Executive Summary:

Cervical cancer still constitutes an important health problem in European countries although screening programs have significantly reduced cervical cancer incidence and mortality. The aetiological link between HPV and cervical cancer has prompted the development of vaccines and of new screening tests. These new developments have led to the need to determine prerequisites and strategies for HPV vaccination in European countries, to predict the impact of vaccination on screening programmes, and to evaluate the impact of novel screening methods. These are the main goals of the PREHDICT consortium which stands for “health-economic modelling of prevention strategies for HPV-related diseases in European countries”, 
a collaborative research initiative of epidemiologists, modellers, biologists, and medical professionals from eight European countries.

The PREHDICT consortium recognized that the variation across European countries in cervical cancer control strategies underlines the need for objective data-supported criteria for future cancer prevention. To derive such criteria, PREHDICT participants have created a large evidence base on HPV-related disease by systematically collecting, updating, and summarizing data on incidence of HPV infections and disease, effectiveness of vaccination, performance of novel screening methods, screening practice, life style, and demographics. This effort includes an EU-wide survey on cost, organization, and quality control of European screening and vaccination programmes. The results of the survey will be used to strengthen guidelines by highlighting strengths and weaknesses of existing prevention efforts. An important research highlight stemming from the data gathering in PREHDICT is a pooled analysis of four European randomized controlled screening trials. The pooled data base enabled the PREHDICT participants to directly estimate the gain in efficacy in preventing invasive cervical cancer by HPV-based screening instead of cytology-based screening.

The data were used to model HPV transmission dynamics by three different research groups. On the basis of their models, the impact of vaccinating adolescent girls on the spread of HPV in the population was assessed as well as the additional impact of vaccinating boys. Furthermore, cost-effectiveness analyses were carried out using both simple and more complex individual-based Markov models. An important finding was that HPV16/18 vaccination of 12-year-old girls was calculated to be very cost-effective in 18 Central and Eastern European countries, where prevention against cervical cancer is scarce and the disease burden is high.

The results of PREHDICT will be disseminated to the general public and to major stakeholders, in particular to decision makers at European, national, and sub-national level. More information about the PREHDICT consortium is available at the World Health Organisation hosted website (www.hpvcentre.net/prehdict) through press information via the network of the European Cervical Cancer Association (www.ecca.info) or by contacting PREHDICT at prehdictmanagement@gmail.com.

Project Context and Objectives:

Cervical cancer is still an important health problem in the European Union (EU) with about 60,000 new cases per year and 30,000 new deaths per year. Cervical cancer screening programmes have been implemented in several European countries and those countries have witnessed a substantial reduction in the occurrence of cervical cancer in the last decades. However, there is a large variation with regard to screening program policies – including screening intensity (screening ages and intervals), invitation method (opportunistic or population-based) and screening financing. Currently, all screening programs are cytology-based, using the PAP smear for the evaluation of morphological abnormalities as indication of (pre-)cancerous lesions. To summarize, cervical cancer remains a common disease in the EU and prevention must be improved.

Cervical cancer is caused by a persistent infection of the human papillomavirus (HPV). There are at least fourteen HPV types that may lead to cancer and these are termed high-risk types (hrHPV). HPV types 16
and 18 are responsible for the majority of cervical cancers. However, hrHPV types are not only implicated in cervical cancers but also in penile cancer in men, vaginal and vulvar cancer in women and in oropharyngeal, laryngeal and anal cancer in both men and women. Low-risk HPV types are rarely found in cancers, but do cause other disease such as genital warts (HPV6/11). The aetiological link between HPV and cervical cancer has prompted the development of vaccines. Currently, two prophylactic vaccines have received registration from the European Medicines Agency (EMEA). In large randomized trials, the vaccines have been shown to be nearly 100% effective against HPV16 and/or HPV18 positive cervical intraepithelial neoplasia grades 2 and 3 (CIN2/3), which are the major cervical cancer precursor lesions. HPV prophylactic vaccines are universally approved for females up to 26 years of age [EMEA; FDA]. However, inclusion into national HPV immunization programs has mostly been restricted to (pre-)adolescent girls, because HPV vaccine trials have demonstrated greatest immunogenicity and efficacy in preventing vaccine-type infections among those without evidence of prior exposure at the time of vaccination. The aetiological link between HPV and cervical cancer has furthermore prompted the development of new screening tests. HPV-based screening is more sensitive than cytology-based screening – indicating that the proportion of women with cervical (pre-)cancerous lesions who test positive is higher with HPV-based screening than with cytology-based screening. However, the test is less specific – resulting in a larger proportion of women testing positive in the absence of disease. HPV-based screening may therefore lead to an increase in the number of women referred for gynaecological examination and the number of detected low-grade lesions. Therefore, implementation of HPV DNA testing in the screening programme requires careful weighing of the expected costs and benefits. In addition to the HPV DNA test, several other tests have been developed to compensate for the imperfections of cytology. Some of the tests examine viral characteristics and include HPV genotyping, HPV RNA testing, and viral load testing. Other tests look for protein activity (e.g. p16) or host cell changes (methylation, chromosomal aberrations). Any of those tests may conceivably be included in a protocol either as a primary screening test or as a triage test for further evaluating samples positive by primary screening tests. Operational issues, most importantly imperfect screening compliance, are important determinants of the successfulness of screening programmes. Some women are not reached by screening and the percentage of women with cervical cancer that have never received a cervical smear is substantial. Attitude studies have shown that non-responders tend to have a negative view on screening. Response rates may improve when non-responders are invited for participation using self-sampling. Finally, HPV vaccination is expected to decrease the incidence of cervical cancer substantially. Because vaccination only targets two hrHPV types (HPV16/18), screening is likely to be necessary also after implementation of vaccination. However, the optimal screening methods are likely to change in a population of HPV16/18-vaccinated women where abnormalities are rare. This may affect the quality of cytological evaluations and leads to a different trade-off between screening efforts and benefits. Coherent prevention strategies that optimally exploit both vaccination and screening need to be developed.

The acronym PREHDICT stands for “Modelling of prevention strategies for HPV-related diseases in European countries” and it is a collaborative research initiative of epidemiologists, modellers, biologists, and medical professionals from eight European countries. The goal of the PREHDICT consortium is to determine prerequisites and strategies for HPV vaccination and cervical screening in European countries, to predict the impact of vaccination on screening programmes, and to evaluate novel screening methods. The consortium has carried out epidemiological analyses, mathematical modelling studies, and a questionnaire survey to evaluate prevention strategies. To carry out the epidemiological and mathematical
analyses, the consortium has built a large database on HPV infections and disease as well as a database of longitudinal screening studies.

Project Results:

MAIN RESULTS

This Section presents the results of the PREHDICT study. We start with a brief description of some key results which are of interest to a wide audience.

MAIN RESULTS

Data collection

The PREHDICT consortium has created two large databases. The first database is an epidemiological database on HPV infection, HPV-associated diseases, life style factors and cancer prevention strategies. This database is built from national registry data, literature searches, and websites. The second database is a pooled database of 3 population-based screening studies (NTCC Italy, POBASCAM The Netherlands, and Swedescreen Sweden). The screening database contains information on cytology, HPV DNA, and histology of women in population-based screening. The database has been extended with cancer incidence data from the ARTISTIC trial (UK). The database contains about 175,000 women. The PREHDICT consortium has also systematically collected information on the organization, quality control, and costs of vaccination and screening programmes via a Europe-wide survey.

Epidemiological analyses

The databases have been used in the project to carry out epidemiological analyses. An important result that could be provided by the pooled screening database is that HPV screening provides greater protection against invasive cervical cancer than cytology. The analysis endorses an HPV-based screening strategy with 5 year screening intervals instead of cytology screening with 3 year intervals. In earlier European studies, the efficacy on HPV-based screening on cancer could not be shown because a very large cohort is required. The joint effort of researchers from different European countries has led to this result which likely speeds up the implementation of HPV-based screening in Europe.

In addition to the joined database analyses, systematic reviews, Cochrane reviews and meta-analyses have been carried out, mainly on HPV screening related outcomes. The meta-analyses included evaluations of the accuracy of HPV tests and biomarkers in different clinical applications (screening, triage of screen-positive women, surveillance after treatment), and adverse effects associated with treatment of cervical cancer. One meta-analysis examined the accuracy of HPV testing on self-collected samples. HPV self-sampling is a promising new technique that may lower the screening barrier for screening non-attenders and be suitable in regions where the organization via smears collected by physicians is not feasible. The meta-analysis showed that HPV testing on self-collected samples was at least as good as cytology on a physician-collected sample. More research is required in this field as HPV self-sampling is likely to play an important role in future cervical screening.
Modelling

An important part of PREHDICT has been the development of mathematical models for the transmission of HPV between males and females. The models have enabled us to assess the impact of HPV vaccination programmes on the occurrence of HPV infections and disease. HPV transmission models were built for Italy, Sweden, and Finland. All models clearly indicated that both vaccinated and unvaccinated women benefit from a female HPV16/18 vaccination programme. Unvaccinated women benefit because vaccination lowers the HPV16/18 prevalence in the population and hence lowers the probability of becoming infected. This indirect preventive effect is known as herd immunity. The herd immunity effect was moderate in the three models. For instance, the Italian model indicated that if 65 percent of the girls are vaccinated, eventually 75 percent will be protected. The interpretation is that herd immunity lowers the disease burden but will not lead to eradication of HPV16/18 unless the vaccination coverage is very high. Herd immunity effects can be boosted by vaccinating boys. The Italian model indicated that additional vaccination of 65 percent of the boys will further increase the protection level among girls to 87 percent. To summarize, the models predicted substantial herd immunity effects which will guide further work on implementing HPV vaccination programmes with the eventual aim of eradicating major hrHPV types.

In addition to transmission modelling, disease models have been developed and cost-effectiveness analyses have been carried out. A main result is that at the current price paid for the vaccine in national immunization programmes, female HPV vaccination is cost-effective in all European countries, also in Eastern European countries with limited resources. Vaccination, however, does not make screening superfluous because the vaccines are designed to protect against 2 of the 14 oncogenic HPV types. Cost-effectiveness analyses indicated that female HPV vaccination combined with HPV-based screening is cost-effective in both Western (The Netherlands) and Central Europe (Slovenia, Poland). The available vaccines also provide some cross-protection against other HPV types. If the reported cross-protection is taken into account, HPV-based screening in vaccinated women remains cost-effective although an extension of the screening interval is recommendable from a cost-effectiveness and screening burden perspective.

RESULTS PER WORK PACKAGE

In the following, a detailed account of the PREHDICT results is given. The results will be presented for the different work packages separately:

Within PREHDICT the following work packages (WP) were assigned:

WP1: Project Management
WP2: Epidemiological data on HPV infection, HPV-associated diseases, life style factors, and cancer prevention strategies
WP3: Parameter estimates from European screening trials
WP4: Organisation, quality, monitoring and evaluation
WP5: Meta-analytical pooling of data providing parameters for modelling
WP6: HPV transmission modelling
WP7: Health economics
WP8: Dissemination of knowledge

The workpackage leaders and how the different workpackages are related are depicted in figure Overview of Prehdict project (in annex).

In the section below, the main results of the different workpackages (WP2-8) are described.

WP2: Epidemiological data on HPV infection, HPV-associated diseases, life style factors, and cancer prevention strategies

Detailed data on the coverage and outcomes of cervical cancer screening and HPV vaccination programmes, as well as the epidemiology and natural history of HPV infection and HPV-associated diseases (cervical cancer, but also cancers of the anus, vulva, vagina, penis and oropharynx/larynx) are needed to guide research on public health economics. These topics have been extensively researched but the resulting data are scattered and heterogeneously formatted and presented. The PREHDICT team has gathered, compiled and published on-line updated data and statistics on the epidemiology of HPV infection, HPV-associated diseases, and other relevant cancer prevention and immunization indicators in the 43 countries included in the project. A European epidemiological database on HPV and a series of country specific and regional reports have been created. The database is publicly available at www.hpvcentre.net/summaryreport.php and consists of the following modules:

Module 1: HPV prevalence and genotype distribution in subjects with and without cancer-related lesions,
Module 2: HPV-related disease burden,
Module 3: Key additional risk factors and co-factors involved in HPV exposure and cervical carcinogenesis,
Module 4: Preventative strategies,
Module 5: Key socio-demographic indicators.

The following is a summary of the burden of HPV infections, HPV-related disease and preventive strategies in European countries.

Genital HPV infection is one of the most common sexually transmitted infections and is commonly found in the anogenital tract of men and women with and without clinical lesions. HPV cervical infection results in cervical lesions ranging from normalcy (cytologically normal women) to different stages of precancerous lesions and invasive cervical cancer. The prevalence of HPV infection increases with the severity of the lesion and is generally accepted that virtually 100% of cervical cancer cases are attributable to HPV infection.

In Europe about 10% of women with normal cytological findings are estimated to harbour detectable HPV infection at a given time. The highest prevalences of infection are observed in Croatia and Lithuania (with 36% and 24% of HPV infection respectively) and the lowest in Turkey and The Netherlands (with 1.5% and 3.9% of infection respectively). Even though, it should be noted that the majority of infections in young
women are self-limited and as a result, HPV prevalence picks in young women and declines in older ages.

HPV 16 is globally the most frequently detected type followed by HPV 18. In Europe, these two HPV types, which are preventable with current HPV vaccines, contribute to 75% of all cervical cancer cases. They are also detected in precancerous cervical lesions (54% of high-grade and 27% of low-grade cervical lesions) and account for 3.5% in women with normal cytological findings. After HPV16/18, the six most common HPV types in Europe, with specific rank order, are namely 33, 45, 31, 52, 35 and 58, although differences in HPV type distribution by lesion severity and cervical histology are observed.

Estimates indicate that every year 56,157 women from Europe are diagnosed with cervical cancer and 25,520 women die from the disease. Eastern Europe is the region showing the highest burden of cervical cancer (56% of new cervical cancer cases and 61% of deaths of cervical cancers). As such, cervical cancer remains as a major public health priority in Europe, ranking as the 7th most frequent cancer among women in Europe, and the 2nd most frequent cancer among women between 15 and 44 years of age in 2008. Cervical cancer also ranks as the 8th cause of female cancer deaths and the 2nd in women aged 15 to 44 years in Europe.

Figure 2.1 (annex) summarizes country specific data on cervical cancer burden showing incidence (the annual number of new cancer cases per 100,000 women) and mortality rates (the annual number of new cancer deaths per 100,000 women). The estimated mortality to incidence ratio in Europe is 37%, with the highest rates observed in Eastern Europe (42%). This suggests a better survival for cervical cancer in Western, Northern and Southern regions of Europe.

Cancers of the anus, vulva, vagina, and penis are much less frequent compared to cancer of the cervix. Data on the burden of these cancers in Europe is limited. Anal cancer incidence reaches 2.2 new cases per 100,000 women in Geneva (Switzerland), 3.5 new vulvar cancer cases per 100,000 women are observed in Malta, 0.9 new vaginal cancer cases per 100,000 women in La Martinique (France), and 1.4 new penile cancer cases per 100,000 men in Murcia (Spain).

The majority of head and neck cancers are associated with high tobacco and alcohol consumption but other etiological factors, such as HPV, are involved. Estimates indicate that every year 58,789 new cases of oral cavity cancer and 26,960 new cases of cancer of the pharynx (excluding nasopharynx) are diagnosed in Europe. Every year oral cavity cancer causes 23,035 deaths and pharynx (excluding nasopharynx) cancer causes 18,088 deaths in Europe. Higher incidence and mortality estimates are generally observed in countries from Western Europe, compared to other regions of Europe (incidence rates of 16.5 new oral cavity cancer cases and 15.2 new pharynx cancer cases per 100,000 men in Hungary).

HPV is also responsible for other benign genital infections such as recurrent juvenile respiratory papillomatosis and genital warts, both mainly caused by HPV types 6 and 11. However, data on their incidence and prevalence in Europe are sparse and not homogeneous within countries. Only 13 countries provide information about genital warts (most of them from the North of Europe) and even less information is available regarding recurrent respiratory papillomatosis, with only data in Denmark and Spain.
The association of HPV DNA with anogenital cancers other than cervical cancer has also been reported, but wide variations among countries are observed in Europe. Globally, in Europe, HPV may cause 80% of anal cancers, 32% of vulvar cancers; 53% of vaginal cancers, and 56% of penile cancers. HPV16 is the most common detected type in all these anogenital locations, but higher contributions are observed among anal and vaginal carcinomas (69% and 53% respectively) and lower contributions among vulvar and penile carcinomas (23% and 43% respectively).

There is also enough evidence for the carcinogenicity of HPV type 16 in the oral cavity, oropharynx (including tonsil cancer, base of tongue and lingual tonsil cancer and other oropharyngeal cancer sites), and limited evidence for laryngeal cancer (Anttila A. et al, 2009). Available information in Europe estimates that 13% of all oral cavity cancers carry HPV infection, 50% of cancers of the oropharynx and 24% of cancers of the hypopharynx. In all these cancer sites HPV16 is by far the most frequent type.

Well-organised cervical cancer screening programmes have significantly reduced cervical cancer incidence and mortality. The introduction of HPV vaccination could also effectively reduce the burden of cervical cancer in the coming decades. There are large variations in cervical cancer screening policies across European countries (refer also to WP6). Cytology is the recommended primary screening test with screening usually starting between 20 and 30 years of age and stopping at age 60 to 70. The screening test interval varies between 1 to 5 years in European countries. Screening was reported as population-based in Denmark, Estonia, Finland, France, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Romania, Slovenia, Spain, Sweden and United Kingdom and as non population-based in Austria, Belgium, Bulgaria, Czech Republic, France, Germany, Greece, Latvia, Lithuania, Luxembourg, Poland, Slovakia and Spain. Finally, no programmewas reported in Cyprus and Malta. Coverage of the screening test within the population-based programme ranges from 10% to 79% in European countries.

In January 2011, all European countries had HPV vaccine licensure. Liechtenstein and Montenegro had licensed the quadrivalent HPV6/11/16/18 vaccine and the Republic of Moldova the bivalent HPV16/18 vaccine, while the other European countries had licensed both vaccines. Twenty two of the countries (including Austria, Belgium, Denmark, France, Germany, Greece, Iceland, Ireland, Italy, Latvia, Luxembourg, Macedonia TFYR, Malta, Netherlands, Norway, Portugal, Romania, Slovenia, Spain, Sweden, Switzerland and United Kingdom) had implemented routine HPV vaccination programmes for adolescent girls, and 10 of them (Austria, Belgium, Denmark, France, Italy, Luxembourg, Netherlands, Portugal, Romania and United Kingdom) had also introduced catch-up programmes for young women.

In addition, male circumcision and the use of condoms have shown a significant protective effect against HPV transmission and may offer an alternative preventive strategy. In Europe male circumcision is not very usual and prevalence of condom use differs by country. The highest prevalences of condom use are observed in Greece (33.9%), Russian Federation (30.3%) and United Kingdom (27.0%)

WP3: Parameter estimates from European screening trials

The objective of WP3 was to obtain large-scale solid pan-European data for comparing the benefits and harms of using cytology or HPV testing for cervical cancer screening. To this end, data from large European randomized controlled trials comparing HPV testing to cytology for primary screening of cervical
cancer precursors were pooled. The PREHDICT team estimated natural history parameters to be used for modelling the impact of vaccination and screening policies. It was also estimated how much earlier HPV testing detected precancerous lesions than cytology and whether it led to overdiagnosis of spontaneously regressive lesions. Furthermore, biomarkers were evaluated that may increase the specificity of HPV-based screening. Finally, type-specific HPV prevalence and occurrence of pre-cancerous and cancerous lesions in women that do not comply with regular screening (i.e. non-responder women) were estimated. A major result was the direct estimate of the gain in efficacy in preventing invasive cervical cancers obtained by HPV testing instead of cytology-based screening and the duration of this additional protection.

Individual data from three randomised controlled trials (Swedescree, POBASCAM, NTCC) were obtained in standardized format and pooled. All randomised trials included examined women for at least two screening rounds. In addition a fourth randomised trial from UK (ARTISTIC) was added in the analysis on invasive cancers, thereby including all European randomised trials that examined women for at least two screening rounds. Overall the analysis included more than 175,000 women representing more than 1 million person-years observed. Given the small number on invasive cancers observed in each single study, the pooled dataset provided a much clearer picture than any previous report and allowed to directly estimate the reduction of invasive cervical cancer with HPV-based screening compared to cytology-based screening. The very large size of the combined analysis allowed to measure the duration of protection against cancer after a negative screening test result. The data also allowed evaluating of age-related efficacy of screening in the context of HPV-based screening.

An initial analysis of one of the included trials, suggested that HPV-based screening could result in increased diagnosis of spontaneously regressive precancerous lesions. However, preliminary analyses on extended follow-up data no longer supported over-diagnosis of spontaneously regressive precancerous lesions by HPV-based screening compared to cytology, even not in younger women. The demonstrated absence of over-diagnosis, is relevant for determining specificity of HPV-based screening and screening-initiation age. Moreover, additional preliminary data analyses showed that HPV testing allows detecting pre-cancerous lesions up to 6-7 years before cytology. In women over age 35 years the gain was 2-5 years for about half of precancerous lesions and this gain seems to be larger in younger women.

The hrHPV prevalence at baseline was calculated and was 4.8% and 5.0% among women in the Dutch and the Italian study respectively. Furthermore, the well-documented variation in age-specific HPV prevalence was confirmed, with a decreasing prevalence of HPV at increasing age. In the Italian study, which included different centres, the age profile was significantly different between centres. Also the HPV type mix was significantly different between centres. The HPV type distribution in women with multiple HPV types at baseline was as expected by chance suggesting no competition between HPV types. This observation is in line with the expectation that massive HPV vaccination is unlikely to result in HPV type replacement due to the elimination of two major HPV types. The most common types were HPV16, 31 18, 45 and 56. Prevalence of vaccine HPV types 16 and/or 18 was 2.1% in the Dutch study, and 2.4% in the Italian study.

In the Dutch study, women with normal screening-test results at baseline were retested after 5 years and the overall incidence of hrHPV among them was 2.6% and decreased with increasing age. The highest incidence was found among the youngest age-group (29-33 years) and the lowest among the oldest age-
group (54-58 years). In the Italian study, the overall incidence of hrHPV among women with normal screening-test results at baseline was 3.3%, decreasing with increasing age. The proportion of hrHPV positive HPV16/18 incident infections did not vary with age and was 36.1% in the Dutch study and 39.1% in the Italian study.

In collaboration with WP6, the age- and type-specific HPV prevalence at baseline was used to estimate some parameters of the natural history of infection, like force of infection, clearance and susceptibility to new infection after clearance. HPV incidence data from prior HPV-negative women were used for validation and their observed frequency was indeed very similar to that predicted by the model.

The PREHDICT team furthermore evaluated if the use of a biomarker, p16INK4A, would increase the specificity of HPV-based screening. p16INK4A is a protein involved in cell cycle control and the results confirmed previous findings that over-expression of p16INK4A reduced the number of HPV-positive women referred for further diagnostic evaluation without losing sensitivity for pre-cancerous lesions in the future. Moreover, p16INK4A was shown to be a good predictor of HPV-positive women most at risk to develop pre-cancerous lesions in the future. The risk of developing a newly detectable pre-cancer in HPV-positive p16-negative women was about 4 times lower than the risk in HPV-positive p16-positive women. The risk in HPV-positive p16-negative women was however higher than the risk in screen-normal women (HPV-negative and/or cytology-negative). Therefore HPV-positive p16-negative women do not need immediate referral for further diagnostic evaluation and can be managed by retesting after an interval longer than that for HPV-positive cytology-negative women (usually 1 year) but shorter than that routinely applied for women with normal cytology.

A different biomarker, based on the methylation status of promoter regions of two human genes (i.e. CADM1 and MAL) was also evaluated as a potential triage tool for HPV-positive women. This biomarker assay was equally discriminatory for CIN3 and cervical cancer as cytology or cytology with HPV16/18 genotyping in HPV-positive women. Moreover, methylation levels of these genes increased proportional to the severity and duration of CIN lesions and were highest in cervical cancer samples. Thus, high methylation levels seem to reflect the presence of advanced CIN lesions and cervical cancer.

Subsequent studies on screening non-attendees revealed that, unlike cytology, methylation marker analysis is also suitable for triage testing on self-collected cervico-vaginal lavage specimens of HPV-positive women. A biomarker panel specific for MAL and miR-124 yielded sensitivities for CIN3 or worse that exceeded that of HPV16/18 genotyping at assay thresholds giving rise to specificities of up to 70% in HPV-positive women. All cervical cancers were positive with this marker panel. Therefore, methylation analysis could be an attractive tool to distinguish HPV-positive women in need of therapeutic intervention, which is particularly useful for self-collected specimens or settings in which cytology is of poor quality or non-existing.

WP4: Organisation, quality, monitoring & evaluation

Screening programmes in Europe have reduced cervical cancer incidence and mortality but the level of success is variable between different countries. Organisation of programmes is essential for equity and cost-effectiveness, but there is variation in effectiveness also among organised programmes. Similarly,
The results of the PREHDICT survey on organization and quality control highlight the diversity of cervical cancer prevention strategies in European countries and associated costs. Designed to be in-line with the recommendations outlined in the 2nd edition of the European guidelines for quality assurance in cervical screening, the survey requested detailed information on each aspect of programme organization, quality assurance efforts, on-going monitoring and evaluation and corresponding line-item costs. Thereby it marks the first attempt to collect such in-depth information and provides a unique opportunity for comparing existing strategies in European countries. The comparison of results can help identify areas of programme implementation that need further attention and also areas of strength that can be used as examples of best practices. The following is a summary of the preliminary results of the survey.

The survey reiterated previous findings that the variation between countries with regard to screening programme policies – screening interval, screening ages, and financing – is significant. The screening interval ranged from 1 year (Czech Republic) to 5 years (e.g. Finland and Romania). Liechtenstein had the lowest recommended age to start screening (age 17) and Finland and Estonia the highest (age 30). The recommended age to stop screening ranged from 59 in Poland to 70 in Latvia. Countries reported that they receive funding through national or local government health care budgets. In the majority of countries, no co-payment is required on the part of the participating women. This is a positive finding as co-payments can limit access to screening among women with lower socio-economic status.

The management structure of screening programmes and the costs associated with running the offices of the programme differed across European countries. While the majority of countries had centralized screening offices and relied on a combination of national and local offices for implementation, a few programmes do not have centralized offices and only Poland was able to submit information regarding costs associated with the centralized screening office. For the other countries, costs for the office of the organized screening programme were included in budgets for general programme implementation or other country-level health authorities. Tracking the individual line-item costs of the organized screening programme is challenging given that screening programmes often make use of existing structures and overlap with other health initiatives.

When asked whether there was a screening quality control programme in place, the majority of responding countries reported that they had a system for quality control (QC) activities and that these efforts were carried out both at the national and the local levels. Data quality forms a critical aspect of the QC programme without which accurate comparisons between groups and over time cannot be made and programme reach cannot be effectively calculated. Countries were surveyed about indicators extracted from Parkin and Bray’s work on comparability, completeness, validity and timeliness and represent key factors in evaluating the quality of screening data (Bray & Parkin, 2009; Larsen et al, 2009; Parkin et al, 2009). While the majority of countries were able to evaluate these indicators, they did so to varying degrees and a minority of countries were not able to track quality of screening data. In general, countries could not split the costs by the line-items. Instead, they submitted general comments regarding the costs
of quality control. On-going monitoring and surveillance efforts at the local and national levels seem to be closely linked with the overall operational budget of the screening program, making the estimation of individual costs difficult. Costs for quality control within the overall screening programme are recommended to be a clearly defined proportion of the overall operating budget, allowing for clear prioritization of these activities.

Through monitoring the profile of cytological and histological test results, programmes can track disease burden in the population and compare across reporting periods and regions to check for possible differences in registration and quality of programme implementation. Costs associated with on-going monitoring of screening programmes include personnel (data management and analysis, IT), data infrastructure and reporting systems, and the costs associated with disseminating the results of monitoring efforts. Screening registries form a critical part of on-going monitoring and evaluation; therefore, the PREHDICT survey put a special focus on issues related to establishing and maintaining screening registries. The majority of countries who reported having a mass-screening registry in place were able to track key monitoring indicators, although the scope of the indicators included in the monitoring efforts varied. Detailed costing information on establishment and maintenance of screening registries was challenging to collect due to, in part, the inter-connectedness of programmes. It is evident that for programmes that have existed longer, fuller integration into the healthcare budget has been achieved compared to newer programmes that must seek funding from other sources or must account for purchasing IT systems for screening information.

With increasing evidence of greater prevention gains with HPV DNA testing, programmes are increasingly moving to incorporate HPV testing. Quality control of HPV testing in screening programmes is crucial to realizing these potential gains. According to the PREHDICT survey, the use of HPV DNA testing in cervical cancer prevention programmes differs across EU and EFTA countries – a minority of programmes have begun to implement primary HPV screening alone while the majority of programmes still rely solely on cytology in primary screening. Of those countries that use HPV testing, the majority use it for triaging cytological abnormalities. Through the WHO HPV LabNet work on quality control of HPV testing, 137 laboratories participated in a global proficiency panel for HPV genotyping. Only about 25% of labs were proficient, demonstrating the need for quality measures in HPV testing.

In estimating the annual costs associated with maintaining proficient HPV testing, materials, auditing, and documentation efforts must be accounted for. In the PREHDICT experience reviewing information regarding screening programme budgets in different EU and EFTA countries, funding for quality assurance and maintenance of the programme is often not specifically earmarked. With the potential for increasing use of HPV testing in screening programmes, costs associated with quality assurance efforts and infrastructure maintenance should be carefully considered in order to ensure that when new programmes are implemented, the results are reliable and perform well against international standards.

Audits of cervical cancer cases are a critical piece of monitoring programme effectiveness and quality assurance in organized screening efforts. When implemented consistently, with the appropriate level of detail and population level data, audits can help to highlight strengths and weaknesses of the screening programme and inform modifications needed to the programme operations (Sasieni & Cuzick, 2001). As proposed in the European guidelines for quality assurance in cervical cancer screening, systematic audits
of organized screening programmes should include detection status of the cancer (screen detected vs. symptomatic), interval cancers, screening history (to identify attendance status), invitation history, and treatment and follow-up compliance (Arbyn et al, 2008). A prerequisite for conducting an audit is the ability to link screening history data with cancer registry data and to include all cases of cervical cancer occurring, allowing for a complete evaluation the cervical cancer prevention impact of the screening program. While individual countries in Europe have conducted audits and published results in the form of programme reports and research articles, very little has been done to compare audit practices across European countries. Our understanding of the key features and costs of conducting audits in different countries is limited. To our knowledge, this survey represented the first time that detailed data have been requested from all European countries regarding cervical cancer audits.

A select few countries were able to provide details of audit practices. Background information regarding the protocols for conducting audits and the indicators collected was submitted by 5 countries and provides a view of the level of detailed analysis possible; however, the same level of detail was not available for the actual costs of conducting audits. In England and Slovenia, the costs of conducting audits were included in the overall costs of screening programme management and quality assurance. In Finland and Sweden, audits have been primarily financed through research grants, and, in the case of Finland, subsidized further through money from the screening registry and participating laboratories. Iceland reported that costs for conducting audits have not been evaluated. The results of audits can have direct influence on programme operations. An example of this is from Sweden where a nationwide audit quantified the risk of cancer in relation to how the clinical investigation and treatment is done after abnormal cytology, providing a solid evidence base for recommendations on quality control of cervical screening programmes.

Previous studies, such as the VENICE surveys, have examined the status of vaccination implementation and target populations. To our knowledge, this was the first time that data regarding HPV vaccination monitoring indicators currently used in programmes and associated costs have been collected. Prophylactic HPV vaccination represents an important opportunity for primary prevention of cervical cancer, and other HPV related diseases. Detailed surveillance efforts should be implemented alongside vaccination programmes to ensure that the programmes have the intended impact and reach the target population. Formalized guidelines for HPV vaccination, as part of cervical cancer prevention, were not included in the 2nd edition of the European guidelines for quality assurance in cervical screening. Instead, an introduction to vaccination was included as an appendix and highlighted as a forthcoming prevention strategy. In the years since licensure, HPV vaccination has begun in many countries in Europe using different delivery strategies.

The results of the PREHDICT survey showed that the most common indicators used to evaluate vaccination programme effect in European countries were cervical cancer incidence, HPV typing of cervical cancer cases, cervical and other HPV-related cancer mortality, screening participating of vaccinated women, and HPV typing of pre-cancerous lesions. Through the PREHDICT survey, costing information was also requested and focused on the costs of establishing vaccination registries (data infrastructure and reporting systems), maintaining registries (staff and data reporting, cleaning, and analysis), and laboratory based-monitoring (HPV prevalence and HPV typing of high- and low-grade lesions and cancers). Countries were not able to provide this level of detail in reporting costs. The gaps in reported information highlighted that this is a new area of health planning and perhaps a topic that should
be re-evaluated to examine progress. While some countries will be able to use existing infrastructure to track data, others will have to create new systems. In conclusion, the majority of countries responding to the survey could provide programme information on HPV vaccination, but only a few countries were able to provide costing information. For some countries, this information is commercially confidential and cannot be released and for others, it is possible that vaccination programmes built on existing infrastructure and therefore could not be separated from pre-existing costs.

In sum, the results of the PREHDICT survey demonstrate significant heterogeneity in screening and vaccination programme organization and quality control. Costs associated with programmes are hard to define which is concerning as this makes it difficult to conduct cost-effectiveness evaluations of different screening and vaccination programme implementation scenarios. The management and budgets of more established screening and vaccination programmes are closely integrated into other healthcare programming while newer programmes must build screening and vaccination programmes that account of the complexity necessary for effective monitoring and evaluation but are sustainably linked to existing structures.

WP5: Meta-analytical pooling of data providing parameters for modelling

Modelling exercises on primary HPV-based versus cytology-based screening and on prophylactic vaccination require parameters on screening and triage algorithms, treatment success rates, accuracy of diagnostic testing etc. These topics have been extensively researched but the resulting data are scattered. The PREHDICT team has performed a number of meta-analyses of such data accounting for different sources of heterogeneity.

HPV testing

In a special issue of Vaccine 2012, dedicated to HPV research, a summary was presented of all recent meta-analyses, performed by the PREHDICT team, on three possible clinical applications of HPV testing: (1) triage of women with equivocal or low-grade cytological abnormalities; (2) prediction of the therapeutic outcome after treatment of CIN lesions, and (3) primary screening for cervical cancer and pre-cancer. What follows below is a technical summary of the results:

In meta-analyses, consistent evidence was available indicating that HPV-triage with the Hybrid Capture-2 assay (HC2) was more accurate (higher sensitivity, similar specificity) than repeat cytology to triage women with equivocal Pap smear results. Several other tests showed at least similar accuracy but APTIMA (HPV E6&E7 mRNA testing) and the biomarker p16INK4a had similarly sensitivity but higher specificity compared to HC2. In triage of low grade lesions (LSIL), HC2 was found to be more sensitive but its specificity was substantially lower compared to repeat cytology. The APTIMA test and, in particular, p16INK4a immunostaining, were more specific than HC2 but for p16INK4a a significant loss in sensitivity was noted. The identification of type-specific HPV16/18 DNA, or RNA from the five most carcinogenic HPV types allowed selecting women at highest risk for the development of CIN3+ but sensitivity and negative predictive value of these markers were lower than complete genotyping of HPV-positive results.

Meta-analyses furthermore demonstrated that after conservative treatment of cervical pre-cancer, HPV
testing picked up more quickly, with higher sensitivity and not lower specificity, residual or recurrent high-grade CIN than follow-up cytology.

Moreover, the analyses found that primary screening for hrHPV generally detected more CIN2, CIN3 or cancer compared to cytology at cut-off ASC-US or LSIL, but at a lower specificity level. Combined HPV and cytology screening provided a further small gain in sensitivity at the expense though of a considerable loss in specificity if women with positive results on either test were referred to colposcopy, in comparison with HPV testing only. Randomised trials and follow-up of cohort studies consistently demonstrated a significantly lower cumulative incidence of CIN3+ and even of cancer, in women aged 30 years or older, who were at enrolment hrHPV DNA negative compared to those who were cytologically negative (see figure 5.1 annex).

The difference in cumulative risk of CIN3+ or cancer for double negative (cytology & HPV) versus only HPV-negative women was small. The loss in specificity associated with primary HPV-based screening could be compensated by appropriate algorithms involving reflex cytology and/or HPV genotyping for HPV16 or 18.

On the basis of these meta-analyses it can be concluded that sufficient evidence exists to recommend HPV testing in triage of women with minor abnormal cytology, in surveillance after treatment of CIN lesions and in primary screening of women aged 30 years or older. The possible advantages offered by HPV-based screening require a well organised programme with good compliance with screening and triage policies.

The accuracy of HPV testing on woman-collected samples

The accuracy of hrHPV testing on a self-sample was found to be similar to that of cytological interpretation of a clinician-obtained sample. However, hrHPV testing on a self-sample was less sensitive and specific than hrHPV testing on a clinician-obtained sample. Self-sampling can increase population screening coverage by reaching the non-responders of the regular screening programme. However, HPV testing on a clinician-obtained sample is still preferred in HPV-based cervical cancer screening, unless it can be shown that for the given test/self-sample combination the accuracy is similar to that of clinician sampling.

Obstetrical adverse effects associated with treatment of cervical precancer

A previous meta-analysis indicated that treatment of cervical precancer by excision was associated with future preterm delivery (Kyrgiou, 2006). Another meta-analysis concluded that aggressive treatment procedures such as cold knife conisation and radical diathermy, but not large loop excision of the transformation zone (LLETZ) were associated with severe preterm delivery and even with perinatal mortality (Arbyn, 2008). Adding 12 new studies, published since then, confirmed findings from these meta-analyses. However, some of the new reports indicated that shallow excision by LLETZ were not or only marginally associated with obstetrical adverse effects. The dimension of the cone excised relative to the size of cervix may explain variability of findings. An individual patient meta-analysis, allowing for better control of findings and containing details about the size of the cone is needed to identify the ranges of oncological and obstetrical safety.
Accuracy of colposcopically directed punch biopsies

A new meta-analysis assessed the accuracy of colposcopy-based punch biopsies to diagnose high-grade cervical intraepithelial neoplasia (CIN), using subsequent excision biopsies as reference standard. The pooled sensitivity for a punch biopsy defined as test cut-off CIN1+ to diagnose CIN2+ disease was 91.3% (95% CI 85.3-94.9%) and the specificity was 24.6% (95% CI 16.0-35.9%). In most of the studies, the majority of enrolled women had positive punch biopsies. Pooling of the four studies where the excision biopsy was performed immediately after the punch biopsy, and where the rate of positive punch biopsies was considerably lower, yielded a sensitivity of 81.4% and specificity of 63.3%. The observed high sensitivity of the punch biopsy derived from all studies was probably due to verification bias.

WP6: HPV transmission modelling

Because screening and vaccination trials have pre-invasive end-points and have only up to 6 years follow-up, mathematical modelling is required to predict the impact of screening and vaccination on life-years, cancer incidence, medical and non-medical costs. To assess the cost-effectiveness of vaccination, it is important to adequately model the natural process of acquiring and clearing an HPV type infection, and of developing temporal or lifelong natural immunity against an HPV type.

By modelling HPV transmission through sexual contact between partners, the effect of low/moderate vaccination coverage can be predicted, the effects of waning immunity can be predicted, the effect of partial cross-protection against non-vaccine high-risk HPV types as well as the effect of type-replacement, and the effects of male vaccination (in addition to female vaccination) can be assessed.

In this WP three models were built using key facts on the dynamic transmission of HPV infection among populations of vaccinated and unvaccinated (adolescent) individuals and using also information on type-specific HPV-transmission probabilities, and duration/completeness of HPV vaccine induced immunity.

The PREHDICT team further developed an age-structured, sexual-activity group-based dynamic transmission model to investigate the natural history of HPV infection (Baussano et al, 2010; Baussano et al, 2011). Two main structural modifications were included in the model developed for this project: A) the established model focuses exclusively on the infectious phase of the natural history of cervical cancer and B) the dynamic of the HPV infection among both men and women accounts for the duration of infection.

In addition, a compartmental transmission dynamic model was developed for single and multiple type hrHPV infections, in which type-specific hrHPV infections transmit through a life-time partner number-based sexual contact structure. The transmission of HPV infection and cervical cancer disease progression were separated into two different models. The transmission model matched to Finnish hrHPV prevalence data (Vänskä et al, 2013, figure 6.1 in annex). HPV infection incidence (force of infection) curves were another outcome of transmission model, and inputs for the progression model and health-economic modelling (WP7).

Finally, the PREHDICT team created a model elaborating clearance of HPV and its progression to clinical
disease, together with viral transmissibility and the duration of naturally-acquired immunity (Johnson et al, 2012). The primary approach involved 3 stages: (A) estimation of parameters from the literature, or directly from Swedish data, (B) the development of 13 separate high-risk and 2 low-risk HPV type-specific deterministic models with identical structures to the individual-based model, which are then fitted to the type-specific data independently using MCMC (Markov Chain Monte Carlo) methods, (C) the posterior distributions for calibrated parameters from the deterministic model are then used as priors in the individual-based models. The models were able to capture the age- and type-specific patterns of HPV prevalences observed in the Swedish data (Johnson et al, 2012).

Individual-based simulation generally requires a great amount of computational resources and takes a long time to deliver precise estimates of population means. For this reason, the PREHDICT team also developed an emulator, i.e. a statistical representation of the individual-based model, which captures the key relations between input variables and outcome measures but can be run in fractions of the computing time required for the original model. By alternating between the original model and this emulator in the stage of model calibration, we were able to search model parameters much more efficiently than if we had applied the original model sequentially in a Markov chain Monte Carlo (MCMC) routine. As a result, we obtained a good fit of the individual-based model in relatively few iterations.

Consequently, the models were used to assess the impact of vaccination.

The impact of vaccination on the relative prevalence of HPV16 and HPV18 women younger than 36 years of age was assessed using the hrHPV infection model (Baussano et al, 2010; Baussano et al, 2011). Improvement of vaccination coverage from 65% (best subsidized programmes) to very high 90% coverage (best school-based programmes) in 11-year-old girls increased the effectiveness against HPV16 infection, within 30 years after vaccination introduction from 75% up to 97%. Due to herd-immunity effect the additional vaccination of 11-year-old boys with the moderate (65%) coverage would raise maximal effectiveness estimates among women <35 years of age to 87% in programmes with 65% coverage among girls and to 99% in programmes with 901% coverage among girls (figure 6.4 in annex).

Catch-up vaccination of 17-to-24 year-old women did not affect long-term effectiveness but substantially anticipated it compared to adolescent vaccination. The anticipation of effectiveness increased as a function of the number of up to four birth cohorts included in the catch-up. In the absence of catch-up, herd-immunity would also partially protect the last unvaccinated birth cohorts. The herd-immunity is, however, expected to decrease among older birth cohorts as a consequence of decrease in sexual mixing with male partners of the vaccinated cohorts.

The second model predicted that vaccinating girls at a base-case, 80% coverage will result in a 55% reduction in the hrHPV prevalence but an even higher 65% reduction in the persistent hrHPV prevalence for females. Herd-immunity explained about 1/3 of the effectiveness of vaccination against hrHPV in the base-case scenario. If the very high (90%) coverage among girls is not reached, vaccinating 80% girls and only 40% of boys corresponded to the same effectiveness (among females).

The second model has furthermore been used to predict the impact of different screening and vaccination strategies on cervical neoplasia rates. The progression model takes into account both organized screening
programme and opportunistic screening practice, which is very heavy in Finland, which was used for model verification.

Finally, verification of the models with results of a community randomized trial (CRT) on the implementation of different HPV vaccination strategies was attempted by comparison of the model predictions on reduction of HPV16 and HPV18 prevalences in 32,500 adolescents born in 1992-1995. Adolescents aged 12-15 years from 33 communities were randomized (at community-level) to one of three strategies: (A) HPV16/18 vaccine (girls and boys); (B) HPV16/18 vaccine (girls) or hepatitis B-virus (HBV) vaccine (boys); or (C) the HBV vaccine (girls and boys, control strategy). Vaccine coverage was equal in the three groups (50% girls and 20% boys). Cervico-vaginal self-collected samples were obtained from girls aged 18.5 years for hrHPV and Chlamydia trachomatis determination. Predictions on the occurrence of HPV16/18 infections (HPV16/18 DNA prevalence) have been made applying the first and second model both for overall (in target-aged vaccinated and unvaccinated community residents) and herd-immunity (in the unvaccinated) effect of the different HPV16/18 vaccination strategies (A and B) as compared to C. Both the models predicted consistently about 50 to 60% overall HPV16 prevalence reduction in girls for both the A and B strategies with slight increase towards the newest birth cohorts. As for the herd immunity effect in the unvaccinated girls the first model predicted twice as high prevalence reduction in the A-communities for newest birth cohorts (30%) than the second model (14%). Verification of the two models is ongoing from the self-collected cervico-vaginal samples of the 1992-1994 born CRT-participants for hrHPV DNA. Altogether 9,983 such samples (from 8,332 vaccinated and 1,651 unvaccinated girls) from the three first birth cohorts have been collected between Q4/2010 and Q1-2/2013, and are being analysed.

WP7 – Development of a microsimulation model and preparation of health-economic evaluations of both HPV vaccination and cervical cancer screening for the different EU countries.

An important goal of PREHDICT is to identify vaccination and screening strategies for European countries that are feasible from a health-economic perspective. As there is substantial variation in the availability of health care resources and in the burden of cervical cancer and other HPV-related disease among European countries, prevention programmes may differ between countries. The health-economic analyses have concentrated on the Netherlands, Italy, and Central and Eastern European countries. PREHDICT offers a unique possibility for health-economic assessments as the cost-effectiveness analyses can be informed by a large disease database (WP2), a large screening database (WP3), questionnaire results on the costs of screening and vaccination programmes (WP4), meta-analyses (WP5), and by transmission models that estimate vaccination-related changes in the HPV type- and age-specific incidences (WP6).

In a health-economic evaluation, the costs and gain in life years of several prevention strategies are compared by means of a cost-effectiveness analysis which identifies strategies that seem good value for money. Cost-effectiveness analyses rely on disease parameters that cannot be directly observed. Models are required to estimate the time from HPV infection to cancer. In WP7, novel mathematical disease models have been developed and consequently used to study the costs and/or effectiveness of (1) HPV16/18 vaccination of 12-year old girls; (2) HPV16/18 vaccination at older age; (3) HPV16/18 vaccination of 12-year old boys; (4) HPV-based screening, and (5) integrated vaccination and HPV-based screening strategies.
Vaccination of 12-year old girls

The cost-effectiveness of vaccinating 12-year-old girls has been widely studied for Western and Northern European countries, usually resulting in a favorable cost-effectiveness of HPV16/18 vaccination. The PREHDICT team concentrated on countries in Central and Eastern Europe and calculated that in each of 18 Central and Eastern European countries, HPV16/18 vaccination is a very cost-effective intervention according to criteria from the World Health Organization (Berkhof et al. Vaccine Monograph 2013). The favourable cost-effectiveness results are related to the high disease burden in Eastern European countries where organised cervical cancer prevention efforts are scarce. However, there was also strong variation among countries with respect to the maximum cost-effective vaccine dose price. The maximum cost of 3-doses of the vaccine and administering the vaccine varied between 100 and 800 international dollars. Fifty-six percent of the variation in the maximum allowable vaccine costs could be attributed to differences in resources (measured by the gross domestic product per capita).

Vaccination of girls older than 16

The use of prophylactic HPV vaccines is universally approved for females up to 26 years of age [EMEA; FDA]. However, inclusion into national HPV immunization programmes has mostly been restricted to (pre-)adolescent girls, because HPV vaccine trials have demonstrated greatest immunogenicity and efficacy in preventing vaccine-type infections among those without evidence of prior exposure at the time of vaccination. New insights in the efficacy of HPV vaccines and reductions in the vaccine price prompted us to investigate the clinical benefit and cost-effectiveness of HPV vaccination for adult women in the Netherlands (research question 2). This was done via model-based simulation of cohorts of women aged 17-25 years in 2010, i.e. those eligible for vaccination but not for reimbursement of the cost of the vaccine. The age-specific HPV incidences in unvaccinated women gradually change with calendar year because of the herd immunity effect (i.e. indirect protection because vaccination lowers the prevalence of HPV in the population). The herd immunity effect was estimated from a transmission model (Bogaards et al. Am J Epidemiol 2010). As a base-case, we assumed the vaccine to offer full protection against HPV16/18 only if no prior exposure to that type had occurred before vaccination. In sensitivity analyses, we considered partial cross-protection against non-vaccine HPV types and efficacy against all future infections, irrespective of previous of current infection status. Our results suggested that 17-year-olds still derived considerable benefit from prophylactic vaccination, but the gain amongst 25-year-olds was marginal under base-case assumptions. The clinical benefit increased moderately if cross-protection was taken into account, but assumptions regarding current or previous infection status had little impact on simulated outcomes. We concluded that, under realistic vaccine price assumptions (about 50 percent lower than the pharmacy vaccine dose price but higher than the tender price paid for national immunisation programmes), refunding the cost of the HPV vaccine to women up to 26 years could be considered cost-effective in the Netherlands.

Vaccination of 12-year old boys

The PREHDICT team also investigated the scope for vaccinating males against HPV16/18. Accumulating evidence for the role of HPV in the etiology of cancer in non-cervical sites, and demonstration that vaccine
efficacy extends to the prevention of HPV-related lesions in males as well as HPV-related non-cervical lesions in females, have prompted initiatives to include boys in the existing female-only HPV immunization programmes. The efficacy of gender-neutral vaccination strongly depends on the extent to which vaccination of girls will mitigate the risk of HPV infection in men, and on the assumed burden of male HPV-related disease. For this purpose, a Bayesian probabilistic model was developed for the burden of male HPV-related cancer, taking account of penile, anal and oropharyngeal carcinomas for which the evidence for a causal link with HPV is considered “strong” at present [IARC]. The influence of female vaccination on the HPV16/18 infection risk in males was informed by an HPV transmission model (Bogaards et al. 2010). The model indicated that female-only HPV immunization programmes already offer considerable health benefits to men, but that the male burden of HPV-associated cancer still remains substantial when only females are vaccinated. The latter also holds when a high coverage among females is achieved. The relation between female vaccination and the health impact of male vaccination is weak for anal cancers due to the high relative risk of anal cancers among MSM and strong for penile cancers. To summarize, male vaccination may have a substantial health impact, but whether the remaining burden is large enough to warrant gender-neutral vaccination depends on the cost and desirability of a gender-neutral HPV vaccination campaign.

Screening model

The cost-effectiveness of HPV-based screening in unvaccinated and vaccinated cohorts was studied by means of individual-based Markov simulation models. The PREHDICT team built a novel Markov-simulation model and applied it to countries with different levels of health resources (the Netherlands, Poland, Slovenia, and the Republic of Georgia). Main input variables to the Markov model are the type- and age-specific HPV incidences calculated in WP6. The progression from CIN2/3 to cancer was estimated using a national database of pathology results in the Netherlands from 2000-2009. The basis for the Markov simulation model is a mathematical statistical model which links HPV incidence to CIN2/3 incidence and cancer incidence. The model provides estimates of the mean duration to cancer and the heterogeneity in the duration to cancer among women (Vink et al. Am J Epidemiol 2013). The latter measure is very important for identifying the optimal screening interval.

To support own modeling initiatives, the individual-based Markov simulation model, can be activated via freely downloadable, user-friendly Excel macros. For local modeling, country-specific data can be uploaded in Excel and country-specific predictions can be obtained. The hope of the PREHDICT team is that a widespread use of the PREHDICT models will contribute to better decisions on the prevention of HPV-related diseases.

Screening in unvaccinated cohorts

In the PREHDICT project, health effects and costs of screening were assessed in countries with different levels of health resources (Netherlands, Slovenia, Poland) using the individual-based simulation model. In all countries, primary hrHPV screening seems a cost-effective alternative to cytology under various assumptions for disease parameters and screening parameters but the laboratory costs of hrHPV testing have to be in the same range as the laboratory costs of cytology. Repeated screening remains necessary although the screening interval can be extended with 1 to 3 years when replacing cytology by hrHPV
testing. The optimal intensity of screening strongly depends on the country’s specific resources and the country-specific burden of disease in unscreened women.

The simulation model can be used to support the choice of the primary screening instrument and to determine the optimal length of the screening interval. However, the instalment of new HPV-based screening programme also requires a suitable triage algorithm for hrHPV positive women. This important subject was studied by means of a decision tree model. This model was constructed from the POBASCAM trial data (Rijkaart et al. Lancet Oncol 2012). Ten different triage strategies for hrHPV positive women were compared (Dijkstra et al. CEPB 2013). The clinical end-point in the model was cervical intra-epithelial neoplasia grade 3 or worse (CIN3+) detected within four years. The decision tree analysis indicated that hrHPV positive women with abnormal cytology should be recommended for colposcopy as they have a substantial risk of CIN3+. The CIN3+ of hrHPV-positive, cytologically negative women is not high enough for immediate referral but those women still have an elevated CIN3+ risk in comparison to HPV-negative women. Therefore, they should be invited for repeat testing after 6/12 months and/or genotyped for HPV16/18.

Screening in vaccinated cohorts

Since the burden of cervical cancer is expected to decline with vaccination, screening guidelines need to be revised in order to reduce the burden of screen positives and to maintain programme efficiency if HPV-based testing is introduced or once vaccinated cohorts reach screening age. In vaccinated cohorts, the optimal intensity of screening is lower than in unvaccinated cohorts although repeated screening at intervals of 5-10 years are still cost-effective (Coupe et al. 2012). The PREHDICT team further estimated that the availability of broad-spectrum vaccines will have a substantial impact on the number of screens, nevertheless a programme with one or two lifetime screens is likely to remain cost-effective.

The efficiency of the current screening programmes for vaccinated cohorts was also studied using HPV type infection risks and abnormal cytology risks observed in Dutch and Italian screening cohorts (POBASCAM and NTCC). In both studies, lifetime risks of screen-detected HPV and abnormal cytology among vaccinated cohorts were almost identical. This indicate that the relatively low specificity of HPV testing in unvaccinated women (Arbyn et al. 2007) will be neutralized in vaccinated cohorts and further supports primary HPV screening.

WP8: Dissemination of knowledge

Technical advice on future prevention strategies of HPV-related diseases resulting from HPV transmission and health economics modelling, quality assessment of screening and vaccination programmes, and feasibility of the implementation of prevention strategies should reach a comprehensive public, and that requires a comprehensive dissemination approach.

The PREHDICT dissemination plan was divided in two different strategies: one targeted to the general public and another one targeted to a professional audience.

A free-access web platform at the European Cervical Cancer Association ECCA (www.ecca.info figure 8.1
Annex has been created for the general public, including information about PREHDICT objectives and outcomes has been published in several European languages including English, French, Italian, Spanish, German, and Russian among others. A media briefing pack was also distributed to journalists specialising in healthcare reporting to ensure they have a good understanding of the background information required for accurate reporting of the topic.

For health professionals and public health stakeholders specific reports on the burden and prevention of HPV infection and related cancers for each of the 43 participating countries of PREHDICT have been posted at the WHO/ICO Information Centre on HPV and Cancer (www.hpvcentre.net; refer also to WP2; figure 8.2 annex). Each report provides key information on cervical cancer, other anogenital cancers and head and neck cancers, HPV-related statistics, factors contributing to cervical cancer, cervical cancer screening practices, HPV vaccine introduction, and other relevant immunization indicators. The most up-to-date data is summarized and presented in a friendly manner (tables and figures) in order to facilitate decisions on current and novel options for the prevention of cervical cancer and other HPV-associated diseases in Europe.

The underlying European HPV Epidemiological Database can also be used to create user-defined tables and figures through a query system (figure 8.3 annex).

A summary of the results of PREHDICT study will also be published shortly after the completion of the project at the same HPV Information Centre site.

A dedicated Vaccine monograph on Eastern Europe has also been produced as part of the ICO Monograph Series on HPV and Disease Prevention (Bosch FX. et al., 2012). The preparation of the Monograph has required the coordination of a well-defined process involving more than 500 key experts in the field, serving as editors, authors or reviewers. One editorial preparation meeting was held for the selection of authors, topics, table of contents and timetables. Section editors and contributing authors for each Monograph were selected based on their research contributions and general expertise in the field. The editorial procedures were adapted to the guidelines issued by the International Committee of Medical Journal Editors Uniform Requirements for Biomedical Journal submissions, which included an independent peer-review process under the publishing organization of Elsevier.

Potential Impact:

WP2: Epidemiological data on HPV infection, HPV-associated diseases, life style factors, and cancer prevention strategies

Understanding the epidemiology of HPV and its prevention tools is a pressing demand from the public health community of European countries. The need to present the information in a comprehensive and unbiased manner becomes a critical task.

The European HPV Epidemiological Database contains the most up-to-date epidemiological information on HPV, related diseases and their prevention. It has been made freely available through the ICO Information Centre on HPV and Cancer website (www.hpvcentre.net) a widely used information source on
HPV and its prevention. The database has been published as a user-friendly, queriable site that produces figures and tables according to the user selection. Moreover, regional and country-specific technical reports have been produced to summarize all these data and have been published in the same site.

The country-specific reports and the database have been used, and have the potential to continue to be used, as the basic epidemiological information source to design prevention HPV strategies in each European country. They facilitate public health officers and other stakeholders the task to gather and select all the information available, work that implies many hours of skilled labor force.

Also, although the European HPV Epidemiological Database and its reports are a tool designed for professional use, the availability to the general public in a more user-friendly way than its original sources (biomedical scientific literature and databases) empowers the public to participate and comprehend current public health policies.

WP3: Parameter estimates from European screening trials

Using data collected in four randomized controlled screening trials, PREHDICT has provided the first large-scale direct and conclusive evidence of increased protection from invasive cancer with HPV screening, in regularly screened women. In addition, the results of the analysis on invasive cancer together with that on the time of detection of pre-cancerous lesions with cytology and with HPV, are important in defining the best HPV-based screening policies. This includes aspects such as screening intervals or age of application and management of HPV-positive women for which direct evidence was not previously available. This new knowledge is likely to have an important impact both on the choice of implementing HPV-based screening and on how to perform it. Studies on new biomarkers have provided options for reducing the number of unneeded colposcopies and biopsies, thereby reducing costs and undesired effects of screening without reducing its efficacy. Particularly biomarkers will reduce the number of short-term recalls, which is disturbing for women and can result in non-participation. Finally, the pooled database enabled the PREHDICT team to refine estimates of the natural history of infection, which are important in order to define the impact of different strategies of vaccination, like catch-up and vaccination of males, on the frequency of HPV infection at a population level.

The results have been published in peer-reviewed journals as well presented during scientific conferences. The results of the pooled efficacy analysis is currently under review by a peer-reviewed journal.

WP4: Organisation, quality, monitoring & evaluation

The results of the work on the survey on organisation, quality and M&E activities will be used to inform guidelines on cervical cancer screening and HPV vaccination programs in Europe. Through careful analysis, the collected information on current quality assurance and monitoring and evaluation activities can be linked to overall program success, allowing for the identification of key program factors associated with greater cervical prevention. Work is ongoing for new chapters regarding quality assurance indicators in the European guidelines for quality assurance in cervical cancer screening. As members of PREHDICT are involved in this process, the results of the survey can be used to strengthen the guidelines by highlighting strengths and weaknesses with existing efforts and potential disconnects between
recommendations and current program practice. To disseminate the results, a variety of channels will be used. Countries responding to the survey have asked to be informed of the final results, which provides us a direct feedback opportunity. Through the European Schools of Screening Management hosted by the International Agency for Research on Cancer, the specific workpackage leaders have established further contacts in screening programs and a network of individuals dedicated to addressing issues of quality assurance in screening. This network will be utilized to further disseminate the findings of the survey. In addition to these direct contacts with agencies and networks, scientific papers will be prepared and presentations at conferences will be given to reach a wider audience of individuals involved with screening and vaccination programs and to motivate further research in the area. These planned publications will strengthen the research evidence base for understanding the key components of organization and evaluation of programs that lead to the greatest preventative effect. Additionally, they will provide a baseline status report on existing efforts that can be used in subsequent years to compare the impact of further developing programs.

WP5: Meta-analytical pooling of data providing parameters for modelling

The results of the meta-analyses conducted over the last four years will be pivotal to the production of evidence-based guidelines for cervical cancer screening. In 2008, the Scientific Institute of Public Health had the responsibility to develop the 2nd edition of the European Guidelines for Quality Assurance in Cervical Cancer Screening. In this 2nd edition it was concluded that sufficient evidence was available to recommend DNA detection of high-risk HPV types in triage of women with equivocal cervical cytology findings and in the follow-up after treatment of cervical precancer. However, for HPV testing in primary screening, insufficient evidence was available. In 2008, meta-analyses had shown that HPV testing in primary screening was more sensitive but less specific in picking up cervical precancer. Indeed, it could not be proven that HPV-screening detected more progressive precancerous lesions or only more regressive lesions compared to cervical cytology. It was anticipated that a reduction in the cumulative incidence of CIN3+ or invasive cervical cancer observed in subsequent screening rounds among women who were in the first round HPV-negative versus cytology negative should constitute the evidence needed to recommend viral instead of cytological screening in Europe. The European Commission has now instructed a team to make a supplement to this second edition which should include guidance on HPV-based cervical cancer screening. Given the evidence derived from meta-analyses and pooled analyses, PREHDICT results will contribute to the major substance and evidence-based for the pending new European guidelines for HPV-based cervical cancer screening.

The results of meta-analyses of the accuracy of molecular markers related to cell cycle – regulation (transcripts of viral oncogenes, protein markers, HPV genotyping, methylation) evaluated in the triage of women with minor cervical cytological lesions will be useful for updating guidelines on management of women with screen-detected cervical lesions. As soon as new data will become available new meta-analyses will address their performance in triage of HPV-positive women identified through HPV-based screening.

The systematic review work done within PREHDICT has highlighted the importance to conduct health-technology assessment within an international network having skills in both synthesis of evidence and having field expertise in prevention and treatment of HPV-related disease. Such an international network
usually can perform better and quicker reviews than teams from national or regional health technology teams. The findings of the meta-analyses produced within the PREHDICT project were presented at scientific conferences dedicated to gynaecology, oncology, virology, cytopathology, epidemiology and public health. The results of the systematic reviews were published in 24 peer-reviewed papers and 3 book chapters.

WP6: HPV transmission modelling

Three different dynamic transmission models were developed which have been/are being parameterized / verified by population-based data from sizeable vaccination and screening cohorts. The model derived force of infection estimates have been utilized by cost-effectiveness analyses but most importantly the versatile models have (in Finland, Sweden) and can be used to advice EU-and other authorities in decision making on HPV vaccination policy (Vänskä et al, 2013; Johnson et al, 2012; Baussano et al, 2013). Data from the community-randomized (effectiveness of) HPV vaccination (strategies) trial in reducing hrHPV prevalence analysis will provide first randomized-trial based evidence on the effectiveness/impact of different HPV vaccination strategies. It will also enable verification of the PREHDICT models with regard to their accuracy on the overall and herd-immunity effects of different vaccination programs that could be implemented in the EU countries.

Publications have been the most important route of dissemination. However, the PREHDICT model based data have been presented on several congresses/scientific symposia, and associated lectures are freely available at www.rokotiitus.net.

WP7: Health Economics

The results of the cost-effectiveness analyses will provide input for decision-taking on screening and vaccination policies. Our analyses clearly showed that HPV vaccination of young females is very cost-effective and may substantially lower the disease burden in Europe. Moreover, the most important parameters for cost-effectiveness of adult vaccination as well boys vaccination were established- including vaccine price, coverage of female vaccination and the remaining cancer burden among males. Cost-effectiveness of vaccination in Eastern European countries had not previously been established and the results will guide policy formulation by local stakeholders. In addition, the modeling results will help to guide the design integrated vaccination and screening programs using novel, molecular HPV-based screening instruments.

The results have been and will further be disseminated via peer-reviewed scientific journals and via scientific conferences. This will provide an effective way to reach a wide audience and to enhance acceptability of the results within the field. The simulation disease model developed by the PREHDICT team is freely downloadable and has been embedded in a user-friendly Excel environment. Our expectation is that this motivates local modeling efforts and will further strengthen the relation with European modelers and policy makers.

WP8: Dissemination of knowledge

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In addition to the dissemination through peer-reviewed journals and presentations at scientific conferences, as described for the workpackages above, the ICO Information Centre on HPV and Cancer is an important dissemination route (www.hpvcentre.net).

The ICO Information Centre on HPV and Cancer is a widely used information source on HPV and its prevention. As of May 2011, the website has received 261,328 visits, at an increasing average of 3,173 visits/month in 2007 to 6,006 visits/month in 2010. Users have accessed the website from 159 countries and 242,619 downloads of indicator data, country- and regional-specific reports have been made. With the post of PREHDICT data, newsletters and mailing will be distributed to increase awareness on the availability of new information.

The ICO Monograph Series on HPV and Disease Prevention is an effort that has been running since 2005 with very satisfactory results. Through an international Think tank forum, the most international recognized professionals on the field of HPV research and prevention are reunited.

Between 2005-2010 five monographs were produced in three different languages. The number of free downloads computed so far is in the range of 200,000 at a constant rate of some 30,000 downloads per year. The number of citations is 1,893 for the 2006 edition, and 500 for the 2008 edition of the general report (last updated September 2012). Distribution is now in place for the English, Spanish (Latin American Report) and Japanese editions (General chapters and chapters on Japan and Korea). One of the chapters has been identified as the top cited paper in the Elsevier evaluation system. These Monographs have been widely used as educational materials at numerous workshops and seminars.

List of Websites:

www.hpvcentre.net/prehdict

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