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EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

GUIDANCE

FOR THE INTRODUCTION OF HPV VACCINES IN EU COUNTRIES

Stockholm, January 2008

ecdc.europa.eu

PREFACE

The purpose of this guidance is to lay down the scientific basis for the potential introduction of human papillomavirus (HPV) vaccines in order to help European Union (EU) Member States to make policy choices. It highlights the issues to be considered and it provides a list of policy options for each of these issues.

This guidance has been developed by a Scientific Panel of experts set up and coordinated by the Scientific Advice Unit of the European Centre for Disease Prevention and Control (ECDC). One of the main tasks of this unit is to provide independent scientific opinions, expert advice, data, and information. Panel members' declarations of interest were reviewed by ECDC and it was considered that there was no potential conflict of interest that would influence the work of the Panel.

HPV vaccines are becoming introduced in an increasing number of countries and EU policy makers are urged to take position on HPV vaccination. This guidance note should help facilitate this process.

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

There are only five-year follow-up data on the HPV vaccines and many questions still need to be answered. This guidance note, made on the basis of current knowledge will probably need to be re-evaluated in six to 12 months.

ACKNOWLEDGEMENTS

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ABBREVIATIONS

ASCUS	Atypical squamous cells of undetermined significance
AIS	Adenocarcinoma *in situ*
BCG	Bacille Calmette-Guérin
CIN	Cervical intraepithelial neoplasia
CT	Chlamydia trachomatis
CI	Confidence interval
DNA	Deoxyribonucleic acid
DT	Diphtheria, tetanus
DTaP	Diphtheria, tetanus, acellular pertussis
ECDC	European Centre for Disease Prevention and Control
EMEA	European Medicines Agency
EU	European Union
HPV	Human papillomavirus
HSIL	High-grade squamous intraepithelial lesion
IPV	Inactivated poliovirus
LSIL	Low-grade squamous intraepithelial lesions
MSM	Men who have sex with men
QALY	Quality-adjusted life year
VE	Vaccine efficacy
VLP	Virus-like particle
WHO	World Health Organization

SUMMARY

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) and the bivalent vaccine, Cervarix® (GlaxoSmithKline Biologicals). Both vaccines are made from virus-like particles and are non-infectious. Both vaccines have a good safety profile. Both vaccines 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, in establishing mechanisms for quality control, and in 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. Also, vaccinated women might have a false sense of security, resulting in lowered 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) begins to become common in that group. Setting the age of vaccination below this age would not prevent many infections and should be avoided until there is evidence that the vaccine has a long duration of 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 of 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 of vaccine uptake may be more difficult here.

Sexual and reproductive health and other medical clinics provided specifically for women may be important sites for immunisation. However, girls may not visit these before the onset of sexual activity and so these are likely to be useful mainly for catch-up programmes for 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 that the message that immunisation is an adjunct, not a replacement for cervical screening, is communicated.

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 the 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 or 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 set of 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 precancer lesions.

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1. CERVICAL CANCER AND HUMAN PAPILLOMAVIRUS INFECTIONS IN THE EUROPEAN UNION

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Key points

- Cervical cancer remains an important problem in the EU.
- The primary cause of cervical cancer is a persistent infection with a cancer-causing genital human papillomavirus (HPV).
- HPV infections are very common and acquired soon after onset of sexual activity.
- Most HPV infections clear spontaneously.
- Persistent HPV infections with a high-risk type can cause cellular changes that can result in cervical cancer.
- HPV 16/18 are together associated with an estimated 73% of cases of cervical cancer in Europe.
- Cervical cancer can be prevented by screening and treating precancerous lesions.
- Cervical cancer is the second most common cancer after breast cancer affecting women aged 15–44 years in the EU. Each year, there are around 33 000 cases of cervical cancer in the EU, and 15 000 deaths.[1]

Trends in cervical cancer in the EU

In the EU, the incidence of cervical cancer per 100 000 females (all ages) per year ranges from less than 8.0 to 29.9 in the EU's eastern Member States.[2] Analysis of cervical cancer mortality in the then 25 EU Member States showed that the burden was lowest in Finland and highest in Lithuania.[3] The risk of developing cervical cancer increases with age and reaches a peak at about 35 to 55 years of age in unscreened populations. Although cervical cancer incidence and mortality have been declining in many European populations in the past few decades, upward trends have been reported in younger women in several countries. These trends are attributed to changing sexual lifestyles and increased transmission of papillomavirus in younger generations of women, although the possibility that women may have been screened differently from one cohort to another should also be considered.[4]

There is consistent and convincing evidence that cervical cancer is a rare consequence of infection of the genital tract by some types of HPVs.[5]

Human papillomaviruses: overview

HPV infects the skin and mucous surfaces of the body. More than 40 types of HPV have been identified which can infect the human genital tract, and these are highly adapted to their human hosts. Transmission of genital HPV types usually occurs during sexual intercourse, although penetration of the penis into the vagina is not necessary. Transmission has been shown to also occur via skin-to-skin contact.

HPV infections are the most commonly diagnosed viral sexually transmitted infections among women and men. Studies have detected asymptomatic HPV infection in 5–40% of women of

reproductive age and most sexually active women and men will become infected with at least one type of HPV during their lifetime.[6,7,8] Prevalence peaks soon after the start of sexual activity and remains high in the 20–29 year age group before sharply declining.[9] Relatively high rates of anal HPV infection have been reported in men who have sex with men (MSM), who also have an increased risk of HPV-related anal cancer.[10]

Only 50–60% of women develop antibodies to HPV after natural infection.[11] A genital HPV infection is often without symptoms, transitory and is usually self-resolving.[12] More than 90% of detected infections clear within two years.[13]

HPVs can be classified as 'low risk' or 'high risk' in terms of their potential to cause cancers.[14] There are at least 13 of these 'high-risk' types which are known to cause cervical cancer. The eight most common high-risk types in Europe are 16, 18, 31, 33, 35, 45, 56 and 58. These account for about 85% of cervical cancer cases in the region. HPVs 16/18 are together associated with an estimated 73% of incidences of cervical cancer in Europe, and each of the next six types cause less than 5% of cases.[15,16]

Some types of low-risk HPVs cause genital warts, and some low-grade cervical disease, but these types have not been causally associated with cervical cancer.

Risk factors for HPV infection

The key determinants for HPV infection for both men and women are related to sexual behaviour. They include being young when starting sexual relations, having a high number of sexual partners in a lifetime and having partners with multiple partners. High-risk HPV is most common in young people, with peak prevalence in women under 25 years of age. In most countries, the prevalence decreases with age over ~35 years.[17,18,19,20,21,22]

Low-risk HPVs and genital warts

HPV 6/11 cause 80–90% of all cases of genital warts.[23,24] The same strains are also responsible for about 80–90% of cases of the rare but serious condition of recurrent respiratory papillomatosis.

HPV 6/11 very rarely cause cancer, so they are considered 'low risk'.[15] Low-risk HPVs cause much of the low-grade, benign, cervical abnormalities detected during cervical screening. These cause much anxiety to patients and incur costs due to the resources required to investigate them, although treatment is not required.

Genital warts are common and infectious. A random sample of women aged 18–45 in Denmark, Iceland, Norway and Sweden suggests that 10% had experienced genital warts before the age of 45, with an increasing occurrence in younger cohorts.[25] Further, the UK National Survey of Sexual Attitudes and Lifestyles in 2000 indicates that that around 4% of all people questioned reported ever being diagnosed with genital warts.[26] However, much lower prevalence levels were found in Slovenia, where the reported lifetime prevalence of genital warts among sexually active Slovenians aged 18–49 years was only 0.4%.[27]

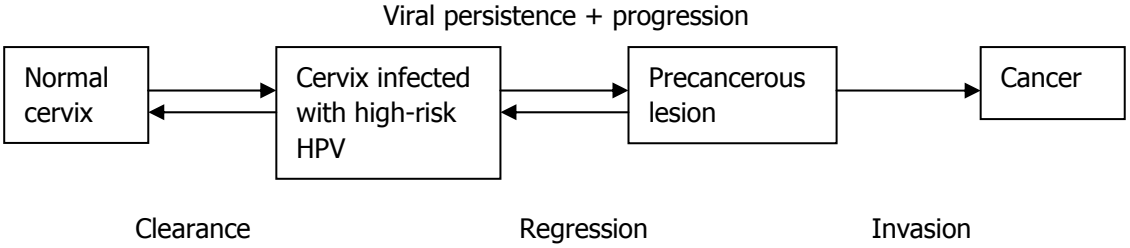
Genital warts are perceived as unsightly and are associated with psychological morbidity and feelings of shame. Most people will seek treatment. However, as treatment is not

straightforward, and there are a large variety of therapies in use, management of genital warts can require large amounts of time and resource. [28]

High-risk HPVs and cervical cancer

Persistence of an infection with a high-risk HPV virus beyond 12 months is associated with an increased risk of cervical cancer.[29] The HPV virus can cause abnormal cellular changes in the infected location (usually the cervix). These abnormal changes are known as cervical intraepithelial neoplasia (CIN). The majority of CIN spontaneously regress, however, they have the potential to develop into invasive cervical cancer (figure 1). CIN are graded into three levels (CIN 1 ['low-grade'], 2 and 3 ['high-grade']) by histopathology on biopsies' tissue, according to how abnormal the cells are and how much of the cervix is affected. The regression rate for CIN 1 is around 60%, while only 10% progress to CIN 2 or CIN 3. Less than 50% of CIN 3 progress to invasive carcinoma, with much lower rates seen in younger than in older women.[30,31,32,33,34]

Figure 1: How cervical cancer can develop after HPV infection.



Source. Adapted from Schiffman M, Castle PE. The promise of global cervical cancer prevention. N Eng J Med 2005; 353(20): 2101—2103

From the time of infection with a high-risk HPV, 10 to 20 years or more are usually needed for cervical cancer to develop. Evidence suggests that less than 10% of women with a persistent HPV infection will develop cervical cancer. [35,36]

High-risk HPV types are also associated with other anogenital cancers and some cancers of the head and neck in both men and women. However, cervical cancer is by far the main burden of HPV-related cancers. [10]

Cofactors increasing probability of cervical cancer development

Although many women become infected with HPV, in most cases this does not progress to cervical cancer. A number of conditions or cofactors have been associated with an increased risk of HPV infection persisting and progressing to cancer. These include:

HPV-related cofactors [37,38]

- viral type: some types, such as HPV 16/18, have a larger oncogenic potential than other types;

- infection with several high-risk HPV types;
- high amounts of virus (high viral load).

Cofactors related to the host

- suppressed immune systems: people with immunodeficiency, caused by HIV infection or organ transplantation, have more persistent HPV infections and a more rapid progression to precancers and cancer;
- parity: the risk of cervical cancer increases with the number of children a women bears.[39]

External factors

- Tobacco smoking;[40,16]
- Use of oral contraceptives for five or more years; [41,42]
- Coinfection with other sexually transmitted diseases, such as *Chlamydia trachomatis* (CT) and herpesvirus type 2. [43,44,45,46,47,48]

The group at highest risk of developing cervical cancer, regardless of cofactors, remains those women who do not attend regular cervical screening.

Current prevention of cervical cancer and HPV infections

The main basis of cervical cancer prevention in Europe currently involves routine sampling and microscopic examination of a sample of cervical epithelial cells ('cytological screening') in order to detect abnormal cervical cells. This form of screening began in the 1960s. In several EU countries, the incidence of cervical cancer has declined significantly since the 1970s, which has been largely attributed to these screening programmes. Organised, population-based, cervical cancer screening programmes with quality assurance at all levels is recommended for all EU countries.[49]

If cell abnormalities are detected, these are investigated with procedures such as a 'colposcopy', where a doctor visually examines the cervix, and a biopsy. Depending on these investigations, treatment may be required. Like other screening tests, cytological screening is not perfect. It is highly dependent on adequate sample collection, slide preparation and correct interpretation by laboratory staff. In addition, a combination of suboptimal screening strategies (in terms of age groups and frequency of screening), variable standards of screening, insufficient coverage by population-based screening programmes (particularly for women with a low socio-economic status) and problems of access to medical services have meant that morbidity and mortality due to invasive cervical cancer are still high in some countries of Europe.[50]

As well as cytological screening, some primary prevention methods such as consistent use of the male condom[i] during vaginal sex and limiting the number of sexual partners are associated with less transmission of HPV and reduce the risk for cervical cancer.[51] There is

[i] Although it could be assumed that the female condom also provides protection, evidence is only available for the male condom.

also some evidence that male circumcision reduces the probability of men carrying HPV and of their female partners developing cervical cancer.[52]

The latest development in primary prevention of cervical cancer, and the subject of this guidance document, is the licensure of vaccines against HPVs 16/18.

Research questions

Is an infection with a high-risk HPV more likely to persist the older a woman is?

Do new HPV infections in older women result in cancer?

Can markers be developed to distinguish between a transient and a persistent HPV infection?

2. THE HUMAN PAPILLOMAVIRUS VACCINE

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Key points

- Two prophylactic human papillomavirus (HPV) vaccines have been licensed in Europe: Gardasil and Cervarix.
- Both vaccines are made from virus-like particles (VLP) and they are non-infectious.
- Both vaccines have a good safety profile.
- Both vaccines protect against the high-risk HPV 16/18, responsible for an estimated 73% of cervical cancer cases in Europe; Gardasil also protects against HPVs 6/11, 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.

In the 1990s, the first vaccines against HPV were created using VLP. These are made using a protein from the outer shell of the virus, which self-assembles in vitro. These particles do not contain viral genetic material, are unable to multiply, and are non-infectious. The particles mimic HPV very well, and together with an adjuvant, induce a strong antibody response after vaccination which is several times higher than the average response after a natural infection.

Using the VLP technology, two vaccines against certain HPV types have been developed. The quadrivalent vaccine Gardasil®, marketed in Europe by Sanofi Pasteur MSD, protects against high-risk HPV types 16 and 18 (these cause an estimated 73% of all cervical cancers in Europe), and low-risk types 6 and 11 which cause genital warts. The bivalent vaccine, Cervarix, manufactured by GlaxoSmithKline protects against high-risk HPV 16/18. Both vaccines have been licensed by the European Commission, after having received a positive opinion from the European Medicines Evaluation Agency.[53,54,55,56]

Both vaccines are prophylactic. They prevent persistent infection with HPVs 16/18 and resultant cervical precancers and invasive cancers (both squamous cell carcinomas and adenocarcinomas) and vulvar and vaginal intraepithelial neoplasias caused by HPVs 16/18 in individuals who have not been previously infected with the HPV types included in the vaccine. The quadrivalent vaccine also prevents infection with HPV 6/11 and associated genital warts. The vaccines are not designed to be therapeutic. The recommended schedule for both vaccines is three doses over a six-month period.

Although HPV 16 is the main cause of cervical cancer, the efficacy of the vaccines against HPV 18 is important since HPV 18 is more closely associated with cervical adenocarcinoma, which is more difficult to detect by screening than squamous cell carcinoma.[57]

Characteristics of the two HPV vaccines and trial populations

	Quadrivalent vaccine	Bivalent vaccine
Manufacturer and trade name	Merck, Gardasil®	GlaxoSmithKline, Cervarix®
VLPs of genotypes	6, 11, 16, 18	16, 18
Substrate	Yeast [S. cerevisiae]	Baculovirus expression system
Composition	20 µg HPV 6, 40 µg HPV 11 40 µg HPV 16, 20 µg HPV 18	20 µg HPV 16, 20 µg HPV 18
Adjuvant	Proprietary Aluminium Hydroxyphosphate Sulfate (225ug) (Merck Aluminium adjuvant)	Proprietary Aluminium Hydroxide (500 µg) plus 50 µg 3-deacylated Monophosphoryl Lipid A (GSK AS04 adjuvant)
Schedule: 3 IM doses of 0.5 ml at	0, 2, 6 months	0, 1, 6 months
Main efficacy trials	Females aged 16–26 years	Females aged 15–25 years
Safety/immunogenicity bridging trials	Females and males 9–15 years	Females 10–14 years Males 10–18 years Women 26–55 years

Adapted from: Cutts et al, 2007[58]

Clinical trials for the quadrivalent and bivalent vaccines

Both vaccines recently underwent randomised, double-blind, placebo-controlled phase III clinical trials in North America, Latin America, Europe and the Asia-Pacific region.

After three doses of either the quadrivalent or bivalent vaccine, almost 100% of women aged 15–26 had detectable antibodies (an immune response) to each HPV type, levels being 10–104 times higher than those seen in natural infections.[59, 60, 61]

Studies of vaccination in girls under age 16 have been carried out using immunogenicity endpoints, since cervical smear testing would be unacceptable and unethical. These have demonstrated an excellent immune response. [62, 63]

Quadrivalent vaccine clinical trial

For the quadrivalent vaccine, 12 167 women aged 16–26 at enrolment were vaccinated with either the vaccine or a placebo.[64] The endpoints measured were cervical intraepithelial neoplasia (CIN) 2/3 (moderate to severe precancers), adenocarcinoma *in situ*, cervical cancer related to HPV 16/18 and genital warts.

In the 5 305 vaccinated women who had no evidence of past or present infections with HPV 16/18, and who received all vaccine doses, the quadrivalent vaccine was found to be 98% effective (95% confidence interval [CI] 86–100) at preventing high-grade cervical precancers (CIN 2/3 and adenocarcinoma *in situ* [AIS]) related to HPV 16/18 after an average follow-up of three years. If those women with less than perfect compliance were also included, vaccine efficacy remained high at 95% (95% CI 85–99), for the same endpoints.

If all 12 167 women enrolled in the trial are included (including the HPV-positive ones and those with presence of precancerous lesions at baseline, the vaccine efficacy against HPV 16/18 related CIN 2/3 or Adenocarcinoma *in situ* was 44% (95% CI 26–58). Most cases of CIN 2/3 among vaccinated women in this population were caused by HPV 16/18 that was present when the woman entered the trial. High efficacy was observed against the types included in the vaccine that these women were not infected with at the start.

The estimated vaccine efficacy against all high-grade cervical lesions, regardless of causal HPV type, in this intention-to-treat population was 17% (95% CI, 1 to 31).

The quadrivalent vaccine that protects nearly universally against the 2 most common oncogenic forms of HPV also provides about 40% cross-protection against other common oncogenic strains of HPV.[65]

Bivalent vaccine clinical trial

Interim results of phase III trials of the bivalent vaccine (Cervarix, GlaxoSmithKline) involving 18 644 women aged 15–25 demonstrated a vaccine efficacy of 90.4% (97.9% CI 53.4–99.3) against CIN 2/3 lesions containing HPV 16/18 DNA in women who were seronegative and DNA-negative for the vaccine HPV types at day 0 of the trial.[66] Follow-ups on women were done for a mean of 14.8 months.

The bivalent vaccine also demonstrated an efficacy of between 21.9% and 38.2% against cervical infections of any oncogenic HPV type persisting for six and 12 months respectively.

Efficacy data from both vaccines

Vaccine efficacy on the prevention of HPV 16/18 related CIN 2/3 or AIS

	Vaccine group		Control group		Efficacy (CI)[i]
	N	Cases	N	Cases	
Gardasil[ii] *(mean follow- up three years)*					
Per protocol population[iii]	5 305	1	5 260	42	98 (86–100)
Unrestricted population[iv]	5 865	3	5 863	62	95 (85–99)
Intention to treat population[v]	5 951	83	5 977	148	44 (26–58)
Cervarix[vi] *(mean follow-up 15 months)*					
Unrestricted population	7 788	2	7 838	21	90 (53–99)

[i] 95% for Gardasil data, 97.9% for Cervarix data.
[ii] Future II study group, New England Journal of Medicine, 2007.
[iii] Defined as subjects naïve to relevant vaccine type at enrollment and through month 7, who received all doses within 1 year and had no protocol deviations. Cases counted after month 7.
[iv] Defined as subjects naïve to relevant vaccine type at enrollment and, who received at least 1 vaccination. Cases counted after month 1.
[v] All subjects regardless of baseline status with respect to HPV and cervical neoplasia, who received at least 1 vaccination. Cases counted after month 1.
[vi] Paavonen et al, Lancet 2007[66].

Vaccine safety

Both vaccines have been evaluated for local and systemic adverse events during the different efficacy trials, including tens of thousands of women from different countries. In June 2007, the World Health Organization's Global Advisory Committee on Vaccine Safety reviewed published and non-published data on the safety of both HPV vaccines. The reviewed data covered local and systemic events in short-term and long-term events up to six years, including pregnancy events. They concluded that the current evidence on the safety of HPV vaccines is reassuring.[67]

People participating in the HPV vaccine's clinical trails reported that its adverse effects were pain, redness and swelling at the injection site. These occurred in about 80% of study participants and were more frequently reported in the vaccine group than the placebo. [64, 66]

During adolescent vaccine campaigns, some mass sociogenic illnesses such as post-vaccination dizziness and syncope have been reported. [67]

Although the trials for both vaccines excluded women who were pregnant, many women inadvertently became pregnant during the trials and have been evaluated. Based on these trial data, both vaccines appear to have good safety profiles during pregnancy.

Continued active follow-up of participants in phase III trials and active assessment of post-licensure phase IV trials will be important to assess the long-term safety of HPV vaccines.

Duration of protection

How long protection will last and whether booster immunisation will be necessary are important questions.[68]

Antibody persistence and protection against persistent infection have been shown for up to five years post-vaccination for both bivalent and quadrivalent vaccines. This has been the longest duration of follow-up where results have been published so far. Antibody levels during this time have remained higher than those seen after natural infection. Follow-ups on both vaccines will be done for the next 15 years.

Cross-protection against other genotypes and possible type replacement

In preliminary analyses, both vaccines have shown some evidence of cross protection against HPV 31/45, closely related HPV types to HPV 16/18, respectively. [60, 66, 65]

In the extended follow-up of the phase II trials of the bivalent vaccine, a significant reduction was found in incident infection with type 45 (one case in 528 vaccinated women and 17 cases in 518 controls; vaccine efficacy (VE) = 94.2% [CI: 63.3–99.9]) and type 31 (14 versus 30 cases, respectively; VE = 54.5% [CI: 11.5–77.7]).

Unpublished data from more than 17 000 women who participated in FUTURE I and II studies of Gardasil were found to have cross-protection for HPV types related to HPV 16.[65] Out of 4 616 women who received the vaccine, HPV types 31, 33, 35, 52, and 58 were identified in

27 women with precancerous lesions, whereas in the control group 48 out of 4 675 women had lesions due to these HPV types. The difference represented a 43% reduction in risk (95% CI 7–66).[65]

For cross protection to be clinically meaningful, it will be necessary to demonstrate that these vaccines effectively reduce the incidence of persistent HPV infection and biopsy-proven CIN caused by HPV types related to HPV 16/18. Studies are continuing for both vaccines. [58]

While the balance of evidence suggests that different HPV types act as independent sexually transmitted infections, low levels of interaction may occur between similar types. There could be competition for ecological niches within the cervix, which means that if infections caused by one type fall, it could be replaced by a different type. Monitoring systems for the surveillance of breakthrough infections and of distribution of vaccine and non-vaccine HPV types will be necessary after introduction of the vaccine. [57]

Populations who could benefit

The very high clinical efficacy in women without evidence of infection with vaccine HPV types shows that vaccinating before an age when females are exposed to HPV would have the greatest impact on cervical cancer incidence, CIN 1/2/3 and genital warts. In addition, immunogenicity studies for both vaccines have shown a higher immunogenicity in young adolescents than in young women over the age of 15.[69] This subject is further discussed in chapter 4.

Although the vaccines provide protection against the most common types of cancer-causing HPVs, screening will still be required for all women to prevent cervical cancer caused by the other high-risk types. See in-depth discussion in chapter 3 for further information.

More clinical data are needed to assess whether other populations might benefit from HPV vaccines. These include:

- Younger age groups: it might be easier to obtain a high coverage by including the vaccination in national immunisation programmes, which are generally administered in the first few years of life. No vaccination trials have yet been undertaken in children under the age of nine, and are unlikely to be.
- Older age groups and women previously exposed to HPVs: data are expected on vaccine efficacy in these groups. In studies of older women aged 26–55, antibody levels induced by the vaccine were also several times higher than after natural infection, although less than that in young women. The clinical efficacy of the vaccines in this older age group is still not known.
- Immunocompromised women: trials of both vaccines among immunocompromised people are still ongoing.
- Heterosexual males: both vaccines could potentially provide protection against HPV 16/18 anogenital cancers. Theoretically, there would be an additional benefit for females as transmission would be reduced. Efficacy studies (for protection against genital warts and immunogenicity) of the quadrivalent vaccine in males are underway.

- Men who have sex with men: much higher rates of anogenital cancers occur in this group. See chapter 4 for a brief discussion of this group as a target population for vaccination.

If vaccination is supported by governmental authorities, target groups and cohorts selected for vaccination will depend partly on the preventable burden of disease (see chapter 4) as well as the logistics and health service structure available for vaccine delivery (see chapter 5 for further discussion) and also on cost-benefit analyses adapted to each national situation (see chapter 6).

Current and future developments

Authorities in several EU countries have already decided to include HPV vaccine in routine immunisation programmes. The primary target group in all of these countries is girls of an age before sexual activity becomes common.

Further generations of HPV vaccines may provide protection against more types of HPV. Therapeutic vaccines may be developed.

Research questions

Will exposure to an HPV virus after vaccination act as a natural booster?

What is the role of cell-mediated immunity in the protection generated by the VLP vaccines?

Some other research questions are currently being addressed by clinical trials:

- What is the effect of HPV vaccine administration at the same time as other vaccines?
- What fraction of cervical cancer incidence overall will be prevented by vaccinating against HPV 16/18?
- What benefits might vaccination confer on adults who are already infected with HPV?

3. HPV VACCINES AND CERVICAL CANCER SCREENING

Patricia Claeys

Key points

- Human papillomavirus (HPV) vaccines do not eliminate the need for cervical cancer screening.
- National authorities should continue their efforts to organise and improve the coverage and quality of screening programmes, independent of vaccine introduction.
- HPV vaccines will have an impact on the efficacy of existing screening programmes, which will need to be monitored closely.
- Women need to be informed and motivated to attend screening programmes, even if they have been vaccinated.

Cervical cancer screening practices within the European Union

Over the last decades, annual numbers of cervical cancer cases and associated deaths have been declining in many European countries as a result of cytology-based screening programmes. The aim of cervical cancer screening is to detect progressive precancerous lesions of the cervix and, by treating them, prevent progression to invasive cancer. It has been shown that the annual number of new cases of cervical cancer has the potential to be reduced by as much as 80–90% among women screened every three to five years between the ages of 35 and 64, using conventional cytology.[70]

In some European countries, e.g. Finland, the Netherlands, the United Kingdom, screening and adequate follow-up of women with abnormal screen results has been very successful in reducing the cervical cancer burden, preventing from 60% to more than 80% of invasive cervical cancer cases or deaths from the disease.[71] Countries where there are organised screening programmes also seem to have much lower lifetime testing and apparently subsequent treatment rates than those with the opportunistic modality alone.[72, 73] Organised screening is therefore more cost-effective than opportunistic screening. [71] However, in many countries, it has not yet been possible to set up programmes that achieve a high coverage of the target population and that assure appropriate follow-up.

The success of screening in preventing invasive cervical cancer depends mainly on the participation of the target population, the quality of the screening test and the adequate treatment of detected precancerous lesions. At the population level, the best results are seen with organised screening programmes, as these are more successful in reaching the women most at risk, in establishing mechanisms for quality control, and in monitoring standardised measures of activity and impact.

The Council of the European Union recommends that screening programmes for cervical cancer are implemented using a systematic population-based approach with quality assurance at all appropriate levels. The test that should be used is the Papanicolaou (Pap) smear. Screening should not start before age 20 years and not later than 30 years. The upper age

limit should depend on the available resources but should preferably not be lower than 60 years.[74] Organised screening is thus capable of preventing cervical cancers across a broad age group among women at risk of the invasive disease and therefore to combat cervical cancer during the next few decades. Introducing organised screening programmes in areas where these do not yet exist seems to be a priority.

While cervical cancer screening exists in all EU Member States, screening policies and organisation in the different countries vary greatly. [4, 73, 75] Organised cervical cancer screening programmes exist in nine EU countries: Denmark, Finland, Slovenia, Sweden, the Netherlands, the United Kingdom, Ireland, Poland and large parts of Italy. In most other countries, screening is still opportunistic, which means that the initiative has to come from the woman or the doctor.

The potential for primary prevention through HPV vaccination offers a new complementary tool to improve the control of cervical cancer. Women vaccinated against HPV 16/18 will still be at risk from other high-risk types.[76] This means that, even after HPV vaccines have been introduced, cervical cancer screening programmes will have to continue, even for vaccinated women. Screening is also essential to protect adult women who have not been vaccinated. It is essentially the combination of primary prevention (HPV vaccination) and secondary (screening) prevention strategies that will further reduce the incidence of, and deaths from, cervical cancer.[77] An important question is how HPV vaccination would interact with existing screening and how to ensure prevention strategies remain cost-effective.

Impact of vaccination on existing cervical screening

In countries where screening programmes are non-existent or deficient, the introduction of HPV vaccination may be an opportunity to organise a cervical cancer prevention programme that includes both vaccination and screening. It should be noted that the testing and treatment rates largely depend upon the recommendations on the screening ages and intervals. In many countries adopting the recommended screening interval of three to five years, instead of a one-year interval, would be meaningful.

Structuring a screening programme in an organised way means clearly defining the target population, introducing an efficient system of notifying patients when their screening test is due and if a test is abnormal ('call-recall' system), attaining high coverage and introducing quality control mechanisms (e.g. for laboratories but also for adequate follow-up, diagnosis, etc), monitoring and evaluation. This means that a patient registry is needed, and that databases have to be linked (e.g. for identification and invitation of the target population, for notification of attendance to the screening programme, and to monitor follow-up of abnormal test results). Where possible, from the start, screening databases, databases of vaccinated girls and cancer registries should be linked in order to measure performance and impact of both screening and vaccination (see chapter 7).[78]

In countries with effective screening programmes with high coverage (e.g. Finland, Denmark, Iceland, the UK, the Netherlands), the benefit of adding vaccines to the screening programme will be relatively small in terms of further reducing cervical cancer-related mortality. Policy makers in these countries will have to carefully evaluate the implications of

introducing HPV 16/18 vaccines. Cost-benefit analyses done in some of these countries, e.g. in Denmark, have shown that vaccination of adolescent girls, in addition to the existing screening programme, can be cost-effective.[i]

The more immediate benefits of using the recently developed quadrivalent and bivalent vaccines in these countries will be a decrease in the number of precancerous lesions. Based on cross-sectional data, it has been estimated that 41–67% of high-grade squamous intraepithelial lesions (HSIL), 16–32% of low-grade squamous intraepithelial lesions (LSIL) and 6–27% of atypical squamous cells of undetermined significance (ASCUS) are HPV 16/18-positive and could thus be prevented using current HPV vaccines. [15] This would result in fewer follow-up examinations, less anxiety for the patients, a smaller number of excisional treatment procedures being performed and fewer short-term and long-term complications due to treatment. Moreover, vaccines will reduce morbidity due to other HPV-induced disease, such as genital warts (for the quadrivalent vaccine only).

HPV vaccination may also negatively affect existing cytology-based screening programmes. Widespread vaccination will result in some decrease of HPV-related cytological abnormalities and a reduction in the positive predictive value of the screening test. This will result in an increasing proportion of false positive results leading to unnecessary investigations and treatments.[79] A lower number of abnormal smears may decrease the alertness of the laboratory staff examining the slides, resulting in reduced sensitivity of the test. Also, vaccinated women might have a false sense of security, resulting in lower attendance at screenings. As a result, the effectiveness of the existing screening programme could be reduced. This risk is an additional reason to organise screening programmes where they are not already present. It will be crucial to continue to inform and to motivate women to attend screening programmes, even if they have been vaccinated.

The overall impact of introducing HPV vaccines in Europe will depend upon its delivery to the sub-groups within a population that most need it like women in low socio-economic groups and women who are less likely to access medical and screening services. This is only possible if vaccines are affordable and widely delivered including among underserved communities. This is more easily obtained in many countries when delivered through public sector health systems or through public-private partnerships. If, in contrast, vaccine access is limited to populations that are most likely to be screened, there will be little or no impact on cervical cancer incidence and mortality. In particular, policy makers should be aware that 'opportunistic' vaccination may not target the groups most at need and that the public health effect of vaccination may be limited if vaccination is not done in a systematic way.

Adapting cytological screening in the era of HPV vaccination

In countries that introduce HPV vaccines, efforts will be needed to monitor and maintain the quality of cervical screening. HPV DNA testing is becoming more important in screening, and results of ongoing trials will show whether the performance of HPV DNA testing is better than cytology as a primary screening tool. HPV testing is more effective in populations with low lesion prevalence and also provides an opportunity to create infection registries that can link

[i] http://www.sst.dk/publ/Publ2007/MTV/HPV/HPV_vaccination_smfatn_en.pdf.

test results from the same women over time, allowing monitoring of vaccinated cohorts. [77] However, if the introduction of the HPV vaccine led to more spontaneous or opportunistic testing for HPV infections particularly among rather young women, this could eventually increase rather than decrease the prevailing screening and cervical intraepithelial neoplasia (CIN) treatment rates. WHO recommends not using HPV-DNA testing in women below the age of 30 because of the high prevalence of transient HPV infections in younger women, resulting in unnecessary follow-up and eventually treatment in this age group. [80]

Adding HPV vaccines to cancer prevention programmes will increase their overall cost, but cost-effectiveness may be improved in future by changes such as extending the screening interval in vaccinated women and probably also by starting screening at a later age. This is especially the case in countries where screening starts at an early age and is done yearly.

However, in countries where international standards are already applied (starting screening at 25 years old and every three to five years) the screening strategy should not be changed in the short term. Close monitoring of vaccinated cohorts will be necessary to inform potential changes to screening practices. Providing adequate information to vaccinated women is essential to keep them aware of the need for regular screening despite vaccination.[81]

Even if it is decided not to introduce widespread HPV vaccination in some EU countries, policy makers have to be conscious that an increasing number of women will be vaccinated outside official programmes and that close monitoring of the effects of vaccination on the screening programme, as well as the design of alternative screening protocols for vaccinated women, will be necessary.

In summary, health authorities of many European countries have reason to be proud of the effective way in which their cytology screening programmes have reduced human suffering due to cervical cancer. HPV vaccines offer new opportunities and challenges and healthcare providers should understand that screening and vaccination are complementary strategies.[82] They should be implemented simultaneously within a comprehensive programme of cervical cancer control. One of the most important challenges will be how to achieve synergy between vaccination and screening in a cost-effective way and with the maximum benefit for women.

Research questions

What are the determinants for compliance of vaccination and screening?

What is the long-term impact of HPV vaccines on screening programmes?

How cost-effective are cervical cancer prevention programmes that include vaccination and screening, taking into account observed data on screening compliance after vaccination?

How should screening programmes be adapted once an increasing number of girls/women are vaccinated?

What is the value of HPV testing as a primary screening tool in vaccinated cohorts?

4. WHO SHOULD BE VACCINATED? DETERMINING TARGET POPULATIONS FOR HPV VACCINATION

Kate Soldan and Daniel Lévy-Bruhl

Key points

- To optimise the impact of the new vaccines on diseases associated with human papillomavirus (HPV), 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 below this age would not prevent many infections and should be avoided until there is evidence that the vaccine has a long duration of 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 to determine the exact year of 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).
- The case for vaccination of women over the age of 26 years and males requires more data on the efficacy and effectiveness of vaccination.
- Routine vaccination of males is very unlikely to be cost-effective.
- Selective vaccination of 'high-risk' groups seems unlikely to be either practical or more effective than vaccinating all girls.

Factors to consider and compare between potential groups, when determining target groups for HPV vaccination include:

- any variation in vaccine safety and licensure;
- any variation in vaccine immunogenicity and efficacy;
- likely herd immunity effects;
- the burden of preventable disease;
- the timeliness of impact on disease;
- the likely acceptability and uptake;
- accessibility for vaccination delivery;
- the existence, coverage and effectiveness of other preventive measures (mainly cervical screening);
- cost-effectiveness (i.e. the economic measure of all these factors together).

Mathematical models have been developed to study the combined effects of these factors. The results of published mathematical models that have assessed the impact of HPV vaccination on cases of cervical intraepithelial neoplasia (CIN) 2/3 lesions and/or cervical cancers can inform the choice of target groups for routine and catch-up vaccination.[83, 84, 85, 86, 87, 88, 89, 90, 91] The results and conclusions from models are dependent on the parameters used

to shape them, including patterns of sexual activity (mainly age at sexual debut and frequency of partner change in the first years of sexual activity). Therefore, one should be careful not to generalise or extrapolate from one country to another if sexual activity patterns (or other parameters) differ significantly between countries.

Routine vaccination of young females

The main part of the total burden of HPV-associated disease, even in countries with effective screening programmes, is due to cervical cancer (and precancers) in women. Reduction of cervical cancer by preventing HPV infections is expected to be greatest if females are protected from infection before beginning sexual activity.

Young women and girls between nine and 26 years of age have been the primary targets of trials and licensure applications for both of the available prophylactic vaccines: the quadrivalent vaccine (Gardasil®) and the bivalent vaccine (Cervarix®). Young females are expected to be the primary target population in countries that introduce HPV vaccination because this group has the greatest potential to benefit from prophylactic vaccination. Consideration of the vaccination of women over 26 years of age requires further data on the efficacy and effectiveness of vaccination at these ages. Further efficacy data on certain sub-groups such as immunocompromised females, and on efficacy in women who are already infected at the time of vaccination are also awaited from trials in progress.

Choice of age for vaccination of girls / women

Vaccine effectiveness is higher if girls are vaccinated before sexual debut, and thus before they are most at risk of developing genital HPV infections. Increasing the target age of vaccination above the age where sexual activity starts to be common decreases the benefits of vaccination, as the proportion of females with a previous or existing infection increases. This has been shown by the mathematical models cited (given their assumptions). Assumptions typically include no or much reduced efficacy in already infected women, and that pre-vaccination testing (for either DNA or antibodies) would not be feasible or helpful.

Decreasing the age of vaccination to below the age of sexual debut delays the impact of vaccination but has the same protective effect in the long term, if it is assumed that there is no substantial waning of vaccine-induced immunity, and no long-term benefit from the greater immunogenicity of vaccination at younger ages. Only longer-term follow-ups of vaccinated cohorts than currently available will resolve uncertainties about the duration of protection and factors associated with duration of protection.

Variations in the cost-effectiveness of HPV vaccination for girls and women aged between ten and 26 years therefore depend heavily on sexual behaviours that determine age-specific risks of HPV infection. Evidence to date suggests that the younger a person is at the time of vaccination (10–15 years compared to 16+ years) the better the immunogenicity. [62] However, all ages of females studied have shown good, very high immune response in naive people and the benefit of relatively higher antibody levels is not known. However, the risk of vaccine-induced immunity waning before the years of high exposure to HPV infections are passed (i.e. before 30 years of age) is greater (if unrelated to initial antibody levels) for younger cohorts

at the time of vaccination. Several models have demonstrated that if vaccine-induced protection lasts for less than 15–20 years, vaccination of very young girls would, in the absence of boosting, result in significantly lower cost-effectiveness and may also result in unexpected outcomes due to susceptibility to infection being shifted to older females. The models show clearly that any waning in vaccine-induced protection during the peak years for HPV incidence (20–25 years of age in females in most populations) could seriously reduce the expected benefits. Therefore, lowering the age of routine vaccination for no real gain in terms of infections prevented should be avoided until more evidence is provided for long-term protection, and/or for benefits associated with higher initial antibody responses.

Other factors should be taken into consideration when choosing the target age group and the delivery strategy (see also chapter 5):

- The mean age at sexual debut and the peak HPV transmission years may vary according to area, so the age at which the vaccine is given should be considered carefully.
- Studies in at least one European country have shown that at least some parents may be reluctant to accept HPV vaccine for prepubescent girls.[92]
- Aversion to needles may be greater or lesser in different age groups, depending on attitudes and experience of other healthcare services.
- Accessibility and ease of vaccination delivery is likely to vary with age, and to depend on country-specific organisation of education and healthcare. For successful HPV vaccine delivery, girls need to be reliably accessible not just at one time point but for three doses over a six-month period. Both the costs of vaccine delivery and the potential for incomplete courses, and associated wastage of vaccine doses may vary with age.

Catch-up vaccination of older girls and women

'Catch-up vaccination' involves the inclusion at the start of the vaccination programme some birth cohorts who are older than the age targeted for routine vaccination. Catch-up programmes therefore vaccinate individuals who would have been vaccinated routinely had the vaccination programme started several years earlier.

The cost of HPV vaccine is high relative to most other vaccines that are used routinely in Europe. As the cost of the vaccines is likely to be a major proportion of the costs of any vaccination programme, the vaccination cost per female in the catch-up programme will be close to the cost per female for the routine programme. Catch-up campaigns will increase the costs of the programme during the catch-up year(s) very significantly.

If a relatively young age is chosen for routine vaccination, the cost-effectiveness of vaccinating some older year-groups may be better than for routine vaccination, as vaccination will occur nearer to the peak risk period of infection and disease.

Three models have explored the impact of an initial catch-up vaccination strategy added to vaccination strategies which vary in terms of age at vaccination and target population (girls only, versus girls and boys). Both models demonstrated the expected result that catch-up improved the timeliness of the vaccination programme's impact and added substantial

decreases to disease in the short term, without changing the proportion of disease prevented per year in the long term once all birth cohorts have experienced routine vaccination (i.e. in 50–70 years' time).

Vaccination of males

Evidence to date suggests that safety and immunogenicity of HPV vaccines amongst males (10 to 15 years of age) is as good as, or better than, that for females. [62] The EU marketing authorisation for Gardasil[93] did not exclude use in males, although noted that efficacy in males was not known. Trials of the efficacy of Gardasil in young men aged 16–23 years are due to be reported in 2009. Trials to determine the safety and immunogenicity of Cervarix in males (aged 10–18 years) are also in progress.

However, routine vaccination of boys and men is not likely to be cost-effective. The burden of disease associated with HPV 16/18 in males is small, as it is related to some anogenital and head and neck cancers and the efficacy of vaccines for the prevention of these relatively rare cancers is not known. Males have 50% (or more, according to some data sources) of the burden of genital warts, the majority of which could be prevented by vaccination against types 6 and 11 (i.e. Gardasil), but the costs and quality of life losses associated with warts are far less than for cervical cancer.

By preventing persistent infection and disease, it is likely that vaccination will reduce the transmission of the vaccine-type HPV infections (i.e. confer 'herd immunity'), although there is as yet no direct evidence (pending large phase IV studies and surveillance of vaccinated populations) about how much vaccination reduces the transmission of infection. If vaccination does prevent transmission, then the benefits of vaccinating males as well as females would be direct protection from genital warts and indirect protection of any unvaccinated female sexual partners (from warts and cancer). Both these benefits would be relatively small if the vaccination coverage of females was high. Alternatively, should vaccination not reliably prevent transmission, then greater benefit would be gained by the direct protection of males from warts but less benefit would be gained by indirect protection of females (from warts and cancers). As the prevention of cancer dominates the cost-effectiveness analyses of HPV vaccination, this second scenario is not likely to favour the vaccination of males either.

Vaccination of boys and men with the aim of preventing cervical disease in women, rather than for the direct health gain of the vaccinated man, may be unacceptable to some people. On the other hand, if the vaccine used protects against warts as well as cervical cancer (i.e. Gardasil is used), the exclusion of males may result in discontent and claims of inequality, particularly if the effects of herd immunity on genital warts in men turn out to be weak. Surveillance of HPV-associated disease in men will be important to evaluate the indirect effects of female vaccination strategies.

Models have shown (given their assumptions) that the impact on cervical cancer of vaccinating boys and men as well as girls and women varies depending upon the age at vaccination and the vaccine coverage. At younger ages, the burden of disease prevented by vaccinating both girls and boys is greater. Once vaccine coverage of both groups exceeds 50% the marginal benefit of vaccinating males as well as females decreases with further

increases in coverage. As the costs of vaccinating males are almost as high as vaccinating females (less only the generic costs of the programme organisation), the conclusion of most assessments tends to be that the vaccination of males has a relatively poor yield and poor cost-effectiveness compared to the vaccination of females (see also chapter 6). The impact of adding male vaccination to female vaccination would only be significant if vaccination coverage is low in females. However, in such a case, improving the coverage of vaccination amongst females would probably be more cost-effective than delivering vaccine to males. Models including catch-up for males have predicted that this would have very little impact on the burden of disease.

Selective vaccination of groups at high risk of HPV-associated disease

The overall high cumulative risk of acquisition of high-risk HPV in the first years of sexual activity for all sexually active girls or women makes it difficult to identify specific high-risk sub-groups for targeted vaccination. One model [90] considered the option of targeting the vaccination towards the most sexually active individuals and showed (given their assumptions) that irrespective of the difficulties of identifying and accessing such individuals, this strategy would probably be less effective than vaccination of all girls. This model is sensitive to sexual mixing patterns and shows that a selective vaccination strategy targeted at individuals with a high level of sexual activity would only be more effective than routine vaccination of girls assuming unexpectedly low rates of mixing between the highest and the lowest sexual activity groups. In most models, the parameters describing sexual activity, compliance with screening programmes and vaccine coverage are assumed to be independent. If there are, in fact, associations between these factors such that high-risk groups have poorer compliance with screening and/or vaccination, special targeting of routine and/or mop-up vaccination at high-risk groups would show a greater benefit.

Men who have sex with men (MSM) have increased rates of anogenital cancers attributed to HPV 16/18 and therefore would potentially benefit from HPV vaccines more than other men assuming that the efficacy of HPV vaccination to prevent HPV 16/18-associated anogenital cancers is similar to the vaccine's efficacy against persistent HPV 16/18 infection and cervical disease in females. However, to gain direct protection from the available prophylactic vaccines, vaccination would have to be delivered to MSM before sexual activity became common (as for young females), and identifying young males who may benefit later on from selective vaccination is likely to be impractical.

Conclusions

Review of the factors that are relevant to determining target groups for HPV vaccination generally concludes that girls aged between nine and 15 years are the priority target group for HPV vaccination. The choice of exact year(s) for vaccination within this age range and the extent of catch-up are likely to depend on country-specific assessment of relevant factors. Vaccination of males in addition to females and selective vaccination of high-risk groups alone is not likely to be as effective as vaccination of young females, nor as cost-effective. The

potential role of selective/opportunistic vaccination of some high-risk individuals in addition to routine vaccination may need further consideration.

It should be remembered that these conclusions regarding age of vaccination, the benefits of catch-up and the benefits of targeting high-risk groups are based on the assumption that HPV vaccines are prophylactic. These conclusions should be reassessed if new data emerge from clinical trials showing high effectiveness of the vaccines (via primary protection or boosting of natural immunity) in individuals who have had previous exposure to HPV.

5. STRATEGY OPTIONS FOR HPV VACCINE DELIVERY IN EU COUNTRIES

Adam Finn

Key points

- School-based immunisation is likely to be the lowest cost option for the delivery of human papillomavirus (HPV) vaccines to pre-adolescent girls. However, local issues, such as whether school-based health services exist, 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 of vaccine uptake may be more difficult here.
- Sexual and reproductive health and other medical clinics provided specifically for women may be important sites for immunisation. However, girls may not visit these before the onset of sexual activity and so these are likely to be useful mainly for catch-up programmes for 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 present to 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 that the message that immunisation is an adjunct not a replacement for cervical screening is communicated.

Scope and limitations

This chapter discusses strategies for vaccine delivery to young adolescent females and briefly discusses catch-up immunisation for older adolescents and young women, anticipating licensure for this group only in the first instance. It does not discuss options for immunisation of boys and men.

It assumes strategies will aim to deliver three doses of vaccine by injection to all recipients over a six-month period. It does not discuss delivery of booster dose(s) or strategies for completing partial immunisation courses.

It considers concomitant administration of HPV vaccines with other vaccines administered to adolescents (specifically DT/IPV & DTaP/IPV [diphtheria, tetanus, acellular pertussis, inactivated polio virus]), although few safety and immunogenicity data on this are yet available.

HPV vaccines will be used, in the first instance, to immunise girls hopefully before the onset of sexual activity, and thus before they have an opportunity to acquire vaccine-type HPV

infection. In most countries, this will involve offering three doses of the vaccine to girls of an appropriate age as part of a rolling programme. National health authorities may also choose to conduct catch-up campaigns for limited periods for older adolescent girls. For younger adolescents, explicit, usually written, parental consent will normally be required as well as assent to the immunisation by the child, whereas older teenagers will be able to consent independently.

As well as routine early childhood immunisation programmes, vaccines are routinely offered to adolescents in many European countries. Although data on uptake are scarce, it is likely that these programmes often achieve lower rates than programmes aimed at young children, although there are examples of successful high uptake adolescent immunisation programmes.[94]

The available delivery strategy options for delivering HPV vaccination in EU countries are:

1. School-based immunisation

Advantages

- School attendance is mandatory or already exists at high rates in nine to 16 year-olds throughout most of Europe (although truancy is a problem in some areas).
- School immunisation programmes are generally trusted and agreed to by most parents.
- Children are already there and registered as present, therefore keeping organisational costs low.[95]

Disadvantages

- Trained staff, time and appropriate space are needed if not already available (thus these programmes are easier to administer where school immunisation and/or health services are already established).
- Payment may be difficult to obtain if vaccine purchase and delivery are not centrally funded.
- Parental consent may be difficult to obtain as parents are not normally present at the time of an immunisation's administration.

Specific issues

- HPV vaccination can be carried out in primary schools (often smaller, more numerous schools where children are seen as 'young' and not yet approaching the age when sexual activity may commence), secondary schools (usually larger, fewer in number, where children are perceived as 'teenagers') or both.

Wherever secondary education with high female attendance is in place, school-based immunisation offers a clear potential place for HPV vaccine delivery. Where adolescent immunisation programmes already exist, such as for diphtheria, tetanus, polio and pertussis, using this platform for HPV vaccine delivery may be the obvious main strategic approach, although investment may be necessary to achieve adequate uptake rates in some places, especially where these are frequently low. Where no such school-based programmes exist, it may be worth establishing them. This may represent an ideal opportunity to deliver several interventions at once (including, for example, other vaccines).

Overall, school-based immunisation is likely to be the lowest cost option in most places. However, where the cost of vaccine purchase and delivery is through personal or personal insurance-based funding, payment systems may only exist through doctors' practices and this may hinder the school-based approach.

Educational organisation in different countries may affect the implementation of HPV immunisation in schools. Specifically, the age of transition from primary to secondary education may influence the chosen target age for immunisation.

Problems related to immunising large numbers of adolescent females in the same place at the same time include fainting related to hyperventilation and consequent injuries. [96, 97] School-based programmes need to be devised so that the risk of mass hysteria is minimised.

Finally, successful immunisation of a large majority of girls in school requires full support from parents, school staff and, not least, the children themselves. This means great care and effort is needed to design, test and implement effective training and education of all these groups before starting any programme.[98]

2. Primary care surgeries and clinics (including private clinics, medical practices and vaccination centres)

Advantages

- They exist, in one form or another, everywhere.
- Personnel are often well known and trusted by parents and children.
- It should be possible to ensure medical and other personnel are well educated about, and willing to promote the use of HPV vaccines.

Disadvantages

- It may be harder to monitor uptake and tracking.
- Young adolescents rarely visit for other reasons, such as illness.
- Organisational costs may be higher, and immunisation cannot occur in such an efficient en masse event, as in a school.

The main way of delivering vaccines to children and adults in many countries is through community-based primary care health clinics and surgeries. Such clinics may be general or speciality-based, and publicly or privately funded. Most families will be able to identify a medical facility they regard as their first contact point for illness management or prevention. In some countries, clinics exist exclusively for vaccination. It is likely that HPV vaccination of young girls and women will be done to some extent through such facilities in all European countries and in some, this may be the main setting for immunisation.

An advantage of such places is that the health professionals responsible for organising and delivering immunisations are usually identifiable and can be targeted for education about immunisation strategy. Indeed, in many areas, this process may already be happening through the vaccine manufacturers, even before government policy is formalised. Where relationships between families and such facilities are established, they usually include a high level of trust which has clear advantages for successful implementation.

However, although these facilities may be well suited to rolling delivery of vaccines to the families who are registered with them, they are not likely to be effective disseminators for mass campaigns. They may not currently have access to adolescents in the way that they have for younger children. In addition, they may not be effective in reaching families in deprived areas and communities or who, for any reason, routinely use acute hospital facilities for medical needs (see 'other settings' below).

Since most children aged nine to 14 are rarely ill and are rarely the target of medical interventions, they rarely routinely attend clinics. The cost and logistical challenges of implementing immunisation in such a place may therefore be higher.

Where information links between such facilities and any form of centralised record-keeping are not established, measures to monitor the success of the programme and identify individuals who have not been immunised or immunised completely, are more difficult than, for example, programmes where larger numbers of individuals are immunised in one place and at one time.

3. Sexual, reproductive health and gynaecological services

Advantages

- These normally cater specifically for sexually active individuals (some clinics may be for females only).
- They are used by the potentially important 'catch-up' population.
- They have the potential to present immunisation and ongoing cervical smear screening as combined prevention by staff already experienced in this area.

Disadvantages

- They are particularly used by women during or after a first pregnancy, i.e. too late for optimal primary prevention.

For an immunisation programme directed exclusively at females, it is logical to deliver it in places already provided specifically or predominantly for females, such as gynaecology and maternity clinics and some sexual health clinics. However, the target population for HPV vaccines are, by definition, not yet sexually active and therefore not likely to be accessing such services. For this reason, this is unlikely to be a major component of national strategies except, potentially, for catch-up programmes, if it is decided to include higher age groups and, possibly, to deliver information to mothers of girls in the target age band (see 'other settings' below). Finally, there may be exceptions where such clinics are well placed to initiate and deliver vaccine; where it is customary for girls to visit a gynaecologist routinely at the onset of menstruation, for example.

4. Other settings: Non-health non-school community settings for young people, parents' groups, hospital emergency departments

Advantages

- May reach 'hard to reach' individuals and groups who may be at high risk.

Disadvantages

- May be costly and complex and require several different approaches to implement effectively.

Maximising the impact of immunisation programmes may include strategies to reach groups who are most likely not to be reached by other strategies such as school-based programmes.[99] It is possible that such groups are also less likely to participate reliably in cervical screening programmes when they get older, giving this kind of approach an added potential public health benefit.

'Hard to reach' groups for vaccination include children living in socio-economically underprivileged communities[100] and immigrants from poorer countries. Such individuals are less likely to attend school reliably, to access and understand educational materials and to access community-based medical services. Other settings may exist which are readily accessible to these children and young people, like youth clubs and centres, young peoples' religious groups, churches and other places of worship and sports clubs. Direct consultation with young people is likely to be the best way to identify other settings and opportunities to immunise and educate young people who are otherwise unlikely to benefit. It is likely that immunisation will be more attractive to young people if there is some sense of ownership and control over the programme by the peer group to be vaccinated.

As with other vaccine programmes,[101] there may be possibilities to 'opportunistically' immunise people who would not otherwise get immunised in hospital emergency departments and other rapid access acute medical facilities. There are several practical problems associated with this approach which include: financing mechanisms for vaccine purchase, record-keeping and ensuring that an immunisation course is completed. Without universally accessible and reliable immunisation records, this approach depends to a greater extent than other approaches upon the need for parents and children to remember accurately whether and how often the child has been immunised with HPV vaccine before. Another problem related to this strategy is ensuring that staff remember to consider offering immunisation to the children present from an age group deemed appropriate to receive it. Strategies to promote this may include automatic flagging of all children within the target age group.

Other considerations

- Whether other programmes or campaigns for adolescent immunisation already exist, are planned or have recently occurred and how well they work (e.g. Bacille Calmette-Guérin, Diphtheria/Tetanus (DT), DT acellular Pertussis (DTaP), polio, hepatitis B, meningococcus, varicella).
- Practical considerations around simultaneous administration of HPV with other vaccines.
- Provision of HPV vaccine as part of broader programmes of health promotion for adolescents may be effective. These may be based at school or elsewhere in the community.

HPV immunisation requires administration of three intramuscular doses of vaccine over a six-month period, which is a dose regimen dissimilar to all other vaccines that are widely used in

adolescents at present (apart from primary courses of hepatitis B vaccine). It is possible that in certain areas many children are being immunised with other vaccines early in the second decade of life. Therefore there are obvious potential advantages to administering a dose of HPV vaccine to adolescent girls who are receiving other vaccines at the same time.

Data exist showing that simultaneous administration of HPV vaccine with hepatitis B vaccine does not reduce the size of antibody responses (Merck, unpublished data). Results of studies with other vaccines are not yet available. Recommendations from the United States indicate that HPV vaccines can be given simultaneously with other vaccines for teenagers such as hepatitis B, quadrivalent meningococcal vaccine and DTaP. This is feasible because HPV vaccines are non-live and do not contain components known to reduce immunogenicity of other vaccines.[102]

To further increase access to HPV immunisation programmes by people who are unlikely to be reached by conventional school or community practice-based strategies, it may be valuable to consider whether HPV immunisation and/or information about this can be combined, or co-localised with other health interventions targeted at adolescents in response to other important health and disease issues. Such activities might include education about preventing HIV and other STIs, Chlamydia screening, provision of contraception and information on avoidance of pregnancy, health promotion activities (information on obesity, exercise, giving up smoking, avoiding drug misuse, etc.)

Conclusions

Several alternative approaches exist for the effective delivery of vaccines to children aged nine to16 years. It is certain that no single strategy will be appropriate throughout Europe and it is likely that more than one strategy will be necessary within many individual countries. National health authorities will need to take account of the resources that they already have in place and assess to what extent they wish to use them. There are obvious potential advantages of cost and rapid implementation where trained, experienced and familiar personnel are already in place whose services can be used. Whatever approaches are used, effective provision of information about what the vaccine is for, the need for three doses for protection and the continuing importance of existing cervical screening programmes will be critical.

Research questions

Does the recommended age of immunisation for girls (in the range nine to 12 years) significantly affect the acceptability of HPV vaccines to parents and children?

Are school-based programmes organisationally feasible using non-central purchasing/charging funding mechanisms?

Which groups are most at risk of high-risk HPV infection and cervical cancer in different countries in the European countries (towards whom immunisation needs to be most effectively targeted)?

Can HPV immunisation be delivered effectively to hard-to-reach communities via non-health non-school community-based settings (such as places of worship)?

Can the effectiveness of immunisation programmes be enhanced by involving young people in their design and the design of information materials associated with them?

Can HPV immunisation programmes be integrated into broader health programmes for adolescents effectively?

Does co-administration of HPV vaccines with other vaccines administered to adolescents result in changed immunogenicity of the vaccines or changed side effect profiles?

6. MODELLING COSTS AND OUTCOMES OF HPV VACCINATION

Paolo Bonanni

Key points

- Human papillomavirus (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 the 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 about the best strategy to prevent cervical cancer.
- Economic evaluations to date seem to indicate that administering HPV vaccination to 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.

Rationale for economic evaluation of vaccination programmes

The decision whether to introduce HPV vaccination (and to which age cohorts) requires, in addition to the demonstration of vaccine efficacy, an evaluation of the economic aspects of its implementation.

In other words, the main question is whether providing HPV vaccination is a good use of healthcare resources. The common approach by decision makers when deciding on whether to invest in an intervention is to determine whether the cost incurred by the society to save a year of life adjusted by its quality (QALY) is similar to other commonly accepted interventions in the medical care sector.

In recent times, the accepted amount of money to consider an intervention worth being implemented has usually been set at below €40 000 per QALY.

Ideally, all European countries should analyse the economics of HPV vaccination before introducing an immunisation programme because costs and economic benefits may be different in the different countries. Within the EU, there are large differences in healthcare spending, and organisation of the national medical care system (such as universal, insurance-based, etc.). Therefore, the results of economic evaluations are not entirely exportable, although they can give a general idea about the convenience of a certain intervention, especially when data are similar in different national contexts. Every EU Member State should at least try to adapt models developed in other countries by changing and individualising all

those factors that can substantially impact on the results of the evaluation (i.e. costs of treatment of HPV-related disease, costs of screening, costs of vaccine, incidence of new infections and prevalence of high-risk HPV types in the population). In reality, decisions are often taken by making rough evaluations of costs and benefits, and political reasons sometimes drive rapid decisions before economic evaluations can be performed. However, economic analysis is important if reasonable decisions are to be taken.

For countries with organised screening programmes, if screening is widely provided by the public or private medical system and involves most women in the country, modelling costs and outcomes can give an idea as to whether investing in vaccination and therefore adding the benefits of vaccination to those of secondary prevention, is economically acceptable vis-a-vis the added costs it implies. If no or very little screening is provided, the impact of vaccination on cervical cancer prevention would be maximised also from an economic perspective. If implementing a screening programme is logistically impossible, economic evaluation of vaccination may not be a priority if the aim is to reduce cervical cancer cases as soon as possible.

Types of economic models

Two approaches have been applied to modelling the costs and the positive impact of HPV vaccination:

- A static model follows the progression of the preventable disease for a hypothetical cohort of subjects for a certain number of years over the cohort's expected lifetime (usually 30–50 years, according to the time extension of the model). For instance, for HPV it would mean following a group of females born in a certain year to see how many develop HPV infection over time, how many of those progress to chronic infection, and eventually to pre-malignant lesions and to HPV-related cancers during the timeframe of the model. A static model is made of several compartments (corresponding to the different statuses just described) with a certain defined probability (or range of probabilities) to pass from one compartment to the other.
- A dynamic model does not track just a single cohort but rather the changing population over time and, hence, individuals constantly enter the model as they are born and exit the model as they die. In a dynamic model, the impact of vaccination on the transmission of the infectious agent (herd immunity effect) is also taken into account. Examples exist where the herd effect on non-vaccinated people due to the reduction or halting of the viral or bacteria circulation is a significant benefit, in addition to the direct protection of vaccinated individuals. However, at present no definitive data exist on the ability of HPV vaccines to confer herd immunity and to impact on infection transmission although it is likely that this will occur, given past experiences with other vaccines.

Input data in economic models

Mathematical models are ideally based on the maximum possible known, reliable data and the fewest possible assumptions and uncertain parameters. Reliable data now exist on HPV vaccine efficacy in clinical trials (close to 100% for prevention of cervical intraepithelial neoplasia (CIN) 2/3 caused by HPV types included in the vaccine), although vaccine

effectiveness (efficacy under real-life or 'field' conditions as opposed to trials) is less well known and is likely to depend on variables such as the fraction of susceptible and already infected women in the population targeted by immunisation programmes. Models must also include data on disease rates in the population under study, the natural history of the disease, the direct and indirect effects of vaccination, the real coverage and effectiveness achieved. There is considerable uncertainty in many for these data inputs. Since this is a new vaccination, assumptions will have to be made concerning immunisation coverage that will be reached within a certain timeframe.

Data should also be available on prices of vaccines in the different countries when supplied by the private and the public market, and the relative percentage of use under the two systems, but also on costs for diagnosis and treatment of all lesions that can be prevented by vaccination (and obviously, data on their incidence).

The HPV vaccine cost is not the same in all EU countries, because many factors influence vaccine pricing like the type of medical care system, whether it is universal or insurance-based, dimension of the vaccine market and the possibility of buying the vaccine by tender rather than in small quantities.

Sensitivity analyses

Another crucial aspect of economic evaluation of health interventions is that of sensitivity analysis. A sensitivity analysis is the analysis of the impact of the possible variation of input parameters (for instance, variation of incidence of the disease and related complications, variation in the price of vaccine, variation in the coverage of vaccination in the target population, etc.) on the economic evaluation. Uncertain input parameters can be varied one by one, leaving the others fixed. Alternatively, it is possible to evaluate the most pessimistic scenario (i.e. all parameters are set at the less favourable extreme for vaccination) and most optimistic (i.e. all parameters are set at the most favourable extreme for vaccination). A good model of the cost-effectiveness of HPV vaccination must include this kind of evaluation, given the high degree of uncertainty in many of the parameters included in models of HPV.

For HPV vaccination, some parameters deserve special attention: the degree of coverage in the target group for vaccination is an estimate when no previous experience with that tool already exists. The same is true for the possible impact of vaccination on compliance with screening programmes. Hopefully, vaccination would bring more attention to cervical screening (secondary prevention), thus increasing offers and acceptance of screening. But it is possible that immunised women may wrongly believe that they are no longer at risk of cervical cancer. Therefore, varying screening compliance parameters has the potential to add useful information to the decision-making process.

Also the duration of immunity after vaccination is an uncertain parameter, and a good economic analysis should forecast both the possibility that HPV vaccination confers life-long protection from precancerous lesions, and the less favourable possibility that a booster dose (or more booster doses) is (are) needed after a certain number of years to confer continuing protection.

A further element for possible discussion is that of the choice of a single cohort or multi-cohort approach to immunisation, and the implications on disease prevention of vaccination of different age cohorts. This is in turn influenced by differences in immunogenicity and efficacy at different ages and on the rate of already infected subjects at a given age. The latter should be investigated by updating knowledge on sexual behaviour and attitudes among the adolescent population in each country.

Comments on some economic models undertaken so far

Several studies have been published on the economic impact of introducing an HPV vaccine[i]. Most of these studies used the same basic model design (a static Markov cohort model, where, as described above, a cohort of subjects is followed for a certain number of years, and simulation is performed of the shift from a compartment – for instance that of susceptibles – to the following compartment – that of infected subjects, according to a certain probability described by an equation), which followed a hypothetical single cohort of girls.

Others, however, used a mixed static-dynamic or a full dynamic approach (a dynamic model also considers the impact of individual immunity obtained thanks to the effect of vaccination on patterns of infection transmission, and therefore takes into account the herd immunity effect). We examine only some of them here to highlight values and drawbacks of different approaches.

The first published studies [88, 89] showed a cost-effectiveness profile favouring vaccination of 12-year-old females, but had a major drawback since the cost of a dose of the vaccine was calculated at values that are far less than the actual price in Europe. The second study, in particular, is interesting for its approach of evaluating costs and positive outcomes of vaccination in a context of variable starting age and intervals of screening policy; a scenario that might also be useful for European countries, where the possibility is being discussed that screening intervals and the kind of test used will be different in the cohorts of vaccinated subjects in the coming decades.

Further elements of interest are present in a third study[103] where the price calculated per vaccine dose is more realistic and, as previously, different alternatives are taken into account. The model analyses the following strategies:

1. vaccination only (initiated at age 12 years);
2. cytological screening only (initiated at 18, 21, 25, 30, or 35 years);
3. combined vaccination and screening strategies, conservatively assuming that vaccination does not alter current screening practice.

Underlying patterns of cervical cancer screening, duration of vaccine efficacy, and the natural history of HPV infection in older women affected are the most important parameters in the sensitivity analysis. The incremental cost-effectiveness ratio (cost per QALY gained thanks to

[i] The study by Elbasha et al. (EID, 2007) is company-funded, the authors work at Merck laboratories. The study by Kulasingam and Myers (JAMA, 2003) was supported by a grant from Merck Research Laboratories. No statement on funding is given in the articles by Saunders and Taira (EID, 2003); The study from Goldie et al was partially supported by a grant from GlaxoSmithKline. The study from Taira, Neukermans and Sanders was funded by university and a public foundation.

the increment of activity (vaccination) compared to the current practice – screening only) of an HPV 16/18 vaccine ranges from $20 600 per QALY with a vaccine that prevents 100% of persistent HPV 16/18 infections, to $33 700 per QALY with a vaccine that prevents 70% of persistent HPV 16/18 infections, reducing the lifetime risk of cervical cancer by 46–66%, compared with current screening.

A more recent study [87] combined the previous static cohort model [89] with a dynamic disease-transmission model (therefore accounting also for herd immunity effects), to estimate HPV prevalence and infection rates due to the introduction of a bivalent HPV 16/18 vaccine. The scope of the study was to evaluate the benefits and cost-effectiveness of adopting a vaccination strategy for both males and females, compared with adopting a female-only strategy in the overall population in the United States.

The authors assumed vaccination of 12-year-old girls with three doses, and a booster injection at 22 years, assuming that the protective effect of the vaccine lasts for 10 years following the most recent booster. A vaccine efficacy of 90% against both HPV 16/18 and 70% coverage of girls in the target group was assumed. In addition, 71% of women were assumed to undergo cervical screening every two years. The HPV vaccine costs amounted to $360 for the initial three doses and $100 for the booster. In this model, routine vaccination of girls by age 12 reduces the lifetime risk for cervical cancer among vaccinated females by 62% with a cost-effectiveness ratio of $14 583 per QALY gained, compared to the current situation. Routine vaccination of girls and boys was found not to be generally cost-effective: $442 039 per QALY.

The recently published evaluation by Elbasha, et al [83] developed a transmission dynamic model to determine the epidemiologic outcomes and the cost-effectiveness of introducing a quadrivalent HPV vaccine (types 6, 11, 16 and 18) in the setting of organised cervical cancer screening and HPV disease treatment practices in the United States. The model simulates HPV transmission and the occurrence of CIN, cervical cancer, and external genital warts in the population divided by age groups. Several scenarios of immunisation of females only, or females plus males at age 12 (with or without catch-up of subjects aged 12–24) were outlined. The strategy of vaccinating both boys and girls at age 12 was found to be less effective and more costly than vaccinating just girls at 12, without ($2 964 per QALY) or with a catch-up campaign in older females ($4 666 per QALY) mainly because HPV-related diseases are much less frequent and serious in males, and male immunisation would mainly have the benefit of reducing HPV transmission. According to this model, in a setting of organised cervical cancer screening, vaccination with the quadrivalent HPV vaccine is most cost-effective (across a reasonably wide range of assumptions) when administered to girls before age 12 years (with or without a catch-up programme), and has a cost-effectiveness ratio near or below (depending on the underlying assumptions of the model) that of several other recommended vaccines.

A recent economic study performed in the United Kingdom by the Health Protection Agency[104] evaluated the impact of duration of protection on cost-effectiveness of vaccination. The study's authors considered the cost of the vaccine, the cost to the health service of treating people with conditions caused by HPV and the effect that cervical cancer and genital warts had on quality of life. The research suggests that the HPV vaccination is likely to be an

effective use of healthcare resources if the vaccine protected girls against the virus for at least 20 years.

Two other recently published European evaluations[i] regarding Denmark and Italy showed a favourable cost-effectiveness profile of HPV vaccines. The Danish economic model concerned the introduction of a vaccine against HPV 16/18, and found a cost per gained year of life of about €11 400 when 12-year-old girls are immunised. The extension of vaccination to the 13 to 15 year age groups would imply only a slight increase of cost per gained year of life to about €11 900. [91] The Italian study evaluated the introduction of the bivalent HPV 16/18 vaccine, in the context of the existing screening programme. The incremental cost per QALY gained, adding vaccination to cytological screening, was about €26 300 in the base case scenario, that took into account cross-protection against HPV types other than 16 and 18. If cross-protection is excluded, the cost per QALY rises to about €29 400. The extension of the vaccination programme to up to four different age cohorts does not substantially modify the cost-utility profile (about €28 000 per additional QALY gained).[105]

Limitations of the main studies so far

Except for the UK study, none of the studies assessed the impact of the reduction in genital warts, although this condition seems to place a substantial burden on healthcare systems. Furthermore, none of the studies took into account the effect of vaccination on other HPV-associated non-cervical cancers, such as head, neck, vulva, penis, and anal cancers.

Three of the economic analyses used static Markov models. This type of modelling design is unable to take into account the dynamics of viral transmission within a host population, and is therefore unable to properly assess herd immunity (i.e. the protective effect conferred on a population by immune individuals within the population). If the contribution of herd immunity is ignored, then the effectiveness and cost-effectiveness of a vaccination programme is likely to be underestimated.

Apart from two studies (in which only costs associated with time needed to perform vaccination and screening were considered, but no indirect benefit connected with prevented diseases was evaluated), all other studies concentrated only on direct costs and direct savings as a result of preventive measures, with no consideration of impact on lost productivity.

All this means that the costs per QALY saved could be lower or higher than those calculated in the presented studies. Moreover, as other data accumulate (for instance on vaccine efficacy and effectiveness in males, impact of vaccination on infection transmission rates, etc.) models will need to be adjusted to incorporate the ever-changing amount of relevant data.

Conclusions

The economic analyses performed to date seem to indicate that adolescent female vaccination strategies when combined with cytological screening have a cost-effectiveness ratio similar or even lower (especially when dynamic models accounting for herd immunity are used) than that of other preventive or therapeutic interventions commonly applied. Catch-

[i] Currently available only in the respective national languages.

up of older female cohorts should be evaluated, taking into account the possible impact of vaccination on screening frequency, age at which the woman first undergoes screening and methods used. At present, male immunisation seems to be too costly as to suggest its implementation. No study looked at the cost-effectiveness of vaccinating men who have sex with men. However, although there are special risk groups who have higher HPV infection rates, it must not be forgotten that HPV is a very easily transmissible virus, and therefore differences between risk groups for HPV infection and the general population are much less than for other sexually transmitted infections.

It must be stressed that, due to the many differences between countries with regard to cost of screening, therapeutic measures and the wide variability of medical services, every country should evaluate the economic impact of HPV vaccination using tailored models reflecting local epidemiological and cost data. As outlined previously, national data are required regarding incidence and prevalence of HPV infections in the population (including information on prevalent HPV types), number of CIN 2/3 lesions diagnosed, costs for the treatment of precancerous lesions, number of cervical cancers occurring each year and cost for their treatment. Also data on offer and compliance with the recommended screening tests for cervical lesions should be collected, together with an evaluation of their costs. Regarding the vaccine, in addition to local price in the private and public market and relevant percentage of use in case of implementation of an immunisation programme, administrative costs should also be calculated.

Research questions

What are the type-specific probabilities of transition of HPV infections to precancerous and cancerous lesions?

What types of models can to be developed that use the prevention of CIN 2/3 as the efficacy endpoint of vaccination (incident and persistent infections might resolve spontaneously)?

How can and what are the types of common quality of life scores that can be used to compare studies performed in different settings?

What other types of HPV-related diseases need to be included in evaluations, in order to fully value the impact of vaccination?

How can worst case and best case scenarios be expanded to make them useful in order to establish the robustness of the underlying assumptions of the models?

7. MONITORING AND EVALUATING THE IMPACT OF HPV VACCINATION

Ahti Anttila

Key points

- Post-licensure evaluation of the human papillomavirus (HPV) vaccines will need to determine the 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 infections, precancerous lesions, or cancers through established or newly developed laboratories or cytology or cancer registries.
- Phase IV trials have also been proposed for evaluating the HPV vaccine's impact on public health. These can provide further information about the incidence of abnormal and precancerous cells as well as cancer incidence and mortality. They could also be useful for assessing potential integration between 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 set of 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.

The purpose of vaccination against human papillomaviruses is to prevent HPV infections as well as reduce the burden of the acute and chronic disease caused by these infections, particularly cervical precancers and cancers. [55,106] Efficacy and safety information from phase II and III trials of both the quadrivalent and bivalent vaccines has been published (chapter 2). Follow-up information on HPV infections and of surrogate end-points for cancer such as rates of cervical intraepithelial neoplasia (CIN) is currently available up to approximately four years of follow-up time. So far, there have been no evidence-based recommendations or guidelines available on the immunisation policies and related practices for the EU. Public health evaluation of the vaccine was not considered in detail as part of the licensure process. However, following licensure, the vaccines are increasingly being used within healthcare services.

Ideally, if any vaccine is administered as part of healthcare services, the consequences, favourable and unfavourable, need to be evaluated systematically.[107,108,106,109] This principle holds for any medical services. The post-licensure evaluation of the HPV vaccines will be needed to determine the 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.

Whatever vaccine monitoring system will be put in place, coordination with 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.

Vaccine uptake and compliance

To evaluate the impact of the HPV vaccine, the penetration of the vaccine within the target population has to be monitored in the first place. Indicators to assess whether the target population is being adequately vaccinated are process indicators. They include: coverage rate (the proportion of the target population that received all three doses) and drop-out rate (the proportion of target population that received less than three doses). These indicators would need to be added to national immunisation information systems, most of which do not have systems for monitoring three-dose vaccines in adolescents. In addition, information on the characteristics of those who get vaccinated, including socio-economic status, will help to assess potential disparities in the penetration of the HPV vaccination within the target population.

Long-term vaccine efficacy and effectiveness

Indicators

Although cervical cancer is the most important clinically relevant endpoint concerning the current HPV vaccines, information on surrogate endpoints or indicators (such as CIN lesions) is needed for evaluation. [108, 106] This is because invasive cervical cancer can take decades to develop and because women with precancerous lesions are treated systematically, not waiting for it to develop. Leaving this condition untreated would be unethical. Confirmed CIN 2/3 lesions can be considered as an acceptable surrogate endpoint for vaccination phase III trials.[110]

Incidence of type-specific and any oncogenic HPV infections can give early information about cross-protection or HPV-type replacement. In addition, cross-protection and type replacement need to be investigated by identifying types of CIN lesions. It is of utmost importance that international standard reagents for calibration and reproducible analytical assessment of HPV test assays, and other recommended analytical quality control procedures are used in these studies and monitoring activities.[111,112,106] In order to survey the effects of vaccines on the incidence of HPV or other infections, it is essential to use appropriate population-based sampling procedures among vaccinated people and among those to whom the vaccine was offered but who did not take part.

For the quadrivalent vaccine, where the vaccine has been designed to also reduce infections of HPV 6/11, information on cases of genital warts would also be valuable to provide timely information on the vaccine effects.

The following can be used as impact indicators:

- HPV-DNA prevalence, particularly, of persistent infections, among those vaccinated.
- Precancerous lesions of the cervix (CIN).

- Genital warts (for vaccine targeting HPV 6/11).
- Cervical cancer incidence and mortality.

Limitations of using surrogate indicators as endpoints for evaluation

For long-term evaluation, intermediate or surrogate indicators of impact have several limitations. Therefore, ideally, evaluation should integrate monitoring and surveillance of the intermediate or surrogate indicators together with the true long-term outcome indicators (e.g. cervical cancer cases) as much as possible, using modelling whenever appropriate. This holds also for cost-effectiveness evaluation and related decision analysis.

If information on the cytologically or histologically confirmed precancerous lesions is used as a surrogate indicator for incidence of fully invasive cancers or related death rates and even life years gained, one needs to remember that only a fraction of these lesions will develop into an invasive cancer. For example, among women aged 18 to 34 years, the regression rate of any CIN lesions has been estimated roughly at 85%, meaning that only a very small fraction will progress. Among older women, the estimated progression rates of CIN lesions range from 19% to 60% depending upon the age of the women and severity of the lesion. [71] It is not known specifically which of the lesions would progress into invasive disease, and which would not do so, if not treated.

In the absence of long-term follow-up studies, estimates on the long-term effects of the vaccines have often been based on cross-sectional information – such as age-specific prevalence of HPV positive women within a range of age groups; or proportions of HPV positive lesions from among any CIN or cervical cancer [15, 10, 113] for the most current information on HPV prevalence. These data need to include information on any oncogenic HPV, or infections specific for the vaccine-related HPV types only. Age-specific prevalences of HPV infections vary a lot between populations, however;[114] and caution is required in inferring natural history or disease outcome

Rationale for phase IV trials

The CIN treatment rates in a given population depend on the screening interval and the target age groups for the screening programmes (chapter 3). The current vaccine trials screened the vaccinated women at rather short intervals of about six months. This makes the information on CINs not directly comparable to the usual screening routine within the target populations, where women are usually not screened at such a young age and at such short intervals. For example, the cumulative incidence of CIN 2 lesions is very high in the vaccination phase II and III trials, compared with those coming from current routine healthcare practices. Furthermore, all significant lesions among HPV- or placebo-vaccinated groups have been treated based on the trial protocols; this has the potential to affect subsequent cervical cancer incidence rates too, in those follow-up studies. In order to provide population-based estimates of vaccine effectiveness and efficacy, along with non-randomised demonstration studies in restricted areas, phase IV trials including random allocation are proposed. [108] Vaccine administration and consequent follow-up needs to be done as much as possible based on the current recommendations on screening and other prevention policies against cervical cancers.

Registration and data collection infrastructures

To evaluate vaccine efficacy and effectiveness, high-quality cancer registries as well as screening registration should be established. It is essential that a cancerous lesion be confirmed by histology as far as possible, that cancers are classified by primary site, histology and disease stage, and that incidence data are linked with any corresponding death records at an individual level. Concerning cervical cancers, data on the fully invasive cancers should be separated from pre-invasive or micro-invasive disease, because it is the fully invasive disease that can cause death. More details on recommended items and procedures are available.[115]

Screening registers are recommended to collect data on screenings whether they took place as part of an organised screening programme, or outside it.[116] Screening registration should include information on screening invitations, visits, cytological and histological findings, and on treatments. Corresponding cytological or pathological files can be used for collecting information on genital warts. It is essential that screening and cancer registries have unique personal identifiers, and that there is national legislation enabling linkages of the registries with other relevant databases as well as using the biological samples.[117, 116] Personally identifiable data collection and linkages need to be set up in accordance with the European Directive on the personal data confidentiality and safety (EU Data Protection Directive 1995).[118]

Provided that vaccine registers are in place, evaluation of the vaccine can be straightforward. Registered information on the vaccinations should include, at a minimum, additional information on people to whom vaccination has been offered, as well as information on the vaccine safety (see the section below about vaccine safety). Information provided to the registry on people who have already been vaccinated should include the purpose of the vaccination, their age when they received it, type of vaccine and doses given. One needs to consider whether the vaccine registry could be linkable with the specific bio-banks becoming available in the country.

When evaluating cervical cancers, historical screening records are also needed. For example, to complete an evaluation of vaccination campaigns targeted at older women or a catch-up programme or possible booster vaccinations, one needs to consider potential selection between screening and vaccination behaviour carefully. This is essential for adjusting the vaccine's effects, because the subsequent cervical cancer incidence or death rate is expected to be very low for a long period of time. [71] On the other hand, if unscreened women were vaccinated (a 'hard to reach' population), one can expect a larger impact on that group than vaccinating screened women.

The infrastructures characterised in this section are available or becoming available in a number of countries, and they are helpful for vaccine evaluation and monitoring. Building up these infrastructures is not a simple issue, and further consultation on this specific matter is recommended.

As a first step, countries that have organised screening programmes could adapt these programmes to monitor vaccine impact on precancerous lesions. Countries that use HPV tests as part of their cervical cancer screening or abnormal cytology follow-up could consider

surveillance for persistent HPV infection in older women that is associated with precancerous lesions. Countries that have cancer registries should explore whether registries that typically conduct surveillance for invasive cancer could be expanded to include incidence of precancerous cervical lesions. Where such programmes do not exist, the setting up of sentinel surveillance programmes in a limited geographic area is acceptable.

Integration with other prevention interventions

The potential impact of the vaccine on other prevention interventions will need to be evaluated. For example, any potential decreases in the coverage and quality of organised cervical screening programmes could result in an increase, rather than a decrease of the cervical cancer burden (see chapter 3). The vaccine could also affect sexual behaviour and result in a decrease in safe sex.

Vaccine safety and adverse effects following immunisation

Several indicators can be used to measure vaccine safety in post-marketing studies. Post-marketing surveillance will be implemented by the vaccine manufacturers in some countries, including the long-term Nordic trials.

Other important sources include post-marketing surveillance for adverse events in Europe though the EMEA system. Before large-scale immunisation, it would be useful to collect background information on the health status of vaccine target groups, including acute, chronic and autoimmune diseases (*ibid.*), which will help to distinguish between vaccine-related events from events unrelated to vaccination that typically first present at the age of vaccination.

All countries where the vaccine is introduced should establish a system to report vaccine-related adverse effects as an essential part of programme monitoring, if feasible. Existing routine reporting, investigation of and response to potential vaccine-related adverse effects should be enhanced to include those following the administration of the HPV vaccines.[119] These systems should also be able to communicate any concerns to healthcare professionals and the public.

Potential research topics

Considering the differences between European countries in terms of vaccination and other relevant healthcare policies and disease burden, what types of assessments of long-term efficacy and effectiveness of the HPV vaccines need to be done?

Provided that systematic individual-level registration is in place for vaccination, screening and cancer, non-randomised demonstration projects (where a vaccination programme would be introduced within a limited area and where also the evaluation and monitoring can be done systematically in order to show that the vaccination programme fulfils its target) can be considered. Reference rates can be approximated from a comparison area, or from time before introducing the vaccine.

Randomised phase IV trials have been proposed for potential vaccination programmes, as they are apparently the most sophisticated and reliable comparison design. [108]

Using these research approaches, it is probably possible to investigate the vaccine impact on the burden of invasive disease and possibly mortality in the future. Because the HPV vaccines can affect many diseases, it is important to assess their impact also upon overall mortality, not only disease specific incidence or mortality.

Even though the current evidence does not justify modifications of organised screening policies (screening intervals and targeted age groups) among vaccinated women, it will be important to assess in the future whether organised screening policies can be changed. New screening methods, such as HPV DNA-based screening and in the future possibly HPV typing, are emerging, and it is essential to assess how the vaccines or their evaluations can be integrated with these. Randomised research policies can be recommended for these research issues as well.

Much of the research on the current HPV vaccines concentrates on the prevention of cervical cancers. HPV infections are related to a number of other cancers and health outcomes as well, and further information is required from the follow-up studies also on the impacts of the vaccines on these.

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