Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Report on the results of the public consultation on the draft health technology assessment (HTA) of extending the national immunisation schedule to include HPV vaccination of boys

4 December 2018

About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent authority established to drive high quality and safe care for people using our health and social care services in Ireland. HIQA's role is to develop standards, inspect and review health and social care services and support informed decisions on how services are delivered.

HIQA aims to safeguard people and improve the safety and quality of health and social care services across its full range of functions.

HIQA's mandate to date extends across a specified range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children and Youth Affairs, HIQA has statutory responsibility for:

- **Setting Standards for Health and Social Services** – Developing person-centred standards, based on evidence and best international practice, for health and social care services in Ireland.
- **Regulation** – Registering and inspecting designated centres.
- **Monitoring Children's Services** – Monitoring and inspecting children's social services.
- **Monitoring Healthcare Safety and Quality** – Monitoring the safety and quality of health services and investigating as necessary serious concerns about the health and welfare of people who use these services.
- **Health Technology Assessment** – Providing advice that enables the best outcome for people who use our health service and the best use of resources by evaluating the clinical effectiveness and cost-effectiveness of drugs, equipment, diagnostic techniques and health promotion and protection activities.
- **Health Information** – Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information about the delivery and performance of Ireland's health and social care service.

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Conflicts of Interest

None

Table of Contents

1.1 Introduction

In June 2017, the Health Information and Quality Authority (HIQA) commenced work on a health technology assessment (HTA) in relation to proposed changes to the national human papillomavirus (HPV) immunisation programme. HIQA agreed to undertake the HTA following a formal request from the Department of Health. The aim of the HTA is to establish the clinical and cost-effectiveness of extending the current immunisation programme, which offers HPV vaccination to all girls in their first year of second level education (12 to 13 year olds), to a programme that also offers the vaccination to boys in their first year.

This report summarises the feedback received from the public consultation process and details HIQA's responses to the issues raised, including any changes that were made to the report as a result.

1.2 The consultation process

The aim of the consultation process was to capture feedback on any issues that may not have been adequately addressed in the report and to expand coverage of material requiring further clarification based on the feedback received.

The draft HTA was published on the HIQA website on 24 July 2018. The public consultation period closed on 7 September 2018. The public were provided with an opportunity to give feedback through a variety of means (postal, email or online) to ensure the consultation process was widely accessible. The consultation webpage contained a link to the draft report, a link to the website www.polldaddy.com for online submission of feedback, and a consultation feedback form that could be downloaded.

A press release was issued at the beginning of the consultation period and the findings of the draft HTA were widely reported in the media. Individuals and organisations with expertise in the area and those who are likely to be affected by the change in the immunisation schedule were targeted directly and requested to provide feedback. This included relevant departments within the HSE, Irish and international experts in vaccinology, clinician groups and patient advocacy groups.

All comments received were saved in an online database. Individuals or organisations who wished to submit comments confidentially were anonymised before being transferred to Microsoft Excel for analysis.

The template for making a submission was unstructured to allow people to be as focused or wide-ranging in their comments as they wished. Character or word limits were not applied to submissions. A copy of the submission template is provided in

Appendix 1A.

1.3 Analysis and discussion

A total of 242 separate submissions were received, 217 from individual respondents and 25 on behalf of organisations or institutions.

Qualitative research methods were used to identify the main themes raised in the submission feedback. This involved reviewing and coding each submission to identify common themes across contributors. A random sample of submissions was coded independently by two people to validate that the groupings of data were consistent with the raw data. Multi-dimensional coding was employed for themes where there was a high degree of conflicting opinion to reflect whether the sentiment being expressed was positive or negative in relation to a given issue. Individual themes were extracted from comments expressing multiple themes. Table 1 provides a list of the main themes identified in the responses to the public consultation, ordered by their overall frequency.

The results of this analysis were used to identify major themes, breaking these down into sub-themes where appropriate. Themes and sub-themes are responded to as a group in the analysis and discussion provided below. While all comments were considered in finalising the HTA and in the writing of this report, for reasons of anonymity and due to the large number of comments received expressing similar or overlapping themes, not all comments submitted are not shown. Examples of comments that were deemed representative of each overarching theme are included within the descriptive analysis. A number of comments were received for which no theme could be identified. General comments were grouped appropriately and are listed in Table 2. HIQA's responses to these comments are provided in Section 1.4.

Commonly emerging themes could generally be grouped according to those in favour or those against extending HPV vaccination to boys. Some comments received related to general queries regarding the implementation strategy or informed consent. Comments in favour of the extension of the current vaccination programme to include boys mainly related to the proven clinical effectiveness of the vaccine and issues of justice, equity and equality. The most common reason for opposing the introduction of a gender neutral vaccination programme was concerns regarding safety of the vaccine (with responses to specific safety concerns provided in Section 1.4.2).

Table 1 Themes identified

Theme	Coding Frequency*
Clinical effectiveness & burden of disease	78
Safety	49
Justice, equity and equality	43
Herd immunity and resilience of immunisation programme	30
Public health importance and health promotion	32
Resource implications and organisational issues	20
Social issues	18
Vulnerable groups	17
Informed consent	16
International experience	15
Cost-effectiveness	13
Process for dealing with adverse events	12
Timing of vaccination/catch-up programme	9
Propagation of false information and social media	9
Lack of Irish data	3
Advertising	3
Errors in report	2

***Figures refer to the number of times theme was identified, not number of submissions**

Table 2, below, provides details of submissions where no theme could be identified. For example, the following submission:

"yes to HPV vaccination of boys"

does not fall into any specific theme, however a positive sentiment was expressed.

Table 2 General submissions

Comment	Coding frequency*
No theme identified but positive sentiment expressed	59
Spoiled comments	6
General query	3
Anecdotal evidence	3
Misunderstanding of instructions	3
No theme identified but negative sentiment expressed	2
Comment regarding process of public consultation	2
Comment beyond the scope of the HTA (e.g. immigration policy, social welfare payments, lifestyles choices)	2

***Figures refer to the number of times general comment was identified, not number of submissions**

Section 1.4, below, provides a summary and discussion of each theme identified in the analysis and Section 1.5 describes any changes made to the HTA report as a result of the issues raised.

1.4 Emergent themes

1.4.1 Clinical effectiveness

The most commonly identified theme related to the clinical effectiveness of HPV vaccines in preventing HPV-related disease. The majority of comments received reflected people's understanding that extending the HPV immunisation programme has direct benefits to males and indirect benefits to females. A total of 78 submissions related to the clinical effectiveness of the HPV vaccine in preventing disease. Thirteen submissions related specifically to the high burden of HPV-related disease in society. Chapters 3 (Epidemiology and burden of disease), 4 (Efficacy) and 5 (Population-level effectiveness) are the chapters of the assessment most relevant to these comments.

The following submission covered many elements relating to the theme of effectiveness:

> *"Female-only vaccination has been shown to be highly effective in reducing HPV infection in both males and females, with a consequent reduction in genital warts in both sexes, and pre-cancerous lesions of the cervix. Offering boys the HPV vaccine would strengthen the community immunity already provided by vaccination of girls, helping to protect anyone (male or female) who is not vaccinated or under-vaccinated. It would help directly protect boys against HPV types that are linked to 90% of anal cancers, 40% of penile cancers, and 90% of genital warts."*

Many responses were received from parents of boys, such as the following:

> *"I hope the HSE will take note and provide the HPV Vaccines for boys. I want my son to be protected and feel we should always adapt a science-led approach. This vaccine is proven to be beneficial in preventing illnesses and protecting against cancers."*

Some related specifically to anogenital warts:

> *"Help sustain the reduction in incidence of anogenital warts that has been seen since the programme was introduced in 2010. The similar trend in both genders reflects the likely herd effect for young men. However such a decrease will not be sustained with the recent decline in vaccine uptake rates*

among girls. This reduction in the rate of ano-genital warts reduces the burden of referrals for treatment of these conditions in primary care and in sexual health clinics."

In the following sections, comments received that refute aspects of the clinical effectiveness of HPV vaccines are addressed, and grouped by sub-themes.

1.4.1.1 Lack of evidence or not clinically indicated

Some comments referred to a perceived lack of evidence of clinical indication to vaccinate boys. Examples of comments include:

"There are no clinical trials in boys aged 12 years old which show effectiveness for any disease outcome"

"*No independent study has proven that the hpv vaccine works, as well as this boys don't have a cervix so how does this vaccine benefit them?"*

"The vaccine is not indicated, nor are there any clinical trials, for penile, oral/throat or head and neck cancers"

"Claiming that this vaccine will prevent head and neck cancers is completely off label marketing. There is little or no clinical trial data to back up this claim."

"The vaccine is not indicated for the prevention (page 15) of: vulvar, vaginal, penile, head, neck or throat cancers."

A summary of the key characteristics of these vaccines including the indications for which they are currently licensed is included in Chapter 2, Table 2.1 of the assessment, and included in Appendix 1B of this document for further clarity. Briefly, HPV vaccines (4-valent and 9-valent) are indicated in the prevention of the following conditions causally related to certain oncogenic HPV types:

- Premalignant anogenital (cervical, vulval, vaginal and anal) lesions
- Cervical cancer
- Anal cancer
- Prevention of anogenital warts (condyloma acuminata) causally related to specific HPV types.

Therefore, HPV vaccines are licensed to prevent cervical cancer (in women), anal cancer (in men and women) and anogenital warts (in men and women). HPV

vaccines are also licensed for the prevention of premalignant anogenital lesions (cervical, vulval, vaginal and anal). These are the necessary precursors to HPV-related cancers in these locations. Prevention of these premalignant states is an accepted proxy for cancer prevention.

In the assessment, it is clearly stated that HPV vaccines are not yet licensed for the prevention of penile or oropharyngeal cancer due to a current lack of efficacy data. Due to the fact that efficacy of the vaccine to prevent these lesions has not yet been demonstrated, the assessment of cost-effectiveness of the HPV vaccine did not include oropharyngeal or penile cancer in the primary (base case) analysis.

Nonetheless, HPV is highly implicated in penile and oropharyngeal cancer cases. A rapidly growing number of oropharyngeal cancers are directly attributable to persistent HPV infection in Ireland, which occurs three to four times more commonly in men than women. As of yet, a precursor lesion for oropharyngeal cancer has not been identified, limiting the conclusions that can be drawn from trial data. Section 3.8 of the report outlines the evidence for an aetiological link between HPV infection and a subset of head and neck cancers (HNCs) at the oropharyngeal site. The evidence is summarised in the key points of Chapter 3:

- Head and neck squamous cell carcinomas most commonly occur in the epithelial lining of the oral cavity. Tobacco use and alcohol consumption are well-known behavioural risk factors; however, strong evidence has also accumulated of an aetiological link between HPV infection and a subset of head and neck squamous cell carcinomas. While HPV is known to be associated with oropharyngeal cancer, it is currently unclear whether HPV has a role in other head and neck cancer sub-sites.

- A recent clinical audit on oropharyngeal cases diagnosed between 2014 and 2018 in Ireland found a 37% increase in cases compared to the 2009-2013 NCRI data. Overall, 77.5% of cases were in men and approximately half are thought to be HPV-driven.

The evidence that underpins the clinical efficacy and immunogenicity of the 4-valent and 9-valent HPV vaccines are presented in Chapter 4. The 4-valent HPV vaccine was shown to be effective at reducing events associated with persistent HPV 6, 11, 16 or 18-related infections (67% reduction), external genital lesions (75-91% reduction) and anogenital warts (79% reduction) in HPV-naïve men.

The effect of HPV vaccines in preventing penile cancer and precursor lesions has also been investigated in clinical efficacy trials. Despite a sizeable reduction in any-HPV type-related penile precancerous lesion (PIN 1 [50%], PIN 2+ [80%]) in a HPV-naïve male population (Chapter 4), there is considerable uncertainty around the effect size of the 4-valent HPV vaccine on PIN lesions and penile, perineal and perianal cancer in men, due to statistical insignificance around reported estimates and very low event rates among study participants.

The following key point from Chapter 4 summarises this information:

- The 4-valent HPV vaccine is also shown to be effective at reducing events associated with persistent HPV 6, 11, 16 or 18-related infections (67%), external genital lesions (75-91%) and anogenital warts (79%) in HPV-naïve men. Despite a sizeable reduction in any-HPV type-related PIN 1 (50%) and PIN 2+ lesions (80%) in a HPV-naïve male population, there is considerable uncertainty around the effect size of the 4-valent HPV vaccine on PIN lesions and penile, perineal and perianal cancer in men, due to statistical insignificance around reported estimates and very low event rates among study participants.

Consistent with the recommendations of the WHO's Strategic Advisory Group of Experts (SAGE) on Immunization, efficacy has been concluded through indirect evidence.[(1)] Clinical efficacy studies of HPV vaccines have not been conducted in the target age for the schools immunisation programme (12 and 13 year old boys and girls). This is due to the ethical and legal constraints in conducting such trials in pre and early adolescents. In order to demonstrate evidence of clinical efficacy in this population, the evidence of efficacy in adults was first established. Subsequently, 'bridging' or 'immunobridging' studies were performed to establish efficacy in other age groups. HPV vaccines have been approved by regulatory agencies (including the European Medicines Agency [EMA] and the Food and Drugs Administration [FDA]) based on bridging studies that generate immunogenicity data to support the extrapolation of data on efficacy from adult cohorts to adolescent cohorts.

1.4.1.2 Duration

A number of comments referred to the duration of the HPV vaccine's effects. Examples include:

> *"Only lasts up to 36 months. So if it wears off so quickly, there is little point in vaccinating so young. It will not prevent any of the forms of cancer proposed*

as they occur in late adulthood, not in adolescent boys"

"I believe states the vaccines efficacy in trials only lasted in males 16 to 26 for 36 months. I find that not good enough that it will be rolled out to 12/13 year olds"

Randomised controlled trials (RCTs) have shown no signs of vaccine efficacy waning after nine years of follow up (as in, no waning throughout the duration of the trial),[(2)] as indicated in Chapter 4 (Section 4.3.1).

There is evidence that the 4-valent HPV vaccine produces durable HPV-antibody responses at a minimum for as long as the trials lasted (that is to say, up to 108 months in adult females and up to 36 months in adult males). The robust and durable nature of the evidence has contributed to an assumption of lifelong duration of efficacy of the 4-valent HPV vaccine. In any case, an analysis was conducted on the potential impact of waning efficacy after 10 years (Chapter 8). This suggested that reduced efficacy after 10 years has a limited impact on the cost-effectiveness of the intervention.

Evidence from Chapter 4 demonstrated that the 4-valent HPV vaccine appears to be effective for at least 108 months for all immunogenicity outcomes in 16 to 23 year old females. Seropositivity rates for HPV 6, 11 and 16 remained at 94.4%, 95.5% and 99.1% by the end of year nine; however, the rates for HPV 18 did taper to 60%. The evidence demonstrated that the 4-valent HPV vaccine appears to be effective for up to 36 months for all immunogenicity outcomes in 16 to 26 year old males. The following key point emphasises the durable nature of seropositivity:

- The immunogenicity data from all bridging studies demonstrates that GMT responses to HPV vaccines persist over time with durable seropositivity rates.

GMT = Geometric Mean Titre

1.4.1.3 Age and sexual transmission

Some comments referred to the age of vaccine recipients. An example is as follows:

"This is an STD vaccine which should be taken by choice by individuals over 18 not children."

"A Chara, I think it is of utmost importance to include the fact that HPV can easily be passed from hand to genital tract and from mouth to genital tract and not solely through intercourse as the term STI can be misleading in this

instance."

HPV vaccines are vaccines that prevent cancer. Up to 90% of people are affected by HPV at some point in their lives, and cases of HPV infection prior to sexual debut have been documented. The HPV vaccine is most effective prior to exposure to the HPV virus and the immune response is most vigorous in the early adolescent years. Vaccination does not alter the course of HPV infection, therefore vaccination should precede exposure.

Importantly, adolescents demonstrate superior immune responses to adults (and only require two doses of the vaccine if aged less than 15 years). This is emphasised in the following key point of Chapter 4:

- The key immunogenicity data for HPV vaccines at seven months demonstrates that adolescents display superior immune responses to adults.

1.4.1.4 Alternatives to vaccination

One comment related to possible alternatives to vaccination:

> *"Informed consent is also lacking in that the HSE material fail to give an alternative to vaccination which is avoiding risk factors like smoking, LT use of the oral contraceptive pill, multi parity, unsafe sex, lack of pap smears and poor diet"*

It is widely accepted that there are no effective alternatives to HPV vaccination to prevent HPV infection and its sequelae. In the case of cervical cancer, the only condition that must be met is persistent infection with HPV; co-factors for disease progression such as smoking may or may not be present. While safe sex is always advocated, barrier protection (such as condoms) does not always prevent HPV transmission as the virus is spread through contact with infected genital skin, mucous membranes or bodily fluids and can be transmitted through intimate contact and sexual intercourse, including oral sex. There is no treatment available to eradicate HPV infection; treatment relates to treating the disease sequelae (such as cancer or anogenital warts).

Another submission referred to immunising the men who have sex with men (MSM) group instead of providing the vaccine to all boys:

> *"MSM men are most at risk for male-associated cancers and the HIQA should recommend a policy of targeting this community ahead of all boys in this*

country which would be more cost effective."

It is indeed true that MSM are at higher risk of HPV-associated disease; however, heterosexual men are still at risk (see Chapter 3: Epidemiology). The HPV vaccine is most effective prior to the onset of sexual activity and the vaccine invokes the most vigorous immune response in young adolescents. Targeting MSM specifically at this age is not possible.

HPV vaccination is currently provided to MSM at sexual health clinics in Ireland. While an important strategy, it is suboptimal, as highlighted by the following submission:

> *"Vaccination in sexual health clinics is a sub-optimal approach. The NCCP advocated for the vaccination of MSM who attend sexual health clinics as a risk reduction measure pending the introduction of a gender neutral vaccination policy. Vaccination at sexual health clinics has been introduced and is welcomed. However, it is a suboptimal approach as most men will have been infected before they ever attend a sexual health clinic. Many at-risk men never attend a clinic at all or do not disclose their sexual identity to a healthcare professional. In addition vaccinating MSM does nothing to protect men who have sex with a woman outside the herd e.g. unvaccinated women in a country where vaccination is offered or women who live in countries where vaccination is not offered."*

1.4.2 Safety

Many comments were received relating to the safety of HPV vaccines, with a number of submissions displaying similarities in content.

The overwhelming conclusion of the HTA was that HPV vaccines are both effective and safe. In the remainder of this section, specific safety concerns received as part of the feedback are addressed. The evidence available from surveillance studies, post-license safety data and trial data (including over 70,000 trial participants and over 20 million individuals in cohort studies in HIQA's systematic review of systematic reviews) did not raise serious safety concerns in relation to HPV vaccines.

1.4.2.1 Included studies

Some submissions referred directly to the studies that were included in Chapter 5: Safety of the assessment. For example,

> *"HIQA's safety profile of the vaccine only looked at two studies. One was the recent review by Cochrane Collaboration and the second was the 2017*

Adelaide HTA review."

HIQA's approach to the assessment of HPV vaccine safety consisted of:

- a systematic review of systematic reviews (also known as an 'overview of reviews'),
- a review of Health Products Regulatory Authority (HPRA) data of adverse event reports in Ireland
- a review of the key assessments conducted by the World Health Organization's (WHO's) Global Advisory Committee on Vaccine Safety (GACVS), the European Medicines Agency (EMA), country-level regulatory agencies and expert narrative reviews not included in the systematic review of systematic reviews.

The systematic review of systematic reviews included 10 reviews that met the inclusion criteria. These reviews evaluated HPV vaccines in over 70,000 trial participants and surveillance of many millions of individuals in cohort studies. Maximum follow up was 10 years.

Due to the abundance of data, analysis was limited to the most recent systematic reviews that were also of highest methodological quality. Most relevant to this assessment was a Cochrane Review on the safety and efficacy of HPV vaccines (published in May 2018) and a health technology assessment, commissioned by WHO, on serious adverse events associated with HPV vaccines (published in February 2017). Of note, significant overlap existed between reviews. While the safety assessment concentrated on two reviews, all 10 were assessed for relevance and scientific rigour and conclusions were consistent across all reviews: no safety concerns were raised in relation to HPV vaccines.

1.4.2.2 Concerns relating to specific medical conditions

Certain submissions listed specific medical conditions, such as:

"*HPV vaccine has been linked to serious adverse events including autoimmune disorders, MS, ALS, Guillan-Barre Syndrome, paralysis, convulsions, chronic fatigue, anaphylaxis, pulmonary embolisms and death. Also menstrual problems and ovarian failure in women."*

There is no evidence to suggest HPV vaccines are causally associated with any of the conditions and syndromes listed.

HIQA's systematic review (Chapter 6, Section 6.2) reviewed 'new-onset chronic

disease' and 'medically significant conditions' in RCTs and did not find any associations. Furthermore, observational studies that included six large, good-quality cohort studies and five self-controlled case series were identified and no increased rates of the following conditions were found in vaccinated versus unvaccinated individuals: autoimmune disorders, venous thromboembolism, multiple sclerosis (MS) and other demyelinating conditions. Individual cohort studies also investigated a range of other conditions, such as Guillain–Barré syndrome, stroke, appendicitis, seizure, syncope and migraine. No observational studies concluded that a verifiable safety concern exists. A rate of 1.7 cases of anaphylaxis per one million doses was noted.

The Global Advisory Committee on Vaccine Safety (GACVS), an independent expert clinical and scientific advisory body, provides the WHO with 'scientifically rigorous advice on vaccine safety issues of potential global importance'. The GACVS first reviewed the safety of HPV vaccines in 2007[(3)] and subsequently in 2008,[(4)] 2009,[(5)] 2013,[(6)] 2014,[(7)] 2015[(8)] and most recently in June 2017.[(9)] In its most recent update, the GACVS reviewed the findings of a comprehensive literature review of further safety data that was generated from the UK, the US and Denmark. Among the new data were studies looking at Guillain-Barré syndrome (GBS), complex regional pain syndrome (CRPS), postural orthostatic tachycardia syndrome (POTS), premature ovarian insufficiency, primary ovarian failure and venous thromboembolism. With large population-level data from several countries, the GACVS has maintained its assertion that there is insufficient evidence for a causal association between HPV vaccine and these conditions. The following key points from Chapter 6 summarises this information:

- This review concurs with the assessments undertaken by WHO's Global Advisory Committee on Vaccine Safety (GACVS) and the European Medicines Agency (EMA) regarding the safety of the HPV vaccine. Both concluded that the HPV vaccine is safe. In its most recent update, the GACVS maintained its assertion that HPV vaccines are not causally associated with Guillain-Barré syndrome, complex regional pain syndrome, postural orthostatic tachycardia syndrome, premature ovarian insufficiency, primary ovarian failure or venous thromboembolism.
- The Adelaide HTA also investigated a range of other important outcomes and included observational data (six high-quality cohort studies and five self-controlled case series) related to safety endpoints. The HPV vaccine was not associated with an increased risk for the following conditions: 'new onset chronic disease', 'medically significant conditions', venous thromboembolism, multiple sclerosis, other demyelinating conditions or autoimmune diseases. Anaphylaxis occurred at a rate of 1.7 per 1,000,000 doses.

1.4.2.3 Concerns relating to adjuvant components of HPV vaccines

A number of submissions related to the use of adjuvants in the placebo arms of clinical trials.

Examples include:

> *"I have serious concerns that the trials were not carried out against a true saline placebo. Across the clinical studies a huge number of the control group had alumimium adjuvant AAHS control = 13,023 subjects where as the saline placebo = 594. How can this give an accurate reflection of the true adverse effects? Seriously flawed"*
>
> *"HIQA failed to see that both lacked integrity as they did not note that the "placebo" used in all studies contained the same aluminium adjuvant plus other excipients found in the vaccine. It was a very similar product and could not be deemed to be inert for the purposes of a clinical trial testing safety. Because of this, both reviews concluded that adverse outcomes were similar in both groups, and this means that the vaccine was safe. This conclusion is not proof of safety."*
>
> *"HIQA failed to comment on the dangers of injecting Aluminium into humans or the dangers of injecting more than one vaccine at a time."*

Safety data relating to adjuvants used in HPV vaccines is detailed in Chapter 6, Section 6.4.5 of the report.

Aluminium is the most abundant metal on earth and is present in food and drinking water. A vaccine adjuvant is a component that increases specific immune responses to an antigen.[(10)] Aluminium adjuvants have been used in vaccines for decades and their safety in this context is well established. The incorporation of adjuvants in vaccines is aimed at enhancing, accelerating and prolonging the immune response to vaccine antigens.[(10)] Aluminium hydroxide and aluminium or calcium phosphate have been used routinely in human vaccines.

In 2012, the World Health Organization's Global Advisory Committee on Vaccine Safety (GACVS) reviewed the US Food and Drug Administration's (FDA's) risk assessment model of aluminium in vaccines.[(11)] The FDA calculations incorporate the most recently published aluminium risk assessments by adjusting for gastrointestinal absorption and uptake from the site of injection. The FDA analysis indicates that the body burden of aluminium following injections of aluminium-containing vaccines

never exceeds safe US regulatory thresholds based on orally ingested aluminium even for low birth-weight infants. The GACVS concluded that this comprehensive risk assessment further supports the clinical trial and epidemiological evidence of the safety of aluminium in vaccines.

The reason aluminium is used as placebo in vaccine trials is that it is desirable that the placebo mimics the formulated product as closely as possible without a therapeutic effect. Aluminium salts therefore serve as a good comparator as aluminium is contained in the active vaccine. When the placebo also contains aluminium, the additional component in the active arm of trials are the HPV L1 protein antigens (L1 proteins are the form of virus-like particles produced in yeast cells by recombinant DNA technology).

The majority of people who received a placebo in HPV vaccine trials received the aluminium adjuvant. However, one large trial, conducted in boys and girls aged nine to 15 years, used a saline placebo.[(12)] The 'saline' solution consisted of water, 9.56 mg sodium chloride, 0.78 mg L-histidine and 50 micrograms polysorbate-80. In this study, 1,184 were randomised to receive the vaccine and 596 randomised to receive the saline solution placebo. The proportion of participants completing the study was similar in each group. The proportion of systemic events was comparable in each group. Transient generalised symptoms, such as fever, were generally mild to moderate in intensity. There were more injection-site reactions in the Gardasil group compared with the placebo group. The subjects were followed up for new medical conditions. A slightly lower proportion of vaccine recipients reported a new medical condition compared with the saline placebo recipients (29% of vaccine recipients versus 31% of placebo recipients).

In summary, adjuvants (especially aluminium) are components that increase specific immune responses to antigens and have been used safely for decades in vaccines. If the purpose of the placebo in trials is to mimic the vaccine as closely as possible without delivering a therapeutic effect, the use of adjuvants in the placebo arm is justified. Of note is that one large efficacy and safety trial did in fact use a true saline placebo on a population of pre-adolescent and adolescent boys and girls.

An example of another comment relating to vaccine adjuvants was:

"They are filled with toxic chemicals like aluminium and mercury."

There is no mercury in HPV vaccines. Aluminium adjuvants are discussed above. Cervarix® contains 500 µg of aluminum hydroxide and 50 µg of 3-O-desacyl-4-monophosphoryl lipid A (AS04). Gardasil® contains 225 µg of amorphous aluminum hydroxyphosphate sulfate (AAHS) adjuvant and Gardasil®9 contains 500 µg of

AAHS. This information is included in Table 2.1 of Chapter 2 (also provided in Appendix 1B of this docuemtn).

Another comment received was as follows:

> *"HIQA failed to see that both lacked integrity as they did not note that the "placebo" used in all studies contained the same aluminium adjuvant plus other excipients found in the vaccine."*

One large trial, conducted on 1,781 sexually naïve children (boys and girls), used a saline placebo.[(12)] This study was included in HIQA's systematic review (contained in the 2017 Adelaide HTA). This trial was excluded in the Cochrane Review due to the fact that aggregate data was presented without reporting on males and females separately (this was an exclusion criteria in their review).

Both reviews, in fact, acknowledged the fact that the 'placebo', in most circumstances, included an aluminium adjuvant. Neither study chose to include or exclude trials based upon the placebo used. The use of a non-saline adjuvant in large vaccine trials is discussed in more detail below (Section 1.4.2.3). Adjuvants are specifically addressed in Chapter 6, Section 6.4.5 'Manufacturer evaluations and the role of adjuvants' of the report.

A final submission relating to adjuvants and contaminants is the following:

> *"The Gardasil contains "non biocompatible and bio-persistent foreign bodies which are not declared by the Producers, against which the body reacts in any case" as highlighted in the research entitled "New Quality-Control Investigations on Vaccines: Micro- and Nanocontamination" by Antonietta M Gatti and Stefano Montanari. These elements identified are: Aluminium (AlPO4 . 2H2O) and the following: CaAlSi, AlSi, SiMgFe, Al,Fe, AlCuFe, FeSiAl, BiBaS, Ti, TiAlSi. The presence of nanosized, inorganic, foreign bodies is alarming and all are to be declared as part of the ingredients or should not be included in any safe and effective vaccine"*

This study[(13)] was heavily criticised by the European Medicines Agency (EMA), the competent authority that regulates medicines across the EU. The EMA has stated that the study study 'does not provide evidence that the quality of these vaccines is compromised'.[(14)] Furthermore, the EMA stated that 'traces of many elements are present everywhere including air, water and food and are constantly being handled by the body. Thus, the presence of trace amounts of inorganic particles in medicines is not unusual and the manufacturing process for vaccines is designed to ensure that any such traces are kept well below safe limits.'

To further allay fears, the EMA pointed to the fact that vaccine manufacturing in the European Union follows 'strict' quality control processes, including batch testing by the network of EU Official Medicines Control Laboratories before vaccines are released by national authorities.[14]

1.4.2.4 Co-administration of vaccines

Some comments received related to the co-administration of HPV vaccines with other vaccines delivered by the schools immunisation programme. Examples include:

> "*The HPV vaccine will be given with other vaccines. HIQA did not examine safety of giving boys this vaccine concomitantly with other vaccines, for which there is little data to support safety for the two other vaccines used by the HSE – Boostrix and Menjugate"*

The co-administration of vaccines is reviewed in Chapter 9, Section 9.3 of the assessment. Currently, the HPV vaccine is co-administered with the tetanus, low dose diphtheria and low dose acellular pertussis (Tdap) booster, and with the meningococcal C (MenC) booster, to girls as part of the schools immunisation programme. Similar to HPV vaccines, the low-dose boosters are also associated with frequent minor injection-site adverse events.[15]

A systematic review that assessed the safety and immunogenicity of co-administered vaccines was discussed in Chapter 4: Efficacy (Section 4.4) and Chapter 9: Organisational issues (Section 9.3). [16] Co-administration of the HPV vaccine with other vaccines is safe, including meningococcal conjugate, hepatitis A, hepatitis B, combined hepatitis A and B, tetanus, diphtheria, acellular pertussis, and inactivated poliovirus vaccines. Safety of vaccine co-administration will be added to Chapter 6: Safety in the final report for additional emphasis.

1.4.2.5 Potential to cause carcinogenicity, genotoxicity or impairment of male fertility

Two comments related to carcinogenicity, genotoxicity and impaired fertility.

> *"As per the FDA's own records, the Gardasil vaccine has not been evaluated for the potential to cause carcinogenicity, genotoxicity or impairment of male fertility (see section 13 on https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm426457.pdf). In other terms, this vaccine has not been tested for the potential to cause cancer (apart from the HPV strands it seeks to protect against), how toxic it is to the human genome or how it affect male fertility. This is unprecedented and presents an unacceptably high risk to the targeted*

population. By law, this information, as well as the full Gardasil leaflet's contents is to be conveyed to the parents in order to assist them in granting informed consent."

"Pre-clinical, clinical and post-licensure safety studies of HPV4 were unable to evaluate ovarian safety."

These comments refer to the following details from the package insert of Gardasil:

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility GARDASIL 9 has not been evaluated for the potential to cause carcinogenicity, genotoxicity or impairment of male fertility. GARDASIL 9 administered to female rats had no effects on fertility [see Pregnancy (8.1)]

In the package insert, 'not been evaluated' may be simply because this type of evaluation was not necessary or appropriate. All necessary pre-clinical or nonclinical testing is performed on vaccines and their components and is required for licensure by agencies such as the EMA (in Europe) and the FDA (in the US). Unless the initial tests indicate a potential issue, clinical testing is not usually warranted. Vaccines are appropriately evaluated for mutagenicity, carcinogenicity and impairment of fertility, when necessary, as a part of pre-clinical or nonclinical studies that occur even before the first studies in people.

Also, as mentioned previously, in its most recent update the WHO's GACVS maintained its assertion that there is insufficient evidence for a causal association between HPV vaccines and premature ovarian insufficiency and primary ovarian failure.[17]

1.4.2.6 Other safety comments

A range of other safety comments were received. For example,

"HIQA failed to obtain Accurate and Factual figures as to the large number of serious adverse reactions to the HPV Vaccine "Gardasil" including cases of anaphylaxis reported to the HPRA."

HIQA obtained safety data from the Health Products Regulatory Authority (HPRA) on 30 April 2018 that represented the most factual and accurate data at that point in time (Chapter 6, Section 6.3.2). Between 01 January 2006 and 31 December 2017, the HPRA received 1,119 reports of suspected adverse reactions associated with the HPV vaccine Gardasil. Figures reported by the HPRA are subject to change as new information becomes available allowing certain cases be identified as duplicates of other cases resulting in merging of cases, as appropriate.

There are three important caveats to be aware of while interpreting reports of suspected adverse reactions to the HPRA.

1) It is important to note that many of the reports received by the HPRA were not medically confirmed. Reports originated from a number of sources, including some directly from patients and family members. The HPRA reviews all data with duplicate cases reconciled under a unique identifying number where possible. The information typically contains variable levels of detail with regards to the nature and onset of symptoms, clinical assessment, investigations pursued and diagnoses received.

2) It is important to note that reports submitted to the HPRA concern 'suspected' adverse reactions. This means that the effects experienced may represent side effects associated with the vaccine or the vaccination process, or may be coincidental in terms of timing, due to an underlying or previously undiagnosed condition that would have occurred in the absence of vaccination.

3) The HPV vaccine is administered in the schools programme with other vaccines (Tdap and MenC). Because of media focus on HPV vaccine, it is possible adverse events associated with the other vaccines are incorrectly ascribed to the HPV vaccine.

Reports of suspected adverse events to the HPRA may not always capture very rare events. For this reason, the systematic review of systematic reviews (Chapter 6) which included over 70,000 trial participants and surveillance of over 20 million individuals in cohort studies should be highlighted. No safety concerns were raised regarding HPV vaccines for a range of conditions. A known rare occurrence of anaphylaxis is recognised (at approximately 1.7 cases per one million doses of the vaccine).

Another comment related to the weight of children:

> *"Children are not weighed before vaccination, yet hospitals weigh patients before they can even administer paracetamol intravenously. The dose of any medication given intravenously is based on the weight of the patient. HIQA should be aware of this and incorporate it into every vaccination programme."*

HPV vaccines are intramuscular injections (not intravenous) and the dosing schedule is based on the age of the recipient and not the weight of the child. The consideration of dosing is thoroughly assessed as part of the licensing of all drugs, including vaccines.

A final comment related to the manufacturer's information leaflet:

> *"While the Manufacturers Package leaflet clearly lists the possible side effects of the vaccine, these are not being disclosed to parent by the NIO/HSE. The HSE refuse to provide parents with the Manufacturers package leaflet in their parent information packs. This is in breach of Regulation 16 of S.I. No. 540/2007 Medicinal Products (Control of Placing on the Market) Regulation. This is in breach of parents Human Rights to make an informed decision as to their child's health care."*

The HSE provides this information on their dedicated website www.hpv.ie. It is the only Irish website that is approved by the World Health Organization. In addition to factsheets in English and Irish, letters for parents and or guardians in English and Irish and a number of other resources, it provides the link to the manufacturer's Summary of Product Characteristics (SPC) and the Patient Information Leaflet (PIL). More detail is available in the information materials provided on the HSE website.

The Evaluation Team has decided to also include links to the PIL and SPC in the report. These will now appear in Chapter 6: Safety.

It is important to note that the information and communications methods employed by the HSE and NIO are consistent with best practice guidelines from the WHO. The WHO requires those consenting to vaccination to receive communications that are easy to understand for a lay person.

1.4.2.7 Dealing with adverse events

A number of respondents to the consultation expressed a feeling that the concerns of the public are not being adequately listened to and addressed. Examples include:

> *"should a reaction occur will there be something in place to treat the boys or will they be told it's all in their heads like the girls?"*

> *"Are you going to ignore the boys who have a reaction to the vaccine like you have done the girls"*

> *"If a side effect is reported then people like Simon Harris will mock and ridicule you and your family on social media, in the Dáil and in any interview and call you and "anti-vaxxer"."*

The concerns of parents who have worries about the safety of the vaccine should be addressed appropriately. This is explored in Chapter 10: Ethical issues, Section 10.2.2. It is critical that in cases in which a vaccine is perceived to have caused harm, these concerns are not dismissed. Parents may perceive that if a clinician dismisses the link between the vaccine and an adverse event, they are not accepting the occurrence or significance of the child's symptoms. Therefore, it is important

that the seriousness of the child's presenting symptoms and how they are treated is not linked to the plausibility of a link to the vaccine.

As a change to the report, this will now be highlighted as a key point in Chapter 10:

- In cases in which a vaccine is perceived to have caused harm, these concerns should not be dismissed. Parents may perceive that if a clinician dismisses the link between the vaccine and an adverse event, they are not accepting the occurrence or significance of the child's symptoms. Thus it is important that the seriousness of the child's presenting symptoms and how they are treated is not linked to the plausibility of a link to the vaccine.

In terms of reporting an adverse event, the Health Products Regulatory Authority (HPRA) is responsible for monitoring adverse event reporting related to medicines and vaccines in Ireland. Members of the public concerned that they have had a side effect to the HPV vaccine can report the issue using the HPRA's online reporting service. Alternatively, a healthcare professional can report the issue to the HPRA on behalf of the individual. The HPRA recommends that any individuals concerned that they have experienced a side effect to a medicine should contact a healthcare professional who can advise on any treatment that may be needed.

In the production of the assessment, safety data specific to Ireland were obtained from the HPRA and are reported in Chapter 6. As stated in Section 6.5 of the report, ongoing surveillance, effective communication and a rapid response to concerns are required to maintain confidence in HPV immunisation programmes.

1.4.3 Herd immunity and resilience of immunisation programme

A number of submissions (29) related to the theme of herd immunity, highlighting the importance of male vaccination to both induce herd immunity and develop resilience in the current programme. Examples include:

> *"Add resilience to the current girls' only programme (which has current uptake rates of 62%) and protect the programme against future changes in female uptake rate."*

> *"A gender-neutral vaccination programme would achieve real herd immunity; without male vaccination men who move outside of the herd, and especially MSM, remain at risk of HPV infection and life-threatening and life-altering HPV related diseases."*

"The HPV vaccine should certainly be extended to boys to improve the chances of herd immunity".

Herd immunity is discussed in Sections 10.2.1 and 10.2.5 of the report. The economic model allowed for the effects of herd immunity. The following key point of Chapter 10 relates to herd immunity:

- On a population level, HPV vaccination of boys provides direct protection against HPV related disease, indirect herd protection to girls, and ensures vulnerable groups are protected who do not benefit from these herd effects (as in, men who have sex with men [MSM] and migrants who are 'outside the herd').

1.4.4 Public health importance and health promotion

Many submissions related to the theme of public health importance and health promotion, acknowledging HPV infection as a major public health threat.

Within this category the importance of an information campaign and provider education is highlighted, for example:

"Health Promotion (p. 345 Section 9.3)

The INMO supports an information campaign for parents of boys in order to educate and allay concerns. A recent survey carried out by Behaviour and Attitudes (Irish Times, 3rd September 2018) found that almost two-thirds of people do not realise that males and females are at equal eisk of HPV infection.

The public awareness campaign needs to deliver information about HPV as a disease for all and not just females. The benefits of the vaccine for boys will need to be highlighted and addressed to boys and their parents. Regaining parental trust and support is ongoing for the girls vaccination programme after the decline in vaccine uptake due to parental concerns about the vaccine safety and this campaign needs to extend to boys.

An educational programme should include all front line nurses and midwives including those working in general practice as all nurses/midwives are trusted by the public as information givers and it is vital that the same evidence based information is disseminated by all health professionals."

> *"The roll out of the 9-valent vaccine to school children must be accompanied by a fully resourced nationwide public education campaign. The IMO is calling for the report's recommendations to be implemented with immediate effect and in full as failure to implement the recommended changes could have potential negative effects on the immunisation programme for the next few years."*

Section 9.3 of the report outlines the importance of an information campaign to address the unique information needs of parents and boys regarding the risk of acquiring HPV infection and the direct benefits of the vaccine for boys. This should also allay any concerns regarding the safety or efficacy of the vaccine and enable informed consent. Consideration would also need to be given to an educational programme for GPs, pharmacists and front-line nursing staff given their important role both in vaccine administration and as a trusted information source for other childhood vaccines as part of the immunisation programme. This has been highlighted in the key points of Chapter 9, Organisational issues:

- If gender-neutral vaccination is adopted, an awareness campaign will be required to include circulation of appropriate materials to address the information needs of parents and boys, as well as healthcare professionals, to enable informed consent to be provided. While international survey data suggest strong support for vaccination of boys, as with HPV vaccination of girls, fear of adverse events, lack of knowledge about male HPV issues and uncertainty around vaccine effectiveness are noted barriers to vaccine uptake.

1.4.5 Justice, equity and equality

Many submissions were received based on the theme of gender equality and equity, all supportive of gender-neutral vaccination. Twenty-five submissions related to this theme. Examples include:

> *"Ensure that access to this vaccine is equitable to both genders."*

> *"I think males should have the same opportunity as females to avail of the protective benefits of the vaccine."*

> *"The protection of the future health of our sons is of equal importance to that of our daughters therefore I would support the extension of the HIQA vaccine to boys as soon as possible."*

Some submissions felt strongly that this was the case:

> *"Boys should get the vaccine as well, this is some absurd cis-heteronormative concept to only give to cis-women!!! Ireland needs to stop being this catholic country run by the church! This makes no sense, only an uninformed stupid person would had made that policy of only giving to cis-girls."*

These issues are covered in Chapter 10: Ethical issues of the report (specifically Section 10.5: Justice and equity).

Some respondents felt that provision of a girls-only programme will contribute to economic inequity:

> *"I had intended paying privately for my son to get the vaccine in a few years so I would welcome the expansion of this scheme."*

> *"By not introducing the vaccine it becomes a public v private argument where those who can afford to will pay for it and those who can't won't. How can that be okay? Well done on commissioning this study and I wish you the best in getting it introduced. Thanks"*

It should be noted, however, that HPV-related *disease* is not equal across genders, despite the fact that HPV infection affects men and women roughly equally. Acknowledging the fact that oropharyngeal carcinoma is increasing rapidly and is more prevalent in men, cervical cancer remains the most deadly HPV-related disease globally (as the ninth most common cause of cancer death worldwide). The HPV vaccine was initially introduced only for girls due to the substantial burden of cervical cancer. Sometimes, it is ethical to only provide vaccination to one group of people, in this case females. In resource-poor settings, such as sub-Saharan African countries, limiting vaccination to girls provides the greatest health benefit and is the most cost-effective strategy in the context of limited vaccine supply. More detail in relation to the different benefit-harm balance for boys and girls is available in Chapter 10, Section 10.2.1, and is summarized in the key point below:

- Based on current knowledge, females benefit more from HPV vaccination than males, as the main contributor to the burden of HPV-related disease is cervical cancer. However, vaccination of boys also confers real health benefits to males that greatly outweighs any potential harms associated with vaccination.

Other comments highlighted another important issue, that the burden of HPV vaccination should not be carried only by women, considering HPV infection is

sexually transmitted. The following comments summarise this view:

> *"It is not equitable to expect girls alone to bear the burden of HPV vaccination, or the responsibility of tackling this sexually transmitted infection."*

> *"Withholding a vaccine from any group of individuals at risk of developing that vaccine-preventable disease is unethical. It is also unfair for females to be expected to carry the responsibility for HPV prevention through vaccination, particularly when HPV is a virus that is sexually transmitted, and affects both sexes so prolifically."*

Given that the burden of HPV-related cancer is higher in females than in males, a female-only vaccination programme could be seen as equitable if the goal of health policy is to allocate resources in such a way as to prioritise those most affected by disease. However, for reasons of non-discrimination (due to the HPV-related health consequences that affect men), non-stigmatisation (falsely believing HPV-related disease is limited to girls) and the need to protect vulnerable groups (MSM and migrants from outside the 'herd'), there are important ethical reasons to consider the inclusion of boys in the national HPV immunisation schedule. This issue has been addressed in Chapter 10, Section 10.5 of the report.

Three submissions directly relate to the ethical argument that an effective prevention tool cannot be withheld. For example,

> *"Withholding a vaccine from any group of individuals at risk of developing that vaccine-preventable disease is unethical."*

> *"From an ethical perspective, to "not fund" a vaccine for any group of individuals at risk of developing a vaccine-preventable disease is questionable; thus, including boys in vaccination campaigns is important to ensure equity in protection from HPV-related diseases."*

In other jurisdictions, such as resource-poor countries with limited vaccine supply, it may be ethical however to limit vaccination to those who will gain the most. This situation is unlikely to apply to Ireland, however. The main ethical issues associated with extending the national immunisation programme to include HPV vaccination of boys are outlined in Chapter 10 of the report, and summarized in the following key points:

- However, the decision to invest in a gender neutral vaccination programme should consider not just the direct benefits and harms to the individual, but also the overall potential population-level benefits and harms.
- On a population level, HPV vaccination of boys provides direct protection against HPV related disease, indirect herd protection to girls, and ensures vulnerable groups are protected who do not benefit from these herd effects (as in, men who have sex with men [MSM] and migrants who are 'outside the herd').

1.4.6 Resource implications

Many submissions were received from both individuals and organisations that relate to the additional resources that will be required if the schools immunisation programme is extended to boys.

Some submissions were of the opinion that the staffing needs are underestimated. Examples include the following:

> *"The model refers to an average immunisation team, that can process up to 100 vaccinations per day, comprising of four staff (senior medical officer, two registered nurses and a clerical officer. This calculation significantly underestimates the resources required in [location] to implement the Secondary School Immunisation programme. If financial costs to implement this campaign are based on the average Immunisation team referred to in the HTA , it will significantly underestimate the costs and jeopardize the implementation of the programme."*
>
> *"I would be concerned the estimated staffing levels for delivery of the current HPV programme underestimates what is actually happening on the ground"*
>
> *"Expecting a vaccination team including 1 doctor and 2 nurses to be able to administer 100 vaccinations in 4 hours in a secondary school is an underestimation of the staff required. At least 1 of these 3 clinicians will not be vaccinating at all as 1 nurse is required to manage the recovery area. It is to be expected that the doctor will also be required to attend to some students in the recovery area from time to time as well as deal with telephone calls to and from parents and queries from vaccinating nurses"*

Another comment is the following:

> *"The assumptions on which the staffing estimates are based represent an underestimate of staffing needs. Hence the costings are also underestimated. Table 8.20 which shows 92eu for vaccine cost (vaccine +administration) per schedule as opposed to 166eu in Sweden and 308-543eu in Norway or Germany supports our argument that the staffing estimates used in the HIQA consultation document significantly underestimate the staffing required to run a safe, quality service. We were poorly resourced when HPV was introduced initially for girls, we cannot sustain a basic level of service if the introduction of HPV for boys is not correctly resourced.*
>
> *We take issue with the following:*
>
> *8.2.3.2. states: It was assumed that, on average, an immunisation team comprises an average of four staff (senior medical officer, two registered nurses and a clerical officer) and took into account PRSI (pay-related social insurance), overheads and pension contributions as per the national guidelines. This is regarded as a very conservative estimate.*
>
> *…an immunisation team can process up to 100 vaccinations per day*
>
> *..It can be argued that teams may be able to cover two smaller schools in a day rather than only one location per day as this HTA was assumed*
>
> *This is a serious underestimate of staffing required currently."*

Another similar comment included:

> *"..We specifically note that the vaccine cost plus administration is assumed as €92 per vaccine (see table 8.20), which is considerably below the national vaccine costs assumed in other developed European countries.."*

In response to these comments, HIQA does acknowledge that the model of four staff (senior medical officer, two registered nurses and a clerical officer) to deliver 100 vaccinations in a day would not apply to all schools and is a simplistic, conservative estimate that gave an average estimate for the purpose of cost-effectiveness modeling. It was not intended that future implementation planning for a gender-neutral vaccination programme should be based on these modelling parameters.

In response to the comment of the difference in cost in Ireland compared to Sweden and Norway, HIQA's estimates for administrative costs were in fact higher than that

used in Sweden or Norway. The difference in cost was due to the difference in cost of the vaccine between countries.

The Irish Nurses and Midwives Organisation (INMO) also outlined the additional staff and investment requirements going forward:

> *"The INMO is concerned that this will put immense pressure on the current school immunisation team, who according to the draft consultation (Section 8.2.3.2, page 305), on average, comprise of four staff including senior medical officer, two registered nurses and a clerical officer.*
>
> *The INMO would like to take this opportunity to outline our concerns:*
>
> - *Additional permanent staff will be required to roll out the extension of the programme*
> - *Redeployment should not be used as ongoing work in the community, which is already understaffed, must not be affected by the programme.*
> - *HPV vaccination cannot be prioritised over all other vaccinations such as childhood and booster vaccinations.*
> - *All staff involved in the programme must be trained prior to its commencement*
>
> *Significant additional investment is required in community nursing in order to ensure the expansion of this service. If recommended engagement and consultation would be required between Department of Health, Health Service Executive and the Irish Nurses and Midwives Organisation to ensure adequate staffing resources are secured and put in place prior to the commencement of the expansion."*

Another comment also highlighted the additional nursing personnel that will be required:

> *"Increased nursing personnel are required to implement this programme for the following reasons:*
>
> - *There will be an increase in staff time to give 2 additional vaccines to boys.*
> - *There will be an additional visit to all boys' only schools within the constraints of the school year.*

- *Currently the South Lee team of PHN's and Vaccination Nurses also deliver the Primary School Screening and Immunisation Programme to schools within the school year."*

Additional follow-up clinics will be required to complete the immunisation schedule for students who may be absent from school or require a clinic setting.

Other comments acknowledged the fact that boys already receive two vaccinations in their first year of secondary school, limiting the impact:

> *"The HPV immunisation programme is already supported and delivered in the secondary school setting. Extension of the HPV programme to boys will require additional resources. However, as the proposed cohort of boys to be vaccinated are already scheduled to receive the diphtheria/tetanus/pertussis (DTP) and Men C vaccines in the school addition of this vaccine the impact of this additional vaccine will be minimised."*

Some comments have pointed to the beneficial impact vaccination will have on STI services. For example,

> *"This reduction in the rate of ano-genital warts reduces the burden of referrals for treatment of these conditions in primary care and in sexual health clinics."*

Chapter 9 acknowledges the resource implications associated with the extension of the current immunisation programme to include boys, taking into consideration the additional burden on the immunisation team both in terms of vaccine delivery and the administrative burden associated with obtaining consent, dealing with queries and concerns, and recording the vaccine administration in the School Immunisation System. The need for additional resources to manage the additional administrative and clinical workload if a gender-neutral HPV immunisation policy is adopted is highlighted in the key points in Chapter 9:

- Additional resources will be required by immunisation teams if a gender-neutral HPV immunisation policy is adopted. Along with the increased administrative burden, an increase in staff time to deliver two additional vaccine doses to boys will be necessary and additional resources will be required to facilitate additional school visits in boys-only schools. Given the need to administer the vaccine at specified intervals within the academic year, this may pose logistical challenges within some areas with surge capacity necessary to reflect the time constraints within which the service must be provided.

1.4.7 Social

In total, 17 comments relate to social context and changing sexual behaviours, all highlighting the need to vaccinate. For example,

> *"Ensure equity of access to young adults from all social backgrounds."*
>
> *"Ensure fair access to HPV by both genders and young adults from all social backgrounds in line with the principals of the Irish Medical Council Guide to Professional Conduct and Ethics for Registered Medical Practitioners. Available data suggests that those from socially disadvantaged backgrounds are more likely to engage in risk taking sexual activity"*
>
> *"The increase in cancers apparent now reflects sexual behaviours from the late 1990s given the lag time of around 20 years from acquisition of HPV infection to progression to invasive cancer. Trend data on STIs suggests that an on-going associated increase in HPV related cancers in the coming years will be seen.""Be an appropriate response to the documented changing sexual behaviour and risk-taking activities of young heterosexual and MSM populations. Data from the Growing Up in Ireland Survey reported on sexual behaviours among young people:*
>
> - *"40% of 17/18-year-olds reported having had oral sex, 33% reported having had sexual intercourse and 42% reported at least one of these activities.*
> - *Males were significantly more likely to report being sexually active (oral sex or sexual intercourse) than females (45% compared to 39%).*
> - *17/18-year-olds from the most socially disadvantaged group were somewhat more likely to report being sexually active (49%) than others (38-42%)."*

As stated in Chapter 9, Section 9.5.3, school-based programmes minimise differences in HPV vaccination uptake between different sub-populations and the general population. Schools-based programmes reduce inequality, particularly in disadvantaged and marginalised communities.[18] Vaccinating in the first year of second level education maximises the likelihood that the child is still at school (although retention rates in second level schools are very high in Ireland, unlike in some other countries).

HPV is highly contagious and affects up to 90% of people at some point in their lives. Therefore, attempts at limiting the number of sexual encounters and avoidance of promiscuous partners provides no guarantee that an individual will not acquire HPV. Further discussion on this matter is addressed in Section 10.2.4 of the report.

1.4.8 Cost-effectiveness

One submission related to the time horizon of the budget impact:

> *"€10.4m for the first 5 years. What are the considerations for 20-30 years which is how long one would expect to see any benefit."*

The budget impact analysis was designed to estimate the net annual financial cost of adopting the technology over a five year time horizon. This is consistent with HIQA's *National Guidelines for the Budget Impact of Health Technologies in Ireland*.[19]

Other comments related to the awareness campaign and the model used for vaccine administration teams:

> "*Awareness campaign – HIQA have not estimated or included this added cost in its effectiveness model."*
>
> *"Additional staff and administration costs not factored into cost effectiveness model – HIQA have not estimated or included this added cost, especially since the burden on staff will largely increase. Additional resources will be needed for boys-only schools."*

It was assumed that, on average, an immunisation team comprises an average of four staff (senior medical officer, two registered nurses and a clerical officer). As outlined in the Chapter 9 (Organisational issues), extending HPV immunisation to boys may necessitate additional staff in some areas or redeployment of staff from other public health activities onto the immunisation teams to provide extra capacity during the targeted periods. Future implementation planning should take into account the requirement for additional resources if a gender-neutral vaccination programme is adopted, and should not be based on these modelling parameters which that are a simplification of reality. An information campaign must also form part of the implementation plan.

Some comments related to the MSM group:

> *"Economic Model – incorrect assumptions: Excluding MSM from the model distorts the effect of the vaccine outcome in heterosexual men."*

The request from the Department of Health for a HTA was to establish the clinical and cost-effectiveness of extending the current immunisation programme, which

offers HPV vaccination to all girls in their first year of second-level education (12 to 13 year olds), to a programme that also offers the vaccination to boys in their first year. Therefore, all modelling parameters were based on the extension of the current programme to include boys. The model assumes that the effects in the MSM population are identical to that in the heterosexual population and are a function of the effects in the female population. It was not possible to single out the MSM population. Extending to boys is therefore extending to MSM and non-MSM individuals. It was not considered feasible to attempt to identify the MSM population in the target age group (12 year old boys).

1.4.9 Vulnerable groups

Fifteen comments referred to the importance of gender neutral vaccination to ensure high risk groups are captured, including the MSM group and 'hard to reach' girls. Examples of such comments include:

> *"A significant proportion of the young women not being fully vaccinated are 'hard to reach', at risk of making other 'poor life decisions', and at higher risk of sexually transmitted infections."*

> *"To optimise the vaccine effectiveness in MSM it should be offered to young MSM prior to sexual debut. Young MSM have low awareness of the vaccine, universal vaccination solves this problem."*

> *"Protect boys falling 'outside the herd' such as men who have sex with men (MSM). Currently, young boys who are MSMs do not have any vaccine protection from HPV. While boys from 16 years old are offered this vaccine in sexual health clinics this may be after they have become sexually active which substantially decreases potential protection from the vaccine."*

As outlined in Chapters 4 and 5, vaccinating boys provides beneficial health impact to males, indirect herd protection to girls and has the ability to ensure vulnerable groups are included who do not benefit from herd effects (as in, men who have sex with men [MSM] and migrants who are 'outside the herd').

Another group that was not specifically mentioned as part of the consultation feedback were migrants and people entering or exiting the 'herd' who may not receive the vaccine. Gender neutral vaccination improves the chances that these individuals will be indirectly protected in later life. Certain parameters of the economic model could be affected by migration, although that would be contingent on Irish rates being very different to those in migrants and for migrant numbers to be very substantial. A related issue regards assumptions around herd immunity and that those who are unvaccinated only acquire immunity while they remain in the

herd. The movement of people in and out of the country and the mobility of the Irish population, particularly amongst those aged 20 to 30 years, mean that herd immunity may not exert a strong effect. However, for the loss of herd immunity to have a strong impact, the unvaccinated population would have to mix with a population with a much higher HPV prevalence than observed locally.

Another submission highlighted the importance of protecting the transgender community:

> *"Although not referenced in the report, the IFPA suggests that the transgender community – a vulnerable population – may also benefit from the introduction of a gender-neutral HPV vaccination programme. The current "girls-only", school-based programme risks misgendering and stigmatising transgender boys who should be offered the HPV vaccine to mitigate their risk of cervical cancer. However, 'outing' these boys in this way violates their right to privacy and could put them at risk of discrimination and harassment from their peers. The introduction of a gender-neutral HPV vaccination programme would address these concerns."*

1.4.10 International experience

Fourteen submissions related to the theme of 'international practice', five of which specifically named Australia as a role model for Ireland in the eradication efforts of the HPV virus. Examples include:

> *"Gender neutral HPV vaccination programmes have been effective in other countries, such as Australia and the United States"*

> *"I was really impressed by studies in Australia where the vaccine has been available for both boys and girls as they are in line to eradicate HPV related cancers within the next decade or so. These results alone are justification for extending the vaccine."*

> *"It's done in Australia already and I trust their research and due diligence having lived there previously."*

> *"I believe both boys and girls should be vaccinated. Australia has a good model which we should be emulating."*

Other submissions highlighted the WHO and JCVI's stances on gender neutral vaccination.

Two submissions incorrectly referred to the HPV vaccine being banned in other countries:

"Why is the government extending this programme when other countries have stopped it altogether."

"This vaccine has been banned in many countries due to horrible side effects which as you know has happened already in this country."

HIQA is not aware of any country that has banned HPV vaccines. HIQA is aware that the Japanese government issued a notice stating that 'cervical cancer vaccinations should no longer be recommended for girls aged 12 to 16' while an investigation was conducted into certain adverse events including pain and numbness in 38 girls in June 2013. In February 2009, the Spanish ministry of health suspended use of one batch of Gardasil after health authorities in the Valencia region reported that two girls had become ill after receiving the injection. Merck has stated that there was no evidence Gardasil was responsible for the two illnesses. While HPV vaccines have been available in India since their approval in 2008, they remain limited to the private sector. There are calls for HPV vaccination to be included in their public health system as over 25% of all cervical cancer deaths in the world occur in India. Current HPV immunisation programmes are detailed in Chapter 2, Section 2.7.1. International experience of implementing male HPV immunisation programmes is discussed in Chapter 9, Section 9.4.

The safety of the human papillomavirus (HPV) vaccine was evaluated in large clinical trials prior to being licensed, and is monitored in post-marketing surveillance systems worldwide. International and Irish data relating to the safety of the HPV vaccine are available in Chapter 6. Specific details of international surveillance activities are given in section 6.4.3.1. Country-level surveillance of the HPV vaccine in the US (including the CDC), UK, Denmark and Sweden do not point to safety signals associated with HPV vaccines.

1.4.11 Propagation of false information and social media

Seven submissions were received that highlighted the dangers of social media and the propagation of false or inaccurate information, as many individuals receive information and make health decisions based on unverified sources.

The decision to implement or extend a health intervention should be based on rigorous scientific methods that are transparent and open to scrutiny.

Examples of comments include:

"Do not allow misinformed people & organisations sway this argument."

"I can't see any reason to delay the rollout of this to boys. Any comments by

AntiVaxxers should be immediately ridiculed and provided with the evidence. Too many people still go by the fake news on Facebook etc. In addition, Facebook et al should be approached to root out and ban these stories as soon as they appear."

"The vaccine should be provided to boys and girls and more should be done to dispel the rumors and hysteria regarding the supposed side effects."

"I think there should be an investigation into the source of the rumors that vaccinations can harm girls and a criminal investigation brought against the source of the rumors if they were spread knowing they were untrue."

"Please don't be discouraged by anti-vaccination groups expressing unfounded fears. Let this decision be made based on the evidence supporting the vaccine, not by public opinion."

Clear and comprehensible information is crucial to obtaining informed consent from parents for vaccination of their children. Informed consent materials must provide sufficient information in a form, manner and language that is comprehensible to parents. The issue of informed consent is dealt with in section 10.3.1. The HSE provides information materials on their dedicated website www.hpv.ie to enable parents to provide informed consent. Links to these documents are now included in Chapter 6 of the report. The following key point of Chapter 10 is also of relevance to this discussion:

- A robust informed consent process must be followed to ensure that the decision to vaccinate is made on the basis of clear, relevant, up-to-date information about the benefits and risks associated with the vaccine. This requires the provision of appropriate and adequate information to parents and children.

1.4.12 Lack of Irish Data

Multiple comments referred to the data sources used. Examples included:

"No irish data on male associated hpv cancers"

"Lack of any data relevant to the prevalence of male HPV-associated cancers in Ireland."

"Data was taken from other countries and from sources, which had no

relevance to the Irish population."

"There is no data relating to Ireland as to prevalence of HPV 16 and 18 in male HPV-associated cancers."

In response to these comments, readers should refer to Chapter 3: Epidemiology. Irish data are available (and heavily referenced in the report) relating to invasive cancer in Ireland associated with HPV infection. The following Irish data sources were accessed and included in the assessment:

1. All invasive HPV-associated cancers diagnosed in Ireland between 2009 and 2013 were obtained, from the National Cancer Registry Ireland (NCRI), a publicly-appointed body that collects and classifies information on all cancer cases which occur in Ireland.

2. Incidence of pre-cancerous lesions of the cervix, from CervicalCheck (Ireland's National Cervical Screening Service).

3. Prevalence of HPV infection in cervical specimens in Ireland, from CERVIVA (a multi-investigator research collaboration), including HPV 16, 18 and other high-risk HPV types.

4. All new anogenital wart notifications in Ireland, from the Health Protection Surveillance Centre (HPSC).

5. The number and HPV positivity, including $p16^{INK4a}$ status, of all available oropharyngeal cancer cases diagnosed at eight treatment centres from 2014 to 2018, from a multicentre Irish audit conducted in 2018.

To estimate the total incidence of precancerous lesions outside the cervix, a literature review to identify countries that routinely collect these data was performed, as no agency routinely screens for these conditions in Ireland (and very few collect this information internationally). The quality, completeness and representativeness international data were assessed. If transferable to the Irish context, the age-specific incidence rates were used to estimate the predicted annual incidence of such lesions in the Irish population.

A similar approach was used to estimate the male carrier prevalence of HPV and to estimate the burden of anogenital warts. Despite receiving data from the HPSC on anogenital warts, international estimates were applied to the Irish population due to the fact that significant under-reporting of anogenital warts takes place in Ireland.

1.4.14 Timing of vaccination and catch-up programme

Two submissions related to the need for a catch-up programme in males:

> *"Having a 13 year old now, I'd be hoping that, there would be a retroactive programme to catch any boys that may have aged out of the first round if and when it comes in"*

> *"I totally agree with the inclusion of HPV vaccintions for boys and would increase the entry point for boys to 5th year"*

In response to these comments, the Evaluation Team modelled a catch-up programme for adolescent males. This is now included in Chapter 8 (Economic evaluation).

There are a number of reasons supporting the administration of the vaccine in the first year of second level education. Vaccinating in the first year of second level school maximises the likelihood that the child is still at school (section 9.5.3). The first dose of the HPV vaccine is co-administered with the tetanus, low dose diphtheria and low dose acellular pertussis (Tdap) booster vaccine in September or October and the second dose is co-administered with meningococcal group C (MenC) low-dose booster vaccine six months later in girls. Boys also receive these booster vaccines in their first year of second level school. School immunisation teams typically visit boys-only schools once (whereby Tdap and MenC are co-administered in the second or third term). Systems are therefore already in place to identify eligible students attending second level and special schools, obtain informed consent and to record vaccine administration.

Furthermore, the systematic review of efficacy of HPV vaccines in boys demonstrated that adolescents display superior immune response compared to adults (Chapter 4). Vaccinating early adolescent girls and boys increases the probability that those receiving the vaccine are HPV naïve at baseline. There is no known treatment for HPV infection. Therefore, the clear benefit of HPV vaccination is the prevention of persistent infection and its sequelae.

1.4.15 Advertising

One submission commented on various aspects of advertising and the law, including the legality of the HSE National Immunisation Office's HPV awareness campaign.

Comments included:

> *"HIQA failed to ensure that the NIO/HSE HPV Vaccination Campaign was Legal."*

and

> *"HIQA refers to the NALA report on page 361 but failed to make adequate /any reference to Irish Laws, Rules, Regulations and Advertising Standards (S.I. No. 541/2007, S.I. No. 540/2007, The Consumer Protection Act 2007, The Ethics Acts, ASAI, BAI, IPHA and HPRA advertising rules) that apply to the advertising / promotion and supply of medicinal products in this country. The HSE/NIO, Department of Health or any Government / State Agency are not exempt from the Law. Consent is not valid unless it is informed consent and obtained legally. The HSE refuse to provide the Manufacturers Package leaflet in their information packs to parents and caregivers. This is in breach of Regulation 16 of S.I. No. 540/2007 (Labelling and package leaflets.) This denies all parents the fundamental right to an informed choice."*

Before a vaccine is licensed for use in Ireland it must be regulated by both the Health Products Regulatory Authority (HPRA) and the European Medicines Agency (EMA). Once vaccines are licensed, both agencies and the vaccine manufacturers continue to monitor and supervise their safety.

The National Immunisation Office (NIO) is responsible for the implementation of the national immunisation programme of the Health Service Executive (HSE) and is responsible for the procurement and distribution of vaccines used in publicly funded programmes. The current HPV vaccination programme is carried out in accordance with Immunisation Guidelines for Ireland. The Schools Immunisation Programme is developed in accordance with the guidance issued by the National Immunisation Advisory Committee (NIAC) of the Royal College of Physicians of Ireland (RCPI) and contained in the Immunisation Guidelines for Ireland. The guidelines specifically state that all information packs for second level schools must be sent as soon as the school year starts for immediate distribution to parents and legal guardians. The NIO also provides information leaflets for the general public and health-care professionals on their website. The need for informed consent has been emphasized in the key points of Chapter 10 of the report.

- A robust informed consent process must be followed to ensure that the decision to vaccinate is made on the basis of clear, relevant, up-to-date information about the benefits and risks associated with the vaccine. This requires the provision of appropriate and adequate information to parents and children.

The laws governing the advertisement of medicinal products are outside the scope of this assessment. However, the Evaluation Team has no reason to believe the HSE's information and education campaign was illegal or inappropriate. The HSE's

efforts to counteract the fall in vaccine uptake rates were successful. In terms of the Patient Information Leaflet and Summary of Product Characteristics, the HSE provides this information on their dedicated website www.hpv.ie. It is the only Irish website that provides information on HPV vaccines that is approved by the World Health Organization.

1.4.16 Errors in report

1.4.16.1 Typographic error in report

Anaphylaxis is estimated to occur at a rate of 1.7 per million doses of Gardasil. This estimate is referred to seven times in the report, correctly in six (pages 232, 234, 237, 253, 357 and 374), however a typographic error is noted in page 291 (where '1 case per 1.7 million doses' should read '1.7 cases per million doses').

1.4.16.2 Error in reference in report

One error in a reference was corrected (reference 459 should be: *Jiménez E, Wisløff T, Klemp M. Cost-Effectiveness of a HPV-Vaccination Catch-Up Program for Females Aged 26 Years or Younger in a Norwegian Setting Oslo, Norway: Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH); 2014 Mar. PMID: 29319987*)

1.5 Changes to the report as a result of consultation process

The following changes were made to the draft report, in response to comments and feedback received through the consultation process:

1) The typographic error in page 291 of the consultation document is corrected.

2) Reference number 459 of the consultation document is amended.

3) A catch-up programme is now included in the assessment and modelled in Chapter 7 (Economic evaluation).

4) The additional resources required and the additional burden that will be placed on schools immunisation teams is highlighted in the key points of Chapter 8: Organisational issues. The need for additional resources to cope with the increased workload and issues surrounding staff shortages are emphasised.

5) Links to the manufacturer's Patient Information Leaflet (PIL) and Summary of Product Characteristics (SPC) are now included in Chapter 6: Safety. (These links are also readily available on the HSE's World Health Organization-approved website, www.HPV.ie).

6) The safety of HPV vaccine co-administration with other vaccines is added to Chapter 6: Safety (whereas previously this information was contained in Chapter 4: Efficacy and Chapter 9: Organisational issues).

7) An additional key point is inserted in Chapter 10: Ethical issues, to address parental concern's relating to the reporting of adverse events:

- In cases in which a vaccine is perceived to have caused harm, these concerns should not be dismissed. Parents may perceive that if a clinician dismisses the link between the vaccine and an adverse event, they are not accepting the occurrence or significance of the child's symptoms. Thus it is important that the seriousness of the child's presenting symptoms and how they are treated is not linked to the plausibility of a link to the vaccine.

In addition to the changes made above, a plain English summary has been provided in the final report. Every attempt has been made in the plain English summary, the Executive Summary and the Advice to the Minister to provide clarity on issues

identified as part of the consultation that were commonly misinterpreted.

1.6 References

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Appendix 1A: Copy of submission feedback form

Health technology assessment (HTA) of extending the national immunisation schedule to include HPV vaccination of boys

1. About you

Name *

_____

Email or telephone no. *

_____

2. Are you replying in a personal capacity or on behalf of an institution or organisation? *

□ Personal

□ On behalf of an organisation

□ On behalf of an institution

□ Name of organisation or institution

3. Are you in favour of extending the HPV immunisation programme to include boys?

□ **Yes**

□ **No**

4. Do you have specific concerns related to the HPV vaccine?

□ **Yes**

If Yes, please give additional information:

_____

_____

□ **No**

5. Comments box. Please outline any general or specific feedback on the report. In your response, where applicable, please specify the section to which you are referring.

6. Keep name and/or organisation confidential

If you wish to do so, you can request that your name and/or that of your organisation be kept confidential and excluded from the published summary of responses.

□ Keep name confidential

□ Keep name of organisation confidential

Note: After the closing date

After the closing date, we will assess all feedback and use it to finalise our documents. The final documents and the Statement of Outcomes (a summary of the responses to the feedback received) will be published on http://www.hiqa.ie.

Please note that we may use your details to contact you about your responses. We do not intend to send responses to each individual respondent.

If you have any questions or would like more information about the consultation process please contact consultation@hiqa.ie

Appendix 1B

Table 2.1 Summary of key characteristics of the licensed HPV vaccines available in Ireland

Vaccine	2-valent	4-valent	9-valent
Trade name	Cervarix®	Gardasil®	Gardasil®9
Manufacturer	GlaxoSmithKline	MSD	MSD
Antigens	2-valent vaccine: Viral L1 protein for HPV types 16, 18	4-valent vaccine: Viral L1 protein for HPV types 6,11,16,18	9-valent vaccine: Viral L1 protein for HPV types 6,11,16,18,31,33,45,52,58
Formulation	Produced using a baculovirus expression system in Trichoplusia ni cells. Each 0.5 mL dose of the 2-valent vaccine contains 20µg of HPV-16 L1 protein and 20 µg of HPV-18 L1 protein adsorbed onto a proprietary adjuvant system containing 500 µg of aluminum hydroxide and 50 µg of 3-O-desacyl-4-monophosphoryl lipid A (AS04).	Produced using yeast substrate and includes amorphous aluminum hydroxyphosphate sulfate (AAHS) as adjuvant. Each 0.5 mL dose of this vaccine contains 20 µg of HPV-6 L1 protein, 40 µg of HPV-11 L1 protein, 40 µg of HPV-16 L1 protein and 20 µg of HPV-18 L1 protein adsorbed onto 225 µg of the adjuvant.	Produced using yeast substrate and includes the AAHS adjuvant. Each 0.5 mL dose of this vaccine contains 30 µg of HPV-6 L1 protein, 40 µg of HPV-11 L1 protein, 60 µg of HPV-16 L1 protein, 40 µg of HPV-18 L1 protein, 20 µg of HPV-31 L1 protein, 20 µg of HPV-33 L1 protein, 20 µg of HPV-45 L1 protein, 20 µg of HPV-52 L1 protein and 20 µg of HPV-58 L1 protein adsorbed on 500 µg AAHS.
Population	Girls and boys ≥9 years	Girls and boys ≥9 years	Girls and boys ≥9 years
Therapeutic indications	Prevention of the following conditions causally related to certain oncogenic HPV types: • Premalignant anogenital (cervical, vulval, vaginal and anal) lesions • Cervical cancer • Anal cancer	Prevention of the following conditions causally related to certain oncogenic HPV types: • Premalignant anogenital (cervical, vulval, vaginal and anal) lesions • Cervical cancer • Anal cancer • Prevention of anogenital warts (condyloma acuminata) causally related to specific HPV types	Prevention of the following conditions causally related to certain oncogenic HPV types: • Premalignant anogenital (cervical, vulval, vaginal and anal) lesions • Cervical cancer • Anal cancer • Prevention of anogenital warts (condyloma acuminata) causally related to specific HPV types

¥Reference: Summary of Product Characteristics – www.medicines.ie accessed 1/9/17[21, 22]
http://www.hse.ie/eng/health/immunisation/hcpinfo/guidelines/chapter10.pdf[23]

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