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

Comments on document under public consultation:

Karsten Viborg, Chairman - Landsforeningen HPV-Bivirkningsramte (Denmark)				
Section of document (e.g. introduction, generic study process)	**Page and line number**	**Comment and rationale**	**Proposed change**	**ECDC reply**
2.2 Human papillomavirus vaccines	Page 11 line 170	The duration is specified for the 3 dose schedule. 9-13 year old girls only get a 2 dose schedule. What is the duration of the 2 dose schedule? Approximately 10 year duration has been in the literature for more than 5 years now. Is the duration limited to 10 years?	Specify duration for all the combinations the HPV vaccines can be administrated in. Including efficacy for the 2 dose schedule.	We removed the text about duration of protection and we are now just referring to the European Medicine Agency's (EMA) Summary of Product Characteristics (SmPC) from the European Public Assessment Report (EPAR) for the most updated information on duration of protection of HPV vaccine products with the different schedules.
2.4 Post-licensure safety and global monitoring of HPV vaccines	Page 14 line 206	Safety of the HPV vaccine is specified as excellent. It's not possible to react to a safety signal, unless there is a predefined limit. How many % must develop adverse events after HPV vaccination? How many % must develop serious adverse events after HPV vaccination? How many % must develop new medical conditions after HPV vaccination?	Setup safety limits in order to be able to act if safety signals occur.	As discussed in Sections 1.1 "Scope and objectives of guidance" and 2.4 "Post-licensure safety and global monitoring of HPV vaccines", in the light of existing up-to-date high-quality evaluations not differing from what was found in the data we reviewed (see evidence tables on safety in the annexes), aspects related to safety of HPV vaccines are not discussed in this guidance. For conclusions on safety of HPV vaccines, please refer to the periodic monitoring performed by GACVS and Cochrane's recent systematic reviews on HPV vaccine.
2.5 Effectiveness and impact of HPV vaccines	Page 15 line 233	The effectiveness is not specified. In order to be able to act on an effectiveness signal, there must be an predefined goal for effectiveness of preventing Cervical Cancer. HPV infections are not sufficient, as more than 90% of HPV infections are cleared naturally.	Setup efficacy goals for the HPV vaccines effectiveness in prevention of Cervical Cancer	Section 2.5 is part of the background of the guidance and is supposed to just provide a brief overview of the evidence currently available. However, this is not part of the assessment performed by this guidance which focuses on the topics indicated in Section 1.1 "Scope and objectives of guidance" and listed in Section 3.1 "Identification of public health questions for guidance". It is not within the scope of this guidance to set efficacy goals for the evidence mentioned in Section 2.5.
Table A34. Incremental cost-effectiveness ratios (ICERs) in local currency from societal perspective and critical parameters	Page 58 and on	Vaccine cost effectiveness ratios is calculated with a vaccine duration from 20 years to livelong. This is NOT in line with the documented/expected duration of 10 years.	Adjust the numbers to match the actual duration. No studies proves efficacy for more than 10 years. 10 years must be used as reference for financial calculations.	In this Table we are just presenting available published studies on cost-effectiveness that were retrieved by the systematic review on cost-effectiveness of adding HPV vaccination of boys. While it is true that the currently demonstrated duration of protection is of (at least) ten years (European Public Assessment Report, EMA), it is not proven that it is just ten years: the evidence available is only until then. Cost-effectiveness is sensitive to duration of protection as discussed in Section 4.4.2. Assumptions on parameters, including duration of protection, are commonly made in cost-effectiveness modelling. Assumptions enable the models to transparently inform on what should be expected as outcome in case the assumption held (which is not necessarily the case). Assumptions are often unverified by definition.
Table A35. Incremental cost-effectiveness ratios (ICERs) converted to EUR from societal	Page 62 and on	Incremental cost effectiveness ratios converted to EUR – The cost for hospitalization, treatment, lost tax income and so on, is not included in the calculation.	Include the expenses for people with adverse events after HPV vaccine. Thousands of children are left without effective treatment; they will demand social security service all their life and never contribute as taxpayers.	These are cost-effectiveness models that were retrieved from published literature. In these tables we are just reporting the results of these models based on what was included as cost and based on the assumptions made in the original studies. The models used are based on the best available evidence at the time, and in this respect it should be noted more recent studies of HPV vaccine safety (*Arbyn et al. Efficacy*

perspective and critical parameters				*and safety of prophylactic HPV vaccines. A Cochrane review of randomized trials. Expert Review of Vaccines 2018; 17(12):1085-91*) have provided robust evidence corroborating previous positive assessments of the safety of these vaccines.
Peter Baker, Campaign Director - HPV Action (UK)				
Section of document (e.g. introduction, generic study process)	**Page and line number**	**Comment and rationale**	**Proposed change**	**ECDC reply**
2. Background	p4 Lines 105-108	It is correct to state that 'no high-quality screening programs are currently available to prevent HPV-related disease other than cervical cancer in women.' However, there should be greater emphasis on the fact that there is no screening for other HPV-related cancers and no screening for any of the cancers that affect men. This is a primary part of the rationale for gender-neutral vaccination	Few pathologies other than cervical cancer offer such a wide range of prevention tools and strategies: cervical cytology for screening, HPV vaccines for primary prevention and more recently HPV detection tests for screening. However, no high-quality screening programs are currently available to prevent HPV-related disease other than cervical cancer in women. One consequence is that no HPV-related cancers in men are detectable through screening. Moreover, despite the unequivocal success of organised population-based cervical screening programs, cervical cancer is still an important cause of morbidity and death among European women. Therefore, vaccination against HPV is can provide a significant added benefit for the prevention of all HPV-attributable diseases in both sexes, especially if delivered on a gender-neutral basis.	We agree we should emphasize more that there is no screening available for HPV-related disease in men, so we modified the sentence as follows: "*Few pathologies other than cervical cancer offer such a wide range of prevention tools and strategies: cervical cytology for screening, HPV vaccines for primary prevention and more recently HPV detection tests for screening. However, no high-quality screening programs is currently available for women or men to prevent HPV-related disease other than cervical cancer in women. One consequence is that no HPV-related cancers in men are detectable through screening. Moreover, despite the unequivocal success of organised population-based cervical screening programs, cervical cancer is still an important cause of morbidity and death among European women. Therefore, vaccination against HPV is expected to provide a significant added benefit for the prevention of all HPV-attributable diseases in both sexes. Evidence on efficacy and effectiveness of HPV vaccines thus needs to be continuously monitored in order to guide public health actions.*"
2.1. Burden of HPV and HPV-related diseases in European countries	p4 Lines 115-152	Some reference should be made to the emerging evidence that HPV might be linked to a range of other diseases including prostate cancer, breast cancer, lung cancer, cardiovascular disease and male infertility. This evidence is not conclusive but it suggests that the current data on the burden of disease could be an under-estimate and that there is a need for accelerated research in this area. This issue should also be added to section 5.4 on Remaining knowledge gaps.	*(New paragraph after line 152)* Recent research, as yet inconclusive, has suggested that HPV could be linked to to a range of other diseases including prostate cancer, breast cancer, lung cancer, cardiovascular disease and male infertility. It may be, therefore, that the current data on the burden of disease is an under-estimate. There is a need for accelerated research in this area.	We understand there is a substantial amount of research undergoing on possible additional causative associations between HPV and other conditions, though currently inconclusive. In this guidance we preferred to refer to the causative associations that are already officially established and recognized by IARC[1]. We added this point in Section 5.4 "Remaining knowledge gaps", as suggested.
4.4. Evidence of cost-effectiveness of adding males to current national HPV vaccination programmes	p18 Lines 608-609	The guidance should be more explicit about the opportunity gender-neutral vaccination offers to eliminate HPV infection and the diseases it causes. This is now an achievable goal.	… health outcomes considered in the analysis (cervical disease, anogenital warts, non-cervical cancers). It should be noted that gender-neutral vaccination offers an opportunity to achieve the goal of eliminating HPV infection and the diseases it causes.	As for the need to be explicit about the opportunity of universal HPV vaccination, this is discussed in Section 5.1 "Possible implications for current national HPV immunization programmes" and in Section 5.1.3 "Ethical considerations" ("*A universal vaccination would also be more equal by giving both sexes the opportunity to get directly protected against HPV-related disease. Additionally, achieving the highest possible indirect (herd) protection and obtaining sustained reduction of HPV circulation in the population may also positively affect people who cannot directly benefit from HPV vaccination, such as those with immunocompromised conditions.*"). The discussion around the possible elimination of HPV infections and of all diseases caused by HPV is beyond the scope of this guidance. Calls for cervical cancer elimination are now mentioned at the end of the introduction of Section 2 "Background". 1 – IARC Monographs 2018. Human papillomavirus. Available from: https://monographs.iarc.fr/wp-content/uploads/2018/06/mono100B-11.pdf

4.4. Evidence of cost-effectiveness of adding males to current national HPV vaccination programmes	p18 Lines 591-613	The guidance should make clear several flaws inherent in most if not all cost-effectiveness analyses: (1) They do not take account of the full economic cost of HPV-related diseases (e.g. the costs to employers or the costs to individuals and their families); (2) They normally look at past morbidity and mortality data and not at future trends (this is especially important for head and neck cancers); (3) They tend to look at past data on sexual behaviours and not at recent changes (e.g. the trends towards riskier sexual behaviours, such as heterosexual anal sex, men who identify as heterosexual having sexual contact with other men, and the increase in sexual contacts facilitated by dating apps). Some modelling has also failed to use up-to-date data on the fraction of cancer cases attributable to HPV. These flaws lead to an under-estimation of the economic benefits of gender-neutral vaccination. It is noteworthy that relatively small errors in the assumptions made in cost-effectiveness modelling can result in much larger variations in outcomes. The guidance should state that several European governments have conducted assessments of the cost-effectiveness of HPV vaccination and decided that boys should be vaccinated, including in countries (eg. the UK) where there is relatively high vaccination uptake in boys. It is also important to stress that decisions on vaccination should not be taken solely on assessments of cost-effectiveness. Issues of equity, ethics and the experience of patients with HPV-related diseases should also be part of the policy-making process. A pan-European multidisciplinary expert group has shown the feasibility of using an extended GRADE framework that includes explicit assessment of cost-effectiveness, medical needs, and patient aspects, ethical and social issues.	*(New paragraphs after line 613)* Cost-effectiveness assessments share several flaws that lead to an under-estimate of the economic benefits of gender-neutral vaccination. They do not take account of the full economic cost of HPV-related, for example, they normally look at past morbidity and mortality data and not at future trends and also at past data on sexual behaviours and not at recent changes. Decisions on vaccination need not be solely based on assessments of cost-effectiveness. Issues of equity, ethics and patient experience can also form an important part of the policy-making process. Nevertheless, several European countries have determined that gender-neutral vaccination is cost-effective even where there is relatively high uptake of vaccination by girls.	We agree that the discussion related to HPV vaccination strategy should not only rely on cost-effectiveness, due to the points correctly raised. In Section 4.4.6 "Conclusions" the first bullet points in fact reads as follows: "*The cost-effectiveness of adding males to female-only HPV vaccination programme depends on several factors and model assumptions that may be context-specific, including vaccine price, vaccination coverage rates in females, duration of protection, vaccine efficacy in males and assumed serotype-specific efficacy of the HPV vaccine against different health outcomes.*" We also agree that other factors like e.g., equity, ethics, values, should be taken into account. In Sections 5.1.1, 5.1.2, 5.1.3, many of these factors are discussed for their potential implications into the national decision making process. In this guidance, we may mention as examples countries that recommended universal vaccination or special schedules, but we do not present and discuss how single countries came up with their decisions as this would be outside of the scope of this guidance. We believe that the very valid point raised is already addressed in the current document in accordance with the scope and objectives of this guidance (Section 1.1).
4.4.6. Conclusions	p20 Line 716	Increasing vaccination coverage among girls may not be easily achieved, especially in countries where there is a lack of vaccine confidence or where vaccination delivery systems are less effective. It is well-established that vaccination programmes delivered via schools are much more likely to achieve higher uptakes. ECDC should explicitly recommend that countries introduce school-based vaccination delivery systems. It should also recommend that countries follow international best practice on measures to increase vaccine confidence in the public. The steps recently taken in Ireland to reverse the slump in vaccine uptake in girls provide a very good example; the measures taken include better training for health professionals, a media campaign and inter-agency collaboration.	While increasing vaccination coverage among girls may appear to be a more cost-effective primary objective it may be hard to achieve in reality especially in the absence of a school-based vaccination delivery system and in countries or among communities where there is a significant lack of vaccine confidence. It is recommended that countries consider the introduction of school-based vaccination delivery systems, where these do not exist, and follow international best practice on measures to increase vaccine confidence in the public.	This guidance did not look into evidence of effective methods for HPV vaccine delivery, therefore we consider this issue beyond the scope of this guidance. Future ECDC outputs are planned and they will discuss HPV vaccine hesitancy-related issues more in detail, including some of the points raised by this comment.
4.4.6. Conclusions	p20 Lines 720-721	The guidance should be more explicit about the opportunity gender-neutral vaccination offers to eliminate HPV infection and the diseases it causes. This is now an achievable goal.	Gender-neutral vaccination offers the opportunity to eliminate all HPV-related disease. In this scenario, HPV vaccination is a much more cost-effective option.	The discussion around the possible elimination of HPV infection and all diseases caused by HPV is beyond the scope of this guidance. In Section 4.4.1 "Evidence of marginal impact of including different health outcomes", this issue is discussed and the last sentence states the following: "*In broad terms, the ICER decreases when incorporating the potential impact of the vaccine on additional HPV-related health outcomes. The consequence is that cost-effectiveness may be underestimated if the analysis is*

				restricted to a subset of disease endpoints." In Section 4.4.6 "Conclusions", the last bullet point reads: "*If the objective of the HPV vaccination programme is to prevent all HPV-related disease, then a universal HPV vaccination may become a more cost-effective option to consider.*" Therefore, we believe that the valid point raised has been already addressed by the current guidance.
5.1.3. Ethical considerations	p22 Lines 824-832	There is an additional argument against a specific vaccination programme for men who have sex with men (MSM) in addition to a girls-only programme. It is very difficult in practice to reach a sufficient number of MSM to create herd protection in the MSM community. In the UK, the MSM programme is delivered opportunistically to men attending sexual health clinics for another reason. This means that MSM cannot attend specifically for a HPV vaccination, thus significantly limiting the reach of the programme. Moreover, the average age of first attendance at UK sexual health clinics for MSM is 32 years by which time they may well have already acquired HPV. It should also be noted that many men who have sex with men do not identify as gay or bisexual or may choose, for a variety of reasons (including a fear of discrimination by health practitioners), not to disclose their sexual identity or that they have or have had sex with men. This means that many men who have sex with men will not be able to participate in a targeted vaccination programme.	Men who have sex with men are at increased risk of HPV infection and transmission …. heterosexual men from the same age group and this could be possibly due to more exposure to HPV. It is also very difficult in practice to deliver a programme targeted at men who have sex with men that will reach a sufficient proportion of that community for herd protection to be achieved. Gender-neutral vaccination of all adolescents would directly (and indirectly for the unvaccinated) protect men who have sex with men without posing any of these challenges. A programme targeted at men who have sex with men would be appropriate only in addition to a gender-neutral programme for adolescents.	We have now amended the text as follows: *"…men who have sex with men appear to have lower immunogenic responses to HPV vaccination compared with heterosexual men from the same age group and this could be possibly due to more exposure to HPV. <u>It is also very difficult in practice to deliver a programme targeted at men who have sex with men that will reach a sufficient proportion of that community for herd protection to be achieved.</u> Gender-neutral vaccination of all preadolescents would directly (and indirectly for the unvaccinated) protect men who have sex with men without posing any of these challenges.* *A universal vaccination would also be more equal by giving both sexes the opportunity to get directly protected against HPV-related disease.* *(…)* *Regardless of the HPV vaccination strategy chosen, it may be optionally considered offering HPV vaccination to men who have sex with men who are no longer in the target (age) groups for routine HPV vaccination in order to provide them with some direct protection against HPV-related disease.*"
5.1.3. Ethical considerations	p23 Lines 833-835	The current statement does not give sufficient weight to the equity issue. It is also erroneous to suggest that this is a matter for 'value judgement'. It is unethical to withhold medical care of proven effectiveness from a group of people on the grounds of their sex. In some countries, this sex discrimination may also be unlawful under the terms of equality legislation. Even though HPV-preventable cancers are more common in women, they are still very significant in men and the burden on men is increasing (especially for head and neck cancers). The overall burden of HPV-related disease is also more equal between the sexes once genital warts are taken into account. There is also an emerging equity issue related to the decision by an increasing number of countries in Europe to introduce gender-neutral HPV vaccination. This will mean that males in these countries will benefit from a level of protection not available to males in other countries. It should also be borne in mind that, in the absence of a funded HPV vaccination programme for boys, parents with sufficient funds and knowledge may well choose to pay for vaccination. This practice would exacerbate in-country health inequalities.	Universal vaccination would also be more equal by giving both sexes the opportunity to get directly protected against HPV-related disease. There is a strong ethical argument that medical care of proven effectiveness should not be withheld from a group of people on the grounds of their sex. Each country may wish to consider whether such action could constitute unlawful sex discrimination. Each country may also wish to consider the equity implications related to the decision by an increasing number of countries in Europe to introduce gender-neutral HPV vaccination. This will mean that males in these countries will benefit from a level of protection not available to males in other countries. Additionally, health inequalities could occur within countries if wealthier and better-informed parents choose to pay for HPV vaccination for their boys.	We removed the sentence "*This is a value judgement that each country should independently consider in light of their local situation and all the previous discussions.*", as suggested. In line with the scope and purpose of this guidance (see Section 1.1), we believe it is enough to mention in Section 5.1.3, under "Ethical considerations", the following: "*A universal vaccination would also be more equal by giving both sexes the opportunity to get directly protected against HPV-related disease.* *Additionally, achieving the highest possible indirect (herd) protection and obtaining sustained reduction of HPV circulation in the population may also positively affect people who cannot directly benefit from HPV vaccination, such as those with immunocompromised conditions.*"
General comments	Whole document	The draft guidance is not sufficiently positive about the case for gender-neutral vaccination on the combined grounds of cost-effectiveness, equity, ethics and public health. Over 30 countries in the world now vaccinate boys, or plan to do so soon. If more countries follow, there is an opportunity for HPV-related diseases to be eliminated. If momentum towards gender-neutral vaccination is not maintained, there is a real risk that health inequalities linked to		We appreciate the importance of HPV universal vaccination, however this guidance does not aim to advocate for or against universal vaccination. Its scope and purpose, outlined in Section 1.1, is to systematically review and appraise the evidence available on efficacy/effectiveness of the 9vHPV vaccine, efficacy/effectiveness of HPV vaccination in boys, efficacy/effectiveness of HPV vaccination of people living with HIV, and the cost-effectiveness of adding boys to girls-only HPV vaccination programmes in the EU/EEA Member States (see section 3.1).

		HPV within and between countries will increase. HPV Action represents over 50 professional and patient groups in the UK (see www.hpvaction.org). It has been making the case for gender-neutral vaccination in the UK since 2013 and was heavily involved in discussions that led to the government's vaccination advisory committee (JCVI) recommending that boys should be vaccinated. It is noteworthy that the JCVI is widely believed to be one of the most rigorous bodies of its kind and that its view is gender-neutral vaccination is cost-effective in the UK even though it has one of the highest uptakes of HPV vaccination by girls in the world as well as a specific vaccination programme for men who have sex with men. The ECDC should clearly state that universal vaccination represents the best way forward in terms of public health, equality and ethics.		In Section 5, possible public health implications of the evidence concerning the topics covered in the guidance are discussed. It is not in the remit of ECDC to recommend EU/EEA Member States which vaccination strategy they should adopt.
Jade Pattyn, Centre for the Evaluation of Vaccination (CEV), Vaccine and Infectious Disease Institute (VAXINFECTIO) - Faculty of Medicine and Health Sciences, University of Antwerp, Belgium				
Section of document (e.g. introduction, generic study process)	**Page and line number**	**Comment and rationale**	**Proposed change**	**ECDC reply**
Executive summary; scope	Page 6 line 10-11	Sentence: This guidance does not address the safety of HPV vaccines observed during the pre- and post-licensing period. Would indicate the reason you mention later in the document	Sentence: This guidance does not address the safety of HPV vaccines observed during the pre- and post-licensing period ***because there are no additional insights.***	In the executive summary, we just define the general scope of the guidance. A more detailed description of how safety has been dealt with in this document is already reported in the second paragraph of Section 1.1 "Scope and objectives of guidance". Additionally, in Section 2.4 of this guidance document, an overview of the current knowledge on safety of HPV vaccines is presented. At the end of the paragraph it is explained that in our reviews we could not find any new information from what is already available from other extensive international reviews on safety, it was thus decided not to report on it in detail. However, in the annexes of this guidance document, supporting tables on the evidence found on HPV vaccination safety are presented.
Executive summary; key conclusions	Page 6; line 34	Spelling- brackets incorrect	males 16–26 years (including men who have sex with men) (evidence quality: high)	We have now corrected the text accordingly.
2 Background; 2.1 Burden of HPV and HPV-related diseases in European countries	Page 9; line 119	Most European populations show a large peak of HPV incidence in the first years after the onset of sexual activity (namely during adolescence and early 20s) decreasing and **stabilising thereafter.**	On EUROGIN2018 a lot of attention was given to a second age-peak. I would check this again and delete the stabilising thereafter if necessary.	We have deleted "decreasing and stabilizing thereafter".
2 Background; 2.2 Human Papillomavirus Vaccines	Page 10 line 166	Spelling- space up to the age of 14 years **for the**	up to the age of 14 years for the	The text has been amended and now he mistake has been removed.
2 Background; 2.2 Human Papillomavirus Vaccines	Page 10 Line 168	Different doses explained, however, you do not mention the 1-dose yet here. I think it would be good to short refer here to the single-dose that its tested but that no evidence yet exists.	than the above indicated ages, the recommended schedule is 3 doses administered at months 0, 1 (or 2) and 6. ***Studies are ongoing to test the efficacy of a single dose.***	As the single dose schedule is yet to be approved, we prefer not to mention it here where we report on current licensure of the different HPV vaccines. We mention the option of a one dose schedule in Section 5.1.1 "Organisational aspects: "*Dose and cost sparing options are under investigation and may provide alternatives in the future"*
2 Background; 2.3 HPV vaccine introduction in Europe; Table 1	Page 12 line Belgium Flanders	Belgium Flanders -Reported coverage 72% (2014/15); incorrect; other % and newer data available (2016)	https://www.zorg-en-gezondheid.be/vaccinatiegraadstudie	As assessment of HPV vaccination coverage is not within the scope of the guidance, and given the heterogeneity of information across EU/EEA Member States, we decided to remove this column from Table 1.
2	Page 12	Lay out of table not practical	Split female male group	We have now amended accordingly.

Background; 2.3 HPV vaccine introduction in Europe; Table 1			Add table headings on every page	
2 Background; 2.4 Post-licensure safety and global monitoring of HPV vaccines	Page 15 Line 232	For discussion on safety of HPV vaccines, refer to periodic monitoring by GACVS and Cochrane's recent systematic reviews on HPV vaccine from 2016–2017. New relevant article from 2018 from M. Arbyn	Reference https://www.ncbi.nlm.nih.gov/pubmed/29740819	This reference has now been added.
5 Implications for public health practice and Research 5.1.1 Organisational aspects	Page 27 Line 789	The Centre d'expertise et de référence en santé publique in Canada recommended a mixed vaccination schedule based on some of these considerations in 2018	I remember from IPV congress in Sydney that there was a serious debate ongoing after presentation of this study. You sure this is now a recommendation from the Centre?	Yes, this a regional recommendation for Quebec (reference quoted in the text). It can be found at: https://www.quebec.ca/en/health/advice-and-prevention/vaccination/human-papillomavirus-hpv-vaccination-program/
Safety of HPV vaccines in females aged 25 years or above Table A34	Page 60 Line 1690	Column ICER (local currency); What is the meaning of ***'Dom'*** not in abbreviations. However not an expert in the field of ICER. Maybe obvious		It means "dominant" which is used in cost-effectiveness analyses to identify an "economically dominant" strategy. We have now added it in the abbreviations under Table A39 in the appendix.

David Winterflood, Director of UK Operations - NOMAN is an Island Campaign (The HPV and Anal Cancer Foundation)

Section of document (e.g. introduction, generic study process)	**Page and line number**	**Comment and rationale**	**Proposed change**	**ECDC reply**
Executive Summary	P1, Line 55 onwards	Even in countries with high vaccination rates in women, discount rates and increased QALY threshold could be applied within an acceptable framework. E.g in the UK where 83% of girls receive the vaccine it is cost effective to vaccinate boys using the accepted rate of 1.5% discount rate and increased QALY threshold. Gender neutral vaccination can bring about the potential to eliminate HPV vaccine types.	A universal HPV vaccination programme could become a cost-effective option once appropriate discount and QALY rates are applied, as the 2018 JCVI recommendation in the UK has shown, despite 83% vaccination rate amongst girls. The WHO target of cervical cancer elimination would be assisted by gender neutral vaccination efforts, in addition to the 5 other cancers caused by the virus.	The discussion about cost-effectiveness is complex, context-specific and subject to many assumptions, as stated in paragraph 4.4.6 "Conclusions": • "*The cost-effectiveness of adding males to female-only HPV vaccination programme depends on several factors and model assumptions that may be context-specific, including vaccine price, vaccination coverage rates in females, duration of protection, vaccine efficacy in males and assumed serotype-specific efficacy of the HPV vaccine against different health outcomes.*" The important discussion about cervical cancer elimination is outside the scope and perspective of this guidance (see Sections 1.1 and 3.1). In this document, we do not provide a general recommendation on which HPV vaccination strategy to adopt, as it is a national decision based on several context-specific factors. We also do not recommend specific values for the parameters of the cost-effectiveness analysis, since they clearly depend on the setting as well.
Executive Summary	P2, Line 63	It is well known that HPV is the causal agent of 5% of cancer, therefore to limit a HPV vaccination programme's objective solely to reducing cervical cancer would be a short sighted approach. This is the greatest opportunity we have had to prevent cancer in decades. - The rates of HPV-related oral cancers in men have overtaken those of cervical cancer in women in the USA. - The taboo that surrounds HPV-related cancers – anal, penile, vaginal and vulvar cancer in particular – prevents fair and equitable conversation around	Imperative that the importance of why gender-neutral HPV vaccination to prevent all HPV-related disease should be stressed for reasons detailed, in the report. At present we would advise that the report does not give full weight to the arguments for gender neutral vaccination, outside of even the equity and ethical reasons for doing so.	Please see above The guidance reports findings and conclusions in line with its scope and objectives (see Sections 1.1 and 3.1). This guidance does not aim to advocate for or against specific HPV vaccination strategies, but to just discuss public health options and related implications, based on the evidence collected and appraised.

		these diseases. - There is a great lack of awareness around the HPV-related cancer burden in Europe. A recent Ipsos Mori study showed that of the respondents: Over 30% are unaware of HPV. More than 50% were unaware of the link between HPV and cancer. 1 in 3 knew that HPV can cause cancer in men. Only recommending a programme to protect against cervical cancer propagates the myth that HPV is a female only problem, and efforts to protect men against HPV-related disease will be undermined.		
2 Background	P4, Line 103	Current phrasing downplays significance of 5 other cancers caused by HPV, by comparison to cervical disease.	HPV is the causal agent of 5% of cancer.	Section 2 of the guidance just provides some background around the issues discussed. In the second paragraph of Section 2.1 "Burden of HPV and HPV-related diseases in European countries", it is stated: "*HR HPV types are not only responsible for virtually all cervical cancer cases, but are also causally related with a variable fraction of other anogenital cancers (vulvar, vaginal, penile and anal cancers) and a subset of head and neck cancers, particularly oropharyngeal cancers."* Moreover, at the end of the third paragraph of the same Section 2.1, it is also stated that: "*In Europe, 14 700 annual cases of anogenital cancers other than cervix are attributable to HPV, with 5 400 cases diagnosed in men (about half in the anus and half in the penis) and 9 300 cases diagnosed in women (4 200 in the anus and 5 100 in the vulva and vagina).* *(…)* *Head and neck cancers also constitute a heavy burden, particularly in men, with an estimated 13 800 cases diagnosed annually (11 000 in males and 2 800 in females). Further, increasing trends in the incidence of HPV-positive head and neck cancers have been consistently observed in the last decade in concomitance with the decline in tobacco use. This increase concerned in particular HPV-positive oropharyngeal cancers among young men in northern Europe and North America."* We have now also added the following sentence at the end of the first paragraph of Section 2.1 "Burden of HPV and HPV-related diseases in European countries": "*Additionally, findings from studies carried out in the US and in Latin America showed that the prevalence of HPV in males is higher than in females and does not seem to decline with age."* We therefore do not agree that the relevance of HPV-related non-cervical cancers has been downplayed.
4.4 Evidence of cost-effectiveness of adding males	P18, Line 605	Adding boys to the programme helps mitigate the risk of the hard to reach girls who are not engaging with vaccination programmes. Eg. If only 40% of girls are receiving the HPV vaccination rate in a specific area, then adding boys to the programme will confer significant benefits. Equally, gender neutral vaccination provides greater stability and protection should there be a dramatic fall in HPV vaccination as seen in Ireland and Denmark in recent years. Vaccinating both sexes means that a greater proportion of the population would be protected.	Such a programme may address certain concerns: - provides a greater opportunity to protect 'hard to reach' girls in the population who don't engage with vaccination programmes. - Provides a greater level of protection to the population in the event of a marked decrease in HPV vaccination rates.	The issue of the resilience of the gender-neutral vaccination against sudden drops in coverage is already reported and discussed in Paragraph 5.1.1 "Organisational aspects", while the issue of reaching under-vaccinated groups is discussed in Section 5.1.2 "Social aspects".
6.1 – Screening in post-vaccination era	P25, Line 911 onwards	Routine screening is only available for one of the 6 cancers caused by HPV; cervical cancer. This lends significant weight to the argument in favour of gender neutral HPV vaccination.	It should be noted that of the 6 cancers caused by HPV only one, cervical cancer, has a routine screening programme. This again lends weight to arguments for GNV.	This is mentioned in Section 2 "Background": "*However, no high-quality screening programs are is currently available for women or men to prevent HPV-related disease other than cervical cancer in women.* (…) *Therefore, vaccination against HPV is expected to provide a significant added benefit for the prevention of all HPV-attributable diseases in both sexes*".

Prof Giampiero Favato, Director of the Institute for Leadership and Management in Health - Kingston university London				
Section of document (e.g. introduction, generic study process)	**Page and line number**	**Comment and rationale**	**Proposed change**	**ECDC reply**
2. Background	Page: 4 Lines: 100-104	The text continues to define the consequences of HPV infection on the basis of sex, de facto discriminating between genders (see the "central role of HPV in the aetiology of virtually all cervical cancers") **HPV is a gender-neutral killer.** The CDC is currently using gender-neutral language in any publicly available material. As an example, the world "girls" or "boys" have been replaced by the gender neutral "kids" or "children"	We strongly urge ECDC to rephrase the entire document avoiding any reference to gender in relation to HPV infection As an example, following find the CDC gender-neutral description of the consequences of HPV infection: "Every year in the United States, 33,700 women and men are diagnosed with a cancer caused by HPV infection. HPV vaccination could prevent more than 90% of these cancers, 31,200 cases ever year, from ever developing."	After careful consideration, we prefer to keep the wording as it is. This guidance is based on public health questions raised by the EU/EEA Member States (please see Section 3.1 "Identification of public health questions for guidance"). As a consequence, in this document an important part of the evidence has been collected and appraised specifically in regards to males, and to the option of expanding the existing girls-only HPV vaccination programmes to males. In fact, in most EU/EEA countries, for some until quite recently, the HPV vaccination programme has been offered only to pre-adolescent girls since the introduction of HPV vaccination (i.e. more than ten years). This fact had a differential impact on the epidemiology of HPV in the two sexes, and it is actually one important argument for considering moving towards an universal programme. Additionally, most of the burden of severe HPV-related disease is associated with cervical cancer, which cannot occur in men, as much as the much rarer, but still severe, penile cancer cannot occur to women.
2. Background	Page: 4 Line:105-106	"Few pathologies other than cervical cancer offer such a wide range of prevention tools and strategies: cervical cytology for screening, HPV vaccines for primary prevention and more recently HPV detection tests for screening." This statement provides one of the main reasons why any EU country should adopt a gender-neutral vaccination programme: there is no screening available for all the other malignancies induced by HPV. Vaccination is the only way to protect our kids. This position is currently supported and promoted by CDC [1]	Acknowledge the fact that screening will not protect individuals from most of the HPV-induced malignancies. Vaccination is the only way	Taking into account the comment, we rephrased the paragraph of the background as follows: "*Few pathologies other than cervical cancer offer such a wide range of prevention tools and strategies: cervical cytology for screening, HPV vaccines for primary prevention and more recently HPV detection tests for screening. However, no high-quality screening program is currently available for women or men to prevent HPV-related disease other than cervical cancer in women. One consequence is that no HPV-related cancers in men are detectable through screening. Moreover, despite the unequivocal success of organised population-based cervical screening programs, cervical cancer is still an important cause of morbidity and death among European women. Therefore, vaccination against HPV is expected to provide a significant added benefit for the prevention of all HPV-attributable diseases in both sexes. Evidence on efficacy and effectiveness of HPV vaccines thus needs to be continuously monitored in order to guide public health actions.*"
2.1 Burden of HPV disease	Page: 4 Lines: 130-142	The summary of the systematic review of the literature fails to provide an overall perspective of the burden of disease at population level. Moreover, most of the incidences of malignancies are derived from broad epidemiological estimates. A recent study entirely based on real-life data from Italian hospital records, concludes that in the burden of HPV-induced malignancies is almost equally split between genders (58% for females and 42% for men)	Provide a balanced, population-based perspective of the burden of disease caused by HPV infections in Europe.	We have used data from sources sanctioned by EU and EU Member State national authorities. It was not within scope of the work to undertake a systematic review of data on burden. This section of the background is therefore not based on a systematic review of the evidence. This is just an introductory overview. Please refer to Section 1.1 "Scope and objectives of guidance" and to Section 3.1 "Identification of public health questions for guidance" for the evidence that has been systematically reviewed and appraised in this guidance.
3.3.2	Page 13: Lines: 362-363	The Joint Committee for Vaccination and Immunization (JCVI), advised by NICE, set the ICER threshold for the incremental cost-effectiveness of adding boys to HPV vaccination at £20,000, using a 1.5% discount rate for both costs and benefits. The 1.5% was chosen as the cost of public incremental debt, the yield of 10-year Treasury Bonds at the time of the discussion. In its final statement, JCVI concluded that: "Using a 1.5% discount rate it is likely that a	Due to the time lapse between vaccination and prevention of malignancies, a discussion should be added to the relevance of the discount rate chosen in the cost-effective analysis.	Discount rates are indeed quite important in many cost-effectiveness assessments, as shown by the recent JCVI assessment on HPV. The choice of the discount rate is however not based on solid epidemiological evidence, but it is based on a value judgement which could vary over time and according to context. In the introductory paragraph of Section 4.4, we have already stated: "*Whether a universal HPV vaccination programme will be deemed cost-effective in any given setting depends on a number of factors, including:*

[1] https://www.cdc.gov/hpv/hcp/hpv-important/more-than-screening-infographic.html

		gender-neutral programme would be cost-effective, and on the basis of these findings JCVI would advise extending immunisation to adolescent boys"[2]		• *health outcomes considered in the analysis (cervical disease, anogenital warts, non-cervical cancers)* • *duration of vaccine protection* • *baseline coverage rates in females (where appropriate)* • *choice of baseline scenario (absence of any HPV vaccination vs. female-only programme)* • *costs of vaccine procurement and delivery; and* • *setting-specific health economic factors (e.g. ICER threshold, discounting rate and payer perspective)."*
4.1.4 Conclusions	Page: 16 Lines: 485	"There is no direct evidence of efficacy of 9vHPV vaccine against HPV-related infection and illness in males." Gardasil9 was approved by FDA with the following indication: GARDASIL 9 is indicated in boys and men 9 through 45 years of age for the prevention of the following diseases: Anal cancer caused by HPV types 16, 18, 31, 33, 45, 52, and 58. Genital warts (condyloma acuminata) caused by HPV types 6 and 11. And the following precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58: Anal intraepithelial neoplasia (AIN) grades 1, 2, and 3.	This sentence would undoubtedly revamp the rampant media campaign sustained by the no-vax movement, potentially jeopardising national vaccination programmes across EU. It is imperative to remove it or to rephrase using a less draconian tone.	The conclusions on the 9vHPV vaccine in Paragraph 4.1.4 read as follow: • *"9vHPV vaccine is efficacious for at least six years in preventing six-month persistent HPV infection and high-grade cervical lesions due to types 31, 33, 45, 52, and 58 in females 16–26 years old not infected with HPV at time of vaccination (evidence quality: high).* • *There is no direct evidence of efficacy of 9vHPV vaccine against HPV-related infection and illness in males.* • *Immunogenicity data show a non-inferior response of 9vHPV vaccine against the four HPV types included into the 4vHPV vaccine, which was already shown to be effective against HPV-related illness caused by serotypes 6, 11, 16 and 18. This can be considered indirect evidence that the 9vHPV vaccine is effective against HPV-related disease caused by serotypes 6, 11, 16 and 18 in females and males (evidence quality: moderate).* • *The 9vHPV vaccine provides stronger immunogenicity against vaccine serotypes in 9–15-year-old males and females compared to 16–26-year-old females.* • *Immunogenicity data on 16–26-year-old males and 9–15–year-old females show a stronger immune response from the 9vHPV vaccine compared to the 4vHPV vaccine against the additional 31, 33, 45, 52, and 58 serotypes contained in the 9vHPV vaccine."* In the first bullet point, it is stated that the 9vHPV vaccine is efficacious among females against a number of clinical outcomes caused by different HPV types. It is additionally mentioned that a very good immunogenicity profile in males was found, which is not inferior to the one of the 4vHPV vaccine (proven to be clinically effective also in males) and also to the one observed among females who were administered the 9vHPV vaccine. Although we could not find direct evidence available of clinical efficacy of the 9vHPV vaccine in males, the efficacy can be inferred from the immunogenicity data. In these conclusions, we just reported the evidence found by the systematic literature review. We believe that the overall tone used is neutral, and we have now slightly rephrased as follows to better contextualise the statement: "*No direct evidence of efficacy of 9vHPV vaccine against HPV-related infection and illness in males was found*" We believe that the document provides a balanced and accurate account of the current state of evidence, and that it is of the utmost importance that the reporting of evidence is transparent.

[2] JCVI statement available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/726319/JCVI_Statement_on_HPV_vaccination_2018.pdf

4.2.2 Efficacy of quadrivalent and bivalent HPV vaccination in males 527 9–15 years old		"The evidence of efficacy of 4vHPV vaccine and 2vHPV vaccine in men is currently limited" Confusing statement. While the bivalent vaccine was never approved for boys, this statement conflicts with 4vHPV approved indications: Vaccination in boys and men 9 through 26 years of age for the prevention of genital warts caused by HPV types 6 and 11 Vaccination in people ages 9 through 26 years for the prevention of anal cancer and associated precancerous lesions due to human papillomavirus (HPV) types 6, 11, 16, and 18 The bivalent vaccine was never approved for boys.	Resolve the confusion between the bi-valent vaccine, never approved for boys, and the quadrivalent vaccine, approved in boys and men 9 through 26 years of age. This statement would also provide fuel for the defamatory no-vax campaign. It is imperative to adequately rephrase, avoiding the conflict with approved indications.	The current indication of the bivalent vaccine in the Summary of Product characteristics (SmPC) of the EPAR from EMA reads as follows: "*Cervarix is a vaccine for use from the age of 9 years for the prevention of premalignant ano-genital lesions (cervical, vulvar, vaginal and anal) and cervical and anal cancers causally related to certain oncogenic Human Papillomavirus (HPV) types.*" https://www.ema.europa.eu/en/documents/product-information/cervarix-epar-product-information_en.pdf We believe that the following two bullet points of the conclusions of Section 4.2 (paragraph 4.2.4) already clarify this possible misunderstanding: • "*There is direct evidence that 4vHPV vaccination is efficacious in 16–26-year-old males in preventing six months persistent infections, genital warts and anal intraepithelial neoplasia (i.e. anal cancer precursor lesion) due to HPV types 6, 11, 16 or 18.* • *There is no direct evidence on the efficacy of 2vHPV vaccine against HPV-related infection and illness in males.*"
4.4 Evidence of cost-effectiveness of adding males to 589 current national HPV vaccination programmes	Page: 18 Lines: 604-605	On equity grounds, some consider it preferential for both males and females to have access to the direct benefits of vaccination		This sentence is the same as the one already written in Section 4.4: "*On equity grounds, some consider it preferential for both males and females to have access to the direct benefits of vaccination.*"
5.1 Possible implications for current national HPV immunisation programmes	Page: 21 Lines: 745-747	"Including men in 745 HPV vaccination programs may be a less efficient strategy if done at the expense of female vaccination coverage for reducing the burden of HPV in the population." Statement based on hypothetical fallacy: if every EU country is already implementing a selective, girls only national vaccination programme, how adding boys can be detrimental to female coverage	Please remove the statement	We replaced the statement with the following: "The overall cost effectiveness of a gender neutral vaccination programme will depend on many factors, and balancing of coverage should there be vaccine supply or resource constraints may require careful consideration" There could be potential issues related to cost and sustainability of the programme and of future supply of the vaccine in some settings. These are possibilities that may not occur but, in our view, they cannot be ignored in a general reflection on public health implications as the one presented in Section 5. Unforeseen consequences on HPV vaccination uptake among girls, after expansion of the programme to boys, cannot be a priori completely ruled out for all EU/EEA contexts.
5.1 Possible implications for current national HPV immunisation programmes	Page: 21 Lines: 765-766	"…vaccinating before the beginning of sexual activity (i.e. before exposure to HPV infection) is generally preferable." The school-based national vaccination programme is the implementation strategy of choice to maximise the coverage of HPV naïve children.	The school-based programme should be recommended as "best practice" to achieve the highest possible coverage of HPV naïve children	Decisions on vaccine programmes implementation, and related recommendations, are under the responsibility of each EU/EEA Member State. In this document ECDC just reports on the evidence within the scope of the guidance (Section 1.1), and discusses potential implications for public health of the different HPV vaccination strategies considered (Section 5). Methods for effective HPV vaccine delivery have not been systematically reviewed in the current guidance.
Markus Kujawa, EU Policy Adviser - Comité Permanent des Médecins Européens / Standing Committee of European Doctors (CPME)				
Section of document (e.g. introduction, generic study process)	**Page and line number**	**Comment and rationale**	**Proposed change**	**ECDC reply**
Executive Summary	Page 1, line 10	Noteworthy is that the document addresses the usefulness of HPV vaccination, but not its safety. This is unfortunate in the current context of vaccine hesitancy.	-	In Section 2.4 of this guidance document, an overview of the current knowledge on safety of HPV vaccines is presented. At the end of the paragraph it is explained that in our reviews we could not find any new information from what is already available from other extensive international reviews on safety, it was thus decided not to report on it in detail. However, in the annexes of this guidance document, supporting tables on the evidence found on HPV vaccination safety are presented.
Aurora Limia, Head of Area Immunization Programme - Directorate General of public health, quality and innovation Ministry of Health, Consumption and Social Welfare				
Section of document	**Page and line**	**Comment and rationale**	**Proposed change**	**ECDC reply**

(e.g. introduction, generic study process)	number			
2.3 HPV vaccine introduction in Europe: Table 1.	Page 7-9, line 198	Difficult reading of the table	Include heading in every page	We have now amended the table accordingly.
2.3 HPV vaccine introduction in Europe: Table 1.	Page 9, line198	-The coverage data for Spain is for females at 13 years of age in 2017 -Even though Spain is highly decentralised and regions are responsible for the establishment of their schedule, the Interterritorial Council Agreements are usually respected. The sentence "Vaccination programs vary by region" can give the fake sensation of different schedules when it is highly homogenous but for the vaccine used (that can also change with time in the different regions). Any changes in the schedule are usually agreed withing the Interterritorial Council. -Incomplete information for Spain.	• Information under "reported coverage…" should appear: 77.8% (13 yo in 2017) • Remove the sentence "Vaccination programs vary by region" at the beginning of the comments referring to Spain Add the following information in the table for Spain: • Since 2015, as agreed by the Interterritorial Council, HPV is recommended for girls at 12 years of age in every region. • Since 2018, HPV has been also recommended for the following risk groups: WHIM syndrome (primary immunodeficiency), women with solid organ and hematopoietic transplant up to 26 years of age , people living with HIV (male and female, with a 3-dose schedule and up to age of 26), people in situation of prostitution up to the age of 26 (3 dose schedule) and women with excisional treatment of the cervix (https://www.mscbs.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/VacGruposRiesgo/docs/VacGruposRiesgo_todas_las_edades.pdf) • Catch-up in females until age 18 (since 2019)	Given the heterogeneity of information on HPV vaccination coverage across EU/EEA Member States and considering that the guidance does not aim to report on coverage data (see Section 1.1), we decided to remove all information about HPV vaccination coverage from Table 1. We have now made the suggested changes to the information concerning HPV vaccination policies in Spain.
		To facilitate the evaluation of the 9vHPV for decision-making, information regarding the most common types associated with different pathologies would be helpful to appear in the document. A table showing this information with the efficacy/effectiveness of the different vaccines would be really helpful. This information can be found in other documents including SPCs, but would be very helpful in this document. Something in line with the one presented in the following reference: Serrano B, Sanjosé S, Tous S, et al. Human papillomavirus genotype attribution for HPVs 6, 11, 16, 18, 31, 33, 45, 52 and 58 in female anogenital lesions. Eur J Cancer 2015; 51: 1732-1741.	Add Table 2 from *Serrano B, Sanjosé S, Tous S, et al. Human papillomavirus genotype attribution for HPVs 6, 11, 16, 18, 31, 33, 45, 52 and 58 in female anogenital lesions. Eur J Cancer 2015; 51: 1732-1741.*	We have added a reference to this article in Section 2.1 "Burden of HPV and HPV-related diseases in European countries".
2.5 Effectiveness …	Page 10; line 242-244	There are data from Spain (only in women) and should be mentioned as well (Purriños-Hermida MJ, Santiago-Perez MI, Treviño M, Dopazo R, Cañizares A, Bonacho I, et al. (2018) Direct, indirect and total effectiveness of bivalent HPV vaccine in women in Galicia,	Include Spain as a country with documentation of reduction in prevalence of HPV vaccine types	Spain has been added to the list of the countries where evidence has been made available and the suggested reference has been added.

		Spain. PLoS ONE 13(8): e0201653. https://doi.org/10.1371/journal.pone.0201653)		
4.3 Efficacy of HPV vaccination in people living with HIV	Page 17; lines 553-554	The section starts saying that direct evidence on the efficacy of HPV vaccination ... for people living with HIV was not found. One article with this information is available (Wilkin TJ, Chen H, Cespedes MS, Leon-Cruz JT, Godfrey C, Chiao EY, et al. A randomized, placebo-controlled trial of the quadrivalent HPV vaccine in HIV-infected adults age 27 years or older. Clin Infect Dis. 2018;67(9):1339–46) Even though was published after the period covered by the systematic review, could be mentioned.	Include that this information is available and has been published after the period covered by the systematic review …	This reference is already mentioned in the text in Section 4.3.1 "Recent evidence not included in systematic review" (second paragraph) on page 18: "*Another study on the efficacy of the 4vHPV vaccine against persistent anal HPV infections and lesions in people living with HIV and older than 27 years was stopped due to futility by the Data and Safety Monitoring Board (Wilkin et al).*"
5.3 Possible implications of HPV vaccine hesitancy	Page 23, line 866-867	Immunization schedules in different countries include HPV in preadolescents. Communication strategies are important to be directed not only to the target groups but also to their parents.	We suggest to add "**and also for parents when appropriate"** after …..tailored to different target groups	We have now added this suggested text.
Thomas Breuer, Chief Medical Officer – GSK Vaccines				
Section of document (e.g. introduction, generic study process)	**Page and line number**	**Comment and rationale**	**Proposed change**	**ECDC reply**
Guidance title	Front page	It should not be expected that stakeholders will go back and read the previous two guides. Instead of an addition, this guidance should encompass all data from previous versions The title is misleading and gives the impression of favoring the introduction of the 9-valent vaccine rather than an update on all HPV vaccines, including the 9-valent.	This guidance should encompass all data and come as a replacement of the previous versions. Suggestion to new title: Introduction of 2-, 4- and 9-vHPV vaccines in European Union countries, 2019.	The topics of this guidance were selected based on requests from the EU/EEA Member States as these were considered priority questions, as described in Section 3.1 "Identification of public health questions for guidance". The scope of this document is not to encompass all topics covered in the previous ECDC guidance documents on HPV vaccination. This guidance is based on a systematic revision and grading of the available evidence specifically concerning the topics outlined in the title and in section 1.1 "Scope and objectives of guidance". The 2- and 4-vHPV vaccines are discussed in this guidance in relation to vaccination of males and to the effectiveness of HPV vaccination in people living with HIV. We have now amended the title of the guidance to make more explicit what is covered in the document.
Scope	Line 6-8, page 1	If the intent is to have this document as a supplement to the guidance edited in 2012, it should be clearly stated in this section. Otherwise, as mentioned above, we suggest making a completely new version, encompassing also data already presented in previous editions.	Add to text: This guidance should be a complement to the two previous ECDC Guidances on introduction of HPV vaccines (+add link).	We have now added a sentence in Section 1.1 to make clear that this guidance is complementing and updating previously presented evidence, and that it is not substituting the previous guidance documents concerning topics that were not covered in this document: "*We still refer to the 2012 ECDC guidance on HPV vaccination for information on the topics that are not covered in this guidance document*" There are references to the previous ECDC guidance documents in Section 1.1 "Scope and objectives of guidance".
Key conclusions	line 40+41, page 1	The text about females should be more complete as there is higher immunogenicity of bivalent vaccine compared to quadrivalent vaccine, administered to females 9 to 55 years for specific HPV types contained in the bivalent vaccine up to 5 years post-vaccination. [Einstein M et al. Human Vaccines & Immunotherapeutics, 10:12, 3435-3445, DOI: 10.4161/hv.36121] This addition is supported by the ref 35: "The 2v-HPV has a very effective adjuvant, ASO4, which results in significantly higher antibody titers than 4vHPV (as demonstrated in a head-to-head trial), and it is likely that this is the mechanism that induces the superior degree of cross-protective efficacy"	higher immunogenicity of bivalent vaccine compared to quadrivalent administered to females 9 to 55 years for specific HPV types contained in the bivalent vaccine up to 5 years post-vaccination [Einstein M et al. Human Vaccines & Immunotherapeutics, 10:12, 3435-3445, DOI: 10.4161/hv.36121]	In this guidance we did not specifically look at immunogenicity, efficacy or effectiveness of 2v- and 4v-HPV vaccines in females (apart from females living with HIV). We mention some overall data on immunogenicity and cross-protection of the 2vHPV vaccine in the Section 2 "Background", but this is not part of the conclusions which are just based on the evidence collected. Please refer to Section 1.1 "Scope and objectives of guidance" for the topics assessed in this guidance.
Key conclusions	Line 42-43, page	There is evidence of higher immunogenicity for 2-vHPV than 4-vHPV vaccine in HIV+	Immunogenicity data in HIV+ subjects suggest:	The conclusions are based on the results of the systematic reviews and grading of the evidence as

	1	females [Folschweiller N on behalf of the HPV-019 study group, abstract HPV17-0979 for oral presentation at HPV 2017, Cape Town, South Africa] [Folschweiller N on behalf of the HPV-019 study group, abstract 00275 for oral presentation at EUROGIN 2018, Lisbon, Portugal]	- Higher immunogenicity of the 2-vHPV vaccine compared to the 4-vHPV vaccine for the types contained in the 2-vHPV vaccine	described in Sections 3.2 and 3.3 of the current document. This guidance does not aim to conclude on the differences in immunogenicity of the existing HPV vaccines, especially given the absence of an immune correlate of protection[1]. It is also already mentioned in Section 4.3 "Efficacy of HPV vaccination in people living with HIV" that: "*In another study comparing the 2vHPV and 4vHPV vaccines in HIV infected adults aged ≥18 years, GMTs for HPV16 did not differ following vaccination with the 2vHPV and 4vHPV vaccines, but they were higher for the 2vHPV vaccine against HPV18 at months 7 and 12 from first immunisation dose (evidence quality: moderate).*" We therefore believe that this point has already been covered. *1- Turner TB, Huh WK. HPV vaccines: Translating immunogenicity into efficacy. Hum Vaccin Immunother 2016; 12(6): 1403–1405.*
Key conclusions	Line 54-55, page 1	Addition to sentence: "irrespective of severity"	If the objective of the HPV vaccination program is to prevent all HPV-related disease irrespective of severity, a universal HPV vaccination may become a more cost-effective option.	According to the evidence reviewed, the universal HPV vaccination becomes increasingly more cost-effective the more outcomes are included in the model (irrespective of their severity). We believe that the suggested point has been already made by stating that increasing vaccination coverage among girls may still be a more cost effective objective if the priority is given to the prevention of cervical disease in women, unless there were persistently low HPV vaccination coverage among females and/or HPV vaccines cost were low.
Possible public health implications	Line 60, page 2	Sentence implies that this is even more important than pre-adolescents - suggest replacing 'particularly' by 'also'	…risk of HPV infection and illness, such as people living with HIV and men who have sex with men, may also benefit…	We understand this concern and we amended the text as suggested.
1.2 Target audience	Line 94-96, page 3	If intent is to have this document as a supplement to the guidance edited in 2012, it should be clearly stated in this section	The target audiences for this document in complement to the ECDC Guidance edited in 2012 (+add link), are public authorities, national policymakers, entities responsible for the planning of healthcare and …	We have added a new sentence explaining this at the end of the first paragraph of Section 1.1 "Scope and objectives of guidance" to clarify this point. We do not think it needs to be repeated under Section 1.2 "Target audience". As this new guidance used a structured evidence-based process and a grading of the evidence following systematic reviews, this cannot be considered a supplement of the previous guidance. It is an additional guidance document that does not cover the same topics of the previous one, despite some overlap (these overlapping topics can be considered as updated by this document).
2.1 Burden of HPV and HPV-related diseases in European countries	Line121-122, page 4	The high-risk HPV types listed here are not aligned with IARC mono 100B where 66 is also oncogenic – available on https://monographs.iarc.fr/wp-content/uploads/2018/06/mono100B-11.pdf Last accessed April 2019	From the more than 200 HPV types identified, only a few are classified as carcinogenic, namely HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66 [5].	In the suggested IARC document, in Section 5 "Evaluation", limited evidence is reported for type 66's (among others') carcinogenicity in humans unlike other types where evidence is deemed "sufficient". It is also reported on page 267 in the last paragraph before the Section "2.1.1 Summary" that "*This categorization scheme leads to the re-classification of HPV-66, for which the evidence of carcinogenicity was previously judged sufficient.*"; and then on page 268 in the Section "2.1.1 Summary" it is reported that "*A re-evaluation of the evidence for HPV 66. The data were re-evaluated and the evidence was judged to be very limited now that more cases have been studied showing that it is very rarely found in cancers despite being relatively common*", and then again that "*there could be harm to public health if the types (53 and 66) are included as carcinogenic in screening assays, which would decrease the specificity and positive predictive value of the assays with virtually no gain in sensitivity and negative predictive value*". We therefore prefer to leave the list of high-risk HPV types unchanged.
2.2 Human papillomavirus vaccines	Line 159-160, page 5	The sentence contradicts the guidance of 2012, where cross reactivity of the 2-vHPV vaccine (Cervarix) is described - see page 10 in the 2012 guidance	Correct to align with previous guidance 2012	The guidance (and its background section) does not have the objective to discuss the comparative effectiveness of the different HPV vaccines. We understand the concern and we decided to rephrase

				the discussion on the attribution of cancer to the HPV types contained in each vaccine rather than to the HPV type-specific vaccines effectiveness. We rephrased as follows: "*The bivalent and the quadrivalent vaccines both contain VLPs of HPV types 16 and 18 which are associated with 71% of all cervical cancer cases worldwide (i.e. those attributable to HPV types 16 and 18), while the nonavalent vaccine contains additional high-risk HPV types cumulatively responsible for 89% of cervical cancer cases [12,20].*"
2.2 Human papillomavirus vaccines	Line 159-162. page 5	If it is true that HPV16/18 are responsible for ~71% of cervical cancer cases, data have demonstrated that the overall efficacy of bivalent vaccine goes beyond the types included in the vaccine and this is reflected in the label. This is also reflected in ref 35, quoting the WHO position paper. It is therefore not the antigen content that matters for the prescriber, but the indication.	Theoretically, the 2- and 4-vHPV vaccines could prevent 71% of all cervical cancer cases worldwide (i.e. those attributable to HPV types 16 and 18), while based on epidemiological projection, the 9-vHPV vaccine could increase the preventive potential to 89% of cervical cancer cases [12,20]. HPV types 31, 33 and 45, the three types against which the 2- and 4-vHPV vaccines are reported to give cross-protection, are associated with 13% of cervical cancer cases. HPV types 31, 33, 45, 52 and 58, against which the 9-vHPV vaccine provides direct protection, are associated with 18% of the cases, i.e. a further 5% compared with the 2- and 4-vHPV vaccines which confer cross-protection against HPV types 31, 33 and 45. [Human papillomavirus vaccines: WHO position paper, May 2017 No 19, 2017, 92, 241–268 available on http://www.who.int/wer last accessed on April 2019]	The background of the guidance (Section 2) does not have the objective to discuss the comparative effectiveness of the different HPV vaccines. In section 2.5 of the guidance, the issue of cross-protection is briefly discussed. We understand the concern and we decided to rephrase the discussion on the association/attribution of cancer to the HPV types contained in each vaccine rather than to the HPV-type specific vaccines effectiveness: "*The bivalent and the quadrivalent vaccines both contain VLPs of HPV types 16 and 18 which are associated with 71% of all cervical cancer cases worldwide (i.e. those attributable to HPV types 16 and 18), while the nonavalent vaccine contains additional high-risk HPV types cumulatively responsible for 89% of cervical cancer cases [12,20].*" (see above)
2.2 Human papillomavirus vaccines	Line 163-164, page 5	In consequence of the above: it is therefore not the antigen content that matters for the prescriber, but the indication. Based on the acknowledged cross-protection, the label does not restrict to vaccine types for the 2- and 4-vHPV vaccines.	The three vaccines are licensed for the prevention of premalignant anogenital lesions (cervical, vulvar, vaginal and anal), cervical cancers and anal cancers ~~causally related to high-risk types included in the vaccines~~ caused by vaccine HPV types for the 9-vHPV vaccine and causally related to certain oncogenic Human Papillomavirus (HPV) types (2- and 4-vHPV vaccines)	The sentence has been rephrased and for each HPV vaccine the corresponding licensure indication according to each EPAR has now been reported separately.
2.2 Human papillomavirus vaccines	Line 172-173, page 6	We do not have 9.4 yrs data on efficacy against non-vaccine types nor irrespective of type.	Protection from infection and cervical lesions attributable to HPV-16 and HPV-18 and cross-reactive type has also been demonstrated with the 2-vHPV vaccine in a 3-dose schedule	In this sentence we are just referring to duration of protection against cervical infection/disease caused by HPV16 and HPV18 types. This sentence quotes the WHO 2017's Position Paper on HPV, where it is stated: "*For the bivalent vaccine, immunogenicity and efficacy of a 3-dose schedule against infection and cervical lesions associated with HPV-16 and HPV-18 have been demonstrated up to 8.4 and 9.4 years respectively*" Text about duration of protection was now removed and references to EMA's EPARs was added instead.
2.3 HPV vaccine introduction in Europe	Line 198, page 7	Vaccination coverage of 72% is cited for Flanders. This website seems to indicate a much higher uptake of 81.5% for a full course: https://www.zorg-en-gezondheid.be/gratis-hpv-vaccinatie-goed-ingeburgerd-in-vlaanderen. T his document: https://www.zorg-en-gezondheid.be/sites/default/files/atoms/files/Vaccinatiegraadstudie%202016.pdf estimates an even higher vaccination coverage but is based on a survey, which is	Correct text according to available references for the vaccination coverage in Flanders.	Given that the presentation of national HPV vaccination coverage data is outside of the scope of this guidance, and given the heterogeneity of information on uptake across EU/EEA countries, we decided to remove this field from Table 1.

		less reliable. This document: https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_theme_file/04_top_geert.pdf) estimates coverage to be around 84%, when adjusting for girls that re-do the same school grade. The document also reports the 72%, of girls that have re-done the same grade but seems to calculate the unadjusted vaccination coverage, based on number of girls in that grade and number of doses/vaccines administered (slide n° 18). This web-page (ministry of health Flanders) estimates HPV vaccination coverage way above 80%: https://www.zorg-en-gezondheid.be/nieuwe-cijfers-tonen-hoge-vaccinatiegraad-bij-vlamingen.		
2.5 Effectiveness and impact of HPV vaccines	Lines 233-253, page 10	Please specify as much as possible which vaccine the data refer to in each of the sections - it seems that most of the data mentioned so far are referring to Gardasil. Particularly when it is about impact on non-vaccine types, this is important as there are papers that demonstrate it. Due to the adjuvants used, the vaccines might not have the same impact, irrespective of the antigens they include. References: - Donken R et al. J Infect Dis. 2018;217:1579–89 - Woestenberg et al. J Infect Dis 2018;217:213–22 - Kudo et al. J Infect Dis. 2019; 219(3):382-390 - Mesher D et al. J Infect Dis 2018; 218:911–21 - Purrinos-Hermida MJ et al. PLoS ONE 13(8): e0201653 - Kavanagh K et al. Lancet Infect Dis. 2017;17(12):1293-1302 - Kumakech E et al. PLoS ONE 11(8): e0160099	Additionally, a 28% reduction in prevalence of HPV types 31, 33 and 45 in same-aged girls and a cross-protective effect in women aged 20–39 years and men under 20 years of age were observed [42]. Reductions in prevalence of HPV vaccine types have been documented so far in vaccinated women in Australia, Belgium, France, Germany, Sweden, Spain, Japan, Uganda, The Netherlands and the UK (England and Scotland separately), non-vaccinated women in the UK [Mesher 2018 and Kavanagh 2017], vaccinated women and men in the US and non-vaccinated men in Australia [35,42–44].	The references were added and placed as suggested.
2.5 Effectiveness and impact of HPV vaccines	Line 246, page 10	Impact of 2-vHPV vaccine on the prevalence of non-vaccine types has been reported from many countries These references should also be included: References: - Donken R et al. J Infect Dis. 2018;217:1579–89 - Woestenberg et al. J Infect Dis 2018;217:213–22 - Kudo et al. J Infect Dis. 2019; 219(3):382-390 - Mesher D et al. J Infect Dis 2018; 218:911–21 - Purrinos-Hermida MJ et al. PLoS ONE 13(8): e0201653 -Kavanagh K et al. Lancet Infect Dis. 2017;17(12):1293-1302 - Kumakech E et al. PLoS ONE 11(8): e0160099	Data from the UK (Scotland) published in 2017, recently confirmed high-level of cross-protection against HPV types 31, 33, and 45 seven years after vaccination with the 2-vHPV vaccine [45] and in several other countries [same ref as for 16/18].	The suggested references have now been added and the text of the guidance has been amended accordingly: "*Data from the UK (Scotland) published in 2017 and 2019, and from the Netherlands published in 2018, recently confirmed high-level of cross-protection against HPV types 31, 33, and 45 years after vaccination with the bivalent vaccine [ref]. Evidence of cross-protection has also been shown in other studies for both bivalent and quadrivalent vaccines [refs]*"
2.5 Effectiveness and impact of HPV vaccines	Line 247, page 10	Decrease of high-grade lesions in the targeted population (vaccinated at age 9-14) has so far been published only for Australia and Scotland from the surveillance based on national screening programs. Other available data are referring to selected samples of girls/women attending sexual health clinics and may suffer from bias as the target populations have not yet reached the age of regular screening. Add reference: - Palmer 2019 on effectiveness on CIN2/3-	The reduction of high-grade CIN observed in the meta-analysis was 31% in women aged 15–19 years [42]. In recent years, a reduction in high-grade cervical precancerous lesions has also been observed in ~~targeted~~ vaccinated populations in several countries such as Australia, Canada, Denmark, Sweden, the UK (Scotland) and the US [35,42,43 Add Palmer 2019].	We made the suggested correction and we added the additional publication by Palmer et al.

		Palmer T et al. BMJ 2019;365:l1161	Australia has now demonstrated reductions in high-grade cervical precancerous lesions in women up to 30 years of age [35].	
3.3 Evidence appraisal and synthesis	Line 283 - 286, page 11	This Guidance loses the sight on the 2-vHPV vaccine because it was described in a previous Guidance of 2012, without using the same analyzing method (GRADE). It is therefore highly questionable if the stakeholders will go back to look into a Guidance, versioned 2012, for comparable 2-vHPV vaccine data.	Include the 2-vHPV vaccine data in this updated report, including in the annex	Please refer to Section 1.1 "Scope and objectives of guidance" and to Section 3.1 "Identification of public health questions for guidance". In the time period covered by the systematic searches of this guidance (see Sections 3.2 "Collection of evidence" and 3.3 "Evidence appraisal and synthesis"), we looked at 2vHPV vaccine effectiveness data on immunogenicity and clinical outcomes only in relation to males and people living with HIV.
3.3.2 Methods for evidence synthesis on cost-effectiveness of adding males to the current HPV vaccination protocols	Line 345-351. page 12	It has been demonstrated that the variable that has the most important impact on the results of a health economical model is the sponsor of the model. References: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4842308/ https://www.sciencedirect.com/science/article/pii/S1542356506008196 https://www.bmj.com/content/326/7400/1167 The disadvantage of selecting literature from academia only may be not reflecting the entire breadth of the discussion field. Although industry sponsored research may be usually biased towards positive results (of the sponsor research), the quality of the research was generally high, sometimes higher than non-industry.	The sponsor-variable of a health economical model should be included in the analysis as well and the selected literature should not be restricted to academia.	We are not aware of a structured system like GRADE able to objectively and independently assess the quality of evidence from cost-effectiveness models, and some degree of subjective judgement on the assumptions made is part of any cost-effectiveness exercise. The general high/superior quality of industry sponsored modelling is also a judgement that would need to be supported by evidence that we do not possess nor are in any position to appropriately assess. Additionally, it would also be quite controversial to include a "sponsor-variable" in the cost-effectiveness model as there is no clarity on the magnitude of its effect on the reported results nor any evidence that this magnitude would be the same across different industry-sponsored studies. The cost-effectiveness studies reported in this guidance come from a systematic review of the literature which is transparently reported and referenced. In this guidance we are just limiting ourselves to discuss the relevant parameters to consider for modelling the cost-effectiveness of adding males to the routine girls-only HPV vaccination and we believe that we have highlighted the relevant ones to consider.
4.1 Evidence of efficacy of 9-valent HPV vaccine	Line 397. page 14	There should be an introductory note to clarify the available data quality. The 9-vHPV additional serotype efficacy data is not as robust as the 2- and 4-vHPV effectiveness and efficacy data.	Include an introductory note: Whereas efficacy and effectiveness data are available for the 2- and 4-HPV vaccines, the 9-vHPV data is based on efficacy only related to the five additional HPV types.	A factual description of the evidence used in the guidance, which was appraised using GRADE (e.g., see conclusions of Section 4.1 "Effectiveness of 9vHPV vaccine"), is already provided for each point of the assessment. We therefore do not think that there is a need for additional specifications.
4.3.1 Recent evidence not included in systematic review	Line 568, page 17	There is evidence of higher immunogenicity for 2- than 4-vHPV vaccine in HIV+ females Reference: - Folschweiller N on behalf of the HPV-019 study group, abstract HPV17-0979 for oral presentation at HPV 2017, Cape Town, South Africa - Folschweiller N on behalf of the HPV-019 study group, abstract 00275 for oral presentation at EUROGIN 2018, Lisbon, Portugal	In a study enrolling a 15-25-year-old cohort of HIV+ and HIV- women, the 2-vHPV vaccine was shown immunologically superior to the 4-HPV vaccine; the antibody response remains over 24 months but appeared lower in HIV+ versus HIV- for both vaccines.	This guidance does not aim to discuss differences in immunogenicity of different HPV vaccines. It is however mentioned already in this Section 4.3 that: "*In another study comparing the 2vHPV and 4vHPV vaccines in HIV infected adults aged ≥18 years, GMTs for HPV16 did not differ following vaccination with the 2vHPV and 4vHPV vaccines, but they were higher for the 2vHPV vaccine against HPV18 at months 7 and 12 from first immunisation dose (evidence quality: moderate).*" We therefore believe that this point was covered in line with the scope and objectives of this guidance.
5.1 Possible implications for current national HPV immunisation programmes	Line 743-746, page 21	It should be specified that the study was with the 2-vHPV vaccine.	Related to this, a Finnish randomized community trial with the 2-vHPV vaccine published in 2018, recently demonstrated that gender-neutral vaccination generates significant herd effects and cross-protection against a number of non-vaccine HPV types in a low-to-moderate coverage scenario [114–115].	We agree this is worthwhile mentioning and we edited the sentence as suggested.
5.1 Possible implications for current national HPV immunisation programmes	Line 761-762, page 21	Refer to above and add 2-vHPV	The current evidence of HPV vaccine efficacy in males is limited and refers to the prevention of persistent HPV infections, genital warts and anal cancers precursor lesions (anal intraepithelial neoplasia) by the 2- and 4- vHPV vaccines.	Evidence of 2vHPV vaccine effectiveness in males was not available during the time period covered by the systematic reviews performed for this guidance, however other publications have shown impact of the 2vHPV vaccine also in males (e.g., Lehtinen et al). We therefore removed "*by the 4vHPV vaccine*" from the sentence so that it is clear that the evidence is not limited to a single vaccine.
5.1 Possible implications	Line 771-7, page	Comparison of the 9-vHpv vaccine has so far, only been made versus the 4-vHPV vaccine	Delete the text: "The introduction of the 9vHPV	We deleted the second part of the sentence in order not to give the impression that there is any evidence of this.

for current national HPV immunisation programmes	21	and reference is based on the epidemiology of oncogenic HPV types. Claiming that the 9-vHPV vaccine will have an impact beyond what has already been observed with the 2-vHPV vaccine is purely speculative and should be confirmed in trials or real-life. Refer again to WHO position paper 2017.	vaccine will likely have an impact on the new additional vaccine HPV types beyond what has been observed with cross-protection from other previously licensed HPV vaccines [119]."	Few rows below we also mention: *"However, the effectiveness of the 9vHPV vaccine should also be compared to the effectiveness of all other available vaccines in order to evaluate options for an optimal immunisation strategy [105,120]."*
5.1.1 Organisational aspects	Line 804-806, page 22	Dose sparing option(s) should also be described	Add a description of dose-sparing option(s)	We added a sentence and references to the one dose schedule and the mixed dose schedule: *"Dose and cost sparing options are under investigation and may provide alternatives in the future."*
5.1.3 Ethical considerations	Line 823, page 22	Ethical considerations in case of a vaccine constrain could be included in the discussion.	include the ethical considerations in a vaccine constrained environment. For instance, if a female and male vaccination strategy lowers the possibility to vaccinate more women.	We added a last sentence in "Section 5.1.3 Ethical considerations" to remind about this: *"In case of limited supply of HPV vaccine, vaccination of girls might be preferred over universal vaccination."*
References	Line 1019-1022, page 27	Reference n° 31 refers to an internet page that is not available anymore	Change of internet reference	We have now provided the right link.
Table A6. 4vHPV vaccine trials for HPV 6, 11, 16 and 18-related outcomes in females 9–15 years old	Line 1378, page 36	In several titles of the tables from the Annex 1, the age group mentioned is not corresponding to the age range of the results presented. Please cross-check carefully as it may give the perception of availability of data that are, in fact, not available.	Table A6. 4vHPV vaccine trials for HPV 6, 11, 16 and 18-related outcomes in females 16-26 years old	The evidence shown is the one used to report on the age groups outlined in the title. Sometimes, the only evidence available is from other age groups, thus there is indirectness. We have modified all the table titles by adding "trials used for" as follows: *"Xv-HPV vaccine trials **USED** for HPV X-related outcomes in males/females XX–XX years old"*
Table A7. 9vHPV vaccine trials for HPV 31, 33, 45, 52 and 58-related outcomes in females 9–15 years old	Line 1383, page 36	Age group not correct	Table A7. 9vHPV vaccine trials for HPV 31, 33, 45, 52 and 58-related outcomes in females 16–26 years old	Same as above.
Table A14. 4vHPV vaccine trials for HPV 6, 11, 16 and 18-related outcomes in males 9–15 years old	Line 1446, page 36	Age group not correct	Table A14. 4vHPV vaccine trials for HPV 6, 11, 16 and 18-related outcomes in males 16–26 years old	Same as above.
Table A15. 9vHPV vaccine trials for HPV 31, 33, 45, 52 and 58-related outcomes in males 9–15 years old	Line 1452, page 36	Age group not correct	Table A15. 9vHPV vaccine trials for HPV 31, 33, 45, 52 and 58-related outcomes in males 9–26 years old	Same as above.
Table A33. Main characteristics of 21 studies that include cost-effectiveness analysis of universal vaccination	line 1684, page 52	Refer also to other comment above: There are demonstrations that the sponsor can be the main variable of HE models	Add Sponsors to the table	Please refer to the reply to the previous comment above.
Rosybel Drury, Regional Director Medical Affairs - MSD				
Section of document (e.g. introduction	**Page and line number**	**Comment and rationale**	**Proposed change (in red)**	**ECDC replies**

, generic study process)				
Executive Summary - Key conclusion	Page 1 Line 19 - 22	Data on efficacy of 9vHPV in preventing Vulvar/ Vaginal precancers is missing. Proposed sentence and corresponding reference has been provided. This sentence can be included at the end of line 22: In a recent comparison of 9vHPV recipient subjects against historic placebo group, Efficacy of 9vHPV vaccine for high-grade vulvar and vaginal disease caused by HPV 6, 11, 16, 18, 31, 33, 45,52,58 (n=4635) was 100% (95%CI: 85.7-100). REF: Giuliano A et al. Nine-valent HPV vaccine efficacy against related diseases and definitive therapy: comparison with historic placebo population. 2019 Gynecologic Oncology	**In a recent comparison of 9vHPV recipient subjects against historic placebo group, Efficacy of 9vHPV vaccine for high-grade vulvar and vaginal disease caused by HPV 6, 11, 16, 18, 31, 33, 45,52,58 (n=4635) was 100% (95%CI: 85.7-100). (Giuliano A et al 2019)**	The suggested study was published after the period covered by the systematic literature review performed for this guidance, therefore it was not retrieved and did not undergo a formal grading assessment. Therefore, the evidence-based conclusions of the guidance cannot be based on its findings. We have now added a new Section 4.1.4 "Recent evidence not included in systematic review", which mentions this recent additional evidence that did not undergo the formal grading assessment in the guidance.
Executive Summary - Key conclusion	Page 1 Line 42-44	"There was no direct evidence on the efficacy of HPV vaccination on HPV-related clinical outcomes in people living with HIV for the period covered by the systematic review, although low quality of evidence of efficacy of the quadrivalent HPV vaccine on oral HPV infection became available in 2018." This sentence can be updated with information available from a study in Canada with QHPV vaccine published in 2019. Furthermore, clearer editing would help the meaning come through more easily for readers, particularly for those for whom English is not a native language. Regarding the data available: HIV-positive Invasive Cervical cancers are more likely to be infected with multiple HPV types (27.8%) than HIV-negative ICC (15.9%). HPV16 was the most frequently detected HPV type in HIV-positive ICC (42.5%), followed by HPV18 (22.2%) and HPV45 (14.4%). (REF 1) There is some direct evidence on the efficacy of HPV vaccination on HPV-related clinical outcomes in people living with HIV Women living with human immunodeficiency virus have a 47–53% prevalence of HPV infection, which is approximately double the prevalence among women without HIV (22–29%). In a trial done in Canada, among 212 women eligible for the PPE population, the incidence rate of newly acquired persistent qHPV was 1.0 per 100 person-years (95% CI, 0.3–2.6). All 4 cases of persistent qHPV were due to HPV18. No cases of qHPV-associated CIN2+ developed among women with normal baseline cytology. (REF 2) 1. Clifford G et al. Effect of HIV Infection on Human Papillomavirus Types Causing Invasive Cervical Cancer in Africa. J Acquir Immune Defic Syndr _ Volume 73, Number 3, November 1, 2016 2. McClymont E et al. The Efficacy of the Quadrivalent Human Papillomavirus Vaccine in Girls and Women Living With Human Immunodeficiency Virus. Clinical Infectious Diseases 2019;68(5):788–94	There was no direct evidence on the efficacy of HPV vaccination on HPV-related clinical outcomes in people living with HIV for the period covered by the systematic review, **although there is evidence on efficacy in persistent infection, as well as ~~although~~** low quality **~~of~~** evidence of efficacy of the quadrivalent HPV vaccine on oral HPV infection became available in 2018	We amended the sentence as follows adding information about the more recent publication: *"..although low quality evidence of efficacy of the quadrivalent HPV vaccine against HPV persistent infection and against oral HPV infection became available in 2018 and 2019."*
Executive Summary - Key conclusion	Page 1 Line 45-46	A general paragraph on the value of gender neutral programs that would summarize the benefits is missing. This points should cover: 1. Secondary prevention (screening): Whereas females have a screening program for	Cost-effectiveness analysis is sensitive to context and context-specific studies should optimally be done to inform decision-making in this area. According to the cost-effectiveness models	In general, the conclusions reported in the Executive Summary are based on the evidence retrieved and appraised during the time period covered by the guidance (see Section 3.2 - Collection of evidence). Further evidence may be added separetely, as additional data, only if relevant for the interpretation of the specific

		Cervical cancer, males on the other hand do not have any screening programs for cancers caused by HPV. (REF 1) 2. Constant HPV prevalence in men: In the HPV Infection in Men (HIM) study, 1,160 males aged 18-70 years from Brazil, Mexico, and the United States were studied and it not only found that HPV prevalence was higher in males than females but also that HPV prevalence in males did not decline with age. (REF 2) 3. Males have very low seroconversion and this seroconversion is not protective: In the HIM Study very few males developed natural HPV antibodies after an Infection with HPV (REF 3). Amongst the males who develop HPV antibodies may not be protected from subsequent incident infection. (REF 4) 4. Higher recurrence of disease in males: The HIM Study also found that recurrence of genital HPV infection with one of nine HPV types studied is common among males and is higher than what has been previously observed in females. (REF 5) 5. HPV transmission from females to males is higher than from males to females. (REF 6) All these factors along with gender equity support the argument for gender neutral vaccination programs. 1. Cubie HA. Virology. 2013;445:21–34 2. Giuliano A et al. Cancer Epidemiol Biomarkers Prev. 2008;17:2036–2043. 3. Giuliano AR et al. Papillomavirus Res. 2015;1:109–115 4. Pamnani SJ et al. Cancer Res. 2016;76:6066–6075 5. Pamnani SJ et al. J Infect Dis. 2018;218:1219-1227. 6. Nyitray AG et al. J Infect Dis. 2014;209:1007–1015	reviewed, if the priority is the prevention of cervical disease in women, adding males to current female-only HPV vaccination programmes becomes increasingly cost-effective with: – persistently lower vaccination coverage among females; and – lower vaccine cost. **Males inclusion in HPV vaccination programs would address their lack of any secondary prevention (screening), their constant HPV prevalence (leading to disease and transmission of HPV due to low natural seroconversion and low natural immune protection) which lead to higher recurrence rates of HPV disease compared to females. In addition, HPV transmission from females to males is higher than from males to females, leaving males at higher risk of infection and further transmission of HPV.**	questions of the current guidance. Our replies point by point are here below: 1. This is a valid point and we modified the text as follows (Section 2 - Background): *"As other less common genital and non-genital cancers have been shown to be attributable to HPV, not only females, but also males may actually suffer from severe consequences of this viral infection. Moreover, virtually all genital warts are due to HPV, contributing to the large burden of HPV-related disease in both sexes.* (…) *However, no high-quality screening programs are is currently available for women or men to prevent HPV-related disease other than cervical cancer in women. One consequence is that no HPV-related cancer in men is detectable through screening.*" 2. We added the following sentence in Section 5.1 "Possible implications for current national HPV immunisation programmes": "*Previous evidence suggested a different age-distribution of HPV infection between sexes, with males seemingly having a constant prevalence over age, though possibly varying according to context, serotype and type of infection [Giuliano et al, 2008].*" 3, 4 and 5. The studies retrieved by this guidance showed high seroconversion rates after HPV vaccination in males similar to what was observed in females following HPV vaccination. However it is true that this does not seem to be the case for the natural immunity and that recurrence of disease has been shown to be higher among males. We have now added to the text in Section 5.1 the higher transmission of HPV from males to females reported by the HIM study. Nonetheless, transmission dynamics are particularly complex in HPV and the aim of this guidance is not to address all their complexities, that may also include non-genital, as well as possible non-sexual, transmission. To take the above mentioned points into account, we added the following sentences to Section 5.1 – Possible implications for current national HPV immunisation programmes: "*The seroprevalence of HPV remains significantly higher among females, as does the burden of disease attributable to HPV, however the Human Papillomavirus Infection in Men (HIM) study reported the following: a different anatomic site-distribution of HPV infections has been observed (e.g., higher HPV infection prevalence in the genital region than in the oral cavity); the immune response against HPV infection differs by anatomic site and seems to be weaker in males against re-infections and recurrences in males; males have shown low seroconversion rates following natural HPV infection and long-term persistence of oral HPV-16 infection; the heterosexual transmission of HPV appears more efficient from female to male than viceversa [Giuliano AR et al 2015 – Eurogin 2014 roadmap; Nyitray AG et al, J Infect Dis 2014; Pierce Campbell CM et al, Cancer Prevention Research 2015; Giuliano AR et al 2015, Papillomavirus Research 1:109-115]. Previous evidence has suggested a different age-distribution of HPV infection between sexes, with males seemingly having a constant HPV prevalence over age, though it may vary according to context, serotype and type of infection [Giuliano A et al. Cancer Epidemiol Biomarkers Prev. 2008;17:2036–2043]."* 5. Ethical considerations (e.g. equity) are already discussed in Section 5.1.3.
Executive	Page 1	"However, increasing vaccination coverage	**~~However,~~ Therefore if the**	A few lines above it has been already mentioned that this

Summary – Key conclusions	Line 51	among girls may still be a more cost-effective primary objective. " This sentence could be misleading if taken out of context. This statement needs to put into context in terms of which strategy will be used as comparator (more cost-effective versus which strategy) and the definition of primary objective is unclear. Because cost-effectiveness studies must be put in context, it is difficult to make a such general statement as according to the specific context, result may vary. Universal vaccination is a cost-effective strategy versus a girl only program and contribute to reduce further the HPV related diseases and cancers in females and males. If the sentence refers to the case when the primary objective is limited to only cervical cancer, then it should be stated to qualify the statement.	**priority is to prevent only cervical cancer,** increasing vaccination coverage among girls may still be a more cost-effective primary objective.	sentence refers to the scenario in which the priority is the prevention of cervical cancer and that this is according to the cost-effectiveness models reviewed in this guidance: "*According to the cost-effectiveness models reviewed, if the priority is the prevention of cervical disease in women, adding males to current female-only HPV vaccination programmes becomes increasingly cost-effective with…*" In the first sentence of this final bullet point of the conclusions, it is also already stated that cost-effectiveness assessments depends on context and resource-availability: "*Cost-effectiveness analysis is sensitive to context and context-specific studies should optimally be done to inform decision-making in this area*". As for the comparator, the conclusions are based on the review of the cost-effectiveness studies included in this guidance. Please refer to tables A36-39 in the appendix for details on the comparator strategy used in each study. The most commonly used was girls-only vaccination, with or without catch-up. This is in line with the vaccination policy initially in place in virtually all EU/EEA Member States.
Executive Summary; Key Conclusions	Page 1 Line 55	Suggest adding a statement that objectives to provide equitable access for direct protection across genders should also be considered. Equitable access and direct protection are referenced in the document (Section 4.4). Propose adding a statement "Objectives to achieve equitable access for direct protection for both males and females are also considerations on program development." These are references to National recommendations in Europe that included equity in their considerations for recommendation of HPV vaccines to boys: References: UK: UK JCVI Boys HPV vaccination (points 23-24) https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/726319/JCVI_Statement_on_HPV_vaccination_2018.pdf Germany: STIKO background paper for boys HPV vaccination (section 12) https://www.rki.de/EN/Content/infections/Vaccination/recommandations/Takla2018_Article_BackgroundPaperForTheRecommend_BGBL_2018-61_HPV.pdf?__blob=publicationFile Belgium: Belgium KCE recommendations https://kce.fgov.be/en/cost-effectiveness-analysis-of-hpv-vaccination-of-boys-in-belgium Ireland: Ireland HIQA HTA evaluation boys extension: https://www.hiqa.ie/reports-and-publications/health-technology-assessment/hta-extending-hpv-vaccination-boys	If the objective of the HPV vaccination programme is to prevent all HPV-related disease, a universal HPV vaccination may become a more cost-effective option. **Objectives to achieve equitable access for direct protection for both males and females are also considerations that European recommendation bodies have taken on account on HPV immunisation program development including males.**	Equity is discussed in Section 5.1.3 "Ethical considerations", for its implications for public health, and is not part of the evidence-based key conclusions of the guidance. We have now modified a sentence in the "Executive Summary" in the paragraph "Possible public health implications", as follows: *It (gender-neutral vaccination) may also favour a more pronounced decrease of HPV viroprevalence and circulation and could more effectively protect all risk groups providing more equitable access to direct protection."*
Executive Summary - Public Health Implications	Page 2 Lines 60-62	The statement that people living with HIV and MSMs as examples of risk populations are considered restrictive given the current knowledge of evidence today. Also, it could lead to believe that only MSMs and HIV positive individuals can benefit from HPV vaccines. REF: Martínez-Gómez *et al.* Multidisciplinary, evidence-based consensus guidelines for human papilloma virus (HPV) vaccination in high-risk populations, Spain 2016. Euro Surveill. 2019;24(7):pii=1700857. https://doi.org/10.2807/1560-7917.ES.2019.24.7.1700857	Subjects at higher risk of HPV infection and illness, include: **HIV infected patients; men who have sex with men; women with precancerous cervical lesions; patients with congenital bone marrow failure syndrome; women who have received a solid organ transplant or hematopoietic stem cell transplantation; and patients diagnosed with recurrent respiratory papillomatosis. ~~such as~~**	Please refer to the scope of this guidance document in Section 1.1 "Scope and objectives of guidance" and to Section 3.2 "Collection of evidence". This guidance focuses on evidence of HPV vaccine efficacy and effectiveness in males (including men who have sex with men) and people living with HIV. This is the reason why these two risk groups are explicitly mentioned. As we have not searched for evidence concerning other high-risk groups, we are not reporting on it. We now made more clear that these examples of risk groups include, but are not limited to, men who have sex with men and people living with HIV, by modifying the sentence as follows: "*Subjects at higher risk of HPV infection and illness, including but not limited to people living with HIV and*

			People living with HIV and men who have sex with men, may particularly benefit from the vaccination despite possibly experiencing lower vaccine efficacy due to increased risk of exposure to HPV types included in the vaccines or lower immune response.	*men who have sex with men, …"*
Executive Summary – Possible public health impact	Page 2 Line 66-68	Female only vaccination is not protecting MSM population, and modelling studies show that female-only programs are less resilient to loss in vaccine coverage rates (REF 124 in the guideline) REF 124: Elfström KM, Lazzarato F, Franceschi S, Dillner J, Baussano I. Human Papillomavirus Vaccination of Boys 1267 and Extended Catch-up Vaccination: Effects on the Resilience of Programs. J Infect Dis. 1268 2016 Jan 15;213(2):199-205.	A female-only HPV vaccination of preadolescent girls is probably more cost-effective at current vaccine cost, but does not ~~**sufficiently**~~ protect men who have sex with men. It is less equitable and ~~**probably**~~ less resilient to sudden drops in vaccine uptake.	This is an issue mainly related to the wording used. Men who have sex with men community is not a 100% closed group when it comes to sexual behavior. Therefore, we cannot state with absolute certainty that they experience zero indirect benefit from HPV vaccination of girls in all settings. Any potential limited indirect benefit would not be sufficient though, as stated by Sauvageaua C et al: "*Although vaccination against HPV types 6, 11, 16 and 18 is currently offered to girls in Québec, unlike heterosexual men, MSM derive little or no benefit from the herd protection that comes from girls vaccination*"[1]. Likewise about resilience, there is no absolute certainty that in real life this would always be the case in all settings at any coverage level and in any population subgroup (depending on e.g. mixing patterns). Nor do we know for sure whether expanding the vaccination to boys would have a positive, negative or neutral impact on the vaccination uptake among girls in different settings. Modelling studies are based on assumptions that are not certain by definition. We still express that an increased resilience is likely to be achieved with a universal (gender-neutral) vaccination programme. 1. Sauvageaua C, Dufour-Turbisb C. HPV vaccination for MSM: Synthesis of the evidence and recommendations from the Québec Immunization Committee. Hum Vaccin Immunother. 2016 Jun; 12(6): 1560–1565.
Executive Summary; Possible public health implications	Page 2 Line 74	Propose adding a reference to calls for elimination of cervical cancer and HPV-related diseases, and country-level considerations to lay groundwork for elimination plans. References: - WHO's call for elimination of cervical cancer (https://www.who.int/cancer/cervical-cancer) - Example of EU organisations calls for action: https://ipvsoc.org/news/stakeholder-collaborations-elimination-hpv-related-disease/ American Cancer Society's call to eliminate all HPV-related cancers (http://pressroom.cancer.org/HPVcancerfreelaunch)	**WHO and numerous global and European coalitions have called for the elimination of cervical cancer. In addition, the American Cancer Society has called for the elimination of all HPV-related cancers. These are indicative of the opportunities to make significant public health advances in the prevention of HPV-related diseases.** Ongoing studies will provide evidence on certain identified research gaps concerning HPV vaccination and allow for 73 additions and updates to this guidance.	We added the following sentence in Section 2 "Background": "*Recently, WHO and a number of scientific and public health coalitions have called for the elimination of cervical cancer, while the American Cancer Society has called for the elimination of all HPV-related cancers.*"
2. Background	P4, Line 99-112	Propose adding a reference to calls for elimination of cervical cancer and HPV-related diseases, and country-level considerations to lay groundwork for elimination plans. References: - WHO's call for elimination of cervical cancer (https://www.who.int/cancer/cervical-cancer) - Example of EU organisations calls for action: https://ipvsoc.org/news/stakeholder-collaborations-elimination-hpv-related-disease/ - American Cancer Society's call to eliminate all HPV-related cancers (http://pressroom.cancer.org/HPVcancerfreelaunch)	**WHO and numerous global and European coalitions have called for the elimination of cervical cancer. In addition, the American Cancer Society has called for the elimination of all HPV-related cancers. These are indicative of the opportunities to make significant public health advances in the prevention of HPV-related diseases.**	We added the following sentence at the introductory paragraph of Section 2 "Background": "*Recently, WHO and a number of scientific and public health coalitions have recently called for the elimination of cervical cancer, while the American Cancer Society has called for the elimination of all HPV-related cancers.*"

2. Background	Page 4 Line 105-112	Whereas the reference to women is made, no reference to males is included in this important paragraph, which points out to the lack of alternative prevention for HPV diseases in males, as there is no screening. There should be clarity in these lines and therefore words missing have been included in our proposal.	Few pathologies other than cervical cancer offer such a wide range of prevention tools and strategies: cervical cytology for screening, HPV vaccines for primary prevention and more recently HPV detection tests for screening. However, no high-quality screening programs are currently available to prevent HPV-related disease **in women or men** other than cervical cancer in women. Moreover, despite the unequivocal success of organised population-based cervical screening programs, cervical cancer is still an important cause of morbidity and death among European women. Therefore, vaccination against HPV **in women and men** is expected to provide a significant added benefit for the prevention of all HPV-attributable diseases **in both sexes**. Evidence on efficacy and effectiveness of HPV vaccines thus needs to be continuously monitored in order to guide public health actions.	We agree with this comment and we amended the text now making reference to males as well.
2.1 Burden of HPV and HPV-related diseases in European countries	Page 4 Line 116-117	*"The overall prevalence of a detectable HPV infection in European women from the general population is estimated to be 14%, although it is highly dependent on age."* Data for prevalence of disease in males can be added here. Proposal and reference: In the HPV Infection in Men (HIM) Study, 1,160 males aged 18-70 years from Brazil, Mexico, and The United States were studied and it found that HPV prevalence was higher in males than females and it did not decline with age.[1] 1. Giuliano A et al. *Cancer Epidemiol Biomarkers Prev*. 2008;17:2036–2043.	The overall prevalence of a detectable HPV infection in European women from the general population is estimated to be 14%, although it is highly dependent on age. **Regarding males, the HPV Infection in Men (HIM) Study, 1,160 males aged 18-70 years from Brazil, Mexico, and The United States were studied and it found that HPV prevalence was higher in males than females and it did not decline with age.**	We now added the following sentence: "*Additionally, findings from studies carried out in the US and in Latin America showed that the prevalence of HPV in males is higher than in females and does not seem to decline with age* [refs]"
2.2. Human Papillomavirus vaccines	Page 5 Line 157-158	Silgard must be removed as the product is no longer licensed in the EU as of Feb. 2019 (*link to EU Commission decision:* http://ec.europa.eu/health/documents/community-register/2019/20190218143884/dec_143884_en.pdf	the quadrivalent HPV vaccine Gardasil**~~/ Silgard~~** (Merck Sharp & Dohme – MSD)	We removed the reference to Silgard.
Section 2.2 Human Papillomavirus Vaccines	Page 5 Lines 163-164	Please correct the indication of Gardasil 9 as it has an indication for prevention of vulvar and vaginal cancer. Of note, Cervarix and Gardasil do not have such indication. REF: SmPC of Gardasil 9 (EPAR): https://www.ema.europa.eu/en/medicines/human/EPAR/gardasil-9	The three vaccines are licensed for the prevention of premalignant anogenital lesions (cervical, vulvar, vaginal and anal), cervical cancers and anal cancers **and for Gardasil 9 also vulvar and vaginal cancers** causally related to high-risk types included in the vaccines. In addition, the quadrivalent and nonavalent vaccines are licensed for the prevention of genital warts.	We revised the text as follows based on what is reported on the SmPC of each vaccine (EPAR): *"The bivalent vaccine is licensed for the protection against the cancer of the cervix (neck of the womb) or anus, and precancerous lesions (abnormal cell growth) in the genital area (cervix, vulva, vagina or anus), caused by certain types of human papillomavirus. The quadrivalent vaccine is licensed for the prevention of premalignant genital lesions (cervical, vulvar and vaginal), premalignant anal lesions, cervical cancers and anal cancers causally related to certain oncogenic human papillomavirus (HPV) types; and genital warts (condyloma acuminata) causally related to specific HPV types. The nonavalent vaccine is licensed for the protection against precancerous lesions (growths) and cancers in the cervix, vulva or vagina and anus, and genital warts, caused by nine types of the human papillomavirus (HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58)."*
Section 2.2 Human Papillomavirus	Pages 5-6 Lines 165-168	Please correct the upper age for the two-dose schedule with Gardasil as per SmPC: two doses can be given to Individuals 9 to	All vaccines are approved from the age of 9 years with a recommended schedule of two	We revised the sentence as suggested based on SmPC of each vaccine (EPAR).

Vaccines		and including 13 years of age; and only after 14 years of age they should pass to a three-dose schedule. As the guideline is written, it could lead to the impression that an individual of 13.1 years needs three doses of Gardasil or that another individual of 14.1 years needs three doses of Gardasil 9, which is not the case. REF: SmPC of Gardasil & Gardasil 9 (EPAR) https://www.ema.europa.eu/en/medicines/human/EPAR/gardasil-9	doses (0–6 months) up to **and including** the age of 14 years **~~forthe~~ for the** bivalent and nonavalent vaccines and up to **and including** the age of 13 years for the quadrivalent vaccine. In individuals older than the above indicated ages **(15 years of age for the bivalent and nonavalent, 14 years of age for the quadrivalent),** the recommended schedule is 3 doses administered at months 0, 1 (or 2) and 6 168 [7,21–23].	
2.2. Human Papillomavirus vaccines	Page 6, Line 170-171	Duration of protection has been demonstrated for at least 12 years for women 16-26 years (*ref to EPAR PI can be added when available, following update by EMA*). REF: CHMP decision no. Gardasil - EMEA/H/C/000703 – II/080 EPAR: https://www.ema.europa.eu/en/medicines/human/EPAR/gardasil (As soon as the EPAR is updated – expected end of April- it can be sent to ECDC) This statement does not reflect LTFU (long term follow-up data) at 14 years from the FUTURE II follow up studies from NORDIC countries: No breakthrough cases of HPV 16/18-related CIN2 or worse were observed in the Long term follow up study of GARDASIL from the Nordic countries. The vaccine effectiveness was 100% in the PPE population through 14 years post dose 1. Persistent and sustained immunogenicity was observed after 14 years of follow up. REF: Nygard M et al.A 14 year Follow- up on the effectiveness, immunogenicity and safety of Gardasil in the Nordic population. (V501, P015). Data presented at Eurogin 2018 in Lisbon, Portugal. (abstract and content available upon request)	The duration of protection from HPV-related cervical and genital disease attributable to serotypes 6, 11, 16 and 18 has been demonstrated for at least **14 ~~10~~** years with the quadrivalent vaccine given in a 3-dose schedule to preadolescents and adolescents **and at least 12 years with the quadrivalent vaccine given in a 3-dose schedule to women 16-26 years old.**	Section 2.2 "Human papillomavirus vaccines" reports on the evidence of vaccination efficacy against cervical and genital HPV-related disease. The reported estimates of duration of protection against HPV-related cervical and genital disease are based on the conclusions of the WHO Position paper from 2017. As we are aware that information on duration of protection is being periodically updated, we will now just simply refer to the most updated SmPC of each vaccine (EPAR) for information on duration of protection. The text now reads: *"The duration of protection from HPV-related cervical and genital disease attributable to HPV serotypes is reported in the WHO position paper on human papillomavirus vaccines and in the EMA's Summaries of Product Characteristics (SmPC) and European Public Assessment Reports (EPAR) [Refs]"*
Section 2.2 Human Papillomavirus Vaccines	Page 6 Line 172-173	*"A duration of 9.4 years of protection from infection and cervical lesions attributable to HPV-16 and HPV-18 has also been demonstrated with the bivalent vaccine in a 3-dose schedule."* The above statement does not specify that the data came from a Phase II study, please include this information.	A duration of 9.4 years of protection from infection and cervical lesions attributable to HPV-16 and HPV-18 has also been demonstrated with the bivalent vaccine in a **Phase II study with a** 3-dose schedule.	Please see the reply to the previous comment
Section 2.2 Human Papillomavirus Vaccines	Page 6 Lines 174-175	Please amend the duration of protection for Gardasil 9, which as indicated in the SmPC, has been demonstrated up to 7.6 years. REF: SmPC of Gardasil 9 (EPAR) https://www.ema.europa.eu/en/medicines/human/EPAR/gardasil-9 "In Protocol 001 registry study, no cases of vaccine HPV types related high-grade CIN were observed through 7.6 years post dose 3 (median follow-up of 4.4years) in women (n=1,782) who were aged 16 to 26years at time of vaccination with Gardasil9."	Finally, **~~5.6~~ 7.6** years of protection from infection and cervical, vulvar and vaginal lesions with the nonavalent vaccine in a 3-dose schedule was shown [7].	Please see the reply to the previous comment
2.3 HPV vaccine introduction in Europe	Page 6 line 177	The sentence "by 2018, all EU/EEA countries had introduced HPV vaccination in their national immunization programs" is not correct as Poland and Romania do not have HPV vaccination in their national immunization program.	Proposal to rephrase: "by 2018, **29/31** EU/EEA countries had introduced HPV vaccination in their national immunization programs"	Given the changes in policy recently occurring in several Member States, we will just write "*most EU/EEA countries*"
2.3 HPV vaccine introduction in Europe	Page 6 Line 185-187	"Several countries (22%) have also expanded or will soon expand vaccination to boys of the same age in recent years, namely Austria, Croatia, the Czech Republic,	"Several countries **(~~22%~~ 13/31; 42%)** have also expanded or will soon expand vaccination to boys of the same	The information in this version of the guidance was updated only until December 2018. We added the suggested countries.

		Denmark [29], Germany [32], Italy, Liechtenstein, Norway [26–28], and the United Kingdom [30–31]. " In the listing of countries who expanded or will soon expand, Ireland, Finland, Belgium, Sweden are missing. References: Ireland: HIQA evaluation boys 4december 2018 (accessed 29 January 2019) https://www.hiqa.ie/sites/default/files/2018-12/HTA-for-HPV-Vaccination-boys.pdf Finland: official Recommendations for boys vaccination 23 January 2019 http://www.julkari.fi/bitstream/handle/ Belgium Wallonia reference: http://www.vaccination-info.be/component/content/category/10-vaccinations-recommandees Belgium Flanders reference: https://www.zorg-en-gezondheid.be/vaccinatie-tegen-hpv	age in recent years, namely Austria, **Belgium,** Croatia, the Czech Republic, Denmark [29], **Finland,** Germany [32], **Ireland,** Italy, Liechtenstein, Norway [26–28], **Sweden** and the United Kingdom [30–31]. "	
2.3 HPV introduction in Europe	Page 6 Line 188	"Other EU/EEA Member States are considering expanding the programme to include boys as well [33]. " Reference 33 refers to Sweden only so the sentence "other member states are considering expanding.." does not match. Sweden has recommended boys Portugal is also evaluating the expansion of HPV vaccination to boys. As reference, we propose the decree-law for the 2019 State Budget (article 212º). The complete reference is the following: Lei n.º71/2018, de 31 de dezembro. Orçamento de Estado para 2019. Diário da República, 1ª série – N.º 251	~~**Other EU/EEA Member States are considering expanding the programme to include boys as well [33].**~~ **Portugal is also evaluating the expansion of HPV vaccination to boys. (REF)** **REF: Lei n.º71/2018, de 31 de dezembro. Orçamento de Estado para 2019. Diário da República, 1ª série – N.º 251**	We have removed the reference about Sweden from this sentence, as it has now (September 2019) officially introduced gender-neutral vaccination in the immunization programme, and we added the reference regarding Portugal.
2.3 HPV vaccine introduction in Europe	Page 6 Line 190	"Finland, Hungary, Iceland, Malta, Norway, Portugal, Spain and the UK have reported national coverage above 70%. " Sweden is missing in the list of countries above 70% VCR During the academic years 2016/17 and 2017/18, HPV vaccination was offered especially for girls born 2004-2006. At the end of June 2018, 78.7 percent of girls born in 2004 vaccinated with one dose and 72.7 percent with two doses of HPV vaccine. Of girls born in 2005, 80.6 percent were vaccinated with one dose and 73.8 percent with two doses. Ref : https://www.folkhalsomyndigheten.se	Finland, Hungary, Iceland, Malta, Norway, Portugal, Spain, **Sweden** and the UK have reported national coverage above 70%.	We checked and this was indeed inaccurate. We have now updated the sentence as suggested.
2.3 HPV vaccine introduction in Europe	Page 6 Line 191-192	In other countries such as France or Germany, coverage has stabilised below 50%, This statement regarding France VCR is misleading as latest VCR published is 21% which is far below 50%. http://invs.santepubliquefrance.fr/Dossiers-thematiques/Maladies-infectieuses/Maladies-a-prevention-vaccinale/Couverture-vaccinale/Donnees/Papillomavirus-humains	In other countries such as ~~**France or**~~ Germany, coverage has stabilised below 50%, **whereas in France coverage is at 21%,**	Section 2 of the guidance just provides background information and does not aim to perform an accurate assessment of the HPV vaccination uptake in the EU/EEA Member States. Here we just wanted to mention that some country consistently cannot reach 50% coverage, we did not want to quantify how below 50% the HPV vaccination coverage is. We rephrased as follows: "*In other countries including France and Germany, coverage has been consistently below 50%, while other countries such as Denmark and Republic of Ireland have faced serious HPV vaccination crises resulting in dramatic drops..*"
Table 1	All table 1 (pages 7-9)	For each of the recommendations, there are currently no references for any of the sources of the data included in the table. As in the ECDC Scheduler, it would be very useful that the corresponding sources of data can be included in the table accordingly.	Table is missing inclusion of all source of data.	The information provided in the table was obtained by the information collected by the Catalan Institute of Oncology (ICO) which drafted the technical report on which he guidance is based on (see acknowledgments at the beginning of the document and Section 3.3 "Evidence appraisal and synthesis"). The references to ICO are already reported at the end of the table. This information was integrated with the data available on the ECDC vaccination scheduler (now added as a

				reference: https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByDisease?SelectedDiseaseId=38&SelectedCountryIdByDisease=-1) and through a survey performed in April-June 2019 among ECDC's national focal points for vaccine-preventable diseases in the EU/EEA Member States. Of course additional changes in policies may have occurred in the meanwhile.
Table 1	Page 7 Belgium	Regional HPV immunization programs for girls were implemented in Flanders in 2010 and in Wallonia in 2011. As of 2019, boys will also be vaccinated in both regions as part of the main vaccinated cohort *Geert T. The HPV vaccination programme in Flanders.* http://www.vaccineconfidence.org/ *Question Santé. Vaccination contre le papillomavirus humain (11-14 ans).* http://www.vaccination-info.be https://www.zorg-en-gezondheid.be/hpv-vaccinatie-ook-voor-jongens http://www.vaccination-info.be/vaccinations-recommandees/ VCR in Flanders is 90%, in Wallonia 36% (reference is the recent KCE report: https://kce.fgov.be/nl/)	Please change **VCR for Flanders to 90% and VCR for Wallonia to 36%** Please change **starting date of the program to 2010 for Flanders and 2011 for Wallonia**	An accurate assessment of national HPV vaccination coverage is not within the scope of the current guidance. Given the difficulty in putting together a comprehensive and coherent picture of the HPV vaccination coverage data across different Member States due to heterogeneities, lack of information, and uncertainties around the denominators in many settings, we decided to remove this information from Table 1. We have updated the table with the information about HPV vaccination introduction.
Table 1	Page 7 Bulgaria	VCR data is quite old, more recent exist In the reference below, it is stated (table 12) that VCR at 12y (after 2 doses) in 2017 was 14.3% NATIONAL CENTER FOR INFECTIOUS AND PARASITARY DISEASES, DEPARTMENT "EPIDEMIOLOGY". ANALYSIS: THE IMPLEMENTATION OF THE ACTIVITIES BY IMMUNOPROPHYLAKTICS IN BULGARIA IN 2017 [Translated from : НАЦИОНАЛЕН ЦЕНТЪР ПО ЗАРАЗНИ И ПАРАЗИТНИ БОЛЕСТИ ОТДЕЛ „ЕПИДЕМИОЛОГИЯ" АНАЛИЗНА ИЗПЪЛНЕНИЕТО НА ДЕЙНОСТИТЕ ПО ИМУНОПРОФИЛАКТИКАТА В БЪЛГАРИЯ ПРЕЗ 2017 ГОДИНА] . 2018. URL; https://www.ncipd.org/	Please correct **VCR for Bulgaria from 17.7% to 14.3%**	Please see above.
Table 1	Page 7 Czech Republic	65.8% at 13y (2015-2017) Ref: https://www.cervix.cz/res/file/aktuality/annex2-hpv-vaccination-coverage-in-czech-regions.pdf	Please put a **VCR for Czech Republic: 65.8%**	Please see above.
Table 1	Page 7 Denmark	VCR for Denmark reported in the document (25%) is below latest published VCR as per SST 2019 report. The Danish Health Authority published April 23rd 2019 a report on vaccine confidence in Denmark citing 73% for 1st dose for the 2005 cohort, and close to 90% for the ones before: https://www.sst.dk/da/nyheder/2019/~/media/02CBB557937E4218AE5F742CA642FA9B.ashx	Please update **VCR for Denmark to 73% (2018)**	Please see above.
Table 1	Page 7 Germany	VCR is not the latest VCR published 31.3% for 15y old girls (2015 data) published in 2018 https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2018/Ausgaben/01_18.pdf;jsessionid=796DC34D04CC74255776965439343 6E2.1_cid390?__blob=publicationFile slight correction of the text for Germany: Since November, 30th 2018 HPV vaccination for all 9–14-year-old girls and boys and catch-up 15-17 years for both girls and boys is in the catalog of mandatory benefits of statutory health insurance.	Please update **VCR to 31.3% (2015) and update text to reflect development in November 2018:** **Since November, 30th 2018 HPV vaccination for all 9–14-year-old girls and boys and catch-up 15-17 years for both girls and boys is in the catalog of mandatory benefits of statutory health insurance.**	Please see above concerning VCR. We have added the update to the text for Germany.
Table 1	Page 8	The VCR for IR is given as 51% and this VCR	Value for VCR should be as	Please see above.

	Ireland	is no longer current – the latest recoding of VCR is 74% REF: recent press declarations from HSE in the Irish Times: https://www.irishtimes.com/news/health/hpv-vaccine-uptake-among-girls-in-ireland-rises-to-70-1.3821784	follows: **70% for first dose (2019)**	
Table 1	Page 8 Italy	VCR is not up to date . 2016 data : 53.14%: 2d at 12Y girls (2016) Ref: Ministero della Salute. Vaccinazione contro il papilloma virus (HPV) - Coperture vaccinali. 16 february 2017 (last update 17 January 2018). URL : http://www.salute.gov.it/portale/documentazione/p6_2_8_3_1.jsp?lingua=italiano&id=27	Please update **VCR with 2016 data: 53.14%**	Please see above.
Table 1	Page 8 Liechtenstein	In the text there's a typo. It should be 11-16 years at the end of the first line VCR is 56% for 16y old girls (data from 2016) Ref: Durchimpfung von 2-, 8- und 16-jährigen Kindern in der Schweiz, 2014–2016. ÜBERTRAGBARE KRANKHEITEN BAG-Bulletin 24 vom 11. Juni 2018. https://www.infovac.ch/docs/public/durchimpfung-kindern-schweiz-2014-2016.pdf	Please **correct typo (16 years) and update VCR to 56%**	Please see above
Table 1	Page 8 Netherlands	VCR is not up to date. 2017 data: 45.5%: 2d at 14Y girls (2017) Ref: Vaccinatiegraad en jaarverslag Rijksvaccinatieprogramma Nederland 2017 (Immunisation coverage and annual report National Immunisation Programme in the Netherlands 2017). RIVM Rapport 2018-0008. https://www.rivm.nl/dsresource?objectid=30c7c6ab-197d-44a0-a901-f9719f916bf9&type=pdf&disposition=inline	**Please update VCR to 45.5% (2017)**	Please see above
Table 1	Page 8 Romania	Program is not funded in Romania so "11-14" should not be displayed, as incorrect and potentially misleading.	**Please remove 11-14y for Romania as program not funded.**	This field just refers to current age targets for vaccination in each country. We have now added in Table 1 a sentence for Romania specifying that the programme is not currently funded.
Table 1	Page 9 Slovakia	HPV vaccination is now fully funded for 2-valent HPV vaccine and partially for 4-valent HPV vaccine for boys and girls since January 2019. Ref: Proceeding related to decision about reimbursement of HPV vaccination (accessed 30 January 2019) http://kategorizacia.mzsr.sk/Lieky/Common/Details/14571 (reimbursement list effective 1 January 2019) http://www.health.gov.sk/Clanok?lieky201901	**Please update funding information to fully funded for 2 valent vaccine and partially funded for 4 valent vaccines for boys and girls**	We have updated the table accordingly.
Table 1	Page 9 Spain line	For HPV the National Spanish Recommendations include the following high risk groups (data from 2018): - WHIM Syndrome (primary immunodeficiency) - Women with solid organ transplantation or hematopoietic progenitors up to 26 years old-HIV Infection: • Child Population: Vaccination of children with a 3-dose regimen • Adult Population: Vaccination men and women up to 26 years old (3-dose guideline) - Men who have sex with men (MSM) up to 26 years (guideline 3 doses) - People in prostitution up to 26 years (guideline 3 doses)	**Vaccination programmes vary by region. The Inter-Territorial Council of the National Health System, the coordination body for the different Health services from the autonomous communities of Spain, approved general recommendation to initiate routine HPV vaccination in Spain in 2007, with a cohort of girls to choose between 11–14 years of age, but with a preference for age 14, and a deadline for implementation until 2010.**	We do not report on policies and recommendations for high-risk groups in the other EU/EEA Member States in Table 1, however, given the recent changes to the recommendations in Spain, we have added the suggested information. For the coverage data, please see above.

		- Women with excisional treatment of cervix REF: Official Spanish National Recommendation for High Risk Groups: link https://www.mscbs.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/VacGruposRiesgo/docs/VacGruposRiesgo_todas_las_edades.pdf VCR is not complete HPV COVERAGES (1º Doses & 2º doses) for girls (12 years old) - 85.6 % (1ª doses) & 77,8 % (2ª doses) Without Andalucia : 88.9 % (1ª doses) & 81.8 % (2ª doses) https://www.mscbs.gob.es/profesionales/ https://www.mscbs.gob.es/profesionales/ since 2019, HPV vaccination is proposed to women <18y not previously vaccinated https://www.mscbs.gob.es/profesionales//Vacunacion_poblacion_adulta.pdf https://www.mscbs.gob.es/profesionales/sCalendarioVacunacion_Todalavida.pdf HPV vaccination in adult and infant risk groups (2019) https://www.mscbs.gob.es/profesionales/saludPublica/prevPromocion/ https://www.mscbs.gob.es/profesionales/saludPublica/prevPromocion/ https://www.mscbs.gob.es/profesionales/saludPublica/CalendarioVacunacion_GRinfantil.pdf	**Afterwards, each autonomous community designed its own implementation programme starting in 3 of them in 2007, and the rest in 2008. In 2018, the following high risk groups have been added to the HPV immunization program:** **- WHIM Syndrome (primary immunodeficiency)** **- Women with solid organ transplantation or hematopoietic progenitors up to 26 years old-HIV Infection:** **● Child Population: Vaccination of children with a 3-dose regimen** **● Adult Population: Vaccination men and women up to 26 years old (3-dose guideline)** **- Men who have sex with men (MSM) up to 26 years (guideline 3 doses)** **- People in prostitution up to 26 years (guideline 3 doses)** **- Women with excisional treatment of cervix** **HPV COVERAGES (1º Doses & 2º doses) for girls (12 years old)** **- 85.6 % (1ª doses) & 77,8 % (2ª doses)** **- Without Andalucia : 88.9 % (1ª doses) & 81.8 % (2ª doses)**	
Table 1	Page 9 UK	VCR data not up to date. 2016/2017 data available: https://www.statista.com/statistics/960801/hpv-immunization-in-uk/ https://assets.publishing.service.gov.uk/government/uploads/_England_2016_to_2017.pdf https://www.isdscotland.org/Health-Topics/C https://www.statista.com/statistics/387799/hpv-immunisation-by-age-in-northern-ireland/	Please update VCR for Scotland, England, Wales, Northern Ireland: **England : 83.1% (2016-2017)** **Scotland : 86% (2016-2017)** **Wales : 85.8% (2016-2017)** **Northern Ireland : 89.6% (2016-2017)**	Please see above about coverage data.
2.5 Effectiveness and impact of HPV vaccines	Page 10 Line 240, 241	Missing data: "Additionally, a 28% reduction in prevalence of HPV types 31, 33 and 45 in same-aged girls and a cross-protective effect in women aged 20–39 years and men under 20 years of 241 age were observed." Results from two recent conference communications are missing. Proposed paragraph is given (in red) REF - Wagner M et al. Variable Cross-Protection Vaccine Effect From a Systematic Literature Review. Data presented at IPV 2018 in Australia. (abstract and content available upon request) Saah A et al. Literature review of neutralizing antibody responses to non-vaccine targeted high-risk HPV types induced by the 2vHPV & 4vHPV vaccines. Data presented at Eurogin 2018 in Lisbon, Portugal. (abstract and content available upon request)	**Cross-protective efficacy against persistent infection appears to be lower and less durable than against HPV types targeted by the vaccine. Real-world evidence for cross-protective effectiveness against infection is inconsistent and its long-term durability remains to be determined.[1] No long term reliable cross protection data is currently available with two doses of HPV vaccine in adolescents. The cross-protection antibody response varies widely and responses are most often detected for the non-vaccine HPV type 31 within 6 months of the 3rd dose; seropositivity rates for other non-vaccine HPV types**	An evaluation with conclusions about magnitude and duration of cross-protection of specific vaccines for specific HPV serotypes, and the corresponding public health implications, is not within the scope of this guidance (see Section 1.1). In this sentence, belonging to the background of the guidance, recent published evidence from Scottish and Dutch data is just mentioned, followed by another sentence acknowledging additional published evidence of cross-protection of the quadrivalent and bivalent HPV vaccines.

			(e.g., 33, 45, 52 and 58) are variable, and neutralizing antibody titers significantly lower than titers against vaccine-targeted types. Long-term data on durability of the cross-protection antibody response beyond two years is very limited and the published study with the largest population suggests limited durability of cross-neutralizing antibodies.[2] In the wake of all these uncertainties, direct protection with HPV types included in the vaccine are more much more reliable than cross protection.	
2.5 Effectiveness and impact of HPV vaccines	Page 10 Line 240, 241	There is missing data: Efficacy of types 31, 33, 45, 52 and 58 in the 9vHPV vaccine has shown to be very high and similar to efficacy seen for types 16 and 18 in the bivalent and quadrivalent vaccines. This is in marked contrast to the much lower levels of efficacy to types 31, 33, 45, 52 and 58 for both the bi- and quadrivalent HPV vaccines based on cross-protection. Taken together, cross-protection is a highly variable, poorly immunogenic phenomenon that is short-lived and does not offer protection that is similar to the 9 valent HPV vaccine. Proposed sentence included (in red) REF: 1. Luxembourg and Moeller, 9-Valent human papillomavirus vaccine: a review of the clinical development program. *Expert Review of Vaccines* 2017;16:11, 119-1139 (refer to Table 4: Efficacy against HPV 31/33/45/52/58-related 6-month persistent infection in clinical studies: cross-protection with quadrivalent and bivalent HPV vaccines vs. type-specific (direct) protection with 9-valent HPV vaccine.)	**In a recent publication (REF 1) looking at the efficacy against HPV 31/33/45/52/58-related 6-month persistent infection in clinical studies, and comparing cross-protection with 4vHPV and 2vHPV vaccines vs. type-specific (direct) protection with 9-valent HPV vaccine it was shown that efficacy of types 31, 33, 45, 52 and 58 in the 9vHPV vaccine has shown to be very high and similar to efficacy seen for types 16 and 18 in the 4vHPV and 2vHPV vaccines. This is in marked contrast to the much lower levels of efficacy to types 31, 33, 45, 52 and 58 for both the bi- and quadrivalent HPV vaccines based on cross-protection.**	The evidence concerning the 9-valent HPV vaccine has been reviewed and appraised in Section 4.1 of the guidance document. It is therefore not included in Section 2.5, which is part of the background. For cross-protection, please refer to the reply to the previous comment above. Please note that cross-protection is not part of the evidence-based assessment nor of the conclusions of this guidance (i.e. Section 4 and Executive Summary).
2.5 Effectiveness and impact of HPV vaccines	Page 10 Line 251, 252, 253	*"The population impact of the quadrivalent HPV vaccine on genital warts has been documented in Australia, Belgium, Canada, Denmark, Germany, Israel, Italy, New Zealand, Spain, Sweden and the US."* Data is also available from UK now to show reductions in Genital warts after implementation of HPV program. REF: Checchi M et al. Declines in anogenital warts diagnoses since the change in 2012 to use the quadrivalent HPV vaccine in England: data to end 2017. Sex Transm Infect 2019;0:1–6.	*"The population impact of the quadrivalent HPV vaccine on genital warts has been documented in Australia, Belgium, Canada, Denmark, Germany, Israel, Italy, New Zealand, Spain, Sweden, UK[1] and the US."*	We added this additional piece of evidence and we amended the sentence as suggested.
3.3.2 Methods for evidence synthesis on cost-effectiveness of adding 336 males to the current HPV vaccination protocols	Page 12 Lines 338-344	"Only those studies from the systematic review that evaluated the cost-effectiveness of universal vaccination were selected for evidence synthesis in this guidance. The systematic review was updated by ICO by adding relevant studies published until 31 December 2017 not included in the original report. The additional articles retrieved were the following: **Bresse 2014 [50], Blakely 2014 [51], Haeussler 2015 [52],**	Please include the 7 publications released in 2016 that have not been taken into consideration regarding the cost-effectiveness of universal vaccination: **Boiron 2016, Brisson 2016, Chesson 2016, Durham 2016, Laprise 2016, Sharma 2016, and Simms 2016.**	The articles included in the guidance were selected through a systematic literature review (see paragraph 3.3.2). Few additional relevant papers published until the end of 2017 were added in agreement with the contractor (Institut Catala' de Oncologia - ICO) and in line with the criteria of the systematic review. The assessment of the specific (and comparative) cost-effectiveness of the different HPV vaccines was not within the scope of this guidance.

		Jiménez 2015 [30], Damm 2017 [53], 341 Qendri 2017 [54], Largeron 2017 [55] and Mennini 2017 [56]. Twenty-one studies were finally identified for assessing the cost-effectiveness of universal vaccination, of which 12 were published in the last four years [50–6970] (Tables A36 – 39)." REFs: • Brisson M, Laprise JF, Chesson HW, et al. Health and Economic Impact of Switching from a 4-Valent to a 9-Valent HPV Vaccination Program in the United States. *J Natl Cancer Inst.* 2016;108(1). • Chesson HW, Markowitz LE, Hariri S, Ekwueme DU, Saraiya M. The impact and cost-effectiveness of nonavalent HPV vaccination in the United States: Estimates from a simplified transmission model. *Human vaccines & immunotherapeutics.* 2016;12(6):1363-1372. • Durham DP, Ndeffo-Mbah ML, Skrip LA, Jones FK, Bauch CT, Galvani AP. National- and state-level impact and cost-effectiveness of nonavalent HPV vaccination in the United States. *Proc Natl Acad Sci U S A.* 2016;113(18):5107-5112. • Boiron L, Joura E, Largeron N, Prager B, Uhart M. Estimating the cost-effectiveness profile of a universal vaccination programme with a nine-valent HPV vaccine in Austria. *BMC infectious diseases.* 2016;16:153. • Simms KT, Laprise JF, Smith MA, et al. Cost-effectiveness of the next generation nonavalent human papillomavirus vaccine in the context of primary human papillomavirus screening in Australia: a comparative modelling analysis. *Lancet Public Health.* 2016;1(2):e66-e75. • Laprise JF, Markowitz LE, Chesson HW, Drolet M, Brisson M. Comparison of 2-Dose and 3-Dose 9-Valent Human Papillomavirus Vaccine Schedules in the United States: A Cost-effectiveness Analysis. *The Journal of infectious diseases.* 2016;214(5):685-688. • Sharma M, Sy S, Kim JJ. The value of male human papillomavirus vaccination in preventing cervical cancer and genital warts in a low-resource setting. *BJOG* 2016;123:917–926. Of note, there are two additional references that have been omitted from the guidance as well (both references have been added to the A33 table in the annexes): - Insinga RP, Dasbach EJ, Elbasha EH, Puig A, Reynales-Shigematsu LM. Costeffectiveness of quadrivalent human papillomavirus (HPV) vaccination		

		in Mexico: a transmission dynamic model-based evaluation. Vaccine 2007;26 (1):128–39. - Kim JJ, Andres-Beck B, Goldie SJ. The value of including boys in an HPV vaccination programme: a cost-effectiveness analysis in a low-resource setting. Br J Cancer 2007;97(9):1322–8.		
Table 2	Page 14	Footnotes do not correspond to table (footnote symbols missing in table)	Clerical error	The errors were now corrected
Table 2	Page 14	Data for efficacy of 9vHPV vaccine for protection of VIN 2/3, Vain 2/3 or worse is now available. REF 1. Giuliano A et al. Nine-valent HPV vaccine efficacy against related diseases and definitive therapy: comparison with historic placebo population. 2019 Gynecologic Oncology	**In a recent comparison of 9vHPV recipient subjects against historic placebo group, Efficacy of 9vHPV vaccine for high-grade vulvar and vaginal disease caused by HPV 6, 11, 16, 18, 31, 33, 45,52,58 (n=4635) was 100% (95%CI: 85.7-100).** [1]	The evidence reported and graded refers to the period covered by the systematic reviews (see Section 3.2 and Paragraph 3.3.1). Given the systematic approach used, we cannot include more recent evidence in the formal assessment. We thus added the Paragraph 4.1.4 informing the reader that this more recent evidence from an indirect comparison is now available, but was not formally appraised in this guidance.
Table 3	Page 15	Footnotes do not correspond to table (footnote symbols missing in table)	Clerical error	The errors were now corrected
4.1.3 Efficacy of 9vHPV vaccine in males 4.2.1 Efficacy of quadrivalent and bivalent vaccines in males 16–26 years	Table 3 (page 15) & Table 4 (page 16)	There is no representation of the data for Japanese trial with QHPV in males. Please include the corresponding reference: Mikamo et al. Efficacy, safety, and immunogenicity of a quadrivalent HPV vaccine in Japanese men: A randomized, Phase 3, placebo-controlled study. Vaccine 2019; 37:1651-1658.	**Efficacy against persistent infection related to HPV6/11/16/18 was assessed in a local registration study in Japan (Protocol 122). This is the first clinical study to evaluate the efficacy of qHPV vaccine against intra-anal HPV infection in HM. The vaccine demonstrated 85.9% (95% confidence interval: 52.7, 97.3; p < 0.001) efficacy against HPV6/11/16/18-related persistent infection. Intra Anal PI Vaccine efficacy was 100% in HM & MSM populations [95% CI: 49.3, 100]** [1]	Please see above. The evidence reported and graded refers to the period covered by the systematic reviews (see Section 3.2 and Paragraph 3.3.1). Given the systematic approach used, we cannot include more recent evidence in the formal assessment. We thus added the paragraph 4.2.3 notifying the reader that this additional evidence is now available but was not formally assessed in this guidance.
4.2.2 Efficacy of quadrivalent and bivalent HPV vaccination in males 9–15 years old	Page 17 Line 536	Data shows immunogenicity only until month 96; whereas long-term follow up data for P020 with QHPV vaccine was presented at EUROGIN congress, in 2018. REF: Long term Follow up data 4vHPV P020 Study: 10 years of follow up. Data presented at EUROGIN 2018 in Lisbon, Portugal. (abstract and content available upon request)	After month 7, a gradual decline in GMTs was observed, although more than 84.8% of males remained seropositive for HPV types 6, 11 and 16 and 60.8% for HPV18 at month 96. **Through 10 years post-Dose 1, administration of 3 doses of qHPV vaccine in young men (age 16–26 years) provides:** • **Durable protection from HPV6/11-related genital warts, HPV6/11/16/18-related EGL, and HPV6/11/16/18-related AIN and anal cancer** • **Generally persistent antibody responses to vaccine HPV types** **The vaccine had an acceptable safety profile**[1]	Please see above. The evidence reported and assessed refers to the period covered by the systematic reviews (see Section 3.2 and Paragraph 3.3.1). Given the systematic approach used, we cannot include more recent evidence in the formal assessment. As this guidance is primarily looking into efficacy of HPV vaccination on HPV-related clinical outcomes, and in the absence of an immune correlate of protection, we chose to report only on the immunogenicity data collected and appraised during the time period covered by the original systematic reviews.
Section 4.2 Evidence on efficacy of	Page 17 Line 541	The guideline is missing data that has already been published in peer-reviewed articles; there are studies of benefits of HPV	Proposal to add new section **4.2.3 Efficacy of**	The articles included in the guidance were selected through a systematic review of the literature (see paragraph 3.3.2). Evidence from the MAM study (different

quadrivalent and bivalent vaccines for boys/men		vaccines in adults (women and men). A paragraph summarising this data is being proposed for insertion after line 541. REFERENCES: 1. Pinto LA et el. Quadrivalent Human Papillomavirus (HPV) Vaccine Induces HPV-Specific Antibodies in the Oral Cavity: Results From the Mid-Adult Male Vaccine Trial. The Journal of Infectious Diseases® 2016;214:1276–83 2. Giuliano AR, Isaacs-Soriano K, Torres BN, et al. Immunogenicity and safety of Gardasil among mid-adult aged men (27–45 years)-The MAM Study. Vaccine 2015; 33:5640–6.	**quadrivalent and bivalent HPV vaccination in males 27 - 45 years old** **One hundred and fifty men from Tampa, FL, US, and Cuernavaca, Mexico who met eligibility criteria (male, 27-45 years old, completed four years of follow-up in the HPV Infection in Men (HIM) natural history study) were enrolled. 100% of men seroconverted to each of the four HPV vaccine components, and the vaccine was generally well-tolerated. The immune response to HPV vaccination in men ages 27-45 was comparable to that observed in younger men, in whom clinical efficacy was demonstrated.[1,2,]**	publications) has been included and reviewed in this guidance. These two studies were captured by the literature search but only Giuliano's paper was eventually included in the final assessment (see supplemental document 2 in the annexes). We have now added a mention to evidence on immunogenicity of the quadrivalent vaccine in the age group 27-45 years old in paragraph 4.2.3.
4.2.2 Conclusions	Page 17 Line 542	*"The evidence of efficacy of 4vHPV vaccine and 2vHPV vaccine in men is currently limited."* We agree that the evidence of efficacy of 2vHPV vaccine in men is currently limited. We have efficacy data from two phase III clinical trials in males with 4vHPV vaccine. Based on the efficacy results in the global study, the EMA granted an indication for 4vHPV for the prevention of anal cancer, anal precancers and genital warts caused by the vaccine HPV types. REF: 1. Giuliano A et al. Efficacy of Quadrivalent HPV vaccine against HPV Infection. N Engl J Med 2011;364:401-11. and disease in males. 2. Palefsky et al. HPV Vaccine against Anal HPV Infection and Anal Intraepithelial Neoplasia. N Engl J Med 2011;365:1576-85. 3. Long term Follow up data 4vHPV P020 Study: 10 years of follow up. Data presented at EUROGIN 2018 in Lisbon, Portugal. (abstract and content available upon request) 4. Mikamo et al. Efficacy, safety, and immunogenicity of a quadrivalent HPV vaccine in Japanese men: A randomized, Phase 3, placebo-controlled study. Vaccine 2019; 37:1651-1658. 5. Ferris D et al. 4-Valent Human Papillomavirus (4vHPV) Vaccine in preadolescents and adolescents after 10 years. Pediatrics. 2017;140(6) 6. Long term Follow up data from 9vHPV P002 Study: 8 years of follow up. Data presented at Eurogin 2018 in Lisbon, Portugal.. (abstract and content available upon request)	**In a phase III clinical trial with QHPV vaccine in 16 to 26 years of age males, the Quadrivalent HPV vaccine was shown to prevents infection with HPV-6, 11, 16, and 18 and the development of related external genital lesions in males.[1,2] Long term data (up till 10 years) from this phase III clinical trial in males (age 16–26 years) with 4vHPV vaccine shows that the vaccine provides:** - **Durable protection from HPV6/11-related genital warts, HPV6/11/16/18-related EGL, and HPV6/11/16/18-related AIN and anal cancer** - **Generally persistent antibody responses to vaccine HPV types** - **The vaccine had an acceptable safety profile[3]** **Efficacy against persistent infection related to HPV6/11/16/18 was assessed in a local Phase III registration study in Japan (Protocol 122). This is the first clinical study to evaluate the efficacy of qHPV vaccine against intra-anal HPV infection in HM. The vaccine demonstrated 85.9% (95% confidence interval: 52.7, 97.3; p < 0.001) efficacy against HPV6/11/16/18-related persistent infection. Intra Anal PI Vaccine efficacy was 100% in HM & MSM populations [95% CI: 49.3,**	Some of the studies quoted (Giuliano 2011, Palefsky 2011, Ferris 2017) were already assessed and included in this guidance. The study that is not included from the proposed list (Mikamo et al) was published in 2019 (i.e. after the reviews that informed this guidance were performed). Paragraph 4.2.3 has now been added and includes relevant recent relevant evidence that was not appraised in this guidance because published outside of the time period covered by the systematic literature review. The publication by Mikamo et al has now been added in paragraph 4.2.3. Regarding the EUROGIN 2018 abstracts, please refer to the reply to a previous comment on additional studies reporting immunogenicity data published outside of the time period covered by this guidance's systematic reviews.

			100] [1] **QHPV vaccine has also been studied in pre adolescents and adolescents. A 3-dose regimen of the 4vHPV vaccine was immunogenic, clinically effective, and generally well tolerated in preadolescents and adolescents during 10 years of follow-up. In the longest follow-up study of the 4vHPV vaccine to date, the10-year follow-up data of the 4vHPV vaccine supported greater, widespread implementation of HPV vaccination in preadolescents and adolescents.[5]** **The 9vHPV vaccine has also been evaluated in adolescent males and females. Durable effectiveness for HPV 6/11/16/18/31/33/45/52/ 58-related persistent infection and disease through 8 years after initiation of vaccination was shown by the 9vHPV vaccine in their study in adolescents. The study also demonstrated that administration of a 3 dose regimen of the 9vHPV vaccine generates robust and persistent immune responses up to 7 years post immunization.[6]**	
4.3.1 Recent evidence not included in systematic review	Page 17 Line 553	*"There is no current direct evidence of clinical efficacy of HPV vaccines in people living with HIV."* The publication from Canada (McClymont et al 2019 – REF 98 in the ECDC gidance), which has been mentioned in the document, yet the conclusions state that there is no evidence of HPV vaccines efficacy in people living with HIV. REF: 1. Clifford G et al. Effect of HIV Infection on Human Papillomavirus Types Causing Invasive Cervical Cancer in Africa. J Acquir Immune Defic Syndr _ Volume 73, Number 3, November 1, 2016 2. McClymont E et al. The Efficacy of the Quadrivalent Human Papillomavirus Vaccine in Girls and Women Living With Human Immunodeficiency Virus. Clinical Infectious Diseases 2019;68(5):788–94	**HIV-positive ICC were more likely to be infected with multiple HPV types (27.8%) than HIV-negative ICC (15.9%). HPV16 was the most frequently detected HPV** **type in HIV-positive ICC (42.5%), followed by HPV18 (22.2%) and HPV45 (14.4%).[1]** **Women living with human immunodeficiency virus have a 47–53% prevalence of HPV infection, which is approximately double the prevalence among women without HIV (22–29%). In a trial done in Canada, among 212 women eligible for the PPE population, the incidence rate of newly acquired persistent qHPV was 1.0 per 100 person-years (95% CI, 0.3–2.6). All 4 cases of persistent qHPV were due to HPV18. No cases of qHPV-associated CIN2+ developed among women with normal baseline cytology.[2]**	The study from McClymont et al is mentioned as additional recent evidence that was not formally assessed in this guidance in paragraph 4.3.1. This is because it was published after the time period covered by the systematic review used (see previous replies to similar comments above, and paragraph 3.3.1 of the guidance document). A sentence was added at the end of paragraph 4.3.1 to explain this. The conclusions of the guidance are only based on the evidence that was formally assessed. However, given the lack of data, the presence of this additional recent evidence has been mentioned for information in paragraph "4.3.2 Conclusions" ("• *New upcoming evidence on the efficacy of HPV vaccination in people living with HIV is emerging from ongoing studies*") and in the executive summary at the beginning of the document.
4.4.6 Conclusions	Page 20 Line 716	*However, increasing vaccination coverage among girls may still be a more cost-effective primary objective.* This sentence could be misleading if taken	***~~However,~~ Therefore if the priority is to prevent only cervical cancer,*** *increasing vaccination coverage among girls*	We believe that the sentence is already put into context by the previous part reported here below (the whole bullet point follows the initial condition): • "*if the priority is the prevention of cervical disease*

		out of context. This statement needs to put into context in terms of which strategy will be used as comparator (more cost-effective versus which strategy) and the definition of primary objective is unclear. Because cost-effectiveness studies must be put in context, it is difficult to make a such general statement as according to the specific context, result may vary. Universal vaccination is a cost-effective strategy versus a girl only program and contribute to reduce further the HPV related diseases and cancers in females and males. If the sentence refers to the case when the primary objective is limited to only cervical cancer, then it should be stated to qualify the statement.	*may still be a more cost-effective primary objective.*	*in women, adding males to current female-only HPV vaccination programmes becomes increasingly cost-effective with:* - *persistently lower vaccination coverage among females; and* - *lower vaccine cost.* *However, increasing vaccination coverage among girls may still be a more cost-effective primary objective."* Please see the previous reply to the same comment to the Executive Summary above for a more detailed explanation.
5.1 Possible implications for current national HPV immunisation programmes	Page 21 Line 751	Include the following references : 1. Wolff 2018 Cost-effectiveness of sex-neutral HPV-vaccination in Sweden, accounting for herd-immunity and sexual behavior https://doi.org/10.1016/j.vaccine.2018.07.018 https://www.sciencedirect.com/science/article/pii/S0264410X18309484 2. Hintze & O'Neill. Strengthening the case for gender-neutral and the nonavalent HPV vaccine. Eur Arch Otorhinolaryngol. 2018 Apr;275(4):857-865. doi: 10.1007/s00405-018-4866-y. 3. Jesús De La Fuente, Juan José Hernandez Aguado, María San Martín,Paula Ramirez Boix, Sergio Cedillo & Noelia López (2019): Estimating the epidemiological impact and cost-effectiveness profile of a nonavalent HPV vaccine in Spain, Human Vaccines & Immunotherapeutics, DOI: 10.1080/21645515.2018.1560770	**Universal HPV-vaccination has been recently evaluated and considered that it would be good value for money and HPV-vaccinating boys would be cost-effective (Wolff 2018; Hintze 2018; De la Fuente 2019).**	The conclusions on cost-effectiveness of adding HPV vaccination in boys, based on the evidence reviewed, has already been made in Section 4 under Paragraph 4.4.6. Section 5 just adds ECDC's reflections on possible implications of the findings for public health of different options (e.g. vaccination strategies) concerning programmatic, organizational, social and ethical aspects.
Section 5.1 Possible implications for current national HPV immunisation programmes	Page 21 Line 756	Ongoing studies suggest that currently licensed vaccines administered to preadolescent girls provide at least 10 years of protection [7]. Note that protection has been demonstrated up to 14 years with qHPVv. REF: Nygard M et al.A 14 year Follow- up on the effectiveness, immunogenicity and safety of Gardasil in the Nordic population. (V501, P015). Data presented at Eurogin 2018 in Lisbon, Portugal. (abstract and content available upon request)	Ongoing studies suggest that currently licensed vaccines administered to preadolescent girls provide at least ~~10~~ **14** years of protection **[**~~7~~].	Few lines above it is stated that: "*Evidence on duration of protection was not assessed in the current guidance".* In this sentence "*Ongoing studies suggest that currently licensed vaccines administered to preadolescent girls provide at least 10 years of protection*" we refer to what is stated in the WHO position paper about duration of protection of HPV vaccines. The only point we are making is that duration of protection is in general an important factor for determining the overall impact of a vaccination. The comparison of duration of protection of different HPV vaccine products is not within the scope of this guidance (see section 1.1).
Section 5.1 Possible implications for current national HPV immunisation programmes	Page 21 Line 772	The reference used is 119 whereas the corresponding reference for that paragraph is ref 42 (Drolet et al 2015)	The introduction of the 9vHPV vaccine will likely have an impact on the new additional vaccine HPV types beyond what has been observed with cross-protection from other previously licensed HPV vaccines **[**~~119~~ **42**].	We amended the text accordingly.
Section 5.1.1 Organisational aspects	Page 21 Line 788 - 789	The guideline refers to a recommendation from Canada on mixed schedules, which is incorrect. This can mislead the reader into considering that the reference provided is a national recommendation. In fact this mixed schedule recommendation reference (which is off label) is only for Quebec, a province of Canada. As the paragraph in the guideline refers to country recommendations and this is a	The choice of which type of HPV vaccine to use should be linked to the evidence of its effectiveness and impact, which may vary between countries due to different epidemiological situations, HPV type distribution and HPV vaccination programme objectives (e.g. prevention of cervical cancer and HPV-related diseases). ~~**The Centre**~~	We now specified that the Centre d'expertise et de référence en santé publique is from Quebec (Canada). The paragraph does not refer to national recommendations only, nor it makes any. We thus do not think that the sentence and the reference need to be deleted as this is a unique vaccination strategy whose outcome (which we cannot anticipate) may provide relevant information for public health (whichever the results).

		province recommendation, we request the reference to be deleted. Otherwise, to be fairly compared, the regional recommendations in Europe would need to also be included in this paragraph. For reference, the most recent recommendation for HPV vaccines in Canada are published by the Canadian NACI (National Advisory Committee on Immunisation): https://www.canada.ca/en/public-health/services/publications/healthy-living/updated-recommendations-human-papillomavirus-immunization-schedule-immunocompromised-populations.html Furthermore, the reference used is 122 where in fact it is ref 123 – therefore, ref 123 in the guideline should also be deleted accordingly: ~~**123. Institut national de santé publique Québec. Advisory report on the Human Papillomavirus (HPV) Vaccination 1265 Schedule. Québec: INSPQ; 2018. Available from: http://www.inspq.qc.ca/en/publications/2458**~~	~~**d'expertise et de référence en santé publique in Canada recommended a mixed vaccination schedule based on some of these considerations in 2018 [122].**~~	
5.3 Possible implications of HPV vaccine hesitancy	Page 23 Line 866	Suggest further strengthening the statement on interventions that can strengthen the resiliency of vaccine ecosystems.	Identifying **proactive and** effective interventions and communications strategies, tailored to different target groups and adapted to the local context, are also critical aspects to consider **in order to drive towards resilient vaccine-coverage rates.**	We do not think strengthening the statement is needed here.
5.4 Remaining knowledge gaps	Page 24 Line 881	*"additional benefit of 9vHPV vaccination for women older than 25 years"* The HPV vaccines are approved for men & women above 26 years, and therefore both genders should be included in the statement.	"additional benefit of 9vHPV vaccination for women **and men** older than 25 years"	We amended the text as suggested.
Section 5.4 Remaining Knowledge gaps	Page 24 Line 891	The area of effectiveness of therapeutic vaccination could be misunderstood and it is worth specifying: 1) If the area is regarding effectiveness of therapeutic vaccines (not yet authorised in EU), then it should be specified. As these vaccines are not yet registered in EU, we consider this group of vaccines is not included in this guideline and therefore out of scope. 2) If the data refers to the effectiveness of current authorised vaccines for the prevention of recurrence of HPV diseases, the it should be stated as adjuvant effectiveness, since prophylactic vaccines have no therapeutic indication. There are many references on the effectiveness of prophylactic HPV vaccination, but they have been summarised in the recent Spanish review referenced below. REF: Martínez-Gómez *et al.* Multidisciplinary, evidence-based consensus guidelines for human papilloma virus (HPV) vaccination in high-risk populations, Spain 2016. Euro Surveill. 2019;24(7):pii=1700857. https://doi.org/10.2807/1560-7917.ES.2019.24.7.1700857	effectiveness of ~~**therapeutic**~~ **adjuvant** HPV vaccination **(using prophylactic HPV vaccines)**	We modified as suggested.
Section 5.4 Remaining knowledge gaps	Page 24 Line 895	• "factors affecting HPV vaccine uptake (including reasons for lower uptake in males in several settings). Recognising the important finding of the significant drop-offs in vaccination rates in	factors affecting HPV vaccine uptake (including reasons for lower uptake in males in several settings) **and sudden drops in the vaccination rate.**	We amended the text as proposed.

		some EU countries, it would be also welcomed to learn more about the factors leading to drop offs in vaccination rates.		
Table A33. Main characteristics of 21 studies that include cost-effectiveness analysis of universal vaccination	Page 52 table A33 Line 1684	Table A33 does not include the full set of evidence regarding the studies that evaluated the cost-effectiveness of universal vaccination and where within the dates of the systematic review carried out by the ECDC. We provide a listing of the references and complete the table accordingly.	Table A33 has been amended below and includes the description of additional 9 studies highlighted in yellow (cf table below)	The studies presented were selected through a systematic approach based on pre-specified criteria. We therefore prefer not to arbitrarily add studies at this stage.