lifelong	380	No vaccination	FM9	11 787 (EUR/QALY)
	CIN, CC, VU, VA, GW, ANA, ORPH, PEN	80%	F 76-100%/M 41-96%	Lifelong	330	No vaccination	FM9	9 982 (EUR/QALY)
	CIN, CC, VU, VA, GW, ANA, ORPH, PEN	50%	F 76-100%/M 41-96%	Lifelong	330	No vaccination	FM9	11 351 (EUR/QALY)
Blakely 2014	CIN, CC, VU, ANA, ORPH, GW	56%/45%	100%	Lifelong	339	No vaccination	FM12	18 800 (NZD/QALY)
	CIN, CC, VU, ANA, ORPH, GW	73%	100%	Lifelong	339	No vaccination	FM12	22 600 (NZD/QALY)
	CIN, CC, VU, ANA, ORPH, GW	93%	100%	Lifelong	339	No vaccination	FM12	31 000 (NZD/QALY)
	CIN, CC, VU, ANA, ORPH, GW	56%/45% vs 73%	100%	Lifelong	339	FM12 (56%/45%)	FM12 (73%)	34 700 (NZD/QALY)
	CIN, CC, VU, ANA, ORPH, GW	73% vs 93%	100%	Lifelong	339	FM12 (73%)	FM12 (93%)	122 500 (NZD/QALY)
Haeussler 2015	CIN, CC, VA, VaIN, VU, VIN, ANA, PEN, PeIN, H&N, GW	90%	CC 78%/ANA 70%/H&N 50%	Lifelong	168	F12	FM12	11 600 (EUR/QALY)

Jiménez 2015	CIN, CC, VU, GW	82%		Lifelong	3340	F12	FM12	1 789 463 (NOK/QALY)
	CIN, CC, VU, GW	82%		Lifelong	750	F12	FM12	351 975 (NOK/QALY)
	CIN, CC, VU, GW	82%		Lifelong	1 500	F12	FM12	765 909 (NOK/QALY)
	CIN, CC, VU, GW	82%		Lifelong	2 250	F12	FM12	1 186 606 (NOK/QALY)
	CIN, CC, VU (2-valent)	82%		Lifelong	3 340	F12	FM12	3 754 854 (NOK/QALY)
	CIN, CC, VU, GW	F92%/M82%		Lifelong	3 340	F12 (92%)	F(82%)M(82%)12	3 815 093 (NOK/QALY)
	CIN, CC, VU, GW, VA, ANA	82%		Lifelong	3 340	F12	FM12	1 538 578 (NOK/QALY)
Olsen 2015	CIN, CC, VA, VU, ANA, PEN, H&N, GW	85%	100%	Lifelong	369	F12	FM12	41 636 (EUR/QALY)
	CIN, CC, VA, VU, ANA, PEN, H&N, GW	85%	100%	Lifelong	277	F12	FM12	31 432 (EUR/QALY)
	CIN, CC, VA, VU, ANA, PEN, H&N, GW	85%	100% (2d)	Lifelong	246	F12	FM12	28 031 (EUR/QALY)
	CIN, CC, VA, VU, ANA, PEN, H&N, GW (time horizon 40y)	85%	100%	Lifelong	369	F12	FM12	47 342 (EUR/QALY)
	CIN, CC, VA, VU, ANA, PEN, H&N, GW	70%	100%	Lifelong	369	F12	FM12	31 615 (EUR/QALY)
	CIN, CC, VA, VU, ANA, PEN, GW	85%	100%	Lifelong	369	F12	FM12	276 642 (EUR/QALY)
Qendri 2017	CC, VU, VA, ANA, PEN, ORPH	F60%/40%M	98% (2d)	Lifelong	34	F12	FM12	9,134 (EUR/LY)
	CC, VU, VA, ANA, PEN, ORPH	F70%/40%M	98% (2d)	Lifelong	34	F12	FM12	13 083 (EURLY)
	CC, VU, VA, ANA, PEN, ORPH	F80%/40%M	98% (2d)	Lifelong	34	F12	FM12	20 631 (EUR/LY)
	CC, VU, VA, ANA, PEN, ORPH	F90%/40%M	98% (2d)	Lifelong	34	F12	FM12	36 363 (EUR/LY)
	CC, VU, VA, ANA, PEN, ORPH	F60%/50%M	98% (2d)	Lifelong	34	F12	FM12	9 935 (EUR/LY)
	CC, VU, VA, ANA, PEN, ORPH	F60%/60%M	98% (2d)	Lifelong	34	F12	FM12	9 412 (EUR/LY)
Damm 2017	CIN, CC, GW	50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4%	20y	450	F12	FM12	117 240 (EUR/QALY)
	CIN, CC, GW	50%	HPV16/18 F 98% HPV6/11 F 100%	20y	300	F12	FM12	73 973 (EUR/QALY)

			HPV16/18/6/11 M 90.4% (2d)					
	CIN, CC (2-valent)	50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4%	20y	450	F12	FM12	130 449 (EUR/QALY)
	CIN, CC (2-valent)	50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4% (2d)	20y	300	F12	FM12	83 602 (EUR/QALY)
	CIN, CC, GW	F20%/M50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4%	20y	450	F12	FM12	46 965 (EUR/QALY)
	CIN, CC, GW	F20%/M50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4% (2d)	20y	300	F12	FM12	26 478 (EUR/QALY)
	CIN, CC (2-valent)	F20%/M50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4%	20y	450	F12	FM12	60 682 (EUR/QALY)
	CIN, CC (2-valent)	F20%/M50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4% (2d)	20y	300	F12	FM12	37 066 (EUR/QALY)
	CIN, CC, GW	F20%/M80%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4%	20y	450	F12	FM12	61 027 (EUR/QALY)
	CIN, CC, GW	F20%/M80%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4% (2d)	20y	300	F12	FM12	36 033 (EUR/QALY)
	CIN, CC (2-valent)	F20%/M80%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4%	20y	450	F12	FM12	74 844 (EUR/QALY)
	CIN, CC (2-valent)	F20%/M80%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4% (2d)	20y	300	F12	FM12	46 525 (EUR/QALY)
Largeron 2017	CIN, CC, VA, VU, ANA, GW	55.6%	F 76-100%/M 41-96% (2d)	Lifelong	280 vs 293	F9-14+CU15–17 (4v)	FM9-14+CU15–17 (9v)	22 987 (EUR/QALY)

	CIN, CC, VA, VU, ANA, GW	55.6%	F 76-100%/M 41-96% (2d)	20 y	280 vs 293	F9-14+CU15–17 (4v)	FM9-14+CU15–17 (9v)	14 827 (EUR/QALY)
	CIN, CC, VA, VU, ANA, GW	70%	F 76-100%/M 41-96% (2d)	Lifelong	280 vs 293	F9-14+CU15–17 (4v)	FM9-14+CU15–17 (9v)	27 986 (EUR/QALY)
	CIN, CC, VA, VU, ANA, GW, PEN, H&N, RRP	55.6%	F 76-100%/M 41-96% (2d)	Lifelong	280 vs 293	F9-14+CU15–17 (4v)	FM9-14+CU15–17 (9v)	14 286 (EUR/QALY)
Mennini 2017	CIN, CC, VaIN, VA, VU, ANA, GW	71%	F 76-100%/M 41-96% (2d)	Lifelong	208 vs 240	F12 (4v)	FM12 (9v)	13 541 (EUR/QALY)
	CIN, CC, VaIN, VA, VU, ANA, GW	60%	F 76-100%/M 41-96% (2d)	Lifelong	208 vs 240	F12 (4v)	FM12 (9v)	11 376 (EUR/QALY)
	CIN, CC, VaIN, VA, VU, ANA, GW	71%	F 76-100%/M 41-96% (2d)	20 y	208 vs 240	F12 (4v)	FM12 (9v)	20 845 (EUR/QALY)
	CIN, CC, VaIN, VA, VU, ANA, GW, PEN, H&N, RRP	71%	F 76-100%/M 41-96% (2d)	Lifelong	208 vs 240	F12 (4v)	FM12 (9v)	7 165 (EUR/QALY)

**: Vaccination coverages separated by / means two different coverages were used in study referring to two separate populations. When numbers are separated by 'vs', two different coverages were compared in different scenarios.*

***: 'Vaccine cost' separated by + means cost of initial vaccination (three) doses plus cost of booster dose.*

Abbreviations

Health outcomes: cervical cancer (CC), cervical intraepithelial neoplasia (CIN), genital warts (GW), vaginal cancer (VA), vulvar cancer (VU), anal cancer (ANA), penile cancer (PEN), oropharingeal cancer (ORPH), head and neck cancer (H&N), recurrent respiratory papillomatosis (RRP)

Sex: females (F), women (W), males (M)

Other: years (y), at (@), dose (d), catch-up (CU), booster (B).

1720 **Table A37. Incremental cost-effectiveness ratios (ICERs) converted to EUR from third-party payer or healthcare system perspective and critical parameters**

Author year	Health outcomes	Vaccination coverage*	Vaccine efficacy	Duration of protection	Vaccine cost (EUR)**	Base strategy (sex, age)	Comparator strategy (sex, age)	ICER (EUR)
Taira 2004	CC	70%	90%	10 y post booster	333+111	F12 + B22F	FM12 + B22FM	491 154
	CC	30%	90%	10 yrpost booster	333+111	F12 + B22F	FM12 + B22FM	45 406
	CC	70%	90%	10 y	333	F12	FM12	57 384
	CC	70%	90%	10 y post booster	333+222	F12+2B(5/5)	FM12+2B(5/5)	431 520
	CC	70%	90%	10 y	333	F12	FM18	64 217
	CC	Highest risk girls 30%	90%	10 yr post booster	333+111	F12 + B22F	FM12 + B22FM	129 348
Elbasha 2007	CIN, CC, GW	70%	90%	Lifelong	290	F12	FM12	Dom
	CIN, CC, GW	70% (50%CU)	90%	Lifelong	290	F12+CU12–24F	FM12+CU12–24F	33 712
	CIN, CC, GW	70% (50%CU)	90%	Lifelong	290	F18+CU18–24F	FM18+CU18–24FM	Dom
	CIN, CC, GW	70% (50%CU)	90%	Lifelong	290	F18+CU18–24F	FM15+CU15–24FM	Dom
	CIN, CC, GW	70% (50%CU)	90%	Lifelong	290	F12+CU12–24F	FM12+CU12–24FM	34 433
	CIN, CC, GW	70% (50%CU)	90%	Lifelong	242	F12+CU12–24F	FM12+CU12–24F	26 991
	CIN, CC, GW	70% (50%CU)	90%	Lifelong	403	F12+CU12–24F	FM12+CU12–24F	49 395
	CIN, CC, GW	70% (50%CU)	90%	10 y	290	F12+CU12–24F	FM12+CU12–24F	44 157
	CIN, CC, GW	70% (50%CU)	100%	Lifelong	290	F12+CU12–24F	FM12+CU12–24F	Dom
	CIN, CC, GW	70% (50%CU)	74%	Lifelong	290	F12+CU12–24F	FM12+CU12–24F	32 250
	CIN, CC, GW	50%	90%	Lifelong	290	F12+CU12–24F	FM12+CU12–24F	19 244
	CIN, CC, GW	90%	90%	Lifelong	290	F12+CU12–24F	FM12+CU12–24F	Dom
	CIN, CC, GW	70% (50%CU)	90%	Lifelong	290	FM12+CU12–24F	FM12+CU12–24FM	36 335
	CIN, CC, GW	70% (50%CU)	90%	Lifelong	242	FM12+CU12–24F	FM12+CU12–24FM	29 162
	CIN, CC, GW	70% (50%CU)	90%	Lifelong	403	FM12+CU12–24F	FM12+CU12–24FM	53 073
	CIN, CC, GW	70% (50%CU)	90%	10 y	290	FM12+CU12–24F	FM12+CU12–24FM	44 297
	CIN, CC, GW	70% (50%CU)	100%	Lifelong	290	F12+CU12–24F	FM12+CU12–24F	Dom
	CIN, CC, GW	70% (50%CU)	100%	Lifelong	290	FM12+CU12–24F	FM12+CU12–24FM	41 481
	CIN, CC, GW	70% (50%CU)	74%	Lifelong	290	FM12+CU12–24F	FM12+CU12–24FM	35 427
	CIN, CC, GW	50%	90%	Lifelong	290	FM12+CU12–24F	FM12+CU12–24FM	29 222
	CIN, CC, GW	90%	90%	Lifelong	290	FM12+CU12–24F	FM12+CU12–24FM	80 982
Kulasingam 2007	CIN, CC	80%	100%	Lifelong	212	No vaccination	FM12	20 640
	CIN, CC	80%	84%	Lifelong	212	No vaccination	FM12	22 650
	CIN, CC	80%	100%	10 y	212	No vaccination	FM12	64 214
	CIN, CC	80%	84%	10 y	212	No vaccination	FM12	66 120
	CIN, CC	70%	100%	Lifelong	212	No vaccination	FM12	17 962
	CIN, CC	70%	84%	Lifelong	212	No vaccination	FM12	21 092
	CIN, CC	90%	100%	Lifelong	212	No vaccination	FM12	23 621
	CIN, CC	90%	84%	Lifelong	212	No vaccination	FM12	24 551
Jit 2008	CIN, CC, GW	80%	100%	Lifelong	310	F12	FM12	765 081

	CIN, CC, GW	80%	100%	10 y	310	F12	FM12	167 421
	CIN, CC, GW	80%	100%	20 y	310	F12	FM12	254 253
Zechmeister 2009	CIN, CC	65%	90%	10 y+booster	330+110	F12+B22F	FM12+B22FM	311 000
Olsen 2010	CIN, CC, GW	70%	100%	-	415	no vaccination	FM12	18 677
Elbasha 2010	CIN, CC, VA, VU, GW, PEN, H&N, ANA, RRP	90% @age26	90%	Lifelong	272	F9–26	FM9–26	17 459
	CIN, CC, VA, VU, GW, H&N, ANA, RRP	90% @age26	90%	Lifelong	272	F9–26	FM9–26	18 715
	CIN, CC, VA, VU, GW, ANA, RRP	90% @age26	90%	Lifelong	272	F9–26	FM9–26	31 958
	CIN, CC, VA, VU, GW, RRP	90% @age26	90%	Lifelong	272	F9–26	FM9–26	42 376
	CIN, CC, VA, VU, GW	90% @age26	90%	Lifelong	272	F9–26	FM9–26	46 965
	CIN, CC, VA, VU	90% @age26	90%	Lifelong	272	F9–26	FM9–26	121 706
	CIN, CC	90% @age26	90%	Lifelong	272	F9–26	FM9–26	13 ,872
Laprise 2014	CC, VU, VA, ANA, PEN, ORPH, GW	80%	95%	Lifelong	186	F9+CU14F	FM9+CU14F	121 971
	CC, VU, VA, ANA, PEN, ORPH, GW	50%	95%	Lifelong	186	F9+CU14F	FM9+CU14F	50 300
	CC, VU, VA, ANA, PEN, ORPH, GW	80%	95%	20 y	186	F9+CU14F	FM9+CU14F	86 861
	CC, VU, VA, ANA, PEN, ORPH, GW	80%	95%	25 y	186	F9+CU14F	FM9+CU14F	124 307
	CC, VU, VA, ANA, PEN, ORPH, GW	50%	95%	25 y	186	F9+CU14F	FM9+CU14F	51 782
	CC, VU, VA, ANA, PEN, ORPH, GW	80%	95%	35 y	186	F9+CU14F	FM9+CU14F	134 599
	CC, VU, VA, ANA, PEN, ORPH, GW	80%	95% (2d)	20 y	124	F9+CU14F	FM9+CU14F	62 920
	CC, VU, VA, ANA, PEN, ORPH, GW	50%	95% (2d)	20 y	124	F9+CU14F	FM9+CU14F	40 446
	CC, VU, VA, ANA, PEN, ORPH, GW	50%	95% (2d)	25 y	124	F9+CU14F	FM9+CU14F	49 647
	CC, VU, VA, ANA, PEN, ORPH, GW	50%	95% (2d)	30 y	124	F9+CU14F	FM9+CU14F	38 450
	CC, VU, VA, ANA, PEN, ORPH, GW	80%	95% (2d)	30 y	124	F9+CU14F	FM9+CU14F	98 869
Pearson 2014	CIN, CC, VU, ANA, ORPH, GW	56%/45%	99%	20 y	193	No vaccination	FM12	23 352
	CIN, CC, VU, ANA, ORPH, GW	73%	99%	20 y	193	No vaccination	FM12	31 023
	CIN, CC, VU, ANA, ORPH, GW	56%/45%	99%	20 y	193	F12	FM12	67 045
	CIN, CC, VU, ANA, ORPH, GW	56%/45% vs 73%	99%	20 y	193	F12 (56%/45%)	FM12 (73%)	84 091
	CIN, CC, VU, ANA, ORPH, GW	73%	99%	20 y	193	F12	FM12	140 341
	CIN, CC, VU, ANA, ORPH, GW	56%/45%	99%	Lifelong	193	F12	FM12	63 068
	CIN, CC, VU, ANA, ORPH, GW	73%	99%	Lifelong	193	F12	FM12	132 955
	CIN, CC, VU, ANA, ORPH, GW	56%/45%	99%	Lifelong	95	F12	FM12	46 193
	CIN, CC, VU, ANA, ORPH, GW	73%	99%	Lifelong	95	F12	FM12	98 295
	CIN, CC, VU, ANA, ORPH, GW	56%/45%	99%	Lifelong	13	F12	FM12	31 420
	CIN, CC, VU, ANA, ORPH, GW	73%	99%	Lifelong	13	F12	FM12	68 750
Bresse 2014	CIN, CC	65%	F 76-100%/M 41-96%	Lifelong	330	No vaccination	FM9	26 701
	CIN, CC, VA	65%	F 76-100%/M 41-96%	Lifelong	330	No vaccination	FM9	26 279
	CIN, CC, VA, VU	65%	F 76-100%/M 41-96%	Lifelong	330	No vaccination	FM9	25 567
	CIN, CC, VA, VU, GW	65%	F 76-100%/M 41-96%	Lifelong	330	No vaccination	FM9	15 820
	CIN, CC, VU, VA, GW, ANA	65%	F 76-100%/M 41-96%	Lifelong	330	No vaccination	FM9	13 850
	CIN, CC, VU, VA, GW, ANA, ORPH	65%	F 76-100%/M 41-96%	Lifelong	330	No vaccination	FM9	10 136
	CIN, CC, VU, VA, GW, ANA, ORPH, PEN	65%	F 76-100%/M 41-96%	Lifelong	330	No vaccination	FM9	10 033
	CIN, CC, VU, VA, GW, ANA, ORPH, PEN	65%	F 76-100%/M 41-96%	20y	330	No vaccination	FM9	19 590

	CIN, CC, VU, VA, GW, ANA, ORPH, PEN	65%	F 76-100%/M 41-96%	Lifelong	281	No vaccination	FM9	8 202
	CIN, CC, VU, VA, GW, ANA, ORPH, PEN	65%	F 76-100%/M 41-96%	Lifelong	380	No vaccination	FM9	11 787
	CIN, CC, VU, VA, GW, ANA, ORPH, PEN	80%	F 76-100%/M 41-96%	Lifelong	330	No vaccination	FM9	9 982
	CIN, CC, VU, VA, GW, ANA, ORPH, PEN	50%	F 76-100%/M 41-96%	Lifelong	330	No vaccination	FM9	11 351
Blakely 2014	CIN, CC, VU, ANA, ORPH, GW	56%/45%	100%	Lifelong	193	No vaccination	FM12	10 682
	CIN, CC, VU, ANA, ORPH, GW	73%	100%	Lifelong	193	No vaccination	FM12	12 841
	CIN, CC, VU, ANA, ORPH, GW	93%	100%	Lifelong	193	No vaccination	FM12	17 614
	CIN, CC, VU, ANA, ORPH, GW	56%/45% vs 73%	100%	Lifelong	193	FM12 (56%/45%)	FM12 (73%)	19 716
	CIN, CC, VU, ANA, ORPH, GW	73% vs 93%	100%	Lifelong	193	FM12 (73%)	FM12 (93%)	69 602
Haeussler 2015	CIN, CC, VA, VaIN, VU, VIN, ANA, PEN, PeIN, H&N, GW	90%	CC 78%/ANA 70%/H&N 50%	Lifelong	168	F12	FM12	11 600
Jiménez 2015	CIN, CC, VU, GW	82%		Lifelong	400	F12	FM12	214 051
	CIN, CC, VU, GW	82%		Lifelong	90	F12	FM12	42 102
	CIN, CC, VU, GW	82%		Lifelong	179	F12	FM12	91 616
	CIN, CC, VU, GW	82%		Lifelong	269	F12	FM12	141 939
	CIN, CC, VU (2-valent)	82%		Lifelong	400	F12	FM12	449 145
	CIN, CC, VU, GW	F92%/M82%		Lifelong	400	F12 (92%)	F (82%) M (82%) 12	456 351
	CIN, CC, VU, GW, VA, ANA	82%		Lifelong	400	F12	FM12	184 040
Olsen 2015	CIN, CC, VA, VU, ANA, PEN, H&N, GW	85%	100%	Lifelong	369	F12	FM12	41 636
	CIN, CC, VA, VU, ANA, PEN, H&N, GW	85%	100%	Lifelong	277	F12	FM12	31 432
	CIN, CC, VA, VU, ANA, PEN, H&N, GW	85%	100% (2d)	Lifelong	246	F12	FM12	28 031
	CIN, CC, VA, VU, ANA, PEN, H&N, GW (time horizon 40 y)	85%	100%	Lifelong	369	F12	FM12	47 342
	CIN, CC, VA, VU, ANA, PEN, H&N, GW	70%	100%	Lifelong	369	F12	FM12	31 615
	CIN, CC, VA, VU, ANA, PEN, GW	85%	100%	Lifelong	369	F12	FM12	276 642
Qendri 2017	CC, VU, VA, ANA, PEN, ORPH	F60%/40%M	98% (2d)	Lifelong	34	F12	FM12	9 134
	CC, VU, VA, ANA, PEN, ORPH	F70%/40%M	98% (2d)	Lifelong	34	F12	FM12	13 083
	CC, VU, VA, ANA, PEN, ORPH	F80%/40%M	98% (2d)	Lifelong	34	F12	FM12	20 631
	CC, VU, VA, ANA, PEN, ORPH	F90%/40%M	98% (2d)	Lifelong	34	F12	FM12	36 363
	CC, VU, VA, ANA, PEN, ORPH	F60%/50%M	98% (2d)	Lifelong	34	F12	FM12	9 935
	CC, VU, VA, ANA, PEN, ORPH	F60%/60%M	98% (2d)	Lifelong	34	F12	FM12	9 412
Damm 2017	CIN, CC, GW	50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4%	20 y	450	F12	FM12	117 240
	CIN, CC, GW	50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4% (2d)	20 y	300	F12	FM12	73 973

	CIN, CC (2-valent)	50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4	20 y	450	F12	FM12	130 449
	CIN, CC (2-valent)	50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4% (2d)	20 y	300	F12	FM12	83 602
	CIN, CC, GW	F20%/M50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4%	20 y	450	F12	FM12	46 965
	CIN, CC, GW	F20%/M50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4% (2d)	20 y	300	F12	FM12	26 478
	CIN, CC (2-valent)	F20%/M50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4%	20 y	450	F12	FM12	60 682
	CIN, CC (2-valent)	F20%/M50%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4% (2d)	20 y	300	F12	FM12	37 066
	CIN, CC, GW	F20%/M80%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4%	20 y	450	F12	FM12	61 027
	CIN, CC, GW	F20%/M80%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4% (2d)	20 y	300	F12	FM12	36 033
	CIN, CC (2-valent)	F20%/M80%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4%	20 y	450	F12	FM12	74 844
	CIN, CC (2-valent)	F20%/M80%	HPV16/18 F 98% HPV6/11 F 100% HPV16/18/6/11 M 90.4% (2d)	20 y	300	F12	FM12	46 525
Largeron 2017	CIN, CC, VA, VU, ANA, GW	55.6%	F 76-100%/M 41-96% (2d)	Lifelong	280 vs 293	F9-14+CU15-17 (4v)	FM9-14+CU15-17 (9v)	22 987
	CIN, CC, VA, VU, ANA, GW	55.6%	F 76-100%/M 41-96% (2d)	20 y	280 vs 293	F9-14+CU15-17 (4v)	FM9-14+CU15-17 (9v)	14 827
	CIN, CC, VA, VU, ANA, GW	70%	F 76-100%/M 41-96% (2d)	Lifelong	280 vs 293	F9-14+CU15-17 (4v)	FM9-14+CU15-17 (9v)	27 986
	CIN, CC, VA, VU, ANA, GW, PEN, H&N, RRP	55.6%	F 76-100%/M 41-96% (2d)	Lifelong	280 vs 293	F9-14+CU15-17 (4v)	FM9-14+CU15-17 (9v)	14 286
Mennini 2017	CIN, CC, VaIN, VA, VU, ANA, GW	71%	F 76-100%/M 41-96% (2d)	Lifelong	208 vs 240	F12 (4v)	FM12 (9v)	13 541

	CIN, CC, VaIN, VA, VU, ANA, GW	60%	F 76-100%/M 41-96% (2d)	Lifelong	208 vs 240	F12 (4v)	FM12 (9v)	11 376
	CIN, CC, VaIN, VA, VU, ANA, GW	71%	F 76-100%/M 41-96% (2d)	20 y	208 vs 240	F12 (4v)	FM12 (9v)	20 845
	CIN, CC, VaIN, VA, VU, ANA, GW, PEN, H&N, RRP	71%	F 76-100%/M 41-96% (2d)	Lifelong	208 vs 240	F12 (4v)	FM12 (9v)	7 165

**: Vaccination coverages separated by / means two different coverages where used in the study referring to two separate populations. When numbers are separated by 'vs', two different coverages were compared in different scenarios.*

***: Vaccine cost separated by '+' means cost of initial vaccination (three) doses plus cost of booster dose.*

Abbreviations

Health outcomes: cervical cancer (CC), cervical intraepithelial neoplasia (CIN), genital warts (GW), vaginal cancer (VA), vulvar cancer (VU), anal cancer (ANA), penile cancer (PEN), oropharingeal cancer (ORPH), head and neck cancer (H&N), recurrent respiratory papillomatosis (RRP)

Sex: females (F), women (W), males (M)

Other: years (y), at (@), dose/s (d), catch-up (CU), booster (B)

1729 # Annex 2. Supplementary material

Code	File	Description
Supp01	Supp01_PICOs_males_efficacy.xlsx	Efficacy of HPV vaccines in males PICO1: Three doses of 4-valent HPV vaccine in 16–23-year-old males versus three doses of placebo in 16–26-year-old males – efficacy outcomes (for HPV 6, 11, 16, 18) PICO2: Three doses of 4-valent HPV vaccine in 16–26-year-old MSM versus three doses of placebo in 16–26-year-old MSM – efficacy outcomes (for HPV 6, 11, 16, 18) PICO3: Three doses of 4-valent HPV vaccine in >=27-year-old HIV-negative MSM versus no treatment in >=27-year-old HIV-negative MSM – efficacy outcomes (any HPV)
Supp02	Supp02_PICOs_males_immunogenicity.xlsx	Immunogenicity of HPV vaccines for boys/men PICO1: Three doses of 9-valent HPV vaccine in 9–15-year-old males versus three doses of 9-valent HPV vaccine in 16–26-year-old females – immunogenicity outcomes (month 7) PICO2: Two doses (0, 6 months) of 9-valent HPV vaccine in 9–14-year-old males versus three doses of 9-valent HPV vaccine in 16–26-year-old females – immunogenicity outcomes (month 7 or 4 weeks after last dose of vaccine) PICO3: Three doses of 9-valent HPV vaccine versus three doses of 4-valent HPV vaccine in 16–26-year-old males -iImmunogenicity outcomes (month 7) PICO4: Three doses of 9-valent HPV vaccine in 16–26-year-old males versus three doses of 9-valent HPV vaccine in 16–26-year-old females – immunogenicity outcomes (month 7) PICO5: Three doses of 4-valent HPV vaccine in 10 to 15-year-old males versus three doses of 4-valent HPV vaccine in 16–23-year-old females – immunogenicity outcomes (month 7) PICO6: Three doses of 4-valent HPV vaccine in –915-year-old males versus three doses of 4-valent HPV in 9–15-year-old females – immunogenicity outcomes (month 7) PICO7: Three doses of 4-valent HPV vaccine in 9–15-year-old males versus three doses of 4-valent HPV in 9–15-year-old females – immunogenicity outcomes (month 18) PICO8: Three doses of 4-valent HPV vaccine in 9–15-year-old males versus three doses of 4-valent HPV in 9–15-year-old females – immunogenicity outcomes (month 96) PICO9: Three doses (0, 2, 12 months) of 4-valent HPV vaccine versus three doses (0, 2, 6 months) of 4-valent HPV vaccine in 18–25-year-old males – immunogenicity outcomes (month 7) PICO10: Three doses of 4-valent HPV vaccine in 2745-year-old males – immunogenicity outcomes (month 7) PICO11: Three doses of 2-valent HPV vaccine in 12–15-year-old males – immunogenicity outcomes (months 7 and 42) PICO12: Three doses of 9-valent HPV vaccine in 16–26-year-old MSM versus three doses of 9-valent HPV vaccine in 16–26-year-old females – immunogenicity outcomes (month 7) PICO13: Three doses of 9-valent HPV vaccine in 16–26-year-old MSM versus three doses of 9-valent HPV vaccine in 16–26-year-old heterosexual males – immunogenicity outcomes (month 7) PICO14: Three doses of 4-valent HPV vaccine in 16–26-year-old MSM versus three doses of 4-valent HPV vaccine in 16–23-year-old heterosexual males – immunogenicity outcomes (month 7) PICO15: Three doses of 4-valent HPV vaccine in 16–26-year-old MSM versus three doses of 4-valent HPV vaccine in 16–23-year-old heterosexual males – immunogenicity outcomes (month 36) PICO16: Three doses of 2-valent HPV vaccine in 10–18-year-old males versus three doses of 2-valent HPV vaccine in 15–25-year-old females – immunogenicity outcomes (month 7)
Supp03	Supp03_PICOs_males_safety.xlsx	Safety and tolerability of the HPV vaccines in males PICO1: Three doses of 9-valent HPV vaccine in 9–1year-old males versus three doses of 9-valent HPV vaccine in 16–26-year-old females – safety outcomes PICO2: Two doses (0, 6 months) of 9-valent HPV vaccine in 9–14-year-old males versus three doses of 9-valent HPV vaccine in 16–26-year-old females – safety outcomes

		PICO3: Three doses of 9-valent HPV vaccine versus three doses of 4-valent HPV vaccine in 16–26-year-old males - safety outcomes PICO4: Three doses of 9-valent HPV vaccine in 16–26-year-old males versus three doses of 9-valent HPV vaccine in 16–26-year-old females – safety outcomes PICO5: Three doses of 4-valent HPV vaccine in 10–15-year-old males versus three doses of 4-valent HPV vaccine (3 doses) in 16–23-year-old females – safety outcomes PICO6: Three doses of 4-valent HPV vaccine versus placebo in 9–15-year-old females and males – safety outcomes PICO7: Three doses of 4-valent HPV vaccine versus three doses of placebo vaccine in 16–26-year-old males – safety outcomes PICO8: Three doses of 4-valent HPV vaccine in 27–45-year-old males – safety outcomes PICO9: Three doses of 2-valent HPV vaccine in 12–15-year-old males versus three doses of HBV vaccine in 12–15-year-old males – safety outcomes PICO10: Three doses of 4-valent HPV vaccine in 16–26-year-old MSM versus three doses of placebo vaccine in 16–26-year-old MSM – Safety outcomes PICO11: Three doses of 2-valent HPV vaccine versus three doses of HBV vaccine in 10–18-year-old males – safety outcomes
Supp04	Supp04_PICOs_9vHPV_efficacy.xlsx	Efficacy of the 9-valent HPV vaccine PICO1: Three doses of 9-valent HPV vaccine versus three doses of 4-valent HPV vaccine in 16–26-year-old females - efficacy outcomes (for HPV types 31, 33, 45, 52, 58) PICO2: Three doses of 9-valent HPV vaccine versus three doses of placebo in 16–26-year-old females - efficacy outcomes (for HPV types 6, 11, 16, 18)
Supp05	Supp05_PICOs_9vHPV_immunogenicity.xlsx	Immunogenicity of the 9-valent HPV vaccine PICO1: Three doses of 9-valent HPV vaccine versus three doses of 4-valent HPV vaccine in 9–15-year-old females - immunogenicity outcomes (month 7) PICO2: Three doses of 9-valent HPV vaccine in 9 to 15-year old females versus three doses of 9-valent HPV vaccine in 16–26-year-old females – immunogenicity outcomes (month 7) PICO3: Two doses (0, 6 months) of 9-valent HPV vaccine in 9–14-year-old females versus three doses of 9-valent HPV vaccine in 16–26-year-old females – immunogenicity outcomes (month 7 or 4 weeks after last dose of vaccine) PICO4: Two doses (0, 12 months) of 9-valent HPV vaccine in 9–14-year-old females and males versus three doses of 9-valent HPV vaccine in 16–26-year-old females – immunogenicity outcomes (month 7 or 4 weeks after last dose of vaccine) PICO5: Three doses of 9-valent HPV vaccine versus three doses of 4-valent HPV vaccine in 16–26-year-old females – immunogenicity outcomes (month 7) PICO6: Three doses of 9-valent HPV vaccine versus three doses of 4-valent HPV vaccine in females 16–26 years – immunogenicity outcomes (month 42) PICO7: Three doses of 9-valent HPV vaccine versus placebo in 12–26-year-old females previously vaccinated with 4-valent HPV (3 doses) - immunogenicity outcomes (month 7) PICO8: Three doses of 9-valent HPV vaccine in males 9–15 years versus three doses of 9-valent HPV vaccine in 16–26-year-old females – immunogenicity outcomes (month 7) PICO9: Two doses (0, 6 months) of 9-valent HPV vaccine in 9–14-year-old males versus three doses of 9-valent HPV vaccine in 16–26-year-old females – immunogenicity outcomes (month 7 or 4 weeks after last dose of vaccine) PICO10: Three doses of 9-valent HPV vaccine versus three doses of 4-valent HPV vaccine in 16–26-year-old males - immunogenicity outcomes (month 7) PICO11: Three doses of 9-valent HPV vaccine in 16–26-year-old heterosexual males versus three doses of 9-valent HPV vaccine in 16–26-year-old females – immunogenicity outcomes (month 7)
Supp06	Supp06_PICOs_9vHPV_safety.xlsx	Safety and tolerability of the 9-valent HPV vaccine PICO1: Three doses of 9-valent HPV vaccine versus three doses of 4-valent HPV vaccine in 9–15-year-old females – safety outcomes PICO2: Three doses of 9-valent HPV vaccine in 9–15-year-old females versus three doses of 9-valent HPV vaccine in 16–26-year-old females – safety outcomes

		PICO3: Two doses (0, 6 months) of 9-valent HPV vaccine in 9– 14-year-old females versus three doses of 9-valent HPV vaccine in 16–26-year-old females – safety outcomes PICO4: Two doses (0, 12 months) of 9-valent HPV vaccine in 9 to 14-year old females and males versus three doses of 9-valent HPV vaccine in 16–26-year-old females – safety outcomesPICO5: Three doses of 9-valent HPV vaccine versus three doses of 4-valent HPV vaccine in 16–26-year-old females – safety outcomes PICO6: Three doses of 9-valent HPV vaccine versus placebo in 12–26-year-old females previously vaccinated with 4-valent HPV (3 doses) – safety outcomes PICO7: Three doses of 9-valent HPV vaccine in males 9–15 years versus three doses of 9-valent HPV vaccine in females 16–26 years – safety outcomes PICO8: Two doses (0, 6 months) of 9-valent HPV vaccine in 9– 14-year-old males versus three doses of 9-valent HPV vaccine in 16–26-year-old females – safety outcomes PICO9: Three doses of 9-valent HPV vaccine versus three doses of 4-valent HPV vaccine in 16–26-year-old males - safety outcomes PICO10: Three doses of 9-valent HPV vaccine in 16–26 years heterosexual males versus three doses of 9-valent HPV vaccine in 16–26-year-old females – safety outcomes
Supp07	Supp07_PICOs_HIV_immunogenicity.xlsx	Immunogenicity of the HPV vaccine in HIV-infected men and women PICO1: Three doses of 4-valent HPV vaccine versus placebo in 7–12-year-old HIV-infected children - immunogenicity outcomes (months 7–24) PICO2: Three doses of 2-valent HPV vaccine in 18– 25-year-old HIV infected females versus three doses of 2-valent HPV vaccine in 18–25-year-old females – immunogenicity outcomes (month 7) PICO3: Three doses of 2-valent HPV vaccine in HIV infected adults (>=18 years old) versus three doses of 4-valent HPV vaccine in HIV infected adults (>=18 years old) – immunogenicity outcomes (months 7–12) PICO4: Three doses of 4-valent HPV vaccine in HIV infected males >18 years old – immunogenicity outcomes (month 7)
Supp08	Supp08_PICOs_HIV_safety.xlsx	Safety of the HPV vaccine in HIV-infected men and women PICO1: Three doses of 4-valent HPV vaccine versus placebo vaccine in 7–12year-old HIV-infected children - safety outcomes PICO2: Three doses of 2-valent HPV vaccine in 18–25-year-old HIV-infected females versus placebo (3 doses) in HIV infected females 18–25-year-old– Safety outcomes PICO3: Three doses of 2-valent HPV vaccine in HIV infected adults (>=18 years old) versus three doses of 4-valent HPV vaccine in HIV infected adults (>=18 years old) – safety outcomes PICO4: Three doses of 4-valent HPV vaccine in HIV infected 16–23-yearld HIV infected females – safety outcomes PICO5: Three doses of 4-valent HPV vaccine in HIV infected males >18 years old – safety outcomes

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