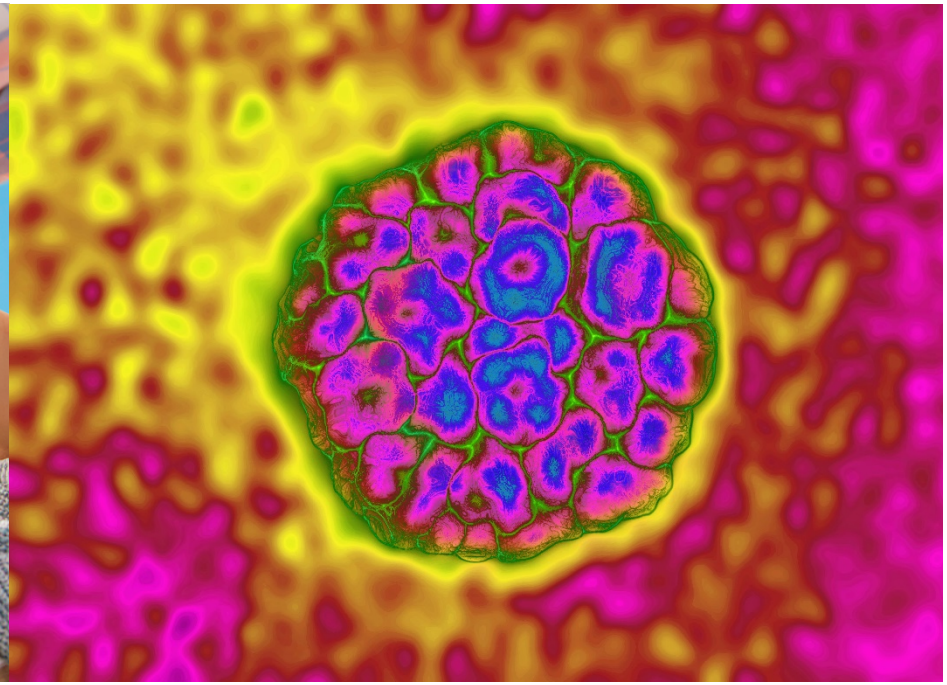
KCE REPORT 308

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

COST-EFFECTIVENESS ANALYSIS OF HPV VACCINATION OF BOYS IN BELGIUM



KCE REPORT 308
HEALTH TECHNOLOGY ASSESSMENT

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- **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.**
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- **Finally, this report has been approved by common assent by the Executive Board.**
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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AGW	Anogenital warts
AIN	Anal intra-epithelial neoplasia
AZG	Agentschap Zorg en Gezondheid
CEA	Cost-effectiveness analysis
CI	Confidence interval
CIN	Cervical intra-epithelial neoplasia
CLB	Centra voor Leerlingen Begeleiding
CPI	Consumer price index
CRPS	Complex regional pain syndrome
CUA	Cost-utility analysis
DMC	Direct medical costs
EMA	European Medicine Agency
EPAR	European public assessment report
FWB	Fédération Wallonie-Bruxelles
GBS	Guillain-barre syndrome
GP	General practitioner
GW	Genital warts
HCP	Health care payer
HCSP	Haut Conseil de la Santé Publique, France
HPV	Human papilloma virus
HPV2	Bivalent HPV vaccine, Cervarix®
HPV4	Quadrivalent HPV vaccine, Gardasil®

HPV9	Nonavalent HPV vaccine, Gardasil 9®
IBM	Individual based model
ICER	Incremental cost-effectiveness ratio
MSM	Men having sex with men
NHS	National health system
NICE	National Institute of Health and Clinical Excellence
NIHDI	National Institute for Health and Disability Insurance (INAMI/RIZIV)
OECD	Organisation for Economic Cooperation and Development
ONE	Office de la Naissance et de l'Enfance
OPC	Oropharyngeal cancer
PIN	Penile intra-epithelial neoplasia
POTS	Postural orthostatic tachycardia syndrome
PPP	Purchasing power parities
PSE	Services de Promotion de la Santé à l'École"
QALY	Quality-adjusted life-year
RR	Risk reduction
RRP	Recurrent respiratory papillomatosis
SHC	Superior Health Council (CSS/HGR)
VaIN	Vaginal intraepithelial neoplasia
VG	Vlaamse Gemeenschap
VIN	Vulvar intraepithelial neoplasia

SCIENTIFIC REPORT

1 BACKGROUND

1.1 HPV infection and disease

The human papillomavirus (HPV) is spread through sexual and oral contacts, i.e. through contact with infected genital skin, mucous membranes, and bodily fluids. More than 80% of sexually active individuals will acquire one or more anogenital HPV infections during their lifetime.[1] The majority of HPV infections do not cause symptoms and are transient, i.e. they clear spontaneously within a few years.[2] Only a small proportion of infected persons (around 10%) develop persistent infection, i.e. lasting 6 months or more.[2] The prevalence of HPV infection, which is around 10-15% among women in European countries, is highest in young and sexually active persons, and is associated with the number of sexual partners in both genders.[2]

The 30 to 40 HPV genotypes that infect the anogenital tract fall into two groups, depending on their oncogenic potential: the “low-risk” types that may cause genital warts, and the “high-risk” types that may cause anogenital and oropharyngeal cancers.[3] There are around 12 high-risk types according to the International Agency for Research on Cancer.[2, 4] Co-infection with different HPV types and subsequent infections are common. Persistent infection with high-risk HPV types may lead to precancerous lesions at the site of infection in a small percentage of persons, which depend on the HPV type involved and host factors. Most precancerous lesions cure spontaneously after a few years, but a small proportion may progress into cancer, if left untreated.[4, 5] The period between infection and development of cancer takes usually 20 years or longer.[2] HPV causes a variable proportion of the following cancers in women and men: cervix, vulva, vagina, penis, anus, and oropharynx. The high-risk types HPV-16 and 18, which are included in all HPV vaccines, are the most frequently involved in these cancers. Infection with low risk HPV types, in particular HPV-6 and 11, may cause anogenital warts, which occur on average 6-12 months after infection and are thus the first and most common clinical manifestation of HPV infection. Some low risk HPV types are also responsible for a rare condition called recurrent respiratory papillomatosis, which causes lesions in the respiratory tract with the risk of airway obstruction.

While the HPV burden continuous to predominate in women, a substantial burden is nowadays recognised in males. In men, HPV is responsible for a proportion of anal, oropharyngeal and penile cancers, and also causes anogenital warts.[6] Men who have sex with men (MSM) are disproportionately affected by HPV, resulting in higher rates of anal, penile and oropharyngeal cancers in this group.[7, 8]

1.2 The HPV vaccines

Three vaccines are currently authorised by the European Medicines Agency (EMA) for the prevention of a number of HPV-related diseases. These vaccines do not provide protection against all HPV-related cancers but against a number of specific pathogenic HPV types that are included in each vaccine, or "vaccine types". The types included and the other characteristics of their authorisation by the EMA are described in Table 1, according to the European public assessment reports (EPAR) of each vaccine.[9-11]

Gardasil and Cervarix were initially indicated for girls only, in 2006 and 2007, respectively. Gardasil has been authorised for males since 2011 to prevent genital warts and since 2014 to prevent anal cancers. Cervarix has been authorised in males since 2016 for the prevention of anal cancers. Gardasil 9 was directly approved for both genders and to prevent anal cancers at its initial authorisation in 2015.

All three vaccines are authorised for the prevention of cervical cancer, as well as for the prevention of precancerous lesions of the cervix, vulva, vagina and anus. Only Gardasil and Gardasil 9 are indicated to prevent genital warts. Gardasil 9 is the only vaccine that has been approved to prevent vaginal and vulvar cancers. However, Cervarix and Gardasil are approved for the prevention of precancerous lesions of the vagina and vulva.

The authorisation from the USA Food and Drug Administration differs from the EMA one for Cervarix, which is, in the USA, only indicated in female - and not in males as in the EU (EMA).[a] Gardasil and Gardasil 9 are both indicated for use in female and male in the USA.[b, c]

The prevention of penile and oropharyngeal cancers, as well as recurrent respiratory papillomatosis, has not been requested to the EMA as indication for any of the HPV vaccines, probably due to the lack of evidence available so far. However, many countries and the international literature consider that HPV vaccines may protect against these diseases.[12-14]

All three vaccines can be administered at a 2-dose schedule given at least 5-6 months apart from 9 up to 13 or 14 years of age (detailed by vaccine, Table 1) and a 3-dose schedule is recommended above that age. If the second dose is given earlier than six months after the first dose, a third dose should always be given for Gardasil and Gardasil 9. The 3-dose schedule can also be used in individuals aged 9 to 13 years.

HPV vaccines protect vaccinated individuals but may also have an effect on unvaccinated persons, if the vaccination programme reaches a sufficient level of uptake. This is called the indirect or herd effect and is due to the decreased level of HPV infection among vaccinated persons, and thereby a decreased transmission of HPV viruses to their contacts, including those that are unvaccinated.[15] Data on the herd effect are described in section 6.

For each vaccine we provide a more detailed description below of the indications and immunisation schedules as stated in the last versions of the EPARs (as of 11/2018).

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a https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm186957.htm

b https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm094042.htm

c https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm426445.htm

Table 1 – HPV vaccines registered by the European Medicine Agency

Vaccine name	Producer	Types included		Date of first EU authorisation	Indication: for the prevention of	Administration schedule	
Cervarix® **Or HPV2**	GSK	2-valent	16, 18	20/09/2007	In males and females ≥ 9 years for: • Precancerous lesions cervix, vulva, vagina and anus • Cancers cervix and anus	9-14 years: 15+ years :	2 doses (0, 5-13 m) 3 doses (0, 1, 6 m)
Gardasil® **Or HPV4**	Sanofi Pasteur MSD	4-valent	6, 11, 16, 18	20/09/2006	In males and females ≥ 9 years for: • Precancerous lesions cervix, vulva, vagina and anus • Cancers cervix and anus • Genital warts	9-13 years: 14+ years:	2 doses (0, 6 m) 3 doses (0, 2, 6 m)† 3 doses (0, 2, 6 m)
Gardasil 9® **Or HPV9**	Sanofi Pasteur MSD	9-valent	6, 11, 16, 18, 31, 33, 45, 52, 58	10/06/2015	In males and females ≥ 9 years for: • Precancerous lesions cervix, vulva, vagina and anus • Cancers cervix, vulva, vagina and anus • Genital warts	9-14 years: 15+ years:	2 doses (0, 5-13 m) 3 doses (0, 2, 6 m)† 3 doses (0, 2, 6 m)

European public assessment reports (EPARs) available from: http://www.ema.europa.eu (Accessed 08/11/2018). The EPARs consulted were last updated on 26/06/2018 (Cervarix), 27/06/2018 (Gardasil) and 23/08/2018 (Gardasil 9). † Alternative posology proposed in the EPAR.

1.2.1 Cervarix

The European Commission granted a marketing authorisation valid throughout the European Union for Cervarix on 20 September 2007. Cervarix is a vaccine for use in males and females from the age of 9 years for the prevention of:

- Premalignant anogenital lesions (cervical, vulvar, vaginal and anal);
- Cervical and anal cancers causally related to certain oncogenic HPV types.

People aged 9 to 14 years can be given two doses, six months apart. If necessary, the second dose can be given between 5 and 13 months after the first dose. People aged 15 and above are given three doses. It is recommended that there is one month between the first and second doses, and five months between the second and third doses. However, the second and third doses can be given after longer gaps if necessary.

1.2.2 Gardasil

The European Commission granted a marketing authorisation valid throughout the European Union for Gardasil on 20 September 2006. Gardasil is used in males and females from the age of 9 years for the prevention of:

- Premalignant anogenital lesions (cervical, vulvar, vaginal and anal);
- Cervical and anal cancers causally related to certain oncogenic HPV types;
- Genital warts (Condylomata acuminata) causally related to specific HPV types.

For people aged 9 to 13 years, Gardasil can be given as two doses six months apart. If the second dose is given earlier than six months after the first dose, a third dose should always be given. For people aged 14 or above, Gardasil is normally given according to a three-dose schedule with the second dose given two months after the first and the third given four months after the second. These same three doses can also be used in individuals aged nine to thirteen years.

1.2.3 Gardasil 9

The European Commission granted a marketing authorisation valid throughout the European Union for Gardasil 9 on 10 June 2015. Gardasil 9 is indicated for active immunisation of individuals from the age of 9 years against the following HPV diseases:

- Premalignant lesions and cancers affecting the cervix, vulva, vagina and anus caused by vaccine HPV types;
- Genital warts (Condylomata acuminata) caused by specific HPV types.

Gardasil 9 is normally given according to a either a two-dose schedule or a three-dose schedule for males and females from 9 to 14 years old and a three-dose schedule for males and females 15 years old and over. For a two-dose schedule, the second dose should be given between five and thirteen months after the first dose. For a three-dose schedule, the second dose should be given two months after the first and the third given four months after the second. There should always be at least one month between the first and the second doses, and at least three months between the second and the third, and all doses should be given within a year.

2 HPV VACCINATION IN BELGIUM

2.1 Recommendations of HPV vaccination

HPV vaccination was first recommended in 2007 by the Superior Health Council (SHC) for girls aged 10-13 years to prevent cervical cancer.[16] In 2017, the SHC updated its recommendations to include the vaccination of males and to add the prevention of other HPV-related diseases, i.e. cancers of vulva, vagina, anus, penis and oropharynx, as well as anogenital warts.[17] In addition, the recommendation states that vaccination may be proposed to older women and men on an individual basis and is recommended for immunocompromised patients.

In Belgium, since 2017, HPV vaccination is thus recommended for:[17]

- All adolescents aged 9-14 years-old, including girls and boys, with a 2-dose schedule (0, 6 months).
- Women and men aged 15 to 26-years-old, as a catch-up vaccination with a 3-dose schedule (0, 1 or 2, 6 months). Vaccination may then be proposed by the general practioner on an individual basis (whether the patient is sexually active or not). MSM should be proposed HPV vaccination up to 26 years old, given their higher risk of infection.
- Immunocompromised patients (transplanted and HIV positive patients), for which a 3-dose schedule is recommended, preferably with Gardasil 9.

Motivations of the SHC for recommending HPV vaccination of boys/men

The main argument of the SHC to expand the recommendation to males is equity as in Europe, the distribution of the new annual cases of HPV-related cancers and anogenital warts is equally balanced between men and women. HPV vaccination of boys would also allow an increase in public health gains, not only through protection of the vaccinees against all HPV-related diseases (including anal, penile and oropharyngeal diseases) but also through a more rapid initiation of herd protection in the general population. Further, vaccinating all boys allows not only to prevent stigmatisation (for a

sexual preference) but also to target future MSM before the onset of sexual activity, when they are still HPV-naïve and when the vaccine is still highly effective. This would further allow a potential impact on health care costs.

An additional argument may be also the mode of transmission of HPV infection, which is sexual and thus involving both genders, and therefore it may constitute a moral responsibility for boys to accept HPV vaccination.[18]

2.2 Organisation and funding

In Belgium, vaccines may be reimbursed by the NIHDI (including a co-payment charged to the patient), delivered free of charge by the vaccination programmes organised by the communities, or simply available in pharmacies at full price. We describe below the different options for the HPV vaccines available.

2.2.1 NIHDI reimbursement

In Belgium, all three HPV vaccines are available and reimbursed by the National Institute for Health and Disability Insurance (NIHDI), but only for girls aged 12-18 (included) years at the time of the administration of the first dose (legal basis: A.R. 21.12.2001 – Chapter IV – §§ 4630000, 4390000 and 8740000). Gardasil and Cervarix are reimbursed since November 2007 and May 2008, respectively, for a maximum of three doses per patient. Gardasil 9 is reimbursed since June 2017, for a maximum of three doses per patient - or two doses when administered at girls aged 12-14 (included) years. The co-payment is €11.90 per dose for regular patients and €7.90 for patients with preferential reimbursements.

According to the rules above, in Belgium currently women aged 19 and over and boys/men have to pay the full public price of the vaccine if they want to be vaccinated.

Table 2 – HPV vaccines in Belgium

Vaccine	Firm	Serotypes	Public price per dose	Co-payment per dose		NIHDI reimbursement rules	Vaccine reimbursed since
				Regular	Preferential		
Cervarix	GSK	16, 18	€68.86	€11.90	€7.90	Females 12-18 years for: • High grade dysplasia cervix • Cancer cervix	1/5/2008
Gardasil	MSD	6, 11, 16, 18	€118.18	€11.90	€7.90	Females 12-18 years for: • High grade dysplasia cervix and vulva • Cancer cervix • Genital warts	1/11/2007
Gardasil 9	MSD	6, 11, 16, 18, 31, 33, 45, 52, 58	€134.45	€11.90	€7.90	Females 12-18 years for: • Precancerous lesions cervix, vulva, vagina and anus • Cancers cervix, vulva, vagina and anus • Genital warts	1/6/2017

Source: CBIP/BCFI (28/09/2017) and NIHDI Programme Web Médicaments/Geneesmiddelen Webtoepassing (16/10/2017).

2.2.2 Vaccination programmes

Beside the reimbursement of the HPV vaccines by the NIHDI, a full schedule is also offered free of charge (with no co-payment) to adolescent girls (around 11-14 years) by the vaccination programmes of the Vlaamse Gemeenschap (VG) and the Fédération Wallonie-Bruxelles (FWB). These programmes are organised by the Agentschap Zorg en Gezondheid (AZG) in VG and the Office de la Naissance et de l'Enfance (ONE) in FWB. The programmes for the HPV immunisation of girls began in September 2010 in VG, using Gardasil from 2010 to 2014, Cervarix from 2014 to 2018, and Gardasil 9 since July 2018.[d] In FWB, the programme started in September 2011 with Cervarix. In both communities, the programme adopted initially a 3-dose schedule, according to the schedule initially authorised by the EMA. Following the EMA authorisation for a 2-dose schedule in early 2014, the programme in both communities adopted a 2-dose schedule in September 2014.[e, 19] The vaccine is offered to girls during the first (VG) or the second year (FWB) of secondary school (i.e. around 11-13 or 13-14 years of age, respectively).

Eligible girls can be vaccinated free of charge by the school health services (Centra voor Leerlingen Begeleiding (CLB) in VG and Services de Promotion de la Santé à l'École (PSE) in FWB). They can also be vaccinated by another physician i.e. GP, paediatrician or gynaecologist; in this case the vaccine is either free of charge if ordered through ONE or AZG, or reimbursed (according to the NIHDI rules, see 2.2.1) if directly bought in a public pharmacy, but the consultation with the physician is paid as usual.

At the time of writing this report (October 2018), a 2-dose schedule of Cervarix is offered during the second year of secondary school in FWB, while a 2-dose schedule of Gardasil 9 is offered during the first year of secondary school in VG. No catch-up vaccination of older girls is organised but those girls wanting to be vaccinated can request reimbursement up to 18 years of age (outside the programme, as described above).

Since the SHC updated their recommendations in 2017 to expand HPV vaccination to boys, the Belgian federated entities have been discussing aspects of public health relevance, feasibility, acceptability, efficiency and costs of expanding the existing programme to boys.

2.3 Vaccine uptake

The vaccine uptake is very high in VG and was estimated at 89.5% (95% confidence interval [CI]: 86.5; 92.4) in 2016 for a full vaccination course of three doses of the HPV vaccine by a study performed in 488 Flemish girls born in 2000, i.e. 3 years after the start of the programme in VG. This uptake reached 91% when the number of appropriate doses are evaluated for the 2- and the 3-dose schedules.[19]

The uptake in FWB is lower and was estimated at 29.2% (95% CI: 28.0; 30.6) in 2012-2013, i.e. 1-2 years after the start of the programme in FWB,[20, 21] and 36.1% (34.7; 37.5) in 2016-2017, i.e. 5-6 years after the start of the programme in FWB, for a full vaccination course (3 doses in 2012-2013, 2 or 3 doses in 2016-2017).[22] However, this last figure is considered to be an underestimation as it is based on vaccination performed in schools and includes only partially vaccination administered in those cohorts by physicians in private practice. The estimated uptake is approximately 50% (personal communication I. Morales, ONE and B. Swennen, PROVAC). We thus considered that the uptake in FWB varies between 36 to 50%.

In the 2013 Health Interview Survey from the Scientific Institute of Public Health, the self-reported percentage of women aged 10-44 years having received at least one dose of the HPV vaccine varied similarly between regions: 24% in Flanders, 11% in Wallonia and 10% in Brussels.[23] The percentages of vaccinated women aged 15-19 years were 62% in Flanders, 37% in Wallonia and 23% in Brussels. Considering the whole of Belgium, the percentages varied by age, with 23% in the 10-14 years, 50% in the 15-19 years, and 38% in the 20-24 years. Percentages then steadily fell from 8% in the 25-29 years to 3% in the 40-44 years.

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d https://www.zorg-en-gezondheid.be/vaccinatie-tegen-hpv (accessed September 2018).

e https://www.zorg-en-gezondheid.be/gratis-hpv-vaccinatie-goed-ingeburgerd-in-vlaanderen (accessed September 2018).

The Surveillance effects of HPV Immunisation in Belgium (SEHIB) study estimated the uptake of HPV vaccination from women attending cervical cancer screening in Belgium between the end of 2010 and early 2014. The HPV vaccination status was queried during the gynaecological consultation (anamnestic HPV vaccination status). The uptake based on self-reported vaccination was estimated at 68% (52; 78%) for women younger than 20 years, 33% (29; 38%) in the 20–24 years, 9% (7; 11%) in the 25–29 years, and 0.3% (0; 1%) in the 30–39 years.[24] In the next sections, we will use the generic names HPV2, HPV4 and HPV9 to replace the commercial names Cervarix, Gardasil and Gardasil 9.

3 RESEARCH QUESTIONS

A research proposal of whether it would be cost-effective to extend the HPV vaccination to boys had been submitted to the KCE before the SHC recommendation was issued. Rationales were the increasing HPV disease burden in males, in particular in MSM, the recent EMA indications of HPV vaccines for boys and anal cancer, the inequity between the female and male gender in the current Belgian situation (HPV offered to or reimbursed for females only) and the fact that the SHC advice does not cover cost-effectiveness analyses. The inequity situation is also reinforced by the fact that the current HPV vaccination of girls may provide some level of indirect protection to unvaccinated males through a reduction of HPV transmission, but this would only protect heterosexual or bisexual men, not MSM, as HPV viruses are mostly transmitted through sexual contacts.

After the new SHC recommendations, both VG and WB decided to revise their HPV vaccination programme. This revision was also triggered by the upcoming calls for tender of vaccines included in their respective programmes that had to take place in 2018 and 2019, respectively. Both FWB and VG needed an economic analysis to inform their decision making on the HPV vaccination programme and to establish the call for tenders. In addition, a number of parliament questions arose in each community and at federal level on whether HPV vaccination should be extended to boys.

In order to best answer the needs of decision-makers, specific research questions were defined with involvement of stakeholders in a scoping meeting gathering the communities (FWB and VG), the agencies in charge of vaccination programmes (ONE and AZG) and the NIHDI. A number of cost-effectiveness questions could only be answered by developing a transmission model that would simulate HPV transmission and HPV vaccination of girls and boys in Belgium. As such model is complex to build and would take an additional year of research, and in view of the short timeframe, it was decided to limit the research questions to those that could be answered by a review of the economic literature.

The selected research questions are considering two groups of indications or diseases preventable by the HPV vaccines:

- the indications authorised by the EMA, to which have been added the cancers of vulva and vagina for HPV2 and HPV4. As said above, HPV2 and HPV4 are indicated to prevent pre-cancerous lesions of vulva and vagina only but the prevention of vulvar and vaginal cancers is not mentioned in their EMA authorisation. However, these outcomes are considered by most economic studies. The expanded EMA indications thus include: cancers of cervix, anus, vagina and vulva for all vaccines, and genital warts for HPV4 and HPV9
- all HPV-related diseases currently identified: cancers of cervix, anus, vagina, vulva, oropharynx and penis for al vaccines, and genital warts for HPV4 and HPV9

The questions are:

1. What is the cost-effectiveness of universal (girls and boys) versus girl-only HPV vaccination, considering the indications authorised by the EMA and considering the current uptakes in the Belgian communities?
2. What is the cost-effectiveness of universal versus girl-only HPV vaccination, considering all HPV-related diseases, and considering the current uptakes in the Belgian communities?
3. Is extending the HPV vaccination to boys more cost-effective than increasing the vaccine uptake in girls, all other factors remaining the same?
4. If universal vaccination is opted for, what is the most cost-effective vaccine?
5. What is the cost-effectiveness of universal versus girl-only vaccination using low vaccine prices?
6. What is the impact of the vaccine duration of protection on the cost-effectiveness?

The recurrent respiratory papillomatosis has not been considered in this study as the disease is very infrequent, no Belgian data are available, and no evidence of a HPV vaccine effect to prevent this disease is available. However, this condition is included in some economic evaluations including all HPV-related diseases.

This report is thus not addressing questions related to the equity, the ethical aspects, the feasibility and the acceptability of HPV vaccination. The question of targeted HPV vaccination of MSM has not been selected by the communities, for ethical and stigmatisation concerns. Although screening for cervical cancers is an important prevention tool, that intervention is not included in our research questions and is assumed to remain equal across the strategies compared in the economic evaluations.

This study is based on literature reviews and a data analysis of the burden of disease. The literature reviews were focused on studies corresponding best to the Belgian situation. In particular, the analysis of the economic literature selected the parameters and analyses that were relevant for the Belgian situation.

4 BURDEN OF HPV DISEASES IN BELGIUM

In this section, we present the estimated morbidity and mortality for HPV-related cancers and genital warts in Belgium.

4.1 Methods

HPV prevalence studies were extracted from the most recent Belgian studies. The number of cancers potentially caused by HPV and the corresponding incidence rates in Belgium reported in 2015 by the Cancer Registry are described in Table 3. For oropharyngeal cancer, as there is no international consensus on which codes should be considered regarding HPV, we selected ICD codes C01, C05.1-9, and C09-10. These codes show a proportion of HPV positive cases above 10% in an EU multicentre study, are included in the oropharynx definition in the 2018 TNM classification of malignant tumours[f] and correspond to the outcomes of the Belgian study on HPV oropharyngeal cancers.[6, 25, 26]

To estimate the diseases that are attributable to HPV, we extracted the proportion of those diseases that were due to HPV in Belgian studies,[26, 27] or, when no Belgian data were available, from recent meta-analyses of European data. We extracted in particular European estimates from large multicentre studies of cancer samples.[6, 25, 28-31] We also extracted the proportion of cases due to the HPV types included in each vaccine, for each disease, from the same sources and from an additional Belgian study.[32]

Temporal trends are based on data from the Cancer Registry for the selected cancers, all causes, and not for HPV-attributable cancers.

4.2 HPV prevalence in Belgium or in similar settings

The largest Belgian study measured HPV prevalence in genital samples in 8729 women 15-85 years of age attending cervical cancer screening in Flanders in the pre-vaccine period (years not reported).[33] The prevalence of high-risk HPV types was 15% overall, 11% in women with normal cytology and 32-93% in women with cytological abnormalities. It peaked in the 20-24 year age group, at 29%, and decreased progressively with increasing age up to 8% in the 55-59 year-olds. HPV-16 was the most common (3.7%), followed by HPV-31, HPV-51 and HPV-53. HPV-16/18 was found in 5% of all women. Another study included cervical samples collected from 6630 women attending cervical cancer screening in Belgium in 2010-14.[24] The overall prevalence of high-risk HPV types was 9%, and peaked in the 20-24 years age group at 20%.

Only one HPV prevalence study in other sites (anal, vulvar, vaginal, penile or oral) was found from Belgium,[34] probably because there is no HPV-related screening programme for other HPV-related cancers in Belgium. We thus also describe data from Western European studies retrieved from recent systematic reviews.

A systematic review on the HPV incidence (not prevalence) and clearance in non-cervical sites covered studies from 1995-2014, and retrieved 10 studies from EU countries.[35] The results suggested that non-cervical genital HPV infections may occur more frequently, with higher clearance rates, than cervical infections. HPV-16 is usually the most prevalent type. In Northern and Southern American studies, the prevalence of genital HPV infection was higher in men than in women, but persistence was less likely. However, comparisons are difficult because detection of HPV in men is influenced by many other factors, such as the sampling site and sampling technique. A recent meta-analysis of 13 HPV prevalence studies among men estimated the prevalence at 49% (95% CI: 35; 62) for all HPV and 35% (26; 45) for high-risk HPV types, but included only two European studies.[36]

[f] https://www.hoofdhalskanker.info/wpavl/wp-content/uploads/TNM-Classification-of-Malignant-Tumours-8th-edition.pdf

A small Belgian study estimated the anal prevalence among 149 HIV-negative women without a history of cervical cancer and attending a colposcopy clinic.[34] HPV was found in 56% of the 96 anal samples (compared to 54% of 149 cervical samples). However, the study sample cannot be considered as representative as 77% of the women had an abnormal smear. Major HPV types found in the anal samples were types 16, 51 and 39; HPV-11 was not found. In other countries, most studies focused on risk groups (HIV-positive and MSM), in which the highest anal HPV prevalence are reported.[4, 35] In those studies, prevalence in MSM (>50%) was twice the prevalence among women (~30%), which in turn was twice the prevalence among heterosexual men (12-15%).[4, 37] Studies in non-risk groups were mostly conducted in North and South America. In women of the placebo arm of the Costa Rica vaccine trial (see 5.2), HPV anal prevalence was 32%.[38] Although anal cancer is rare (see 4.3.2), anal HPV infection is thus common among women and men without risk factors.[37] Studies that measured concomitantly cervical and anal HPV infection in women, as in the Belgian study,[34] show comparable prevalence estimates at both anatomic sites.[37] A decline in anal HPV prevalence with increasing age has been observed in women but not in men.[4]

The prevalence of HPV infection of the penis is not available from Belgium and varies across studies. Penile HPV prevalence was 34% (114/337) in Danish soldiers 19-22 years of age,[39] 13% (19/147) in men attending a clinic for non HPV-related reasons in Sweden,[40] and above 50% in men attending STI clinics in the Netherlands and Spain.[41, 42] HPV prevalence was stable across ages.[37]

Oral HPV prevalence was not available from Belgium, but it varies considerably between studies from different geographical regions.[43] Oral HPV prevalence was estimated at 7.5% in a meta-analysis from nine studies (including one EU study) involving 3762 HIV-negative and cancer-free subjects.[43] The median time to clearance varied from 6.5 to 18 months. Type distribution was similar to cervical infections and HPV oral infection was strongly related with sexual behaviour. Prevalence was considered to be 5-10 fold lower than cervical prevalence, 2 to 3-fold higher in men compared to women.[43-46] This difference across gender is not easily explained by differences in sexual behaviour, which suggests difference between gender in natural history and exposure to cofactors.[44]

4.3 Burden of HPV-related cancers

Table 3 describes for each of these cancers (cervix, vulva, vagina, penis, anus, and oropharynx) the incidence rate, number of new cases and mean age per gender, the proportions of those that are due to HPV and the proportion of HPV-attributable cancers that are due to the HPV types included in each vaccine. The proportions of HPV-attributable cancers vary across studies and settings, especially for penile and oropharyngeal cancer (OPC).[27, 47] Differences are due to geographical and population factors and also depend on the method used, the type and method of sampling, and the recruitment of subjects.[48] For those reasons, we selected Belgian estimates or European multi-country estimates to derive these proportions, instead of worldwide estimates. As these proportions do not differ substantially across gender,[6] we did not stratify them by gender in Table 3.

In Belgium, the incidence of OPC, all causes, were 2.6 times more frequent in men than in women and anal cancer was 1.5 times more frequent in women. The mean age of cases of non-cervical cancers, all causes, ranges from 59 to 73 years in Belgium, and is higher compared to cervical cancers (53 years). This implies that non-cervical cancers occur at a later point in life after HPV infection compared to cervical cancers (see Table 3).

The studies that provided the proportion of HPV-attributable cancers and proportions of HPV types in Europe are described under each specific cancer (see 4.3.1 to 4.3.6). HPV-16 type is found in the large majority of these cancers, usually in more than 70%. Table 3 shows that a higher proportion of anal, vulvar and OPC cancers are associated with HPV2 types (16 and 18) compared to cervical cancer. Low risk HPV types 6 and 11 are responsible for around 6% of anal cancers, a few vaginal, vulvar and penile cancers, and for most genital warts (see 4.4). The five additional types included in HPV9 (HPV9 non-HPV4 types) were responsible for 17% of cervical cancers, 10-14% of penile, vulvar and vaginal cancers but only 5% and 3% of OPC and anal cancers, respectively. HPV9 types were found in 85-95% of HPV-attributable cancers.

Table 3 – Incidence rates, numbers and mean age of selected HPV-related cancers (due to any cause), by gender, Belgium, 2015 (Cancer Registry) and proportion of those attributable to HPV types (literature)

Disease	Incidence in men per 100 000 (number)	Mean age in men in years	Incidence in women per 100 000 (number)	Mean age in women in years	% due to HPV	% of HPV positive cancers		
						due to HPV2 types	due to HPV4 types	due to HPV9 types
Cancer cervix	-	-	10.0 (634)	53 years	100%	73%	73%	90%
Cancer anus	1.1 (79)	63.5 years*¥	1.6 (130)	64 years*¥	88%^	87%	93%	95%
Cancer vulva	-	-	2.5 (218)	72 years*	18%∞	84%	84%	94%
Cancer vagina	-	-	0.5 (42)	73 years*	71%ᵛ	71%	73%	87%
Cancer penis	1.3 (94)	69 years*	-	-	32-61%†	73%	75%	85%
OPC (C01, 05.1-9, 09-10)	7.5 (503)	59 years*	2.9 (207)	60 years*	25%**	85%	85%	90%

** In Flanders only. ** 2000-10, van Limbergen.[26] ^ Alemany 2015.[29] † Alemany 2016 and D'Hauwers.[6, 27] ∞ de Sanjose.[31] ᵛ Alemany 2014.[30] ¥ Median age. OPC: oropharyngeal cancer.*

Based on the data from Table 3, we estimated the number of cancers attributable to HPV in Belgium in 2015 and those due to the HPV types included in each vaccine, per gender (Table 4). These numbers are approximations as no systematic HPV testing is applied on cancer cases in Belgium and we used different sources for cases (Cancer Registry) and for the proportion of HPV types by disease (literature). For penile cancers, we selected the Belgian study for the proportion of HPV-attributable penile cancers, i.e. 61%, although this might be an overestimation.[27]. Overall, we estimated that 1122 new cancers were attributable to HPV in Belgium in 2015, and nearly half (44%) of these were non-cervical cancers. More than three quarter of all HPV-attributable cancers were found in women (869/1122), and 73% of these were cervical cancers. Among the 253 (22% of all) HPV-attributable cancers reported in men, 50% of these were OPC cancers.

The total number of cancers attributable to the HPV types included in HPV2, HPV4 and HPV9 vaccines in Belgium in 2015 is estimated at 869, 882 and 1019 cases, respectively. In other words, the seven types contained in HPV9 and not in HPV2 caused around 150 cancers in 2015, including 110 cervical cancers. Figure 1 presents the estimated number of HPV attributable cases by vaccine HPV types, by gender.

The burden and characteristics of each HPV-related cancer and relevant sources are further described in the next sections (4.3.1 to 4.3.6). The burden of anogenital warts is presented under 4.4.

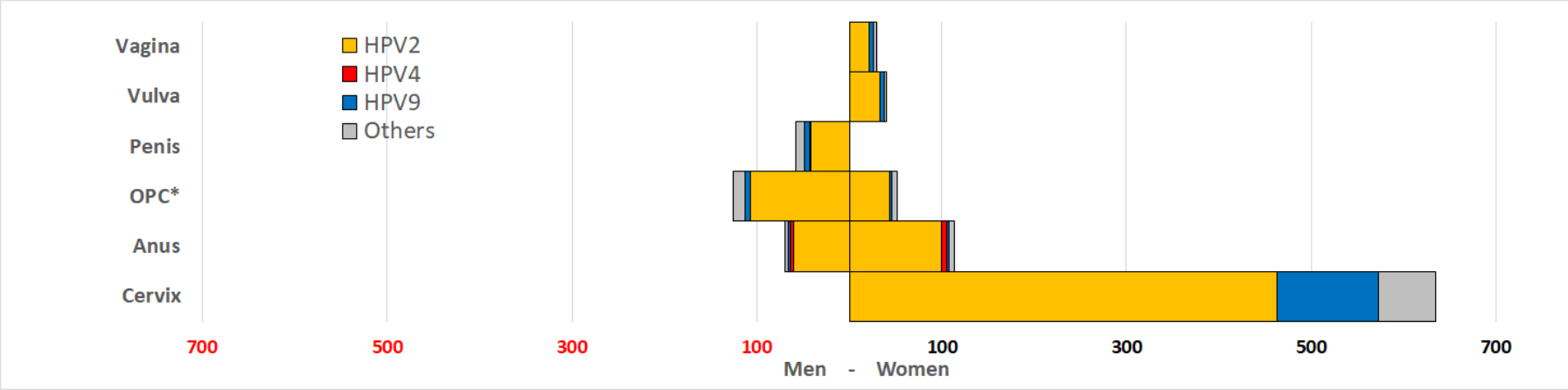
An increase in the number of oropharyngeal, anal and penile cancers has been reported in many countries.[14] The trends in Belgian incidence over 2004-15, based of Cancer Registry data, are shown in Figure 2. The trends specific for each cancer are described below under each type of cancer (4.3.1 to 4.3.6). The age-specific incidence rates of cancers for the year 2015 is shown in Figure 3.

Table 4 – Estimated numbers of HPV-attributable disease, for any HPV and HPV types included in each vaccine, per gender, in Belgium in 2015 (Cancer Registry and literature)

Disease	Number cases attributable to HPV			Number cases attributable to HPV2		Number cases attributable to HPV4		Number cases attributable to HPV9	
	Men	Women	Total	Men	Women	Men	Women	Men	Women
Cancer cervix	-	634	634	-	463	-	463	-	573
Cancer anus	69	114	183	60	99	64	105	66	108
Cancer vulva	-	40	40		33	-	34	-	38
Cancer vagina	-	30	30		21	-	22	-	26
Cancer penis	57	-	57	42	-	43	-	49	-
OPC (C01, 05.1-9, 09-10)	126	52	178	107	44	107	44	113	46
Total HPV-attributable cancers*	252	869	1122	209	661	214	668	228	792
Genital warts (estimates)*									
High	9833	9833	19 666						
Low	6785	6785	13 570						

** Totals may not add up due to rounding. OPC: oropharyngeal cancer.*

Figure 1 – Estimated numbers of HPV-attributable cancers in Belgium, by gender and groups of HPV types included in the vaccines, 2015



** ICD10 codes: C01, 05.1-9, 09-10. OPC: oropharyngeal cancer. Source studies for the proportion of vaccine types found in the cancers that are HPV attributable: vaginal: Alemany 2014;[30] vulvar: de Sanjose;[31] penis: Alemany 2016;[6] OPC: Castelsague;[25] anal: Alemany 2015;[29] cervical: Tjalma.[32]*

Figure 2 – Incidence rates of cancers potentially due to HPV, all causes, in Belgium, 2004-15, all ages, Cancer Registry. Left: females; right: males.

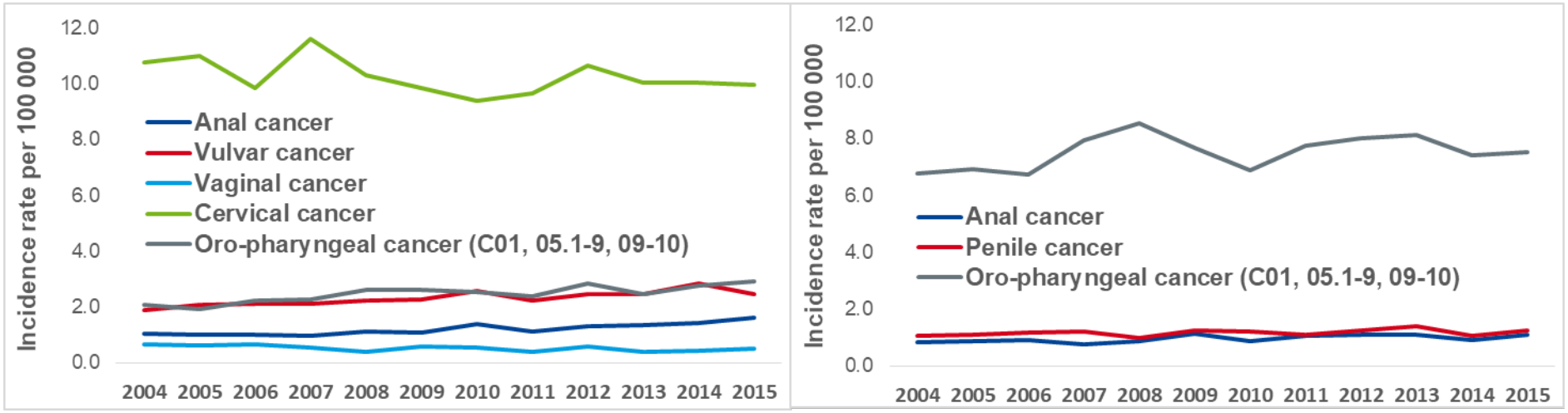
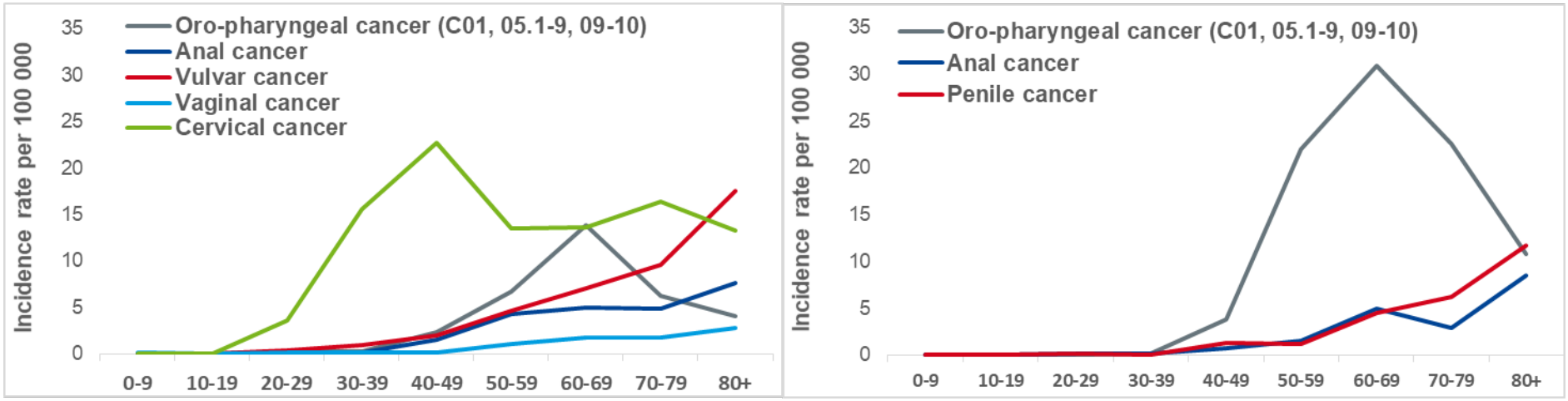


Figure 3 – Age-specific incidence rates of cancers potentially due to HPV, all causes, in Belgium in 2015, Cancer registry. Left: females; right: males.



4.3.1 Cervical cancer

The Cancer Registry reported 634 cases of cervical cancers in Belgium in 2015, or an incidence rate (standardised for European population) of 10 cases per 100 000 women (Table 3 and Table 4). Compared to 2004, this represents a 7% decrease in incidence (Figure 2). In 2015, the highest incidence rates were observed in the 35-50 year-olds (above 10 per 100 000) and the mean age at diagnosis was 53 years (see Figure 3). The survival at 5 years was estimated at 68% of the cases in 2011-2015.[49]

All cases of cervical cancer are attributed to HPV infection.[50] A Belgian study included samples of invasive cervical cancers from 255 Belgian patients collected in 2001-08 and found that types HPV-16, HPV-18, HPV-31 and HPV-33 were present in 62%, 11%, 8% and 6%, respectively, of all cases. Overall, HPV types included in HPV2 and HPV4 vaccines were found in 73% of cases and those included in the HPV9 vaccine in 90% of cases.[32] These proportions are similar to those reported in a recent European review, i.e. 73% and 89% for HPV2/HPV4 and HPV9 types, respectively.[6] The low risk HPV types HPV-6 and HPV-11 were not described in any cervical cancers in Belgium.[51] Note that the prevalence of HPV-16/18/45 types is always higher in invasive cervical cancers than in high grade CIN.[32]

We thus estimated that the HPV types included in HPV2/HPV4 and HPV9 vaccines would cause 463 and 573 new cases of invasive cervical cancer, respectively, in Belgium in 2015 (Table 4)

4.3.2 Anal cancers

The Cancer Registry reported 209 cases of cancers of the anal canal (all causes) in 2015. Around two third were found in women, with incidence rates of 1.6 and 1.1 cases per 100 000 inhabitants, in women and men respectively (Table 3). Anal cancer rates are particularly high in MSM and HIV infected men and women,[29] but no Belgian data are available on these risk groups. The median age at diagnosis was around 64 years for both genders in Flanders in 2004-07, and incidence increases with increasing age in both genders. The survival at 5-year after diagnosis was 69% of the cases in Flanders in 2001-10, and slightly better for females (73%) than for males (67%).[52]

The incidence of anal cancers is increasing in many countries due to changes in sexual behaviour.[53-55] In Belgium, the incidence of anal cancer increased in both genders, by 31% in men and by 55% in women over an 11-year period (2004-2015, Figure 2).

A multi-centre study included 169 samples from 9 European countries collected in 1986-2011 and found that 88% (148/169) of invasive anal cancers were HPV-attributable, based on HPV DNA detection and p16 expression (cyclin-dependent kinase-4 inhibitor or $p16^{INK4a}$).[29] No differences in the proportion of HPV-related anal cancers were observed across genders. Among European HPV-related cases, HPV-16 was the most frequent type (84%) and the HPV types included in HPV2, HPV4 and HPV9 vaccines contributed to 87%, 93% and 95% of cases.[29]

We thus estimated that 183 new cases of anal cancers would be attributable to HPV in Belgium in 2015, 114 in women and 69 in men, and the HPV types included in HPV2, HPV4 and HPV9 vaccines would be involved in 160, 169 and 174 new cases of anal cancer, respectively, in both genders (Table 4).

4.3.3 Vulvar cancer

The Cancer Registry reported 218 cases of vulvar cancer (all causes) in 2015, or an incidence rate of 2.5 cases per 100 000 inhabitants (Table 3). The mean age at diagnosis is 72 years in Flanders, and incidence increases with increasing age (Figure 3). The survival at 5-year after diagnosis has been estimated in Flanders at 66% of the cases in 2004-07.[52] In Belgium, the incidence of vulvar cancers has increased by 31% between 2004 and 2015 (Figure 2).

In a large multi-centre study, 18% of 903 European samples from invasive vulvar cancer were attributable to HPV, based on HPV DNA detection and $p16^{INK4a}$ expression.[31] Interestingly, a much higher proportion of pre-cancerous vulvar lesions were related to HPV in the same study, i.e. 87% of 312 vulvar intraepithelial neoplasia or VIN cases. This study noted that the HPV contribution in invasive vulvar cancers has probably been overestimated in previous studies, which may be due to other diagnostic criteria to consider a tumour to be HPV-related, and different distributions of vulvar cancer sub-types.[31]

HPV-16 was the most frequent type, found in 73% of HPV-related cancers worldwide. Types from HPV2, HPV4 and HPV9 vaccines were found in 84%, 84% and 94% of HPV-related vulvar cancers in Europe.[6, 31g]

We estimated that 40 new cases of vulvar cancers would be attributable to HPV in Belgium in 2015, and the HPV types included in HPV2, HPV4 and HPV9 vaccines would be involved in 33, 34 and 38 new cases of vulvar cancer, respectively (Table 4).

4.3.4 Vaginal cancer

Vaginal cancer is rare, with 42 cases (all causes) reported by the Cancer Registry in 2015, or an incidence rate of 0.5 cases per 100 000 inhabitants (Table 3). The mean age at diagnosis was 73 years in Flanders, and incidence increases with increasing age (Figure 3). Mortality is higher than for other cancers described in this section, and survival at 5-year after diagnosis has been estimated in Flanders at 35% of the cases in 2004-07.[52] The incidence of vaginal cancers has decreased by 24% between 2004 and 2015 (Figure 2).

In a large multi-centre study, 71% (108/152) of European samples from invasive vaginal cancer were related to HPV, based on HPV DNA detection, with a predominance of HPV-16 (67% of HPV positive samples).[30] Types from HPV2, HPV4 and HPV9 vaccines were found in 71%, 73% and 87% of the 108 HPV-positive European cases.

We estimated that 30 new cases of vaginal cancers would be attributable to HPV in Belgium in 2015, and the HPV types included in HPV2, HPV4 and HPV9 vaccines would be involved in 21, 22 and 26 new cases of vaginal cancer, respectively (Table 4).

4.3.5 Penile cancer

Penile cancer is a rare disease, with 94 cases (all causes) reported by the Cancer Registry in 2015, or an incidence rate of 1.3 cases per 100 000 inhabitants (Table 3). The mean age at diagnosis was 69 years in Flanders, and age specific incidence rates increase rapidly and continuously after 45 years (Figure 3).[52] The survival at 5-year was estimated at 70% of cases from Flanders in 2001-2010.

Several countries, such as the Netherlands, Denmark and England, reported an increasing incidence of penile cancers in recent years, after an initial decline.[56] In Belgium, the incidence of penile cancers has also recently increased, by 17% between 2004 and 2015 (Figure 2).

HPV has been detected in 32% of 419 samples of invasive penile cancers in European samples of a recent multi-centre study.[28] A study assessed penile pre-cancers and cancers from four Belgian university hospitals using PCR, and detected HPV in 61% (22) out of the 36 samples of invasive penile cancers that were adequate for HPV targeting.[27] Authors explained the difference in HPV prevalence in Belgian samples compared to other European studies by geographical factors, differences in risk factors and changes in detection methods.

HPV-16 was found in 71% of the HPV-positive Belgian samples, and low-risk HPV-6 and HPV-11 were found in one sample each (1/22 or 5%).[27] As the number of samples was small in this study, we derived the proportions of HPV types from samples of the multi-centre study mentioned above: among 135 HPV-positive European samples, HPV-16 was found in 73% cases, and types from HPV2, HPV4 and HPV9 vaccines were found in 73%, 75% and 85% penile cancer cases, respectively.[28]

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g As no data were found on the prevalence of HPV-6/11 in European HPV-related samples, we derived it from worldwide samples (0.9%).

We thus estimated that 57 new cases of penile cancers would be attributable to HPV in Belgium in 2015, and that the HPV types included in HPV2, HPV4 and HPV9 vaccines would be involved in 42, 43 and 49 new cases of penile cancers, respectively (Table 4).

4.3.6 Oropharyngeal cancers

The Cancer Registry reported in 2015 710 cases of cancers due to base of tongue, soft palate, tonsil and oropharynx in general (ICD codes C01, C05.1-9, C09 and C10), all causes, and 71% cases were reported in men. The highest incidence was reported in tonsils. We did not include cancers of the oral cavity, nasopharynx or larynx in this analysis because only a small proportion of these cancers are considered to be related to HPV (<5% in Western European samples from a multi-centre study of head and neck cancers).[25]

The much higher incidence of oropharyngeal cancer (OPC) in men, 7.5 compared to 2.9 per 100 000 in women in 2015, is also observed in other EU countries such as England, Denmark and Norway.[44, 57-59] HPV prevalence of the oral cavity is systematically lower (about 2 to 3-fold) in women compared to men but the mechanisms of HPV transmission to the oral cavity are poorly understood.[45, 46]

The median age at diagnosis in Flanders (2004-07) was 59 years for males and 60 years for females. Incidence increases rapidly from the age of 40 years in males and 45 years in females and decreases after 60 years (Figure 3). The relative survival at 5-year after diagnosis has been estimated at 45% of the cases in Flanders in 2001-10, and was higher in women (56%) than in men (41%).[52] HPV-positive cases were older (62 years) at diagnosis than the HPV-negative cases (58 years) in a multi-centre Belgian study of 249 cases tested for HPV.[26]

A continuous increase in the OPC incidence has been reported in several EU countries, in particular for oral squamous cell carcinoma and among males, and is mostly driven by HPV-positive cases.[57-59] In Belgium, the incidence of OPC, all causes, increased in both genders, although relatively more in women (+40%) than in men (+11%). However, the changes in HPV-attributable OPC incidence are unknown in Belgium.

The proportion of HPV-positive OPC may vary from 15 to 80% according to studies.[44, 47, 60] This is partly due to substantial variations across countries, which are attributed to differences in tobacco use, drinking habits, oral sexual behaviour, and periods of sampling as the proportion tends to increase with time.[47] For instance, a higher HPV prevalence is expected among cases who have never been smokers or drinkers, as these persons developed the disease in the absence of these risk factors.[47] HPV-related OPC are considered to constitute a distinct epidemiological, molecular and clinical form as compared to non HPV-related ones. Other reasons for differences in reported HPV prevalence are the method and site of sampling as the proportion of HPV also varies across cancer localisation.[25]. A Belgian study estimated that 25% of 249 OPC evaluable cases were attributable to HPV, based on HPV DNA detection and p16 expression.[26] The proportions were similar among men and women. This estimate is comparable to the proportion of HPV-positive European OPC cases (22%) in a large multi-centre study of head and neck cancers.[25]

In the Belgian study, the HPV types were not reported. In the large multi-centre international study, types from HPV2, HPV4 and HPV9 vaccines were found in 85%, 85% and 90% of the 271 HPV-positive OPC cases.[25] These results are for all countries confounded because no type estimates are provided for European cases only, but they represent 74% of all OPC cases of that study.

We thus estimated that 178 new cases of OPC would be attributable to HPV in Belgium in 2015, including 126 in men and 52 in women, and the HPV types included in HPV2, HPV4 and HPV9 vaccines would be involved in 151, 151 and 159 new cases of OPC, respectively (Table 4).

4.4 Burden of anogenital warts

There are no precise estimates on the incidence of anogenital warts (AGW) or genital warts (GW) in Belgium. A study based on medical claims for imiquimod (reimbursed treatment for AGW) estimated the incidence of treated GW in 2009-13 at 77 and 92 per 100 000 among men and women of 16-59 years of age, respectively (Table 5).[61] However, this is an underestimation because it does not include cases for which imiquimod was not used or not reimbursed. A systematic review found higher estimates for the incidence of any new AGW in three EU countries, as could be expected, ranging from 118 to 170 per 100 000 in studies published in 2001-12 (from Germany, UK and Spain).[62] However, these estimates are restricted to patients seeking care. The review showed relatively similar rates among men and women in studies providing incidences for both genders. AGW incidence peaks in a younger age in women compared to men in all studies comparing males and females, before 24 years of age in women and between 25 and 29 years in men in the systematic review.[62] The reported median time between infection and the development of genital warts is 11-12 months in men and 5-6 months in women.[4, 62] The review also found high incidence rates of recurrent AGW but case definition varied.

As no comprehensive data on anogenital warts were found for Belgium, we derived the number of AGW from the incidence rates reported in that systematic review and applied them to the Belgian population. This would correspond to a total range of 13 570 to 19 665 new AGW seeking medical care in Belgium per year, and we assume equal share of cases in both genders (Table 4).

Before HPV vaccine introduction, the incidence of AGW tended to increase in industrialised countries such as the United Kingdom, the Netherlands, and the Nordic countries.[4] After the introduction of HPV vaccination programmes with HPV4, a substantial reduction in the AGW incidence was observed in vaccinated and non-vaccinated men and women of several countries.[63] A mild decrease was also observed among women in Belgium (Table 5).[61] Another Belgian study from a sentinel surveillance network of general practitioners found that 18% of GW were reported in MSM in 2013-14.[64, 65] No mortality is associated with AGW.[62]

HPV types 6 and 11 account for the majority of AGW cases.[4] In the placebo arm of two HPV4 efficacy trials (FUTURE-I/II, see 1.1.1) involving 8800 women 15–26 year-olds, 538 AGW were diagnosed in 351 women. HPV-6 and/or HPV-11 were detected in 95% of HPV-positive lesions.[66] In four studies, HPV-16/18 were also found in around 10-30% of AGW, usually in association with types 6 or 11.[48, 66-68] However, the proportion that can be attributed to the different vaccine types is difficult to estimate because the wart surface does not accurately reflect the HPV types present within a wart lesion that is the potential cause.[69]

Table 5 – Incidence rates of genital warts from Belgian studies and a recent meta-analysis

Study, country	Age group	Period	Source, method	Incidence in men /100 000 (95%CI)	Incidence in women /100 000 (95%CI)	Overall incidence /100 000 (95%CI)
Dominiak 2016, Belgium (treated cases)[61]	16-59 years	Pre-vaccine 2006	Sick-funds. 1st reimbursement imiquimod (surrogate)	71 (64; 79)	114 (110; 124)	92 (86; 98)
		Post-vaccine 2009-13		77 (72; 82)	92 (87; 98)	85 (81; 88)
Patel 2017, Germany, UK and Spain[62]	14-65 years	Pre-vaccine (2005-06)	Systematic review, including three EU studies providing incidence data	137 to 168	100 to 191	118 to 170

4.5 Other complications of HPV infection

A number of *in vitro* and epidemiological studies have revealed that HPV infection in men and women is associated with alterations in fertility.[70] HPV infection in men may result in infection of the semen. A systematic review retrieved at least seven clinical studies showing an association between HPV infection and alteration of semen quality, in particular when HPV-16 or 31 were involved.[70] HPV was shown to be more prevalent in infertile men compared to fertile men.[70] HPV infection in women was significantly associated with a higher risk of failure of *in vitro* fertilisation in three studies. Two studies showed an association between cervical HPV infection and spontaneous abortion or premature rupture of membrane.[70] Although HPV cannot be considered as being the main cause for these events, HPV infection of men and women represents a risk factor for reduced fertility. Many questions remain unanswered on the underlying mechanisms of HPV effects on both the female and male reproductive system.

4.6 Gender differences in HPV-related diseases

HPV infection and occurrence of HPV-attributable cancers differ between men and women.

As described above, men tend to have a higher prevalence of genital HPV infection, which stays relatively stable across age, as opposed to women in whom rates of HPV infection decrease with increasing age.[2, 4, 37] Thus in women, the rate of acquiring a new infection decreases with age while it does not vary by age in men. However, once HPV is acquired, the duration of infection is comparable between men and women.[37] Men also have a lower immune response, as seen by the lower prevalence of HPV antibodies in men compared to women, across all ages.[71] This could explain that the stronger immune response in women may protect them against reinfection while men do not develop that protection.[48]

The time between infection and cancer also differs across genders: in Belgium, cervical cancer peaks in women at the age of 45 years, while penile cancer peaks in men at 80 years of age, showing that non-cervical cancers occur later after HPV infection. A similar pattern is observed for AGW, for which the median time between infection and diagnosis of warts is 11-12 months in men and 5-6 months in women, which implies that AGW incidence peaks in a younger age in women compared to men: before 24 years of age in women and between 25 and 29 years in men (4.4).[4, 62]

As shown above, the incidence of OPC is 2-3 times higher in men than in women and anal cancer is 1.5 times more frequent in women. MSM are the most affected group by HPV disease, in particular HIV-positive MSM. Furthermore, MSM have a disproportionately high prevalence of anogenital and oral HPV infection and related disease compared to heterosexual men, which translates into higher rates of anal, penile and oropharyngeal cancers.[7, 8]

5 VACCINE EFFICACY AND SAFETY

5.1 Methods

The first objective was to compare the most recent efficacy estimates from published studies to those used in the economic evaluations, to assess the credibility of the parameters selected. We thus initially focused on the vaccine efficacy against vaccine types in a naïve population (i.e. not previously infected by HPV) measured in large trials, usually considered as "per protocol" analysis, and on the efficacy against the types not included in the vaccine being evaluated (i.e. cross-protection). The second objective was to inform Belgian decision makers on the protection and safety that could be expected from the different HPV vaccines in public health terms, i.e. protection against all HPV-related diseases (all HPV types) and adverse events related to the vaccine, according to the most recent knowledge. We thus extracted vaccine efficacy against disease due to any HPV strain, in the naïve and the total population (individuals with and without previous HPV infection), and information on safety.

We performed a pragmatic search to retrieve data on clinical efficacy and safety of the HPV2, HPV4 and HPV9 vaccines in young subjects (i.e. around 14-25 years). We searched for available systematic reviews on the efficacy and safety of each vaccine in both males and females. For males, six systematic literature reviews were retrieved.[2, 17, 72-75] Recent and relevant primary studies were additionally retrieved. Efficacy data against cervical cancer was extracted from the last Cochrane review (2018) and further details were searched in the primary studies when required.[76] Efficacy data in females against other outcomes (cancers vulva, vagina, anus, and oropharynx, as well as anogenital warts) were extracted from systematic reviews or the last publications of the main trials (see below per outcome). For outcomes for which there was no appropriate trial (e.g. oropharynx), we also searched for the most recent observational studies.

5.2 Vaccine efficacy

Five major trials measured vaccine efficacy against HPV infection or against pre-cancerous lesions and cancers in young subjects and are described in Table 6. Only one randomized, double-blind, controlled trial (V501-020) investigated vaccine efficacy (with the HPV4 vaccine) in males.[77-79] In females, four main trials were conducted on the three vaccines, PATRICIA, CVT, FUTURE and V503-001.

None of the clinical trials presented efficacy results against cancer outcomes so far because they were not large enough or of sufficient duration to evaluate cancer outcomes.[76] Indeed cancer mostly occur 20 years or more after infection and the longest follow-up period of trials is around 10 years (see 5.5). We found only one 10-year follow-up study of large trials that included a number of cancers.[80] For that reason, we present here pre-cancerous outcomes, i.e. intraepithelial neoplasia grade 2 (IN2) and 3 (IN3), [h] that have a high probability of progressing into cancer.[2] When available, we present efficacy results for intraepithelial neoplasia grade 3 and above (IN3+), as it was the most immediate and widely accepted precursor of cancer by the licensing agencies at the time of EMA authorisation, for cervical cancer in particular.[81] When efficacy against IN3+ is not available, efficacy against IN2+ are presented. For some cancers for which this information is not available, we present other (earlier) outcomes that are available from published studies such as HPV infection (e.g. for anal, vulvar and oropharyngeal cancers). Immunogenicity results are not shown as there is no recognized correlate of protection, with the exception of "bridging" studies that have been conducted to "bridge" results in adults to those in the target group of adolescent girls and boys (5.3).

The values for vaccine efficacy were extracted according to the populations analysed. To represent best the total population, which comprises individuals with and without previous HPV infection, the results from the "intention-to-treat" analyses are reported. To represent the naïve population,

[h] Premalignant intra-epithelial lesions are classified according to their progression and histopathology. E.g. for cervical cancer, grade 1 is for mild dysplasia, grade 2 for moderate to marked dysplasia and grade 3 for severe dysplasia to carcinoma in situ. Grade 1 and above (IN1+), grade 2 and above (IN2+), or grade 3 and above (IN3+) also include adenocarcinoma in situ and cancers.

which only includes individuals not previously infected by any HPV type (or sometimes by the HPV vaccine-types), the results from the "completely-naïve" or the "per-protocol" analyses were reported. The definitions of these populations are:

- ITT or intention-to-treat population: subjects that received ≥1 dose of the vaccine and returned for ≥1 follow-up visit, irrespective of previous or current HPV status (i.e. previously or currently infected or not).
- PP or per-protocol population: subjects that were never infected by the vaccine-types, i.e. HPV seronegative and HPV DNA negative at baseline, and that received 3 doses of the vaccine and were in line with the protocol.
- CN or completely-naïve population: subjects that are HPV seronegative and HPV DNA negative at baseline for all the HPV types tested in the study (not only the vaccine-types) and that received ≥1 dose of the vaccine.

For all outcomes, vaccine efficacy is higher in the naïve population compared to the efficacy in the total population. As this study covers the vaccination of young adolescents in Belgium, the efficacy in the naïve population (not infected with HPV) represents best the protection that can be achieved by vaccinating a group that is not yet sexually active (sexually naïve) - for most of them. Efficacy is also highest against the types included in the vaccine. We also present the efficacy against all HPV types, i.e. all lesions or cancers due to HPV, as it represents the outcome of public health interest. The sections below present the efficacy against any, vaccine and non-vaccine types, when available. The efficacy against non-vaccine types, or cross protection, is further discussed under Cross Protection (see 5.3). In the tables of the next section, the number of cases are reported for information when there are less than 10 cases per arm, to highlight the uncertainty due to small numbers.

Table 6 – Characteristics of the main HPV vaccine efficacy trials[81, 82]

Characteristic	PATRICIA	CVT	V501-020	FUTURE I/II	V503-001
Vaccine type	HPV2	HPV2	HPV4	HPV4	HPV9 (vs HPV4)
Population gender	Females	Females	Males	Females	Females
Age range in years	15-25	18-25	16-26*	15-26	16-26
Number of participants	18 644	7466	4065$	17 622	14 215
Duration in years	4	4	3#	4	6
Funding	GSK	US National Cancer Institute	Merck&Co	Merck&Co	Merck&Co
Number of countries	14	1 (Costa Rica)	18	24	18

** Heterosexual men 16-23 years and males-having-sex-with-males (MSM) 16-26 years. $ Of which 602 MSM. # Duration reported as median follow-up.*

5.2.1 Cervical cancers

Results of the major trials for HPV2, HPV4 and HPV9 are presented in Table 7 for the most advanced outcomes that are reported (cervical intra-epithelial neoplasia grade 3 and over or CIN3+), and which were confirmed in a recent meta-analysis.[76] In large trials involving each 14-17 000 subjects in total, the efficacy of ≥1 dose of each of the three vaccines against CIN3+ due to respective **vaccine types** (or the 5 additional types for HPV9) was 100% in the HPV naïve population, Table 7. In the total population, the efficacy of ≥1 dose against vaccine type CIN3+ was also similar between HPV2 and HPV4 at 46% (Table 7).

Analyses per protocol included women naïve to HPV-16/18, and efficacy against vaccine type CIN3+ was lower for HPV2 at 80% (95% CI: 9; 96) than for HPV4 at 97% (57; 100) for three doses.[83] This lower efficacy of HPV2 in women naïve for HPV-16/18 types after 3 doses in the PATRICIA trial contrasts with the high efficacy of HPV2 in totally naïve women for the same outcome and for at least one dose (100%, Table 7). In an additional analysis of the PATRICIA trial using a "HPV type assignment algorithm" to attribute a causal association between a lesion and the HPV type, the efficacy of HPV2 in women naïve for HPV-16/18 types against vaccine type CIN3+ after 3 doses increased to 100% (36; 100).[83]

Efficacy of ≥1 dose against CIN3+ **due to any type** was higher (93%) for HPV2 compared to HPV4 (46%), but were measured in different trials (PATRICIA for HPV2, FUTUREI/II for HPV4), both involving around 10 000 women. A similar pattern was observed for CIN2+, at 65% (53; 74) for HPV2 vs. 43% (24; 56) for HPV4 among naïve women.

Further, a large follow-up study of three HPV2 trials (including PATRICIA) and based on the Finnish cancer registry followed over 18 000 Finnish women (15 627 unvaccinated and 2465 vaccinated) during 4.5 to 10 years. Seventy-five (75) cases of CIN3 and 4 cases of invasive cervical cancers were detected in the unvaccinated cohort, against 4 CIN3 cases in the vaccinated women.[80] The protective effect of HPV2 against CIN3+ of any HPV type was 66% (8; 88).[80] Due to small numbers, there was no separate efficacy results against invasive cervical cancer.

The only trial assessing HPV9 efficacy, the V503-001 study involving more than 14 000 women (ITT), used HPV4 vaccinees as control group and estimated at 100% the additional protection against CIN3+ due to the five additional vaccine types in a naïve population.[82, 84, 85] However, in this trial only a small number of CIN3+ cases were involved (0 vs 7 in vaccinated and controls, respectively).[82, 84] No additional protection was conferred by HPV9 compared to HPV4 in the total population against CIN2+ due to the five vaccine types (16% not significant) or when any HPV type was considered, i.e. 0% (-17; 14), despite high numbers of cases (325 vs 326).[84] However, the cross-protection of HPV4 (control group) against these five additional types would tend to underestimate the additional protection conferred by HPV9 measured in that trial.

No cases of invasive cervical cancer were reported in the trials investigated for the three vaccines, but cancer outcomes were reported in the follow-up (observational) HPV2 study in Finland (see above).[80]

A 2018 meta-analysis summarised the HPV2 and HPV4 efficacy based on published trials.[76] HPV2 efficacy against CIN3+ due to any HPV type from two trials, i.e. PATRICIA with around 17 000 women (ITT) enrolled, and a small Japanese trial involving 1000 women (ITT). As expected, efficacy against CIN3+ was close to the estimates from the Patricia trial, at 92% (77; 97) in the naïve population and 45% (29; 57) in the total population.[76] The Japanese trial is not described according to our selection criteria. For HPV4, only the results of the FUTURE I and FUTURE II trials were summarised in the meta-analysis, which correspond to the efficacies reported in Table 7. The Nordic Cochrane has recently criticised the Cochrane systematic review cited above,[76] claiming that it was incomplete and ignored important evidence of bias.[86] Although the debate is not solved, the data reported are in line with the original studies and with our selection criteria.

Table 7 – Vaccine efficacy against cervical outcomes

Vaccine	Trial Country	Population Trial duration	Number of participants in		Outcome	HPV types	Vaccine efficacy (95% CI) in % in	
			Total population*	Naïve population**			Total population*	Naïve population**
HPV2	PATRICIA[87] America, Asia, Europe	15-26 years Mean follow-up: 2.9-3.7y	HPV2: 8694 Control: 8708	HPV2: 5466 Control: 5452	CIN3+	Any	46 (29; 59) (≥ 1 dose)	93 (79; 99) (≥ 1 dose)
						Vaccine	45 (23; 62) (≥ 1 dose)	100 (86; 100) (≥ 1 dose)
HPV4	FUTURE I,[88] and FUTURE I/II[89] in Arbyn review[76] America, Asia, Europe, Australia	15-26 years Mean follow-up: 3-3.6y	HPV4: 8562 Control: 8598	HPV4: 4616 Control: 4680	CIN3+	Any	19 (4; 31) (≥ 1 dose)	46 (18; 64) (≥ 1 dose)
						Vaccine	45 (30; 56) (≥ 1 dose)	100 (82; 100) (≥ 1 dose)
HPV9	V503-001[82, 84, 85] America, Asia, Europe	16-26 years Follow-up: 6y	HPV9: 7099 HPV4: 7105	HPV9: 2976 HPV4: 3009	CIN2+ or CIN3+	Five vaccine types (HPV9 non HPV4)	CIN2+: 16 (-6; 34) (≥ 1 dose)	CIN3+: 96% (76; 100) (≥ 1 dose)
						Any	CIN2+: -0.3 (-17; 14) (≥ 1 dose)	-
						Non-HPV9	-	CIN2+: 14 (-49; 49) (≥ 1 dose)

** Corresponds to the intention-to-treat population. ** Corresponds to the completely-naïve population (i.e. a "best-case" scenario valid when vaccination is done before sexual debut). CIN2+: cervical intra-epithelial neoplasia grade 2 and over (i.e. CIN2, CIN3, adenocarcinoma in situ and cervical cancer). CIN3+: cervical intra-epithelial neoplasia grade 3 and over (i.e. CIN3, adenocarcinoma in situ and cervical cancer). CI: confidence interval.*

5.2.2 Anal cancer

Table 8 – Vaccine efficacy against anal outcomes

Vaccine	Trial Country	Population Trial duration (years)	Number of participants in		Outcome	HPV types	Vaccine efficacy (95% CI) in % in	
			Total population*	Naïve population**			Total population*	Naïve population**
HPV2	CVT[90] Cost Rica	Female, 18-25y Median follow-up: 4.1y	HPV2: 2103 Control: 2107	HPV2: 1003 Control: 986	Anal infection	Vaccine	62 (47; 73) (≥ 1 dose)	84 (67; 93) (3 doses)
						Non-HPV2†	49 (30; 64)† (≥ 1 dose)	62 (43; 75)† (3 doses)
HPV4	V501-020[77, 78] Australia, Brazil, Canada, Croatia, Germany, Mexico, Spain, United States	MSM, 16-26y Mean follow-up: 2.5-2.8y	HPV4: 299 Control: 299	HPV4: 194 Control: 208	AIN2 and AIN3	Vaccine	54 (18; 75) (≥ 1 dose)	75 (9; 95) (3 doses)
					AIN1+	Any	26 (-1; 46) (≥ 1 dose)	55 (8; 79) (3 doses)
				HPV4: 129 Control: 129		Non-HPV4 high risk‡	12 (-39; 44)‡ (≥ 1 dose)	-35 (-581; 71)‡ 5 vs 4 cases (≥ 1 dose)
HPV9	Not available							

** Corresponds to the intention-to-treat population. ** Corresponds to the completely-naïve population (i.e. a "best-case" scenario valid when vaccination is done before sexual debut) or to the per-protocol population when the previous results are not available. † Efficacy against non-vaccine-types 31, 33 and 45. ‡ Efficacy against non-vaccine types 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59. AIN2 and AIN3: anal intra-epithelial neoplasia grade 2 or 3. AIN1+: anal intra-epithelial neoplasia grade 1 and over. CI: confidence interval, CVT: Costa-Rica vaccine trial, MSM: men having sex with men.*

The only efficacy trial against anal lesions involved HPV4. This trial (V501-020) was performed in 18 countries and involved 602 MSM subjects only (Table 8).[81] However, the reported evidence of vaccine efficacy against precancerous anal lesions is limited, measured in a specific population at higher risk, and involves a small number of cases with large confidence intervals as a result.[77, 78] No case of anal cancer has been reported during the study period. HPV2 and HPV9 obtained the EMA authorisation based on non-inferiority studies based on immunological outcomes only, i.e. comparing antibody responses after HPV2 or HPV9 vaccination with those of HPV4.

The HPV2 efficacy against anal HPV infection was assessed in a trial performed in Costa Rica among 2000 (naïve population) to 4000 (ITT population) women. [90] HPV2 efficacy against anal infection due to vaccine type was relatively high in both the naïve and the total populations at 84% and 62% respectively. There was also a moderate cross-protection of HPV2 against the three high-risk types 31, 33 and 45 in both populations. However vaccine efficacy estimates against HPV infections should be interpreted with caution as most of them clear spontaneously.

5.2.3 Vulvar and vaginal cancers

Table 9 – Vaccine efficacy against vulvar and vaginal outcomes

Vaccine	Trial Country	Population Trial duration (years)	Number of participants in		Outcome	HPV types	Vaccine efficacy (95% CI) in % in	
			Total population*	Naïve population**			Total population*	Naïve population**
HPV2	CVT[91] Costa Rica	18-25 years Follow-up: 4y	HPV2: 508 Control: 536	-	Vulvar infection	Vaccine	54 (5; 79) (≥ 1 dose)	-
HPV4	FUTURE I/II including V501-007[92] America, Europe, Asia	16-26 years Mean follow-up: 3y	HPV4: 9087 Control: 9087	HPV4: 7811 Control: 7785	VIN2 and VIN3 (vulvar)	Vaccine	62 (10; 85) (≥ 1 dose)	100 (42; 100) 0 vs 8 cases (3 doses)
						Any	51 (9; 75) (≥ 1 dose)	-
					VaIN2 and VaIN3 (vaginal)	Vaccine	82 (17; 98)	100 (31; 100) 0 vs 7 cases (3 doses)
						Any	43 (-22; 74) (≥ 1 dose)	-
HPV9	V503-001[82, 85] America, Europe, Asia	16-26 years Follow-up: 6y	HPV9: 7099 HPV4: 7105	HPV9: 6009 HPV4: 6012	VaIN2+ (vaginal)	Five vaccine types (HPV9 non HPV4)	-	100 (-72; 100) 0 vs 3 cases (3 doses)

** Corresponds to the intention-to-treat population. ** Corresponds to the completely-naïve population (i.e. a "best-case" scenario valid when vaccination is done before sexual debut) or to the per-protocol population when the previous results are not available. VIN2 and VIN3: vulvar intra-epithelial neoplasia grade 2 or 3. VaIN2 and VaIN3: vaginal intra-epithelial neoplasia grade 2 or 3. VaIN3+: vaginal intra-epithelial neoplasia grade 3 and over (i.e. VaIN2, VaIN3 and vaginal cancer). CI: confidence interval.*

No HPV2 efficacy trial has been conducted against vulvar or vaginal pre-cancers or cancers but the HPV2 efficacy against vulvar HPV infection due to vaccine types has been assessed in the Costa Rica Vaccine Trial (CVT). In the ITT population involving 1000 women, HPV2 efficacy against infection due to vaccine types was moderate at around 50%.[91] The efficacy of HPV4 was assessed in the FUTURE trials, against vulvar and vaginal intra-epithelial neoplasia (VIN and VaIN), and was high against grade 2 and 3 VIN and VaIN due to vaccine types in the naïve population (about 15 000 women) and moderate at around 50% against all types in the total population (about 18 000 women), see Table 9. The efficacy of HPV9 was assessed against VIN and VaIN in a multicentre trial involving more than 14 000 women (ITT) and where the control group was vaccinated by HPV4. In this trial, no cases of VIN were reported. The additional protection against VaIN2+ conferred by HPV9 compared to HPV4 was estimated at 100% in the naïve population but was not significant due to small numbers of cases (0 vs 3 cases in the HPV9 and HPV4 vaccinees, respectively).[82] No cases of vulvar or vaginal cancers were reported in any trial.

5.2.4 Penile cancer

Table 10 – Vaccine efficacy against penile outcomes

Vaccine	Trial Country	Population Trial duration (years)	Number of participants in Total population*	 Naïve population**	Outcome	HPV types	Vaccine efficacy (95% CI) in % in Total population*	 Naïve population**
HPV2	Not available							
HPV4	V501-020[77, 79] Africa, Australia, Europe, America	Male, 16-26y Median follow-up: 2.9y	HPV4: 1817 Control: 1815	HPV4: 1275 Control: 1270	PIN2 and PIN3	Any	-49 (-1683; 83) 3 vs 2 cases (≥ 1 dose)	100 (-426; 100) 0 vs 2 cases (≥ 1 dose)
						Vaccine	-	100 (-426; 100) 0 vs 2 cases (≥ 1 dose)
						Non-HPV4 high risk†	Not available	100 (-3751; 100)† 0 vs 1 cases (≥ 1 dose)
HPV9	Not available							

** Corresponds to the intention-to-treat population. ** Corresponds to the completely-naïve population (i.e. a "best-case" scenario valid when vaccination is done before sexual debut); or to the per protocol population when the previous results are not available. † Efficacy against non-vaccine types 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59. PIN2 and PIN3: penile intra-epithelial neoplasia grade 2 or 3. CI: confidence interval.*

The only trial on penile lesions involved HPV4 and included 2500 (naïve population) to nearly 4000 men (ITT), see Table 10.[77, 93] Although efficacy in the naïve population is estimated at 100% against penile intra-epithelial neoplasia grade 2 or 3 (PIN2/3), it is non-significant and the large confidence interval is due to very low numbers of cases (0 vs 2 cases of PIN2/3 in vaccinated and control arms, respectively).[77] The point estimate for efficacy was even negative for PIN2/3 caused by any type in the total population, likely due to small numbers (3 vs 2 cases of PIN2/3 in vaccinated and control arms, respectively).[93] No case of penile cancer was reported.

5.2.5 Oropharyngeal cancer

Table 11 – Vaccine efficacy against oropharyngeal outcomes

Vaccine	Trial Country	Population Trial duration (years)	Number of participants in		Outcome	HPV types	Vaccine efficacy (95% CI) in % in	
			Total population*	Naïve population**			Total population*	Naïve population**
HPV2	CVT[94] Costa Rica	Female, 18-25y Median follow-up: 4.6y	HPV2: 2910 Control: 2924	-	Oral infection	Any	46 (7; 69) (≥ 1 dose)	-
						Non-HPV2[†]	13 (-61; 54)[†] (≥ 1 dose)	
						Vaccine	93 (63; 100)	
HPV4	NCT01461096[95] Brazil, United States	HIV-infected MSM and female, >27y[‡] Median follow-up: 3.4y	HPV4: 288 Control: 286	-	Persistent oral infection	Vaccine	88 (2; 98) 1 vs 8 cases (≥ 1 dose)	-
HPV9	Not available	-	-	-	-	-	-	-

** Corresponds to the intention-to-treat population. ** Corresponds to the completely-naïve population (i.e. a "best-case" scenario valid when vaccination is done before sexual debut) or to the per protocol population when the previous results are not available. † Efficacy against non-vaccine types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68-73. ‡ The percentages of MSM/female in the population are 82/18%. CI: confidence interval.*

None of the trials evaluated the efficacy of HPV vaccines against oral pre-cancer lesions or cancers. Two trials investigated the efficacy of HPV2 and HPV4 vaccines against oral infection in both genders (Table 11).[94, 95] One trial (using HPV2) involved a general female population of about 6000 women and the other trial involved HPV4 in nearly 600 HIV infected subjects. The difficulty to demonstrate efficacy against HPV-related lesions is related to the difficulty in diagnosing oral disease, as explained in the section 4.3.6. In addition, the levels of oral antibodies needed to protect against oral HPV infection is still unknown, as well as the duration of protection.

Although available trial data are limited, similar patterns are observed as for other cancers: high efficacy against vaccine type (persistent or not) infection (88-93% for both HPV2 and HPV4) and moderate efficacy against any type, at 46% for HPV2.[94, 95] The results for HPV4 should be interpreted with caution given the small sample size and the resulting wide confidence interval.

In addition, an observational US survey conducted among 2627 males and females aged 18-33 years showed that oral HPV infection among subjects vaccinated with HPV4 was reduced by 88.2% (6; 99) compared to non-vaccinated subjects.[96]

5.2.6 Anogenital warts

Table 12 – Vaccine efficacy against genital warts

Vaccine	Trial Country	Population Trial duration (years)	Number of participants in		Outcome	HPV types	Vaccine efficacy (95% CI) in % in	
			Total population*	Naïve population**			Total population*	Naïve population**
HPV2	Not available	-	-	-	-	-	-	-
HPV4	Tejada, 2017[74] meta-analysis (FUTURE I/II, V501-007, V501-019, V501-020)	(Fe)male, 15-45y Follow-up: 2.2-5y***	HPV4: 12 897 Control: 12 904	HPV4: 10 912 Control: 10 917	Genital warts	Vaccine	62 (55; 68) (≥ 1 dose)	95 (75; 99) (3 doses)
HPV9	V503-001[82] America, Asia, Europe	Female, 16-26y Follow-up: 6y	-	HPV9: 6009 HPV4: 6012	Genital warts	Five vaccine types (HPV9 non HPV4)	-	100 (-12; 100) 0 vs 4 cases (3 doses)

** Corresponds to the intention-to-treat population. ** Corresponds to the completely-naïve population (i.e. a "best-case" scenario valid when vaccination is done before sexual debut) or to the per protocol population when the previous results are not available. *** Most studies had follow-up periods between 26 and 36 months, except for one study with a follow-up of 60 months. Only 56.3% of women were enrolled in the extended follow-up phase (37-60 months), and groups were not comparable in percentage and reasons of loss of follow-up during this second phase of the study. CI: confidence interval.*

No HPV2 trial has measured the efficacy against genital warts and this is not an authorised indication for HPV2, which does not contain the types 6 and 11 that are responsible for the majority of genital warts. However, the PATRICIA trial evaluated the efficacy against persistent infection with types 6 and 11 (due to cross-protection, see 5.3) at 11% (-7; 26) and 35% (11; 52) among total (nearly 16 000 women) and naïve (about 10 500 women) populations, respectively, in women aged 15-25 years.[97] A few observational studies have assessed the effect of HPV2 on anogenital warts but the effect among vaccinated subjects was not measured.

A 2017 meta-analysis has summarised the HPV4 efficacy against genital warts from five trials involving women and one trial involving men, totalling more than 25 000 individuals (ITT), and showed a high efficacy at 95% in naïve subjects and a significant efficacy of 62% in the total population of 15-45 years of age (Table 9).[74]

The efficacy of HPV9 against genital warts was assessed in a trial involving 12 000 naïve women and where the control group was HPV4 vaccinees. The additional protection against genital warts conferred by HPV9 compared to HPV4 was estimated at 100% in the naïve population but was not significant due to small numbers of cases (0 vs 4 cases in the HPV9 and HPV4 vaccinees, respectively).[82]

A retrospective study in Belgium evaluated the population level effect and impact of vaccination with HPV4 on the prevalence of genital warts in females and males.[61] Vaccine effectiveness against treated genital warts was 88% (79; 93) in fully vaccinated women, higher when the first dose was given younger and remained high for over 4 years post-vaccination in all ages.

5.2.7 Additional results for HPV9

Two trials compared HPV9 to HPV4 vaccines, one in women and one in men. The trial in women assessed HPV9 efficacy compared to HPV4 vaccination, i.e. against disease due to the five additional types over a 6-year period and results are described in Table 7 and Table 9.[82, 84] The two trials also measured immunogenicity and showed that the levels of antibodies generated by HPV9 were comparable (non-inferior) to those elicited by HPV4 against the types that are in common in both vaccines.[84, 98]

One study compared the immune response elicited by HPV9 among MSM, heterosexual men and women. The specific antibody response was higher in heterosexual men than in women but lower in MSM.[3]

5.3 Bridging studies

Efficacy in pre- and early-adolescents, the primary targets for HPV vaccination, has not been demonstrated in trials that usually target older individuals (generally above 15 years). To support the authorisation of HPV vaccines in younger age groups, in which pre-cancerous outcomes would appear much later, immunogenicity studies have been conducted and compared to immunogenicity results from the trial population (bridging studies). Young adolescents have demonstrated strong immunogenicity results in bridging studies of the HPV2 and HPV4 vaccines.[81] In a US study enrolling 506 girls and 510 boys (10-15 years of age) and 513 women (16-23 years of age), 3 doses of HPV4 induced geometric mean titers (GMTs) in girls and boys that were 1.7–2.0 and 1.8–2.7-fold higher, respectively, than the titers induced in women.[99] Similarly, in a Danish study enrolling 158 girls aged 10-14 years and 458 women aged 15–25 years, 3 doses of HPV2 induced GMTs in girls that were 2.1–2.5-fold higher than those induced in women, as measured by ELISA.[100] Response with a 2-dose schedule was non-inferior to a 3-dose schedule.[81]

For HPV9, an international study (including 17 countries) that enrolled 1800 girls and 600 boys aged 9-15 years and 400 women aged 16-26 years demonstrated that 3 doses of HPV9 vaccine induced anti-HPV antibody responses in girls and boys that were non-inferior to responses in young women.[101]

These result supported bridging the HPV vaccine efficacy results from young women aged 16-26 years of age to girls and boys 9-14 years of age.

5.4 Cross-protection

HPV vaccines may provide some protection against the HPV types that are not included in the vaccines, called cross-protection, at least against cervical lesions. A number of studies have shown that both HPV2 and HPV4 provide some level of cross-protection against high-risk HPV types other than 16 and 18, in particular 31, 33 and 45, which are included in the HPV9 vaccine.[2] We did not find data on cross protection conferred by HPV9, likely because non-HPV9 types cause a very small proportion of cancers (see 4.3).

For cervical lesions, two meta-analyses assessed the cross-protection of HPV2 and HPV4 against the five high-risk types not included in both vaccines (31, 33, 45, 52 and 58) and concluded that cross-protection is higher for HPV2 compared to HPV4.[76, 102] For instance an analysis of the most comparable trial populations (FUTURE I/II and PATRICIA) showed that HPV2 cross-protection against CIN2+ for the types 33 and 45 was 82% and 100% compared to 24% and -52% for HPV4.[102] Two HPV2 trials not included in the above meta-analysis found significant efficacy against types 31, 33 and 45.[76] An analysis of the PATRICIA trial also found an HPV2 efficacy against CIN3+ due to all non-HPV2 high-risk types at 91% in the naïve and 48% in the total population.[103] The better cross-protection of HPV2 may partly explain the higher HPV2 efficacy against CIN3+ due to any type compared to HPV4 (Table 7).[76] The HPV9 efficacy against non-HPV9 types could not be assessed by the main trial because HPV9 vaccinees were compared to HPV4 vaccinees. However, it suggests that the level of cross-protection of HPV9 against non-HPV9 types is not better than the one of HPV4, as no additional efficacy against CIN2+ due to the non-HPV9 types was observed in those vaccinated with HPV9 compared to those vaccinated with HPV4 (14% not significant).[82, 84]

For anal outcomes, a HPV2 efficacy trial in women (Table 8) showed a significant cross-protection against anal infection in total and naïve populations, at 49% and 62% for three non-HPV2 types, respectively, but no high grade lesions were included.[90]

In males, the HPV4 trial did not show significant efficacy against disease due to non-vaccine types, i.e. anal and penile high grade lesions and anogenital warts.[77, 78, 93]

For OPC, HPV2 did not show efficacy against oral infection due to 17 non-HPV2 types (13%, Table 8).[94]

5.5 Duration of protection

The duration of protection has been evaluated mostly in women for cervical cancer as this was the first indication of HPV vaccines. The 2018 Cochrane meta-analysis on cervical cancer showed that HPV2 and HPV4 efficacy against CIN2+ remained stable throughout the trial duration (around four years), in both naïve women and total population.[76] The longest duration of follow-up for which protection data are reported was around 8-10 years for both HPV2 (PATRICIA) and HPV4 (FUTURE I/II) and continued protection was observed at the end of the follow-up period.[104, 105] The trial comparing HPV9 to HPV4 vaccinees showed a sustained efficacy of HPV9 against genital lesions in women up to 6 years in the naïve population, but no longer follow-up is yet available.[82]

As described in 5.2.1, the study based on the Finnish cancer registry followed Finnish women enrolled in three HPV2 trials during 4 to 10 years, and detected 78 cases of CIN3 and 4 cases of invasive cancers.[80] The protective effect of HPV2 against CIN3+ any HPV type was 66% over the follow-up period.[80] However, the analysis does not present efficacy stratified by time after vaccination.

The 10-year protection of HPV4 against HPV-related genital lesions, including genital warts, was measured in preadolescents and adolescents (9-15 years) of both genders, vaccinated in an earlier trial. No case of genital HPV-related disease due to vaccine types had been detected in the study.[105]

The duration of cross-protection was also assessed. Although waning of cross-protection of HPV2 was suggested by a 2012 review,[102] a 2018 review found HPV2 cross-protection against infection with types 31, 33 and 45 to last more than nine years in two recent studies (efficacy between 35% and 71%).[76] Cross-protection of HPV4 was noted up until 4 years after vaccination in women for CIN1+ (not for CIN2+),[103] but no cross-protection against HPV-related genital lesions was shown at 10 years in a follow-up study.[105] Cross-protection in males was not reported (see 5.4).[77]

As conclusion, the protection conferred by HPV vaccines against HPV-related diseases seems to last as long as 10 years in women against cervical lesions, and in both gender against anogenital warts. However, no longer follow-up is available and whether the same level of protection can be expected for men or for other types of cancers is still unknown. The high level of cross-protection of HPV2 seems to last longer than HPV4 cross-protection (more than 9 years versus up to 4 years), but this needs to be confirmed in comparative (head to head) trials.

5.6 Efficacy of shorter schedule

Most efficacy trials used a 3-dose schedule. A number of studies have shown that a 2-dose schedule provides a similar level of protection against clinical outcomes such as persistent cervical infection.[76, 90]

In the CVT trial, HPV2 efficacy against persistent 12-months cervical infection with vaccine types was 81% (71; 88) for 3-dose (5967 subjects) and 84% (50; 96) for 2-dose (802 subjects) with a follow-up of four years.[106] However, an important question is whether a 2-dose protects for a similar duration and provides a similar level of cross-protection compared to a 3-dose schedule.[106] A post-hoc analysis combined CVT and PATRICIA subjects and found similar and significant efficacy estimates against cervical incident infection due to vaccine types after three (77%), two (76%) and one doses (86%) after four years.[107] Similar findings were observed for non-HPV2 types HPV-31/33/45 with 60%, 38% and 37% for three, two and one doses, respectively. Another follow-up study of the CVT trial monitored persistent infections in vaccinated subjects for 7 post-vaccination years.[108] Vaccine efficacy could not be computed because no placebo group was possible as they were all offered the vaccine at the end of the trial period. The cumulative incidence of persistent infection with vaccine types remained low and similar between groups having received one, two or three doses during the trial period.[108] The prevalence of (non-HPV2) types 31/33/45 was also low and similar across vaccine groups. The 2018 Cochrane meta-analysis also concluded that no significant difference in protection was observed when fewer than three doses were given.[76] Additional studies

looked at the duration of antibody titres in a 2-dose vs a 3-dose schedule but these outcomes are more difficult to interpret.

Four studies also found a high vaccine effectiveness of a single dose of HPV2 of HPV4. However, the interpretation of these studies is hampered by selection biases and limited sample size.[2]

5.7 Comparison across vaccines

HPV2 and HPV4 confer similar protection against cervical lesions associated with HPV-16/18 types. However, the trials suggest that HPV2 has a higher efficacy than HPV4 against any CIN3+ (i.e. due to any HPV types) in the naive and in the total population: 93% vs. 46% in naïve and 46% vs. 19% in total population, Table 7.[76] This difference may be due to differences in the populations enrolled in the trials, differences in laboratory methods used, but also to better cross-protection of HPV2 (see 5.4). One study also showed that neutralizing antibodies against HPV-16 and HPV-18 were around 4 and 7-fold higher, respectively, for HPV2 compared to HPV4 in women 18–26 years of age seven months after vaccination.[2, 17, 109, 110] Five years after vaccination, antibodies levels were 2-12 times higher in those vaccinated with HPV2 compared to HPV4, across all age groups. However, the clinical significance of antibody levels is still unclear as no immunological surrogate of protection has been defined.

No trial has yet compared HPV2 to HPV4 or HPV9. Studies using both vaccines (head-to-head) and comparing diseases endpoints would be needed to determine whether differences exist in protection and in the duration of vaccine-induced protection.

5.8 Vaccine safety

The recent reviews that assessed safety did not find an increased risk of serious adverse effects following the three HPV vaccines.[2, 72, 76] Two 2018 systematic reviews of trials, one in females and one in males, concluded that the risk of mild or serious adverse events was similar between controls and those vaccinated.[2, 72] As for any vaccine, the short-term local adverse events were more common in vaccines compared to those in the control group.[76] A WHO committee reviewed in 2016 the post-licensure surveillance data from many countries, and concluded that systemic reactions were generally mild and self-limiting.[2]

It should be noted that the safety in males has been less investigated compared to females, as trials were smaller and HPV vaccines started recently to be used in that group, at least in the EU.

However, a number of safety concerns have been raised in recent years. In 2015, a complaint was submitted to the EMA by the Danish health authorities regarding two safety signals, the complex regional pain syndrome (CRPS) and the postural orthostatic tachycardia syndrome (POTS).[111] An expert group assessed additional pre- and post-licensure data but concluded that no causal relation could be established between HPV vaccines and these health problems.[111] In 2015, a report from the French drug agency suggested an increased risk on Guillain-Barre syndrome (GBS) related to HPV vaccination,[112] and the WHO Global Advisory Committee on Vaccine Safety (GACVS) recommended to conduct further studies. A large observational self-controlled case series study from the UK involved 101 GBS episodes ascertained from a population given approximately 10.4 million HPV vaccine doses, and did not find any significant increased risk for GBS after any dose of the HPV vaccine.[113]

The WHO GACVS conducted an update review of post-licensure safety data in 2017 and concluded that no safety concerns have arisen during the pre-licensure clinical trials or in post-licensure surveillance.[114] They also reviewed data from a Danish national cohort study involving 540 805 pregnancies and US data from >92 000 eligible pregnancies, and concluded that no adverse outcomes in terms of birth defects were observed. Based on additional data on POTS and CRPS, the GACVS concluded that there is still no evidence to suggest a causal association between HPV vaccine and CRPS and POTS.

A 2018 Australian review of 109 studies, including 15 population-based studies in over 2.5 million vaccinated persons across six countries, also confirmed that no increased risk for serious adverse events, including CRPS and POTS, could be associated with HPV vaccination.[115]

6 HERD EFFECTS OF HPV VACCINATION

6.1 Methods

In this section, we describe data on the herd effect generated by HPV vaccination programmes, i.e. on unvaccinated individuals. We retrieved the most recent systematic reviews on the topic and added recent results from Australia as this is the first country in the world to include boys in the HPV vaccination programme. However all these studies assessed herd effects on early outcomes, such as HPV infection, genital warts and CIN, due to the insufficient duration of existing HPV vaccination programmes.

6.2 Systematic reviews

Two systematic reviews described the herd effects of girl vaccination based on 28 studies undertaken in 9 high-income countries.[15, 116] The magnitude of the herd effects depends on vaccine uptake and is higher in high uptake countries.[15, 116] In the meta-analyses, the effects of vaccinating girls, mostly below 20 years of age, with HPV2 or HPV4 on unvaccinated subjects were measured up to 4 years after the start of the programmes. In countries with girl uptake ≥ 50%, significant decreases between the pre- and post-vaccination periods were observed in the incidence of anogenital warts in boys aged 15-19 years (-34%), in men aged 20-39 years (-18%) and in women aged 20-39 (-32%), which suggests herd effects. There was also a trend towards herd protection against HPV-16/18 infection in those populations, but results were not significant. In women aged 20-39 years an increase in CIN2+ is observed, which is inconsistent. In countries with low girl uptake (< 50%), there was no indication of significant herd effects on anogenital warts or HPV-16/18 infection. However herd effects take even longer to become evident where uptake is lower and those results are thus not seen as a reason to rule out herd effects in settings where uptake is low.

Table 13 – Herd effects of girl-only vaccination with HPV2 or HPV4, stratified by gender, age and uptake in girl-only vaccination

Change in % (relative risk, 95%CI)	Population	< 50% uptake in girls	≥ 50% uptake in girls
CIN2+	Women (20–39 years)	-3% (0.97, 0.92-1.02)	+11% (1.11, 1.10-1.12)
Anogenital warts	Women (20–39 years)	+2% (1.02, 0.90-1.16)	-32% (0.68, 0.51-0.89)
	Boys (15–19 years)	+7% (1.07, 0.93-1.22)	-34% (0.66, 0.47-0.91)
	Men (20-39 years)	+13% (1.13, 0.95-1.33)	-28% (0.82, 0.72-0.92)
HPV-16/18 infection	Women (20–39 years)	-4% (0.96, 0.77-1.18)	-58% (0.42, 0.16-1.10)
	Boys (15–19 years)	-	-63% (0.37, 0.12-1.10)
	Men (20-39 years)	-	-15% (0.85, 0.35-2.03)

CIN2+: cervical intra-epithelial neoplasia grade 2 and over (i.e. CIN2, CIN3, adenocarcinoma in situ and cervical cancer).

6.3 Australia

Australia was one of the first countries to implement a fully publicly-funded, school-based HPV vaccination program. It started in 2007 with the immunisation of girls aged 12-13 years with 3 doses of HPV4, and was followed in 2013 by the immunisation of boys aged 12-13 years. In addition, 2-year catch-up programmes targeted older subjects (12 to 26 year-old females and 14 to 15 year-old males). High vaccine uptakes have been achieved, at 70-80% for boys and girls.

A 2014 cross-sectional study compared the prevalence of HPV infection in Australian women aged 18-24 years and recruited in the pre-vaccination (2005-2007, n=202) and in the post-vaccination (2010-2012, n=1058) era with HPV4.[117] Compared to the pre-vaccination sample, the reduction in the prevalence of HPV4 vaccine types after initiation of the Australian HPV vaccination programme was 35% (4; 57) in unvaccinated women, which suggests herd immunity.

The herd effects observed in young males as a result of the female program are described in a recent study. A cross-sectional study compared the presence of antibodies (seropositivity) to HPV types 6, 11, 16 and 18 in Australian men aged 15-39 years whose serum samples were collected before (in 2005, n=546) and after (2012-2013, n=735) the start of the girl HPV immunisation, and in any case before implementation of the male immunisation programme.[118] Compared to the baseline 2005 seroprevalence of the HPV4 vaccine-types, substantial reductions were observed in unvaccinated males across all age groups (15-19, 20-29 and 30-39 years). Seropositivity to HPV types 6, 11, 16 and 18 in the 15-19 year-old males was 4.8% (2.1; 9.3) in the girl pre-vaccination period and 1.4% (0.1; 5.1) in the post-vaccination period. In the 20-29 age group seropositivity was 24.9% (19.2; 31.3) and 8.9% (6; 12.6), and was 40% (32.6; 47.8) and 12.4% (8.7; 16.7) in the 30-39 age group, in the girl pre- and post-vaccination periods respectively, and the differences were statistically significant. HPV infection was not measured.

7 HPV VACCINATION OF MALES IN OTHER INDUSTRIALISED COUNTRIES

An overview of the status of male HPV vaccination in other countries is provided in the next sections and summarised in Table 14, and has been last updated in December 2018.

7.1 Boys

Based on a recommendation published in November 2011 by the Pharmaceutical Benefits Advisory Committee,[i] **Australia** became in February 2013 the first country in the world to extend their school-based HPV immunisation programme to include boys aged 12-13 years of age.[119] Since 2018, Gardasil 9 is used in the school-based National HPV Vaccination Program. It replaced Gardasil which was in use between 2007 and 2017.[j]

In **Canada**, in January 2012, the National Advisory Committee on Immunisations recommended immunisation for boys and men aged 9 to 26. Since then, all Canadian provinces and territories have gradually expanded their publicly-funded HPV vaccination programs (originally targeted to females) to cover school-age boys between 2013 and 2018.[120] The age at vaccination varies across provinces/territories but vaccination usually occurs around 9-12 years of age. The vaccine currently administered is Gardasil 9,[k] except in the province of Quebec that recently opted for a mixed schedule made of 1 dose of Gardasil 9 followed by 1 dose of Cervarix.[l]

In August 2013, **Austria** was the first European country to recommend gender-neutral adolescent HPV vaccination as early as 9 years of age.[121] Since February 2014, HPV vaccination is offered free of charge to all children around 9 years of age as part of the existing school vaccination programme.[122] The vaccine currently administered is Gardasil 9.[m, n]

In **Italy**, free of charge HPV vaccination of 11-year-old boys started in 2015-16 in several regions.[o] In 2017, Italy made HPV vaccination of boys aged 11 years part of the "Livelli Essenziali di Assistenza", a list of essential services that must be made available to all Italian residents free of charge. Regions and Provinces had 2 years to implement this decision. Free of charge HPV vaccination of 11-year boys was then introduced in 2017 in 10 regions; the remaining regions introducing it this year (2018).[p] In most regions, Gardasil 9 is administered.

In **Israel**, the Ministry of Health recommends that all boys and girls aged 13-14 years should be vaccinated against HPV and receive Gardasil as part of the school-based routine vaccination programme. HPV vaccination of girls at middle school was introduced in 2013, while boys vaccination begun in the 2015-2016 academic year.[q]

In **New Zealand**, the HPV Immunisation Programme started in September 2008 for girls and in January 2017 for boys. HPV immunisation is funded for everyone aged 9–26 years. The vaccine is available free of charge through general practices from 9 years of age and is also offered to boys and girls through participating schools at around 12 years of age. Gardasil has been used since 2008 and was replaced by Gardasil 9 from the beginning of 2017.[r]

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i http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2011-11/pbac-psd-quadrivalent-nov11

j http://www.hpvvaccine.org.au/

k http://www.cancerview.ca/preventionandscreening/hpv-vaccination-programs-across-canada/

l https://www.inspq.qc.ca/en/publications/2458

m https://www.bmgf.gv.at/home/EN/Health_care_services/Free_vaccinations/

n https://www.sciencedaily.com/releases/2017/10/171030095616.htm

o https://www.apss.tn.it/-/piano-delle-vaccinazioni-aggiornato-il-calendario

p http://www.regione.piemonte.it/sanita/cms2/notizie-87209/notizie-dalle-asl-e-dalle-aso/285-25-6-2018-vercelli-parte-la-campagna-di-vaccinazione-anti-hpv-anche-per-i-ragazzi

q https://www.health.gov.il/English/Topics/Vaccination/HPV/Pages/default.aspx

r https://www.health.govt.nz/your-health/healthy-living/immunisation/immunisation-older-children/human-papillomavirus-hpv

Table 14 – Status of HPV vaccination of males in some other industrialised countries (update December 2018)

Male HPV vaccination		Girl uptake (%)^	Recommendation		Vaccination funded#		
			Start date	Age (years)	Start date	Age (years)	Vaccine
Boys							
Australia		70-80	2011	12-13	2013	12-13	Gardasil 9
Canada	Quebec	80	2012	9-26	2018	9-12*	Gardasil 9 + Cervarix§
	Elsewhere		2012	9-26	2013-2018*	9-12*	Gardasil 9
Austria		60-65	2013	>9	2014	9	Gardasil 9
Italy		NF	2017	11	2015-2018*	11	Gardasil 9
Israel		NF	NF	NF	2015	13-14	Gardasil
Switzerland		NF	2015	11-26	2016†	11-13	Gardasil
New Zealand		NF	NF	NF	2017	9-26	Gardasil 9
Norway		70-80	NF	NF	Autumn 2018	12	Cervarix
Germany		~50	June 2018	9-14	Sept 2018	-	Cervarix or Gardasil 9
UK		>85	July 2018	12-13	Next years	-	(Gardasil)‡
Ireland		65% (2018)	December 2018	12-13	2019	12-13	Gardasil 9
Denmark		NF	NF	NF	Next years	12	NF
Sweden		80	-	-	Ongoing discussions	-	-
Netherlands		60	-	-	Ongoing discussions	-	(Cervarix)‡
France		17.2 (2014)	NF	NF	Ongoing discussion	-	-
MSM							
Canada		80	Quebec		2016	< 26	Gardasil 9
			British Columbia		NF	< 26	Gardasil 9
			Prince Edward Island		NF	No limit	Gardasil 9
France		17.2 (2014)	2016	< 26	NF	< 26	Gardasil 9
Ireland		NF	NF	NF	2017	< 26	Gardasil
UK		>85	NF	NF	2018	< 45	Gardasil

** Depending on the provinces/regions. § One dose of Gardasil 9 followed by one dose of Cervarix in the Québec since 2018. † Not all Swiss cantons implement HPV vaccination of boys yet. ‡ Vaccine currently administered in girls. ^ Girls uptake at the time of the recommendation. # Vaccination is either reimbursed or implemented in an organised vaccination programme. NF: information not found.*

In **Switzerland**, HPV vaccination is recommended by the Federal Office of Public Health and the Swiss Commission for Vaccination for all girls (since 2007) and boys (since 2015) aged 11 to 26 years (i.e. general vaccination for 11-14 years, catch-up vaccination for 15-19 years and case-base vaccination for 20-26 years).[st] However the extend of this programme considerably varies between cantons (e.g. simple distribution of educational material, informing parents that vaccination is available, school-based vaccination). Most Swiss cantons integrated gender-neutral HPV vaccination in their cantonal vaccination programme and started school-based free of charge vaccination of boys in the 9th grade (11-13 years) with Gardasil. This is the case for example in the cantons of Fribourg,[u] Neuchâtel,[v] Berne,[w] and Geneva[x] since the school year 2016-2017, or in the canton of Jura since the school year 2017-2018.[y]

In **Norway**, the HPV vaccine has been offered to girls at around 12-year-old since the 2009/2010 school year. In August 2018, the Norwegian Institute for Public Health announced that HPV vaccination will also be offered to all boys of the same age from the school year 2018/2019. The vaccine used so far in the Norwegian immunisation programme for girls is Cervarix,[z] and this vaccine will also be used for boys (Personal communication B. Winje, Norwegian Institute of Public Health).

In **Germany**, free of charge HPV vaccination for girls started in 2007. In June 2018, the German Standing Committee on Vaccination (STIKO) recommended HPV vaccination for boys aged 9 to 14 years with either Cervarix or Gardasil 9.[aa, 12, 123] Reimbursement of the vaccine by the German statutory Health insurance was decided in September 2018.

In its 2017 interim statement the **UK** Joint Committee on Vaccination and Immunisation (JCVI) expressed a negative advice against the extension of HPV immunisation to boys, as it was considered as likely not cost-effective.[13] The JCVI revised its advice and in July 2018, issued a final statement which recommends a gender-neutral HPV vaccination programme to all adolescents aged 12-13 years.[14] Following this advice, the Public Health Minister announced that adolescent boys will effectively be offered HPV vaccination.[bb] So far, Gardasil is routinely offered to girls aged 12 to 13 years, and provided free on the NHS up to the age of 18.[cc]

In **Ireland**, the Health Information and Quality Authority (HIQA) has recently published its assessment report (December the 7th 2018) and advised to extend HPV vaccination to boys aged 12-13 years and to adopt Gardasil 9.[124] On the same day, the Minister of Health announced that HPV vaccination will be extended to boys in 2019, subject to a favourable review of the content of the HIQA report by officials in the Department of Health.[dd, ee] The vaccine used so far in the Irish immunisation programme for girls is Gardasil.[124]

s https://www.bag.admin.ch
t https://www.infovac.ch
u https://www.fr.ch/smc/sante/prevention-et-promotion/vaccination-contre-les-papillomavirus-humains-hpv
v https://www.ne.ch/autorites/DFS/SCSP/medecin-cantonal/maladies-vaccinations/Pages/hpv.aspx
w https://www.gef.be.ch/gef/fr/index/gesundheit/gesundheit/infektionskrankheiten impfungen/hpv-impfung.html
x http://ge.ch/enfance-jeunesse/promotion-de-sante-prevention/visite-de-sante-accompagnement/controle-vaccinations
y https://www.jura.ch/CHA/SIC/Centre-medias/Communiques-2017/Vaccination-contre-les-HVP-aussi-pour-les-garcons-des-la-rentree-scolaire-2017-2018.html
z https://www.fhi.no/en/id/vaccines/childhood-immunisation-programme/vaccines-in-CIP/vaccine-against-hpv-human-papilloma-virus/
aa https://www.rki.de/EN/Content/infections/Vaccination/recommandations/recommendations_node.html
bb https://www.gov.uk/government/news/hpv-vaccine-to-be-given-to-boys-in-england
cc https://www.nhs.uk/conditions/vaccinations/hpv-human-papillomavirus-vaccine/
dd https://www.thejournal.ie/hiqa-hpv-boys-4381319-Dec2018/
ee https://health.gov.ie/blog/press-release/minister-harris-welcomes-hiqa-recommendation-to-proceed-with-hpv-vaccine-for-boys/

In **Sweden**, the Public Health Agency reports on its website (updated 10/07/2018) that it is currently investigating whether HPV vaccination of boys should be included in the national vaccination programme.[ff]

In **Denmark**, the Ministry of Health and Elderly recently announced (October the 25th, 2018) that young boys aged 12 years will also receive free HPV vaccination in the future.[gg]

In the **Netherlands**, the Dutch Health Council is discussing whether the advice on vaccination should be adjusted to cover men.[hh] RIVM confirms that the extension to boys has been decided, but the vaccine is not decided yet. They currently use Cervarix and do not discard it as vaccine to be used for the extension phase. The uptake in girls is low (Personal communication, M Knoll, RIVM).

In **France**, the "Haut Conseil de Santé Publique (HCSP)" assessed in 2016 the opportunity of expanding their girl HPV vaccination to boys.[125] Based on a literature review they estimated that universal HPV vaccination is rarely cost-effective and advised against it. The current recommendation in France for HPV vaccination focuses then on increasing the uptake in girls aged 11-14 years (in 2014 the uptake was 17.2%) and offering vaccination to MSM (see below). In February 2018 however, the "Haute Autorité de Santé" decided to reconsider this position and new recommendations on HPV vaccination of boys are expected by the first trimester of 2019.[ii] In October 2018, the French Senate approved the vaccination of boys in 2 departments (Grand Est and Auvergne-Rhône-Alpes), as an experimentation.[jj]

7.2 Men having sex with Men

In **Canada**, three provinces currently provide free of charge HPV vaccination with Gardasil 9 to MSM. British Columbia[kk] and Québec[ll] (since January 2016) offer the vaccine to men aged up to 26 years who have sex with other men (both provinces), or who are not yet sexually active but are questioning their sexual orientation (British Columbia), or who plan to have sex with men (Québec). In the Prince Edward Island, the vaccine is offered to MSM without upper limit in age.[mm]

In **France**, since 2016, the "Haut Conseil de la Santé Publique" recommends HPV vaccination to MSM aged up to 26 years. HPV vaccination is offered free of charge if the vaccine is administered in public vaccination centres or in so called "Centre Gratuit d'Information, de Dépistage et de Diagnostic".[nn, oo] The HCSP further recommended that any new HPV vaccination should be initiated with Gardasil 9.[125, 126]

In **Ireland**, since January 2017, MSM aged under 26 years have access to HPV vaccination (Gardasil) through publicly funded sexually transmitted infection clinics.[pp, 124]

In the **UK**, MSM vaccination is recommended by the JCVI since 2015 and from April 2018, MSM up to and including the age of 45 are eligible for free HPV vaccination on the NHS when they visit genitourinary medicine clinics and HIV clinics.[13] The vaccine offered is Gardasil.[qq]

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ff https://www.folkhalsomyndigheten.se/the-public-health-agency-of-sweden/communicable-disease-control/vaccinations/ny-sidachanges-in-the-national-vaccination-programme/

gg http://sum.dk/Aktuelt/Nyheder/Sundhedspolitik/2018/Oktober/Regeringen-vil-styrke-vaccinationsindsatsen-med-nyt-udspil.aspx

hh https://www.rivm.nl/en/Documents_and_publications/Common_and_Present/Newsmessages/2017/HPV_vaccination_not_only_protects_against_cervical_cancer

ii http://www2.assemblee-nationale.fr/questions/detail/15/QE/9653

jj https://www.publicsenat.fr/article/parlementaire/la-recommandation-du-vaccin-anti-hpv-etendue-aux-garcons-dans-deux-regions

kk https://immunizebc.ca/hpv

ll https://www.quebec.ca/en/health/advice-and-prevention/vaccination/human-papillomavirus-hpv-vaccination-program/eligibility/

mm https://www.princeedwardisland.ca/sites/default/files/publications/aidetailed_sch_jan2018.pdf

nn https://vaccination-info-service.fr/Les-maladies-et-leurs-vaccins/Infections-a-Papillomavirus-humains-HPV

oo https://solidarites-sante.gouv.fr/IMG/pdf/calendrier_vaccinations_2018.pdf

pp https://www.hse.ie/eng/health/immunisation/hcpinfo/othervaccines/hpvadults/

qq https://www.nhs.uk/conditions/vaccinations/hpv-human-papillomavirus-vaccine/

8 ECONOMIC EVALUATIONS OF UNIVERSAL HPV VACCINATION

8.1 Methods

The cost-effectiveness of universal (i.e. girls and boys) HPV vaccination was inferred from a review of the economic evaluations as the number of rather good quality studies published on this topic allowed to answer the majority of the research questions (see 3). This decision was further driven by time constraints as the development of a dynamic transmission model tailored to Belgium was not possible within the given timelines.

A rapid and pragmatic search was performed on Medline(OVID) in March 2018 to identify recently published (i.e. after 2015) systematic reviews of economic evaluations including boy HPV vaccination, and primary economic evaluations published after the last search date of the literature reviews or not included in the reviews yet. Eight (8) reviews were identified,[120, 121, 125-130] covering 52 potentially eligible economic evaluations. The 2018 review by Ng et al. was not included as it was published after the limit of our search date (March 2018).[131] This publication builds however on a 2016 WHO report, that was well included in our review.[128] Ng et al. did not identify other economic evaluations than the ones already covered, and their conclusions and key parameters remain the same as in the WHO report. Updating the reviews up to March 2018 generated another 10 potentially eligible primary economic evaluations. The full-texts of the 62 economic evaluations were screened to select relevant publications (see Table 33 in Appendix).

The inclusion criteria was full economic evaluation of universal (boys and girls) HPV vaccination in economically developed countries. Partial economic evaluations were excluded, i.e. where only health outcomes are evaluated. Studies focusing on HPV vaccination in females only,[132-154] in males only,[155] and in specific target groups (e.g. HIV-positive males,[156] or MSM[157-160]) were excluded, conform to our research questions (see 3). Studies performed in economically emerging countries were also discarded.[161-163] Abstracts and conference proceedings were not considered. In total 29 relevant economic evaluations were retained (see Table 33 in Appendix).

In a second step, from those 29 economic evaluations, only studies presenting similar characteristics to the Belgian setting and HPV vaccination were selected, according to the following criteria:

- The comparator to universal vaccination is girl vaccination, as it is the current situation in Belgium. Comparisons versus no vaccination were not retained as they would bias the studies towards more favourable results.
- The same vaccine is used in boys and girls. Using different vaccines per gender is unlikely to be an option in Belgium as it would raise logistical and organisational issues, and acceptability concerns. It would further potentially decrease the purchasing power of the Belgian federated entities due to reduced volume per type of vaccine.
- The clinical impact of HPV vaccination is assessed on more HPV-related diseases than cervical cancer only, according to the 2017 SHC recommendations to consider other HPV-related cancers.[17]
- No catch-up vaccination is modelled and the age at vaccination is between 9-14 years, as this is the case in Belgium where single cohorts of girls aged 11-14 years are vaccinated, and as the SHC recommends to vaccinate adolescents aged 9-14 years old.[17]
- The girl uptakes simulated are similar (as much as possible) to the rates observed in the Vlaamse Gemeenschap (90%[19]) and in the Fédération Wallonie-Bruxelles (36-50%), see 2.3.

A total of 15 economic evaluations were retained.[164-178]

In the sections below, all values are reported in Belgian Euro from the year 2017. Local currencies used in the original economic evaluations were converted into 2017 Belgian Euro values using the country-specific consumer price index before applying the purchasing power parities for gross domestic product. Both datasets were obtained from the Organisation for Economic Cooperation and Development website (http://stats.oecd.org, accessed on 24/05/2018).

Results of the economic evaluations are expressed as incremental cost-effectiveness ratio (ICER) or additional cost per life-year (LY) or quality-adjusted life-year (QALY) gained.

As such however an ICER alone do not allow to conclude on the cost-effectiveness of an intervention but only informs on its relative cost-effectiveness. Such conclusion requires to compare the ICER with a reference value or a "threshold", above which an intervention would not be considered cost-effective (because the additional cost for an additional unit of effect is too high). Below this threshold, the intervention would be considered cost-effective. However Belgium does not have or use such an explicit threshold, which makes the interpretation of cost-effectiveness results complex.[179] To simplify the interpretation of our results, the ICER in this report are compared with the ICER estimated in 2007 for HPV vaccination of 12 year-old girls in Belgium (€33 000 per QALY gained).[180] This is in line with the upper limit of the standard UK NICE threshold ranging £20 000 to £30 000 (€22 500 to €33 800).

To further put those values into perspective, we provide also (base-case) ICER estimates from other past KCE reports for vaccines either approved or rejected to be implemented in the Belgian routine vaccination programme.

- Childhood vaccination with the 10 or 13-valent pneumococcal conjugate vaccine was implemented in the routine vaccination calendar based on an estimated €12 400 per QALY gained for 2+1 doses, compared to the previously used 7-valent vaccine.
- With an ICER ranging €50 000–68 000 per QALY gained, infant vaccination against rotavirus is reimbursed by NIHDI but was not approved to be implemented in the routine vaccination calendar of the communities.[181]
- With an ICER estimated at >€85 000 per QALY gained depending on the modelled time horizon and assuming exogenous boosting (i.e. exposure to chickenpox reduces the risk for herpes zoster), varicella zoster-virus vaccination with two doses in children was not approved for inclusion in the routine vaccination calendar of the communities and was not reimbursed by the NIHDI.[182] Universal childhood hepatitis A vaccination (2 doses) was estimated at €262 000 per QALY gained and was not approved for inclusion in the routine vaccination calendar of the communities, nor for NIHDI reimbursement.[183] With cost-effectiveness ratios above €400 000 per QALY assuming no herd immunity, childhood meningococcal B vaccination was not included in the vaccination calendar of the communities and was not reimbursed neither.[184]

However, caution should be taken when comparing the results of the current study with other interventions since we know that not only economic factors but also other factors (e.g. therapeutic value, ethical and organisational issues) have been considered in the decision-making process. Moreover comparison with ICERs calculated in the past is only warranted if the ICERs are obtained in the same way, i.e. using the same methodology and under the same conditions (costs, existing technologies, experience, etc.).

8.2 Characteristics of the selected studies

We describe below the technical characteristics and main parameters used in the 15 economic evaluations. Whenever available we compare those parameters with the best evidence available (i.e. vaccine efficacy) and with Belgian data (i.e. HPV-related burden of disease).

8.2.1 Technical characteristics, vaccine costs and diseases modelled

The studies were published between 2009 and 2017. Nine out of the 15 studies were financed by sources independent from the industry, i.e. public or academic institutions without sponsoring.[165-168, 171, 172, 176-178] Six studies were industry-sponsored.[164, 169, 170, 173-175]

Nine studies were European, 5 were performed in the USA and 1 in New-Zealand. All studies had outcomes expressed as quality-adjusted life-years (QALY), except for one study that expressed outcomes as life-years, i.e. without adjustment for the quality of life.[177] The models simulated HPV vaccination over a period that ranges from 55 years to a lifetime, which is long enough to capture the long-term consequences of HPV-related cancers. The majority of the studies (12) discounted future costs and clinical benefits (e.g. QALYs) at a rate of 3-4% for both. In Belgium, the guidelines for economic evaluations recommend a lower discount rate for clinical benefits (1.5%) than for costs (3%), to avoid penalizing medical interventions that generate most of their benefits in the future such as vaccination programmes.[185]

All but two economic evaluations included direct medical and intervention costs as cost categories. These studies were thus performed from the perspective of the health care payer / national health system, although some

of them report they used a societal perspective (see Table 15). Two studies performed their analysis from a societal perspective, including also direct non-medical costs (such as transport costs) and patient time costs.[166, 172]

All studies took into account the indirect benefits of girls HPV vaccination on non-vaccinated female/male populations (herd immunity, see 1.2). The models used were dynamic population-average state-transition models (8 studies),[164, 167-169, 171, 173, 174, 178] individual-based dynamic models (2 studies),[165, 175] or hybrid models combining a dynamic state-transition model for HPV transmission and a static individual-based model for disease progression (2 studies).[166, 172] Three studies used static models and herd immunity was induced by integrating the output predicted by previously published dynamic models (static model with forced decreased HPV incidence).[170, 176, 177]

Most studies (10) adopted a 3-dose vaccination schedule, three of them also considering a 2-dose schedule in their sensitivity analysis.[166, 171, 175] Five studies adopted a 2-dose schedule in their base-case analyses.[164, 173, 174, 177, 178]

Table 15 – Technical characteristics, vaccine costs and diseases modelled

	Country	Sponsor	Time horizon	Discount rate	Reported perspec-tive	Resour-ces valued	Nbr of doses	Vaccine cost per dose (€ 2017)				Vaccine	Diseases modelled							
								HPV2	HPV4	HPV9	Admin		GW	CER	VUL	VAG	ANA	OPC	PEN	RRP
Nonavalent vaccine																				
Largeron et al. 2017[173]	Germany	Industry	100y	C: 3% O: 3%	NHS	DMC	2	€149	€149	€156	€10	HPV9 HPV4 HPV2*	x*	x	x	x	x	No†	No†	No†
Mennini et al. 2017[174]	Italy	Industry	100y	C: 3% O: 3%	NHS	DMC	2	€119	€119	€138	€8	HPV9 HPV4 HPV2*	x*	x	x	x	x	No†	No†	No†
Brisson et al. 2016[165]	USA	Public	70y	C: 3% O: 3%	Societal	DMC	3	-	€132	€143	Included‡	HPV9 HPV4	x	x	x	x	x	x	x	No
Boiron et al. 2016[164]	Austria	Industry	100y	C: 3% O: 3%	HCP	DMC	2	-	€116	€142	€13	HPV9 HPV4	x	x	x	x	x	x	x	x
Chesson et al. 2016[168]	USA	Public	100y	C: 3% O: 3%	Societal	DMC	3	-	€111	€122	€13	HPV9 HPV4	x	x	x	x	x	x	x	x
Bivalent and/or quadrivalent vaccine																				
Wolff et al. 2017[178]	Sweden	Public	100y	C: 3% O: 3%	NHS	DMC	2	€78	-	-	Included‡	HPV2	No	x	x	x	x	x	x	No
Qendri et al., 2017[177]	Netherlands	Public	Life	C: 3% O: 3%	HCP	DMC	2	€26	-	-	€14	HPV2	No	x	x	x	x	x	x	No
Haeussler et al. 2015[170]	Italy	Industry	55y	C: 3% O: 3%	NHS	DMC	3	-	€65	-	€8	HPV4	x	x	x	x	x	x	x	No

	Country	Sponsor	Time horizon	Discount rate	Reported perspec-tive	Resour-ces valued	Nbr of doses	Vaccine cost per dose (€ 2017)				Vaccine	Diseases modelled							
								HPV2	HPV4	HPV9	Admin		GW	CER	VUL	VAG	ANA	OPC	PEN	RRP
Olsen et al. 2015[175]	Denmark	Industry	62y	C: 3% O: 3%	HCP	DMC	3 §	-	€138	-	€18	HPV4	x	x	x	x	x	x	x	No
Jimenez et al. 2015[171]	Norway	Public	100y	C: 4% ^ O: 4% ^	NHS	DMC	3 §	-	€95	-	No	HPV4 HPV2*	x*	x	x	No†	No†	No	No	No
Burger et al. 2014[166]	Norway	Public	Life	C: 4% O: 4%	Societal	PTC, DMC, DnonMC	3 §	-	€69 (19-148)	-	€13	HPV4	x	x	x	x	x	x	x	x
Pearson et al. 2014[176]	New-Zealand	Public	98y	C: 3% O: 3%	NHS	DMC	3	-	€66	-	€73-82	HPV4	x	x	x	No	x	x	No	No
Chesson et al. 2011[167]	USA	Public	100y	Not stated	Societal	DMC	3	-	€107	-	€11	HPV4	x	x	x	x	x	x	x	x
Elbasha et al. 2010[169]	USA	Industry	100y	C: 3% O: 3%	NS	DMC	3	-	€122	-	Included‡	HPV4	x	x	x	x	x	x	x	x
Kim et al. 2009[172]	USA	Public	100y	C: 3% O: 3%	Societal	PTC, DMC, DnonMC	3	€118	-	-	NS	HPV2	No	x	x	x	x	x	x	No

*The "x" means that protection against this disease was considered for all the vaccines listed, except otherwise stated. * HPV2 assessed in the sensitivity analysis assuming no impact from HPV2 on GW. † Disease considered in the sensitivity analysis. ‡ Administration costs included in the vaccine cost per dose. § A two-dose schedule is considered in the sensitivity analysis. ^ The discount rates (costs and outcomes) are 4% during the first 40 years of the program, 3% from year 41 to 75 and 2% beyond year 75 of the program. ANA: anal cancer, CER: cervical cancer, DMC: direct medical costs, DnonMC: direct non-medical costs (e.g. transport), GW: genital warts, HCP: health care payer; NHS: national health system, NS: not stated, OPC: cancer of the oropharyngeal region (head & neck / oropharynx, base of tongue and tonsil), PEN: penile cancer, PTC: patient time cost, RRP: recurrent respiratory papillomatosis, VAG: vaginal cancer, VUL: vulvar cancer.*

8.2.2 Vaccine efficacy and duration of protection

Efficacy estimates against vaccine types were consistently assumed to be high (around 90-100%) for the three vaccines and to correspond to a naïve population, which is consistent with published data in naïve populations for cervical, vulvar, vaginal, and anal lesions (though efficacy is slightly lower ranging 75-84% for this last outcome). Models assumed high vaccine efficacies against penile and oropharyngeal lesions, though this cannot be confirmed by the literature yet (see Table 16, 5.2.4 and 5.2.5). Models assessing the cost-effectiveness of HPV9 assumed the same vaccine-type efficacy as for HPV4.

None of the studies assumed a cross-protective effect of HPV2 against non-HPV2 types, although this effect is documented in many studies. Only cross-protection of HPV4 against non-HPV4 types was considered in three studies.[165, 168, 170] This choice is likely to underestimate the overall efficacy of HPV2 against any HPV-related cancer (see 5.3).

Most (13) models assumed that HPV vaccines protect over the entire lifetime; five of them also assumed a shorter duration of protection in their sensitivity analysis (18-20 years).[164, 165, 173, 174, 177]

Table 16 – Vaccine efficacy and duration of protection

Author	Country	Vaccine	Vaccine-type efficacy against		Duration of protection	HPV types modelled	Cross-protection
			Infection	Disease			
Nonavalent vaccine							
Largeron et al. 2017[173]	Germany	HPV9 HPV4 HPV2	Transient F: 76-96%† M: 41-62%† Persistent F: 98% M: 79-96%†	CIN, VIN, VaIN: 98-100%†	Life (20y in SA)	HPV9 types	No
Mennini et al. 2017[174]	Italy	HPV9 HPV4 HPV2	Transient F: 76-96%† M: 41-62%† Persistent F: 98% M: 79-96%†	CIN, VIN, VaIN: 98-100%†	Life (20y in SA)	HPV9 types	No
Brisson et al. 2016[165]	USA	HPV9 HPV4	95%	-	Life (20y in SA)	HPV9 + 35, 39, 51, 56, 59, 66, 68, 73, 82	HPV4: 46, 29, 8, 18 and 6% efficacy against 31, 33, 45, 52 and 58 (lifelong) ‡
Boiron et al. 2016[164]	Austria	HPV9 HPV4	Transient F: 76-96%† M: 41-62%† Persistent F: 98% M: 79-96%†	CIN, VIN, VaIN: 98-100%†	Life (20y in SA)	HPV9 types	No
Chesson et al. 2016[168]	USA	HPV9 HPV4	95% (85-100)	-	Life	HPV9 types	HPV4: 46, 29, 8, 18 and 6% efficacy against 31, 33, 45, 52 and 58 (lifelong) ‡
Bivalent and/or quadrivalent vaccine							
Wolff et al. 2017[178]	Sweden	HPV2	100%	-	Life	HPV2 types	No
Quendri et al., 2017[177]	Netherlands	HPV2	-	98%	Life (18y in SA)	HPV2 types	No
Haeussler et al. 2015[170]	Italy	HPV4	-	CER: 78% ANA: 70% OPC: 50%	Life	HPV4 + 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	HPV4: 32.5% efficacy against 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 (5 years)
Olsen et al. 2015[175]	Denmark	HPV4	100%	-	Life	HPV4 types	No
Jimenez et al. 2015[171]	Norway	HPV4	Persistent infection: F: 74% M: 67%	CIN: 20% VIN/VaIN: 51% AIN (F&M): 54% GW (F&M): 61%	Life	HPV4 types	No
Burger et al. 2014[166]	Norway	HPV4	-	F: 100% M: 90%	Life	HPV4 types	No

Author	Country	Vaccine	Vaccine-type efficacy against		Duration of protection	HPV types modelled	Cross-protection
			Infection	Disease			
Pearson et al. 2014[176]	New-Zealand	HPV4	99%	-	20 years	HPV4 types	No
Chesson et al. 2011[167]	USA	HPV4	F: 95% (75-100) M: 90% (60-100)	-	Life	HPV4 types	No
Elbasha et al. 2010[169]	USA	HPV4	Transient / Persistent F: 76-96%† / F: 98% M: 41-62%† / M: 79-96%†	CIN, VIN, VaIN, GW (F):98-100%† GW (M): 84-91%†	32 years	HPV4 types	No
Kim et al. 2009[172]	USA	HPV2	F: 100% M: 85%	F: 100% M: 90%	Life	HPV4 types	No

† Efficacy varies per HPV-vaccine type. ‡ Base-case results are presented both with and without cross-protection against non-vaccine types. AIN: anal intraepithelial neoplasia, ANA: anal cancer, CER: cervical cancer, CIN: cervical intraepithelial neoplasia, F: female vaccination, GW: genital warts, HPV9: nonavalent HPV vaccine, HPV4: quadrivalent HPV vaccine, HPV2: bivalent HPV vaccine, M: male vaccination, OPC: cancer of the oropharyngeal region (head & neck / oropharynx, base of tongue and tonsil), SA: sensitivity analysis, VaIN: vaginal intraepithelial neoplasia, VIN: vulvar intraepithelial neoplasia, y: year.

8.2.3 Outcomes considered

As the last HPV vaccine authorised (HPV9 in 2015) has been granted the indication of vulvar and vaginal cancers, most studies assumed that HPV4 and HPV2 (authorised in 2006 and 2007 respectively) and that are indicated for the prevention of pre-cancerous lesions of the vagina and vulva are also effective to prevent these cancers. This group of expanded EMA indications, that also includes vulvar and vaginal cancers for HPV2 and HPV4, is named "EMA+" indications in this report. Protection against anogenital warts is considered for HPV4 and HPV9 only, not for HPV2.

Two main groups of outcomes were considered in the economic evaluations:

- EMA+ indications
- All HPV-related diseases (see 3).

Four studies considered EMA+[171, 173, 174, 176] and 13 studies considered all HPV-related diseases.[164-170, 172-175, 177, 178] The outcomes considered per study can be found in appendix.

8.2.4 Disease burden and HPV attribution fraction

8.2.4.1 Incidence of HPV associated diseases

Four studies provided calibrated incidence values (model output) calculated by multiplying observed incidence values with the percentage of disease that can be attributed to some (not all) HPV types (i.e. incidence related to the HPV types contained in the 4- or in the 9-valent vaccine).[165, 169, 173, 174] Six studies provided observed population-based incidence data, usually obtained from cancers registries.[164, 166-168, 171, 172] In 5 studies, incidence values were not reported or not exploitable (see Table 17).[170, 175-178]

When age-specific (instead of overall) incidence data were used in the studies (usually per 5-year age groups), reports the incidence of the age group that included the average age at which Belgian patients typically develop HPV-related diseases. As described in the section on the burden of disease (see 4.3), the average age at diagnosis is for female 53 years for cervical cancer (50-54 age group), 72 and 73 years for vulvar and vaginal cancers (70-74 age group), 64 years for anal cancer (60-64 age group) and

60 years for oropharyngeal cancer (60-64 age group); for male 63.5 years for anal cancer (60-64 age group), 59 years for oropharyngeal cancer (60-64 age group) and 69 years for penile cancer (65-69 age group). For both female and male the age group considered are 20-24 years for genital warts, and 0-18 years for juvenile RRP.

The baseline incidence rates used in the economic evaluations in the absence of male vaccination do not differ substantially from the rates reported for Belgium, despite differences in data sources (i.e. measured from national data or generated by the models, see 4.3 and Table 17). The incidence rates from the two Norwegian studies tend to be higher than Belgian rates, especially for the incidence of cervical and oropharyngeal cancers and for anogenital warts.[166, 171]

Table 17 – Disease burden: incidence of HPV-related events (per 100 000)

	Country	Source of data	HPV types	Female outcomes							Male outcomes				
				CER	VUL	VAG	ANA	OPC	GW	RRP	ANA	OPC	PEN	GW	RRP
Overall incidence rates															
***KCE, see* 4.3**	*Belgium*	*Cancer registry 2015 and % HPV*	*All HPV type*	*10*	*0.5*	*0.4*	*1.4*	*0.7*	*118-170*	*-*	*1.0*	*1.9*	*0.4-0.8*	*118-170*	*-*
Largeron et al., 2017[173]	Germany	Model output	HPV9	8.82	0.26	0.19	1.17	NR	170	NR	0.86	NR	0.44	133	NR
Menini et al., 2017[174]	Italy	Model output†	HPV9	7	NR	NR	1.2	NR	175	NR	1	NR	NR	250	NR
Boiron et al., 2016[164]	Austria	Cancer registry 2015 and % HPV	HPV9	7.5	0.5	0.67	1.42	0.53	127	NR	0.79	1.27	0.41	132	NR
Burger et al., 2014[166]	Norway	Cancer registry 2008-10	All HPV type	12.6	3.4	0.6	1.9	1.5	2-714‡	0.17	0.9	3.8	2	1-885‡	NR
Elbasha et al., 2010[169]	USA	Model output	HPV4	6.5	0.46	0.24	1.14	1.13	161.7	0.72	1.08	4.6	0.79	155.6	0.72
Age-specific incidence rates – Age categories considered (years):				***50-54***	***70-74***	***70-74***	***60-64***	***60-64***	***20-24***	***0-18***	***60-64***	***60-64***	***65-69***	***20-24***	***0-18***
KCE	*Belgium*	*Cancer registry 2015*	*All*	*21*	*6.5*	*4.9*	*3.2*	*5.4*	*254*	*-*	*2.5*	*22.7*	*4.7*	*67*	*-*
Brisson et al., 2016[165]	USA	Model output†	All HPV type	10.5	3.5	3.5	5.1	3.2	410	-	2.5	18	1.6	225	-
Jimenez et al., 2015[171]	Norway	Cancer registry 2002-12	All	18.07	9.96	1.85	4.49	-	1400	-	2.26	-	-	1400	-
Chesson et al., 2016[168]	USA	Cancer registry 2006-10	All	12.2	6.4	1.7	4.9	4.8	459	0.735	2.6	24.8	2.60	236	0.735
Chesson et al., 2011[167]	USA	Cancer registry 2008-10	All	12.3	6	1.7	5.12	4.67	459	0.735	2.75	21.91	2.82	236	0.735
Kim et al., 2009[172‡]	USA	Cancer registry 1975-2001	All	4.2-62.8	0.2-19.6	0.1-6.0	0.0-5.6	0.2-13.9	-	-	0.1-4.3	0.1-17.7	0.0-7.6	-	-
Pearson et al., 2014[176]	New Zealand	Cancer registry 2011	All	NR	NR	-	NR	NR	NR	-	NR	NR	-	NR	-
Qendri et al., 2017[177*]	Netherlands	NR	NR	NR	NR	NR	NR	NR	-	-	NR	NR	NR	-	-
Wolff et al., 2017[178]	Sweden	Cancer registry 2010-14	All	NR	NR	NR	NR	NR	-	-	NR	NR	NR	-	-

	Country	Source of data	HPV types	Female outcomes							Male outcomes				
				CER	VUL	VAG	ANA	OPC	GW	RRP	ANA	OPC	PEN	GW	RRP
Haeussler et al., 2015[170]	Italy	NR	NR	NR	NR	NR	NR	NR	NR	-	NR	NR	NR	NR	-
Olsen et al., 2015[175]	Denmark	NR	NR	NR	NR	NR	NR	NR	NR	-	NR	NR	NR	NR	-

*The "-" mean that the outcome is not modelled. For age-specific incidences, the age groups considered are 50-54 years for cervical cancer, 70-74 years for vaginal / vulvar cancer, 60-64 for anal cancer (both genders), 60-64 for OPC cancer (both genders) and 65-69 for penile cancer. † Incidence rates observed on the figures from the publication. ‡ Overall or age-specific incidence rates are not reported, but only a range of values. * Cumulative incidence rates over 90 years are reported but are not exploitable here. ANA: anal cancer, CER: cervical cancer, GW: genital warts, NR: not reported, OPC: cancer of the oropharyngeal region (head & neck / oropharynx, base of tongue and tonsil), PEN: penile cancer, RRP: recurrent respiratory papillomatosis, VAG: vaginal cancer, VUL: vulvar cancer.*

8.2.4.2 HPV attribution fraction

The percentage of HPV-related diseases attributable to HPV types used in the economic evaluations are reported in Table 19 (per study) and summarised in Table 18. Four studies did not report this information.[169, 170, 174, 175]

Despite the various sources used, the proportions were rather consistent and comparable to our estimates from Belgian or European sources (see 4, and Table 18). There were however larger variations in the HPV attributable fractions for oropharyngeal and penile cancers, which can be explained by geographical and population differences, and for vulvar cancers. The 2018 JCVI statement on HPV vaccination concluded however that varying (from 30 to 60%) the attributable fraction of HPV for oropharyngeal cancer had no impact on the results, the incidence of this cancer in the population being low.[14]

Table 18 – Range of HPV attributable fractions used in the economic evaluations

	Attributable to HPV2 or HPV4 types	Attributable to HPV9 or any HPV type	Estimate for Belgium (any HPV type)
Sources	164, 166, 167, 171-173, 176, 177	164, 165, 168, 173, 178	See 4.3
Anogenital warts	90-100%	90-100%	100%
Cancer cervix	68-78%	81-100%	100%
Cancer anus	69-87%	79-92%	88%
Cancer vagina	32-66%	61-78%	71%
Cancer penis	16-46%	34-64%	32-61%
Cancer vulva	14-44%	16-69%	18%
Cancer oropharynx	14-60%	14-74%	25%

Table 19 – HPV attributable fractions

	Country	Female outcomes							Male outcomes					Source
		CER	VUL	VAG	ANA	OPC	GW	RRP	ANA	OPC	PEN	GW	RRP	
***KCE** Belgium (all HPV types)*		*100%*	*18%*	*71%*	*88%*	*25%*	*100%*	-	*88%*	*25%*	*32-61%*	*100%*	-	*See* 4.3
HPV2 vaccine types (16, 18)														
Qendri et al., 2017[177]	Netherlands	68%	14.2%	44.3%	69.4%	25.7%	-	-	69.4%	25.7%	16%	-	-	Alemany et al., 2014, 2015, 2016[28-30] de Sanjose et al., 2010[186] Ndiaye et al., 2014[187]
HPV4 vaccine types (6, 11, 16, 18)														
Largeron et al. 2017[17]	Germany	72.8%	14.2%	50.7%	76.3%	17.8%	90%	NR	76.3%	18.5%	34.4%	90%	NR	Hartwig et al., 2015[188]
Boiron et al. 2016[164]	Austria	72.8%	14.2%	50.7%	76.3%	13.6%	90%	NR	76.3%	16.5%	34.4%	90%	NR	Hartwig et al., 2015[188]
Jimenez et al. 2015[171]	Norway	100%†	90%‡	90%‡	82.8%	-	100%	-	82.8%	-	-	100%	-	Local reasoning
Burger et al. 2014[166]	Norway	72%	44%	66%	82%	54%	90%	100%	82%	54%	46%	90%	100%	WHO ICO database
Pearson et al. 2014[176]	New-Zealand	77.7%	32%	-	72%	19.8%	99%	-	72%	19.8%	-	99%	-	National data
Chesson et al. 2011[167]	USA	70%	44%	56%	87%	60%	90%	90%	87%	60%	31%	90%	90%	Gillison et al., 2008[189] Watson et al., 2008[190]
Kim et al. 2009[172]	USA	70%	32%	32%	82.8%	24%	-	-	82.8%	24%	25.2%	-	-	Hartwig et al., 2015[188]
HPV9 vaccine types (6, 11, 16, 18, 31, 33, 45, 52, 58)														
Largeron et al. 2017[17]	Germany	89%	16.2%	60.6%	78.7%	17.8%	90%	NR	78.7%	18.5%	34.4%	90%	NR	Hartwig et al., 2015[188]
Boiron et al. 2016[164]	Austria	89%	16.2%	60.6%	78.7%	13.6%	90%	NR	78.7%	16.5%	34.4%	90%	NR	Hartwig et al., 2015[188]
Chesson et al. 2016[168]	USA	81%	63%	73.4%	90.3%	60.3%	90%	90%	83%	67.8%	57%	90%	90%	Saraiya et al., 2015[191]
All HPV types														
Wolff et al. 2017[178]	Sweden	100%	15-48%*	78%	88%	74%	-	-	88%	74%	51%	-	-	Plummer et al., 2016[192] Nasman et al., 2015[193]
Brisson et al. 2016[165]	USA	100%	69%	75%	92%	63%	90%	-	89%	72%	63%	90%	-	Saraiya et al., 2015[191]

*The "-" mean that the outcome is not modelled. † Percentage attributable to all HPV types. ‡ Percentage attributable to all types of vulvar intraepithelial neoplasias (not only to those HPV-related). * Age dependant. ANA: anal cancer, CER: cervical cancer, GW: genital warts, NR: not reported, OPC: cancer of the oropharyngeal region (head & neck / oropharynx, base of tongue and tonsil), PEN: penile cancer, RRP: recurrent respiratory papillomatosis, VAG: vaginal cancer, VUL: vulvar cancer, WHO - ICO: World Health Organization - Institut Catala d'Oncologia.*

8.2.4.3 *Mortality of HPV associated cancers*

The HPV-related cancer mortality modelled in the studies is described in Table 20. When reported, data are expressed as mortality rates or 5/10-year survival rates. Data are further usually stratified per age and disease stage (local, regional and distant cancer). Though some consistency emerges across studies, it is hard to make an assessment due to the diversity of the reporting formats.

Table 20 – HPV-related cancer mortality

	Country	Source	Stratification	Female cancer					Male cancer		
				CER	VUL	VAG	ANA	ORP	ANA	ORP	PEN
Mortality rate (per 100 000 person-year)											
Largeron et al. 2017[173]	Germany	German cancer registry, EUROCARE-5	by age (15-44, 45-54, 55-64, 65-74, 75+) and stage (local, regional, distant)						See table in publication		
Mennini et al. 2017[174]	Italy	EUROCARE-5, BEST II	by age (15-44, 45-54, 55-64, 65-74, 75+) and stage (local, regional, distant)						See table in publication		
Boiron et al. 2016[164]	Austria	EUROCARE-5	None	4.1	0.9	0.2	0.3	0.8	0.3	2.5	0.3
Elbasha et al., 2010[169]	USA	US cancer registry	by age (15-29, 30-39, 40-49, 50-59, 60-69, 70+ OR 15-54, 55-64, 65+) and stage (local, regional, distant)						See table in publication		
5-year relative survival (%)											
Wolf et al., 2017[178]	Sweden	Sweden cancer registry	by age (<50, 50+) and stage (local, regional, distant)						See table in publication		
Brisson et al. 2016[165]	USA	US cancer registry	None †	18-91†	67	67	69	61	69	61	68
Chesson et al. 2016[168]	USA	US cancer registry	<50 years	77.4	84.4	70.5	77.4	63.4	62.9	74.3	75.5
			50+ years	57.1	63.2	52.4	72.3	56.0	54.4	63.5	66.7
Jimenez et al., 2015[171]	Norway	Norway cancer registry	by stage (local, regional, distant)							Not reported	
Burger et al., 2014[166]	Norway	Norway cancer registry	None †	20-91†	72.8	48.6	70.4	57.6	51.3	60.3	81
Pearson et al., 2014[176]	New Zealand	New Zealand data	by sex, age, ethnicity and deprivation							Not reported	
Chesson et al., 2011[167]	USA	US cancer registry	by age (<50, 50+) and stage (local, regional, distant)						See table in publication		
Kim et al., 2009[172]	USA	US cancer registry	None †	16-92†	77.8	55.7	66.2	62.6	64.1	57.6	75
10-year relative survival (%)											
Quendri et al., 2017[177]	Netherlands	Dutch cancer registry	by age (45-74 years) ‡	60	66	34	55	34	51	28	69
No information reported											
Haeussler et al., 2015[170]	Italy	Not reported	Not reported							Not reported	
Olsen et al., 2015[175]	Denmark	Not reported	Not reported							Not reported	

† Stratification per disease stage for cervical cancer only. Rates for local, regional and distant cancers are 91%, 58% and 18% in Brisson et al.;[165] 91%, 66% and 19.9% in Burger et al.;[166] and 92%, 55.7% and 16.5% in Kim et al.[172] ‡ Data for other age groups (<45 and 75+ years) are not reported. ANA: anal cancer, CER: cervical cancer, EUROCARE: European Cancer Registry, ORP: cancer of the oropharyngeal region PEN: penile cancer, VAG: vaginal cancer, VUL: vulvar cancer.

8.3 Assessment of the selected studies

8.3.1 Criteria

The **quality** of the 15 economic evaluations was assessed based on the following two criteria:

1. The extent to which ICER are computed based on a true incremental analysis, i.e. all vaccination strategies are identified (in terms of vaccine choice, uptake and target group), and every strategy is compared with the previous most cost-effective strategy ("efficiency frontier approach") and not only with the current situation.[185]
2. The extent to which uncertainty is considered in the study, i.e. whether the sensitivity analyses performed (if any) are probabilistic (i.e. a probability distribution is defined for all input parameter) or deterministic (a selected number of parameters are varied in univariate and/or multivariate analyses). The number of parameters varied (ideally all uncertain input parameters) and whether these were appropriately selected and varied is also assessed.

Beside this, the **funding source** of the study was collected, i.e. whether the study is industry-funded or independent from industry sources. There is indeed indication that industry-sponsored studies report more favourable base-case cost-effectiveness ratios, whatever their quality.[194]

As there was no economic evaluation of HPV vaccination performed in Belgium, we also assessed to which extent the results of these studies may be **inferred to the Belgian situation**. The input parameters (vaccine price, vaccination schedule, burden of disease, % HPV) and structural choices (discount rate) used in the base-case and in the sensitivity analyses of the studies were compared to the Belgian situation.

8.3.2 Results

Quality assessment

Almost all studies followed the principle of an incremental analysis (at least partially) when computing their ICER. A comprehensive incremental analysis in which all vaccination strategies in terms of vaccine choice (HPV9 versus HPV4), uptake (different %) and target group (girls and boys versus girls) were identified and compared with each other was performed in 2 independent studies.[165,176] In 10 studies the analyses were incremental according to the target group only (girls and boys versus girls) while the other parameters were usually explored in sensitivity or scenario analyses (see Table 21). Three studies (2 sponsored and 1 independent grey coloured in Table 21) presented methodological flaws when computing their ICER, not respecting the incremental analysis principle.[173, 174, 168]

Although all studies conducted some form of sensitivity analysis, 5 studies (3 sponsored, 2 independent grey coloured in Table 21) only conducted one-way sensitivity analysis,[173, 174, 164, 178, 172] which is generally considered inadequate to explore parameter uncertainty.

Based on those two criteria, 2 studies (which were industry sponsored) were assessed as being of lower quality.[173, 174]

Inference to Belgium

The base-case vaccine prices (per dose) simulated in the studies were similar to or lower than the Belgian public vaccine prices in 11 studies. Eight studies adopted a 2-dose schedule in their base-case, [164, 173, 174, 177, 178] or in their sensitivity analyses, as is currently the case in Belgium.[166, 171, 175] In all studies, an equal discount rate was applied to both costs and health outcomes. A lower discount rate for outcome, as currently recommended in Belgium (e.g. 3% for costs and 1.5% for outcomes) was explored in the sensitivity analyses of 5 studies.[173,174,175,177,178]

The percentage of HPV-related diseases attributable HPV types used in the studies were all comparable to the data derived for Belgium. The baseline incidence rate used in the studies did not differ much from the rates derived for Belgium, except in 2 Norwegian studies with high incidence rates.[166,171]

Table 21 – Assessment of the selected economic evaluations of universal HPV vaccination and correspondence with Belgium (base-case)

	Largeron et al. 2017[173]	Mennini et al. 2017[174]	Brisson et al. 2016[165]	Boiron et al. 2016[164]	Chesson et al. 2016[168]	Wolff et al. 2017[178]	Qendri et al., 2017[177]	Haeussler et al. 2015[170]	Olsen et al. 2015[175]	Jimenez et al. 2015[171]	Burger et al. 2014[166]	Pearson et al. 2014[176]	Chesson et al. 2011[167]	Elbasha et al. 2010[169]	Kim et al. 2009[172]
Quality of the studies															
1. Incremental analysis															
• **The ICER are computed following a true comprehensive incremental analysis target group and vaccine choice and uptake) OR**	no	no	yes	-	no	-	-	-	-	-	-	yes	-	-	-
• **The ICER are computed following a partial incremental analysis (target groups only or vaccine choice only)**	no	no	-	yes	no	yes	yes	yes	yes	yes	yes	-	yes	yes	yes
2. Sensitivity analysis															
• **The SA is probabilistic, all (or at least the most important) parameters are jointly varied and the variations are ad hoc OR**	no	no	yes	no	-	no	yes	yes	-	yes	-	yes	yes	yes	no
• **The SA is deterministic but multivariate analyses are performed in which the most important parameters are jointly varied and the variations are ad hoc**	no	no	-	no	yes	no	-	-	yes	-	yes	-	-	-	no
Funding source of the studies															
The study is financed by sources independent from the industry	no	no	yes	no	yes	yes	yes	no	no	yes	yes	yes	yes	no	yes
Inference to Belgium (input parameters and methodological choices)															
1. Public vaccine prices are roughly similar to Belgium (base-case)	no	yes	yes	yes	yes	yes	-	-	no	yes	-	no	yes	yes	no
2. Lower vaccine prices are used (potential simulation of the result of a public procurement procedure in a Belgian situation)															
• **In the base-case**	no	-	-	-	-	-	yes	yes	no	-	yes	no	-	-	no
• **In the sensitivity analysis**	no	-	-	-	-	yes	-	-	no	yes	yes	no	-	-	no
3. A two-dose schedule is simulated, as in Belgium															
• **In base-case**	yes	yes	no	yes	no	yes	yes	no	-	-	-				no
• **In sensitivity analysis**	-	-	no	-	no	-	-	no	yes	yes	yes	no	no	no	no

	Largeron et al. 2017[173]	Mennini et al. 2017[174]	Brisson et al. 2016[165]	Boiron et al. 2016[164]	Chesson et al. 2016[168]	Wolff et al. 2017[178]	Qendri et al., 2017[177]	Haeussler et al. 2015[170]	Olsen et al. 2015[175]	Jimenez et al. 2015[171]	Burger et al. 2014[166]	Pearson et al. 2014[176]	Chesson et al. 2011[167]	Elbasha et al. 2010[169]	Kim et al. 2009[172]
4. The discount rate for health outcomes is lower than the discount rate for costs, as recommended in Belgium															
• **In base-case**	-	-	no	no	no	-	-	no	-	no	no	no	no	no	no
• **In sensitivity analysis**	yes	yes	no	no	no	yes	yes	no	yes	no	no	no	no	no	no
5. The baseline incidence rates of HPV-related diseases used in the studies are comparable to the Belgian situation	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	no	yes	yes	yes	yes
6. The HPV attribution fractions used in the studies are comparable to the fractions derived for Belgium	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes

The cell coloured in grey indicate that the criteria was not adequately met by the study.

8.4 Cost-effectiveness of extending HPV vaccination to boys in contexts similar to Belgium

An overview of the vaccination strategies compared for each research question is presented in Table 22. The table specifies which interventions are compared and the girl vaccine uptake used in the economic evaluations (in the base-case and sensitivity analyses). Analyses with uptake rates in girls above 80% (or 70% when no other info is available) were used to best represent the VG situation, while comparisons with rates ranging between 25-60% were used to reflect the FWB situation.

For each comparison between vaccination strategies, the results are presented for the EMA+ indications and for all HPV-related diseases considered, when available.

Whenever available, we present the results where universal vaccination is compared to girl-only vaccination with HPV2 or HPV9, as the vaccines currently administered to girls are HPV2 in the FWB (since 2011) and HPV9 in the VG (HPV4 in 2010-2014, followed by HPV2 in 2014-2018 and HPV9 since July 2018, see 2). Comparisons with HPV4 are also reported as the impact on cancers would be similar to that obtained with HPV2.

Compared to HPV4 and HPV9, there were relatively few studies exploring vaccination strategies with HPV2. HPV2 is not registered for use in men in the USA (see 1.2); in Europe, where HPV2 is registered for men, this vaccine was only adopted in few countries. This limits the number of economic evaluations assessing HPV2 to 5 studies.[171, 172, 177, 178, 173] There were more studies (12) assessing HPV9 and/or HPV4; however comparison with HPV9 used in both strategies (universal vs girl-only vaccination) was not found.

Table 22 – Cost-effectiveness of universal HPV vaccination: comparisons available in the selected studies (number of studies and uptake in girls)

Vaccination strategies compared		EMA+ indications †		All HPV-related diseases ‡	
Intervention	**Comparator**	**VG situation**	**FWB situation**	**VG situation**	**FWB situation**
Universal vaccination (boys and girls) vs vaccination of girls?				*12 studies (7 independent, 5 sponsored)*	
Universal HPV2	**Girls HPV2**	1 (82%)[171]	0	2 (80, 90%)[177, 178]	3 (50%, 60%)[172, 177, 178]
Universal HPV4	**Girls HPV4**	2 (73, 82, 92%)[171, 176]	1 (47%)[176]	3 (80, 85, 90%)[166, 170, 175]	2 (25, 30%)[167, 169]
Universal HPV9	**Girls HPV9**	0	0	0	0
Universal HPV9	**Girls HPV2**	0	1 (40%)[173]	0	0
Universal HPV9	**Girls HPV4**	2 (70%)[173, 174]	2 (40, 60%)[173, 174]	0	2 (40, 60%)[173, 174]
Improve the uptake in girls or add boys to girls' vaccination?				*4 independent studies*	
Increased uptake in girls HPV4	**Universal HPV4**	1 (From 82% to 92%)[171]	1 (From 47% to 73%)[176]	1 (From 71% to 90%)[166]	1 (From 30% to 45%)[167]
Universal vaccination with which vaccine?				*4 studies (2 independent, 2 sponsored)*	
Universal HPV9	**Universal HPV4**	1 (71%)[174]	0	0	3 (40, 46, 55, 60%)[164, 165, 168]
Duration of vaccine protection: 18-20 years (instead of lifelong)				*5 studies (2 independent, 3 sponsored)*	
Universal HPV9	**Girls HPV4**	1 (70%)[174]	1 (40%)[173]	0	0
Universal HPV2	**Girls HPV2**	0	0	0	1 (60%)[177]
Universal HPV9	**Universal HPV4**	1 (70%)[174]	0	0	2 (40, 60%)[164, 165]

The "%" reflect the vaccine uptake in girls assumed in the studies. † Considering the 3 HPV vaccines have an impact on cervical, anal, vaginal and vulvar cancers; and on genital warts (except for the bivalent vaccine). ‡ Considering the three HPV vaccines have an impact on cervical, anal, vaginal, vulvar, oropharyngeal and penile cancers; and on genital warts and recurrent respiratory papillomatosis (except for the bivalent vaccine). FWB: Fédération Wallonie-Bruxelles, HPV9: nonavalent HPV vaccine, HPV4: quadrivalent HPV vaccine, HPV2: bivalent HPV vaccine; VG: Vlaamse Gemeenschap.

8.4.1 What is the cost-effectiveness universal (girls and boys) versus girl-only HPV vaccination for the EMA+ indications?

The EMA+ indications include the cancers of the cervix, anus, vagina and vulva for all three vaccines (see 8.2.3). Protection against genital warts is considered for HPV4 and HPV9 only. The cancers of the oropharynx and penis are not considered here.

If the uptake in girls is similar to the Vlaamse Gemeenschap

When the same vaccine is used to compare universal and girl-only HPV vaccination (i.e. the only change is to add boys to the vaccination programme), extending HPV vaccination to boys is not found to be cost-effective in two independent studies. At a 73 to 92% uptake rate in girls, incremental costs are higher than €118 000 per quality-adjusted life-year (QALY), with either the HPV2 or the HPV4 vaccine (Table 23).[171, 176] Comparisons with the HPV9 vaccine used in both strategies were not found.

When boys are added to the vaccination together with a vaccine change (i.e. vaccination of boys and girls with HPV9 is compared with the vaccination of girls with HPV4), universal HPV vaccination is cost-effective at a 70% uptake rate in girls in two studies (ICERs below €30 000 per QALY, Table 4).[173, 174] In those industry-sponsored studies however, the positive results for universal vaccination with HPV9 are rather attributable to the use of the new vaccine in girls than to the addition of boys to the vaccination. Indeed, at 70% uptake, switching from HPV2 or HPV4 to HPV9 in girl-only resulted in low ICERs below €5200 per QALY.[173, 174] No cross-protection was assumed for HPV2 and HPV4 which, together with other favourable assumptions, may overestimate the results for HPV9. Note that we did not perform a formal review of the cost-effectiveness of HPV9 versus HPV2 and HPV4 in girl-only.

If the uptake in girls is similar to the Fédération Wallonie-Bruxelles

Given the lower uptake in girls (36%) in Brussels/Wallonia, the potential gain from universal HPV vaccination is higher. This translates into more favourable results.

Using the same vaccine to compare universal and girl-only vaccination (such that the impact on adding boys is isolated), one study reports an incremental cost of €68 600 per QALY at 47% uptake in girls.[176] Although this cost remains high, it is nonetheless much lower than when higher uptake rates are used (Table 23). Further, a 3-dose schedule is used in this study, and vaccine and administration costs are high at €139-148 per dose. Many studies, including this one, report a quasi-proportional decrease in the ICER with decreasing vaccination costs.[166, 171, 176] In Belgium, lower prices may be obtained through public procedures and vaccination schedule consists in 2 doses. It is thus most likely that the results for universal vaccination of the above study would be favourable if transposed to the Belgian context.

Two industry-sponsored studies found that when an extension of the vaccination to boys is considered together with a change from HPV2 or HPV4 to HPV9, universal HPV vaccination is cost-effective at 40-60% uptake in girls, with incremental costs ranging from €12 350 to €24 500 per QALY (see Table 23).[173, 174]

Though universal vaccination seems favourable from a cost-effectiveness point of view when a 30-50% uptake in girl-only vaccination is reached, two independent studies found that it is more cost-effective to improve the uptake rate in girls than to extend vaccination to boys (see also 8.4.3).[171, 176] As an illustration, one study reports that universal vaccination with HPV4 is associated with an ICER of €68 600 per QALY at 47% uptake for both genders while improving the uptake in girl-only vaccination from 47% to 73% is associated with an ICER of €19 500 per QALY.

Tender-based vaccine prices and discount rates

All economic evaluations modelled vaccine costs based on their official list prices, which are higher than those that could be obtained by call for tender or negotiation procedures in a widescale vaccination programme. Some (older) studies further assumed a three-dose vaccination schedule,[171, 176] and in one study administration costs were as high as €73-82 per dose, while ranging between €0 to €10 in other studies.[176] All this contributes to high vaccination costs that push towards less cost-effective results of universal vaccination. In Belgium however, childhood vaccines are integrated in the regional immunisation programmes and are obtained through public procurement procedures (occasionally negotiation procedures in case of monopolistic position of the vaccine provider). Vaccine prices in the immunisation programmes can thus be substantially lower than their list (public) prices. For example, according to the data from the Tenders Electronic Daily (TED) website of the European Union, a tender-based price of €24.38 (VAT inclusive) per HPV2 dose was obtained in 2014 in Flanders.[rr] By comparison, the HPV2 list (i.e. public) price is €69 per dose.

The discount rates for the future costs and health benefits used in the studies varied between 3 to 4%, while the Belgian guidelines for economic evaluations recommend a lower rate for health benefits (1.5%) than for costs.[185] A lower discount rate for health benefits translates into more QALYs gained while the costs remain unchanged, thus resulting in lower ICERs.

Given current cost reductions due to tender pricing, the 2-dose schedule, and the lower discount rate for health effects (1.5%) than for costs (3%), as it all applies to Belgium, it is thus probable that universal HPV vaccination would be a cost-effective intervention, even when limited to EMA+ indications.

[rr] Data from the TED website were used in a recent publication on tender-based HPV vaccine prices in Europe.[110] Though the data reported are correct, the Belgian price per dose computed in this publication differs from our results.

Table 23 – Cost-effectiveness of universal versus girl-only HPV vaccination, for EMA+ indications† (Summary)

Vaccination strategies compared (intervention versus comparator)		With uptake similar to VG				With uptake similar to FWB			
		Uptake in girls	Vaccine cost per dose	ICER	Source	Uptake in girls	Vaccine cost per dose	ICER	Source
Same vaccine in both strategies									*2 independent studies*
Universal HPV2	**Girls HPV2**	82%	€47 €95	>€153 000	P[171]	-	-	-	-
Universal HPV4	**Girls HPV4**	73 -92%	€66 €95	>€118 700	P[171, 176]	47%	€66	€68 600	P[176]
Different vaccines per strategy									*2 sponsored studies*
Universal HPV9	**Girls HPV2**	-	-	-	-	40%	€156/149*	€12 350	I[173]
Universal HPV9	**Girls HPV4**	70%	€138/119* €156/149*	€15 500 - €30 000	I[173, 174]	40 -60%	€138/119* €156/149*	€13 000 - €24 500	I[173, 174]

*† EMA+ indications are cancers of the cervix, anus, vagina and vulva for all 3 vaccines, and genital warts for the HPV4 and HPV9 vaccines. * Cost per dose of the HPV9 vaccine / cost per dose of the HPV4 vaccines. EMA: European medicine agency, FWB: Fédération Wallonie-Bruxelles, HPV2: bivalent HPV vaccine, HPV4: quadrivalent HPV vaccine, HPV9: nonavalent HPV vaccine, I: Industry-sponsored study, ICER: incremental cost-effectiveness ratio, P: Independent study from the public/academic sector, VG: Vlaamse Gemeenschap.*

Table 24 – Cost-effectiveness of universal versus girl-only HPV vaccination, for EMA+ indications

Author	Country	Disease	Cost (Belgian Euro 2017)				Intervent°	Compar-ator	Cross-protect°	Doses	Uptake in girls & boys	ICER	Premium vaccine cost ‡	Thres-hold ‡
			HPV2	HPV4	HPV9	Adminis-tration								
Belgium		List prices:	€69	€118	€134									
Universal vaccination with HPV2 versus girl-only vaccination with HPV2														
Jimenez et al., 2015[171]	Norway	EMA+ minus GW, ANA, VAG†	€95	-	-	No	HPV2 FM	HPV2 F	No	3	82%	€320 000	-	-
			€47	-	-	No	HPV2 FM	HPV2 F	No	3	82%	€152 780	-	-
Universal vaccination with HPV4 versus girl-only vaccination with HPV4														
Jimenez et al., 2015[171]	Norway	EMA+	-	€95	-	No	HPV4 FM	HPV4 F	No	3	82%	€132 400	-	-
		EMA+ minus ANA/VAG†	-	€95	-	No	HPV4 FM	HPV4 F	No	3	82%	€152 800	-	-
			-	€95	-	No	HPV4 FM	HPV4 F	No	2	82%	€118 700	-	-
			-	€95	-	No	HPV4 FM	HPV4 F	No	3	92%	€272 000	-	-

Author	Country	Disease	Cost (Belgian Euro 2017)				Intervent°	Compar-ator	Cross-protect°	Doses	Uptake in girls & boys	ICER	Premium vaccine cost ‡	Thres-hold ‡
			HPV2	HPV4	HPV9	Adminis-tration								
Pearson et al., 2014[176]	New Zealand	EMA	-	€66	-	€73-82	HPV4 FM	HPV4 F	No	3	47%	€68 570	-	-
		EMA	-	€66	-	€73-82	HPV4 FM	HPV4 F	No	3	73%	€143 500	-	-
Universal vaccination with HPV9 versus girl-only vaccination with HPV2														
Largeron et al. 2017[173]*	Germany	EMA+ (no GW for HPV2)	€149	-	€156	€10	HPV9 FM	HPV2 F	No	2	40%	€12 350	-	-
Universal vaccination with HPV9 versus girl-only vaccination with HPV4														
Largeron et al., 2017[173]*	Germany	EMA+	-	€149	€156	€10	HPV9 FM	HPV4 F	No	2	40%	€24 500	€64	€40 000
		EMA+	-	€149	€156	€10	HPV9 FM	HPV4 F	No	2	70%	€29 800	-	-
Menini et al., 2017[174]*	Italy	EMA+	-	€119	€138	€8	HPV9 FM	HPV4 F	No	2	60%	€13 080	-	-
		EMA+	-	€119	€138	€8	HPV9 FM	HPV4 F	No	2	70%	€15 490	€156	€40 000
		EMA+	-	€119	€138	€8	HPV9 FM	HPV4 F	No	2	70%	€15 490	€78	€20 000
Additional results: girl-only vaccination with HPV9 versus girl-only vaccination with HPV4														
Largeron et al., 2017[173]*	Germany	EMA+	-	€149	€156	€10	HPV9 F	HPV4 F	No	2	40%	€350	-	-
		EMA+	-	€149	€156	€10	HPV9 F	HPV4 F	No	2	70%	€745	-	-
Menini et al., 2017[174]*	Italy	EMA+	-	€119	€138	€8	HPV9 F	HPV4 F	No	2	60%	€4930	-	-
		EMA+		€119	€138	€8	HPV9 F	HPV4 F	No	2	70%	€5160	€112	€40 000
		EMA+	-	€119	€138	€8	HPV9 F	HPV4 F	No	2	70%	€5160	€73	€20 000
Additional results: girl-only vaccination with HPV9 versus girl-only vaccination with HPV2														
Largeron et al., 2017[173]*	Germany	EMA+ (No GW for HPV2)	€149	€149	€156	€10	HPV9 F	HPV2 F	No	2	40%	Dominant§	-	-
Menini et al., 2017[174]*	Italy	EMA+ (No GW for HPV2)	€119	€119	€138	€8	HPV9 F	HPV2 F	No	2	70%	Dominant§	-	-

*EMA+ indications are cancers of the cervix, anus, vagina and vulva for all 3 vaccines, and genital warts for the HPV4 and HPV9 vaccines. * Industry-sponsored study. ‡ Premium vaccine cost is the maximum cost difference per dose between the vaccine used in the intervention and the vaccine used in the comparator, such that the intervention strategy remains cost-effective at a given threshold (cost per QALY). † EMA minus anal and vaginal cancers = impact considered on cervical and vulvar cancers. § An intervention is dominant when it generates more heath gains and less costs than its comparator. ANA: anal cancer, EMA: European medicine agency, F: female vaccination, FM: female and male vaccination, GW: genital warts, HPV9: nonavalent HPV vaccine, HPV4: quadrivalent HPV vaccine, HPV2: bivalent HPV vaccine, ICER: incremental cost-effectiveness ratio, VAG: vaginal cancer, VUL: vulvar cancer.*

8.4.2 What is the cost-effectiveness of universal (girls and boys) versus girl-only HPV vaccination for all HPV-related diseases?

In this section, the cancers of the oropharynx and the penis are added to the EMA+ indications. Recurrent respiratory papillomatosis (RRP) is also sometimes considered for HPV4 and HPV9 (see Table 26).

The cost-effectiveness of adding boys to the girl-only HPV vaccination programme improves compared to the results for the EMA+ indications. This could be expected because the additional indications are mainly found in men (oropharyngeal and penile cancers).

If the uptake in girls is similar to the Vlaamse Gemeenschap

At an 80-90% uptake rate in girls, universal vaccination with either HPV2 or HPV4 is favourable with ICERs ranging from €3460 to €39 000 per QALY in five studies.[166, 170, 175, 177, 178] Comparisons involving HPV9 were not found. The highest ICER (€39 000 per QALY) refers to a Norwegian study using a 4% discount rate for health benefits.[166]

If the uptake in girls is similar to the Fédération Wallonie-Bruxelles

Five studies compared universal versus girl-only vaccination using the same vaccine at a 25-60% uptake in girls. Adding boys to girl-only vaccination with HPV2 or HPV4 was cost-effective in four studies, with ICERs ranging from €7300 to €23 600 per QALY.[167, 169, 178] One study reported a higher ICER of €61 000 per QALY at 50% uptake but assumed a 3-dose schedule, a high cost of HPV2 (€118 per dose) and a 3% discount rate for clinical benefits.[172] This ICER would substantially decrease with a 2-dose schedule, a lower vaccine cost per dose (e.g. HPV2 tendering price was €24.38 per dose in 2014 in Flanders, see 8.4.1), and a 1.5% discount rate as it is the case in Belgium.

Table 25 – Cost-effectiveness of universal versus girl-only HPV vaccination, for all HPV-related diseases† (Summary)

Vaccination strategies compared (intervention versus comparator)		With uptake similar to VG				With uptake similar to FWB			
		Uptake in girls	Vaccine cost per dose	ICER	Source	Uptake in girls	Vaccine cost per dose	ICER	Source
Same vaccine in both strategies								*8 studies (5 independent, 3 sponsored)*	
Universal HPV2	**Girls HPV2**	80 -90%	€26, €39, €78	€13 700 - €37 200	P[177, 178]	50 -60%	€26, €78, €118	€7300 - €61 000	P[172, 177, 178]
Universal HPV4	**Girls HPV4**	80 -90%	€65, €69, €138	€3500 - €39 000	P[166], I[170, 175]	25 -30%	€107, €122	€23 000 -€23 600	P[167], I[169]
Different vaccines per strategy								*2 sponsored studies*	
Universal HPV9	**Girls HPV4**	-	-	-	-	40 -60%	€156/149* €138/119*	€8300 - €15 200	I[173, 174]

*† All HPV-related diseases are cancers of the cervix, anus, vagina, vulva, penis and oropharynx for all 3 vaccines; and genital warts and recurrent respiratory papillomatosis for the HPV4 and HPV9 vaccines. * Cost per dose of the HPV9 vaccine / cost per dose of the HPV4 vaccines. FWB: Fédération Wallonie-Bruxelles, HPV2: bivalent HPV vaccine, HPV4: quadrivalent HPV vaccine, HPV9: nonavalent HPV vaccine, I: Industry-sponsored study, ICER: incremental cost-effectiveness ratio, P: independent study from the public/academic sector, VG: Vlaamse Gemeenschap.*

Table 26 – Cost-effectiveness of universal versus girl-only HPV vaccination, for all HPV-related diseases

Author	Country	Disease	Cost (Belgian Euro 2017)				Intervent-ion	Compar-ator	Cross-protect°	Doses	Uptake in girls & boys	ICER	Premium vaccine cost ‡	Thres-hold ‡
			HPV2	HPV4	HPV9	Adminis-tration								
Belgium		List prices:	€69	€118	€134									
Universal vaccination with HPV2 versus girl-only vaccination with HPV2														
Wolff et al., 2017[178]	Sweden	All minus GW/RRP	€78	-	-	Included	HPV2 FM	HPV2 F	No	2	80%	€36 480	-	-
			€39	-	-	Included	HPV2 FM	HPV2 F	No	2	80%	€13 660	-	-
			€78	-	-	Included	HPV2 FM	HPV2 F	No	2	50%	€7290	-	-
Qendri et al., 2017[177]	Nether-lands	All minus GW/RRP	€26	-	-	€14	HPV2 FM	HPV2	No	2	60% ^	€9350	€87.5	€40 000
			€26	-	-	€14	HPV2 FM	HPV2	No	2	70% ^	€13 400	€57.5	€40 000
			€26	-	-	€14	HPV2 FM	HPV2	No	2	80% ^	€21 100	€27.5	€40 000
			€26	-	-	€14	HPV2 FM	HPV2	No	2	90% ^	€37 200	€2.5	€40 000
Kim et al., 2009[172]	USA	All minus GW/RRP	€118	-	-	NS	HPV2 FM	HPV2 F	No	3	75%	€112 550	-	-
			€81.6	-	-	NS	HPV2 FM	HPV2 F	No	3	75%	€61 900	-	-
			€118	-	-	NS	HPV2 FM	HPV2 F	No	3	50%	€61 000	-	-
Universal vaccination with HPV4 versus girl-only vaccination with HPV4														
Haeussler et al., 2015[170]*	Italy	All minus RRP	-	€65	-	€8	HPV4 FM	HPV4 F	Yes†	3	90%	€13 350	-	-
Olsen et al., 2015[175]*	Denmark	All minus RRP	-	€138	-	€18	HPV4 FM	HPV4 F	No	2	85%	€3460	-	-
			-	€138	-	€18	HPV4 FM	HPV4 F	No	3	85%	€5140	-	-
		All minus RRP/OPR	-	€138	-	€18	HPV4 FM	HPV4 F	No	3	85%	€34 180	-	-
Burger et al., 2014[166]	Norway	All	-	€69	-	€13	HPV4 FM	HPV4 F	No	2	80%	€39 190	-	-
		All	-	€139	-	€13	HPV4 FM	HPV4 F	No	2	80%	€78 090	-	-
Chesson et al., 2011[167]	USA	All	-	€107	-	€11	HPV4 FM	HPV4 F	No	3	30%	€23 000	-	-
Elbasha et al., 2010[169] *	USA	All	-	€122	-	Included	HPV4 FM	HPV4 F	No	3	25%	€23 615	-	-
		All minus PEN	-	€122	-	Included	HPV4 FM	HPV4 F	No	3	25%	€25 310	-	-
		All minus PEN/OPC	-	€122	-	Included	HPV4 FM	HPV4 F	No	3	25%	€43 230		-

Author	Country	Disease	Cost (Belgian Euro 2017)				Intervent-ion	Compar-ator	Cross-protect°	Doses	Uptake in girls & boys	ICER	Premium vaccine cost ‡	Thres-hold ‡
			HPV2	HPV4	HPV9	Adminis-tration								
Universal vaccination with HPV9 versus girl-only vaccination with HPV4														
Largeron et al., 2017[173]*	Germany	All	-	€149	€156	€10	HPV9 FM	HPV4 F	No	2	40%	€15 210	-	-
Menini et al., 2017[174]*	Italy	All	-	€119	€138	€8	HPV9 FM	HPV4 F	No	2	60%	€8260	-	-

*All HPV-related diseases are cancers of the cervix, anus, vagina, vulva, penis and oropharynx for all 3 vaccines; and genital warts and recurrent respiratory papillomatosis for the HPV4 and HPV9 vaccines. * Industry-sponsored study. ‡ Premium vaccine cost is the maximum cost difference per dose between the vaccine used in the intervention and the vaccine used in the comparator, such that the intervention strategy remains cost-effective at a given threshold (cost per QALY). † Cross-protection of HPV4 against non-vaccine types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 is 32.5% (6.0%–51.9%) during 5 years. ^ Uptake rate in girls, the uptake rate in boys remains constant at 40%. ANA: anal cancer, F: female vaccination, FM: female and male vaccination, GW: genital warts, HPV9: nonavalent HPV vaccine, HPV4: quadrivalent HPV vaccine, HPV2: bivalent HPV vaccine, OPC: cancer of the oropharynxl, PEN: penile cancer, RRP: recurrent respiratory papillomatosis, VAG: vaginal cancer, VUL: vulvar cancer.*

8.4.3 *Is extending HPV vaccination to boys more cost-effective than increasing the vaccine uptake in girls?*

Four studies explored whether it is more cost-effective to improve the uptake of a girl-only vaccination programme, or to extend vaccination to boys while keeping the uptake rate in girls as it is.[166, 167, 171, 176] With initial uptakes in girls ranging from 30% to 80%, all studies concluded that it is more cost-effective to improve the uptake in girls than offering the vaccine to boys, whatever health outcomes are considered (EMA+ or all HPV-related diseases). Such conclusion rests however on a purely economic reasoning without any consideration for, e.g. ethical or organisational aspects. It does not preclude that universal vaccination may also be cost-effective. No study assessed whether increasing the uptake in girls would still be cost-effective when this uptake is as high as 90%, as is the case in Flanders.

In two studies, universal vaccination produced less health benefits (i.e. was less effective) and was more costly than increasing the uptake of girl-only vaccination.[166, 176] In the two other studies, universal vaccination was also more costly but produced more health benefits than increasing the uptake of girl-only vaccination. Compared to girl-only vaccination, universal vaccination in those studies was associated with ICERs of €23 000 per QALY at a 30% uptake and €152 800 per QALY at an 82% uptake. By contrast, increasing the uptake in girls from 30 to 45% and from 82 to 92% was associated with lower ICERs of €7545 and €28 760 per QALY, respectively.[167, 171]

Table 27 – Cost-effectiveness of extending HPV vaccination to boys versus increasing the uptake for girl-only vaccination (Summary)

Vaccination strategies compared (direct comparison of intervention versus comparator)		With uptake similar to VG				With uptake similar to FWB			
		Uptake	Vaccine cost per dose	ICER	Source	Uptake	Vaccine cost per dose	ICER	Source
Considering the EMA+ indications†									*2 independent studies*
Universal HPV4	**Girls HPV4 uptake+**	Universal: 82% Girls: 92%	€95	€326 000	P[171]	Universal: 47% Girls: 73%	€66	Dominated	P[176]
Considering all HPV-related diseases‡									*2 independent studies*
Universal HPV4	**Girls HPV4 uptake+**	Universal: 71% Girls: 90%	€46, €69, €139	Dominated	P[166]	Universal: 30% Girls: 45%	€107	€95 200	P[167]

*† EMA+ indications are cancers of the cervix, anus, vagina and vulva for all 3 vaccines, and genital warts for the HPV4 and HPV9 vaccines. ‡ All HPV-related diseases are the EMA+ indications plus cancers of the penis and oropharynx; and recurrent respiratory papillomatosis (except for HPV2). * Dominated: universal vaccination generates less health benefits and more costs than increasing the uptake in girl-only vaccination. EMA: European medicine agency, FWB: Fédération Wallonie-Bruxelles, HPV4: quadrivalent HPV vaccine, I: Industry-sponsored study, ICER: incremental cost-effectiveness ratio, P: independent study from the public/academic sector, VG: Vlaamse Gemeenschap.*

Table 28 – Cost-effectiveness of extending HPV vaccination to boys versus increasing the uptake for girl-only vaccination

Author	Country	Disease	Cost (Belgian Euro 2017)				Intervention	Comparator	Cross-protect°	Doses	Uptake universal vaccination	Uptake girl-only vaccination	ICER
			HPV2	HPV4	HPV9	Adminis-tration							
Belgium		List prices:	€69	€118	€134								
Direct comparisons													
Burger et al., 2014[166]	Norway	All	-	€69	-	€13	HPV4 FM	HPV4 F	No	2	71%	90%	Dominated
		All	-	€46	-	€13	HPV4 FM	HPV4 F	No	2	71%	90%	Dominated
		All	-	€139	-	€13	HPV4 FM	HPV4 F	No	2	71%	90%	Dominated
Pearson et al., 2014[176]	New Zealand	EMA minus VUL plus OPC	-	€66	-	€73-82	HPV4 FM	HPV4 F	No	3	47%	73%	Dominated
Chesson et al., 2011[167]	USA	All	-	€107	-	€11	HPV4 FM	HPV4 F	No	3	45%	30%	€95 240
Jimenez et al., 2015[171]	Norway	EMA minus ANA/VAG	-	€95	-	No	HPV4 FM	HPV4 F	No	3	92%	82%	€325 800
Indirect comparisons													
Jimenez et al., 2015[171]	Norway	EMA minus ANA/VAG	-	€95	-	No	HPV4 FM	HPV4 F	No	3	82%	82%	€152 800
			-	€95	-	No	HPV4 F	HPV4 F	No	3	92%	82%	€28 760
Pearson et al., 2014[176]	New Zealand	EMA minus VUL plus ORP	-	€66	-	€73-82	HPV4 FM	HPV4 F	No	3	47%	47%	€68 570
			-	€66	-	€73-82	HPV4 F	HPV4 F	No	3	73%	47%	€19 470
Chesson et al., 2011[167]	USA	All	-	€107	-	€11	HPV4 FM	HPV4 F	No	3	30%	30%	€23 000
			-	€107	-	€11	HPV4 F	HPV4 F	No	3	45%	30%	€7545

EMA+ indications are cancers of the cervix, anus, vagina and vulva for all 3 vaccines, and genital warts for the HPV4 and HPV9 vaccines. All HPV-related diseases are the EMA+ indications plus cancers of the penis and oropharynx; and recurrent respiratory papillomatosis (except for HPV2). ANA: anal cancer, EMA: European medicine agency, F: female vaccination, FM: female and male vaccination, HPV9: nonavalent HPV vaccine, HPV4: quadrivalent HPV vaccine, HPV2: bivalent HPV vaccine, GW: genital warts, NS: not stated, OPC: cancer of the oropharyngeal region (head & neck / oropharynx, base of tongue and tonsil), PEN: penile cancer, RRP: recurrent respiratory papillomatosis, VAG: vaginal cancer, VUL: vulvar cancer.

8.4.4 *If universal (girls and boys) vaccination is opted for, which vaccine is cost-effective?*

Four studies (two of them sponsored) explored the cost-effectiveness of switching from universal vaccination with HPV4 to universal vaccination with HPV9.[164, 165, 168, 174] There was no comparison between HPV2 and HPV9.

Assuming no cross-protection, all studies conclude that it is cost-effective to use HPV9 instead of HPV4 in universal vaccination (ICERs below €17 300 per QALY). Two studies further confirm that, when cross-protection for HPV4 is considered, using HPV9 instead of HPV4 in universal vaccination remains cost-effective. However less health benefits are gained by universal HPV9 vs universal HPV4 in this situation than when no cross-protection is assumed (Table 29)

In these studies, the price difference between the HPV9 and the HPV4 vaccines varied from €11 to €26 per dose. This is in line with Belgium where the difference in list (public) prices is €16 (€118 for HPV4 against €134 for HPV9).

Table 29 – Cost-effectiveness of a vaccine change for universal vaccination (Summary)

Vaccination strategies compared (intervention versus comparator)		With uptake similar to VG				With uptake similar to FWB			
		Uptake	Vaccine cost per dose	ICER	Source	Uptake	Vaccine cost per dose	ICER	Source
Considering the EMA+ indications† and no cross-protection									*1 sponsored study*
Universal HPV9	**Universal HPV4**	71%	€138/119*	€12 000	I[174]	-	-	-	-
Considering all HPV-related diseases‡ and no cross-protection									*3 studies (1 independent, 2 sponsored)*
Universal HPV9	**Universal HPV4**	-	-	-	-	40%, 46%, 55%, 60%	€143/132* €142/116* €122/111*	€17 300 – Dominant§	I[164] P[165, 168]
Considering all HPV-related diseases‡ and HPV4 cross-protection§									*2 public studies*
Universal HPV9	**Universal HPV4**	-	-	-	-	40%, 46%, 55%	€143/132* €122/111*	€7300 – Dominant§	P[165, 168]

*† EMA+ indications are cancers of the cervix, anus, vagina and vulva for all 3 vaccines, and genital warts for the HPV4 and HPV9 vaccines. ‡ All potential HPV-related diseases are the EMA+ indications plus cancers of the penis and oropharynx; and recurrent respiratory papillomatosis (except for HPV2). * Cost per dose of the HPV9 vaccine / cost per dose of the HPV4 vaccines. § Lifelong HPV4 cross-protection is 46/29/8/18/6% against non-vaccine types 31/33/45/52/58. § An intervention is dominant when it generates more health effects and less costs than its comparator. EMA: European medicine agency, FWB: Fédération Wallonie-Bruxelles, I: Industry-sponsored study, ICER: incremental cost-effectiveness ratio, I: independent study from the public/academic field, VG: Vlaamse Gemeenschap.*

Table 30 – Cost-effectiveness of a vaccine change for universal vaccination

Author	Country	Disease	Cost (Belgian Euro 2017)				Intervent°	Compar-ator	Cross-protect°	Doses	Uptake	ICER	Premium cost ‡	Thres-hold ‡
			HPV2	HPV4	HPV9	Adminis-tration								
Belgium		List prices:	€69	€118	€134									
Menini et al., 2017[174]*	Italy	EMA	-	€119	€138	€8	HPV9 FM	HPV4 FM	No	2	71%	€12 050	€61	€40 000
		EMA	-	€119	€138	€8	HPV9 FM	HPV4 FM	No	2	71%	€12 050	€39	€20 000
Brisson et al., 2016[165]	USA	All	-	€132	€143	Included	HPV9 FM	HPV4 FM	No	3	F: 40% M: 15%	Dominant	-	-
		All	-	€132	€143	Included	HPV9 FM	HPV4 FM	Yes†	3		Dominant	€13.6	€0
		All	-	€132	€143	Included	HPV9 FM	HPV4 FM	No	3	F: 55% M: 35%	Dominant	-	-
		All	-	€132	€143	Included	HPV9 FM	HPV4 FM	Yes†	3		€4180	-	-
Boiron et al., 2016[164]*	Austria	All	-	€116	€142	€13	HPV9 FM	HPV4 FM	No	2	F: 60% M: 40%	€17 300	€45	€30 000
		All	-	€116	€142	€13	HPV9 FM	HPV4 FM	No	2		€17 300	€3.2	€0
Chesson et al., 2016[168]	USA	All	-	€111	€122	€13	HPV9 FM	HPV4 FM	No	3	F: 46% M: 29%	Dominant		
		All	-	€111	€133	€13	HPV9 FM	HPV4 FM	No	3		€14 200		
		All	-	€111	€122	€13	HPV9 FM	HPV4 FM	Yes†	3		€7310		

** Industry-sponsored study. † Cross-protection for HPV4 against non-vaccine types 31 / 33 / 45 / 52 / 58 is 46% / 29% / 8% / 18% / 6% lifelong. ‡ Premium vaccine cost is the maximum cost difference per dose between the vaccine used in the intervention and the vaccine used in the comparator, such that the intervention strategy remains cost-effective at a given threshold. EMA: European medicine agency, F: female vaccination, FM: female and male vaccination, HPV9: nonavalent HPV vaccine, HPV4: quadrivalent HPV vaccine, HPV2: bivalent HPV vaccine.*

8.4.5 What is the cost-effectiveness of universal (girls and boys) versus girl-only vaccination using low vaccine prices?

In Belgium, vaccine prices in the vaccination programmes are the results of public procurement procedures with vaccine providers, and are usually lower than their list (public) prices. We extracted the results of the studies using vaccine (and administration) prices that are lower than the Belgian list prices, i.e. €69 for HPV2, €118 for HPV4 and €134 for HPV9.

Considering the EMA+ indications, at €47 per HPV2 dose (in a 3-dose schedule) and no administration costs, the ICER of universal vaccination versus girl-only vaccination with a 82% uptake is high (€153 000 per QALY, equal discount rate at 4%).[171] In this study, doubling the vaccine cost at €95 per dose led to a proportional increase of the ICER, at €320 000 per QALY.

Considering all HPV diseases, two European studies using a HPV2 strategy report lower ICERs with vaccination costs of ~€40 euro per dose).[177, 178] ICERs were below €9350 per QALY for a girls uptake at 50 to 60%, and ranged from €13 660 to €37 200 for a girls uptake at 80 to 90%. With an HPV4 vaccine cost of €65 plus €8 administration costs (3-dose schedule), an Italian study reports lower ICER at €13 350 per QALY for universal vaccination with a 90% uptake in girls.[170] Using slightly higher vaccination costs for HPV4 (€69 per HPV4 dose plus €13 administration costs in a 2-dose schedule), a Norwegian study reports an ICER of €39 000 per QALY at an 80% uptake in girls (equal discount rate at 4%).[166] In this last study the

ICER changed proportionally to the vaccine price (ICER of €78 000 with a cost of €139 per HPV4 dose).

The studies that compared extending the vaccination to boys to increasing the uptake in girls showed results that are less sensitive to vaccine price assumptions as both strategies require an increased number of vaccine doses administered. In Burger et al., increasing the uptake in girls was always the preferred option, generating clinical benefits and cost-savings compared to universal vaccination, whatever the vaccine prices used for HPV4 (i.e. €46, €69 or €139 per dose, with €13 administration costs in a 2-dose schedule).[166]

The Pearson et al. study were not used as, although the price per HPV4 dose in this study is low at €66, a 3-dose schedule is modelled and administration costs are high (€73-82 per dose) which make vaccination costs very high and not relevant for Belgium.[176]

8.4.6 What is the impact of the vaccine duration of protection on the incremental cost-effectiveness ratio?

Five studies explored the impact of a reduced duration of vaccine protection (18-20 years versus lifelong) on the cost-effectiveness results.[164, 165, 173, 174, 177]

In all studies, reducing the duration of protection from lifelong to 18-20 years only moderately increased the ICERs without modifying the studies' conclusions. In one study reducing the duration of protection improved the cost-effectiveness results, which is not plausible and is not justified by the authors.[173]

Table 31 – Impact of vaccine duration of protection on the cost-effectiveness of universal vaccination (Summary)

Vaccination strategies compared (intervention versus comparator)		With uptake similar to VG				With uptake similar to FWB			
		Uptake	Duration vaccine protection	ICER	Source	Uptake	Duration vaccine protection	ICER	Source
									5 studies (2 independent, 3 sponsored)
Universal HPV9	**Girls HPV4**	70%	Life	€15 500	I[174]	40%	Life	€24 500	I[173]
			20 years	€25 000			20 years	€15 750*	
Universal HPV2	**Girls HPV2**	-	-	-	-	60%	Life	€9350	P[177]
							18 years	€19 500	
Universal HPV9	**Universal HPV4**	70%	Life	€12 000	I[174]	40-60%	Life	Dominant - €25 000§	I[164]
			20 years	€20 900			20 years	Dominant - €26 000§	P[165]

** Not plausible and not justified by authors. § An intervention is dominant when it generates more health effects and less costs than its comparator. FWB: Fédération Wallonie-Bruxelles, HPV4: quadrivalent HPV vaccine, HPV9: nonavalent HPV vaccine, I: Industry-sponsored study, ICER: incremental cost-effectiveness ratio, P: independent study from the public/academic field, VG: Vlaamse Gemeenschap.*

Table 32 – Impact of vaccine duration of protection on the incremental cost-effectiveness of universal vaccination

Author	Country	Disease	Cost (Belgian Euro 2017)				Intervent°	Comparator	Cross-protect°	Doses	Uptake	Duration protection	ICER
			HPV2	HPV4	HPV9	Adminis-tration							
Belgium		List prices:	€69	€118	€134								
HPV9 FM versus HPV4 F													
Largeron et al., 2017[173] *	Germany	EMA	-	€149	€156	€10	HPV9 FM	HPV4 F	No	2	40%	Life	€24 500
		EMA	-	€149	€156	€10	HPV9 FM	HPV4 F	No	2	40%	20 years	€15 750
Menini et al., 2017[174] *	Italy	EMA	-	€119	€138	€8	HPV9 FM	HPV4 F	No	2	70%	Life	€15 490
		EMA	-	€119	€138	€8	HPV9 FM	HPV4 F	No	2	70%	20 years	€24 920
HPV9 FM versus HPV4 FM													
Menini et al., 2017[174] *	Italy	EMA	-	€119	€138	€8	HPV9 FM	HPV4 FM	No	2	70%	Life	€12 050
		EMA	-	€119	€138	€8	HPV9 FM	HPV4 FM	No	2	70%	20 year	€20 885
Boiron et al., 2016[164]*	Austria	All	-	€116	€142	€13	HPV9 FM	HPV4 FM	No	2	F: 60%	Life	€24 880
		All	-	€116	€142	€13	HPV9 FM	HPV4 FM	No	2	M: 40%	20 years	€26 180
Brisson et al., 2016[165]	USA	All	-	€132	€143	Included	HPV9 FM	HPV4 FM	No	3	F: 40%	Life	Dominant
		All	-	€132	€143	Included	HPV9 FM	HPV4 FM	No	3	M: 15%	20 years	Dominant
		All	-	€132	€143	Included	HPV9 FM	HPV4 FM	Yes†	3	F: 40%	Life	Dominant
		All	-	€132	€143	Included	HPV9 FM	HPV4 FM	Yes†	3	M: 15%	20 years	Dominant
HPV2 FM versus HPV2 F													
Qendri et al., 2017[177]	Netherl-ands	All minus GW/RRP	€26	-	-	€14	HPV2 FM	HPV2 F	No	2	F: 60%	Life	€9350
			€26	-	-	€14	HPV2 FM	HPV2 F	No	2	M: 40%	18 years	€19 550

** Industry-sponsored study. † Cross-protection for HPV4 against non-vaccine types 31 / 33 / 45 / 52 / 58 is 46% / 29% / 8% / 18% / 6% lifelong. EMA: European medicine agency, F: female vaccination, FM: female and male vaccination, HPV9: nonavalent HPV vaccine, HPV4: quadrivalent HPV vaccine, HPV2: bivalent HPV vaccine.*

8.5 Questions that cannot be addressed from the literature

Despite the numerous economic evaluations already published, not all questions could be answered based on the available material. This is mainly because cost-effectiveness studies involving the recent HPV9 are still relatively scarce compared to studies with HPV2 or HPV4. More precisely, the following comparisons are missing:

- The cost-effectiveness of universal vaccination with HPV9 versus girl-only vaccination with HPV9.
- The cost-effectiveness of universal vaccination with HPV9 versus girl-only vaccination with HPV2. This comparison is highly relevant for Belgium as HPV2 is administered to girls (up to July 2018 in VG). The only study making this comparison used a low uptake and considered EMA+ indications only. Results for uptake similar to VG and for all HPV-related diseases were not available.
- The cost-effectiveness of universal vaccination with HPV9 versus universal HPV2 vaccination.

In addition, the clinical impact of the different strategies in published evaluations could not be used for the Belgian context because they were based on diverging baseline situations, comparisons and indicators. Furthermore, the clinical impact reported by the studies was expressed in absolute number of cases, in the specific setting, and could not be extrapolated to Belgium.

Despite those limitations, inference from the many other comparisons available has been done and provides a consistent view of the conditions where universal HPV vaccination could be considered cost-effectiveness of in Belgium.

9 DISCUSSION

9.1 Clinical aspects

In Belgium, an estimated 1122 cases of cancers were attributable to HPV in 2015, including cancers of cervix, vulva, vagina, penis, anus, and oropharynx, and 44% of these were non-cervical cancers. During the period 2004-2015, the overall incidence of penis, anus, and oropharynx cancers (HPV-attributable or not) has increased in Belgium by 11-55% (depending on the cancer and gender), but it is unknown whether this is due to an increase in HPV infections. In addition, an estimated 13 000 to 20 000 genital warts occur in Belgium every year. The total number of cancers attributable to the HPV types included in HPV2, HPV4 and HPV9 vaccines in Belgium is estimated at 869, 882 and 1019 cases, respectively, in 2015. The seven types contained in HPV9 and not in HPV2 are thus estimated to have caused around 150 cancers in 2015 in both genders.

In 2015, 22% (n=253) of all HPV-related cancers were reported in men. More than half of them were oropharyngeal cancers, whose incidence was 2-3 times higher in men than in women. There are no Belgian data on the HPV burden in MSM, but the international literature suggests that this group has disproportionately higher rates of anal, penile and oropharyngeal cancers.

To date, there are still no data available from trials on the efficacy of HPV vaccines against cancers. However, all three vaccines have shown a very high efficacy against high-grade pre-cancerous lesions and cancers (grouped together) due to vaccine types in HPV-naïve subjects, exceeding mostly 95%. One exception however is anal cancer, against which the efficacy was around 75-84% (for HPV4) for vaccine types in naïve MSM. The efficacy of HPV vaccines against lesions due to any HPV type, which represents the true burden of HPV disease, was always lower and not exceeding 50% for most high-grade lesions. An exception was the high efficacy of HPV2 against cervical cancer due to any HPV type in a naïve population (92% against grade 3 or more), compared to 46% for HPV4. Besides potential differences in trials, HPV2 showed a higher level of cross-

protection, compared to HPV4, against the types not included in those two vaccines.

There are no or few data on the efficacy of HPV vaccines against pre-cancerous lesions of the penis and the oropharynx, and HPV vaccines are not officially indicated for those two cancers, but available data suggests an effect against HPV infection of the oropharynx.

Based on current knowledge, HPV vaccines are considered safe. However, new concerns may always arise due to potential temporal associations between vaccination and the onset of a disease. It is crucial to guarantee a good monitoring of potential safety signals, as for other vaccines.

In 2017, the SHC updated its recommendations to expand the current vaccination of girls to boys based on the two main arguments: equity and non-stigmatisation of sexual behaviour. Indeed, vaccinating all boys also includes potential future MSM, and targets boys before the onset of sexual activity (thus when they are HPV-naïve), a group is which vaccine efficacy is highest. Furthermore, MSM have the highest burden and are not protected by the indirect effect of the current girl-only vaccination programme. These two factors have motivated a number of countries to develop HPV vaccination targeting MSM (Table 14). A strategy targeting MSM was not selected by the Belgium health authorities and has therefore not been covered by our analysis.

9.2 Economic aspects

No economic criteria is taken into account in the SHC advises and the federated authorities have asked the KCE to produce an economic analysis. Due to time constraint, and the high number of economic analyses published on our research questions, we opted for a review of the economic literature. A transmission model simulating the vaccination of successive cohorts of girls and boys in Belgium would answer to many questions but was not possible to develop within the timeframe of our study. The economic evidence gathered in our report emerges thus from 15 published studies presenting similar characteristics to Belgium (setting and HPV vaccination characteristics), published between 2009 and 2017, and 6 of them were industry-sponsored.

Vaccine-type efficacy assumptions used in the economic studies were consistent with the published clinical literature. Assumed efficacies against penile and oropharyngeal lesions were high though this has yet to be confirmed. Models assessing the cost-effectiveness of the HPV9 assumed the same vaccine-type efficacy as for HPV4. No cross-protection was assumed for HPV2 while it was assumed for HPV4 in three studies. All studies took herd immunity effects from girl vaccination into account. The burden estimates (incidences and HPV attributable fractions) used in the economic studies were generally consistent and comparable to our Belgian (or European) estimates, except for two Norwegian studies (see Limitations below).

The cost-effectiveness of expanding the HPV vaccination of girls to boys depends primarily on which outcomes are considered to be prevented by HPV vaccination. If only the EMA+ indications are considered, universal HPV vaccination presents ICERs that are well above the one estimated for the HPV vaccination of girls in 2007 (> 118 000 per QALY vs €33 000 in 2007) compared to girl-only vaccination when the uptake in girls is high (as in VG) and when the same vaccine (HPV2 or HPV4) is used (based on 2 public studies). However two lower quality industry-sponsored studies suggest that if the vaccine used in girls (HPV2 or HPV4) is replaced by HPV9 for the universal vaccination, the ICER would be below the one estimated for the HPV vaccination of girls in 2007, whatever is the level of uptake in girls. When the girl uptake is low (30-50%) as in FWB and there is no change of vaccine, universal vaccination is more attractive than when uptake in girls is high (based on 1 independent and higher quality study) but the ICER reported is above the one estimated for the HPV vaccination of girls in 2007. In this study however, higher vaccination costs compared to Belgium were used (including a 3-dose schedule) and it is thus most likely that universal vaccination would be cost-effective when transposed to the Belgian context. Direct sensitivity of the ICERs to changes in vaccination costs is indeed documented in many economic evaluations. When all HPV-related diseases are considered (i.e. HPV vaccines are assumed to be efficacious against OPC and penile cancers), universal HPV vaccination present ICERs that are close to or lower than the one estimated for the HPV vaccination of girls in 2007, at whatever vaccine uptake in girls (between 25 to 90%) and vaccine

used (based on 10 studies, of which 5 sponsored). However, there were no studies that used HPV9 in both strategies being compared.

Studies that assumed low vaccination costs per dose (for vaccine and administration, ranging €40-47 for HPV2, and €72-82 for HPV4) showed that ICERs are extremely sensitive to vaccine prices. All studies discounted the health benefits at 3 to 4% rate and some of them used a 3-dose schedule. In a Belgian situation with a 1.5% discount rate for health outcomes, a 2-dose schedule and much lower vaccine prices (e.g. through tenders), we cannot exclude that universal vaccination would reach an ICER below the one estimated for the HPV vaccination of girls in 2007, whatever outcomes are considered.

When the uptake in girls is low, increasing the uptake in girls was more cost-effective than extending the vaccination to boys (based on 2 independent studies) whatever diseases are considered. Such conclusion however does not take equity into account and it does not preclude that universal vaccination may also be cost-effective. Reducing the duration of vaccine protection only had a moderate impact on the results in the studies that investigated it, and the conclusions are unchanged.

There were relatively few studies exploring vaccination strategies with HPV2 as it is not registered for use in men in the US and it is not broadly adopted in Europe. The comparison between a universal vaccination with HPV9 and a girl vaccination with HPV2 is very interesting for the FWB situation, but was explored in only one industry-sponsored study of lower quality which reported results that were very favourable for HPV9 (universal HPV9 vaccination with ICER of €12 350 per QALY). This study however did not assume any cross-protection of HPV2. The comparison between a universal vaccination with HPV9 and a girl vaccination with HPV9, of interest for the VG, was also not available.

In the UK, the JCVI first expressed a negative advice against the extension of HPV vaccination to boys as it was considered as likely not cost-effective based on an equal 3.5% discount rate for costs and health benefits.[13] In July 2018, JCVI revised its advice and used a discount rate of 1.5% for health benefits, according to UK economic guidelines for public health interventions with long-term health benefits, as vaccination.[195] This puts more weight on the clinical benefits and, under equal costs, improves the ICERs. The new evaluation concluded that extending immunisation to adolescent boys is likely cost-effective.[14] In Belgium the recommendation is to use a lower discount rate for health effects (1.5%) than for costs (3%).[185]

9.3 Other aspects

Clinical and economic aspects are not the only factors to decide on the implementation of a vaccination programme. The expansion of the HPV vaccination to boys also involves feasibility and acceptability concerns. Feasibility must be investigated at the level of each community as boys from this age group are not targeted by the current vaccination programme, and the impact on the school health service organisation will be substantial. There are also many concerns for the acceptability of a universal HPV vaccination as the current HPV vaccination of girls is facing vaccine hesitancy, especially in Wallonia where the uptake is lower and the anti-vaccine lobbies are more active.

Ethical aspects are also involved in this question but are not covered here. Budget impact issues were not explored neither.

9.4 Limitations

The following limitations must be taken into account when interpreting these results:

- It was not possible to estimate the expected clinical impact of the different strategies in Belgium (see above).
- Some methodological choices made and some input parameters selected by the studies do not fully correspond to the Belgian setting:
  - The burden of disease differs across studies and with the Belgian burden estimates. In general the incidence rates do not differ substantially from the rates reported for Belgium, except for two Norwegian studies in which higher rates of disease were used, especially for oropharyngeal cancers and anogenital warts.[166, 171] However this should not change the conclusion for the comparisons using EMA+, as the ICERs are high and would be higher with a lower burden (as less disease would be prevented). In the comparison using all outcomes, the Norwegian study found an ICER at around €39 000 which would be higher if a lower burden is considered.[166] However the two other studies in that comparison are very favourable. No sensitivity analysis on the burden of disease could help to improve the inference to Belgium.
  - The vaccine prices used by most evaluations are higher than the tender-based prices that may be expected in Belgium. The conclusions of the studies are thus likely to underestimate the cost-effectiveness of the same comparison in Belgium.
  - The discount rates used in the studies are similar for costs and health benefits, at 3 or 4%; while the Belgian guidelines recommend the use of a lower discount rate for health benefits (1.5%) than for costs (3%). The conclusions of the studies are thus likely to underestimate cost-effectiveness of the same comparison in Belgium.
- Some choices and parameters of older studies do not fully correspond to the current state of knowledge. In particular, cross-protection of HPV2 (i.e. against non-HPV2 types) was not taken into account in any study, and cross-protection of HPV4 was considered in only three studies.[165, 168, 170] This is in contradiction with two meta-analyses that conclude that cross-protection is higher for HPV2 compared to HPV4.[76, 102] This likely leads to underestimate the overall efficacy of HPV2 against any HPV-related cancer and thus the cost-effectiveness of strategies using HPV2 – and to some extent HPV4 – compared to HPV9.
- All studies were based on the vaccine efficacy against vaccine HPV type infection and/or pre-cancerous lesions, as these surrogates are the outcomes available in published studies. However, the real HPV vaccine efficacy to prevent HPV-related cancers (due to vaccine types or any type) is not yet known.
- Six studies were sponsored by the industry producing the vaccine being evaluated, and results were usually more favourable than in publicly sponsored studies. We report in every analysis the type of sponsoring of the involved studies, and this aspect should be taken into account by those using this report.
- Fewer economic analyses involved HPV2 strategies, probably because HPV2 is not authorized for boys in the US and fewer countries in EU use HPV2 in their vaccination programme.
- No study was found in which the incremental cost-effectiveness of universal HPV9 versus girl-only HPV9 vaccination was the focus of the analysis and subjected to proper uncertainty analysis.

9.5 Conclusions

In Belgium, more than 1000 new cases of cancer are attributable to HPV every year, and 22% of these were reported in males in 2015. In addition, 13 000 to 20 000 genital warts occur in Belgium every year in total. HPV vaccines have been shown to be effective at preventing pre-cancerous lesions of most HPV-related cancers and are considered to be safe.

Our review of the economic literature suggests that the cost-effectiveness of expanding the HPV vaccination of girls to boys depends primarily on the outcomes that are included in the analysis and were defined as preventable by the vaccination:

- When the outcomes considered are all HPV-related diseases (cancers of cervix, anus, vagina, vulva, penis and oropharynx, and genital warts for HPV4/9), universal HPV vaccination compared to girl-only vaccination presents ICERs that are generally lower than the ones estimated for the HPV vaccination of girls in 2007 (€33 000). This conclusion prevails whatever the vaccine uptake in girls and whatever the vaccine used in the studies i.e. HPV2 or HPV4 in girls also used for universal vaccination, or HPV4 in girls replaced by HPV9 for universal. There was no study whose focus was to compare HPV9 in both universal and girl-only vaccination.
- When considering the authorised indications only (EMA + indications i.e. cancers of cervix, anus, vagina and vulva, and genital warts for HPV4/9), the cost-effectiveness results depend on the vaccine used and the uptake in girls.
    - When the uptake in the girl-only situation is high, as in the Vlaamse Gemeenschap, universal HPV vaccination compared to girl-only vaccination presents ICERs that are above the ones estimated for the HPV vaccination of girls in 2007 when there is no change of vaccine, i.e. HPV2 or HPV4 are used in both vaccination strategies that are compared (girl-only and universal vaccination).
    - When the uptake in the girl-only situation is low (30-50%), as in the Federation Wallonie-Bruxelles, and there is no change of vaccine, universal vaccination is more cost-effective than when the uptake in girl-only is high. Furthermore that strategy is likely to be cost-effective in a Belgian context with lower prices obtained through public procurement procedures and a 2-dose schedule.
    - For both communities, if the vaccine used in girls (HPV2 or HPV4) is replaced by HPV9 for the universal vaccination, ICERs are below the one estimated for the HPV vaccination of girls in 2007, according to two lower quality industry-sponsored studies for levels of uptake in girls between 40 and 70%.

In Belgium, with a lower discount rate for health outcomes, a 2-dose schedule and much lower vaccine prices (e.g. through tenders) than considered in those studies, we cannot exclude that universal vaccination would reach an ICER below the one estimated for the HPV vaccination of girls in 2007, whatever the outcomes considered.

When the uptake in girls is low, as in Federation Wallonie-Bruxelles, increasing the uptake rate in girls is even more cost-effective than extending the vaccination to boys, whatever diseases considered. This conclusion, however, do not take equity into account and it does not preclude that universal vaccination may also be cost-effective.

A model simulating the Belgian situation could have provided more accurate answers and to some additional questions, but this analysis of the economic literature thoroughly explored all results (including all sensitivity analyses) of the studies, and allowed us to answer to the key questions required by the stakeholders.

APPENDICES

APPENDIX 1. ECONOMIC EVALUATIONS OF UNIVERSAL HPV VACCINATION

Appendix 1.1. Literature selection

Table 33 – Selection of primary economic evaluations of universal HPV vaccination

SOURCE FOR PRIMARY ECONOMIC EVALUATION	PUBLISHED LITERATURE REVIEWS (Author, year)								KCE UPDATE (up to March 2018)	ELIGIBILITY OF THE IDENTIFIED ECONOMIC EVALUATIONS	
	Sinisgalli, 2015[129]	Ben Hadj, 2015[121]	Chaiyakunapruk, WHO, 2016[128]	Brisson, WHO, 2016[127]	HCSP, 2016[125]	Foerster, CADTH, 2017[120]	HCSP HPV9, 2017[126]	Sujikerbuijk, 2017[130]		Study selection	Reason for exclusion
Number of economic evaluations	**15**	**14**	**28**	**11**	**15**	**6**	**8**	**18**	**10**	**29**	
Taira, 2004[196]		x	x	x	x					Yes	
Danish Centre HTA, 2007[197]					x					Yes	
Elbasha, 2007[198]	x	x	x		x					Yes	
Insinga, 2007[161]	x		x							No	Mexico
Kim, 2007[162]	x		x							No	Brazil
Kulasingam, 2007[199]	x	x			x					Yes	
Dasbach, 2008 (UK)[135]			x							No	Females only
Dasbach, 2008 (Taiwan)[136]			x							No	Females only
Dasbach, 2008 (Norway)[137]			x							No	Females only
Jit, 2008[200]	x	x	x	x	x			x		Yes	
Kim, 2008[145]								x		No	Females only
Usher, 2008[150]			x							No	Females only
Elbasha, 2009[140]			x							No	Females only
Kim, 2009[172]	x	x	x	x	x			x		Yes	
Zechmeister, 2009[201]	x	x	x	x	x					Yes	
Dasbach, 2010[138]			x							No	Females only
Elbasha, 2010[169]	x	x	x	x	x			x		Yes	
Kim, 2010[158]		x			x					No	MSM only
Olsen, 2010[202]	x	x		x	x					Yes	
Chesson, 2011[167]	x	x	x	x	x			x		Yes	

Jit, 2011[142]								x			No	Females only
Westra, 2011[151]			x								No	Females only
Kawai, 2012[143]			x								No	Females only
Tully, 2012[148]			x								No	Females only
Brisson, 2013[133]								x			No	Females only
Luttjeboer, 2013[147]								x			No	Females only
Turner, 2013[149]			x								No	Females only
Yamabe, 2013[152]			x								No	Females only
Blakely, 2014[132]								x			No	Females only
Bresse, 2014[203]	x		x					x			Yes	
Burger, 2014[166]	x	x			x			x			Yes	
Deshmukh, 2014[157]		x			x						No	MSM only
Drolet, 2014[139]			x	x			x	x			No	Females only
Kiatpongsan, 2014[144]			x								No	Females only
Laprise, 2014[204]	x	x	x		x			x			Yes	
Pearson, 2014[176]	x	x			x			x			Yes	
Bogaards, 2015[205]						x					No	No econ eval
Graham, 2015[155]						x					No	Boys only
Haeussler, 2015[170]			x			x		x			Yes	
Jit, 2015[141]								x			No	Females only
Olsen, 2015[175]	x		x					x			Yes	
Boiron, 2016[164]				x			x				Yes	
Brisson, 2016[165]				x		x	x	x			Yes	
Chesson, 2016[134]				x			x				No	Females only
Chesson, 2016[168]							x				Yes	
Durham, 2016[206]							x				Yes	
Laprise, 2016[207]							x				Yes	
Liu, 2016[146]			x								No	Females only
Sharma, 2016[163]			x								No	Vietnam
Vargas, 2016[156]						x					No	HIV + males
Largeron, 2017[173]							x				Yes	
Lin, 2017[159]						x					No	MSM only
Jimenez, 2015[171]										x	Yes	
Simms, 2016[208]										x	Yes	

Damm, 2017[209]	x	Yes	
JCVI, 2017[13]	x	Yes	
Kuie, 2017[153]	x	No	Females only
Menini, 2017[174]	x	Yes	
Qendri, 2017[177]	x	Yes	
Vorno, 2017[154]	x	No	Females only
Wolff, 2017[178]	x	Yes	
Zhang, 2017[160]	x	No	MSM/boys

Appendix 1.2. Overview of the systematic reviews of economic evaluations of universal HPV vaccination

Sinisgalli et al., 2015[129]

Sinisgalli et al. performed a review of 15 economic evaluations of universal HPV vaccination, all considering 3 doses of HPV2 or HPV4.[129] They report that extending HPV vaccination of girls to include boys is likely to be cost-effective when considering the current decreasing vaccine prices and the two-dose schedule.

A review of 13 former reviews of cost-effectiveness studies on HPV vaccination including boys was also performed. In the oldest reviews universal vaccination was not found to be cost-effective compared to girl-only vaccination or to increasing the uptake among girls. The most recent reviews, instead, suggested that adding boys could be cost-effective if vaccine costs were reduced, if girl uptake did not increase, and if all HPV-related diseases were taken into account.

Ben Hadj Yahia et al., 2015[121]

Ben Hadj Yahia et al. reviewed 14 original economic evaluations (17 minus 3 redundant publications) of universal HPV vaccination, all published between 2004 and 2014, and using three-dose vaccine series.[121] The analyses were grouped by clinical outcome with a separate analysis for MSM.

Extending vaccination to boys was rarely cost-effective at the current vaccine price and for the health outcomes for which the vaccines are licensed. Cost-effectiveness ratios became more attractive when all HPV-related diseases were considered (cervical, vaginal, vulvar, penile, anal, and oropharyngeal cancers, recurrent respiratory papillomatosis and genital warts), and when girl uptake was below 40%. MSM vaccination was found to be the best option with respect to gender equity and cost-effectiveness; but this specific population is hard to capture at young ages.

WHO Strategic Advisory Group of Experts meeting on HPV immunisation, 2016[127, 128]

Two short reviews on the cost-effectiveness of HPV immunisation were written for the WHO Strategic Advisory Group of Experts (SAGE) meeting on HPV vaccination that took place on 18-20 October 2016 in Geneva.[127, 128]

One study reviewed 28 economic evaluations (including low income countries) pertaining to immunisation with HPV9 (versus HPV2 or HPV4), gender-neutral vaccination (versus girl-only) and multiple age cohort vaccination (versus single age cohort).[128] Their literature search was performed up to June 2016. Economic evaluations of HPV9 used in girls were scarce such that the authors could not conclude on its cost-effectiveness.[139, 144] Based on 14 studies, universal immunisation was reported to be potentially cost-effective depending on the girl uptake, the vaccine price, the duration of vaccine protection and the HPV-related clinical outcomes considered in males. If the uptake in girls is greater than 70-80%,

extending vaccination to boys is not found to be cost-effective. This WHO report was recently published in Ng et al.[131]

In the second review the methods used for study selection were poorly described.[127] For girl-only HPV vaccination, based on 4 economic evaluations, switching to HPV9 is predicted to be cost-effective in Canada, Austria, and cost saving in the US, if the cost per dose for HPV9 is assumed to be no more than 10-15% greater than the cost for HPV4. For universal vaccination, based on two previously published reviews,[210, 211] if the girls uptake is greater than approximately 50%, gender-neutral vaccination is unlikely to be cost-effective (versus girl-only vaccination).

Haut Conseil de la Santé Publique, 2016 (HPV vaccination of boys)[125]

In 2016, the French Haut Conseil de la Santé Publique (HCSP) reviewed the cost-effectiveness of universal and targeted (MSM) HPV vaccination of boys.[125] They searched the literature from 2001 to 2014 and identified 14 studies all (but one) using a 3-dose schedule with HPV2 or HPV4. One study considered a 2-dose schedule.[204] HPV vaccination of boys was not found cost-effective when the clinical outcomes considered in the studies were limited to the EMA indications. By contrast, extending HPV vaccination to boys was found to be cost-effective when:

- all clinical outcomes were considered (including oropharyngeal and penile cancer, recurrent respiratory papillomatosis), or
- the vaccine cost ranges $40-80 per dose, or
- vaccination is targeted to MSM.

They further reported that in all studies, if the girl uptake is <40%, HPV vaccination of boys becomes cost-effective provided a high uptake in boys is reached.

Foerster et al., Canadian Agency for Drugs and Technologies in Health, 2017[120]

The Canadian Agency for Drugs and Technologies in Health (CADTH)[120] performed an update of the previous reviews by Sinisgalli et al.[129] and Ben Hadj Yahia et al.[121] Six new economic evaluations were identified (search up to 24/02/2017). Most studies assessed HPV4.

From those additional studies, CADTH concluded that the economic analyses on the HPV immunisation of boys and young men were generally favourable although dependent on factors such as the cost to purchase and administer the vaccine, and the dosage schedules.

Haut Conseil de la Santé Publique, 2017 (HPV9 vaccination)[126]

The French HCSP reviewed 8 economic evaluations of HPV9, all performed in developed countries (2 in Europe and 6 in North America).[126] Their literature search spanned from 01/2013 to 07/2016. HPV9 was compared with HPV4; there was no comparison against HPV2. Most studies considered a three-dose vaccination scheme.

A change from HPV4 to HPV9 to immunize girls only was found to be cost-effective (at local thresholds) if the cost difference between the vaccines (HPV9 versus HPV4) was below €6-25 per dose. Results for universal vaccination were unclear. They stressed that most studies used optimistic assumptions (e.g. in terms of vaccine efficacies and duration of protection); and highlighted that the cost-effectiveness of HPV9 was highly sensitive to the local distribution of additional HPV types contained in Gardasil 9 and to the HPV-related diseases considered.

Suijkerbuijk et al., 2017[130]

Suijkerbuijk et al. from The Netherlands reviewed the impact of including non-cervical cancers on the cost-effectiveness of universal versus girl-only vaccination.[130] They included 18 economic evaluations, published up to 18/01/2016, considering cervical cancer plus at least one other HPV-related cancer. Most studies investigated HPV4, two the HPV9 vaccine.[139, 165] A three-dose schedule was used, except in 2 recent studies that used a two-dose schedule.[141, 204]

The cost-effectiveness of universal versus girl-only vaccination resulted in ICERs ranging between €113 778 and €292 159 per QALY gained when only cervical cancer was considered. In studies including other HPV-associated diseases, the ICERs varied between €13 700 and €261 866 per QALY. They conclude that including non-cervical diseases in economic evaluations of HPV vaccination programs makes it more likely that the ICER falls beneath accepted cost-effectiveness thresholds and therefore increases the scope for gender-neutral vaccination.

Appendix 1.3. Overview of the 29 economic evaluations of universal HPV vaccination

Appendix 1.3.1. Technical characteristics

Table 34 gives an overview of the technical characteristics of the 29 economic evaluations.

High-income countries was the focus of this review. Studies were carried out in North America (9 in USA and 1 in Canada), in Europe (3 in Austria, 3 in Denmark, 2 in Germany, 2 in Italy, 2 in UK, 2 in Norway, 1 in Sweden), in Australia (2) and New Zealand (1).

More than one third of the studies had conflicts of interest with (all) authors being affiliated with and/or the analysis being sponsored by Sanofi-Pasteur-MSD. All other studies explicitly acknowledged of support that did not include private industry, generally from public (academic or government) sources.

All but two studies were cost-utility analyses, with outcomes expressed as quality-adjusted life years (QALY), or disability-adjusted life years in Pearson et al.,[176] therefore capturing both years of life lost due to premature death and loss of quality of life due to morbidity. Zechmeister et al.[201] and the DCHTA study[197] used a cost-effectiveness design, with outcomes expressed as life years, and considered improvement in life expectancy only.

Virtually all economic evaluations focused on direct medical and intervention costs as cost categories. These studies were thus performed from the perspective of the health care payer / national health system, although some of them report they used a societal perspective. Two studies performed their analysis from a societal perspective, including also direct non-medical costs (such as transport costs) and patient time costs.[166, 172]

In almost all studies the time horizons were long enough to capture the relevant long-term clinical consequences related to HPV diseases (e.g. HPV-related cancers and deaths), and varied from 52 years[201] up to a lifetime (or 100 years). As a consequence those studies had to extrapolate the results from the clinical trials far beyond their observed periods (e.g. for vaccine duration of protection) which generates uncertainties in the long-term predictions of the models. The study by Durham et al.[206] was limited to a horizon of 35 years which may not be long enough to capture all relevant endpoints.

In Table 34, economic evaluations were classified according to the vaccine(s) evaluated: the recently licenced HPV9 vaccine or the HPV2 and HPV4 vaccines. Studies were further stratified according to the HPV-related diseases modelled in their base case, to assess the cost-effectiveness of extending HPV vaccination to boys. Six cost-effectiveness studies considered cervical cancer as the only disease targeted by the HPV vaccines.[196, 197, 199, 201, 206, 208] Four of those studies were old with publication dates between 2004 and 2009, but the two other studies were recent (2016) and assessed HPV9.[206, 208] Four cost-effectiveness studies considered cervical cancer combined with genital warts as the only targeted diseases, all of them evaluating HPV4 (and HPV2 in Damm et al.[209]) and with publication years spanning 2007 to 2017.[198, 200, 202, 209] The remaining 18 cost-effectiveness studies considered (almost) all HPV-related diseases, i.e. cervical, vulvar, vaginal, anal, penile and head and neck (oropharyngeal) cancers, juvenile or/and adulthood-onset recurrent respiratory papillomatosis and genital warts. Their publication years ranged from 2009 to 2017. Due to sparse evidence however, the impact on recurrent respiratory papillomatosis and on penile and oropharyngeal cancer was often discarded (in 11, 4 and 3 studies respectively) or only explored in sensitivity analyses.

Table 34 – Technical characteristics of the 29 economic evaluations of universal HPV vaccination

	Country	Sponsor	Analytic technique	Reported perspective	Resources valued	Time horizon (years)	Vaccine assessed (intervent°)	Diseases modelled							
								GW	CER	VUL	VAG	ANA	OPC	PEN	RRP
Nonavalent vaccine															
Largeron et al. 2017	Germany	Industry	CUA	NHS	DMC	100	HPV9	x	x	x	x	x	No†	No†	No†
Mennini et al. 2017	Italy	Industry	CUA	NHS	DMC	100	HPV9	x	x	x	x	x	No†	No†	No†
Brisson et al. 2016	USA	Public	CUA	Societal	DMC	70	HPV9	x	x	x	x	x	x	x	No
Boiron et al. 2016	Austria	Industry	CUA	HCP	DMC	100	HPV9	x	x	x	x	x	x	x	x
Chesson et al. 2016	USA	Public	CUA	Societal	DMC	100	HPV9	x	x	x	x	x	x	x	x
Laprise et al. 2016	USA	Public	CUA	Societal	DMC	100	HPV9	x	x	x	x	x	x	x	No
Simms et al. 2016	Australia	Public	CUA	NHS	DMC	?	HPV9	No	x	No†	No†	No†	No†	No	No
Durham et al. 2016	USA	Public	CUA	Societal	DMC	35	HPV9	No	x	No	No	No	No	No	No
Bivalent and/or quadrivalent vaccine															
Wolff et al. 2017	Sweden	Public	CUA	NHS‡	DMC‡	100	HPV2	No	x	x	x	x	x	x	No
JCVI. 2017	UK	Public	CUA	NR	NR	NR	NR	x	x	x	x	x	x	x	No
Qendri et al., 2017	Netherlands	Public	CEA	HCP	DMC	Life	HPV2	No	x	x	x	x	x	x	No
Haeussler et al. 2015	Italy	Industry	CUA	NHS	DMC	55	HPV4	x	x	x	x	x	x	x	No
Olsen et al. 2015	Denmark	Industry	CUA	HCP	DMC	62	HPV4	x	x	x	x	x	x	x	No
Jimenez et al. 2015	Norway	Public	CUA	NHS‡	DMC‡	100	HPV4	x	x	x	No†	No†	No	No	No
Bresse et al. 2014	Austria	Industry	CUA	NR	DMC	100	HPV4	x	x	x	x	x	x	x	x
Burger et al. 2014	Norway	Public	CUA	Societal	PTC, DMC, DnonMC	Life	HPV4	x	x	x	x	x	x	x	x
Laprise et al. 2014	Canada	Public	CUA	HCP	DMC	70	HPV4	x	x	x	x	x	x	x	No
Pearson et al. 2014	New-Zealand	Public	CUA	NHS	DMC	98	HPV4	x	x	x	No	x	x	No	No
Chesson et al. 2011	USA	Public	CUA	Societal	DMC	100	HPV4	x	x	x	x	x	x	x	x
Elbasha et al. 2010	USA	Industry	CUA	NS	DMC	100	HPV4	x	x	x	x	x	x	x	x
Kim et al. 2009	USA	Public	CUA	Societal	PTC, DMC, DnonMC	100	HPV2	No	x	x	x	x	x	x	No
Damm et al. 2017	Germany	Public	CUA	NHS	DMC	100	HPV4, HPV2*	x	x	No	No	No	No	No	No
Olsen et al. 2010	Denmark	Industry	CUA	HCP	DMC	62	HPV4	x	x	No	No	No	No	No	No
Jit et al. 2008	UK	Public	CUA	NHS	DMC	100	HPV4	x	x	No	No	No	No	No	No

	Country	Sponsor	Analytic technique	Reported perspective	Resources valued	Time horizon (years)	Vaccine assessed (intervent°)	Diseases modelled							
								GW	CER	VUL	VAG	ANA	OPC	PEN	RRP
Elbasha et al. 2007	USA	Industry	CUA	NHS	DMC	100	HPV4	x	x	No	No	No	No	No	No
Zechmeister et al. 2009	Austria	Public	CEA	HCP	DMC	52	HPV2	No	x	No	No	No	No	No	No
Kulasingam et al. 2007	Australia	Industry	CUA	NHS	DMC	73	HPV2	No	x	No	No	No	No	No	No
DCHTA 2007	Denmark	Public	CEA	Society	DMC	62	HPV2	No	x	No	No	No	No	No	No
Taira et al. 2004	USA	Public	CUA	NR	DMC	Life	HPV2	No	x	No	No	No	No	No	No

** Bivalent vaccine (HPV2) assessed in the sensitivity analysis. † Disease considered in the sensitivity analysis. ‡ A societal perspective was also adopted in which direct medical and productivity (time) costs were included. ANA: anal cancer, CEA: cost-effectiveness analysis, CER: cervical cancer, CUA: cost-utility analysis, DMC: direct medical costs, DnonMC: direct non-medical costs (e.g. transport), GW: genital warts, HCP: health care payer; NHS: national health system, NR: not reported, PEN: penile cancer, PTC: patient time costs, RRP: recurrent respiratory papillomatosis, OPC: cancer of the oropharyngeal region (head & neck / oropharynx, base of tongue and tonsil), VAG: vaginal cancer, VUL: vulvar cancer.*

Appendix 1.3.2. Vaccination schedules, interventions and comparators

All but three studies compared universal HPV vaccination with vaccination of girls only. In three studies universal vaccination was compared to no vaccination.[197, 202, 203] With such comparison however the indirect benefits to boys derived from girl-only vaccination via herd immunity is ignored which may unduly favour the results towards universal vaccination. Universal vaccination with HPV2 was assessed in 5 studies and compared with girl-only HPV2 vaccination.[178, 196, 199, 201, 209] Universal vaccination with HPV4 was assessed in 12 studies and compared with girl-only vaccination with the same vaccine.[166, 167, 169-172, 175, 176, 198, 200, 204, 209] The cost-effectiveness of universal vaccination with HPV9 was explored in 8 studies. Two studies compared it with HPV4[173, 174] or HPV2[173] vaccination of girls. In five studies the cost-effectiveness of switching from HPV4 to HPV9 for universal HPV vaccination was explored.[164, 165, 168, 206, 208] Beside, Brisson et al.[165] and Chesson et al.[168] assessed scenarios where boys and girls are not offered the same vaccine, i.e. switching females only to HPV9 while boys remain with HPV4. In Laprise et al.[207] the cost-effectiveness of a 2- versus 3-dose schedule with HPV9 was explored.

Twenty-two studies considered a 3-dose schedule in their base-case, four of them also considering a 2-dose schedule in their sensitivity analysis.[166, 171, 175, 209] A 2-dose schedule was taken into account in the base-case of 6 recent studies.[164, 173, 174, 178, 204, 207, 208] In the oldest studies by Zechmeister et al.[201] and Taira et al.[196] the 3-doses primo-vaccination was followed by a booster dose administered 10 years later.

In most studies, single age cohorts were vaccinated, usually at 12 years old or in the age range 9-17 years. Some studies also considered a temporary catch-up programme during the first years of the programme, targeted at older females (age range 13-26 years).[167, 198, 204, 208] In three studies vaccination was administered to multiple age cohorts with cumulative uptake rates gradually increasing with age (9-17 years in Largeron et al.,[173] 12-26 years in Chesson et al.[168] and 9-26 years in Elbasha et al.[169]).

Table 35 – Vaccination strategies of the 29 economic evaluations of universal HPV vaccination

	Country	Number of doses	Age (years) at vaccination	Single or multiple cohort vaccination / Catch-up	Interventions	Comparators
Nonavalent vaccine						
Largeron et al. 2017	Germany	2	9-17	Multiple	HPV9 FM HPV9 FM *HPV9 F* *HPV9 F*	HPV4 F HPV2 F *HPV4 F* *HPV2 F*
Mennini et al. 2017	Italy	2	12	Single	HPV9 FM *HPV9 F* *HPV9 F* *HPV9 FM*	HPV4 F *HPV4 F* *HPV2 F* *HPV4 FM*
Brisson et al. 2016	USA	3	13-17 (?)	Single	*HPV9 F + HPV4 M* *HPV9 FM* *HPV9 FM*	*HPV4 FM* *HPV9 F + HPV4 M* *HPV4 FM*
Boiron et al. 2016	Austria	2	9	Single	*HPV9 FM*	*HPV4 FM*
Chesson et al. 2016	USA	3	12-26	Multiple	*HPV9 F + HPV4 M* *HPV9 FM*	*HPV4 FM* *HPV4 FM*
Laprise et al. 2016	USA	2 and 3	13-17 (?)	Single	*HPV9 FM 3d*	*HPV9 FM 2d*
Simms et al. 2016	Australia	2	12-13 + CU F	Single + Catch-up	*HPV9 FM*	*HPV4 FM*
Durham et al. 2016	USA	3	13-17 (?)	Single	*HPV9 FM*	*HPV4 FM*
Bivalent and/or quadrivalent vaccine						
Wolff et al. 2017	Sweden	2	10-12	Single	HPV2 FM	HPV2 F
JCVI. 2017	UK	2 and 3	NR	NR	NR	NR
Qendri et al., 2017	Netherlands	2	12	Single	HPV2 FM	HPV2 F
Haeussler et al. 2015	Italy	3	12	Single	HPV4 FM	HPV4 F
Olsen et al. 2015	Denmark	3 †	12	Single	HPV4 FM	HPV4 F
Jimenez et al. 2015	Norway	3 †	12	Single	HPV4 FM	HPV4 F
Bresse et al. 2014	Austria	3	9	Single	HPV4 FM	No vaccination
Burger et al. 2014	Norway	3 †	12	Single	HPV4 FM	HPV4 F
Laprise et al. 2014	Canada	2 and 3	9 * + CU F14	Single + Catch-up	HPV4 FM	HPV4 F
Pearson et al. 2014	New-Zealand	3	12	Single	HPV4 FM	HPV4 F
Chesson et al. 2011	USA	3	12 12 + CU F13-26	Single Single + Catch-up	HPV4 FM	HPV4 F
Elbasha et al. 2010	USA	3	9-26	Multiple	HPV4 FM	HPV4 F

	Country	Number of doses	Age (years) at vaccination	Single or multiple cohort vaccination / Catch-up	Interventions	Comparators
Kim et al. 2009	USA	3	12	Single	HPV2 FM	HPV2 F
Damm et al. 2017	Germany	3 †	12	Single	HPV4 FM HPV2 FM	HPV4 F HPV2 F
Olsen et al. 2010	Denmark	3	12	Single	HPV4 FM	No vaccination
Jit et al. 2008	UK	3	12	Single	HPV4 FM	HPV4 F
Elbasha et al. 2007	USA	3	12 12 + CU F12-24	Single Single + Catch-up	HPV4 FM	HPV4 F
Zechmeister et al. 2009	Austria	3+1 ‡	12 + booster 22	Single	HPV2 FM	HPV2 F
Kulasingam et al. 2007	Australia	3	12	Single	HPV2 FM	HPV2 F
DCHTA 2007	Denmark	3	12	Single	HPV2 FM	No vaccination
Taira et al. 2004	USA	3+1 ‡	12 + booster 22	Single	HPV2 FM	HPV2 F

*† A two-dose schedule is considered in the sensitivity analysis. ‡ Three-dose schedule followed by a booster dose administered ten years later. * Vaccination at 12 years old explored in the sensitivity analysis. CU: catch-up vaccination, F: female vaccination, FM: female and male vaccination, HPV9: nonavalent HPV vaccine, HPV4: quadrivalent HPV vaccine, HPV2: bivalent HPV vaccine.*

Appendix 1.3.3. Model structure and filiation

The filiation between the HPV transmission models used in the cost-effectiveness studies was investigated. Studies in Table 36 are classified according to the original model they were based on. Model structure was characterised following three attributes:[212]

1. the force of infection (i.e. the rate at which susceptible individuals become infected) in order to estimate incidence changes over time (dynamic) or not (static);
2. any changes in the model occur randomly (stochastic or probabilistic) or the rules of changes are pre-specified (deterministic);
3. the population's behaviour in the model is simulated using aggregate variables of which values are population averages (aggregate) or the behaviours of individuals in the population are tracked (individual based).

The structure of the HPV transmission models evolved over time and the majority of the most sophisticated models (e.g. dynamic individual based stochastic models) were found in cost-effectiveness studies published in the last 4 years.[165, 175, 204, 207, 208] Men having sex with men (MSM) are difficult to model for young cohorts and were therefore rarely explicitly included in population models. MSM were separately modelled in three studies only, representing 2.5-3% of the male population (proportion not reported in Haeussler et al.).[170, 178] Those studies modelled an increased relative risk of disease in MSM versus the heterosexual population: 17 for anal cancer[170, 204] and 3 for genital warts, penile and oropharyngeal cancers.[204] (RR 3). Other studies modelled heterosexual partnerships only and therefore did not reflect HPV transmission among MSM, who may realise a greater benefit from HPV vaccination.

A series of 6 industry-sponsored cost-effectiveness studies used the same HPV dynamic transmission model initially developed by Elbasha et al.[169, 198] for the USA, or an updated version of it.[164, 169, 173, 174, 198, 203] The model is a deterministic, dynamic state-transition model (Susceptible-Infected-Recovered-Susceptible) that simulates the genotypes of the HPV4 vaccine

(HPV 6, 11, 16, 18) for the older studies and those of the HPV9 vaccine (HPV 6, 31, 33, 45, 52, and 58) for the most recent studies. Non-vaccine types are not modelled and no vaccine cross-protection is assumed. The model simulates the heterosexual transmission of HPV; the impact of HPV vaccination on MSM is ignored.

Three cost-effectiveness studies were based on updated versions of an early model developed at the Centre for Disease Control and Prevention by Chesson and colleagues, to assess the 4- or the 9-valent vaccine in the US.[167, 168, 171] The model is a deterministic, dynamic, population-based model simulating the heterosexual transmission of HPV. Jimenez et al.[171] performed a Norwegian adaptation of this model to make it probabilistic. In this study further vaginal, anal, penile or oropharyngeal cancers were not included in the base case, while they all were included in the original model. In its last version the model was expanded to incorporate cross-protection from HPV4 against the 5 additional types contained in HPV9.[168]

Another series of 4 cost-effectiveness studies used HPV-ADVISE, a stochastic individual-based transmission-dynamic model of 18 HPV type infections (HPV9 vaccine types plus 35, 39, 51, 56, 59, 66, 68, 73, 82) and diseases (anogenital warts, cancers of the cervix, vulva, vagina, anus, penis and oropharynx).[165, 204, 207, 208] Simms et al. slightly differed from this and focused on the HPV9 vaccine types and on cervical cancers.[208] HPV-ADVISE was originally developed to inform HPV vaccination policy in Canada and was created by researchers under the supervision of Marc Brisson. Later the model was adapted and recalibrated to represent the United States (HPV-ADVISE-US). One study considered the benefits to the MSM population (who do not benefit from the herd effects of girl-only vaccination) of adding boys to an HPV vaccination programme.[204] Cross-protection from HPV4 was assumed in three studies.[165, 204, 208] In Brisson et al. given the uncertainty in the cross-protection from HPV4 against the 5 HPV9 non-HPV4 vaccine types, base-case results were presented with and without cross-protection.[165]

Olsen et al.[175, 202] used an individual-based dynamic model initially developed by the independent Danish Centre for Health Technology Assessement.[197] Though the initial model was developed independently, the two studies using revised version of this model were funded by an unrestricted grant from Sanofi-Pasteur MSD. The initial model exclusively simulated the heterosexual transmission of two HPV types (16 and 18) and was later extended with HPV types 6 and 11. No cross-protection was assumed.

Burger et al.[197] and Kim et al.[172] used a hybrid model combining a dynamic state transition model for HPV heterosexual transmission and a static individual-based model for disease progression. No cross-protection was assumed.

The remaining studies, among which no cluster of HPV transmission model was identified, were all population-average state-transition models. Most of them were dynamic, taking herd immunity into account. In three cost-effectiveness studies however the models were static but herd immunity offered by vaccination was considered by integrating the output predicted by previously published dynamic models.[170, 176, 199] Most models focused on vaccine-specific HPV types and did not assume cross-protection against non-vaccine types in their base-case. Three cost-effectiveness studies modelled non-vaccine HPV types and assumed cross-protection.[170, 206, 209] In Durham et al.[206] 10 HPV types were independently modelled (i.e. HPV9 vaccine types, minus 6/11, plus 35/39/51). Damm et al.[209] modelled 6 groups of HPV strains: 16, 18, high-risk types with potential for cross-protection (31/33/35/39/45/51/52/56/58/59), other high-risk types without potential for cross-protection, 6/11, and other low-risk types. Cross-protection was considered in their sensitivity analysis. Haussler et al. modelled the HPV4 vaccine types together with 10 additional non-vaccine types (31/33/35/39/45/51/52/56/58/59) against which cross-protection was assumed.[170]

Table 36 – Structure and filiation of the models in the 29 economic evaluations of universal HPV vaccination

	Country	Model source	Model attributes			Model type	Impact on MSM	HPV types modelled	Cross protection
			Static / Dynamic	Deterministic / Stochastic	Aggregate / individual based				
Root model: Elbasha (AP-MSD sponsored)									
Largeron et al. 2017	Germany	Elbasha 2007 & 2010	Dynamic	Deterministic	Aggregate	State-transition	No	HPV9 types	No
Mennini et al. 2017	Italy	Elbasha 2007 & 2010	Dynamic	Deterministic	Aggregate	State-transition	No	HPV9 types	No
Boiron et al. 2016	Austria	Elbasha 2007 & 2010	Dynamic	Deterministic	Aggregate	State-transition	No	HPV9 types	No
Bresse et al. 2014	Austria	Elbasha 2007 & 2010	Dynamic	Deterministic	Aggregate	State-transition	No	HPV4 types	No
Elbasha et al. 2010	USA	Elbasha, 2007	Dynamic	Stochastic	Aggregate	State-transition	No	HPV4 types	No
Elbasha et al. 2007	USA	-	Dynamic	Deterministic	Aggregate	State-transition	No	HPV4 types	No
Chesson root model (No industry sponsor)									
Chesson et al. 2016	USA	Chesson 2011	Dynamic	Deterministic	Aggregate	State-transition	No	HPV9 types	Yes
Jimenez et al. 2015	Norway	Chesson 2011	Dynamic	Stochastic	Aggregate	State-transition	No	HPV4 types	No
Chesson et al. 2011	USA	Chesson 2008	Dynamic	Deterministic	Aggregate	State-transition	No	HPV4 types	No
HPV-ADVISE root model (No industry sponsor)									
Brisson et al. 2016	USA	HPV-ADVISE-US	Dynamic	Stochastic	Individual	IBM	No	HPV9 + 35, 39, 51, 56, 59, 66, 68, 73, 82	Yes
Laprise et al. 2016	USA	HPV-ADVISE-US	Dynamic	Stochastic	Individual	IBM	No	HPV9 + 35, 39, 51, 56, 59, 66, 68, 73, 82	No
Simms et al. 2016	Australia	HPV-ADVISE	Dynamic	Stochastic	Individual	IBM	No	HPV9 types	Yes
Laprise et al. 2014	Canada	HPV-ADVISE	Dynamic	Stochastic	Individual	IBM	Yes. 3% MSM. RR 17 for anal cancer, 3 for GW	HPV9 + 35, 39, 51, 56, 59, 66, 68, 73, 82	Yes
Danish Centre for HTA root model									
Olsen et al. 2015	Denmark	Olsen 2010 & DCHTA 2007	Dynamic	Probabilistic (partially)	Individual	IBM	No	HPV4 types	No

Olsen et al. 2010	Denmark	DCHTA, 2007	Dynamic	Deterministic	Individual	IBM	No	HPV4 types	No
DCHTA 2007	Denmark	-	Dynamic	Deterministic	Individual	IBM	No	HPV2 types	No
Kim and Goldie root model (No industry sponsor)									
Burger et al. 2014	Norway	Kim & Goldie 2009 & 2008	Dynamic Static	Deterministic	Aggregate	State-transition (HPV transmission) IBM (disease progression)	No	HPV4 types	No
Kim et al. 2009	USA	Kim & Goldie 2008	Dynamic Static	Deterministic	Aggregate	State-transition (HPV transmission) IBM (disease progression)	No	HPV4 types	No
Other (no filiation between the models of the studies)									
Durham et al. 2016	USA	-	Dynamic	Stochastic	Aggregate	State-transition	No	16, 18, 31, 33, 35, 39, 45, 51, 52, 58	Yes
Wolff et al. 2017	Sweden	-	Dynamic	Deterministic	Aggregate	State-transition	Yes. 2.5% MSM.	HPV2 types	No
JCVI. 2017	UK	-	Dynamic	Stochastic	Individual	IBM	Yes	Vaccine types (at least), HPV9	NR
Qendri et al., 2017	Netherlands	Bogaards, 2015[205]	Static *	Stochastic	Aggregate	State- transition	Yes. 7% MSM. RR 31 anal cancer, 3 OPC	HPV2 types	No
Damm et al. 2017	Germany	Horn, 2013	Dynamic	Deterministic	Aggregate	State-transition	No	All types (split in 6 groups)	No‡
Haeussler et al. 2015	Italy	Favato, 2012	Static *	Stochastic	Aggregate	State-transition	Yes. RR 17 for anal cancer	HPV4 + 31, 33, 35, 39, 45, 51, 52, 56, 58, 59	Yes
Pearson et al. 2014	New-Zealand	Blakely, 2014	Static *	Stochastic	Aggregate	State-transition	No	HPV4 types	No
Zechmeister et al. 2009	Austria	Neilson, 2007	Dynamic	Deterministic	Aggregate	State-transition	No	HPV2 types	No
Jit et al. 2008	UK	Choi, 2007	Dynamic	Stochastic	Aggregate	State-transition	No	HPV4 types	No
Kulasingam et al. 2007	Australia	-	Static *	Deterministic	Aggregate	State-transition	No	All (low-risk, 16/18, non-16/18 high-risk)	No
Taira et al. 2004	USA	-	Dynamic Static	Stochastic	Aggregate	State-transition (HPV transmission) State-transition (disease progression)	No	HPV2 types	No

*‡ Cross-protection against non-vaccine types was explored in the sensitivity analysis. * Static HPV-transmission model with forced decreased incidence to consider herd immunity. GW: genital warts, IBM: individual-based model, RR: relative risk (MSM versus heterosexual population), MSM: men having sex with men.*

Appendix 1.3.4. Vaccine assumptions

Vaccine-type efficacy and duration of protection

Whatever the vaccine considered, most (15) studies assumed high vaccine-type efficacies against infections or against HPV-related diseases (over 90% in females and over 85% in males), with lifelong protection.[165-168, 172, 175, 178, 197-199, 202, 204, 206-208] In those studies, usually, the same efficacy is assumed to be similar for cervical diseases and other HPV-related diseases, and for both sexes. Shorter vaccine durations of protection were largely explored in sensitivity analyses. Three older studies assumed 90-100% vaccine efficacy against infection for a shorter period of 10 years.[196, 201] to 20[200] As a consequence two of those studies considered adding a booster dose at 22 years of age, 10 years after their initial 3-dose vaccination.[196, 201] Two recent studies also assumed high vaccine efficacies of limited duration (20 years on average).[176, 209]

Five studies relying on the same AP-MSD model made a distinction between the level of protection against HPV infection and again the disease resulting from a breakthrough infection, and considered different efficacy values for each.[164, 169, 173, 174, 203] In those studies lifelong vaccine type-specific protection was 76-96% (female) and 41-62% (male) against transient infection; and 98% (female) and 79-96% (male) against persistent infection, depending on the HPV genotype and the site of infection. Efficacies against genital warts were 99% (HPV6) and 100% (HPV11) for female; and 84% (HPV6) and 91% (HPV11) for male. Efficacy values against diseases were 98-100% (both gender) for vaccine-type related cervical, vaginal and vulvar intraepithelial neoplasia. In those studies thus vaccinated girls that still contract an infection were assumed to be protected against the most severe forms of HPV-related diseases (cervical, vaginal and vulvar diseases). The degree of protection of the vaccine against other HPV diseases (on anus, penis, head and neck, and RRP) was zero and assumed to be conferred through protection against infection only.

Haeussler et al.[170] and Jimenez et al.[171] considered lower lifelong efficacies against HPV-induced diseases. Haeussler et al.[170] assumed vaccine-type efficacies of 78% against cervical diseases, 70% against anal diseases and 50% against oropharyngeal diseases. In Jimenez et al.[171] vaccine effect (any HPV type) was 20% against cervical diseases, 51% against vaginal or vulvar diseases, 54% against anal diseases for both genders and 61% against genital warts for both genders.

Cross-protection and duration of protection

Six (6) studies assumed HPV4 would confer protection against non-vaccine types in their base-case.[165, 168, 170, 204, 206, 208]

In three studies based on the HPV-ADVISE model[165, 204, 208] and in the recent Chesson et al. study,[168] HPV4 efficacies against the 5 additional types contained in HPV9 were obtained from the meta-analysis by Malagon et al.(2012),[102] and were 46.2 / 28.7 / 7.8 / 18.4 / 5.5% against the 5 HPV9-nonHPV4 types 31 / 33 / 45 / 52 / 58. Duration of protection was lifelong[165, 168] or assumed to last for 10 years.[204, 208] In Durham et al. the rate of cross-protection was 46% against HPV type 31 for HPV4, and protection was assumed to last over life.[206] In Haeussler et al.[170] cross-protection conferred by HPV4 against the HPV types 31/33/35/39/45/51/52/56/58/59 was estimated at 32.5% (6.0%–51.9%) during 5 years.[213, 214]

In Damm et al.[209] cross-protection was considered in a scenario analysis with an efficacy of 68.4% (for HPV2) and 32.5% (for HPV4) against HPV types 31/33/35/39/45/51/52/56/58/59 during 20 years on average.

Uptake

Uptake rates varied considerably. Baseline uptakes modelled in girls were high (≥ 80%) in 9 studies, moderate (between 40 and 80%) in 15 studies and low (≤ 40%) in 4 studies (Table 37). In most studies the uptake for boys' vaccination was set equal to the uptake for girls. In 6 recently-published (2016) studies however, all of them comparing universal vaccination with HPV9 to universal vaccination with HPV4, uptake in boys was assumed to be lower than the uptake in girls.[134, 164, 165, 206-208] Different uptakes for girls and boys were also explored in the sensitivity analysis in Damm et al.[209]

Uptakes for the temporary catch-up vaccination programmes (females aged 13 to 26 years) were assumed to be lower than the uptakes for the primo-vaccination, with the exception of one study that used similar uptakes (80%[204]).[167, 198, 204, 208] In Elbasha et al.[198] uptake for the catch-up program increased linearly from 0% up to 50% during the first 5 years and was then stopped. In Chesson et al.[167] uptake was 5% (3%, 10%) for ages 13–18 years and 1.25% (0.75%, 2.5%) for ages 19–26 years. Both studies modelled their catch-up programme in a scenario analysis. In Simms et al.[208] uptakes modelled were 16–41%, depending on the age of the cohort targeted.

Safety

Two studies modelled vaccine adverse events.[171, 206] In Durham et al.,[206] based on a recent review,[215] assumed rates were 105/100 000 vaccinated for mild adverse reactions (syncope, skin infection) and 9/100 000 vaccinated for severe reactions. Jimenez et al.[171] modelled serious cases of adverse events defined as a reaction that required either admission to hospital or prolonged stay at the hospital, and that was attributed to HPV4. Data came from the national registry of the Norwegian Medicines Agency and the rate of serious adverse event per 100 000 doses was valued at 8.

All other economic evaluations did not consider vaccine adverse-event in their study.

Table 37 – Uptake, vaccine efficacy and duration of protection in the 29 economic evaluations of universal HPV vaccination

Author	Country	Vaccines	Uptake		Vaccine-type efficacy against			Duration of protection	Cross-protection
			Girls	Boys	Infection		Disease		
Nonavalent vaccine									
Largeron et al. 2017	Germany	HPV9 HPV4 HPV2	16.3% at 10y 37.7% at 12y 55.6% at 17y	16.3% at 10y 37.7% at 12y 55.6% at 17y	Transient F: 76-96%† M: 41-62%†	Persistent F: 98% M: 79-96%†	CIN, VIN, VaIN: 98-100%†	Life (20y in SA)	No
Mennini et al. 2017	Italy	HPV9 HPV4 HPV2	71%	71%	Transient F: 76-96%† M: 41-62%†	Persistent F: 98% M: 79-96%†	CIN, VIN, VaIN: 98-100%†	Life (20y in SA)	No
Brisson et al. 2016	USA	HPV9 HPV4	38%	14%	95%		-	Life (20y in SA)	HPV4: 46/29/8/18/6% against 31/33/45/52/58 (lifelong) †
Boiron et al. 2016	Austria	HPV9 HPV4	60%	40%	Transient F: 76-96%† M: 41-62%†	Persistent F: 98% M: 79-96%†	CIN, VIN, VaIN: 98-100%†	Life (20y in SA)	No
Chesson et al. 2016	USA	HPV9 HPV4	45.5% at 13y 63.9% at 26y	28.6% at 13y 44.1% at 26y	95% (85-100)		-	Life	HPV4: 46/29/8/18/6% against HPV 31/33/45/52/58 (lifelong) †
Laprise et al. 2016	USA	HPV9	39.7%	21.6%	95%		-	3d: life 2d: 10y to life	No

Author	Country	Vaccines	Uptake		Vaccine-type efficacy against		Duration of protection	Cross-protection
			Girls	Boys	Infection	Disease		
Simms et al. 2016	Australia	HPV9 HPV4	70%	65%	F: 95% M: 85%	-	Life (20y in SA)	HPV4: 46/29/8/18/6% against HPV 31/33/45/52/58 (10 years)
Durham et al. 2016	USA	HPV9 HPV4	39.70%	21.60%	HPV4: 99-100%† HPV9: 94.8-100%†	-	Life	HPV4: 46% against HPV 31 (lifelong)
Bivalent and/or quadrivalent vaccine								
Wolff et al. 2017	Sweden	HPV2	80%	80%	100%	-	Life	No
JCVI. 2017	UK	NR	NR	NR	NR	NR	Life (20y in SA)	NR
Quendri et al., 2017	Netherlands	HPV2	60%	40%	-	98%	Life (18y in SA)	No
Haeussler et al. 2015	Italy	HPV4	90%	90%	-	CER: 78% ANA: 70% OPC: 50%	Life	HPV4: 32.5% against HPV 31/33/35/39/45/51/52/56/58/59 (5 years)
Olsen et al. 2015	Denmark	HPV4	85%	85%	100%	-	Life	No
Jimenez et al. 2015	Norway	HPV4	82%	82%	Persistent infection: F: 74% M: 67%	CIN: 20% VIN/VaIN: 51% AIN (F&M): 54% GW (F&M): 61%	Life	No
Bresse et al. 2014	Austria	HPV4	65%	65%	Transient F: 76-96%† M: 41-62%† Persistent F: 98% M: 79-96%†	CIN, VIN, VaIN, GW (F):98-100%† GW (M): 84-91%†	Life (20y in SA)	No
Burger et al. 2014	Norway	HPV4	71%	71%	-	F: 100% M: 90%	Life	No
Laprise et al. 2014	Canada	HPV4	80% (50% in SA)	80% (50% in SA)	95%	-	3d: 20y to life 2d: 10y to life	HPV4: 46/29/8/18/6% against 31/33/45/52/58 (10 years)
Pearson et al. 2014	New-Zealand	HPV4	47%, 73%	47%, 73%	99%	-	20 years	No
Chesson et al. 2011	USA	HPV4	30% (20-75 in SA)	30% (20-75 in SA)	F: 95% (75-100) M: 90% (60-100)	-	Life	No
Elbasha et al. 2010	USA	HPV4	25% at 12y 80% at 26y	15% at 12y 48% at 26y	Transient F: 76-96%† M: 41-62%† Persistent F: 98% M: 79-96%†	CIN, VIN, VaIN, GW (F):98-100%† GW (M): 84-91%†	32 years	No

Author	Country	Vaccines	Uptake		Vaccine-type efficacy against		Duration of protection	Cross-protection
			Girls	Boys	Infection	Disease		
Kim et al. 2009	USA	HPV2	75% (50% in SA)	75%	F: 100% M: 85%	F: 100% M: 90%	Life	No
Damm et al. 2017	Germany	HPV4 HPV2	50% (20%, 80% in SA)	50% (20%, 80% in SA)	F: 98-100%† M: 90.4%	-	20 years (life in SA)	In SA: 68.4% (HPV2) and 32.5% (HPV4) against HPV 31/33/35/39/45/51 /52/56/58/59 (20 years)
Olsen et al. 2010	Denmark	HPV4	70%	70%	100%	-	Life	No
Jit et al. 2008	UK	HPV4	80%	80%	100%	-	20 years	No
Elbasha et al. 2007	USA	HPV4	70%	70%	90%	100%	Life (10y in SA)	No
Zechmeister et al. 2009	Austria	HPV2	65%	65%	90%	-	10 years	No
Kulasingam et al. 2007	Australia	HPV2	80%	80%	-	100% (93-100)	Life	No
DCHTA 2007	Denmark	HPV2	70%, 85%	70%, 85%	100%	-	Life	No
Taira et al. 2004	USA	HPV2	70%	70%	90%	-	10 years	No

*† Efficacy varies per HPV-vaccine type. ‡ Administration costs included in the vaccine cost per dose. * Base-case results are presented both with and without cross-protection against non-vaccine types 2d: two-dose vaccination schedule, 3d: three-dose vaccination schedule, AIN: anal intraepithelial neoplasia, ANA: anal cancer, CER: cervical cancer, CIN: cervical intraepithelial neoplasia, F: female vaccination, GW: genital warts, HPV9: nonavalent HPV vaccine, HPV4: quadrivalent HPV vaccine, HPV2: bivalent HPV vaccine, M: male vaccination, NR: not reported, OPC: cancer of the oropharyngeal region (head & neck / oropharynx, base of tongue and tonsil), SA: sensitivity analysis, VaIN: vaginal intraepithelial neoplasia, VIN: vulvar intraepithelial neoplasia, y: year.*

Appendix 1.3.5. Vaccination costs

Vaccination costs were reported with different base years and different currency units. To facilitate the comparison between studies and with Belgian prices, all currencies were converted into 2017 Belgian Euro values, using the country-specific consumer price index (CPI) before applying the purchasing power parities for gross domestic product (PPP). Both datasets were obtained from the Organisation for Economic Cooperation and Development (OECD) website (http://stats.oecd.org, accessed on 24/05/2018).

Vaccine prices varied largely, with €78 to €171 for HPV2, €61 to €171 for HPV4 and €104 to €156 for HPV9 (per dose, see Table 38). Vaccine administration costs were fairly consistent between studies, ranging from €8 to €19 per dose. The study by Pearson et al.[176] assumed administration costs as high as €73 (school-based) to €82 (primary care) per dose. Funds to cover program management were included in their costs, which is not the case in other studies.

As a comparison, the public prices (per dose, reference year 2017) of the HPV vaccines in Belgium are €69 for HPV2, €118 for HPV4 and €134 for HPV9.

Table 38 – Vaccination costs in the 29 economic evaluations of universal HPV vaccination

Author	Country	Costing year	Original currency	Cost per dose in original currency and costing year				Cost per dose in Belgian Euro (2017)			
				HPV2	HPV4	HPV9	Administration	HPV2	HPV4	HPV9	Administration
Nonavalent vaccine											
Largeron et al. 2017	Germany	2014	EUR	NS	€140	€147	€9	€149	€149	€156	€10
Mennini et al. 2017	Italy	2014	EUR	€104	€104	€120	€6.6	€119	€119	€138	€8
Brisson et al. 2016	USA	2010	USD	-	$145	$158	Included‡	-	€132	€143	Included‡
Boiron et al. 2016	Austria	2014	EUR	-	€110	€135	€12	-	€116	€142	€13
Chesson et al. 2016	USA	2013	USD	-	$130	$143	$15	-	€111	€122	€13
Laprise et al. 2016	USA	2013	USD	-	-	$143	$15	-	-	€122	€13
Simms et al. 2016	Australia	2013	AUD	-	NS	NS	NS	-	NS	NS	NS
Durham et al. 2016	USA	2016	USD	-	$113.5	$126	$21.8	-	€94	€104	€18
Bivalent and/or quadrivalent vaccine											
Wolff et al. 2017	Sweden	2014-5	SEK	SEK 852	-	-	Included‡	€78	-	-	Included‡
JCVI. 2017	UK	NR	GBP	NR	NR	NR	£10	NR	NR	NR	€12
Quendri et al., 2017	Netherlands	2014	EUR	€25.60	-	-	€13.81	€26	-	-	€14
Haeussler et al. 2015	Italy	NR†	EUR	-	€56.1	-	€6.64	-	€65	-	€8
Olsen et al. 2015	Denmark	2008	EUR	-	€123	-	€16	-	€138	-	€18
Jimenez et al. 2015	Norway	2014	NOK	-	NOK 1113.4	-	No	-	€95	-	No
Bresse et al. 2014	Austria	2012	EUR	-	€110	-	€10.30	-	€120	-	€11
Burger et al. 2014	Norway	2010	USD	-	$75 (20-160 in SA)	-	$14	-	€69 (19-148 in SA)	-	€13
Laprise et al. 2014	Canada	2010	CAD	-	$85 (40 in SA)	-	Included‡	-	€61 (29 in SA)	-	Included‡
Pearson et al. 2014	New-Zealand	2011	NZD	-	NZ$ 113	-	NZ$ 126-141	-	€66	-	€73-82
Chesson et al. 2011	USA	2008	USD	-	$116	-	$17	-	€107	-	€11
Elbasha et al. 2010	USA	2008	USD	-	€133	-	Included‡	-	€122	-	Included‡
Kim et al. 2009	USA	2006	USD	$120	-	-	NS	€118	-	-	NS
Damm et al. 2017	Germany	2010	EUR	€150.4	€150.4	-	€7.50	€171	€171	-	€9
Olsen et al. 2010	Denmark	2007	EUR	-	€122.3	-	€16	-	€142	-	€19
Jit et al. 2008	UK	2006-7	GBP	-	£60	-	£4.37	-	€89	-	€6
Elbasha et al. 2007	USA	2005	USD	-	$120	-	Included‡	-	€122	-	Included‡
Zechmeister et al. 2009	Austria	2007	EUR	€110	-	-	€10	€134	-	-	€12
Kulasingam et al. 2007	Australia	2005	AUD	AU$115	-	-	AU$12	€82	-	-	€9
DCHTA 2007	Denmark	2007	DKK	DKK 924.52	-	-	DKK 115	€144	-	-	€18
Taira et al. 2004	USA	NS†	USD	$100	-	-	NS	€110	-	-	NS

† When the costing is not reported, the publication year minus two years was used. ‡ Administration costs included in the vaccine cost per dose. HPV9: nonavalent HPV vaccine, HPV4: quadrivalent HPV vaccine, HPV2: bivalent HPV vaccine, NR: not reported.

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