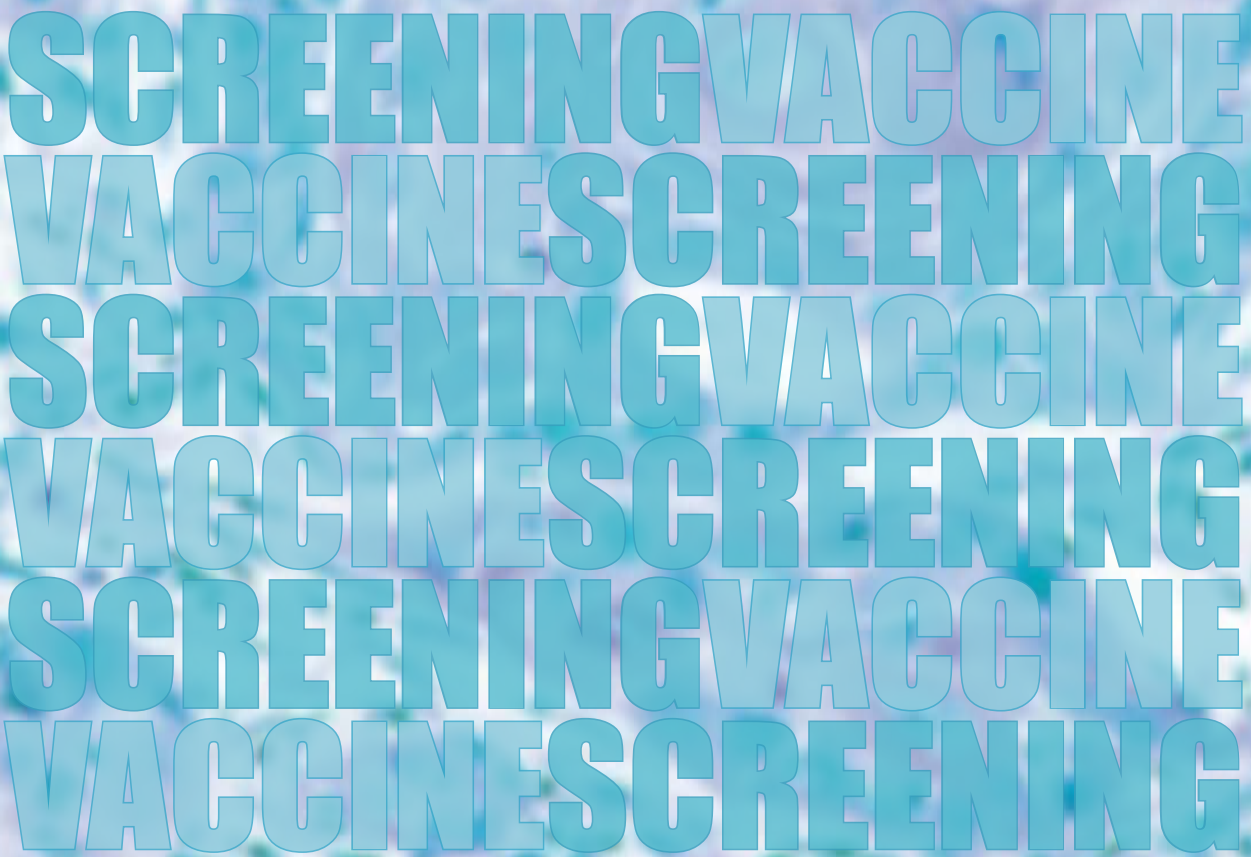
# CAN WE PREVENT CERVICAL CANCER?

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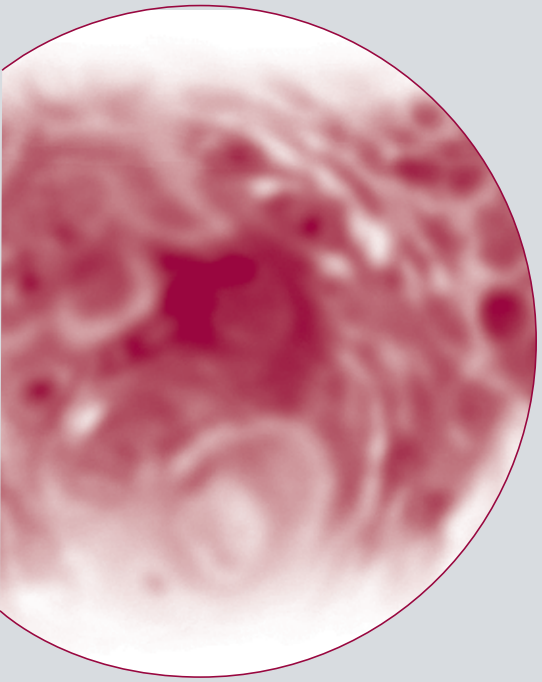
## THE *ENTRE NOUS* EDITORIAL ADVISORY BOARD

# EDITORIAL

**Gudjón Magnússon**

**2007 has begun as every new year with new expectations and hopes. In 2007 the European Magazine on Sexual and Reproductive Health *ENTRE NOUS* will celebrate its 25th anniversary and evaluate successes and failures as well as make new plans for the future. This publication has always tried to focus on topical issues of sexual and reproductive health and inform its readers on the latest policies, achievements, best practices or barriers to reach the goals set by the international community. It is therefore no surprise that the current issue of *ENTRE NOUS* is covering the topic of cervical cancer and its prevention.**



Cancer of the cervix is the second most common cancer among women worldwide with about 500 000 new cases and 250 000 deaths every year. Despite the progress made by scientists in identifying the causes of cervical cancer and policy makers introducing a comprehensive approach to preventing and controlling cervical cancer, every year 30 000 women die from this preventable disease in the WHO European Region alone. Many more women will experience suffering and long and exhausting treatment that would be unnecessary, if the precancerous lesions would be diagnosed in time.

In recent years several Member States of the WHO European Region have asked for assistance and advice in improving screening and management of cervical cancer in their countries. All 53 Member States have approved the WHO European strategy for the prevention of non-communicable diseases during the Regional Committee meeting last year.

For health care providers, working in this area, 2006, will remain the year when human papillomavirus (HPV) vaccines have been approved. This edition of *ENTRE NOUS* aims to inform policy makers and programme managers about the scale of the cervical cancer problem in Europe and present the future research of the HPV vaccine and the possible place of the HPV vaccine in the present national screening programmes. Finally, it will present some country examples on current prevention and management of cervical cancer.

The "Questions and answers" section is based on the queries received from the WHO Country Offices, where our colleagues have been approached by the staff of the Ministries of Health, by health care providers or mass media people. Not all questions can be answered as some answers only will be available in the next five to ten years; however, it is important to be informed of the existing evidence to assist countries in strengthening informed decision-making on prevention of cervical cancer.

Besides the technical issues and up-to-date information, cervical cancer is an area of public health that requires well-coordinated collaboration and partnership. We cannot expect any progress if the efforts and interests of every woman and every community member will not be joined with those of governments, professional and civil society organizations. It provides an opportunity as well as a challenge for representatives of different areas of health care, such as national immunization and sexual and reproductive health and cancer control programmes, to work together.

I would like to use this possibility to thank Jacqueline Bryld, the Editor of the latest four issues of *ENTRE NOUS*, for her professionalism, collaboration and contribution in this project and wish her success in her future career.

**Gudjón Magnússon**
Director of Division of Health Programmes
WHO Regional Office for Europe

# WHO'S ACTION PLAN AGAINST CERVICAL CANCER

**Cervical cancer causes up to 257 000 deaths and was in 2005 responsible for up to 500 000 new cases.**

Despite its human cost, advances in science and medical practice have the potential to eliminate cervical cancer as a killer of women. A range of prevention and intervention measures exist, from vaccines to screening that can prevent women from being infected with the virus that causes the cancer or detect lesions before the cancer takes hold. Palliative care and pain management are also essential elements of cervical cancer control.

But at least 90% of cervical cancer deaths occur in low and middle-income countries where access to screening, treatment and palliative care is often non-existent or insufficient.

Cervical cancer is caused by oncogenic types of human papilloma virus (HPV) mainly type 16 and 18, and the infection is generally transmitted sexually. HPV can evolve during a period of 10 to 20 years through precancerous lesions to invasive cancer and death. According to WHO projections, cervical cancer deaths will rise to 320 000 in 2015 and 435 000 in 2030.

To curb such growth, WHO has developed a comprehensive action plan against cervical cancer that encompasses primary prevention, early detection and screening, treatment and palliative care. These measures fall under the umbrella of national cancer control programmes (1). Its fight against cervical cancer is backed by several World Health Assembly resolutions, including WHA 57.12 and WHA 58.22. To achieve its goals, WHO works in partnership with key stakeholders including the United Nations Population Fund (UNFPA) and the International Atomic Energy Agency (IAEA).

## A new WHO guide

A powerful tool to combat cervical cancer is World Health Organization's Comprehensive Cervical Cancer Control guide to essential practice that was launched in 2006 by both the Departments of Chronic Diseases and Health Promotion, and the Department of Reproductive Health and Research (see "Resources" page 30).

The guide, crafted following consultations with a wide range of international stakeholders, offers current evidence-based recommendations to prevent, treat and palliate cervical cancer for healthcare providers.

## Approaches to prevent HPV infection

One of the guide's key recommendations is making health education an integral part of any national cervical cancer control strategy. Raising awareness on condom use is vital, as young people are particularly vulnerable to HPV infections.

Although condoms offer only partial protection against HPV transmission, correct and consistent use allows faster virus clearance in men and women, increases regression of cervical lesions and therefore lowers cancer risk. Furthermore, it lowers the risk of genital warts. Condoms also protect against other sexually transmitted infections, including chlamydia and HSV-2, which are possible co-factors for cervical cancer. Whether female condoms (which cover part of the vulva) offer the same or additional HPV protection as male condoms is as yet unknown.

But the role men can play in reducing cervical cancer does not stop at condom use. While cervical cancer is a chronic health burden suffered by women, men - as HPV carriers - must be made aware of their role in the disease's sexual transmission. WHO recommends clinical and community health settings deliver messages to men about cervical cancer prevention and HPV's sexual transmission, plus urging them to encourage their partners to undergo screening and necessary treatment.

## A new vaccine against HPV infection

Treatment may become a thing of the past, however, if a new HPV vaccine takes hold. Versions of this powerful primary prevention option have been either licensed or are in advanced clinical testing. The vaccine has proven to be able to prevent 65-76% of HPV infections, depending on the local prevalence of oncogenic HPV types (2). HPV vaccine

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trials have shown 100% efficacy against moderate and severe pre-cancerous cervical lesions caused by the HPV types 16 and 18, included in the vaccine.

But WHO has recognized several implementation and applied research challenges in using the vaccine (3,4). New delivery strategies must be developed and evaluated because current WHO routine vaccine programmes generally target young infants, while the HPV vaccine is aimed at pre-adolescent girls.

Vaccine delivery costs, therefore, are likely to be much higher, adding to the already high costs of the drug itself, although vaccine producers are expected to practice tier-pricing. The vaccine also possesses culturally sensitive issues, like sexual behaviour, sexually transmitted infection and genital cancer. Such factors could also present a challenge for implementation.

Decisions on introducing the vaccine will rest on the burden of cervical cancer in any given country and the priorities set by policymakers.

Another consideration is the sustainable funding of future HPV vaccine programmes in the context of financing of screening programmes. It might take 10 to 30 years from the vaccine's introduction before reduced cancer incidence and mortality can be measured, which underscores the need for continued screening.

## Screening for cervical cancer

Screening plays a fundamental role in WHO's cervical cancer control strategy. It promotes organized screening programmes to detect precancerous lesions and invasive cancer and determine appropriate management.

Among various screening technologies is cytology screening, the most widely used and effective tool to detect precancerous lesions of the cervix and, in turn, potentially reduce cervical cancer burden. But this requires appropriate health service infrastructure, technical resources and a well-defined referral system to treatment services. Such fundamentals often do not exist or are limited in developing countries.

Women should undergo regular screening from the age of 25 years, WHO recommends. But when new screening programmes are established, screening should start with women aged 30 years or more. Younger females should be included only once the older and highest-risk group has been covered.

In terms of frequency of screening, WHO recommends a three-year interval for women aged 25-45 years and a five-year gap for women aged above 50. If a woman can be screened only once in her life, the best age is between 35 and 45 years. Screening is not required for women over 65 years provided the last two previous smears were negative.

Alternative screening techniques suitable for low-resource countries, like visual inspection with acetic acid (VIA) followed by cryotherapy, are being investigated in various parts of the world, including Africa, by WHO's Department of Reproductive Health and Research (RHR) and the WHO International Agency for Research on Cancer (IARC). WHO, however, does not recommend using such procedures outside research programmes.

In conjunction with cytology and other screening procedures, HPV DNA testing is being conducted as another possible detection method. But WHO recommends that such tests, for now, be conducted within pilot projects or closely monitored settings. People aged 30 years or under should not be subjected to HPV DNA-based screening.

## Diagnosis and treatment

If screening leads to diagnosis of precancerous lesions or cervical cancer, the next step is to formulate the most effective treatment for the individual concerned.

To properly manage a cervical cancer patient, it is vital to understand the extent or "stage" of her disease at the time of diagnosis. A number of staging systems are used for cancer based on tumour size and the extent of spread of disease in the pelvis and distant organs. The classification of the international Federation of Gynecology and Obstetrics (FIGO) is recommended by WHO for staging of invasive cervical cancer.

After assessing the cancer's stage, a healthcare provider can determine how the cancer can be treated and what the likely outcome will be.

In the case of precancerous lesions, WHO recommends that outpatient services be used to treat people. Both cryotherapy and the loop electrosurgical excision procedure (LEEP) are suitable outpatient services depending on eligibility criteria and available resources.

Only specialists with focused training in gynecological cancer surgery at central-level facilities should perform the required invasive surgery. Surgery can be undertaken with a curative intent, removing the primary tumour with all its extensions, with the aim to cure the patient. Palliative surgery is usually used to relieve distressing symptoms.

Radiotherapy plays a central role in treating most invasive cervical cancers, and is used primarily for cases with bulkier tumours and those with extensive involvement of the lymph nodes seen on laparotomy. It is also used to manage cancers in patients unable to tolerate general anesthesia. Along with its curative role, radiation can also alleviate symptoms, especially bone pain and vaginal bleeding. The availability of a basic radiotherapy unit (teletherapy and brachytherapy) allows for the effective treatment and palliation in all cases of invasive cancer.

Chemotherapy is not a primary cervical cancer treatment mode, but it may be used concurrently with surgery or radiation to treat bulky tumours. Cisplatin is the most commonly used drug in chemotherapy and is included in WHO's Model List of Essential Medicines (5).

## Palliative care

Despite the best systems and efforts to prevent and screen for HPV and cervical cancer, many women are diagnosed with or will develop advanced disease and will, in turn, require palliative care and pain control.

Palliative care can help people with advanced disease to have dignity and peace

during difficult and final phases of life. A broad combination of medical and non-medical means can ensure that pain is effectively controlled in 90% of advanced cervical cancer cases.

WHO recommends all national health programmes set the goal of providing a system of palliative care to avoid unnecessary suffering and improve the quality of life of women with advanced cervical cancer. Symptom control and end-of-life care are key steps in this process.

As families to are also emotionally affected by the suffering of the patient, healthcare providers must also provide emotional assistance, spiritual support and bereavement care to next-of-kin. Patients and their caregivers need training, ongoing support and supplies for palliative care, including for symptom management at home.

WHO urges pain control measures be introduced to give relief to sufferers from the physical torment they may be enduring, but pain control remains vastly underutilized in many countries. WHO recommends national health services ensure opioid, non-opioid and adjuvant analgesics, particularly orally administered morphine, be made available to patients suffering from advanced cervical cancer. Restrictive drug regulations must be modified to allow for pain control.

## Treatment considerations

Despite comprehensive treatment and screening practices being in operation, concerns linked with social and cultural norms can prevent people using such facilities exist. WHO recognizes this and advocates health facilities ensuring counseling, screening and treatment occur in private and confidential settings to guarantee the privacy and dignity of the patient.

Inherent with cervical cancer are sensitivities surrounding sexually transmitted infections and sexuality. This can impact on the delivery of prevention messages or stop people seeking screening and treatment.

If a patient feels there is lack of privacy in a clinic or that the provider is disapproving or may reveal information to others, she may choose to withhold important details on her condition or attend a distant clinic, in doing so wasting precious time. Even worse, she may not seek care at all.

Ensuring privacy and confidentiality is key, particularly in health facilities that may be in bustling and crowded areas. Access to patient data must be restricted to relevant staff, while measures must be taken to ensure a person's treatment regime does not become something of workplace or public gossip.

## What next?

Cervical cancer is clearly preventable and curable, but such outcomes require strong commitment from healthcare providers, governments and stakeholders to ensure universal access to the means of prevention. Only by implementing comprehensive national cervical cancer control programmes focusing on prevention, early detection, treatment and palliative care, can this be done. Such programmes must also use and establish a monitoring system based on cancer registries. Recognizing this increasing interest, the 120th Executive Board of the World Health Organization (WHO 2007) has placed on its agenda an item on promoting comprehensive cervical cancer control (6). WHO supports raising attention surrounding cervical cancer, an entirely preventable disease.

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# HUMAN PAPILLOMAVIRUS, CERVICAL CANCER AND HPV VACCINES: PUBLIC HEALTH ISSUES

**Cancer of the cervix is the second most common cancer among women worldwide.**

The data on incidence of the cervix uteri cancer in Europe are available on the Health for All Data Base (http://data.euro.who.int/hfadb/), most of them collected by the National Cancer Registries (Figure 1). However, the system of registration and/or estimates differs among the Member States of WHO European Region and needs additional information if more detailed analyses is to take place.

Virtually all cervical cancer cases (99%) are linked to genital infection with human papillomavirus (HPV), which is the most common viral infection of the reproductive tract. There are 40 different genotypes of HPV that can infect the genital area of men and women, including the skin of the penis, the vulva (the area outside the vagina), and anus, and the lining of the vagina, cervix, and rectum. Two "high-risk" genotypes (HPV 16 and 18) are responsible for the majority of cancers of the cervix, vulva, vagina, anus and penis worldwide. Two "low-risk" genotypes (HPV 6 and 11) cause a substantial proportion of low-grade cervical dysplasia (i.e. cell abnormalities) detected in screening programmes and more than 90% of genital warts. The peak incidence of HPV infection occurs between the ages of 16 and 20 years. HPV infection usually resolves spontaneously, but it may persist, and precancerous cervical lesions may follow. If untreated, these may progress to cervical cancer over a period of 20–30 years. During the period of persistent HPV infection, precancerous changes can be detected in the cervix; early detection of these changes is an effective strategy for prevention of cervical cancer (Figure 2).

HPV is highly transmissible, with peak incidence soon after the onset of sexual activity, and most individuals acquire the infection at some time in their lives. Factors contributing to development of cervical cancer after HPV infection include immune suppression, multiparity, early age at first delivery, cigarette smoking, long-term hormonal contraception use, and sexually transmitted diseases such as chlamydia trachomatis and herpesvirus simplex 2.

A comprehensive approach to prevention and control of cervical cancer encompasses interventions along the continuum of care, from primary prevention to early detection, treatment and palliative care. In high-income countries, deaths from cervical cancer have been greatly reduced through wide coverage of cytology-based screening programmes, which allow early detection and treatment of precancerous lesions. Even if cervical cancer is only detected at early invasive stages, it can be treated through surgery or radiotherapy, which has a high cure rate.

One of the objectives of the WHO European Regional Strategy on Sexual and Reproductive Health (http//www.euro.who.int/document/e74558.pdf) is to reduce the incidence of cervical cancer. The expected result is implementation of "the screening programmes for early detection and early treatment of cervical pre-cancer, and for management of invasive cancer". This strategic document urges countries to:

- provide population-based screening for early detection of cervical cancer,
- improve the quality of screening and early treatment,
- provide cross-sectional training to general practitioners, obstetricians and gynaecologists, dermatologists, and others,,
- advocate use of screening and protection from sexually transmitted infections,
- emphasize male responsibility in all prevention activities, and
- systematically use monitoring for improvement for screening programmes and case management.

**Figure 1. Cervical cancer incidence in WHO European Region (HFA DB)**

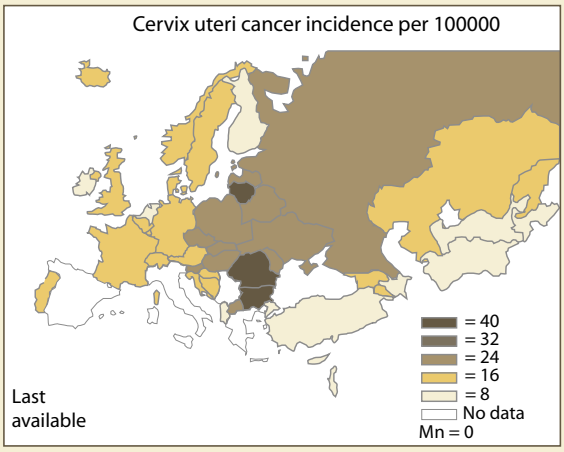
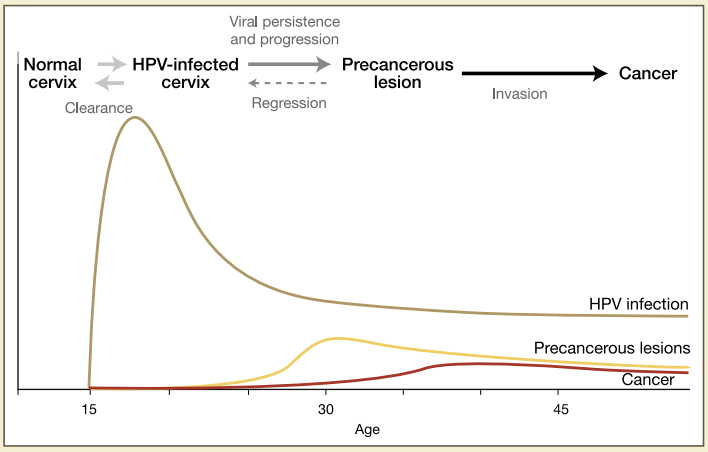
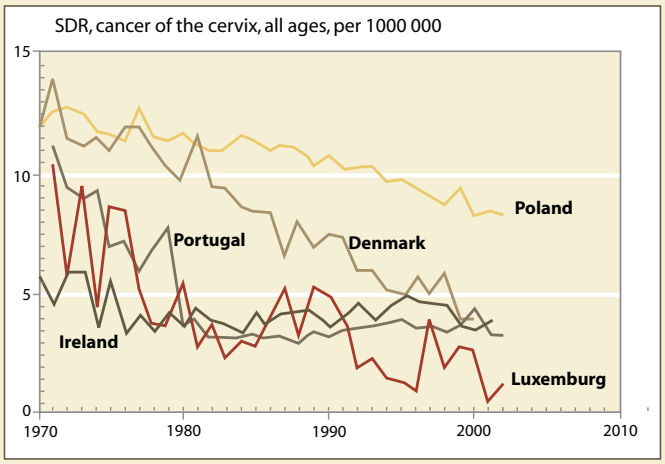


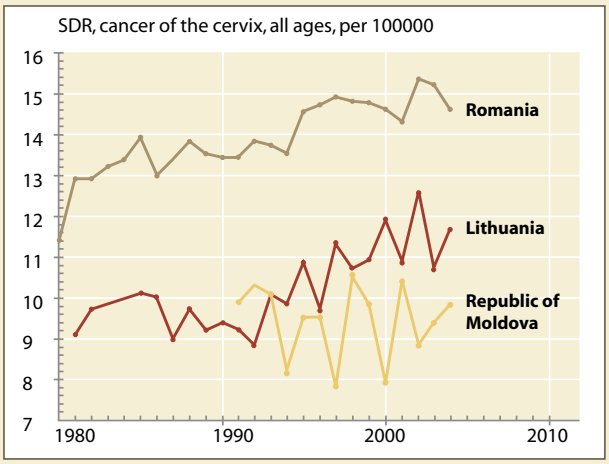

**Figure 2. Prevalence of HPV infection, preccancerous lesions and cervical cancer by age of women**






*Source: Health For All database, 2006*

**Figure 3. Changes of the age-standardized death rate (ICD-10 code: C53) all ages, per 100000 since 1970 in Denmark, Ireland, Luxemburg, Poland and Portugal (HFA DB, 2006)**




*Source: Health For All database, 2006*

**Figure 4. Changes of the age-standardized death rate (ICD-10 code: C53) all ages, per 100 000 since 1980 in Lithuania, Republic of Moldova and Romania (HFA DB, 2006)**

In the most developed countries, the primary economic burden of HPV disease is related to the early detection and management of precancerous lesions. Not all developed countries, however, have successfully controlled their cervical cancer burden through screening and early treatment programmes and that results in diversity of age-standardized death rate among the EU countries (Figure 3). The potential for primary prevention through vaccination offers a new complementary tool to improve cervical cancer control. Keeping in mind that many countries have improved the registration of the cervical cancer morbidity and mortality, number of deaths cases from this disease are increasing in some countries and is a clear signal that more should be done to change the situation (Figure 4).

The potential for primary prevention through vaccination offers a new complementary tool to improve cervical cancer control. HPV vaccines are prepared from virus-like particles (VLPs), produced by recombinant technology. A quadrivalent vaccine (GardasilTM) has recently been licensed and a bivalent vaccine (Cervarix TM) is in advanced clinical testing. These HPV vaccines are designed to prevent infection and disease due to HPV 16 and 18; the quadrivalent vaccine also protects against low-risk genotypes 6 and 11. The vaccines are not designed to treat persons who have already been infected with these genotypes. They are given in a series of three 0.5 ml intramuscular injections over a six-month period. HPV vaccines induce high levels of serum antibodies in virtually all vaccinated individuals. Injection site adverse events (pain, erythema and oedema) occur more often in vaccine than placebo recipients, but no increase in serious adverse events has been found in any of the trials.

In women who have no evidence of past or current infection with the HPV genotypes in the vaccine, both vaccines show >90% protection against persistent HPV infection with those genotypes. In large, multicentre phase III trials of the quadrivalent vaccine that covered four continents, almost half the women enrolled were from European countries. The quadrivalent vaccine showed 100% protection (95% confidence interval: 92.9%, 100) against moderate or severe precancerous lesions associated with HPV 16 or 18. Results from a phase II trial of the bivalent vaccine that enrolled 1,113 women, showed an efficacy of 100% (95% confidence interval: -7.7, 100) against moderate precancerous cervical lesions. Data from larger trials of the bivalent vaccine are expected soon. Data on vaccine effects among women who had already been infected with HPV 16 and 18 are only available for the quadrivalent vaccine, and no protective effect of vaccine against moderate or severe precancerous lesions was seen. Because only a very small minority of women had already been infected with all four HPV vaccine-types at baseline, benefit could accrue to all vaccinated women because efficacy was demonstrated to those HPV genotypes to which women were susceptible.

The very high clinical efficacy in women, without evidence of infection with vaccine HPV types and lower efficacy among those already infected shows that vaccinating at an age before females are exposed to HPV would have the greatest impact. Although the duration of protection is not yet known, there is evidence of protection for at least five years after vaccination, and large studies are ongoing in Nordic countries to evaluate the longer-term duration.

HPV vaccine cost is a major determinant of the predicted cost-effectiveness of HPV vaccination. Delivery costs are also likely to be important, since in many settings new systems will be needed to reach young adolescents. If a two-dose schedule could be used, or vaccination could be given at an earlier age when other vaccines are given (e.g. school-entry, or even infancy), costs of vaccine and its delivery could be reduced. Evaluation of these options is therefore very important and such



studies are being planned.

HPV vaccines can improve comprehensive cervical cancer control programmes as well as stimulate new partnerships for advocacy, information and communication, as well as service delivery, stewardship and financing. HPV vaccines that protect against types 16 and 18 have the potential to reduce, but not eliminate, the risk of cervical cancer (since women will still be at risk from other high risk genotypes), and other interventions including cervical screening will still be required. Taken together, early vaccination of adolescents with screening and adequate evidence-based treatment could be components of a comprehensive strategy with the long-term goal of eliminating cervical cancer.

There are critical issues of equity associated with introducing these new vaccines. International organizations, national governments and private foundations must address, at the highest level, how to minimize delays in accessing the vaccines in poor countries and to ensure access is equitable. Public spending on health is so low in those countries that have the greatest disease burden that external finance mechanisms to subsidize the purchase of vaccines will be necessary. According to the World Bank data (http://devdata.worldbank.org/wdi2006/contents/index2.htm) the Gross National income (GNI) in 7 countries of WHO European Region is below US$ 1000 per capita (Azerbaijan, Georgia, Kyrgyzstan, the Republic of Moldova, Tajikistan, Ukraine and Uzbekistan). This criterion is used by the Global Alliance for Vaccines and Immunisation (http://www.gavialliance.org/) to provide assistance in subsidizing purchase of vaccines. According to the WHO estimates (HFA DB) public health expenditure on health as percentage of total government expenditure in these countries is very low (2.9% in Azerbaijan, 4.6% in Tajikistan and 4.7% in Georgia) in comparison the average in the European Region – 12.29 % (2004).

We understand enough about the science and the social issues to generate realistic prevention strategies. However, the challenge of delivering a vaccine that prevents both a sexually transmitted infection and cancer to an adolescent population will make it necessary to inform and educate not only adolescents but also their parents and the health-care providers. There is lack of reliable information on provider and client knowledge of cervical cancer. The reproductive health survey carried out in 2005 provides information on the most important reasons for not having a cervical cancer screening test among sexually experienced women were lack of recommendation of the test by a health provider (44%), lack of awareness (35%), and belief that cervical cancer screening is unnecessary (17%) (1). This must be seen as an opportunity, given the need to educate adolescents at an early age about risk-taking and general health. Current adolescent vaccination programmes usually provide only single-dose boosters, for example, of tetanus toxoid and diphtheria-containing vaccines, and the three-dose HPV vaccination series represents a challenge; but it is also an opportunity to strengthen adolescent vaccination services. The HIV/AIDS community recognizes that introducing an HPV vaccine may provide a platform for the introduction of an AIDS vaccine in the future, given the probable need to vaccinate the same target population of adolescents.

The HPV vaccine addresses a critical public health need, and is one element of a comprehensive cervical cancer control strategy. Ensuring universal access to cervical cancer prevention, screening and treatment services will be the key to reducing the burden of cervical cancer worldwide. There are critical issues of equity associated with the introduction of these new vaccines, which should not go unaddressed. If due attention is not given to reaching poorer women, the new vaccine risks increasing health inequities, rather than contributing to the achievement of reproductive health for all. The challenge for policy-makers and opinion-leaders is to acknowledge lessons learned from prior initiatives to introduce vaccines, and to ensure that this gender-specific disease has the necessary priority on the public health agenda. High-level advocacy and a partnership among immunization, cancer-control and the reproductive health sectors must emerge to ensure that the right initiatives are implemented rapidly to prevent this disease that characterizes health inequity today.

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For more information on HPV and HPV vaccines, see:
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# CERVICAL CANCER PREVENTION IN EUROPE

## Burden of cervical cancer

Cervical cancer (CC) still remains a considerable public health problem in Europe, in spite of the strong evidence that well-organised screening with cytology can reduce the incidence and mortality up to 80% (1). Cancer of the uterine cervix primarily affects rather young women with the majority of cases appearing between the ages of 35 and 50, an age when many women are actively involved in their careers or caring for their families. According to the most recent estimates for the first years of the 21st century, approximately 65,000 women in the European WHO Region get cervical cancer and almost 32,000 die from the disease each year (2, 3). An obvious west-east gradient in the burden of cervical cancer can be observed (see Table 1). The lowest mortality (world-age standardised rate $\leq 2$) has been observed in Finland, Switzerland, Iceland and Italy, whereas mortality is high (range: 7.5-9.0, shaded in red in Figure 1) in the former Yugoslav Republic of Macedonia, the Republic of Moldova, Latvia, Kazakhstan, Kyrgyzstan, Bosnia and Herzegovina, Bulgaria) and very high (shaded in brown) in Albania (9.8), Lithuania (10.0), Serbia and Montenegro (10.1) and Romania (13.0).

Over the last decades, substantial reductions in incidence and mortality were noted in the Nordic countries, and the extent of these reductions correlated with the level of implementation of organised screening. By improving screening coverage and quality in the UK, near the end of the 1980s, the rising trend in young cohorts could be reversed. More recently, in Norway, organised screening including nation-wide registration of all Pap smears was introduced only in 1995. The population coverage rose in spite of a reduced number of Pap smears and was subsequently accompanied by a 20% reduction of CC incidence. In Italy, it was shown that, by organised screening, cervical cancer incidence could be reduced further in areas with pre-existing opportunistic screening. Opportunistic screening also resulted in a drop of cervical cancer incidence and mortality in several other West-European countries. Nevertheless, in Ireland, Spain and Portugal, a tendency of increasing mortality is observed, which can be explained by the absence of a high-quality screening programme or the insufficient effectiveness of opportunistic screening in the past. The current dramatic contrast between West- and Eastern Europe could even rise in the near future since trends are even increasing in some high-risk countries such as Romania, Bulgaria and Lithuania, unless effective prevention programmes could be set up in all countries.

### Screening systems in Europe

In 2003, the European Council adopted a recommendation to implement population based screening for cervix and breast cancer in women and colo-rectal cancer in men and women in all member states of the European Union (4). Cytological screening should start between the age of 20 and 30 years and be continued at three to five year intervals up to the age of 60-64 years. Non-screened older women should benefit from screening beyond that age. Moreover, the European Council recommends that high quality should be assured at all steps of the screening process (invitation, screening, diagnostic confirmation and treatment of lesions, and follow-up after treatement) and therefore proposes that screening be offered in organised settings whereas opportunistic screening should be discouraged. Monitoring systems, including linkage between appropriate databases should be set up in order to verify performance and impact. Before all, high population coverage should be achieved. Women should be informed approriately of the advantages but all also of the limits of screening and treatment of screen-detected lesions. Soon, the European Commission will publish the second edition of the European Guidelines for Qualtiy Assurance in Cervical Cancer Screening, which are in line with the recent WHO guidelines recommendations (5, 6).

Organised CC screening programmes only exist in nine European countries (Denmark, Finland, Iceland, Norway, Slovenia, Sweden, The Netherlands, UK and large parts of Italy). Screening programmes are being initiated in the Baltic countries and Hungary. In most other countries, screening remains opportunistic, depending on the initiative of the individual woman or her doctor. Such opportunistic screening is often characterised by: a high coverage in selected parts of the population, screened too frequently; low coverage in other socio-economically less-developed population groups; and heterogeneous quality. Little information is available on the screening situation in eastern European, Caucasian and central Asian republics but it is expected that, in general, coverage and quality is poor.

### New technologies

The recognition that persistent infection with high-risk HPV types is a necessary but insufficient cause of CC has prompted the development of a series of HPV tests and vaccines. From an updated meta-analysis of the diagnostic properties of HPV testing compared to cytological screening , it was concluded that sufficient evidence exists to recommend HPV testing for triage of women with atypical cytology and in surveillance after treatment of CIN lesions (7). No worldwide consensus exists with respect to the choice of the primary screening test. There is no doubt that validated HPV tests are more sensitive and more reproducible than cervical cytology but they are also less specific. HPV screening may allow longer intervals if the test is negative. But to translate this theoretical advantage into practice, a well-established organisational framework will be required, with adequate management algorithms and counselling for HPV positive women. In the United States, combined cytology and HPV testing with the Hybrid Capture-2 assay is approved for primary screening in women older than 30 years. However, in Europe, cytology-based screening still remains the standard screening method. The European Union screening policy will be reviewed based on the longitudinal outcomes of randomised population trials, which are currently underway. These results are expected by 2007-2008.

Liquid-based cytology (LBC) reduces

the proportion of inadequate smears, require less time for microscopic interpretation compared to conventional Pap smears and allow ancillary molecular testing (for instance HPV test if atypical cells of undetermined significance). However, LBC is more expensive and not more sensitive or specific for the detection of histologically confirmed high-grade cervical precancer.

## HPV vaccination

Meanwhile, prophylactic trials have demonstrated that a vaccine containing L1 virus-like particles (VLPs) are safe and trigger production of type-specific antibodies lasting for at least five years. The vaccine offers an excellent protection against persistent infection with the target HPV types and cervical precancerous lesions associated with those types, if administrated to young women who are not infected with the HPV types included in the vaccine.

The vaccines do not protect against an established HPV infection, and for this reason, the vaccine should be administered preferentially before onset of sexual activity, for instance to girls of 11-13 years. Screening policies should not be modified for women, who currently are 25 years or older. Since the vaccine does not protect against all oncogenic HPV types, screening cannot be obviated, but could start later and might be offered less frequently.

Currently, national regulatory agencies are defining recommendations for vaccine use and funding. Active surveillance systems must be set up to verify the long-term vaccine efficacy, safety and occurrence of HPV type replacement. In the future – over 10 to 20 years – new screening policies for vaccinated cohorts need to be defined, based on new data from phase 4 studies (trials and surveillance) addressing the costs and benefits of screening and vaccination combinations.

## Conclusion

The highest level of protection against cervical cancer can be reached if screening is well organised following an evidence-based, acceptable and economically affordable policy. Cost-ineffective opportunistic screening should be discouraged. Population coverage and quality should be maximized and actively monitored.

New technologies should be introduced only after through evaluation of efficacy and cost-effectiveness. HPV vaccination offers new opportunities of primary prevention but will not obviate the need of screening for the next two decades.

WHO and European Union guidelines can assist national and regional health authorities in defining practice standards and rational policies for cervical cancer prevention. Particular attention should be given to the high burden of CC in East-Europe.

**Table 1.** Mortality from cervical cancer in 49 countries of the European WHO Region: number of deaths, crude and world-age standardised rate (WASR, per 100,000 women-years). The estimates are derived from a recent study of the burden of cervical cancer in member states of the European Economic Area for 2004 (3), and from GLOBOCAN 2002 (2) for the other countries; figures are adjusted for mortality from not other wise specified uterine cancer.

| Country | Deaths | W-ASR (/100,00 women-years) | Country | Deaths | W-ASR (/100,00 women-years) |
|---|---|---|---|---|---|
| Member states of the European Union (estimates for 2004) | | | | | |
| Austria | 253 | 3.3 | *Before January 2007* | | |
| Belgium | 367 | 3.8 | Latvia | 166 | 7.9 |
| Cyprus | 25 | 5.6 | Lithuania | 283 | 10.0 |
| Czech Republic | 495 | 5.8 | Luxembourg | 12 | 3.0 |
| Denmark | 178 | 3.9 | Malta | 9 | 2.7 |
| Estonia | 83 | 6.9 | Netherlands | 305 | 2.3 |
| Finland | 61 | 1.1 | Poland | 2,216 | 7.4 |
| France | 1,562 | 3.0 | Portugal | 376 | 4.3 |
| Germany | 2,582 | 3.4 | Slovakia | 225 | 5.8 |
| Greece | 210 | 2.1 | Slovenia | 70 | 4.0 |
| Hungary | 555 | 7.2 | Spain | 775 | 2.3 |
| Ireland | 75 | 3.0 | Sweden | 248 | 2.7 |
| Italy | 1,090 | 2.0 | UK | 1,430 | 2.9 |
| 3 member states of the European Economic Area (estimates for 2004) | | | | | |
| Iceland | 4 | 2.0 | | | |
| Norway | 107 | 3.1 | Switzerland | 105 | 1.6 |
| 21 other countries from the European WHO Region (estimates for 2002) | | | | | |
| Albania | 146 | 9.8 | | | |
| Armenia | 130 | 5.6 | Macedonia | 99 | 7.6 |
| Azerbaijan | 113 | 2.8 | Republic of Moldova | 220 | 7.8 |
| Belarus | 436 | 5.2 | Romania | 2,094 | 13.0 |
| Bosnia Herzegovina | 227 | 8.0 | Russian Federation | 7,784 | 6.5 |
| Bulgaria | 506 | 8.0 | Serbia & Montenegro | 815 | 10.1 |
| Croatia | 209 | 5.0 | Tajikistan | 70 | 3.5 |
| Georgia | 225 | 5.9 | Turkey | 726 | 2.4 |
| Israel | 82 | 2.3 | Turkmenistan | 96 | 5.2 |
| Kazakhstan | 729 | 7.9 | Ukraine | 2,578 | 6.4 |
| Kyrgyzstan | 186 | 7.9 | Uzbekistan | 379 | 3.9 |

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# INTEGRATION OF THE VACCINE AGAINST HUMAN PAPILLOMAVIRUSES INTO NATIONAL VACCINATION PROGRAMMES

**Human papillomaviruses (HPVs) cause the most common sexually transmitted infections (STIs) in up to 35% of young adults. Infections with oncogenic high risk HPV types progress in 10 to 20 years to anogenital cancers in 1/100 infected individuals, and are the major known cause of mortality from cancer among females with 270 000 annual deaths from cervical cancer alone.**

The facts in the order of marketing value and public health impact are: 1. Two vaccines against the high-risk HPV types 16 and 18 based on DNA-free virus-like particles comprising viral L1 structural protein will have been licensed by the end of 2007. 2. The majority of high-risk HPV-associated neoplastic diseases, an be prevented by vaccination, and 3. High-risk HPV types can probably be nearly eradicated by systematic vaccination of early adolescents. How to implement prophylactic vaccination of early adolescents both against cancer and against the most common sexually transmitted infection (STI)? That is the question of the year in public health. To guarantee all achievable health benefits to the young, national vaccination programmes should provide free HPV vaccination to early adolescents.

Past infection with oncogenic high risk HPV types 16, 18, 31 and 45, as well as with several other high risk HPV types (33,35,52,58,66), is the cause of cervical cancer and many other anogenital cancers that appear >10 years later. In affluent societies an increase in sexual risk-taking behavior since the 1970's has increased the prevalence of high risk HPVs up to 35% in women under 25 years of age (1). Good longitudinal data for developing countries is missing but the trends are probably in the same direction. Co-infections with high risk HPV types (2) and co-infection with the high risk HPV and Chlamydia trachomatis (Lehtinen et al. unpublished) are common up to the age of 30, and probably help to establish the first step in cervical carcinogenesis: persistent high risk HPV infection. In phase II trials virus-like particle (VLP) -vaccines have showed >95% vaccine efficacy (VE) in preventing incident and persistent infection and pre-cancerous lesions associated with vaccine HPV types up to 5 years.(3, 4) Next carcinogenic steps, however, are beyond reach of the VLP induced neutralizing antibodies, and these prophylactic vaccines should be administered before the onset of sexual activity.

The registered/soon to be registered tetravalent (HPV6/11/16/18, Merck & Co. Inc.) and bivalent (HPV16/18, GlaxoSmithKline Biologicals) vaccines are administrated intramuscularly, like the first genetically engineered human cancer vaccine hepatitis B-vaccine, in three doses during a conventional 6-month schedule. Interim analyses of multinational phase III trials have shown/are expected to show high VE against clinical manifestation of persistent HPV16/18 infection i.e. cervical intraepithelial neoplasia (CIN2+). However, CIN2 lesions have a high regression probability, and it is ethically impossible to judge from the active phase III trial data, whether the vaccine is equally effective against HPV16/18 infections and CIN2 that would have progressed to cancer as against HPV16/18 infections and CIN2 that would have regressed1.

In this context, 6,600 16- to17-year old girls, comprising about 20% of all the 15- to 25-year old women (and the vast majority of <18-year old women) who received the experimental tetravalent or bivalent HPV vaccines or placebo in the phase III trials, have been enrolled in a population based study in Finland.(1) To completely assess direct, indirect and total long-term VEs of the intervention 17 000 18- to 19-year old non-vaccinated young women have also been enrolled. A proportion of placebo recipients and non-vaccinated young women will accept the freely available licensed HPV-vaccine(s) at the end of the trial or purchase the vaccine(s) in the future, but they can all be identified through the Finnish National Agency for Medicines. The majority of the controls are, however, not expected to take the HPV vaccine but attend organized screening for cervical cancer. Furthermore for many of those opportunistically vaccinated the vaccination comes too late, i.e., after acquisition of the high risk HPV infection. Thus, passive follow-up of all the 23 600 young women by Finnish Cancer Registry will yield true VEs of HPV16/18 VLP-vaccination against localized cervical carcinoma (carcinoma in situ, CIS) by 2015.

While each previously HPV uninfected vaccinated woman directly benefits from HPV vaccination, the vaccine additionally confers indirect population-level benefit on unvaccinated women by reducing transmission and thereby reducing the likelihood of being exposed to the infection. This effect of herd immunity means that vaccine coverage of 90% can prevent greater than 90% of infection leading to the possibility of near-eradication (Figure 1). Even with vaccine coverage not exceeding 50% the contribution of herd-immunity is strong. However, complete eradication of an STI is hard to achieve because of heterogeneity in sexual behaviour. This suggests that targeted control programs may be useful and also raises the role of catch-up vaccination (5).

With the newly reported 16/31 and 18/45 cross-reactivity (3) the proportion of cervical cancer preventable by the HPV16/18 vaccine is 80-85% in the developed and 70-75% in the developing countries. The latter might especially benefit from the inclusion of some of the other high risk HPV types (33,52,58,66) into the vaccines. It might also be important to avoid high risk HPV type-replacement, i.e., emergence of new high risk HPV types not included in the vaccine into the ecological niches created by vaccination. In this context it is important to note that the fierce competition between the two

vaccine manufacturers (Merck & Co. Inc. and GSK Biologicals) probably guarantees a flow of multivalent HPV vaccines to the market in the coming years.

The duration of vaccine protection in adolescents is also important for the effectiveness of high risk HPV vaccination against cervical cancer both in the developed and the developing countries, especially for women who might acquire new infections later in life. In the worst-case scenario waning of immunity in five years would result in low or no reduction of cervical cancer incidence from HPV vaccination. On the other hand, assuming 10 to 30 year protection from a combination of HPV16/18 vaccination at the age of 12-years and one lifetime high risk HPV-screening would most cost-effectively decrease the incidence of cervical cancer compared to conventional screening.

Finally, even the affluent societies offer few health services that the adolescents recognize as promoting their personal health and well-being. In this context screening for Chlamydia trachomatis, of which the population attributable fraction in cervical cancer is at least 30% according to a recent meta-analysis (Lehtinen et al., unpublished), in young adults can be highly synergistic with the herd immunity induced by HPV vaccination programmes. Eradication of the high-risk HPVs from the new birth cohorts entering sexually active life is the ultimate goal, but it is also necessary to evaluate the effectiveness, effectiveness of vaccinating girls and boys, and population level safety (e.g. type-replacement) of the vaccines. A community-randomized trial in Finland will yield this data, and in implementing the first STI vaccine models a variety of interventions against common STIs in the adolescents will be identified1. Self-evidently, the acceptance of the interventions starting from the appropriate age of HPV vaccination varies by country. Furthermore, securing commitment from various stakeholders for sexual health education for adolescents and young people is a challenge.

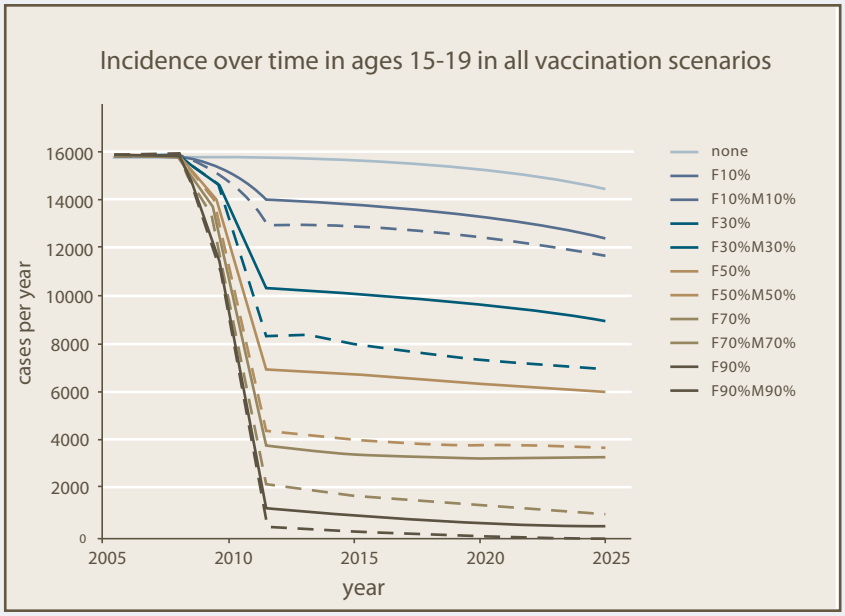


**Figure 1. Model of reduction of HPV16 infected individuals following population based vaccination of 13- to 15-year old adolescents in Finland by different coverage of HPV16 vaccine.**

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# THE EUROPEAN CERVICAL CANCER ASSOCIATION AND THE PREVENTION OF CERVICAL CANCER IN EUROPE

**Worldwide, cervical cancer is the second most common cancer in women after breast cancer. About 500 000 women develop this cancer and 250 000 die from it every year with most cases occurring in areas of the world where there is no screening or the screening is not effective (1). In Europe as a whole, about 50 000 women develop cervical cancer and almost 25 000 women die from it every year (2). However, these summary statistics do not reveal the dramatic differences that exist in Europe where cervical cancer rates are much higher among lower socioeconomic groups where lack of awareness and competing priorities result in reduced attendance to screening programmes, and in some Eastern European countries where effective screening programmes are lacking.**

While the statistics for cervical cancer are deplorable, perhaps the biggest tragedy with cervical cancer is that we already know how to prevent the overwhelming majority of cases and yet it remains a significant source of disease and death across Europe and around the world. It has been well established that effective organised screening programmes can prevent up to 80% of cervical cancers (3). The benefits of such programmes have been clearly demonstrated in Finland, the UK and other countries or regions where they have been established, and the same results could be achieved anywhere there is the political will to do it. In addition, new technologies such as HPV testing and HPV vaccination, if properly implemented within the context of an organised prevention programmes, offer the potential to make an even greater impact on cervical cancer rates. As a result, the main battle against cervical cancer has now moved from the research arena to the political arena where those responsible for allocating money to public health programmes and those responsible for implementing them must be encouraged to prioritise cervical cancer prevention programmes.

It was in recognition of this change that the European Cervical Cancer Association (ECCA) was established in 2002, with the overarching objective to raise awareness of cervical cancer and the means by which it can be prevented among all relevant target audiences including:

- women in the general public who must understand the benefits of prevention programmes to ensure they access the services that are available to them,
- medical professionals who must be able to provide accurate advice to their patients and advocate for changes to the healthcare systems within which they work,
- public health officials who must fully understand the importance of organised cervical cancer prevention and public health education programmes so that they receive due priority when setting healthcare policy.

The foundation of all of the ECCA's activities is a cervical cancer education programme that is coordinated at a European level through a network that now involves more than 60 cancer societies, medical associations, university departments and patient groups from across Europe. Together, these organisations bring an enormous wealth of expertise in all aspects of cervical cancer and they all are involved in the initial development of the core materials and programmes that are produced by the ECCA. Subsequently, these same organisations are responsible for adapting the core materials to meet the national requirements of each country and then translating them into the local language. In this way, the ECCA network is able to develop consensus agreed core materials that are essentially 'peer reviewed' by Europe's leading cervical cancer experts, but then adapted and translated to meet local requirements. Importantly, this process ensures that the factual content of the materials remains consistent from one country to the next and thereby minimises the opportunities for people to be exposed to inconsistent or conflicting messages, which would undermine the educational process.

### The current set of educational materials includes:

- 3 introductory brochures on 1) cervical cancer screening, 2) the Human papillomavirus (HPV) and cervical cancer, and 3) the follow-up of an abnormal Pap smear. These brochures have been designed so they can be

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read in less than 5 minutes and therefore only introduce a limited number of basic concepts but then provide further sources of information for those who desire to learn more.

- 2 booklets that constitute one of the sources of further information and present a more complete picture of 1) cervical cancer prevention including information on HPV's involvement in cervical cancer development, HPV testing and HPV vaccination, and 2) the follow-up of an abnormal Pap smear including information on the various stages of cervical disease together with the options for their treatments.
- A website that offers a comprehensive range of information from the very basic to the very advanced and allows people to find as much or as little information as they desire at the time.

The ECCA uses a variety of means to disseminate these materials. For the general public, the primary method is to work with cancer societies, medical associations and other organisations, often in conjunction with a local sponsor, to make the materials available through the medical professionals. Importantly, this process also serves to educate the medical professionals as they are exposed to the educational materials and the website. In addition, all the materials produced by the ECCA are freely available on the ECCA website for people to download and use free of charge for non-commercial purposes. At this point in time, the brochures are available in 10 languages and the booklets are available in 4 languages and the website is available in 5 languages, although other language versions of all the materials are in the process of being prepared.

For communicating with politicians and public health officials, it should be remembered that the ECCA is a European organisation and its focus is therefore naturally on European policy development. In Brussels, the ECCA works closely with and provides the secretariat for the European Parliament Cervical Cancer Interest Group (CCIG) that was launched on 31 May 2006 and currently includes 36 Members of the European Parliament. Together with the CCIG, the first project that was undertaken was the preparation of a series of 8 fact-sheets on cervical cancer prevention in Europe that were delivered monthly to the Members of the European Parliament, and are currently available on the ECCA website. These fact sheets have been also been translated by members of the ECCA for delivery to politicians and public health officials in their own countries.

For raising awareness among all target audiences, the ECCA has now launched the European Cervical Cancer Prevention Week (ECCPW) to be held each year during the 3rd week of January (the week of 21-28 January 2007). The primary objective of this event is to attract media attention to the issue of cervical cancer and thereby facilitate the dissemination of key prevention messages to European women. The ECCPW will be launched by the Cervical Cancer Interest Group with an event in the European Parliament to be held on 23 January which will include Members of the Parliament, European Commission Officials and representatives of cancer societies, medical associations, patient groups, etc. In addition, the ECCA will hold the 'Working Together to STOP Cervical Cancer' workshop in Brussels and Members of the ECCA will be organising many national events across Europe.

The ECCA is very interested to work with any organisation or individual involved in the prevention of cervical cancer in Europe. If you would like to find out more about the ECCA or participate in our programmes, please go to the website (www.ecca.info) or contact any of the authors note below.

## Resources


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# CERVICAL CANCER SCREENING – EFFECTIVENESS AND IN ICELAND

**Cervical cancer has long been connected with life-style and sexual behaviour and the common risk factors are high parity, age at sexual debut, number of sexual partners, use of oral contraceptives, smoking and sexually transmitted infections (STI). However, the world-standardized incidence varies between countries, depending on the cytological screening activity in each country.**

## Cytological screening

The effectiveness of cervical cancer screening is evaluated by time trends in incidence and mortality rates in countries with established screening procedures. The Nordic countries, except Norway, started organized screening around 1962-1964 (1) with the most intensive target age group and screening intervals in Iceland and the least intensive in Finland (see table 1). In spite of these differences the reduction in the mortality rate up to 2000-2004 has been similar in both these countries or around 82-83%, indicating that the Icelandic women have been over-screened and over-treated (2).

## The Icelandic screening experience

After the start of screening in Iceland in 1964 both the incidence and mortality rates decreased significantly. The incidence, however, did increase temporarily between 1981-1985, mainly among younger women, and the mortality rate levelled out. Re-evaluation of the screening program (3) confirmed a low regular attendance in the target age group of 25-69 together with an increased rate of moderate to high-grade preinvasive disease (cytology: HSIL; histology: CIN 2-3/AIS). The screening program was reorganized with a computerized call and recall system, and intensified re-screening at 2-3 year intervals and follow-up of women with abnormal screening results.

A new re-evaluation in 1987 confirmed that the prevalence of preinvasive disease had continued to increase, beginning at age 20. This resulted in a decision to decrease the lower age limit to age 20 in 1988 (4). The latest re-evaluation of the program in 2005 (5,6) showed that the rates of moderate to high-grade preinvasive disease continued to increase until 1998, but levelled out thereafter. Analyses of the cumulative incidence of the lesions at a fixed risk level showed that the number of earlier normal visits did not lead a decision to prolong screening intervals until after age 35, thus supporting 2-3 year screening intervals before age 35.

The age-specific incidence of invasive disease was significantly higher after 1980 in women under 35, but had decreased significantly after age 40. The increased incidence below age 35 was due to the in-

**Table 1. Organized Cervical Cancer Screening the Nordic countries up to 2000-2004**

| | Iceland | Finland | Sweden | Denmark | Norway |
|---|---|---|---|---|---|
| Start of organized screening | 1964 | 1963 | 1964 | 1962 | 1995 |
| Targeted age groups up to 1985 | 20-69 | 30-55 | 23-49 | 23-50 | |
| Screening interval | 2-3 | 5 | 4 | 4 | |
| Target age groups since 1985 | 20-69 | 30-60 | 23-60[1)] | 23-75 | 25-69 |
| Screening interval (Years) | 2-3 | 5 | 3-5[2)] | 3-5[3)] | 3 |
| Five-year period with highest incidence rate[6)] | 1966-70 | 1961-65 | 1961-65 | 1961-65 | 1971-75 |
| Reduction in overall world adjusted incidence rate | | | | | |
| through 1981-'85 | 45% | 66% | 46% | 45% | 26% |
| through 2000-´04 | 64% | 72% | 60% | 64%[4)] | 50% |
| Five-year period with highest mortality rate[6)] | 1966-70 | 1966-70 | 1961-65 | 1961-65 | 1956-60 |
| Reduction in ovarall world adjusted mortality rate | | | | | |
| through 1981-'85 | 62% | 60% | 46% | 37% | 33% |
| through 2000-´04 | 83% | 82% | 71%[5)] | 68%[4)] | 63%[5)] |

1) Sweden: age 20-60 at 3 year intervals in 1985-1997; 2) Since 1998 at 5 year in the age 51-60 year age group
3) Denmark: at 5 year intervals in the 60-75 age group; 4) incidence and mortality rates though 1997-2001
5) Sweden and Norway: mortality rates through 2000-2003
6) Incidence and mortaltity rates based on data from the Nordic Cancer Registries

# IMPLICATIONS OF HPV VACCINES

Kristjan Sigurdsson

creased rate of squamous cell carcinoma and adenocarcinoma diagnosed at an early stage whereas the rate of more advanced disease (stage IIA+) had decreased significantly in all age groups.

At age 20-34 the incidence of microinvasive disease (stage IA) had increased at a significantly higher rate than stage IB, and the cumulative incidence of stage IA had already started to accumulate within three years after the last normal smear. These findings can be regarded as showing the success of the reformed screening program, as diagnosis of microinvasive disease enables fertility-sparing treatment in these younger women.

The Icelandic conclusions are therefore that screening should start at or soon after age 20 (IARC´s recommendation (7) is age 25) with a maximum of 3 year screening intervals, but that the intervals can be extended to five years at age 40 and screening stopped at age 65 among adequately screened women.

## Younger women

The Icelandic recommendations find support in other data. In Finland the age-specific incidence under age 50 increased after 1995 connected with changes in lifestyle and sexual behaviour, and an increased rate of HPV 16 infections (8). In the UK a nearly fourfold increase in the age-specific incidence occurred in some areas at age 25-29 after 1970, followed by a 40% increased death rate in this age group between 1977 to 1988 (9). In the 20-24 age group the rate of moderate to high-grade histological preinvasive disease increased more than 60% from 1993 to 2000. Concurrent with these changes the number of women having intercourse before age 16 increased from 1% to 24%, the number of women with more than four sexual partners increased from 11% to 26%, and the frequency of gonorrhoea, chlamydia and syphilis more than doubled.

## HPV

The sexually transmitted human papilloma virus (HPV) is the main etiological factor in cervical cancer (10) virus is a necessary but not a sufficient cause, meaning that certain co-factors such as other STIs smoking, hormonal contraceptives, etc. are needed for development of the disease. There are more than 200 types, subtypes and variants of HPV and about 40 are classified as anogenital. Of the latter about 15-18 types are classified as oncogenic, of which the most common are HPV 16 and 18 found in approximately 70% of cervical cancer cases (11). The oncogenic types are said to act independently and convey a statistically similar risk of developing cervical cancer (12). The natural history of the different HPV types and determinants of immune response are, however, still unclear.

## HPV vaccines

Studies in the UK using the Hybride Capture 2 test have confirmed a prevalence s high as 33% at age 20-29 (9) and even higher with PCR analyses. The prevalence decreases with age and levels out after the age of 30-35. It has been shown that the non-oncogenic L1 HPV capsid self-assembles into virus-like particles (VLP) in yeast and baculovirus culture systems. Trials with VLP have found that these induce neutralizing antibodies. Two vaccines, one from Merck based on HPV VLP 16/18 and 6/11 (Gardasil™) and one from Glaxo Smith Kline based on HPV VLP 16/18 (Cervarex™), are under evaluation.

## Phase I-III studies

Phase I and II studies confirm that these vaccines are well tolerated, the immune response is good and protection is offered against persistent HPV infections (13). Although a limited cross-reaction between HPV types has been reported recent data from the GSK trial indicate a potential cross-reaction between HPV 16/31 and 18/45, but confirmation awaits further test results.

Phase III studies are ongoing and an interim analysis of Merck's Phase III trial (Future II which enrolled 12,167 women at age 15-26, thereof 710 from Iceland) confirmed a 100% efficacy in preventing HPV 16/18 related CIN 2-3/AIS endpoints in women free from such infections at enrolment. The Merck vaccine (Gardasil™) has been approved by the FDA for use in the 9-26 year age group, and the marketing process started immediately after approval.

## Unresolved issues

Age of vaccination: The vaccines have no effect after the virus has been integrated into the genes. The target group for public health vaccination programs should therefore be naïve girls but the optimal age is, however, still unclear.

Duration of the vaccination effect: Whether and when a booster vaccination is needed is still unclear.

Vaccination of young males: The inclusion of young males in future vaccination programs is dependent on the disease burden caused by these viruses in men and the cost-effectiveness of such an approach.

Vaccines based on multiple HPV types: Including HPV 16, 18, 31, 33, 45, 52, 58 is estimated to increase the reduction in the cancer incidence from 70% to 87% (11). The cost-effectiveness of adding more types to the current available vaccines is, however, still unclear.

## Integration into existing screening programs

Studies on cost-effectiveness (C/E) of HPV vaccines are based on computer-based mathematical simulation models that take into account age at vaccination, cost of vaccination, duration of the vaccination effect, the natural history of cervical carcinogenesis etc. All these models are highly sensitive to variations in the included variables. The study conclusions take into consideration that current screening practice can give 85% reduction in the lifetime cancer risk and that a C/E ratio less than $75,000 is regarded as good value for resources in the USA.

Some of the studies indicate that the most effective approach is vaccination at age 12 combined with cytological screening from age 24-25 at 2-3 year intervals. This approach has been estimated to reduce the lifetime cancer risk by 83-

94% with an incremental C/E ratio of <$60,000 per Quality Adjusted Life Year, and including young males was not considered cost-effective (14, 15).

## Implications on current screening practices

HPV 16/18 vaccines will undoubtedly be a blessing in countries unable to accomplish an effective cytological screening program. The cost of vaccination, however, may be of concern, especially for the developing countries. Health authorities in countries with well established organized screening programs or planning to start such screening should, however, carefully evaluate implications of future vaccination programs with HPV 16/18 vaccines.

The vaccines will decrease the prevalence of the disease and thereby decrease the positive predictive value of screening. The decreased prevalence of abnormal smears will decrease the alertness of the cyto-screeners, thus stimulating to incorporation of more expensive screening techniques. This may decrease the cost-effectiveness of the combined approach and press decision makers to change the age limits and prolong the screening intervals to cope with increased costs.

These implications, together with the potential decreased attendance among the vaccinated women (false security), may lead to an increased rate of invasive disease among the younger women. These risks may, however, be counterbalanced by keeping the vaccine prices at the lowest possible profit level, increasing the vaccine efficacy by adding multiple HPV types to the current vaccines, and informing and educating the public, health care personnel and policy makers.

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# CERVICAL CANCER SCREENING IN LITHUANIA

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**Despite the extensive and often costly screening effort, approximately 27 000 new cases of cervical cancer are diagnosed each year in the European Union and 11 000 women die from the disease. In the whole of Europe, almost 50 000 women develop and 25 000 women die from cervical cancer every year. The number of women living with cervical cancer is more than 175 000 (1).**

Lithuania exhibits one of the highest incidence rates for cervical cancer in the Baltic countries and Europe. During the last five years the incidence ranged from 23.6 to 31.1 per 100 000. The incidence of cervical cancer in Lithuania is fivefold higher than in Finland, thrice as high as in Sweden and 2.5 times as high as in Norway. In year 2000 the mortality from cervical cancer in Lithuania reached the second highest place in Europe. Mortality rate ranged from 11.5 to 13.6 per 100 000. During the last five-year period the mortality and incidence rates have increased every year. These figures in Lithuania are markedly higher than in Latvia and Estonia, the other two Baltic countries with almost the same standards of living. The high mortality rate is associated with late diagnosis: about 50% of cases are diagnosed at an advanced stage (III-IV) (2).

## Cervical cancer screening during 1993-2003: what has happened?

The screening for cervical pathology in the last decade of the 20th century was unorganized, chaotic and totally opportunistic. According to the recommendations of the Ministry of Health of Lithuania every sexually active woman older than 18 years is supposed to be screened with a Pap smear once a year. Some women were examined a few times per year whereas other women (usually women from high risk groups) were never examined. Very often women did not know if a specimen for cytological examination had been taken from their cervix during their visit to the doctor. Often they were not informed about the results and were not told when this test should be repeated. In 1993 the Ministry of Health endorsed the establishment of the National Cancer Control Program (NCCP). According to this program from 1993 till 1999 screening for cervical cancer was carried out in six districts of the country under the supervision of the high-qualified oncological specialists from the Lithuanian Centre of Oncology. There is not yet available any published data about the organization, methodology, coverage of target population and results of this screening program. However, the statistic data of the Lithuanian Cancer Register Database showed that neither this screening system organized as a part of the NCCP nor opportunistic screening according to general recommendations of Ministry of Health in the remaining part of Lithuania functioned very well. This was due to lack of resources, absence of systematic testing, no quality assurance system, no information system and no follow-up.

The national program for cancer control was prepared in 1990. The results from various epidemiological studies show that there is a tendency of increasing number of cases of cervical cancer, in Lithuania. In 1990 there were 370 cases of cervical cancer and in 2000 this number had already grown to become 468. According to the data provided from the Lithuanian Cancer register 48.4% of all cases of cervical cancer were Stage I and II, widespread disease Stage III and Stage IV - 51.6%. With a high proportion of widespread disease, it is clear that the mortality rate also increases. According to WHO, the death rate from cervical cancer in Lithuania is one of the highest in Europe. In member countries of the European Union and other Eastern European countries, the death rate from cervical cancer has greatly decreased whereas in Lithuania, Latvia, and Estonia, this rate has a tendency to rise. This shows that these counties had no strategy for secondary preventive measures.

The plans of the Lithuanian NCCP were to carry out a cervical cancer screening pilot study during 1998-2000; from 2000 to expand screening based on experience accumulated in the pilot regions and then expand the pilot study to all the country covering 80% of women over 20 years. These plans of the NCCP were practically not carried out. The target of the NCCP from 2001 was to continue and continuously improve cervical, breast and prostate cancer screening in all of the country. However, no detailed description and schedule for implementation or measurable criteria for evaluation were provided.

With changing tendencies in oncology, there was a larger role to be played by the family doctors working in the primary health care centres, where clear-cut restructuring took place in 2003. The main responsibility of preventing cervical cancer lies with the public and the primary health care providers, who can play a major role in educating the general public. Cervical cancer is not only a medical problem; the knowledge of the women concerning this problem is insufficient, thus there is a need for unified efforts to supply information for the general public about this problem through advertisement, TV and radio.

## Nation-wide cervical cancer screening: experience from 2004

In the new National Cancer Control Program for 2003-2010, the priority was given for the screening of the pathology of the uterine cervix. The working group for creating a cervical cancer screening program, consisting of primary health care providers, specialists from various fields and representatives from public organizations was established by the Ministry of Health of Lithuania. The "Guidelines of implementation of cervical cancer screening program" were developed by

this working group in the beginning of 2004 and confirmed by the order of the Minister of Health. The nation-wide organized cervical cancer screening was implemented along the state insurance based health care system, which seems to be a reasonable approach for cervical cancer screening. The government allotted the resources to the State Patient Fund (SPF), which is responsible to provide the reimbursement for the services. Five Territorial Patient Funds are responsible to manage contracts with Primary Health Care Centres (PHCC). There are more than 350 PHCC around the country. They are responsible to join the screening program and to implement the screening procedures. The visit of the women to PHCC in Lithuania is free of charge if she is registered on the list of the centre. The SPF follows the system and does not allow simultaneous registration of the women at different centres. Each General Practitioner (GP) is supposed to serve 1500 – 2500 of population. According to the National Screening Guidelines the GP's or gynaecologists working in PHCC are responsible for the invitation, the smear test and assessment of the results of the Pap test. The GPs provide information to the women about the screening program during visits to the centre or at home. Ten pathology laboratories around the country are certified to examine the Pap smears.

The nation-wide cervical cancer screening started at July 1, 2004. The aim of this program is to reduce the mortality from cervical cancer by 15% and morbidity by 30%. The objectives of this program are:

- to actively inform the society and the community about the problem;
- to diagnose women with preinvasive cervical conditions and to treat them;
- to ensure easy access and effective treatment of the precancerous lesions and cancer of the uterine cervix;
- to collect the information necessary to evaluate the effectiveness of the program, and the effect of its separate components on the results and the disadvantages;

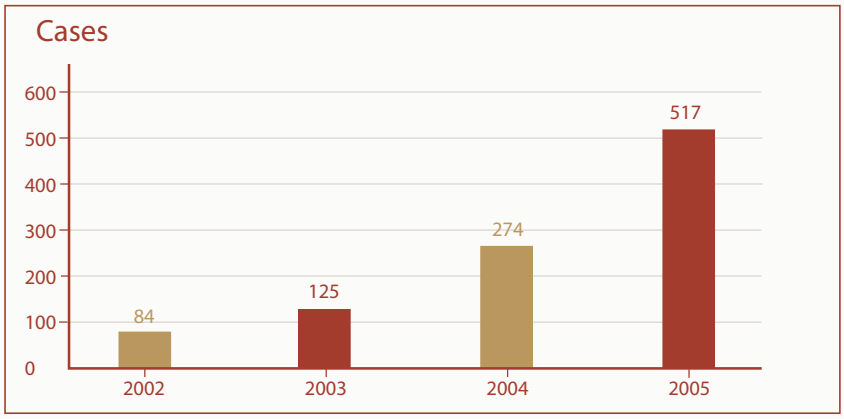


**Figure 1 The dynamics of the Ca in situ**


**Figure 2 The dynamics of the Ca in situ and invasive cancer**

- to ensure a quality control of the performed cytological examinations.

The results of this screening program can only be expected after 10 or 15 years - as can be seen from the experience of Finland, which was the first in Europe to start the implementation of the organized screening program in 1963. In Norway, the screening program was started 10 years ago, and cervical cancer incidence started to decrease as well.

The target group of this program is women between 30 and 60 years of age. There are about 750 000 women on the target. The screening interval is 3 years. During a 3-year period, the plan is to examine 80% (about 600 000) of the target group. The implementation of the program includes an invitation, smear test and assessment of the results, Pap examination. The invitation of women and smear taking is not centralized, and this gives an opportunistic feature to the program. The National cervical cancer screening coordinating committee, consisting of pathologists, gynaecologists, GP, epidemiologist, was organized by the Ministry of Health in 2004. The primary task of this committee is to review the results and provide the advice to make necessary changes in the guidelines. The implementation of nation-wide organized cervical cancer screening along the state insurance based health care system was a new and reasonable approach for cervical cancer screening in the country having low health economy resources. During one year 90% of primary health care centres have joined the program. Since the beginning of this program 267.000 of the women participated in the program - 38 percent of the total target group. From 2003 the Ca in situ cases have doubled ev-

**Table 1 The changes in the reimbursement made by the State Patient Fund in Euro (€)**

| | 2004 | 2006 |
|---|---|---|
| Information/invitation | 0,43 € | 0,71 € |
| Collection of Pap | 1,57 € | 2,11 € |
| Reading of Pap smear | 3,49 € | 4,00 € |
| From September, 2006: | | |
| Biopsy procedure | - | 11,11 € |
| Histological evaluation | - | 16,69 € |

ery year (Figure 1). It shows the effectiveness of the program and gives some optimism for the future. The ratio between Ca in situ and invasive cancer was about 0.1 before the screening program started. The situation has changed in the recent two years. The ratio between early detection of cervical cancer and invasive cancer exceeded "1"in 2005 (Figure 2). This ratio is about 5 or 10 in the countries in which screening runs very effeciently. From the beginning of the program 176 cases with the cytological symptoms of Ca (0,07%), 2865 – HSIL and Ca in situ (1,07%), 2048 – LSIL (0,77%) were diagnosed.

The first years experience has shown that the program still carries the opportunistic features. The program is strongly dependent on the frequency of women visiting the GP, the activity of the GP and experience of the team, presence of qualified Pap smear takers at each centre. During the last year the changes in the reimbursement were made by the State Patient Fund (Table 1) and 2 new services appeared in the list - biopsy procedure (11.11€) and histological evaluation (16.69€).

## High risk HPV types infection among rural and urban Lithuanian women

In Lithuania the national cervical cancer screening program is based on cytology. Primary prophylaxis is considered to include prophylactic vaccines and the knowledge of avoidance of factors related to the development of the disease, or reduction of their influence.

Changes in the incidence rate and mortality rate of cervical cancer in Lithuania show that the evaluation of the prevalence of HPV infection and factors, increasing the risk of HPV prevalence and persistence, will be helpful in applying primary and secondary prophylaxis. The prospective cohort study, analyzing the high risk HPV infection, prevalence, persistence and factors increasing the risk of HPV infection was carried out in 1998 - 2001 testing urban and rural women of reproductive age (3). The aim of the study was to investigate the prevalence, persistence and risk factors of high oncogenic risk human papillomavirus (HPV) among urban and rural women of reproductive age coming to consult a gynaecologist. The data was collected in eight health care institutions. HPV DNA was determined by molecular hybridisation method (hybrid capture version II) determining HPV of high oncogenic risk. 1120 women participated in the study. Prevalence of high-risk HPV among the studied women was 25.1%. It was higher among the urban women than among the rural women.

High risk HPV prevalence increased when having two or more sexual partners during the last 12 months (OR-2.81; 95% CI 1.83–4.32), 19 years or younger age (OR-2.68; 95% CI 1.47–4.91), smoking (OR-1.81; 95% CI 1.16–2.81) and secondary or lower education (OR-1.43; 95% CI 1.01–2.04). This infection was obviously associated with high and low-grade squamous intraepithelial changes of the cervix (OR-1.66, 95% CI=1.08 – 2.53).

The young and low educated women were found to be the group most exposed to HPV; therefore public health interventions and education seem to be essential in cervical cancer reducing programs. Because the study included the women who were seeking for gynaecologist consultation voluntarily, the HPV prevalence of all population could be different and population-based study need to be conducted. The national screening for high risk HPV infection or national vaccination program may be useful after large population-based study having the possibility to determine HPV type distribution. The understanding of the problem by women and their personal efforts to be healthy are of great importance in straining overreach this disease.

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# RECENT TRENDS IN CERVICAL CANCER CONTROL IN POLAND

Although cervical cancer is one the very few malignancies that are potentially preventable, it is one of the most common types of cancer found among Polish women. Despite full access to Pap smear testing for many years now, the lack of a national actively organized and controlled screening programme in Poland results in unfavourable epidemiological indicators. Low coverage of previous versions of screening was due to the very low level of awareness in the society and insufficient knowledge about the need for screening both among health care professionals and women. The implementation of actively organized screening together with the introduction of vaccines against oncogenic types of human papillomavirus (HPV) by the end of 2006 will hopefully improve the cervical cancer statistics over the coming years.

## The burden of the problem

By most recent data (1) in 2003, 3439 women were diagnosed and 1825 died of cervical cancer in Poland, which makes it the fifth most common and the seventh most lethal cancer among Polish women. Despite the decrease in incidence of the disease in Poland for 40 years, other European countries worked more effectively on the problem. Poland and Denmark had almost the same SDR per 100 000 women in the 1970s but effective prophylactic measures in Denmark led to a substantial reduction of the burden of the disease over the last 35 years. Nowadays SDR of cervical cancer in Poland is almost two fold higher compared to Denmark. A high incidence of invasive cervical cancer and a high mortality rate is caused by the low detection rate of precancerous lesions and late diagnosis of invasive cancers.

## Pap smear screening programmes in Poland

Pap smear testing is available for all women in Poland but attendance for testing is low and cannot be fully monitored. These facts remain the main cause of the high mortality from cervical cancer. Pap smear can be performed in three ways: in gynaecological clinics possessing a contract with the National Health Fund for the screening programme, in gynaecological clinics possessing a contract with the National Health Fund for general gynaecological service and by private care gynaecologists. Although the course of the national screening programme can now be entirely monitored, the number of Pap smears collected outside the programme can only be estimated. There are also limited means to control frequency and quality of service outside the screening programme.

In the 1990s and the beginning of this century sporadic local screening programmes existed but they were ineffective from a countrywide perspective. The national screening programme started in 2004 and was carried out with minor changes until the end of 2006, when a major reorganization was implemented. For the first three years the programme was inactive (opportunistic) and had a very low coverage rate (Table 1). At the end of 2005 and in 2006 the Polish Gynaecological Society lead by Professor Marek Spaczyński elaborated on the modifications, which are supposed to increase the efficacy of the screening and decrease incidence and mortality from cervical cancer by years 2012-2014 (2). Once in three years every Polish female aged 25-69, who is insured through the National Health Fund and has not taken part in the screening for three years, will receive an individual personal invitation to undergo a Pap testing. The invitations will be sent by the National Health Fund and will inform about neighbouring gynaecological clinics and offices, where free Pap smear service is available within the programme. Women at higher risk of cervical cancer (with history of HPV infection, treated for cervical cancer and precursors, immunodeficient) will be invited every year or more frequently. A central nationwide database was developed in the summer 2006 and will be used by all screening centres from the beginning of 2007. It provides complete control of the course of the programme. Women may undergo Pap smear testing in about thousand gynaecological sites all over the country (3). The Pap smear slides are processed and evaluated by cytological laboratories, which fulfil the criteria of a minimal number of annually evaluated slides and quality control. The results are presented in Bethesda and additionally in the Papanicolaou system. In cases of a positive test result patients are referred to colposcopy centres for final diagnosis and treatment. Results of colposcopy/histology can be monitored by the database. The screening programme is coordinated by 16 regional coordination centres and a central coordination centre. Apart from control of the screening, the personnel of the coordination centres train, inspect and consult programme providers. However the main task of coordinating centres is to increase the screening coverage and attendance of women. The screening is therefore accompanied by a national media campaign promoting cervical cancer prophylaxis through radio and TV spots, brochures, posters and direct meetings with programme participants and health professionals.

However, the main problem at the moment is the low coverage of the screening programme. The situation is complicated by the fact that presumably only about 10-20% Pap smears collected annually in the country are performed within the programme. The rest are performed mainly by private care gynaecologists and in clinics, which do not have a contract for screening with National Health Fund. In these cases women undergoing Pap smears are not registered within the central database the number, frequency, quality of tests and follow-up of positive results cannot be fully monitored. The organizers of the programme are however attempting to find a solution to this situation, so that most if not all Pap smears could be registered.

Vaccinations against oncogenic types of human papillomavirus – a breakthrough in cervical cancer prevention in Poland?

Since the end of 2006 the first vaccine against HPV, the aetiological factor of cervical cancer is available on the Polish (and European) pharmaceutical market. The vaccine of the second manufacturer will presumably be accessible in the next few months. Administration of the three-

**Table I. Coverage of cervical cancer screening programme in Poland**

| Year | 2004 | 2005 | 2006 (first 8 months) |
|---|---|---|---|
| Approximate numebr of women eligible for screening | 9.000.000 | 9.000.000 | 9.000.000 |
| Approximate number of women screened in the programme | 160.000 | 290.000 | 245.000 |

dose vaccination against HPV types 16 and 18 in young women prior to their sexual debut result in approximately 70% reduction of life-time risk of cervical cancer development. The use of the vaccine among older sexually active women may also be potentially beneficial, however the efficacy of the vaccine in this group is expected to be slightly lower, and is not yet completely known. The HPV vaccination is not likely to become a part of a Polish national immunisation programme very soon, mainly due to the costs, although it would be one the most effective ways of cervical cancer prevention. The attitude towards vaccination against HPV in the Polish society has not yet been evaluated. The extent of vaccine use will depend both on the awareness of the benefits of being vaccinated and the acceptability of its high price. One might expect that women of high socioeconomic status, who are already aware of the necessity of cervical cancer prevention and regularly attend cytological screening, will be the first line of vaccine beneficiaries, as they will be able to afford it. At the same time there is a danger that poor women with little knowledge of the problem, who never or seldom attend cervical screening, will not be vaccinated because of the high cost of the product and low awareness of the disease. It is difficult to predict how parents of 10 to 12 year-old girls will perceive costly vaccination of their daughters against a sexually transmitted disease. We therefore reckon that HPV vaccines should be advertised and marketed as an anticancer not a STI preventing product. If the vaccine is not funded by the National Health System, alternative sources of finance should be searched, particularly for indigent societies who are the main risk groups of cervical cancer development. In some regions local initiatives emerged to find resources for vaccination of girls from poorest environments e.g. orphan houses.

HPV vaccinations are most likely to be performed mainly by three groups of specialists: paediatricians and family practitioners, who routinely deal with great majority of obligatory and recommended immunisations, and also gynaecologists who are responsible for secondary cervical cancer prevention in Poland. Paediatricians and family practitioners will carry out vaccination of young girls, whereas gynaecologists also will vaccinate adolescent girls and older women. Making these three groups of specialists entirely aware of the burden of the cervical cancer problem and potential benefits of HPV vaccinations is essential. Substantial demand for expert information to guide health-care providers for indications, limitations and effective use of vaccines is also expected. Because vaccines do not provide 100% protection, the definite obligation for continued Pap smear screening of vaccinated women must be stressed at all occasions. Some data based on mathematical models from highly developed countries suggest extending the intervals between routine Pap smears in the era of HPV vaccinations. In the authors' opinion it is far too early to implement such recommendations in Poland, where the general public awareness of the need for screening and coverage of the screening programme is low. Promotion of extending intervals between Pap smears could result in a misleading opinion that vaccinated women are entirely protected from cervical cancer. Besides, long-term observations of vaccine efficacy still need to be elucidated.

However both the implementation of the active form of screening and media campaign promoting vaccines led by competing pharmaceutical companies are likely to increase knowledge and awareness of the problem of cervical cancer in Poland. The impact of HPV vaccinations on cervical cancer incidence and mortality in future decades remains to be evaluated and depends mainly on affordability of the vaccines to entire population of Polish women.

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# IMPLEMENTATION OF THE NATIONAL PROGRAM ON PREVENTION OF CERVICAL CANCER IN ARMENIA,

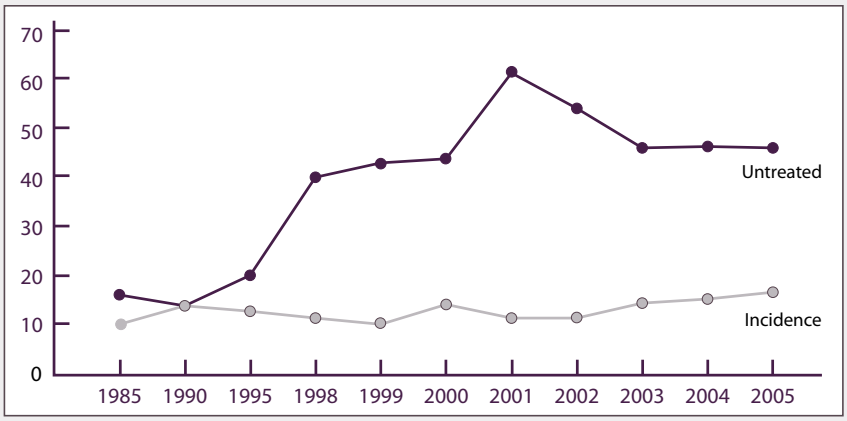
Cancer in Armenia is the third leading cause of morbidity among women. Prevalence of cervical cancer among malignancies of reproductive system is in the second place, following breast cancer. In Armenia during the last decade the cervical cancer incidence has been in the range of 11-14 per 100 000 women. In fact, in the Russian Federation cervical cancer morbidity is 15.94 per 100 000 population, in Latvia - 25.09, in France - 11.1, in Finland - 5.2 (1). However, in recent years increasing trends in morbidity associated with cervical cancer are observed. In 2001 the cervical cancer incidence rate was 10.9 per 100 000 women, whereas in 2004 and 2005 the incidence rates were already 13.8 and 14.4 respectively (2). Moreover, there is a two-fold increase in cases detected in late untreated stages of the disease (see Figure 1).

In addition, nowadays in Armenia malignancies, and particularly, cervical cancer is registered among younger age groups compared to earlier. In fact, every 4th case (27% of cases) is registered among women aged 25-35, making the problem even more prominent. The observed growth in morbidity rates can be attributed to the high prevalence of sexually transmitted infections (STIs), decreased utilization of health services, lack of evidence-based medical approaches in detection and treatment, and poor awareness among the population.

In 2004, with the support from UNFPA, a representational survey on prevalence of cervical cancer and STIs was conducted among 2650 women aged 18-49 (3). Prevalence of gonorrhea was very low, with only 11 cases revealed from the total number of 2650 women, whereas every 10th women had been diagnosed with chlamydiosis. The highest prevalence of clamydiosis was revealed in the 29-33 age group (13.8%), the lowest in the 18-23 age group (8.8%). There was no significant urban-rural difference in the prevalence of chlamydiosis.

The need for prevention of cervical cancer has been acknowledged and reflected by a number of governmental policies including in the poverty reduction strategy paper, mother and child health protection strategy, and the 2004-2010 National programme on the improvement of women status and increasing their role in the society.

**Figure 1. Incidence of Cervical Cancer in Armenia, 1985-2005**




*Source: Ministry of Health of the Republic of Armenia*

In the framework of the Biennial Collaborative Agreement 2004-2005 between the Armenian Ministry of Health and the WHO Regional Office for Europe, a national strategy and programme on prevention of cervical cancer was developed. In March 2005, an orientation meeting was organized with participation of the WHO experts, during which a situational analysis on cervical cancer was presented, action plan developed, main principles of national guidelines elaborated, and a working group established.

## National program on diagnosis, treatment, and prevention of cervical cancer in Armenia, 2006-2015 (4)

The aim of the programme is to reduce morbidity and mortality due to cervical cancer, timely diagnose and effectively treat pre-cancer, and improve quality of life of women suffering from cancer. The national programme on control of cervical cancer includes the following main components:

- Primary prevention
- Early detection through increased awareness of women and correctly organized screening programmes
- Diagnosis and treatment
- Palliative care in untreated cases

Based on the results of discussions with all stakeholders in the area and due to the financial situation in the country, it was agreed that improved opportunistic screening of cervical cancer will be introduced in Armenia and will be the basis for organized screening in the future.

- In implementation of the national programme on cervical cancer in 2005, national guidelines, programme and training modules were developed, reviewed by WHO experts and approved. In 2006, the Government of Armenia approved provision of the state-supported free-of-charge prevention for cervical cancer as stipulated by the national guidelines.
- At present opportunistic screening of cervical cancer is recommended to all women aged 30-60, once in three years. A lot of activities are taking place to increase access to screening by providing women the opportunity to undergo screening in out-patient health care facilities at the place of residence and in mobile health care units that were involved in antenatal care, and are trained to provide cervical cancer screening in remote areas.
- In 2005, 2001 Bethesda classification for interpretation of cytological investigations and FIGO classification for cervical cancer were adopted in Armenia, and training of trainers among cytologists took place, involving specialists from Iceland. Strengthening or establishment of regional cytological laboratories took place all

# DIAGNOSES, TREATMENT AND 2006-2015

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over the country by improving the quality of screening for cervical cancer at all stages, including taking the smear, its fixation, transfer of slides to the laboratory and investigating and interpreting the results.

The Ministry of Health of Armenia is actively involved in provision of all outpatient medical facilities with necessary medical equipment to conduct cervical cancer screening and has approached international organizations to assist the country in this process. During 2005-2006, with the support from WHO experts, a team of national trainers was prepared to conduct training of health care providers. Cascade trainings of service providers have been completed throughout the country by the end of 2006. To ensure sustainability in capacity building efforts, the corresponding changes in the under- and post-graduate curriculum are carried out.

Awareness raising of the population on prevention of cervical cancer, the necessity of screening, access to health services, healthy life style, increased risk of cervical cancer among smoking women, safe sexual behavior, mutual monogamy, prevention of STIs are all important parts of the national programme on prevention and management of cervical cancer. However, at this stage much more needs to be done to involve community leaders, non-governmental organizations and health care professionals to forward the message to every inhabitant in Armenia.

## Monitoring

The suggested criteria for assessment and monitoring of effectiveness of the programme are:

- Percent of women screened
- Percent of women with pre-invasive and invasive cancer that have received treatment and follow-up assistance
- Percent of low quality, non-informative smears
- Percent of smears with false-negative results (through internal quality control)
- Percent of smears with false-positive results (through internal quality control)
- Correlation percent of cytological and histological investigations
- Verification percent of normal and pathologic smears at in- and inter-country levels

**Table 1 Programme Implementation Expected Results**

| Indicator | 2005 | 2010 | 2015 |
|---|---|---|---|
| Incidence rate | 13.8/100,000 | Decrease by 30% | Decrease by 50% |
| Mortality rate | 8.6/100,000 | Decrease by 25% | Decrease by 50% |
| Percent of patients who have not received treatment | 47% | Decrease by 50% | Decrease by 70% |
| Screening coverage percent | - | 50 % | 80% |
| Percent false- negatives | - | Decrease by 25% compared to 2006 | Decrease by 60% |

*Data collection and analysis is implemented through the oncology registry system established on the basis of the National Oncology Centre.*

We hope that the implementation of the national programme on diagnosis, treatment, and prevention of cervical cancer in Armenia, 2006-2015 will prove that cervical cancer can be prevented, diagnosed early and treated well and should not be the cause of mortality of women in the 21st century (see table 1).

## Challenges

In the process of the programme implementation certain barriers and problems were observed:

- In particular, the finances provided by the government for the Pap smear investigations are still very small.
- Women's involvement and their motivation in taking care of their own health remains low.
- The quality of the evaluation of Pap smears in some laboratories requires control and improvement.
- The investigation of Pap smears in some laboratories is too long.
- The knowledge and understanding of the cervical cancer prevention programme is not sufficient (in community as well as among health care providers)
- Insufficient involvement of mass media (radio, TV, press) in reaching the goals of the national program on diagnosis, treatment and prevention of cervical cancer in Armenia.
- The reimbursement of the services related to cervical cancer prevention at the primary health care level remains insufficient.

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# CERVICAL CANCER SCREENING IS EFFECTIVE

*– the Finnish experience*

**Screening for cervical cancer can be highly effective. The working group for the International Agency for Research on Cancer, IARC, has concluded that well-organised screening prevents more than 80% of the deaths and incident cases of the disease. The scope of this article is to discuss the currently available information on screening impact, how the screening programme has been organised, and also to discuss the new technological alternatives that are emerging in cervical cancer control in Finland – a country with one the largest population-based screening impact.**

## Effect of organised screening

In Finland (population 5 million), the organised screening programme for cervical cancer was launched in the early 1960s, and the programme became nationwide and with a high coverage within the targeted age groups in the early 1970s. When compared to the rates in the time before screening, the age-adjusted incidence and mortality rates have decreased, historically, with 75%-85% (Figure 1). Currently the age-standardised incidence rate is about 4.0 /100,000 woman-years and the death rate is 1.0 /100,000 woman-years.

There are currently about 160 incident cases annually, and 60 deaths from the disease. Based on estimation of historical trends and population data, it has been estimated that currently nearly 300 deaths are prevented each year, due to cervical cancer screening. There is some increase in the rates among women in ages 25 to 39, even though based on small numbers of cases (Figure 2). Noteworthy, death rates from the disease among women below 50 of age are very low.

The decrease in the disease rates has been largely obtained thanks to the screening programme. Follow-up studies among women invited to screening have confirmed that the decrease in the cervical cancer risk only took place among those women who participated. The incidence and death rates from the disease are continuously very low among the ones who participated. There are nowadays also other smears than those used strictly in the programme, but effectiveness from them is apparently not as good as that of the organised programme. In total about 98% of women in the whole target population is estimated to have given at least one smear ever in their lifetime.

In addition to follow-up studies on screened and not-screened women, there is nowadays a systematic audit system in the screening programme. Screening records are regularly linked with cancer registry data, and in case of invasive cervical cancers diagnosed after a negative screen, those screening samples, together with a couple of control samples, are subjected to systematic re-readings. This is a cost-effective tool to locate and correct for potential errors and diagnostic challenges. The re-reading programme is nowadays recommended e.g. in the quality assurance guidelines of the European Union.

## How screening takes place

Women between the age 30 to 60 years are invited to the cervical cancer screening programme with a five-year interval, with the help of a population registry. Some municipalities start screening at age 25. Screening is free of charge for the women; the costs are covered from the primary health care budget maintained by the municipalities. Trained nurses or midwives usually take samples at the health-care centres or other primary health care clinics.

There are about 15 cytological screening laboratories contracted by the municipalities in the programme all over the country (in July 2006 it was estimated that Finland had a population of 5,231,372. Women are informed of the result by letter from the laboratories – even in cases with negative results. About 72% of the invited women attend and about 1% of them are referred to colposcopy or other further examination. There are about 200,000 screenings in the programme each year. Pre-cancerous lesions are diagnosed and treated in about 0.3-0.5% of the screened, depending upon the region. About 7% are re-tested within a year if there is a borderline cytological finding.

In addition to the high quality in the screening service, high compliance and systematic follow-up among those who need follow-up or treatment is characteristic for the Finnish programme. There are practically no dropouts, when a referral for confirmation has been made. This can be controlled well using the screening registration systems.

## Challenges in screening

Well-organised screening programmes have been proved effective. However, there is wide variation in screening practices over countries. Mainly the rich

Ahti Antilla

countries, also Finland, have wide 'opportunistic' overuse of the services, whereas a proportion of the target population remains actually unscreened. Limitations in the coverage of screening connect to suboptimal effectiveness. Meanwhile, there are countries, e.g., among the new European Union members or accession states that have much lower resources in health care and that are with very high disease rates with very little, if any, change in the cervical cancer rates. Those countries are in the need of cancer prevention. The question is how equity can be obtained among women in the whole Europe?

Organisation and access of screening needs to be improved throughout Europe. This is important, because well-organised screening is cost-effective. In addition to the conventional cytological screening, evidence on new test methods is also emerging. Even though the conventional cytological test can work well, alternative methods such as human papillomavirus (HPV) tests can introduce a higher sensitivity to recognise pre-cancerous changes. Performance of HPV tests can be good in areas, where conventional test quality is a problem. Subsequently cancer rates after HPV screening are not yet known, but first follow-up studies on severe precancerous lesions or a worse outcome (CIN3+) will become available soon, and they seem to be promising.

In Finland, currently about 10% of the screening tests in the programme are primary HPV tests. HPV screening has been integrated using an individually randomised evaluation design. The first results have shown that the HPV test is highly sensitive. On the other hand, the HPV test recognises more such mild precancerous lesions that could regress naturally, even without their diagnosis and treatment. To overcome this potential adverse aspect, with HPV-testing we need to reduce the number of screenings during lifetime. To avoid unnecessary actions and increased costs, possibly to 3 or 4 invitations would be required. It remains to be seen in the on-going quite long-lasting follow-up studies how valid the HPV

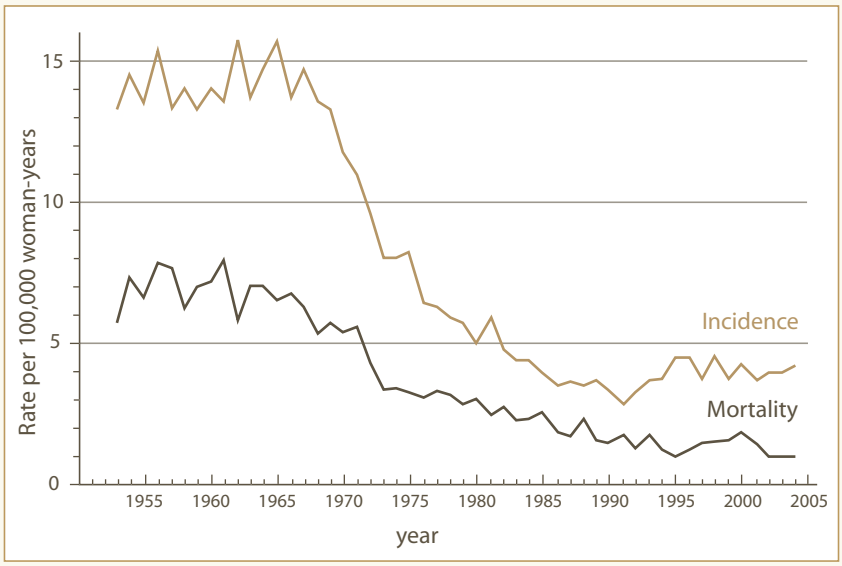


**Figure 1. Incidence and mortality rates of cervical cancer in Finland in 1953-2004, adjusted for age to the World standard population (Finnish Cancer Registry).**

screening programme can be and how many tests are required.

Also attendance in screening has been quite low among young targeted age groups (25 to 35 years of age). Increasing the participation is a continuous challenge.

## Effectiveness of HPV vaccines unresolved

The first results of efficacy of preventive L1 VLP HPV vaccines have been excellent. The vaccines have prevented almost 100% of type-specific persistent HPV infections and related type-specific CIN2+ lesions among HPV-naïves. Efficacy was reported among those who were negative for HPV 16 and 18 types based on DNA or serological test. The vaccine was provided to 16-26 year olds, and the development of pre-cancers was monitored through visits with 6-month intervals.

Because acquisition of new HPV infections, as well as the natural history of HPV and cervical lesions differ by age, effectiveness of the prophylactic vaccines is likely to differ among girls or women vaccinated in different ages. The US Food and Drug Agency administrative report estimated that the effect among all vaccinated in the above studies, including also HPV positives, on type-specific CIN2+ lesions was 40%. There was no material impact among those who were HPV type positive at vaccination.

It is important to evaluate effectiveness of the HPV vaccines when administered to girls, possibly also boys, in an age before the sexual debut. It is not known explicitly, which would be the optimal age to give the vaccine; and whether the males also need to be vaccinated. Currently, also in Finland, there are rather large-scale evaluation studies on-going, aiming to demonstrate within 5-10 years' time the population-based vaccine efficacy against CIN3+ or comparable lesions. The National Public Health Institute, that evaluates vaccination programmes and other such programmes on the sexual health among adolescents, will soon start cost-effectiveness evaluations for the prophylactic HPV vaccines.

## Scenarios on cervical cancer prevention

When evaluation of new technologies for cervical cancer prevention was planned about ten years ago, there were just two or three candidates available and additionally few candidates in a very intensive developmental phase. Since then, availability of new methods has increased sharply. An intensive bio-medical development

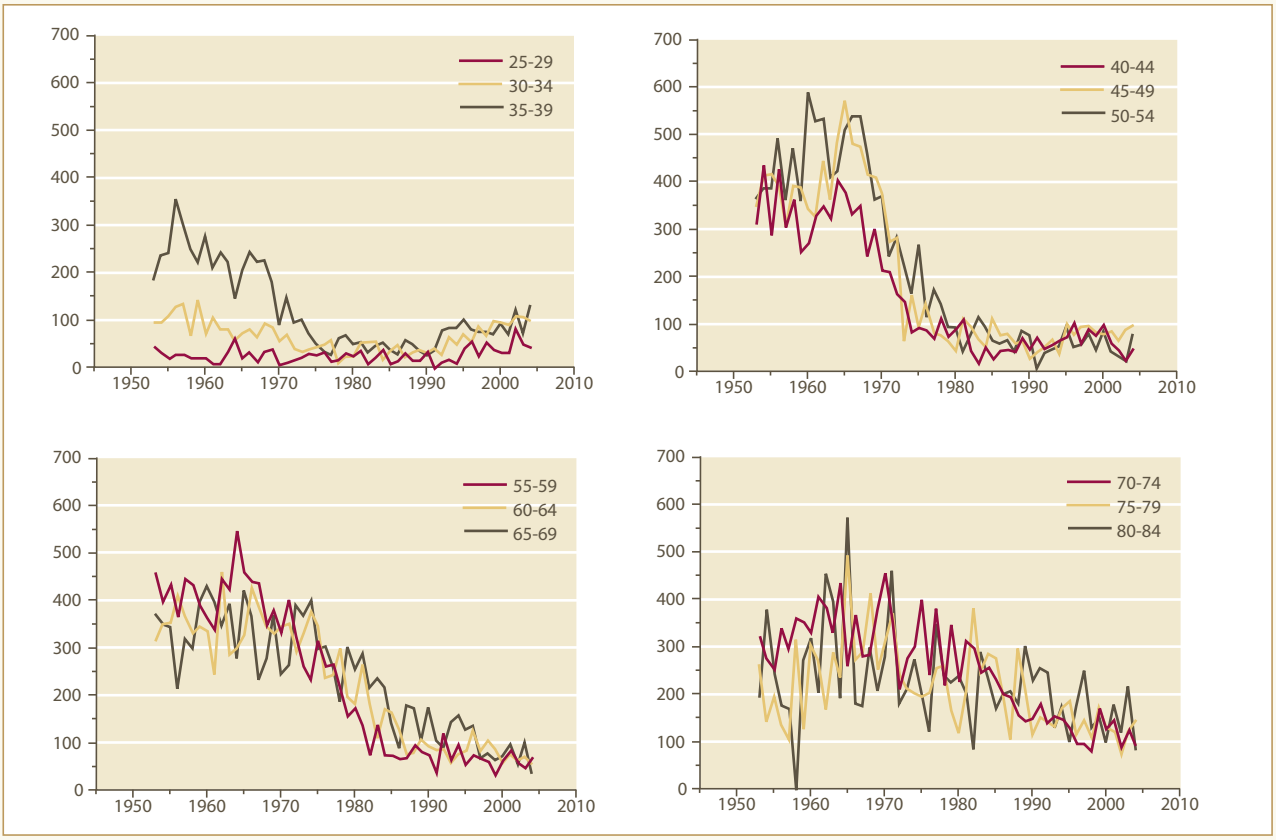


**Figure 2. Age-specific incidence rates of cervical cancer in Finland during 1953 to 2004 (Finnish Cancer Registry)**

continues. When looking, e.g., at 10 or 20 years' perspective in the future, the prospects look very good to combat cervical cancers with more and more sophisticated diagnostic markers and related therapeutic and other preventive options.

Even though conventional screening for cervical cancer has been effective, it is reasonable to conclude that new methods can add to cancer prevention. However, for any option, the additional benefit in preventing cervical cancers in comparison with other techniques is quite small. Cost-effectiveness and quality of life issues may give another picture; therefore, comparisons on theoretical and local cost-effectiveness are essential.

In a country without an established organised screening programme, one can immediately prevent more cancers by introducing an organised screening programme with three or four cytology or HPV tests, compared to shots of preventive vaccines. Vaccines will not substitute the need of organising screening. But one may decrease need of screening and treatments in the very long term, if introducing a vaccine, as well as affect other HPV-induced diseases.

The main aim for introducing any of the new methods discussed here should be to combat cervical cancers. Therefore, any method should be investigated in an independent fashion from the commercial interests. Prevention must be introduced in an organised manner where the need is large.

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# QUESTIONS AND ANSWERS

*Common questions related to prevention of cervical cancer and the HPV vaccine*

**Gunta Lazdane**

## 1. How much will the vaccination cost?

Although the vaccine is not yet widely available, where it has been licensed the current price of the vaccine is over 100 US$ per dose (with three doses required to achieve full protection). Manufacturers have declared their willingness to tier prices for countries of different economic settings. The price at which the vaccine is available is almost certainly going to be a major determinant of the cost and affordability of any vaccine programme.

Administration costs are likely to vary by country and region. Very few countries have universal programmes for delivering healthcare to pre-adolescents and adolescents. Discussions are under way to obtain access to international financing mechanisms (e.g. through the Global Alliance for Vaccines and Immunization), which could potentially subsidize the vaccine for low-resource settings until mature, affordable prices are achieved.

## 2. What about cervical cancer screening in the countries where HPV vaccine is available?

It is very important to ensure that comprehensive cervical cancer screening, diagnosis and treatment are available to respond to health-care needs of older women. Women and girls given HPV vaccine will need to be screened at the time recommended by the national cervical screening programme, i.e. generally some 10-15 years later for women vaccinated in early adolescence. Likewise, women considered too old for vaccination, or who are likely to have already been exposed to HPV, should be screened accordingly to national guidelines.

## 3. Should we diagnose HPV infection through cytology or is it enough to do the HVP screening?

Most probably the author of the question meant, whether it is necessary to perform cervical cancer screening using cytology or it is enough to do HPV DNA-based screening. Based on the available evidence cytology (conventional Pap smear or liquid-based cytology) is recommended for large-scale cervical cancer screening programmes, if sufficient resources exist. HPV DNA tests as primary screening methods, at this time, are recommended for use only in pilot projects or other closely monitored settings. They can be used in conjunction with cytological or other screening testes, where sufficient resources exist. HPV DNA-based screening should not begin before 30 years of age.

## 4. What is the effectiveness of the HVP vaccine? - Lifelong? Limited?

Data on longevity of immune response have been published up to 54 months for the bivalent (HPV 16, 18) vaccine and 60 months for the quadrivalent (HPV 6, 11, 16, 18) vaccine. Notably, it is not yet known, whether or not seropositivity correlates with clinical protection. Early results from a study in which vaccinated women were given a fourth dose of the quadrivalent vaccine five years after enrolment, suggest that immune memory is induced by HPV vaccine. Protection against persistent infection or a combined endpoint of persistent infection and all genital diseases has been demonstrated for up to five years post –enrolment. This is the longest reported follow-up so far. Further studies are planned to evaluate more fully the duration of protection.

## 5. What about boys?

Potentially, both vaccines could provide direct benefit by preventing HPV16, 18 – related anogenital cancers. Although vaccinating males could theoretically reduce transmission of HPV to females, preliminary results of modelling studies in Finland suggest that, in settings with high vaccination coverage of the female population, the additional benefit in terms of cervical cancer reduction – over and above that resulting from vaccinating women alone – is marginal. However, modelling studies of the benefit of male vaccination where vaccination rates are moderate are still continuing.

## 6. Only vaccinate before sexual debut, or also after? Untill which age?

In defining the target population for immunization, a key consideration is that HPV infection is sexually transmitted and is usually acquired within the first few years following sexual debut. Ideally, therefore, the vaccine should be administrated before sexual debut, i.e. before any risk of exposure to HPV.

The HPV vaccines are licensed for use in girls and women aged 9-26 years. Vaccination has been shown to result in high seroconversion rates in all age groups studied, but bridging immunogenicity studies for both vaccines (Merck – Gardasil and Glaxo Smith Kline – Cervarix) have demonstrated higher immunogenicity in young adolescents than in women over 15 years. The target age range will be specified in national licensing standards.

Trials are also under way to evaluate the effects of vaccine administration to women older than 25 years, and those who have, or have previously had, infection with HPV 16 or 18.

## Relevant reports and articles


**Bosch, F.X, Cuzick, J., Schiller, J.T. Garnett, G.P., Meheus A., Franco, Wright, T.C. (Eds.) HPV Vaccines and Screening in the Prevention of Cervical Cancer, Vaccine, Volume 24, Supplement 3, August 2006. (www.elsevier.com/locate/vaccine)**

This recent issue of 'Vaccine' comprehensively covers the issue of prevention of cervical cancer. It deals with the topic in seven sections respectively: (I) HPV as a major public health issue, (II) Screening for cervical cancer: what has been achieved and what can be achieved, (III) Prophylactic HPV vaccines, (IV) Integrating HPV vaccines and screening, (V) Public health aspects of HPV vaccine introduction, (VI) Research needs and opportunities in HPV-based vaccination and prevention and (VII) Summary.

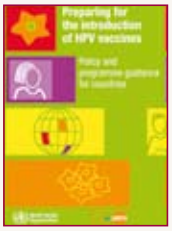
**Anttila, A. et al. Cervical cancer screening programmes and policies in 18 European countries British Journal of Cancer (2004) Published online 27 July 2004.**

A questionnaire survey was conducted by the Epidemiology Working Group of the European Cervical Cancer Screening Network, and the International Agency for Research on Cancer, IARC, between August and December 2003 in 35 centres in 20 European countries with reliable cervical cancer incidence and/or mortality data in databanks held at IARC and WHO. The results of this survey can be read in this article. 28 centres from 20 countries completed the questionnaire. The final tables included information on 25 centres from 18 countries.

## Recent WHO documents and publications


**Comprehensive Cervical Cancer Control: A guide to essential practice, Geneva, World Health Organization, 2006.**

The Guide is intended to help those responsible for providing services aimed at reducing the burden posed by cervical cancer for women, communities and health systems. It focuses on the knowledge and skills needed by health care providers, at different levels of care in order to offer quality services for prevention, screening, treatment and palliation of cervical cancer. The Guide presents guidelines and up-to-date, evidence-based recommendations covering the full continuum of care. The guide can be downloaded at: http://www.who.int/reproductive-health/publications/cervical_cancer_gep/index.htm




**Preparing for the introduction of HPV vaccines: Policy and programme guidance for countries, World Health Organization and United Nation Population Fund, Geneva, 2006.**

This guidance note is based on a UNFPA/WHO Technical Consultation on HPV Vaccine and Sexual and Reproductive Health Programmes held in March. It is intended to alert a broad array of stakeholders – in sexual and reproductive health, immunization, child and adolescent health, and cancer control programmes – to some of the key issues surrounding the upcoming introduction of HPV vaccines against cervical caner. The paper is available at: http://www.who.int/reproductive-health/publications/hpvvaccines/

**Human Papillomavirus and HPV vaccine: Key information for policy makers, Geneva, World Health Organization, in print.**

This document aims to provide health professionals with key information on HPV, HPV-related diseases and HPV vaccines, and to underpin the guidance recently published by WHO and UNFPA.


**Gaining health. The European Strategy for the Prevention and Control of Noncommunicable Diseases, 2006.**

Investing in prevention and improved control of noncommunicable diseases would improve the quality of life and well-being of people and societies. No less than 86% of deaths and 77% of the disease burden in the WHO European Region are caused by this broad group of disorders, which are linked by common risk factors, underlying determinants and opportunities for intervention. A more equitable share of the benefits from effective interventions would make the greatest impact as well as bring significant health and eco-

nomic gain to all Member States. This action-oriented strategy, adopted by the WHO Regional Committee for Europe in September 2006, promotes a comprehensive and integrated approach to tackling diseases in the European Region. The strategy is available at: http://www.euro.who.int/InformationSources/Publications/Catalogue/20061003_1

## Relevant websites

The U.S National Library of Medicine and the National Institutes of Health have set up Medline Plus, which among other things contains an online medical encyclopaedia. The section on cervical cancer contains relevant information regarding cervical cancer and in particular has some excellent illustrations explaining different cervical cancer related issues. You can access this part of the encyclopaedia on the following website: http://www.nlm.nih.gov/medlineplus/ency/article/000893.htm

The website of the European Cervical Cancer Association is an extremely useful site to visit for anyone interested in the Cervical Cancer situation in Europe. Also for clients this is a useful website, as it contains advice related to the frequency of screening, screening methods etc. For more information please visit: http://www.ecca.info/webECCA/en/

This WHO website 'Cancers of the reproductive system' provides you with the latest relevant WHO publications within this field. For more information please visit: http://www.who.int/reproductive-health/pages_resources/listing_cancer.en.html

## Upcoming events


### International workshop on human papillomaviruses and consensus recommendations for cervical cancer prevention & coloscopy training, April 18-21, 2007, Hotel Croatia, Dubrovnik-Cavtat, Croatia.

The aim of this workshop is to bring together the leading experts in all areas of cervical cancer prevention to present the latest research findings on cervical cancer screening, HPV testing and HPV vaccination, to discuss how these results will impact on cervical cancer prevention practices and to develop consensus recommendations for implementation of these new technologies within the context of the organised cervical cancer screening programmes that have been called for by the Council of the European Union. For more information please visit: http://www.irb.hr/hpvccp/



### "Strengthening cervical cancer prevention in Europe", 29-31 May 2007

WHO European Regional meeting of policy makers and programme managers will take place 29-31 May, 2007 in Copenhagen where representatives of all 53 Member States as well as international partners will be invited. General objective of the meeting is to assist countries in strengthening informed decision-making on prevention of cervical cancer. It is planned to present and discuss the recent WHO strategies and publications relating to prevention and management of cervical cancer and introduction of HPV vaccines in countries and to assist the Member States in development their national policies and programmes in introduction of HPV vaccines within the broader context of cancer control and reproductive health.

### 7th Congress of the European Society of Gynecology, 10th October 2007, Paris, France

One of the topics included in the programme of the Congress is "Cervical Cancer in Europe: screening controversies. Anti HPV vaccination". More information: http://www.seg-web.org/congseg/

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*The European Magazine for Sexual and Reproductive Health*

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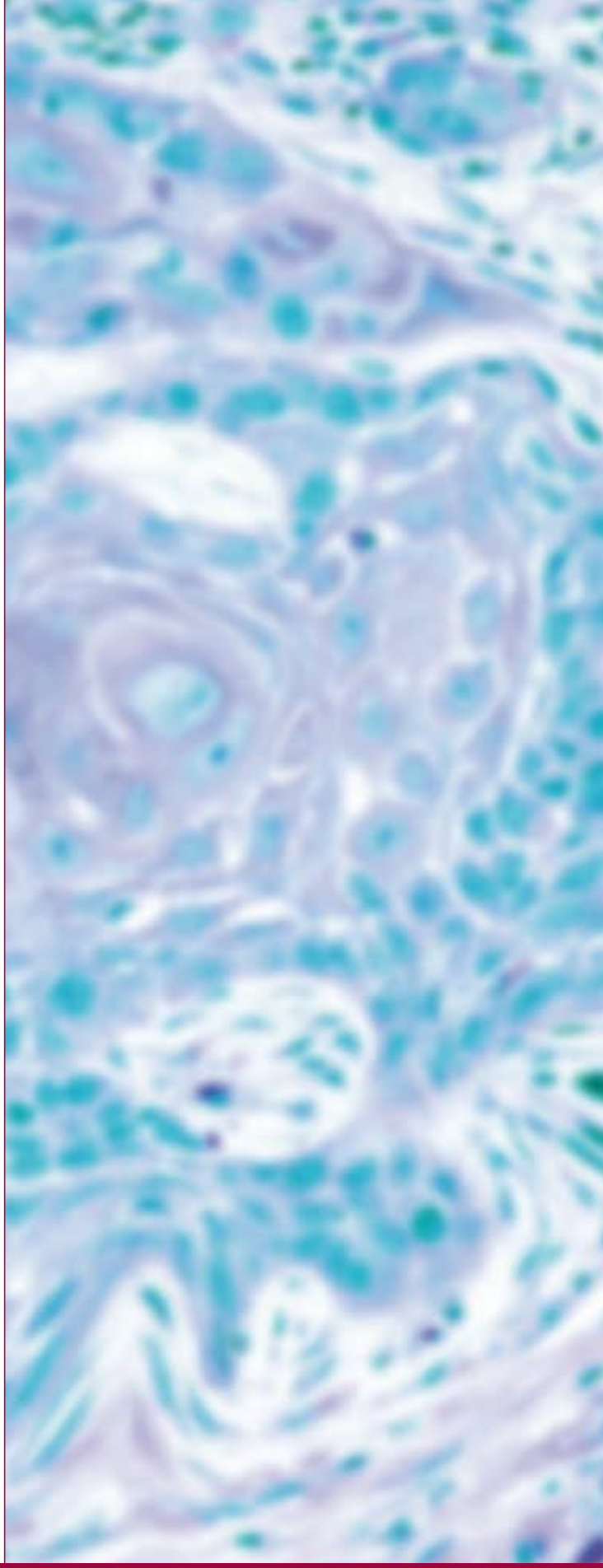

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