ECDC **GUIDANCE**

Introduction of HPV vaccines in European Union countries – an update

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Introduction of HPV vaccines in European Union countries – an update

This report was commissioned by the European Centre for Disease Prevention and Control (ECDC) and coordinated by Benedetto Simone, Paloma Carrillo-Santisteve and Pierluigi Lopalco.

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Contents

Abbreviations

AAHS	Amorphous aluminium hydroxyphosphate sulphate
AS04	500 µg aluminium hydroxide and 50 µg 3-O-desacyl-4'-monophosphoryl lipid A
AIS	Adenocarcinoma in situ
CDC	Centers for Disease Prevention and Control
CIN	Cervical intraepithelial neoplasia
CI	Confidence interval
DNA	Deoxyribonucleic acid
ECDC	European Centre for Disease Prevention and Control
GMT	Geometric mean titre
HR-HPV	High-risk human papillomavirus
HPV	Human papillomavirus
HSIL	High-grade intraepithelial lesion
ICER	Incremental cost-effectiveness ratio
ITP	Intention to treat population
LSIL	Low-grade intraepithelial lesion
LYG	Life years gained
MSM	Men who have sex with men
QALY	Quality-adjusted life years
RR	Risk-ratio
VENICE	Vaccine European New Integrated Collaboration Effort
VaIN	Vaginal intraepithelial neoplasia
VIN	Vulvar intraepithelial neoplasia
VLP	Virus-like particles

Preface

In January 2008, a panel of ECDC experts produced the *Guidance for the introduction of HPV vaccines in EU countries*. Since then, the European Union has come a long way: most countries have implemented national vaccination programmes for adolescent girls and a significant number have also introduced catch-up programmes for young women.

Research on the human papillomavirus (HPV) vaccines has been intense over the past four years: literature published since 2008 has provided new evidence and filled some knowledge gaps. Meanwhile, new questions have arisen: one of the main issues is whether vaccination protocols should include boys as well as girls, while another pressing concern is the unsatisfactory immunisation coverage rate achieved in most countries.

The current document has been produced to review the main developments in relation to HPV vaccination. Nevertheless, the 2008 Guidance is still a useful reference for more consolidated knowledge on the topic.

The target audiences for this guidance are national immunisation programme managers, policy makers at the EU level and in ministries of health and other relevant ministries, and experts involved in the decision-making process for the introduction of HPV vaccines in-country (e.g. oncologists, gynaecologists, paediatricians, epidemiologists, specialists in infectious disease, adolescent and sexual health, primary care physicians and others.)

The following points have been addressed in the current update:

- Current status of HPV vaccine introduction in the EU countries, Norway and Iceland
- Efficacy and safety of vaccines against HPV infection and HPV-related morbidity among women
- Efficacy, immunogenicity and safety of HPV vaccines in boys and men
- Models of effectiveness/cost-effectiveness of adding boys and men to the current HPV vaccination protocols
- New perspectives for HPV administration (alternative vaccination schedules, less-than-three-dose protocols)
- Parental acceptance and attitudes of healthcare workers towards the HPV vaccination.

For each point, the ECDC collected the scientific evidence available, focusing on literature published after 2007, and provided a list of knowledge gaps and open questions that need to be addressed by future research.

Executive summary

Current status of HPV vaccine introduction in EU countries

Since 2008, HPV vaccination programmes have been implemented in most EU countries. By May 2012, 19 out of 29 countries in the EU (including Norway and Iceland) had implemented routine HPV vaccination programmes, and 10 countries had also introduced catch-up programmes. Despite the efforts made by individual Member States, coverage rates – where data are available – are lower than expected in many EU countries. Furthermore, target age, system of financing and delivery of the vaccines differ from one country to another and coordination among EU countries is lacking.

New evidence on efficacy and safety of prophylactic vaccines against cervical HPV infection/HPV-related diseases among women

The HPV vaccines currently in use for girls are generally safe, well tolerated and highly efficacious in the prevention of persistent infection, cervical cancer and cancerous and precancerous lesions related to the vaccine-HPV serotypes. The vaccines also confer some degree of cross-protection against non vaccine-HPV serotype infection and precancerous cervical lesions. There are still, however, concerns about the duration of protection of vaccination beyond nine years (based on vaccine trials) and the possibility that a booster dose of the vaccine might be necessary to guard against waning immunity.

Current evidence on efficacy, immunogenicity and safety of HPV vaccines for boys/men

There is much speculation on the possibility of including boys in the vaccination programmes. The rationale is that vaccine coverage in boys would be effective in the prevention of HPV-related conditions in men, such as condylomata, anal cancer and oropharyngeal cancer. Furthermore, universal vaccination for men would prevent cervical cancer in women via herd immunity. Only the tetravalent HPV vaccine has been evaluated for efficacy in men and is approved for use in males. The bivalent vaccine has not been assessed. The clinical trials on efficacy, immunogenicity and safety of HPV vaccines for boys are limited and relatively recent, but current data indicate that the vaccines elicit the same, if not a higher, degree of immunogenicity in boys, compared to girls of the same age groups. The vaccines are also well tolerated and safe. Despite the short follow-up time of the studies, the efficacy of the tetravalent vaccine in preventing persistent infections and HPV-related morbidities in boys seems to be high.

Models of effectiveness and cost-effectiveness of adding boys/men to the current HPV vaccination protocols

In spite of the benefits of the vaccination, current economic models show that including boys in the current HPV vaccination programmes is unlikely to be cost-effective. However, one major limitation is that the models published in literature reflect assumptions that are not entirely evidence-based, such as duration of protection, coverage rates in girls, and incidence of HPV-related morbidities in the general population. Nevertheless, in all scenarios economic analyses render a much higher cost-effectiveness ratio for campaigns aimed at improving vaccination coverage rates in females. The cost-effectiveness of including boys in HPV vaccination programmes can be re-assessed when more solid data are available for baseline assumptions, and especially if vaccination costs are significantly reduced in the future. When more data on vaccine protection against HPV re-infection are available, one strategy worth exploring is that of targeted immunisation programmes for men who have sex with men (MSM). MSM may benefit more from HPV vaccination than the general male population, and might be an important group for targeted vaccination campaigns. Despite foreseeable obstacles in implementation, offering vaccination to MSM, even after sexual debut and exposure to HPV, might prove cost-effective.

Perspectives on HPV vaccine administration schedule

Vaccination against HPV is expensive and the regime of three doses in six months is difficult to implement. The expense of the vaccine may have resulted in some countries not promoting its availability as actively as they might given pressures on government budgets, and three doses in such a short time may be a deterrent to some individuals. These two compounded are the primary reasons why coverage rates are low. A clinical trial showed no significant difference in the efficacy of the bivalent vaccine at four-year follow-up, irrespective of whether one or two doses were administered, compared to the recommended three-dose protocol. If confirmed, these findings will have a great impact on costs and strategies for HPV vaccination programmes. Furthermore, some literature provides evidence that alternative vaccination schedules are no less effective than the recommended protocol. This knowledge might help to ensure the completion of the three-dose vaccination cycle.

Parental acceptance of HPV vaccination and attitudes of healthcare professionals

Since the recommended age for vaccination is 10–14 years in most EU countries, parental acceptance is necessary for successful implementation of the immunisation programmes. Studies in literature show that intent to vaccinate and rates of vaccination rose during the first years when the HPV vaccine was introduced but have subsequently fallen. The initial enthusiasm for the vaccine was probably due to greater visibility and debate on the issue at the time of vaccine introduction. HPV awareness therefore needs to be increased and maintained among parents through the use of ad hoc policies. Furthermore, knowledge, attitudes and practices of healthcare professionals need to be analysed. An important issue for parents and healthcare professionals is the perceived negative impact of the vaccine on the sexual conduct of adolescent girls. This perception needs to be addressed in order to improve vaccination coverage. Fear of adverse reactions to the vaccine, justified or otherwise, needs to be addressed by providing recipients, parents and those prescribing with appropriate, evidence-based information on the benefits and risks of HPV immunisation.

Social behaviour, which is partly country-specific, is another issue that needs to be reviewed and studies should be carried out to identify high vaccine coverage rates in Europe.

Summary from 2008 guidance document for the introduction of HPV vaccines in EU countries

Cervical cancer and human papillomavirus infections in the European Union

Cervical cancer is the second most common cancer after breast cancer affecting women aged 15–44 in the European Union (EU). Each year, there are around 33 000 cases of cervical cancer in the EU, and 15 000 deaths. The primary cause of cervical cancer is a persistent infection of the genital tract by a high-risk human papillomavirus (HPV) type.

Genital HPV infections are very common and acquired soon after onset of sexual activity. Most of these infections are spontaneously cleared. However, persistent HPV infections with a high-risk HPV type can cause cellular changes in the cervix that can result in cervical cancer. High-risk HPV types are also associated with other anogenital cancers, and head and neck cancers in both men and women. Some low-risk HPV types cause genital warts in both men and women.

The human papillomavirus vaccine

Two prophylactic HPV vaccines have been licensed in Europe: the quadrivalent vaccine, Gardasil® (Sanofi Pasteur MSD)/Silgard® (Merck Sharp & Dohme), and the bivalent vaccine, Cervarix® (GlaxoSmithKline Biologicals). Both are inactivated subunit vaccines and are non-infectious. Both vaccines have a good safety profile and protect against the high-risk HPV types 16 and 18, responsible for an estimated 73% of cervical cancer cases in Europe. Gardasil also protects against HPV 6 and 11, which cause most cases of genital warts. In large phase III trials both vaccines have been shown to prevent more than 90% of precancerous lesions associated with types 16 or 18 among HPV-naive women. The vaccines are given in three doses over a six-month period.

HPV vaccines and cervical cancer screening

Well organised cervical cancer screening programmes that achieve high coverage and include effective follow-up and treatment of women with abnormal cytology have been proven to reduce cervical cancer incidence by over 80%. Organised screening programmes are more successful than opportunistic screening in reaching the women most at risk, establishing mechanisms for quality control and monitoring standardised measures of activity and impact.

The HPV vaccine offers a new, complementary tool to improve the control of cervical cancer. However, it does not eliminate the need for cervical cancer screening, even for women vaccinated against HPV types 16 and 18 who will still be at risk from other high-risk types. National authorities should continue their efforts to organise and improve the coverage and quality of screening programmes, independent of vaccine introduction. Organising screening programmes where they do not exist appears to be a priority.

HPV vaccines will have an impact on the effectiveness of existing screening programmes, which will need to be monitored closely. Widespread vaccination will result in some decrease of HPV-related cytological abnormalities and vaccinated women might have a false sense of security, resulting in lower attendance at screenings. Women need to be informed and motivated to attend screening programmes, even if they are vaccinated. One of the most important challenges will be to achieve synergy between vaccination and screening in a cost-effective way and with the maximum benefit for women.

Who should be vaccinated? Determining target populations for HPV vaccination

To optimise the impact of the new vaccines on HPV-associated disease, the primary target group to consider for routine vaccination is girls at the age just before sexual activity (and therefore HPV infections) begin to become common in that group. Setting the age of vaccination lower would not prevent many infections and should be avoided until there is evidence that the vaccine can offer long-term protection (more than 15–20 years). Targeting slightly older girls and young women with catch-up vaccination at the start of a routine vaccination programme is likely to accelerate the impact of the vaccination programme and increase vaccination benefits in the short term.

Country-specific factors will be important in determining the exact age for routine vaccination, and the ages for any catch-up vaccination. These factors include: average age of sexual debut, age-specific prevalence of HPV infections (when available), vaccine delivery strategies and acceptance of vaccination by the target group (and their guardians).

Selective vaccination of 'high-risk' groups alone seems unlikely to be either practical or more effective than vaccinating all girls. However, the potential role of selective/opportunistic vaccination for some high-risk individuals in addition to routine vaccination may need further consideration.

Strategy options for HPV vaccine delivery in EU countries

School-based immunisation is likely to be the lowest-cost option for delivery of HPV vaccines to pre-adolescent girls. However, local issues, such as whether there are school-based health services, funding arrangements for vaccine purchase and administration and obtaining parental consent may affect the feasibility of this approach.

Clinic or practice-based immunisation is a universally available, additional or alternative option for HPV vaccine delivery. This may be more expensive than school-based immunisation and monitoring vaccine uptake may be more difficult.

Sexual and reproductive health and other medical clinics provided specifically for women may be important sites for immunisation. However, girls may not visit them before the onset of sexual activity and so they are likely to be useful mainly for catch-up programmes targeting older adolescents and women. Other settings may exist for provision of HPV vaccine to girls in 'hard to reach' communities and for opportunistic immunisation when girls visit medical services for other reasons. Using these might help improve overall uptake.

Existing immunisation programmes for adolescents and other ongoing health promotion activities should be taken into account when planning delivery strategies for HPV vaccine. Wherever vaccination is provided, it is vital to communicate the message that immunisation is an adjunct and not a replacement for cervical screening.

Modelling costs and outcomes of HPV vaccination

HPV vaccination should be evaluated not only for its efficacy, but also from an economic point of view. Economic evaluation aims to determine whether the cost incurred by society to save a year of life adjusted by its quality (quality-adjusted life year or QALY) due to HPV vaccination is similar to that of other commonly accepted interventions in the medical care sector.

Economic evaluations are not entirely exportable, due to the variability of costs and healthcare systems in different countries. Therefore, an effort should be made by each country to perform such an evaluation (also taking into account the kind of cervical screening in place) before making a decision on the best strategy to prevent cervical cancer.

Economic evaluations made to date seem to indicate that HPV vaccination of pre-adolescent girls (with or without catch-up of older age groups) has an acceptable cost-effectiveness profile. The results are more favourable when dynamic simulation models are used, where the effect of vaccination on transmission rates is also taken into account.

Monitoring and evaluating the impact of HPV vaccination

Post-licensure evaluation of the HPV vaccines will need to determine vaccine uptake and compliance, long-term efficacy and effectiveness of the vaccines, integration of vaccination with other strategies, such as organised cervical cancer screening, and vaccine safety. Coordination between vaccine monitoring and cancer control programmes will be critical to assess the impact of the vaccine and its benefits compared with other existing prevention interventions such as screening.

Methods to assess the impact of vaccines on clinically relevant disease endpoints might include surveillance for vaccine-related HPV infection, precancerous lesions, or cancers through established or newly developed laboratories or cytology/cancer registries.

Phase IV trials have also been proposed for evaluating the HPV vaccine impact on public health. These can provide further information about incidence of abnormal and precancerous cells, as well as cancer incidence and mortality. They could also be useful for assessing potential integration of cervical screening and vaccination programmes. Monitoring based on systematic registration of HPV vaccination and linkage studies using relevant healthcare registries can be used to assess vaccine effectiveness under field conditions.

The minimum information to monitor HPV vaccination should include data on vaccine coverage, monitoring of adverse events following immunisation and at least a sentinel surveillance of impact on pre-cancer lesions.

1 Current status of HPV vaccine introduction in EU countries

Key points

- A total of 19 out of 29 countries in the EU/EEA (Norway and Iceland but not Liechtenstein) have implemented a routine HPV vaccination programme and 10 countries have introduced catch-up programmes.
- Target age, financing and delivery of the vaccines are very different from one country to another.
- Coverage rates, where data are available, range from 17–84% and are generally lower than expected.

The HPV vaccines have been introduced in most EU/EEA countries (Table 1). As of May 2012, the vaccination advisory bodies in 22 of the 29 countries had made a recommendation in favour of HPV vaccination, compared to 12 out of 27 countries in February 2008 [1].

Cyprus, Estonia, Finland, Hungary, Lithuania, Malta, Poland and Slovakia have not yet introduced a national immunisation programme, nor have their vaccination advisory boards produced recommendations for the introduction of HPV vaccination.

In two countries, Bulgaria and Czech Republic, the recommendation has been produced but the HPV vaccination has actually been integrated into the national immunisation programme.

In 19 countries (Austria, Belgium, Denmark, France, Germany, Greece, Iceland, Ireland, Italy, Latvia, Luxembourg, the Netherlands, Norway, Portugal, Romania, Slovenia, Spain, Sweden, the United Kingdom) the programme is currently active, and ten of them have also introduced catch-up programmes for women (Table 2).

Data collected by the VENICE[1] 2 Group in 2010 register a high heterogeneity in the strategies for implementation of the HPV vaccination in the EU/EEA countries. Recommendations for the vaccination age are diverse, ranging from 9 to 18 years, as they are for catch-up rounds, where they range from 12 to 40 years. The adopted vaccination policy targets girls/women in all the countries where HPV vaccine has been introduced, except for Austria, where boys/men are also targeted.

In most cases the vaccination programmes are financed by the national health systems. However, in Austria the vaccination is entirely covered by the recipient, and Belgium and France have adopted a co-financed system, where the vaccine recipient contributes to the payment (25% and 35%, respectively).

The public health and school health services are the most common infrastructure used in the EU/EEA for vaccine delivery. Six countries rely entirely or mainly on private infrastructure (Austria, Belgium, France, Germany, Greece and Luxembourg).

As for catch-up immunisation, the ten countries where this is currently implemented have fully public-funded programmes (Denmark, Italy, Luxembourg, the Netherlands, Portugal, Romania and the United Kingdom) or partial public funding (Belgium and France). In Austria the vaccination is fully covered by the recipient. Vaccine delivery is evenly split between public and private structures.

Vaccine coverage (full three-dose, routine administered) rates are suboptimal. In 2010, out of seven countries for which data were available, only Portugal and the United Kingdom had vaccination coverage rates of ≥80%; Denmark and Italy ranged from 50–60%; France, Luxembourg and Norway had rates of ≤30%. The same applied to catch-up coverage which ranged from 29–73%. However, more recent data from some countries where the vaccination programmes were approved in 2007–2009 show higher coverage rates for the youngest vaccinated cohorts (girls born in 1996/1997): 84% coverage in Portugal (personal communications), 79% in Denmark (81% for catch-ups), 63% in Norway [2], 64% in Spain [3], 58% in the Netherlands (personal communication from EVAG expert) and 55% in Slovenia (personal communication from EVAG expert).

In Italy, the transfer of responsibility for health to regional authorities has resulted in a diverse situation within the country: only seven out of the 21 Italian regions and autonomous provinces have introduced catch-up programmes, covering around 1/4 of the national population. The target age groups for catch-up immunisation are also variable from region to region.

As of 2010, thirteen countries (Denmark, France, Ireland, Italy, Latvia, Luxembourg, the Netherlands, Norway, Portugal, Romania, Slovenia, Sweden and the United Kingdom) had declared that there was a national HPV vaccination coverage monitoring system in place for routine immunisation. Five of these countries (France, Italy, the Netherlands, Norway and Sweden) reported the existence of systems in place to follow up on adults/adolescents [4].

[1] Vaccine European New Integrated Collaboration Effort

Knowledge gaps and research questions

- Does the heterogeneity in vaccine policies from one country to another have an impact on coverage rates? Is the vaccination coverage assessment methodology the same in all EU/EEA countries?
- Would a more coordinated strategy among EU/EEA countries have an impact on vaccination costs?

Table 1. Current status of HPV immunisation programmes in EU/EEA countries (data adapted from the VENICE 2 Report, WP 3, Dec 2010 [4] and from the official national immunisation programmes)

	Introduction	Target age group	Coverage (three doses, %)	Financing	Delivery infrastructure
Austria [5]	2006	9-15 (female and male)	n/a	Fully covered by patient	Private sector (100%)
Belgium [6]	2007	10-13	n/a	75% supported by national health authorities	Private sector (100%)
Bulgaria [7]	No*	-	-	-	-
Cyprus [8]	No	-	-	-	-
Czech Republic [9]	No*	-	-	-	-
Denmark [10]	2008	12	79 (2011)§	Fully covered by national health authorities	PH (100%)
Estonia [11]	No	-	-	-	-
Finland [12]	No	-	-	-	-
France [13]	2007	14	24 (2008)	65% supported by national health authorities	PH (5%), Private sector (95%)
Germany [14]	2007	12-17	n/a	Fully covered by national health authorities	PH (5%), Private sector (95%)
Greece [15]	2008	13-18	n/a	Fully covered by national health authorities	PH (30%), Private sector (70%)
Hungary [16]	No	-	-	-	-
Iceland [17]	2011	12	n/a	Fully covered by national health authorities	SHS (100%)
Ireland [18]	2008	~12-13**	n/a	Fully covered by national health authorities	SHS (100%)
Italy [19]	2007–2008 (a)	12	65 (2011)	Fully covered by national health authorities	PH (100%)
Latvia [20]	2009	12	n/a	Fully covered by national health authorities	PH (95%), SHS (4%), Private sector (1%)
Lithuania [21]	No	-	-	-	-
Luxembourg [22]	2008	12	17 (2009)	Fully covered by national health authorities	Private sector (100%)
Malta§† [23]	2012	12	n/a	Fully covered by national health authorities	PH (100%)
Netherlands [24]	2010	12-13	58 (2011)§	Fully covered by national health authorities	PH (100%)
Norway [25]	2008	12-13	63 (2011)§	Fully covered by national health authorities	SHS (100%)
Poland [26]	No	-	-	-	-
Portugal [27]	2007	13	84 (2011)§	Fully covered by national health authorities	PH (100%)
Romania [28]	2008	12	n/a	Fully covered by national health authorities	PH (5%), SHS (95%)
Slovakia [29]	No	-	-	-	-
Slovenia [30]	2009	11-12	55 (2011)§	Fully covered by national health authorities	SHS (100%)
Spain [31]	2007	11-14	64 (2011)§	Fully covered by national health authorities	PH (50%), SHS (50%)
Sweden [32]	2008	10-12	n/a	Fully covered by national health authorities	SHS (100%)
UK [33]	2007	12-13	80 (2009)	Fully covered by national health authorities	PH (6%), SHS (94%)

*HPV: Human papillomavirus; n/a: no information available; PH: public health/primary care doctors/public health nurses/vaccination clinics; SHS: school health services; * Recommended by expert advisory board; ** First year of secondary level school; (a) depending on the region*

§ New data reported by national experts.

†New data reported by national experts, August 2012. Malta is in the process of implementing its vaccination programme.

Table 2. Current status of HPV catch-up programmes in EU/EEA countries (data adapted from the VENICE 2 Report, WP 3, Dec 2010 [4] and the official national immunisation programmes)

	Introduction	Target age group	Coverage (three doses, %)	Financing	Delivery infrastructure
Austria [5]	2011	18-40 (female and male)	n/a	Fully covered by patient	Private sector (100%)
Belgium [6]	2008	13-18	n/a	75% supported by national health authorities	Private sector (100%)
Bulgaria [7]	No	-	-	-	-
Cyprus [8]	No	-	-	-	-
Czech Republic [9]	No	-	-	-	-
Denmark [10]	2008	15-17	81 (2011)§	Fully covered by national health authorities	PH (100%)
Estonia [11]	No	-	-	-	-
Finland [12]	No	-	-	-	-
France [13]	2007	15-18	30 (2008)	65% supported by national health authorities	PH (5%), private sector (95%)
Germany [14]	No	-	-	-	-
Greece [15]	No	-	-	-	-
Hungary [16]	No	-	-	-	-
Iceland [17]	No	-	-	-	-
Ireland [18]	No	-	-	-	-
Italy [19]	2007-2010 (b)	14/15/16/17/24/ 11-18 (a)	44.3-80 (2011)	Fully covered by national health authorities	PH (100%)
Latvia [20]	No	-	-	-	-
Lithuania [21]	No	-	-	-	-
Luxembourg [22]	2008	15-16	29 (2009)	Fully covered by national health authorities	Private sector (100%)
Malta [23]	No	-	-	-	-
Netherlands [24]	2009	13-16	45 (2009)	Fully covered by national health authorities	PH (100%)
Norway [25]	No	-	-	-	-
Poland [26]	No	-	-	-	-
Portugal [27]	2009	17	82 (2011)§	Fully covered by national health authorities	PH (100%)
Romania [28]	2010	12-24	n/a	Fully covered by national health authorities	PH (30%), SHS (30%), private sector (20%), public hospitals (20%)
Slovakia [29]	No	-	-	-	-
Slovenia [30]	No	-	-	-	-
Spain [31]	No	-	-	-	-
Sweden [32]	No	-	-	-	-
United Kingdom [33]	2008	13-17	32 (2009)	Fully covered by national health authorities	PH (70%), SHS (30%)

*HPV: Human papillomavirus; n/a: no information available; PH: public health/primary care doctors/public health nurses/vaccination clinics; SHS: School health services; *Recommended by expert advisory board, not implemented; (a) depending on the region; (b) 6/21 regions implemented a catch-up programme, covering 19.4% of the population.*

2 New evidence on efficacy and safety of prophylactic vaccines against cervical HPV infection/HPV-related diseases among women

Key points

- The HPV vaccines currently in use for girls are safe, well tolerated and highly efficacious in the prevention of persistent infection, cervical cancer and other cancerous and precancerous lesions related to the vaccine-HPV serotypes.
- The vaccines confer some degree of cross-protection against non vaccine-HPV serotype infection and precancerous cervical lesions.

A systematic review and meta-analysis published in 2011 [34] evaluated efficacy and safety of the HPV vaccines up to 31 July 2009. Seven randomised controlled trials were selected (Appendix 1). The primary efficacy endpoint was defined as the occurrence of high-grade cervical lesions or worse (cervical intraepithelial neoplasia grades 2 and 3, adenocarcinoma in situ or cervical carcinoma). Type-specific persistent infection was chosen as the secondary endpoint. Occurrence of adverse events was examined for assessment of vaccine safety.

The seven trials included 44 142 females globally. Data collected showed that the vaccines are safe, well tolerated and highly efficacious in preventing persistent infections and cervical diseases associated with vaccine-HPV types in young females. The data also support the notion that the vaccines provide some degree of cross-protection from persistent infections and cervical diseases associated with non vaccine-HPV serotypes. Details are shown in Table 3.

Since July 2009, one new trial [35] and two updates of older trials [36, 37]have been published on the efficacy and safety of the bivalent vaccine among women. So far results are in line with what is already known, both as regards efficacy and safety. Literature published after July 2009 confirms the high efficacy of the bivalent vaccine on HPV-related conditions in young women up to 7.3 years (8.9 years according to the summary of product characteristics on the website for Cervarix®) [38]. Cross-protection against non vaccine-HPV serotypes and the high safety profile of the vaccine are also confirmed (see Appendix 2).

The new scientific evidence therefore supports the choice made by most European countries to introduce HPV universal coverage in girls and could act as a further stimulus for the introduction of a vaccination programme in those EU countries where it is still not in place.

It is worth mentioning, however, that the published data (relative to the bivalent vaccine) on immunised women with the longest follow-up period only covers 7.3 years since vaccine administration, even though the summary of product characteristics on the website for Cervarix® reports 8.9 years of follow-up [38]. It is still unknown how long effective immunity will last and whether boosters will be required. Data on long-term immunogenicity of the vaccines show that in most cases geometric mean titres (GMTs) remain several times higher than natural infection levels up to seven years after immunisation. On the other hand, GMTs are shown to drop within two years of the first vaccination and to continue decreasing at a slower rate after that. Another issue worth considering is that, although efficacy of HPV vaccines was found to be above 90% in the according-to-protocol cohorts, the intention-to-treat cohorts showed less encouraging results. Further studies on long term efficacy and immunogenicity of vaccines should therefore to be encouraged [39].

For these reasons, it is necessary to stress once again that the HPV vaccines cannot replace or modify current routine cervical cancer screening protocols. It is imperative that national screening programmes are maintained and that the impact of vaccines on screening programmes is monitored closely.

Lastly, although all current analyses of the long-term benefits and costs of HPV vaccination on girls show that the vaccines are cost-effective [40] (see *Guidance for the introduction of HPV vaccines in EU countries*), these analyses are complicated by the uncertainties of waning immunity and the impact of incomplete vaccination. Re-assessment will therefore be necessary once more data on the topic are made available.

Knowledge gaps and research questions

- How long does the immunity conferred by the vaccines last?
- Will booster doses be necessary?
- If waning immunity is a possibility and women will be exposed and susceptible to HPV at an older age because of the vaccination, what consequence will this have on the epidemiology and morbidity of HPV-related conditions?
- What is the impact of incomplete vaccination on the benefits and cost-effectiveness of vaccination programmes?
- What is the long-term impact of vaccines on screening programmes?

Table 3. Efficacy and safety of HPV vaccines (from Lu et al. 2011)

	Vaccine		Control		Risk ratio
	Events	Total	Events	Total	IV, fixed, 95% CI
Efficacy					
CIN2+ associated with HPV 16					
Intention to treat populations	85	14506	232	14523	0.47 [0.36, 0.61]
Per-protocol populations	3	11617	93	11323	0.04 [0.01, 0.11]
CIN2+ associated with HPV 18					
Intention to treat populations	8	14023	53	14030	0.16 [0.08, 0.34]
Per-protocol populations	2	11849	26	11716	0.10 [0.03, 0.38]
CIN1+ associated with HPV 16					
Intention to treat populations	67	10922	174	10969	0.43 [0.33, 0.58]
Per-protocol populations	0	2643	63	2597	0.02 [0.00, 0.11]
CIN1+ associated with HPV 18					
Intention to treat populations	9	10425	44	10460	0.22 [0.10, 0.44]
Per-protocol populations	0	2102	16	2120	0.03 [0.00, 0.51]
Persistent HPV 16 infection of ≥ six months					
Intention to treat populations	25	5974	173	5990	0.15 [0.10, 0.23]
Per-protocol populations	31	7332	475	7153	0.06 [0.04, 0.09]
Persistent HPV 18 infection of ≥ six months					
Intention to treat populations	16	6456	69	6492	0.24 [0.14, 0.42]
Per-protocol populations	9	7056	193	6952	0.05 [0.03, 0.09]
CIN2+ associated with HPV 31/33/45/52/58					
Intention to treat populations	267	17213	341	17263	0.79 [0.67, 0.92]
Per-protocol populations	74	12478	130	12533	0.58 [0.43, 0.77]
Persistent infection of ≥ six months associated with HPV 31, 33, 45, 52 and/or 58					
Intention to treat populations	1092	10262	1418	10262	0.77 [0.72, 0.83]
Per-protocol populations	661	8700	922	8672	0.72 [0.65, 0.79]
Safety					
Serious adverse effects	825	21916	829	21940	1.00 [0.91, 1.09]
Injection-related serious adverse effects	15	21916	8	21940	1.82 [0.79, 4.20]

HPV: Human papillomavirus; CIN: Cervical intraepithelial neoplasia

3 Current evidence on efficacy, immunogenicity and safety of HPV vaccines for boys/men

Key points

- Clinical trials on immunogenicity and safety of HPV vaccines on boys are few and relatively recent.
- The vaccines seem to elicit the same, if not a higher degree of immunogenicity in boys than in girls of the same age groups.
- The vaccines are well tolerated and safe.
- Only the tetravalent vaccine has been assessed for efficacy and reported to be effective in the prevention of persistent infections and HPV-related morbidity in boys.

The rate of genital HPV infection is similar in males and females [41, 42] but there are differences in the immune-response to natural infection. Overall, 17.9% of females are seropositive, compared to only 7.9% of males, and antibody titres are generally higher in females [43, 44]. Natural lower immune response to HPV in males probably explains the higher prevalence of HPV infections compared to that observed among females [41] [43,44].

In recent years there has been much speculation on the possibility of extending vaccine coverage to boys [45] and the justification is very sensible. First, if the male population were to be immunised it would reduce the risk of females being infected, via herd immunity. Second, although the major burden of HPV is cervical disease, the virus is also associated with other morbidities affecting men as well as women (e.g. anogenital warts, penile, anal and oropharyngeal cancers and respiratory papillomatosis) [46, 47] and, although less prevalent than cervical cancer, these conditions still incur varying degrees of morbidity, mortality and cost. Third, even if all women were immunised, the HPV chain of transmission would still be maintained through men who have sex with men (MSM). Some authors have also speculated that limiting vaccination to women might increase the psychological burden on women by confirming a perceived inequality of the sexes [48]. Finally, previous experience in gender-restricted vaccination programmes has demonstrated a substantially lower effectiveness than universal vaccination [49].

Scientific literature on vaccination in men/boys is not as prominent as that associated with women/girls. There are fewer trials concerning the male population and they are more recent than those conducted on females. So far however, the trials conducted on men/boys have showed similar patterns of safety and reactogenicity [44], [50-52] to those for women/girls of the same age. Two trials [51,52] on immunogenicity of the HPV-16/18 vaccine showed substantially higher immune response in young males compared with females of similar age groups. Post-vaccination antibody levels for the HPV-type vaccines were up to three times higher in males than in females. Similar in both males and females was the fact that the vaccines elicited higher antibody levels in younger age groups (10–14 years compared to 15–18 years) [51].

Vaccine efficacy in females and males is somewhat difficult to compare, since cervical disease is the primary end point in most studies conducted on girls/women. To date, only the efficacy of the quadrivalent HPV vaccine has been assessed on men.

One recently published trial [44] [53] involved 16–26 year-old males and focused on the occurrence of condylomata acuminata (warts), the most common HPV-related lesion, and on anal intraepithelial neoplasia.

Point efficacy estimates for warts (see Table 4) were lower than those for females in previous studies. However, confidence intervals overlap, suggesting that vaccine efficacy may be similar for the two sexes. The study also provides efficacy data in a potential high-risk category – MSM. Efficacy against external genital lesions in this group was reported as 79% and was statistically insignificant (95% CI: –88–100%) in the per-protocol population (efficacy among heterosexual men: 92%; 95% CI: 70–99%); the intention-to-treat analysis yielded an efficacy comparable to that for heterosexual men (44%, 95% CI: 20–61%; 50%, 95% CI: 36–62%, respectively). It should be noted that, although the subpopulation of MSM consisted of a relatively small sample size (275 MSM in the ITP (Intention to treat population), compared to 1 542 heterosexual men), the rate of HPV-persistent infection was five times higher in MSM than in heterosexual men.

As for anal intraepithelial neoplasia associated with HPV-6, 11, 16, or 18, the quadrivalent vaccine showed an efficacy of 50.3% (95% CI: 25.7–67.2) in the intention-to-treat population and 77.5% (95% CI: 39.6–93.3) in the per-protocol; the corresponding efficacies against anal intraepithelial neoplasia associated with HPV of any type were 25.7% (95% CI: –1.1–45.6) and 54.9% (95% CI: 8.4–79.1) respectively. Rates of anal intraepithelial neoplasia per 100 person-years were 17.5 in the placebo group and 13.0 in the vaccine group of the intention-to-treat population and 8.9 in the placebo group and 4.0 in the vaccine group of the per-protocol efficacy population. The rate of grade 2 or 3 anal intraepithelial neoplasia related to infection with HPV-6, 11, 16, or 18 was reduced by 54.2% (95% CI: 18.0–75.3) in the intention-to-treat population and by 74.9% (95% CI: 8.8–95.4) in the per-protocol efficacy population. The corresponding risks of persistent anal infection with HPV-6, 11, 16, or 18 were reduced by 59.4% (95% CI: 43.0–71.4) and 94.9% (95% CI: 80.4–99.4) respectively.

In conclusion, scientific evidence on the efficacy and safety of HPV vaccine in men is promising but needs to be strengthened by further studies and follow-up of the closed trials. In particular, no data are available on the efficacy of the HPV vaccine in preventing oropharingeal and penile cancers. However, current evidence does suggest that HPV vaccines in boys/men are beneficial in the prevention of HPV-related conditions in the male population.

Knowledge gaps and research questions

- Why is the natural immune response to HPV lower in males than in females?
- What is the long-term immunogenicity pattern and safety profile of the vaccine in males? Does this differ from that for females?
- What is the long-term efficacy of the vaccine in preventing HPV-related conditions in men (in particular oropharingeal and penile cancers)?
- What is the risk that vaccination of men will cause their female partners to develop HPV-related conditions?

Table 4. Efficacy of quadrivalent HPV vaccine in males (from Giuliano et al. 2011)

	Vaccine		Control		Efficacy (%)
	Events	Person-yr at risk	Events	Person-yr at risk	[95% Confidence intervals]
Efficacy					
External genital lesions					
ITP	36	4612.6	89	4538.6	60.2 [40.8, 73.8]
PPP	6	3172.9	36	3081.1	83.8 [61.2, 94.4]
External genital lesions related to vaccine HPV types					
ITP	27	4625.7	77	4556.5	65.5 [45.8, 78.6]
PPP	3	2830.9	31	2812.2	90.4 [69.2, 98.1]
Persistent infection with vaccine HPV types					
ITP	148	4094.3	273	3942.6	47.8 [36.0, 57.6]
PPP	15	2549.4	101	2469.3	85.6 [73.4, 92.9]
Detection of vaccine HPV types DNA at any time					
ITP	384	3851.1	511	3736.5	27.1 [16.6, 36.3]
PPP	136	2455.3	241	2404.1	44.7 [31.5, 55.6]

HPV: Human papillomavirus; ITP: Intention to treat populations; PPP: Per-protocol populations.

4 Models on effectiveness and cost-effectiveness of adding boys/men to the current HPV vaccination protocols

Key points

- Including boys in the current HPV vaccination programmes is likely to be beneficial to both sexes.
- The models published in literature originate from assumptions that are not fully evidence-based.
- Vaccinating boys is unlikely to be cost-effective in the current economic conditions.
- Most economic analyses render a much higher cost-effectiveness ratio for campaigns aimed at improving vaccination coverage rates in females.
- The cost-effectiveness of including boys in HPV vaccination programmes can be re-assessed if vaccination costs are significantly reduced in the future.
- MSM may benefit more from HPV vaccination and targeted vaccination campaigns than the general male population.
- Vaccination of MSM might be cost-effective even after sexual debut and exposure to HPV infections.

General male population

Even if extending HPV vaccination to boys/men would to some extent be beneficial to both sexes, the matter of cost-effectiveness remains controversial.

Provided that the efficacy and safety of HPV vaccines are comparable in men and women, and that anogenital warts in men have a higher impact on quality of life than previously assumed [54], the most effective strategy to prevent HPV-related morbidity would be universal coverage. However, cervical disease accounts for a major part of HPV-related burden of disease and, at present, HPV vaccination programmes are costly.

Several models have been produced in recent years that include boys/men in HPV vaccination programmes. A detailed table of analyses available from literature is reported in Appendix 3. The models are based on a series of assumptions: effective vaccine coverage rates among girls; duration of vaccine protection; definition and epidemiology of HPV-attributable conditions [55]. These assumptions still need to be verified through further research in order to provide a complete set of evidence-based data. Different baseline assumptions, as well as different choices for the modelling, have generated wide discrepancies in the cost-effectiveness estimates for vaccinating boys.

However, although vaccinating boys may have some benefit on the reduction of cervical cancer rates among females (via herd immunity) and on other HPV-related conditions among both males and females, this benefit seems unlikely to be cost-effective, especially if high vaccination coverage can be provided to the female population and the duration of protection is long.

In November 2011, the American Centers for Diseases Prevention and Control (CDC) recommended that young boys as well as girls should get immunised against human papillomavirus. In particular, CDC officials said that the disappointing coverage rate in girls had encouraged them to review the matter. Male vaccination is most cost-effective when coverage of females is low and, in 2010, only 49% of adolescent girls in the US had received at least the first of the recommended three HPV shots [56]. In January 2012, Canada's National Advisory Committee on Immunization also recommended extension of the tetravalent vaccination to males aged between nine and 36 years. The Committee, however, leaves it to the States and Territories to decide whether to adopt this recommendation on the basis of economic considerations and so far no Canadian State has done so [57].

For the time being, it is imperative that clinical trials on male vaccination programmes carry on, but at present universal coverage for boys appears to be too costly in proportion to the potential benefits. This consideration is of paramount importance in most EU countries, where vaccination programmes are funded – fully or in part – by public health systems. The case of Austria is emblematic: vaccination is recommended for both girls and boys, but the cost of vaccination is covered by the recipients.

Most economic analyses render a much higher cost-effectiveness ratio for campaigns aimed at improving vaccination coverage rates in females. Covering boys has an impact on girls, but herd immunity works both ways, and its effects are optimised by increasing coverage in girls rather than including boys in a programme. Assuming coverage is independent in girls and boys, theoretically if 100% of girls and 0% of boys were to be vaccinated, then 100% of heterosexual partnerships would have at least one person vaccinated. Yet under similar conditions and with the same expenditure on vaccine provision, if 50% of girls and 50% of boys were to be vaccinated, on average only 75% of heterosexual partnerships would have at least one partner vaccinated [58].

On this topic, it is worth mentioning a recent, publicly-funded Dutch study [59] that addresses the question of whether female-only or male-and-female vaccination makes a difference in reducing the prevalence of sexually transmitted diseases such as HPV. The authors used a range of two-sex transmission models with varying detail to

identify general criteria for allocating a prophylactic vaccine between both sexes. The most effective reduction in the population prevalence of infection was always achieved by single-sex vaccination. Increasing vaccine uptake among pre-adolescent girls resulted in more effective reduction of HPV infection than including boys in existing vaccination programmes.

Furthermore, it is reasonable to assume that coverage might not be independent in girls and boys, but that there are close overlaps between the social networks of girls likely to be vaccinated and boys likely to be vaccinated. This would lead to a higher proportion of heterosexual partnerships where both males and females are vaccinated and a lower proportion of partnerships where only one partner is vaccinated, with the lowest return in terms of cost-effectiveness. Similarly, the greatest health benefit will be for females in that they will avoid cervical cancer through immunisation, meaning that prospects are good for the acceptance of vaccination. There is less of a health gain for males and it is therefore unrealistic to assume that introducing male vaccination would automatically lead to the same coverage levels as achieved in females.

The cost-effectiveness of vaccinating boys could therefore be re-assessed when new evidence is available, especially if regimens of less than three vaccine doses are proven to be just as efficacious as the current standard vaccination protocols, meaning that costs can be significantly reduced (see Section 5).

Men who have sex with male partners

One strategy that deserves more attention is the targeted immunisation of high-risk categories of men, such as MSM, who are particularly susceptible to developing HPV-related anal cancer. Data from the US on incidence of anal cancer show that it is much lower than that of cervical cancer, but the risk of anal cancer among MSM (especially HIV-positive men) is comparable to that of cervical cancer before routine cytology-based screening was introduced [55]. MSM may benefit more from HPV vaccination than the general male population, and might be an important target population, even though identification of MSM might not occur until after sexual initiation and exposure to HPV infections, resulting in lower vaccine effectiveness.

A cost-effectiveness modelling analysis of vaccinating MSM in the USA estimated that, even if MSM were vaccinated at 20 or 26 years of age (that is, after potential exposure to HPV infections) the cost-effectiveness ratios were less than USD 50 000 per QALY under most scenarios. For example, HPV vaccination of MSM at 26 years would cost USD 37 830 per quality-adjusted life-year when previous exposure to all vaccine-targeted HPV types was assumed to be 50% [60].

Given the limited amount of data available from clinical trials, the knowledge gaps on the epidemiology and nature of HPV-related conditions in men, and the potential challenges to the administration of the vaccine to MSM, it is currently impossible to assess the cost-effectiveness of targeting MSM for immunisation. Although this topic needs to be investigated further, it does seem plausible that countries where only girls are routinely vaccinated could benefit from the implementation of targeted immunisation programmes for MSM.

Knowledge gaps and research questions

- Which outcomes (clinical conditions) should be considered HPV-related in men and to what extent? How should they be defined?
- What is the exact epidemiology of these outcomes?
- What is the cost of the psychological impact of HPV-related morbidities, such as condylomata?
- Which economic model best fits in order to take into account the impact of herd immunity on the female population?
- What is the epidemiology and the cost of HPV-related morbidities in MSM compared to heterosexual men?
- To what extent does the vaccine confer protection against re-infection in MSM?
- Which strategies could be implemented to promote early uptake of HPV vaccine among MSM?

5 Comparative economic evaluations of quadrivalent and bivalent vaccines

Key points

- Several models have been produced comparing the cost-effectiveness of the two vaccines. However, they are based on numerous assumptions and are of limited use due to the differences between the two vaccines.
- Considering new evidence on the burden of disease of anogenital warts, the models estimate that the bivalent vaccine should cost EUR 20–42 less than the quadrivalent vaccine per dose to be equally cost-effective.

Several countries procure one of the two vaccines currently on the market for publicly funded vaccination programmes, and a number of economic models have been produced to compare the cost-effectiveness of the two vaccines. Based on these models the quadrivalent vaccine was procured by Denmark and France, whereas the Netherlands procured the bivalent vaccine. The UK originally procured the bivalent vaccine and in 2011 switched to the quadrivalent vaccine, following a new economic evaluation.

The procurement of one vaccine instead of the other is not an obvious choice. The two vaccines are very different in valency, licensed indications, cross-protective potential, long-term immunogenicity and tender price. Furthermore, all cost-effectiveness models are based on a series of theoretical assumptions that have yet to be proven.

The latest study from the UK, published in late 2011 [61], concluded that the bivalent vaccine needs to be cheaper than the quadrivalent vaccine to be equally cost-effective, mainly because of its lack of protection against anogenital warts. The price difference per dose ranges from a median of GBP 19–35 (EUR 23–42) depending on the scenario. This study integrates a previous analysis performed in 2008 to inform vaccine procurement for the UK HPV immunisation programme, where the median additional price per dose for an equally cost-effective quadrivalent vaccine was estimated to be about GBP 15–23 (EUR 18–27) per dose. The estimates were reconsidered, mainly on the basis of new evidence on the quality of life detriment due to episodes of warts [54].

An Irish study [63] found that, assuming lifelong vaccine duration, the bivalent vaccine would have to be 22% (or about EUR 20 per dose) cheaper to be as cost-effective as the quadrivalent vaccine because of lack of protection against anogenital warts. A Canadian study [64] estimated the difference to be around CAD 35 (around EUR 27) per dose.

Knowledge gaps and research points

- What is the effective burden and impact on quality of life of anogenital warts?
- What is the cost-effectiveness of the vaccines in different environments/countries?

6 Perspectives on HPV vaccine administration schedule

Key points

- Vaccination against HPV is expensive and difficult to complete: this partly explains why coverage rates are low.
- A clinical trial showed no significant difference in vaccine efficacy whether two doses or one dose were administered, compared to the recommended three-dose protocol. These findings need to be verified. If confirmed, however, they will have a great impact on costs and strategies for HPV vaccination programmes.
- Some literature provides evidence of non-inferiority of alternative vaccination schedules compared to the recommended protocol. This knowledge might help to ensure the completion of the three-dose vaccination cycle.

Efficacy of fewer than three doses of HPV vaccine

A recently published study [65] has evaluated the efficacy of fewer than the recommended three doses of the bivalent HPV vaccine. The study was nested within the Costa Rica HPV Vaccine Trial (funding: GlaxoSmithKline), which started in 2004. Although all the young women (18–25 years) enrolled in the trial were assigned to receive three doses of the HPV 16/18 vaccine or a control vaccine, four years after the trial start 5 967 received three vaccine doses (2 957 HPV vs. 3 010 control), 802 only received two doses (422 HPV vs. 380 control), and 384 received one dose (196 HPV vs. 188 control). The reasons for receiving fewer doses and other pre- and post-randomisation characteristics were diverse but balanced within each dosage group between women receiving the HPV and control vaccines. The study reports no significant difference in efficacy at four years follow-up, irrespective of whether one or two doses of vaccine were administered, compared to the recommended three-dose protocol. Efficacy, in terms of HPV 16/18 persistent infection incidence, was reported to be 80.9% for three doses of the HPV vaccine (95% CI: 71–88%), 84% for two doses (95% CI: 50–96%), and 100% for one dose (95% CI: 67–100%).

Three-dose regimens for HPV vaccines are expensive and difficult to complete, especially in settings where the need for cervical cancer prevention is greatest. The validity of this study is limited by the small sample size. Furthermore, long-term efficacy of two- or one-dose protocols, compared to the standard three-dose regimen, needs to be assessed. Nevertheless, the results reported in the study do provide a strong justification for carrying out ad hoc clinical trials on the matter. If a one- or two-dose regimen of HPV vaccination does in fact elicit a good and durable immune response, these findings will have a great impact on costs and strategies for HPV vaccination programmes throughout Europe. Although there is insufficient evidence at this time, British Columbia (Canada) and Switzerland are already recommending a two-dose schedule of HPV vaccine for females of 9–13 years and under 15 years, respectively.

Evidence on alternative vaccination schedules

The three-dose schedule over a six-month period can be a potential barrier to vaccine introduction and this is particularly relevant for countries with limited resources. However, given the low coverage rates achieved even in high-income European countries [see Section 1], alternative vaccination schedules represent an attractive perspective, especially as regards catch-up campaigns for women.

Three experimental studies in literature have focused on alternative HPV vaccination schedules (see Appendix 4). The studies focus on immunogenicity and the safety aspects of vaccination and provide some evidence that alternative vaccination schedules are not inferior to the standard schedule (e.g. third vaccine dose administered 12 months instead of six months after the first dose). This knowledge might help to ensure that young women complete the three-dose vaccination cycle.

While on the subject of alternative schedules, it is worthwhile mentioning that the Canadian States of Quebec and British Columbia [66] have adopted a 0, 1 and 60-month vaccination calendar, while Portugal allows women to finish the vaccination schedule up to the age of 25 years (personal communications).

Knowledge gaps and research questions

- What is the long-term immunogenicity trend of fewer than three vaccine doses?
- What is the long-term efficacy of fewer than three vaccine doses as regards incidence of persistent infection and of HPV-related conditions?
- How will this finding, if confirmed, impact on cost-effectiveness models?
- What are the long-term safety, immunogenicity and efficacy profiles of alternative HPV vaccination schedules?
- Would having multiple HPV vaccination schedules be cost-effective?

7 Parental acceptance of HPV vaccination and attitudes of healthcare professionals

Key points

- Current vaccine uptake is low. Widespread parental acceptance is necessary for the successful implementation of the HPV vaccination programmes.
- Intent to vaccinate and rates of vaccination rose during the first years following introduction of the HPV vaccine but have subsequently fallen in many western European countries
- One major issue, for some parents and healthcare professionals is the perception of the vaccine's negative impact on the sexual conduct of adolescent girls.
- HPV awareness needs to be increased and maintained among both parents and healthcare professionals by means of ad hoc policies.

In spite of an active offer of HPV immunisation programmes in most EU countries, vaccine uptake remains low (see Section 1). Much literature has been produced on the topic and there are essentially four reasons suggested for the low vaccine uptake rate: 1) scarce knowledge of HPV and the HPV vaccine; 2) high costs in countries where they are covered by the recipient; 3) perceived low efficacy of the vaccine; 4) alleged and real adverse events to vaccines. Since prophylactic vaccination is most effective if administered before sexual debut, immunisation programmes throughout the EU countries target girls (and in the case of Austria, boys) aged 10–18 years. In most cases, vaccination programmes target the 10–14 year age group. Therefore, one of the key factors for successfully implementing HPV vaccination programmes is parental acceptance [67].

A recent systematic review [67] collected all the evidence produced from 2001 to 2011 on parental knowledge, attitudes and behaviour towards HPV vaccines. Of the 53 studies included, 15 were produced within the EU, involving over 22 000 European parents. Moreover, the vast the majority of studies came from high-resource settings (EU, United States, Canada, Australia and New Zealand), and present relatively homogeneous results, which can be extremely useful for enhancing strategies to improve vaccination coverage rates in the EU countries. Some of the key results from the review are reported below.

Knowledge focus: the percentage of parents who had heard about HPV clearly rose over time (from 60% in 2005 to 93% in 2009). Parents' understanding of the link between HPV infection and cervical cancer also increased (from 70% in 2003 to 91% in 2011).

Behaviour focus: during the era of vaccine approval in the US and in most European countries (2006–2008), there appeared to be a stronger awareness of the vaccines which has waned with time. This same pattern is seen in the percentage of parents whose children received the HPV vaccine (84% in 2010; 36% in 2011).

Attitude focus: parental intention to have a child vaccinated against HPV reached a peak when the national authorities approved the use of the vaccines and decreased in subsequent years.

Barriers against the vaccine: a common pattern from the studies included in the review is that parents still have concerns regarding safety and side-effects and want more information. Parents sometimes view the vaccine in a similar vein to the oral contraceptive pill and prefer to postpone vaccine administration until their children are sexually active. Parents look to their physicians to recommend the vaccine.

In conclusion: awareness of the vaccine, intent to vaccinate and rates of vaccination rose during the first years after the HPV vaccine was introduced but have fallen in subsequent years. Parents need more information and reassurance from healthcare workers about the safety and effectiveness of the vaccines. Policy programmes, to increase HPV vaccination uptake as part of an overall HPV strategy to reduce the incidence of cancers and infections caused by the virus, will need to heed parents' concerns and communicate the appropriate information.

Given the lower-than-expected coverage rates in all EU countries, attitudes, knowledge and practices of healthcare professionals towards the vaccination should be studied in detail. In a literature search, only three articles from EU countries focused on this aspect. A survey of physicians in the Rhône-Alpes region of France found that opinion on the HPV vaccine was favourable (80.8%) and that it was widely used. However, there were some concerns in relation to the potential for side effects and the recommended target age of recipients due to the fact that the vaccine had only recently been introduced. In particular, according to physicians, the concern about age was related to the need to discuss sexually transmitted infections with adolescent patients. Another study from the Provence-Alpes-Cote d'Azur region of France also reported 89.6% of physicians as being in favour of the vaccination. Here too, concerns emerged in relation to the possible negative effects on the image of sexuality and cervical cancer screening. The great majority of school nurses interviewed in a British study declared they had little information on HPV and the vaccine, despite having to discuss the safety and the role of the HPV vaccination with adolescents and parents (see Appendix 5).

It should be noted that social factors and behaviour affecting vaccine acceptance, such as the sexual conduct of adolescent girls, are in part country-specific and need to be addressed at a national level.

Knowledge gaps and research questions

- Which strategies would be most appropriate in order to raise and maintain a high HPV awareness among parents?
- Would routine cervical screening be a useful forum for informing young mothers about HPV vaccines for their children?
- What are the attitudes, knowledge and practices of healthcare practitioners in EU countries in relation to the HPV vaccine?
- Why is the HPV vaccine associated with possible negative effects on sexual behaviour, when the same does not apply to other vaccines for sexually transmitted diseases, e.g. the hepatitis B virus?
- What social factors and behaviour affect vaccine acceptance at a national level?

Appendix 1. Characteristics of the randomised controlled trials included in Lu, et al.

Table 1. Randomised controlled trials included in Lu, et al.

	Koutsky & Mao (1, 2)	Harper (3, 4)	Villa (5, 6)	FUTURE I (7, 8, 9)	FUTURE II (8, 9, 10)	PATRICIA (11, 12)	Muñoz (13)
Phase	III	III	II	III	III	III	III
No. of study sites	16	32	5	62	90	135	38
Countries included	1	3	5	16	13	14	7
Year of study enrolment	10/1998–11/1999	11/2003–07/2004	Not reported	01/2002–03/2003	06/2002–05/2003	05/2004–06/2005	06/2004–04/2005
Funding source	Merck	GlaxoSmithKline	Merck	Merck	Merck	GlaxoSmithKline	Merck
Inclusion criteria							
Age	16–25	15–25	16–23	16–24	15–26	15–25	24–45
Lifetime no. of sexual partners	≤ 5	≤ 6	≤ 4	≤ 4	≤ 4	≤ 6	No restriction
Exclusion criteria	Pregnancy, history of abnormal Pap smear.	History of abnormal Pap smear, or ablative or excisional treatment of cervix; ongoing treatment for external condylomata; seropositive for HPV 16 or 18; DNA positive for any of 14 HR HPV in past 90 days.	Pregnancy, history of abnormal Pap smear.	Pregnancy, history of abnormal Pap smear or genital warts.	Pregnancy, history of abnormal Pap smear.	History of colposcopy, pregnancy, breastfeeding, autoimmune diseases or immunodeficiency.	Pregnancy, history of genital warts, present or past cervical disease, immuno-compromised.
Intervention and comparator							
Vaccine component	HPV 16 VLPs	HPV 16, 18 VLPs	HPV 6, 11, 16, 18 VLPs	HPV 6, 11, 16, 18 VLPs	HPV 6, 11, 16, 18 VLPs	HPV 16, 18 VLPs	HPV 6, 11, 16, 18 VLPs
VLP amount (µg)	40	20/20	20/40/40/20	20/40/40/20	20/40/40/20	20/20	20/40/40/20
Vaccine adjuvant	225 µg AAHS	AS04 (500 µg/50 µg)	225 µg AAHS	225 µg AAHS	225 µg AAHS	AS04 (500 µg/50 µg)	225 µg AAHS
Comparator	Placebo	Placebo	Placebo	*Placebo/Placebo + hepatitis B vaccine	Placebo	Hepatitis A vaccine	Placebo
Comparator adjuvant	225 µg AAHS	500 µg aluminium hydroxide	225 or 450 µg AAHS	225 µg AAHS	225 µg AAHS	500 µg aluminium hydroxide	225 µg AAHS
Administration schedule	Month 0,2,6	Month 0,1,6	Months 0,2,6	Month 0,2,6	Month 0,2,6	Month 0,1,6	Month 0,2,6
Clinical Protocol							
Frequency of HPV DNA test	6-month interval	6-month interval	6-month interval	6-month interval	6-month interval	6-month interval	6-month interval
Frequency of cytology test	6-month interval	6-month interval	6-month interval	6-month interval	12-month interval	12-month interval	6-month interval
Length of trial (months)	41	Initial trial: 27 Follow-up study: 53	Initial trial:36 Follow-up study:60	36.0 (mean)	36.0 (mean)	39.4 (mean)	26.4 (mean)

	Koutsky & Mao (1, 2)	Harper (3, 4)	Villa (5, 6)	FUTURE I (7, 8, 9)	FUTURE II (8, 9, 10)	PATRICIA (11, 12)	Muñoz (13)
Endpoints							
Primary	Persistent HPV 16 infection	Incidence infection with HPV 16, and/or 18.	Combined incidence of HPV 6, 11, 16 and/or 18-associated 6-month persistent infection, CIN1-3, AIS, VIN1-3, VaIN1-3, external genital warts and cervical, vulvar or vaginal cancer.	Incidence of HPV 6, 11, 16, and/or 18-associated genital warts, CIN1-3, VIN1-3, VaIN1-3, AIS, and cervical, vulvar or vaginal cancer	HPV 16 and/or 18-associated CIN 2-3, AIS and cervical cancer	HPV 16/18-associated CIN2+	Combined incidence of six-month persistent infection, CIN1-3, VIN1-3, VaIN1-3, AIS, cervical, vulvar or vaginal cancer, and genital warts associated with HPV 6, 11, 16 or 18, or with HPV 16 or 18 alone.
Secondary	Transient or persistent HPV 16 infection.	Persistent infection with HPV 16, 18 or 16/18; HPV 16/18-associated LSIL, HSIL, CIN1-3 and cancer.		Combined incidence of HPV 6, 11, 16 and/or 18-associated CIN1-3, AIS and cancer; persistent infection, CIN1-3 and AIS associated with HPV 31, 33, 45, 52, 58.	Persistent infection, CIN1-3 and AIS associated with HPV 31, 33, 45, 52, 58.	Persistent infection with HPV 16, 18 or other oncogenic types; HPV 16/18-associated CIN1+; immunogenicity and safety.	Combined incidence of 6-month persistent infection, CIN1-3, VIN1-3, VaIN1-3, AIS, cervical, vulvar or vaginal cancer, or genital warts associated with HPV 6 or 11.
Populations for efficacy analysis							
Per-protocol population (PPP)	All subjects that received three doses of vaccine or placebo; DNA negative for HPV 16 in cervical swab and biopsy from Day 1 to month 7; seronegative for HPV 16 on Day 1; had no protocol violation; had a Month 7 visit within 14–72 days after the third vaccination.	All subjects that received three doses of vaccine or placebo; DNA negative for 14 HR HPV on Day 1; cytologically negative and seronegative for HPV 16 and 18 on Day 1; had no protocol violation.	All subjects that received three doses of vaccine or placebo within a year; seronegative and DNA negative for HPV 6, 11, 16 or 18 on Day 1; remained DNA negative for the same HPV type(s) through month 7; had no protocol violation.	All subjects that received three doses of vaccine or placebo within a year; seronegative and DNA negative for HPV 6, 11, 16 or 18 on Day 1; remained DNA negative for the same HPV type(s) through Month 7; had no protocol violation.†	All subjects that received three doses of vaccine or placebo within a year; seronegative and DNA negative for HPV 16 or 18 on Day 1; remained DNA negative for the same HPV type(s) through Month 7; had no protocol violation.†	All subjects that received three doses of vaccine or placebo; seronegative to HPV 16 or 18 on Day 1; DNA negative to HPV 16 or 18 on Day1 and Month 6; had normal or low-grade cytology at baseline, had no protocol violation.	All subjects that received three doses of vaccine or placebo within a year; seronegative and DNA negative in cervico-vaginal swab and/or biopsy samples for HPV 6, 11, 16 or 18 on Day 1; remained DNA negative to the same HPV type(s) through Month 7; had no protocol violation; had one or more follow-up visits after Month 7.
Intention-to-treat (ITT)/Modified Intention-to-treat (MITT) population	MITT2: All subjects that received ≥1 dose of vaccine or placebo.	ITT: All subjects that received ≥1 dose of vaccine or placebo; DNA negative for 14 HR HPV on Day 1; had data available for outcome measurement.	MITT: All subjects that received ≥1 dose of vaccine or placebo; seronegative and DNA negative to HPV 6, 11, 16 or 18 on Day 1.	ITT: All subjects that had undergone randomisation regardless of their baseline HPV status or evidence of HPV-associated anogenital disease.	ITT: All subjects that had undergone randomisation regardless of their baseline HPV status or evidence of cervical neoplasia.	ITT: All subjects that received ≥1 dose of vaccine or placebo; DNA negative to HPV 16 or 18 on Day 1; had data available for outcome measurement.	ITT: All subjects that received ≥1 dose of vaccine or placebo; had one or more follow-up visits after Day 1.

	Koutsky & Mao (1, 2)	Harper (3, 4)	Villa (5, 6)	FUTURE I (7, 8, 9)	FUTURE II (8, 9, 10)	PATRICIA (11, 12)	Muñoz (13)
Methodological quality							
Allocation concealment	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate
Blinding	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate	Adequate
Dropout/loss-to-follow-up reported	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Expected efficacy (1-RR)	0.75	0.7	0.8	0.8	0.80-0.90	0.85	0.8
Sample size calculation performed	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	α = 0.05 (one-sided) β = 0.10	α = 0.05 (two-sided) β = 0.20	α = 0.05 (two-sided) β = 0.10	α = 0.0125 (one-sided) β = 0.09	α = 0.02055 (one-sided) β = 0.10	α = 0.05 (two-sided) β = 0.06	β = 0.13

HR HPV: High-risk HPV includes HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68; CIN: Cervical intraepithelial neoplasia; AIS: Adenocarcinoma in situ; CIN1+: Cervical intraepithelial neoplasia grade 1 or worse, including CIN1-3, AIS and cervical cancer. CIN2+: Cervical intraepithelial neoplasia grade 2 or worse, including CIN2-3, AIS and cervical cancer; LSIL: Low-grade intraepithelial lesion; HSIL: High-grade intraepithelial lesion; VIN: Vulvar intraepithelial neoplasia; VaIN: Vaginal intraepithelial neoplasia. VLPs: Virus-like particles; AAHS: Amorphous aluminium hydroxyphosphate sulphate. AS04: 500 µg aluminium hydroxide and 50 µg 3-O-desacyl-4'-monophosphoryl lipid A; RR: Risk ratio, the ratio of event rates of vaccine and control group.

** A subset of 466 subjects in the treatment arm received quadrivalent vaccine and hepatitis B vaccine and 467 subjects in control arm received placebo and hepatitis B vaccine.*

† Per-protocol population for evaluation of cross-protection included subjects who received ≥1 vaccination and at enrolment were seronegative and DNA negative for each of vaccine HPV types (6, 11, 16, and 18); were DNA negative for each of 10 non-vaccine types (31, 33, 35, 39, 45, 51, 52, 56, 58, and 59); and had a normal Pap test result.

References – Appendix 1

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Appendix 2. Literature search of randomised controlled trials on HPV vaccine efficacy, immunogenicity and safety in girls/women since July 2009

The following provides an overview of the studies published on efficacy, immunogenicity and safety of HPV vaccines in adolescent girls and young women since Lu et al. produced their systematic review (search updated to July 2009).

Search (run 20 November 2011) on Medline, Cochrane and clinicaltrials.org:

String: 'efficacy and "papillomavirus vaccines" [MeSH] and (wom$ or girl$ or femal$) and trial'

Inclusion and exclusion criteria: no language restrictions. Time restriction: search from 1 July 2009. Study design: randomised controlled trials.

The methodology for data extraction follows the criteria proposed in Lu B, Kumar A, Castellsague X and Giuliano AR. Efficacy and safety of prophylactic vaccines against cervical HPV infection and diseases among women: a systematic review & meta-analysis. BMC Infectious Diseases 2011, 11:13.

Studies focusing on immunogenicity and safety alone were not considered, as they lack information which is any more recent than the older trials included in Lu et al.

Results

- 91 studies retrieved
- 70 discarded after reading title/abstract
- 15 doubles
- six articles included (see Table 6).

Of the six articles included, two are further end-of-study analyses of the PATRICIA trial, (reported in Appendix 1). One of the studies focuses on specific efficacy endpoints (4), the other on cross-protection from non-vaccine HPV strands (5). The results of the latter two studies are reported here but not included in the table.

Lehtinen et al. (4) showed that vaccine efficacy against CIN3+ associated with HPV-16/18 was 100% (95% CI 85.5–100) in the total vaccinated cohort (TVC) naive and 45.7% (22.9–62.2) in the TVC. Vaccine efficacy against all CIN3+ (irrespective of HPV type in the lesion and including lesions with no HPV DNA detected) was 93.2% (78.9–98.7) in the TVC-naive and 45.6% (28.8–58.7) in the TVC. In the TVC naive, vaccine efficacy against all CIN3+ was above 90% in all age groups. In the TVC, vaccine efficacy against all CIN3+ and CIN3+ associated with HPV-16/18 was highest in the 15–17 year age group and progressively decreased in the 18–20 year and 21–25 year age groups. Vaccine efficacy against all AIS was 100% (31.0–100) and 76.9% (16.0–95.8) in the TVC-naive and TVC, respectively. Serious adverse events occurred in 835 (9.0%) and 829 (8.9%) women in the vaccine and control groups, respectively. Only ten events (0.1%) and five events (0.1%) respectively, were considered to be related to vaccination. PATRICIA end-of-study results show excellent vaccine efficacy against CIN3+ and AIS irrespective of HPV DNA in the lesion. Population-based vaccination incorporating the HPV-16/18 vaccine and high coverage of early adolescents might have the potential to substantially reduce the incidence of cervical cancer.

Wheeler et al. (5) showed consistent vaccine efficacy against persistent infection and CIN2+ (with or without HPV-16/18 co-infection) across cohorts for HPV-33, HPV-31, HPV-45, and HPV-51. In the most conservative analysis of vaccine efficacy against CIN2+, where all cases co-infected with HPV-16/18 were removed, vaccine efficacy was noted for HPV-33 in all cohorts, and for HPV-31 in the ATP-E and TVC-naive. Vaccine efficacy against CIN2+ associated with the composite of 12 non-vaccine HPV types (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), with or without HPV-16/18 co-infection, was 46.8% (95% CI 30.7–59.4) in the ATP-E, 56.2% (37.2–69.9) in the TVC naive and 34.2% (20.4–45.8) in the TVC. Corresponding values for CIN3+ were 73.8% (48.3–87.9), 91.4% (65.0–99.0) and 47.5% (22.8–64.8). Data from the end-of-study analysis of PATRICIA show cross-protective efficacy of the HPV-16/18 vaccine against four oncogenic non-vaccine HPV types—HPV-33, HPV-31, HPV-45, and HPV-51—in different trial cohorts representing diverse groups of women.

Results so far are in line with what is already known as regards efficacy and safety. Literature published after July 2009 confirms the high efficacy of the vaccines on HPV- related conditions in young women for up to 7.3 years and the high safety profile of the vaccine.

It should be noted that studies have only followed those immunised for 7.3 years. It is still unknown how long effective immunity will last and whether boosters will be required. Data on long-term immunogenicity of the vaccines show that GMTs are maintained several times higher than natural infection levels for up to seven years after immunisation. However, GMTs are shown to drop within two years of the first vaccination and then to keep decreasing at a slower rate. Moreover, although efficacy of HPV vaccines was above 90% in the according-to-protocol cohorts, the intention-to-treat cohorts showed less encouraging results. Further studies on long term efficacy and immunogenicity of vaccines are therefore required.

Table 6. Randomised controlled trials published after July 2009 on efficacy, immunogenicity and safety of HPV vaccines in girls/women

	De Carvalho (subset of GSK HPV-007), 2010 (1)	Konno, 2010 (2)	GSK HPV-007, 2009 (3)
Phase	III	II	III
No of study sites	5	13	27
Countries included	1	1	3
Year of study enrolment	11.2003–07.2004	04.2006–02.2009	11.2003–07.2004
Funding source	GlaxoSmithKline	GlaxoSmithKline	GlaxoSmithKline
Inclusion criteria			
Age	15–25	20–25	15–25
Lifetime of sexual partners	<=6	No restriction	<=6
Exclusion criteria	History of abnormal PAP smear, or ablative or excisional treatment of cervix; ongoing treatment for external condylomata; seropositive for HPV 16 or 18; DNA positive for any of the oncogenic HPV types in past 90 days	Pregnancy; history of vaccination with HPV vaccine or hepatitis A vaccine, MPL administration, hepatitis A infection and clinically significant diseases, previous colposcopy examination to evaluate abnormal cervical cytology	History of abnormal PAP smear, or ablative or excisional treatment of cervix; ongoing treatment for external condylomata; seropositive for HPV 16 or 18; DNA positive for any of 14 HR HPV in past 90 days
Intervention & comparator			
Vaccine component	HPV 16, 18 VLPs	HPV 16, 18 VLPs	HPV 16, 18 VLPs
VPL amount (µg)	20/20	20/20	20/20
Vaccine adjuvant	AS04 (500 µg/50 µg)	AS04 (500 µg/50 µg)	AS04 (500 µg/50 µg)
Comparator	Placebo	Hepatitis A vaccine	Placebo
Comparator adjuvant	500 µg aluminium hydroxide	500 µg aluminium hydroxide	500 µg aluminium hydroxide
Administration schedule	Month 0, 1, 6	Month 0, 1, 6	Month 0, 1, 6
Clinical protocol			
Frequency of HPV DNA test	6 month interval	6 month interval	6 month interval
Frequency of cytology test	6 month interval	12 month interval	6 month interval
Length in trial (months)	initial trial: 27; first follow-up study: 53; current follow-up study: 11 (overall: 88)	24	77
Endpoints			
Primary	Incident infection, 6-month and 12 month persistent infection, cytological abnormalities (>= ASC-US and >=LSIL), histopathologically confirmed CIN1+ associated with HPV 16 and/or 18	Persistent infection with HPV-16/18 in women seronegative at study entry and DNA negative for the corresponding HPV DNA at months 0 and 6	Incident infection with HPV 16 and/or HPV 18
Secondary	Incident infection, 6-month and 12 month persistent infection, cytological abnormalities (>= ASC-US and >=LSIL), histopathologically confirmed CIN1+ associated with any oncogenic HPV type	Incident and 2-month persistent cervical infections, cytological and histopathological abnormalities associated with HPV-16/18 or any oncogenic HPV types; immunogenicity; safety	Incident and persistent infection and cytological and histopathological abnormal changes associated with oncogenic HPV types; long term vaccine safety and immunogenicity
Population for efficacy analysis			
PPP	All subjects that received three doses of vaccine/placebo; DNA negative for 14 HR HPV on day 1; cytologically negative and seronegative for HPV 16 and 18 on Day 1; had no protocol violation	All subjects complying with the three-dose schedule, with normal or low-grade cytology at month 0, evaluable for efficacy	All subjects that received three doses of vaccine/placebo; DNA negative for 14 HR HPV on Day 1; cytologically negative and seronegative for HPV 16 and 18 on Day 1; had no protocol violation.
ITT / modified ITT (MITT)	ITT: All subjects that received >=1 dose of vaccine/placebo; DNA negative for 14 HR HPV on Day 1; had data available for outcome measurement	All subjects who received >=1 dose of vaccine/placebo; normal or low grade cytology at Month 0, can be evaluated for efficacy	ITT: All subjects that received >=1 dose of vaccine/placebo; DNA negative for 14 HR HPV on Day 1; had data available for outcome measurement.

	De Carvalho (subset of GSK HPV-007), 2010 (1)	Konno, 2010 (2)	GSK HPV-007, 2009 (3)
Methodological quality			
Allocation concealment	Adequate	Adequate	Adequate
Blinding	Adequate	Adequate	Adequate
Dropout/loss to follow-up reported	Yes	Yes	Yes
Expected efficacy (1-RR)	0.7	0.7	0.7
Sample size calculation performed	Yes α=0.05 (two-sided) β=0.20	Yes α=0.045	Yes α=0.05 (two-sided) β=0.20
Trial Sample size			
PPP	Vaccine (n=206 for efficacy cohort, 180 for immunogenicity cohort)	Vaccine (n=501 for efficacy cohort, 370 for immunogenicity cohort)	Vaccine (n=465)
ITT/MITT	Vaccine (n=222)	Vaccine (n=519)	Vaccine (n=560)
Summary of main findings	During current follow-up, no cases of infection or cytohistological lesions associated with HPV-16/18 were observed. Vaccine efficacy up to 7.3 years was 94.5% (CI 82.9-98.9) for incident infection, 100% (CI 55.7-100.0) for 12-month persistent infection and 100% for CIN2+. Antibody titres for total IgG and neutralising antibodies remained several folds above natural infection levels and >=96% of women were seropositive. Vaccine safety was similar to placebo.	Vaccine efficacy in PPP against six-month infections associated with HPV-16/18 was 100% (95.5% CI 71.3-100.0). Efficacy against CIN1+ associated with HPV oncogenic types was 64.9% (95.5% CI 4.9-89.0%). At 24 months from trial start, geometric mean antibody titres against HPV-16 and HPV-18 were 51- and 28-fold higher than titres from natural infection, respectively. SAEs were reported by 18 women (3.5%) in the HPV vaccine group and 19 women (3.6%) in the control group.	Vaccine efficacy against incident infection with HPV 16/18 was 95.3% (95% CI 87·4-98·7) and against 12-month persistent infection was 100% (81.8–100). Vaccine efficacy against CIN2+ was 100% (51.3–100) for lesions associated with HPV-16/18 and 71.9% (20.6–91.9) for lesions independent of HPV DNA. Antibody concentrations by ELISA remained 12 times or more higher than after natural infection (both antigens). Safety outcomes were similar between groups: during the follow-up study, 30 (8%) participants reported a serious adverse event in the vaccine group versus 37 (10%) in the placebo group, none judged related to vaccination.

AAHS: Amorphous aluminium hydroxyphosphate sulphate; AIS: Adenocarcinoma In Situ; AS04: 500 µg aluminium hydroxide and 50 µg 3-O-desacyl-4'-mophosphoryl lipid A; ASC-US: Atypical Squamous Cells of Undetermined Significance; CIN: Cervical Intraepithelial Neoplasia; EGL: External Genital Lesion; HPV: Human papillomavirus; ITT: Intention To Treat; LSIL: Low-grade Squamous Intraepithelial Lesion; PPP: Per-protocol Population; RR: Risk Ratio of event occurrence in vaccine and control groups; SAE: Serious Adverse Events; VaIN: Vaginal Intraepithelial Neoplasia; VIN: Vulvar Intraepithelial Neoplasia; VLP: Virus-Like Particles

References – Appendix 2

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Appendix 3. Models of effectiveness and cost-effectiveness of adding boys to current HPV immunisation programmes

At present, a universal vaccination programme which includes boys has yet to be introduced. However, many models have been developed to assess the effectiveness and cost-effectiveness of adding boys to HPV vaccination programmes. These models have been reviewed in Table 7 below.

Methods

Search (run 10 October 2011) on Medline, Cochrane and clinicaltrials.org:

String:'papillomavirus vaccines [MeSH] AND (men or man or male or boy or boys) AND (model$)'

Inclusion and exclusion criteria: no time/language restrictions, HPV vaccines were conducted among males and measured prophylactic effectiveness or cost-effectiveness against HPV infection or HPV-related conditions. Ad hoc subgroup analyses on potential high-risk categories, such as MSM, were not considered.

The methodology for data extraction follows the criteria proposed in Jeurissen S and Makar A. Epidemiological and economic impact of human papillomavirus vaccines. Int J Gynecol Cancer 2009 May;19(4):761-771.

Results

- 47 studies retrieved
- 25 discarded after reading title/abstract
- 11 doubles
- 11 articles included (see Table 7.)

Table 7. Models of effectiveness and cost-effectiveness of adding boys to current HPV immunisation programmes

	Taira (1)	Elbasha (2)	Insinga (3)	Kim (4)	Kulasingam (5)	Jit (6)	Elbasha (7)	Zechmeister (8)	French (9)	Choi (10)	Brisson (11)
Year	2004	2007	2007	2007	2007	2008	2010	2009	2007	2010	2011
Country	USA	USA	Mexico	USA	Australia	UK	USA	Austria	Finland	UK	Canada
Model	Hybrid	Dynamic	Dynamic	Dynamic	Markov	Dynamic	Dynamic	Dynamic	Dynamic	Hybrid	Dynamic
Vaccine used	HPV-16/18	HPV-6/11/16/18	HPV-6/11/16/18	HPV-6/11/16/18	HPV-16/18	HPV-6/11/16/18	HPV-6/11/16/18	HPV-16/18	HPV-16	HPV-6/11/16/18	HPV-16/18
Vaccine cost	Vaccination USD 300; catch-up: USD 100 (USD 2001)	USD 360 (2005)	USD 240 (2005) - non medication costs not included in the study	USD 360 (2006)	Vaccination AUD 381; catch-up: AUD 146 (2005)	GBP 191–252 (2007)	USD 399 (2008)	EUR 340 (2008)	nd	nd	nd
Discount rate	3%	3%	3%	3%	5%	3.50%	3%	5%	nd	nd	nd
Modelled population	Cohort based on US population	Cohort based on US population	Cohort based on Mexican population	Cohort based on US population	Cohort based on Australian population.	Cohort based on UK population.	Cohort based on US population	Cohort based on international epidemiological data.	Cohort based on Finnish population.	Cohort based on UK epidemiological data.	Heterosexual, open, stable population.
Morbidities considered in the model.	Cervical cancer	Cervical cancer, CIN 2/3, genital warts in males and females.	Cervical cancer, high-grade cervical precancer, genital warts.	Cervical cancer and other HPV-related neoplasms, genital warts, respiratory papillomatosis in males and females.	All HPV-16/18 associated diseases.	Cervical cancer & other HPV-related neoplasms, warts in males and females.	Cervical cancer and other HPV-related neoplasms, CIN-1,2,3, genital warts, respiratory papillomatosis in males and females.	Cervical carcinoma, CIN-1,2,3.	Cervical cancer	Cervical cancer, CIN-1,2,3, CGIN-1,2,3, anogenital warts.	nd
Fraction of cervical cancers attributable to vaccine types.	100%	100%	70%	70%	70%	100%	100%	70%	Only CC due to HPV-16 modelled (but a fraction of 56% assumed)	98%	nd
Base assumptions											
Age at vaccination	12	12	12	12	12	12–25	9– 26	12	12, 15, 18 or 21 (four separate scenarios modelled).	12	12
Catch-up	At age 22	No catch-up; 12–24 year-old females and males catch-up.	No; 12–24 years for females and males.	No	No	No catch-up	No	No	No catch-up; three-year catch-up.	No	nd

	Taira (1)	Elbasha (2)	Insinga (3)	Kim (4)	Kulasingam (5)	Jit (6)	Elbasha (7)	Zechmeister (8)	French (9)	Choi (10)	Brisson (11)
Vaccine efficacy	90%	90%	90%	100% among females; 85% among males.	100%	100%	90%	90%	100%	100%	99%
Duration of protection	10 years	Lifelong	Lifelong	Lifelong	Lifelong	>10 years (varying time modelled)	Lifelong	Lifelong (booster at year 10)	Lifelong	10 years, 20 years, lifelong	20 years
Coverage	70%	70%	70%	75%	80%	80%	75% by age 18.	65%	70%	80%	70%
Screening status	71% compliance with biannual screening	Current US screening programmes	Current US screening programmes	Current US screening programmes	Current Australia screening programmes	Current UK screening programmes	Current US screening programmes	30% compliance with biannual screening	From 25/30 to 60 years at five-year intervals	Current UK screening programmes	nd
Sensitivity analysis											
Natural history	No	No	One-way	Multivariate	No	Multivariate	No	One-way	nd	Multivariate	nd
Vaccine parameters	One-way	One-way	One-way	Multivariate	One-way	One-way	One-way	One-way	nd	Multivariate	nd
Economic parameters	One-way	One-way	One-way	Multivariate	One-way	Multivariate	One-way	One-way	nd	nd	nd
Cost of vaccinating boys per QALY/LYG (Life Years Gained)	USD 442 039 compared to female-only vaccination	Vaccination girls and boys: dominated. Vaccination girls and boys plus 12–24 year-old females catch-up: USD 41 803. Vaccination girls and boys plus 12–24-year-old females and males catch-up: USD 45 056.	Vaccination girls and boys: dominated compared to girls-only vaccination programme. Vaccination girls and boys plus female catch-up: incremental USD 16 663 compared to vaccinating girls plus females catch-up. Further incremental USD 16 702 for male catch-up programme.	Incremental USD 114 510–120 300 (depending on the screening strategy used) compared to vaccinating girls only.	AUD 33 644 compared to no vaccination programme.	Incremental GBP 113 846 (71 099–176 749) compared to vaccination plus catch-up aged 12–25 years for females, if 10 years' vaccine protection is assumed. Incremental GBP 172 892 (112 230–289 698) compared to vaccination plus catch-up aged 12–25 years for females if 20 years' vaccine protection is assumed. Incremental GBP 520 255 (304 798–986 917) compared to vaccination plus catch-up aged 12–25 years for females if lifetime vaccine protection is assumed.	USD 25 700 (13 600–48 800) if vaccination protects against all HPV-6/11/16/18-associated diseases. USD 69 000 (37 700–152 300) if it only protects against diseases currently in the vaccine indication.	Increase of 6 324 undiscounted or 1 220 discounted LYG (0.0004 LYG per person) if boys are vaccinated. Discounted incremental cost effectiveness ratios (ICER) for HPV vaccination of girls and boys are EUR 311 000 per LYG and EUR 299 000 per LYG from a healthcare system and a societal perspective respectively, compared to HPV-vaccination programme for girls only.	nd	nd	nd

	Taira (1)	Elbasha (2)	Insinga (3)	Kim (4)	Kulasingam (5)	Jit (6)	Elbasha (7)	Zechmeister (8)	French (9)	Choi (10)	Brisson (11)
Other outcomes and conclusions	Adding boys to vaccination programmes will reduce risk of cervical cancer by 63.9% (61.8% with girls-only vaccination). As vaccine coverage increases, the number of cervical cancer cases decreases. The male-female programme always results in less cervical cancer cases, but the difference is only large when levels of female vaccine penetration are low.	Including men and boys is the most effective strategy, reducing the incidence of genital warts, CIN and cervical cancer by 97%, 91% and 91%, respectively. Cost-effectiveness ratio near or below that of several other recommended vaccines, when implemented as a strategy combining vaccination of boys and girls before age 12 and a 12–24 years catch-up programme.	Universal vaccination plus females and males catch-up programme will reduce by 84–98% HPV-6/11/16/18-related cervical cancer, high-grade cervical precancer and genital wart incidence during year 50 following vaccine introduction.	Vaccinating boys is unlikely to be cost-effective if vaccine coverage and efficacy are high among girls. Vaccinating both sexes falls below USD 100 000 per QALY only under scenarios of high, lifelong vaccine efficacy against all HPV-related conditions.	In a setting with an effective screening programme, such as Australia, vaccinating boys is likely to be cost-effective when the morbidity of the screening programme is taken into account (QALY), but not when only mortality associated with cervical cancer is considered (LYG).	Unlikely to be cost-effective, even if vaccination results in lifelong protection. At 80% coverage of females it is likely that most HPV-16/18-related cervical cancers and anogenital warts will be prevented, therefore the benefits of vaccinating boys are few.	Compared to girls-only programmes, further decrease of the cumulative mean number of genital wart cases, CIN-2/3 cases, cancer cases and cancer deaths in the US by 5 146 00, 708 000, 116 000 and 40 000, respectively, within 100 years of the vaccination programme start.	20% HPV-16-associated cervical cancer reduction for vaccination at 21 years, 40% at 18 years, 67% at 15 years and 68% at 12 years, with an incremental reduction for male vaccination of 15.1% at 12 years, 15.5% at 15 years and 1% at 21 years.		Extending vaccination to boys provides additional benefits in terms of reduction of cervical cancer and anogenital warts.	Relative reduction in HPV prevalence at equilibrium compared with no vaccination. Girls only: 65% female, 62% male. Girls and boys: 85% female, 88% male. Girls only: 61% female, 58% male relative reduction of incidence of vaccine-type infection over the first 70 years compared to no vaccination. Boys and girls: incremental reduction of 16% female, 23% male. Reduction in vaccine-type prevalence at equilibrium/vaccine coverage: girls only: 64%/35%. Girls and boys: incremental 24%/35%. Incremental gains of vaccinating boys are limited.

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Appendix 4. Alternative HPV vaccination schedules

HPV vaccine programmes have a very high potential for decreasing HPV-related mortality and morbidity. However, the three-dose schedule over a six-month period may represent a barrier to introducing the vaccine. This is particularly relevant for low-resources countries, but, given the low coverage rates even in high-income European countries (see Section 1), alternative vaccination schedules are attractive, especially as regards catch-up campaigns for women. Studies in literature on alternative administration schedules have been analysed.

Methods

Search on Medline (run 24 October 2011)

Search query: (alternative OR alternate) and (administration OR schedule) and (vaccin$ OR immunizat OR immunisat) and (hpv or papillomavirus)

No time/language restrictions set.

Results

- 23 results yielded
- 15 excluded after reading title or abstract
- Five excluded as not experimental design
- Three eligible studies considered:

Neuzil et al. 2011 (1): Immunogenicity and reactogenicity of the quadrivalent vaccine were analysed using three alternative dosing schedules to the standard in a sample of 903 adolescent girls (11—13 years on enrolment) in an open-label, cluster-randomised, non-inferiority study at 21 schools in Vietnam. Serum anti-HPV geometric mean titres were measured one month after administration of the last vaccine dose. Dosing schedules were: (1) 0, 2 and 6 months (standard protocol, reference group); (2) 0, 3 and 9 months; (3) 0, 6 and 12 months; (4) 0, 12 and 24 months. Non-inferiority criteria were met for the alternative schedule groups 2 and 3. Reactogenicity and safety were comparable in all the alternative schedule groups.

Esposito et al. 2011 (2): Immunogenicity and safety of the bivalent vaccine were analysed using an alternative dosing schedule (0, 1 and 12 months) to the standard in a sample of 804 healthy women aged 15—25 years. The study, a randomised open design trial, was conducted at 18 centres in Romania, Slovakia and Italy. Serum anti-HPV geometric mean titres were measured one month after administration of the second and third vaccine dose. Non-inferiority criteria were met for the alternative schedule group. Safety was comparable to the standard dosing schedule.

Zimmerman et al. 2010 (3): Immunogenicity of the bivalent vaccine was analysed using an alternative dosing schedule (0, 2 and 12 months) to the standard in a sample of 200 women aged 18—23 years. The study was conducted among women of the community at the University of Pennsylvania, USA. Serum anti-HPV geometric mean titres were measured 2—6 weeks after the third vaccine dose. Non-inferiority criteria were met for the alternative schedule group.

Conclusions

The results of these studies indicate that alternative vaccination schedules (in particular, third dose at 12 months instead of six) are no less effective than the standard schedule. This knowledge might help to ensure that young women who are working or studying complete the three-dose vaccination cycle.

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Appendix 5. Knowledge, attitude and practice of healthcare workers towards HPV vaccines

Vaccination coverage rates in EU countries have proven to be lower than expected. Attitudes, knowledge and practices of healthcare professionals towards the HPV vaccination should be considered possible reasons for the unsuccessful implementation of current policies. European studies in literature on the topic were analysed.

Methods

Search on Medline and Embase (run Nov 21st 2011)

Search query: (knowledge OR attitude OR practice) and (doctor$ OR physic$ OR gp OR practitioner$ OR nurse$ OR (("health care" OR "healthcare") and (worker$ OR providers))) and (hpv or papillomavirus) and (vaccine or vaccines or vaccination or immunisation or immunization)

No time/language restrictions set.

Results

- 144 results yielded
- 122 not relevant
- 19 from non-European countries.

Three eligible studies considered:

Lutringer-Magnin et al. 2011 (1): A total of 80.8% of GPs reported a favourable opinion of HPV vaccination, 17.4% were uncertain and 1.8% were opposed. The main justification for a favourable opinion related to the public health benefits of the HPV vaccination (cited by 60% of those favouring vaccination). The main justification for an 'opposed or uncertain' opinion was that the vaccine had been introduced so recently (cited by 43.4%). The main difficulties in providing HPV vaccination were patients' concerns about potential side effects (cited by 37% of the respondents) and the target age of 14 years (28.9%). Interviews suggested that the concern about age may relate to the need, as perceived by GPs, to discuss sexually transmitted infections with adolescent patients.

Piana et al. 2009 (2): In this study, 89.6% of family physicians answers were in favour of HPV. The ideal age for vaccination was between 11 and 13 years for 34.4% and between 14 and 15 years for 53.9%. The family physicians most in favour of vaccination were those involved in screening for STDs, those who did not think that the vaccine would have a negative effect on the image of sexuality and screening for cervical cancer, and those who were confident of the vaccine's safety. The study identified the negative elements concerning HPV in order to optimise information strategies among family physicians.

Mammas et al. 2010 (3): School nurses in Wirral, UK were interviewed to identify the level of their knowledge and attitudes towards HPV vaccination. A total of 25 out of 33 (75.8%) nurses returned the questionnaires: 92% declared that they had little information on HPV and the vaccine, while only 16% considered their knowledge of HPV vaccine adequate. All school nurses (100%) considered that they could play an important role in discussing the safety and role of the HPV vaccination with adolescents and parents. They also considered important their role to promote the participation of adolescents in the national HPV vaccination programme. These findings demonstrate the will of British school nurses not only to inform adolescents about HPV but also to have an active role in the HPV vaccination programme.

Conclusions

European studies on attitudes, knowledge and practices are very scarce. There is a strong justification for encouraging more authors to address the topic throughout the EU.

Studies conducted so far show that acceptance of general practitioners is generally high, but some concerns should be addressed. In particular, concerns on long-term vaccine efficacy and possible consequences of the vaccination on adolescent sexual behaviour.

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