Report on the health technology assessments on human papillomavirus and rotavirus vaccinations in Europe.

VENICE 2

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Coordinated by
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Executive summary

In 2006 and 2007, two vaccines against rotavirus (RV) infections and two against human papillomavirus (HPV) infections were granted licensing authorisations by the European Medicines Agency (EMEA). Since then, Member States (MS) have been facing the decision about introducing or not these vaccinations into their national immunisation schedules. Two VENICE 2 surveys have been carried out in 2009/2010 to investigate the decision-making process undertaken regarding the potential introduction of the HPV or RV vaccinations into MS national immunisation programmes as well as to investigate the modalities of implementation of the vaccination programmes.

Within the decisional process of introducing new vaccines, a multidisciplinary appraisal regarding the impact of those vaccines, known as health technology assessment, has been adopted by some countries. The implementation of a health technology assessment process requires expertise from various disciplines in order to evaluate the different dimensions affected by the vaccine introduction into the population. At the current stage of introduction of HPV and RV vaccination, this evaluation process implementation has been heterogeneous amongst European countries. Indeed, some countries have carried out and fully achieved the assessment process and others still have the process on-going or have not the objective of completing such an analysis. Furthermore, although an extensive literature does exist on RV vaccination regarding its economical and epidemiological impacts, no HTA reports on RV vaccination was available during the collection phase of this project.

For HPV vaccination, it has been shown that under the assumption of a long-life protection, the programme would be cost-effective while under the assumption of a shorter length of protection, it would still remain cost-effective but less than in the first scenario. Furthermore, the access of women to screening programme should be strengthened and encouraged by adequate information in order to preserve the benefits of the vaccination programme. Girls should be targeted by the vaccination programme before the age of their sexual debut in order to maximize the impact of the vaccine. Beyond, adequate information should be provided to the population for optimizing the individual decision-making.

For RV vaccination, the introduction process into the National Immunization Schedule has been effective in far less countries than for HPV vaccination - 5 countries have introduced the RV vaccine instead of 18 countries for the HPV vaccine. The health technology assessment process will most probably grow and develop as the vaccine introduction process evolves.

Aim of the VENICE 2 Project

On the 23rd of December 2008, VENICE II, a new project funded by the European Centre for Disease Prevention and Control (ECDC) was launched.

VENICE II is coordinated by the National Centre for Epidemiology, Surveillance and Health Promotion of Istituto Superiore di Sanità (Italy). The following partners gathered in the Venice II Consortium are involved in the project: the Institut de Veille Sanitaire (France), the Health Protection Surveillance Centre (Ireland), the National Institute of Public Health (Poland) and the CINECA consortium of public universities for Information and Communication Technology (Italy). VENICE II has 29 participating countries/institutions listed below:

- Austria - Federal Ministry of Health, Family and Youth, Directorate General Public Health
- Belgium-University of Antwerp, Campus 3 Eiken Epidemiology and Social Medecine - Institute of Public Health - Epidemiologie
- Bulgaria- National Center of Infectious and Parasitic Diseases Department Epidemiology and Surveillance of Communicable Diseases
- Cyprus- Medical and Public Health Services Surveillance Unit
- Czech Republic-National Institute of Public Health, Centre Epidemiology and Microbiology
- Denmark- Statens Serum Institut, Department of epidemiology
- Estonia-Health Protection, Inspectorate Epidemiological Department
- Finland- National Public Health Institute
- France- Institut de Veille sanitaire, Département des maladie infectieuses
- Germany-Robert Koch Institute Immunization Unit
- Greece-Hellenic Centre for Diseases Control & Prevention, Department of epidemiological Surveillance & Intervention
- Hungary-National Center for Epidemiology, Department for Communicable Disease Epidemiology
- Iceland- Directorate of Health, Centre for Infectious Disease Control
- Ireland- National disease Surveillance Centre
- Italy- Istituto Superiore di Sanità - CNESPS
- Latvia-Public Health Agency, Department of epidemiological Surveillance of Infectious Diseases

- Lithuania-Centre for Communicable Diseases Prevention and Control, Immunization Department
- Luxemburg-Ministère de la Santé-Direction de la Santé - Division de l'Inspection Sanitaire
- Malta- Ministry for Social Policy
- Netherlands- National Institute of Public Health and the Environment, Department Public Health
- Norway- Norwegian Institute of Public Health, Department of Vaccination and Immunity
- Poland- National Institute of Public Health - National Institute of Hygiene, Department of Epidemiology
- Portugal-Communicable Diseases Division Directorate General of Health
- Romania-Institute of Public Health, Epidemiology Institute of Public Health
- Slovakia-Public Health Authority of the Slovak Republic, Section of Epidemiology
- Slovenia- Institute of Public Health of the Republic of Slovenia, Centre for Communicable Diseases
- Spain-Instituto de Salud Carlos III, Centro Nacional de Epidemiologia
- Sweden-Smittskyddsinstitutet-Department of epidemiology
- United Kingdom-Health Protection Agency Communicable Disease Surveillance Centre

Built on the first VENICE project, the general aim of VENICE II is:

- To collect information on the national vaccination programmes through a network of professionals;
- To share the collected information and to build up a knowledge base endeavouring to improve the overall performance of the immunisation systems;
- To follow up the impact of newly introduced vaccinations in selected member states.

VENICE II will also address the lack of information related to sub-national variations and different population groups. In some countries, in fact, there is significant disparity in the vaccination programmes at sub-national, regional, area or district level, not always well known at national level. Moreover, there is evidence that no vaccination programme will be able to control or eliminate vaccine preventable diseases without efforts dedicated specifically

to risk groups and hard to reach populations, including ethnic minorities, migrants and refugees.

1.2. Objectives of this report

An updated follow up survey of the previous VENICE I on HPV and RV vaccines introduction in the EU and EEA/EFTA countries have been carried out in 2009/2010. For each country; the following information has been collected:

- Current state of decision/recommendation of HPV and RV vaccinations programmes (at national and sub-national levels for HPV)
- On-going and available studies amongst which health technology assessment reports
- Data on vaccination coverage and information on the delivery infrastructures and the financing mechanisms for HPV specifically.

The Institut de Veille Sanitaire has been responsible for the coordination of this WP3.

1.3 Context and objectives of the health technology assessment on HPV and RV vaccinations

Vaccination remains one of the most powerful public health interventions in terms of preventing infectious diseases and within the last years, new vaccines have been licensed and used for preventing acute diseases but also chronic conditions such as cancers. Given the dynamics of vaccines innovation and the high public funds generally devoted for subsidizing vaccination expenditures, health technology assessment (HTA) has been designed for providing public health authorities wide insights into vaccination impact so as to make the most appropriate decisions.

Health Technology Assessment can be defined as a multidisciplinary tool that aims to explore the clinical, economic, ethical, juridical, organizational, and social implications of the implementation of a new technology. Therefore, HTA can be considered as a bridge between scientific research and decision-making.

As health technology assessment has recently been applied to vaccination and requires bringing together expertise of various disciplines, health institutions and researchers teams have increasingly been involved and concerned by that health technology assessment process.

Amongst the new technologies assessed, HPV and RV vaccines have been or will be targeted and the impact of their introduction within countries highlighted in reports and scientific articles. Although the HTA process has extended to a growing number of countries in Europe, only some of them have carried out a complete HTA and most of them have focused on HPV vaccination. Regarding the current disparities between countries on that topic, sharing information and methodologies could highly contribute to the ambition of developing common procedures to optimize the decision in vaccination by presenting the main findings and results of HTA.

HPV and cervical cancer: a brief overview

Genital HPV infections are transmitted by sexual intercourse. HPVs are highly transmissible and most sexually active individuals will acquire an HPV infection. Despite the fact that most HPV infections are benign, certain viral genotypes can cause persistent genital infections which can develop into a cancer. Diseases caused by HPVs include predominantly cancers of the cervix but also cancers of the vagina, vulva, penis and anus, some head and neck cancers and anogenital warts and recurrent respiratory papillomatosis. In 2005, WHO has estimated that 500.000 cases of cervical cancer have occurred worldwide with an estimated 260.000 deaths. Genital warts are frequent among sexually active people and usually occur in young adults and adolescents. Countries with well organized screening and management programme for early detection and treatment of precancerous abnormalities and early stage of cervical cancer can prevent up to 80% of these cancers. More than 100 HPV genotypes are known but HPV 16 and 18 are responsible for about 70% of all cases of cervical cancer with genotype 16 having the greatest oncogenic potential. The low-risk HPV 6 and 11 are responsible for about 90% of anogenital warts and recurrent respiratory papillomatosis. Persistent HPV infection may lead to cervical intraepithelial neoplesia (CIN) of moderate (2) or severe (3) grade or to adenocarcinoma in situ, that can develop to cervical cancer. On average, the period time between initial HPV infection and cervical cancer is at least 20 years.

HPV vaccine summary

A quadrivalent vaccine protecting against the HPV types 6, 11, 16 and 18 (GARDASIL®) was licensed in September 2006. This vaccine is designed for the prevention of high-grade cervical dysplasia (CIN 2/3), cervical carcinoma, high-grade vulvar dysplastic lesions (VIN 2/3), and external genital warts (condyloma acuminata). The primary vaccination series consists of 3 separate 0.5 ml doses administered intramuscularly according to the following

schedule: 0, 2, 6 months. The vaccine has demonstrated efficacy in adult females aged 16 to 26 years old and immunogenicity in 9- to 15-years old children and adolescents. A second bivalent vaccine protecting against the HPV types 16 and 18 (CERVARIX®) received EMEA approval in September 2007.

Rotavirus infection: a brief overview

Rotaviruses are the most common cause of severe diarrhoeal disease in young children throughout the world. According to WHO estimates, 527.000 children aged less than 5 years die each year from vaccine-preventable rotavirus infections.

Rotavirus vaccination summary

Two vaccines against rotavirus infections were licensed in 2006. Both vaccines, Rotarix® and Rotatec®, are indicated for the active immunisation of infants for prevention of gastro-enteritis due to rotavirus infection. Vaccination with Rotarix® consists of 2 doses and vaccination with Rotateq® consists of 3 doses. For both vaccines, the first dose may be administered from the age of six weeks and there should be intervals of at least 4 weeks between doses. The full course must be completed by 24 (Rotarix®) or 26 weeks (Rotateq®) of age due to the theoretical risk of occurrence of intussusception in children aged over 6 months.

Licensing of these vaccines means that Member States (MS) have been facing the decision about their introduction into their national immunisation schedules. These circumstances provide a unique opportunity for countries to assess the future impact of the introduction of a new vaccine on different aspects: epidemiological, economical, organizational, social, legal and ethical. The objective of this report is to have a better knowledge of the HTA process undertaken in Europe and to share the main findings obtained through the application by countries of this multidisciplinary approach to new vaccines.

2.0. Method

Two separate surveys were developed in 2009/2010, one for exploring the introduction of HPV vaccination and the modalities of its implementation and the other one for investigating the decision making process for the introduction of RV vaccination.

The electronic survey questionnaires were each piloted in four MS (IT, IE, FR, and PL) and posted on VENICE 2 website in February 2010 for HPV vaccination and in July 2010 for RV

vaccination. The questionnaires were filled in online by the gatekeepers/contact points in each MS participating in the VENICE 2 project and saved on the website.

The questionnaires focused on several aspects of the decision-making process and implementation. One of the questions specifically addressed the health technology assessment status with four answers possibilities regarding the implementation and status of achievement of a health technology assessment: "Completed", "On-going", "Planned" and "Not planned". Once the questionnaire fully completed, the countries that have answered either "Completed", "On-going" or "Planned" have been contacted and asked to deliver, when appropriate, the HTA reports achieved. Subsequently, a review of the different reports has been carried out and the main findings regarding countries where HTA has been fully achieved summarized in this report. No complete HTA work on RV vaccination has been identified although epidemiological and economical aspects have been explored in several countries.

A methodological proposition based on a typical HTA multidisciplinary approach has been formulated by some researchers (La Torre G. and al.) and a framework for HTA applied to the vaccination field has been developed. Most of the following points have been dealt with in the different national HTA reports.

1. Evaluation of the epidemiology of infection and related diseases by a systematic review of scientific literature;
2. Assessment of the disease burden in terms of morbidity (hospitalizations, drugs consumption, etc...) and mortality through the consultation of National Discharge Cards or Database and direct interviews of clinicians;
3. Study of current preventive measures to avoid infection and practices to treat the disease/infection;
4. Evaluation of effectiveness and safety of the new vaccine through a systematic review of scientific evidences;
5. Investigation of biotechnological aspects and of the views of the manufacturers;
6. Elaboration of a mathematical model predicting epidemiological and economical impact of vaccination;
7. Economic evaluation of immunization by a cost-effectiveness analysis with the computation of cost per QALY (Quality Adjusted Life Year) gained;
8. Evaluation of ethic, legal and social issues related to the infection and to the introduction of new vaccine;

9. Study of organizational aspects and vaccination impact on the health system, both at micro-, meso- and macro-level.

3.0. Results for the HPV vaccination

Status regarding HPV vaccination introduction in the national immunization schedule

In 21 countries of the 29 MS, a recommendation to introduce HPV vaccination in their national immunisation schedule has been made by the national advisory body. The national health authorities in 18 countries have taken the decision to introduce the vaccination as of July 2010 (Table 1).

Table 1: Status of countries regarding the introduction of HPV vaccination

Status regarding HPV vaccination introduction	**Countries**		
	n	*%*	
Recommendation made by expert advisory body (N=29)	21	72	AT BE BG CZ DK DE ES FR GR IS IE IT LU LV NL NO PT RO SI SE GB
Decision taken by national health authorities (N=29)	18	62	AT BE DE DK ES FR GR IE IT LV LU NL NO PT RO SI SE GB

*Results extracted from the Finalised report on the decision making process, modalities of implementation and current country status for the introduction of human papilloma virus and rotavirus vaccination into national immunisation programmes in Europe.

Status regarding achievement of a health technology assessment

Six countries (20.7%) reported having undertaken a health technology assessment to support the decision making process for HPV vaccination introduction, 1 country (3.4%) has an on-going HTA and 2 countries (6.9%) have planned to undertake this type of study (Table 2).

Table 2: Status of countries regarding HPV health technology assessment (N=29).

Status of HPV health technology assessment	**Countries**		
	n	*%*	
Completed	6	20.7	BE DE DK IR IT SE
Ongoing	1	3.4	FI
Planned	2	6.9	AT RO

Not planned	20	69.0	BG CY CZ ES EE FR GR HU IS LI LU LV MA NL NO PL PT SI SK GB

*Results extracted from the Finalised report on the decision making process, modalities of implementation and current country status for the introduction of human papilloma virus and rotavirus vaccination into national immunisation programmes in Europe.

Although six countries have declared to have completed a HTA on HPV vaccination, HTA reports for only 5 countries could be collected: Belgium, Denmark, Germany, Ireland and Italy.

Mains findings of the Health Technology Assessment

1. **Belgium : Health Technology Assessment on HPV vaccination for the prevention of cervical cancer in Belgium (KCE reports vol.64B)**

This HTA report on HPV vaccination for the prevention of cervical cancer in Belgium elaborated by the Expert Federal Centre on Health Care has been published in 2007.

Epidemiological context

In Belgium, the cervical cancer is the tenth most frequent cancer amongst the female cancers. Its annual incidence has been estimated to be 600 cases accounting for 2.8% of all cancer cases. An opportunistic screening programme for the prevention of invasive cervical cancer has been run by the country and the participation rate has been estimated to be 80% of the targeted population.

Economical impact

Several scenarios have been developed to estimate the economical impact of the introduction of the HPV vaccination. Most of the information and data used to assess the HPV vaccination economical impact have focused on Gardasil because Cervarix data have been considered as insufficient in a modelisation perspective.

Given the high uncertainty related to some crucial hypothesis, a static Markov model developed with a Multi State Life table and applied to the Belgian data has been elaborated in order to assess the influence of uncertain values on the estimations of the Incremental Cost Effectiveness Ratio (ICER).

The main sources of uncertainty have been identified as linked to the following variables:

1. Impact on the participation rate to screening programme after HPV vaccination
2. Discounting rates for costs
3. Uncertainty on vaccination duration protection

The model is used in a theoretical context of a public vaccination programme rather than an opportunistic programme and different scenarios with various hypotheses have been developed:

1. A reduction of the vaccination protection duration throughout time requiring a booster dose after 10 years with discounting rates for costs of 3% and for effects of 1.5% has led to the following results:
    - ➔ ICER = 33.000 Euros / QALY gained (CI 95%: [17.000-68.000] Euros)
    - ➔ 20% of the number of cervical cancers avoided

2. A life-long immunity protection and therefore no need for a booster dose and discounting rates for costs of 3% and for effects of 1.5% have led to the following results :
    - ➔ ICER=14.000 Euros
    - ➔ 50% of the number of cervical cancers avoided

3. A life-long immunity protection and therefore no need for a booster dose and discounting rates for costs of 3% and for effects of 3% have led to the following results:
    - ➔ ICER = 56.000 Euros
    - ➔ 50% of the number of cervical cancers avoided

Once stabilized, HPV vaccination would account for a net annual investment of 24 millions Euros in the health budget. However, the implementation of a systematic and optimal screening programme rather that an opportunistic screening programme as organized currently would involve substantial economical savings and the possibility of financing a vaccination programme.

Organizational and health system impact

A universal immunization programme rather than an opportunistic immunization programme should be favoured in order to improve the vaccination coverage and to reach specifically deprived populations.

A reduction in the participation of women to the screening programme could result in a dramatic reduction in the potential benefits of HPV vaccination. Indeed, given the 60% HPV

genotypes vaccine coverage (16, 18), 40% of cervical cancers are caused by genotypes different than the genotypes 16 and 18 included in the vaccine. Furthermore, HPV vaccination is not so effective in women that have been previously exposed and infected with HPV. Therefore, a universal HPV vaccination programme could impact the participation rate of women to the screening programme by missing opportunities of detection of pre-cancerous lesions amongst vaccinated women who do not comply with the recommendations of being screened.

The benefits of a vaccination programme would be maintained only if the screening programme participation rate was maintained at a high level. Indeed, the estimations made by the Markov model have shown that for a population of young women, the risks of developing a cervical cancer given a life-long immunity for the vaccine are very different according to the screening participation and vaccination status (Table 3).

Table 3.Risk of developing a cervical cancer

	Vaccination	**No vaccination**
Screening	1/556	1/217
No screening	1/70	1/28

It has been demonstrated that a 10% reduction in the screening programme participation rate would dramatically affect the benefits of HPV vaccination. The implementation of a screening register and a vaccination register could contribute to a high level of screening and vaccination participation rates.

2. Denmark : Reduction in the risk of cervical cancer by vaccination against human papilloma virus; A Health Technology Assessment (Health Technology Assessment 2007; 9(1))

This report, published in 2007, has been elaborated by the Danish Centre for Health Technology Assessment (DACE-HTA).

Epidemiological context

In Denmark, more than 400 women are annually diagnosed with cervical cancer and approximately 175 women die of the disease. The cervical cancer screening programme introduced in Denmark at the beginning of the 1960's and provided more systematically since 1989 has contributed to a dramatic reduction in the number of cases of cervical cancer. Indeed, 14.800 women are annually found to have a preliminary stage of cervical cancer which accounts for a significant disease burden. Despite this screening programme performance that reaches an estimated 70% of the women aged 23 to 60 years old, Denmark still has one of the highest incidences of cervical cancer in the European Union.

Human Papillomavirus vaccination programme should be combined with an organized screening programme. Indeed, some characteristics inherent to the HPV vaccine would lead a vaccination programme to lose its benefits when used without a screening programme because of the missed opportunities of early detection of pre-cancerous lesions that cannot be prevented by the vaccination.

Firstly, it has been demonstrated that the vaccines genotype coverage - HPV 16 and 18 - is associated with 70% of cervical cancers leaving 30% of cervical cancers not targeted by any of the 2 vaccines. Furthermore, most of the vaccines have been tested in studies with a maximum follow-up of 5 years, which is a short-time period compared to an estimated 20 years for a cervical cancer to develop from the time of infection. Hence, there is still uncertainty regarding the life-time protection of the vaccine and consequently the risk of emergence of the disease even after a vaccination. Another aspect concerns the HPV vaccine protection conferred to women that have already been infected with HPV given the preventive characteristic of the vaccine which is recommended before HPV exposure. Those arguments demonstrate that the HPV vaccination would be effective only if cervical cancer screening programme participation rate is maintained at a high level.

Personal aspect

A literature review has shown that the attitude and acceptance towards the HPV vaccine is context dependent, encouraging the Danish researchers to conceive and carry out specific qualitative studies applied to the Danish population for exploring the personal dimension regarding the introduction of the HPV vaccination. Parents of children aged 9 to 22 years old structured in several focus groups have been interviewed. The main findings of the discussions demonstrate that the parents were positive towards a cervical cancer vaccine despite the fact they are concerned about its safety and would like to be better informed on the potential longer term adverse effects of the HPV vaccine. Furthermore, they underline the financial aspect and mention the importance of an equal access to the vaccine. It has been argued that 12 years old children would be the ideal target age for the administration of the vaccine given and that boys could be targeted as well by the vaccination programme.

Ethical aspect

Since there is no experience of using the vaccine on a large-scaled population, there is still uncertainty regarding potential adverse reactions and non specific effects. The population should then be properly informed on the limited experience with HPV. Furthermore, as cervical cancer is a serious threatening disease, equal economic access to HPV vaccination should be considered.

Organizational aspect

As the vaccine should be given before the sexual life debut, the age for administration of the vaccine should be between 9 and 12 years old and a catch-up campaign could be implemented in order to rapidly acquire a herd immunity effect.

The integration of the HPV vaccination into the childhood immunization programme would correspond to a complete payment of its costs by public finances and therefore favour and equal access to the vaccine. A high rate of participation to the screening programme should be encouraged in women when reaching the relevant age and a vaccination register should be established in order to evaluate in the longer term the effect of the HPV vaccine on cervical cancer and other cervical cellular changes.

Economical aspect

A literature review and a specific mathematical simulation model of the HPV infection known as a individual-based simulation model have been made in order to estimate the economical impact of a vaccination programme based on different scenarios.

1. The target vaccination group of 12 years old girls and a vaccination coverage assumed to be 70% without a catch-up programme have led to the following results :

   ➔ **CER: 11.400 Euros /LYG (life years gained)**

2. The target vaccination group of 12 years old girls and a vaccination coverage assumed to be 70% with a catch-up programme targeting the girls from 13 to 15 years old have led to the following results :

   ➔ **CER: 11.900 Euros /LYG**

3. The target vaccination group of 12 years old girls and boys and a vaccination coverage assumed to be 70% without a catch-up programme have led to the following results :

   ➔ **CER is doubled compared to scenario 1**

4. The target vaccination group of 12 years old girls and boys and a vaccination coverage assumed to be 70% with a catch-up programme targeting girls and boys from 13 to 15 years old have led to the following results :

   ➔ **CER is doubled compared to scenario 2**

Vaccinating 12 years old girls should be privileged as it is the most cost-effective scenario and implementation of a catch-up campaign of girls aged between 13 and 15 years old should be considered as well. The cost-effectiveness for this catch-up scenario (2) is just above the one for the scenario 1, with the additional benefit of a herd immunity probably reached in a shorter time.

3. Germany

In Germany, a systematic literature search has been done by two independent experts and the findings extracted from 9 medical, 24 economical and 19 ethical, social and legal sources that have been considered for the analysis.

Epidemiological context / impact

In Germany, since the implementation of the screening programme in the 1970's, cervical cancer incidence has dramatically been reduced. Currently, the annual number of cases of cervical cancer has been estimated to be around 6.200 women and the mortality rate 2.8 cases

per 100.000 women. Fatal cases in women account for 1.7% of the total deaths caused by cancer.

Although the duration of protection of the HPV vaccine has not been determined because of the short randomized control trials (RCT) follow-up period, it has been estimated that both available HPV vaccines are effective in preventing HPV 16 and 18 infections.

The HPV vaccine can be considered as secure although very rare events, if any, could most probably not have been detected given the limited number of cases enrolled in the RCT.

Beyond, the HPV vaccination programme has been demonstrated to be successful and to bring optimal benefits only if it is combined with a high participation rate in the cervical cancer screening programme.

Economical impact

The economical studies suggest that under the assumption of a lifelong protection of the HPV vaccine, there is a high probability that the cost-effectiveness ratio of the HPV vaccination falls under a threshold of 50.000 Euros per QALY. As there is no current evidence of such an assumption, it is not possible to conclude on the cost-effectiveness in the German context.

Ethical / social / legal impact

The extrapolation to the German context of results from studies carried out in other countries is not feasible. However they show that parental acceptance appears as an important factor for HPV vaccination. However, it has been shown that the acceptance of the vaccination is very high throughout the population except in some groups of the population, frequently the most conservative, who seem to be more reticent because of the sexually transmitted specificity of the HPV infection.

4. Ireland: The role of human papillomavirus vaccines in reducing the risk of cervical cancer in Ireland. A health technology assessment. 25th February 2008.

This report has been prepared by the Health Information and Quality Authority and the National Centre for Pharmacoeconomics (NCPE).

Epidemiological context / impact

In Ireland, cervical cancer is the 8th most frequently diagnosed cancer in women. In 2004, 200 women were diagnosed with cervical cancer with more than 90 women dying from the disease. A national cervical cancer programme is due to be rolled out in Ireland in 2008 and it

is anticipated that women in the programme will be screened every 3 years between the ages of 25 and 44 years and then every five years up to 60 years of age.

Economical impact

Although most of the economic models available have been elaborated by manufacturers, the NCPE has used an independent economic model elaborated by the Danish National HTA Agency and applied this model to the Irish setting. The estimates and data incorporated into the model were extracted from published RCT, Irish databases and consultations with experts groups. A number of assumptions have been made for the implementation of the economic model:

- Targeted population : girls in 1st year of secondary school (12 years old)
- Vaccination coverage (3 doses) : 80%
- Screening programme coverage : 80%
- Vaccine efficacy : 95% (16,18) in women that were HPV infection free at the time of the vaccination
- Life-long protection
- Cost for one dose of HPV vaccine : 100 Euros
- Cost for administration of one dose of vaccine (school-based programme) : 30 Euros

In this scenario, the incremental cost-effectiveness ratio (ICER) per Life Year Gained (LYG) has been estimated to be 17.383 Euros.

The cost-effectiveness of different catch-up scenarios in the 1st year of the vaccination have been evaluated for several age groups 13-15, 13-17, 13-19, 13-26 and the most cost-effective is the one that targets the 13 to 15 years old girls group, although vaccinating 12 years old girls is the most cost-effective amongst all the scenarios. Indeed, the vaccine becomes less effective for individuals that have been exposed to HPV which means that the vaccine efficacy decreases as age increases.

The implementation of a catch-up programme designed for girls aged 13 to 15 years old combined to a 12 years old girls vaccination would incur an additional cost of 29.2 million Euros in the 1st year of the vaccination programme which corresponds to an estimated ICER in the 1st year of vaccination of 52.968 Euros per life year gained.

The extension of the catch-up programme from the 13 to 15 years old group to the 16 and 17 years old girls is not cost-effective and corresponds to an ICER of 1.071.532 Euros /LYG.

After the 1st year, the annual cost for vaccinating 12 years old girls has been estimated to be 9.7 million Euros.

Impact of varying the assumptions was evaluated and the conclusion was that the vaccination of 12 years old girls remained cost-effective. However, with duration of protection shortened with a booster dose 10 years after the primary series, the vaccination programme would be less cost-effective, the ICER increasing from 17.383 Euros to 24.320 Euros per life year gained.

Those results should be interpretated cautiously as they have been made under certain assumptions that have to be confirmed by future evidence.

Organizational impact

Vaccination programme should be combined with an organized screening programme in order to control and prevent cervical cancer in the Irish setting and specific information designed to encourage both vaccinated and unvaccinated women to participate in the cervical cancer screening programme.

5. Italy

Since in Italy there is not a national HTA agency, the information below are from two HTA reports produced by the Institute of Hygiene of Catholic University of the Sacred Heart in Rome (La Torre G, Chiaradia G, Mannocci A, de Waure C, Ricciardi W, Capri S, et al. Health Technology Assessment della vaccinazione anti-HPV [Health Technology Assessment of HPV vaccination]. Ital J Public Health 2007;4(2S):1-60; La Torre G, Chiaradia G, de Waure C, Nicolotti N, Monteduro A. Report HTA del vaccino quadrivalente anti-HPV Gardasil [Health Technology Assessment of tetravalent HPV vaccine]. Ital J Public Health 2009;6(Suppl.2):S1-S66), funded partially or totally by GlaxoSmithKline and Sanofi Pasteur MSD.

Epidemiological aspects

The prevalence of HPV infection is within the range 8.8%-24.1%, with a pooled HPV prevalence of 19% (95%CI: 10-30%), in women with normal cytology, and of 60% (95%CI: 40-80%), in women with abnormal Pap test.

The mean incidence of cervical cancer is 9.8 cases per 100,000 women per year, that means almost 3,500 new cases per year, and the adjusted mortality rate is 2.2 deaths per 100,000 women per year.

According to national data, 70.9% of women from 25 to 64 years submitted to pap test at least one time in own life and 82.5% of them repeated the screening more than once.

Vaccine efficacy

The systematic review and the meta-analysis of the literature were used as key tools to evaluate the epidemiological aspects with a focus on the national and international context and to assess HPV vaccine efficacy. Considering all the studies, a 10-fold decreased risk of HPV 16 persistent infection was observed in vaccinated subjects (RR:0.10, CI95%:0.07-0.15).

The efficacy of bivalent and tetravalent vaccines in preventing persistent cervical infections was 87% (RR:0.13; 95%CI:0.09-0.20) for infections due to HPV16 and 78% (RR:0.22; 95%CI:0.13-0.38) for those sustained by HPV 18.

A meta-analysis of scientific papers on tetravalent vaccine show an efficacy of 99% in preventing CIN2-3 and adenocarcinoma in situ, of 94% in preventing vulvar and vaginal in situ neoplasia and of 98% of condiloma.

Clinical and economic impact

Clinical Impact

Vaccination of primary target population (12 years old girls) plus screening would greatly reduce the burden of disease, if compared to the only screening option. Introducing the HPV vaccination could lead, if cross-protection is considered, to a 67% reduction of the incidence and the mortality of the cervical cancer. The absolute risk reduction of developing a cervical cancer was maximally reduced when the HPV vaccine was given in combination with screening.

Cost-effectiveness analysis

The incremental cost-effectiveness ratio (ICER) of vaccination plus screening compared to screening alone would be € 22,055/QALY for the bivalent vaccine and € 19,053/QALY for the quadrivalent HPV vaccine, that indicates a very good cost-effective profile. The most important factors influencing ICER in the sensitivity analysis were discount rate and age at vaccination.

Social and ethical aspects

A specific survey demonstrated that educational campaigns are still needed to fill the knowledge gap on HPV and other sexually transmitted diseases, as well as to correctly promote HPV vaccine. Moreover, while 88% of women over 18 years declared to be willing to be vaccinated although the vaccine is not free of charge for this age-group, only 55.8% of them supported to provide the vaccination before the first sexual intercourse.

Concerning ethical aspects, as shown in the international literature the parental acceptance of the HPV vaccination seems to be a critical point, as well as the uncertainties about the burden of side effects due to the vaccination. These aspects need to be taken carefully into account in the vaccination administration process.

Conclusion

- The HTA process in the vaccines field is a recent acquisition, and is strictly linked to the increasing availability of vaccines. There is increasing evidence that applying HTA to the evaluation process of introducing new vaccines could represent a useful strategy both to meet population health needs and best allocate economic resources.

- Both bivalent and quadrivalent vaccines against HPV show positive assessments, considering all the aspects of HPV infection/diseases.

- HPV vaccination is cost-effective under the assumption of a life-long protection. However, evidence for this assumption is still expected and although it has been shown that the vaccination still remains cost-effective, it is less with a shorter period of protection (10 years of protection).

- Screening programme for cervical cancer and HPV vaccination programme should be complementary because of the importance of detecting cervical cancer abnormalities in women that have not been vaccinated, in women vaccinated but affected by other genotypes than the ones in the vaccine and in women vaccinated but previously exposed to the HPV. The missed opportunities for cervical cancer or cervical cancer precursors would impact the overall performance of the HPV vaccination, leading to a dramatic loss of benefits for the programme.

- Organizational aspects need to be taken into account, including an adequate training of health care workers of the vaccination facilities, as well as the synergic intervention between primary and secondary prevention for HPV related diseases. Moreover, health promotion programme in the field of sexually transmitted infections needs to be implemented at the school level.

- HPV vaccination should target girls before the debut of their sexual life, depending on the country.

- HPV vaccination of boys has not been demonstrated as bringing significant epidemiological benefits and has not been shown as being cost-effective.

- Communication to population on the HPV vaccine should be made by the health authorities to inform the population on the various aspects of the HPV vaccination, included what is unknown on the vaccine, for instance its length of protection and the potential risk for rare or delayed adverse events that could not have been detected yet, given the limited follow-up period of randomized control trials and number of cases enrolled.

- Catch-up campaigns targeting certain age groups (for instance 13-15 years old) could be combined to routine vaccination programme.

- These data are based on the present knowledge and in a long term vision, it is necessary monitoring the prevalence of the oncogenic HPV types to verify eventual replacement with other HPV types. Furthermore studies linking screening programmes with vaccine immunization registries should be performed to evaluate the HPV vaccine effectiveness.

4.0. RV vaccination results

Status of countries concerning the introduction of RV vaccination

The decision of introducing or not the RV vaccination in the national immunisation schedule has been taken by the National health Authorities in 8 countries and amongst them, 5 countries have decided to integrate the vaccine (Table 1).

Table 1. Decision regarding the introduction of RV vaccination in countries where the national health authorities have taken a decision (N=8).

Decision taken by national health authorities	Country
Integration into national immunization schedule	AT BE FI LU LV
No integration into national immunization schedule	ES FR
Other (Recommendation without integration)	BG

*Results extracted from the Finalised report on the decision making process, modalities of implementation and current country status for the introduction of human papilloma virus and rotavirus vaccination into national immunisation programmes in Europe.

Health technology assessment

Only four countries have declared to have completed or have an on-going health technology assessment project.

Table 2. Status of countries concerning RV vaccination Health technology Assessment undertaken (N=29).

Status concerning RV HTA	Countries		
	n	*%*	
Completed	3	10.3	FI IE LU
Ongoing	1	3.5	NO
Planned	0	0	-
Not planned	25	86.2	AT BE BG CY CZ DE DK ES EE FR GR HU IS IT LI LV MA NL PL PT RO SE SK SI GB

*Results extracted from the Finalised report on the decision making process, modalities of implementation and current country status for the introduction of human papilloma virus and rotavirus vaccination into national immunisation programmes in Europe.

Only 5 countries have included RV vaccination into their national immunization programme, whereas 18 have done so for HPV vaccination. As already mentioned, several countries have published results regarding the epidemiological and economical potential impact of RV vaccine introduction, but no completed HTA report could be collected for this report.