Implications of varied patterns of cervical cancer screening for introduction of human papillomavirus vaccines in Europe

Avrupa'da farklı servikal kanser tarama programlarına Human papilloma virus aşılamasının girişi

Achim Schneider[1], Olivier Gleizes[2], Pekka Nieminen[3], Evrim Erdemoğlu[1], Fausto Boselli[4], David Jenkins[5]

[1]*Department of Gynecology, Campus Benjamin Franklin and Campus Mitte, Charité University, Berlin, Germany*

[2]*Smart Pharma Consulting, Paris, France*

[3]*Department of Obstetrics and Gynecology, Jorvi Hospital, Helsinski University, Helsinski, Finland*

[4]*Department of Obstetrics and Gynaecology, University of Modena and Reggio Emilia, Modena, Italy*

[5]*GlaxoSmithKline Biologicals, Rixensart, Belgium*

Abstract

Objective: To identify patterns of variation in cervical cancer screening programmes in Europe to support planning public health human papillomavirus (HPV) vaccination strategies in cervical cancer prevention.

Material and Methods: A three-phase approach was designed to evaluate programmes in different countries and to identify drivers and barriers to vaccine introduction. Countries were clustered according to their structure, process, and outcomes of current secondary prevention programmes for cervical cancer. Main outcome measures: Detailed description of cervical cancer secondary prevention programmes (organisation, target population, screening algorithms, financing) was compared. Outcome based criteria were incidence rate, mortality rate, and coverage rate of women (proportion of women actually screened).

Results: A wide range of variation was found in structure, process and outcomes for cervical cancer screening programmes in Europe, but countries could be clustered on the basis of screening practice and outcomes. There was a relation between the quality of cervical cancer prevention programmes and the continuing cervical cancer burden.

Conclusion: There are several different patterns of current cervical cancer secondary prevention in Europe. Implementation of vaccination against the major oncogenic HPV types 16/18 provides a potentially important tool to supplement these cervical screening and achieve optimal cervical cancer prevention. The challenges are different in each country cluster.

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Key words: Cervical cancer, screening programmes, European countries, vaccination

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Özet

Amaç: Avrupadaki servikal kanser tarama programlarındaki varyasyonların belirlenerek servikal kanserin önlenmesinde toplumda human papillamovirus (HPV) aşılama programlarının ve stratejilerinin gelişimini incelemektir.

Gereç ve Yöntemler: Farklı ülkelerdeki aşılama programlarını, buna etki eden olumlu ve engel olan faktörleri incelemek için üç fazlı bir dizayn yapılmıştır. Ülkeler yapılarına, işlemlerine, ve şu anki sekonder servikal kanser önleme programlarına göre sınıflanmıştır. Ana çıktılar: Sekonder servikal kanser tarama programlarının detaylı tanımı (organizasyon, hedef populasyon, tarama algoritimleri, finans) karşılaştırılmıştır. Sonuçlar şu kriterlere bağlı kalarak verilmiştir; insidans, mortalite oranı, ve taramayla kapsanan kadınların oranı.

Bulgular: Servikal kanser taramasında Avrupa ülkelerinde organizasyon, işlem ve sonuçlar açısından çok farklılıklar olmasına rağmen ülkeler tarama programlarına ve sonuçlarına gore gruplandırılabilir. Servikal kanser tarama program kalitesiyle servikal kanser riski arasında ilişki vardır.

Sonuç: Avrupa'da sekonder servikal kanser önleme programları arasında farklılıklar mevcuttur. Major onkojenik HPV 16 ve 18 tiplerine karşı aşılama bu programların tamamlanması ve iyileştirilmesini sağlayacaktır. Her gruptaki ülkelerin karşılaştığı güçlükler farklıdır.

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Anahtar kelimeler: Servikal kanser, tarama programı, Avrupa, aşılama

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Introduction

European screening programmes in 18 countries have recently been reviewed by the Epidemiology Working Group of the European Cervical Cancer Screening Network and the International Agency for Research on Cancer, who concluded that screening recommendations are met only in few European countries and health authorities need to consider stronger measures and incentives than those laid out in the current set of recommendations (1).

Studies have shown the efficacy of vaccination with HPV-16/18 VLPs composed of the viral L1 protein in uninfected women is up to 100% against type-specific prevalent persistent infections and associated abnormal cytology and pre-can-

Address for Correspondence / Yazışma Adresi: *Achim Schneider MD, MPH, Charité Universitaetsmedizin Berlin Campus Benjamin Franklin and Campus Mitte Department of Gynaecology Hindenburgdamm 30 12200 Berlin, Germany Phone: +49-30-8445 2591 Mobile: +49-30-8445 4477 e.mail: achim.schneider@charite.de*

cerous lesions (2-8). Successful implementation of HPV-16/18 vaccination requires careful consideration of the background against which this takes place and includes (1,7) the identification of the target population and existing health infrastructure to deliver vaccination to this population, (2) support from health authorities and public health policy makers, (3) awareness of the disease, and (4) potential interactions between established programmes such as secondary prevention cervical cancer screening and the introduction of a prophylactic vaccine.
In order to provide information regarding the challenges of integrated cervical cancer prevention based on vaccination and screening, we evaluated patterns of variation in current cervical cancer survival programmes in Europe in order to lay the ground for discussions on cancer vaccination strategies.

Methods

The project focused on the 25 member-countries of the European Union as well as Romania and Russia. A three-phase approach was designed to evaluate programmes in different countries and to identify drivers and barriers to vaccine introduction. In the first phase, countries were clustered by the criteria for quality of the screening programme and by outcome defined; and countries with nationally organised screening programmes (existence of national guidelines for the definition of age intervals, frequency, type of test used for primary screening, management of abnormal findings, existence of a formal process to access the target population (invitation and recall-systems in place), national registry to register and follow-up screenings on an individual basis as well as assessed performance of screening).
Outcome based criteria were incidence rate, mortality rate, and coverage rate of women (proportion of women actually screened). Standardized mortality rate was available for all countries in the scope of the study. Coverage rate was considered as the most relevant value, however, it was not available for all countries.
Information was gathered by structured interviews with epidemiologists and opinion leaders from 12 countries who are listed in the appendix and supplemented by additional desk research (Smart Pharma Consulting, Paris, France).
Presence or absence of a national organized screening programme was the first criterion applied and countries were separated in two groups (Figure 1). Countries without a national organized screening programme were further subdivided in three groups according to their mortality rate being lower than five, five to less than ten, and ten and more per 100.000 women per year. Using these criteria, countries were allocated to four clusters keeping in mind that the quality of cancer registries with respect to incidence and mortality varies considerably between and inside clusters. Also problematic is the allocation of Denmark to cluster 3 due to the high incidence and mortality in Greenland, although a national screening program and excellent cancer registry is in place. In each cluster one country was chosen as cluster-head. The selection of cluster head countries was random and based exclusively on the availability and commitment of the experts approached for collaboration in the study. A detailed description of cervical cancer secondary prevention programmes (organisation, target population, screening algorithms, financing) was provided for each cluster head. The performance of the existing screening programmes was assessed.
The cluster results were compared by the expert panel of the European Cervical Cancer Prevention Board to evaluate the potential implications of difference in cervical screening practice and outcomes within Europe for the introduction of HPV-16/18 vaccination.

Results

A detailed description of the "cluster-head" screening programmes is given for each of the four clusters (Table 1). Crude incidence and mortality rates are shown in figure 2.
In cluster 1, screening is offered to all women and an acceptable coverage rate is achieved due to an efficient invitation process. Regular training of health care professionals allows for

Table 1. Clusterisation of countries into four groups based on a three-phase approach. Each cluster head in the study is highlighted. Clustering of countries: Finland, Italy, Germany, and Poland are the proposed "cluster-heads", respectively for cluster 1, 2, 3, and 4

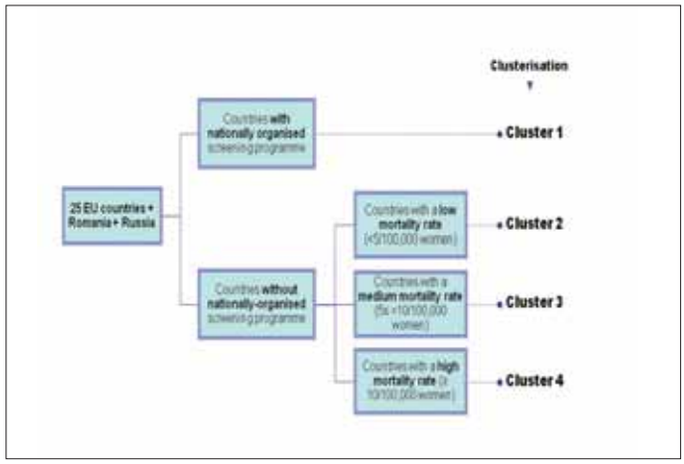

Figure 1. Clustering of countries algorithm. Presence or absence of organized "national screening programmes" was applied to define the first cluster, and remaining countries are further separated based on their mortality rate

the collection of good quality samples. National registries allow for excellent monitoring of epidemiological parameters and screening performance. Screening results are always communicated to the women, even if negative.

Head for cluster 1 countries was Finland. An organized screening programme was introduced in 1963 with regular updates. Guidelines recommend a starting age of screening at 30 years, although cases of severe cervical dysplasia are reported as early as 25 years of age. National guidelines have defined the target population, screening intervals and management of abnormal findings since 1992. Organisation and financing of screening are part of a national health care system. Implementation of screening is the responsibility of the 431 municipalities, but most of screening activities are coordinated and supervised by the Finnish Cancer Society.

Target population of women between 30 and 60 years of age is approximately one million, and they are screened at five-year intervals. Some municipalities start at age 25 and end at the age of 65, the target population in this age group is 1.4 million. Women are identified from the population registry and each woman receives a personal invitation by mail, and an appointment. A recall letter is sent if a woman does not attend the examination. Screening for cervical cancer according to screening guidelines is free of charge to women, including the additional tests required in case of positive initial screening results. Funding is public, and provided from direct taxation through the national health system More than 90% of women 30 years and older are invited and on average 70% of women follow the invitation. Rate of spontaneous screening is not registered.

A detailed screening algorithm is defined for primary screening as well as the management of abnormal findings, based on the Finnish guidelines. The management of abnormal cervical findings is aligned to the guidelines of the European and American Societies for Colposcopy and Cervical Pathology. Pap smear is the primary screening tool, performed by trained health professionals in health care centres, ensuring a low rate of inadequate smears (below 1%).

National Cancer Registry provides complete data on cancer incidence and mortality since 1953. The Mass Screening Registry records and files screening invitations and results for cervical, breast, and prostate cancer. Every municipality has to submit data to both registries, which are maintained by the Finnish Cancer Society. Existence of national registries allows for a thorough monitoring of the epidemiology and screening performance nationally. Outcome evaluation shows an 80% reduction of incidence and mortality rates since the 1960s with a slight increase in incidence recently (Figure 3).

In cluster 2, well designed screening programmes are usually in place. Registries maintained are at regional levels, giving accurate although partial information on country situation.

Head of cluster 2 was Italy. Organised cervical cancer screening on a national basis was introduced in 1996. National guidelines for cervical screening are produced by Italian Ministry of Health. Organisation and financing of screening belongs to National

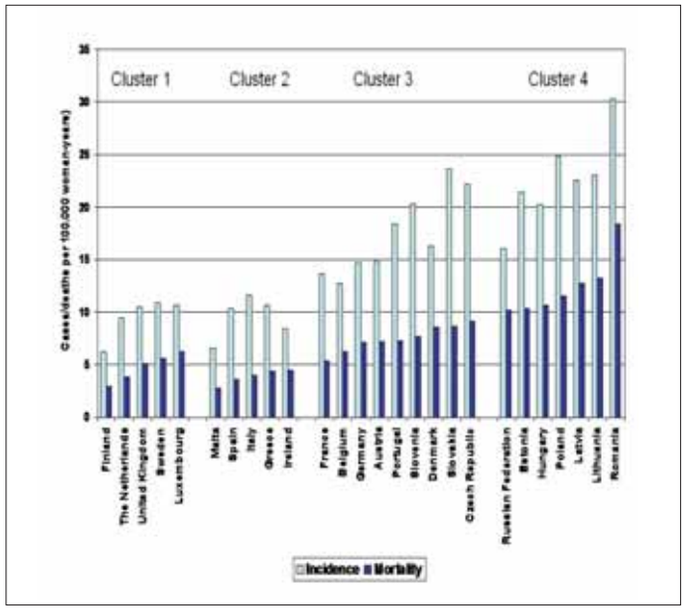

Figure 2. Incidence and mortality of cervical cancer in European countries by cluster (crude rates)

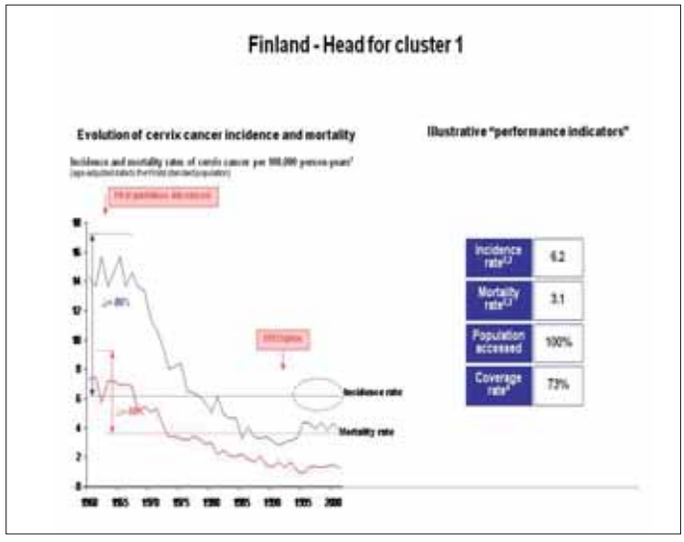

Figure 3. Assessment of the outcome of the current cervical cancer screening programme in Finland, representing Cluster 1

Health Service. Implementation of screening activities is delivered by regional health services of 21 regions in Italy. To date, 17 out of the 21 regions (covering 80% of the population) have decided to implement these guidelines, with implementation starting in 2005.

Target population of women between 25 to 64 years of age is approximately 16 million. Women are screened at 3 year intervals and one-third of the target population is invited each year through general practitioners. Each woman in the target population receives an individual invitation by mail from regional health services, and an appointment. If the woman does not attend, two recall invitations are sent, and if she still does not attend, she will be re-invited three years later. The results are always communicated to women, even if negative.

Screening for cervical cancer is free of charge for women within the national guidelines, including additional tests required in case of positive results. In the regions that have not implemented the national programme yet or for screening between the recommended intervals, women have to pay a lump sum for the Pap smear.
The National screening programme captures approximately 39% of the women. Opportunistic screening in private practices captures approximately 40% of the women; in addition, there is no registration of the screening results.
A detailed algorithm has been defined in Italy for the primary screening and management of abnormal findings, although not implemented in all regions. Pap smear is the primary screening tool and quality assurance systems are in place.
There is a regional registry in which performance indicators of the screening programme are collected and evaluated. Submission of screening data by regions to this registry is mandatory. Regional registries are consolidated in a national observatory for oncological screening monitoring cancer prevention performance which has existed since 2000. Regional registries contain information on activities carried out within the national programme exclusively. Screening tests implemented outside the programme are not recorded. Information from the regional/national registry seems reliable, although reflecting only a part of the country, and national epidemiological data on cervical cancer are extrapolated from regional information. Regional cancer registries are also in place, although covering only 15-20% of the Italian population. Only a limited linkage exists between screening and cancer registries. Incidence rate of cervical cancer has dropped over the last 11 years by 20%, whereas the mortality rate remains stable (Figure 4).
In cluster 3 there is a partly organised system with a mixed invitation/voluntary attendance, targeting the majority of women in the relevant age-group. A very large age-interval is covered with a yearly frequency of smears. New technology is available free of charge in case of abnormal findings. A self-referral system has not allowed the coverage of all women by an invitation

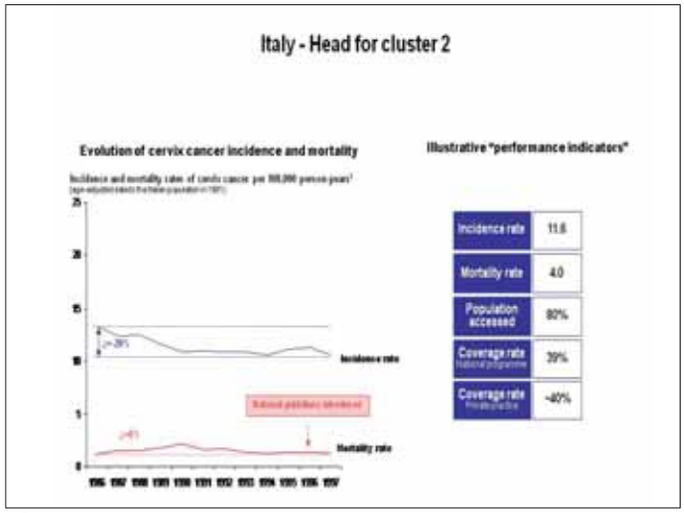

Figure 4. Assessment of the outcome of the current cervical cancer screening programme in Italy, representing Cluster 2

system and there is no control of whether or not the women are reached by screening. There is a lack of information about the performance of a screening programme on a national level and therefore limited ability to improve the process and optimisation of financial spending. There is a lack of harmonisation of the quality of cytology across regions and management of abnormal findings across physicians.
Head of this group was Germany. A statutory cancer screening programme was introduced in West Germany in 1971 with a predominant focus on breast cancer and cancer of the colon. In 1991, this programme was extended to former East Germany. A cervical cancer screening programme is partly organised at a national level. Guidelines are defined by scientific committees. They include age, frequency and type of primary screening tools, classification of Pap smear findings as well as quality assurance protocols. Those guidelines are implemented and controlled by health insurances (450 statutory and 100+ private companies).
Screening is offered as early as 20 years of age on a yearly basis and no age limit is mandatory but is decided by physicians and patients. Size of the target population is approximately 25 million. Recruitment is mainly a voluntary system. A proportion of women are covered by an invitational system from the insurance company. This invitation is a form to be filled in by a gynaecologist and cytologist and sent to the insurance. Women still have to fix the appointment with their physician and there is no recall of women in case of no show (due to data protection measures).
There is not a single national screening registry in Germany. Cancer registries are managed on the level of federal states and their contents vary according to the extent of data protection offered to individuals. In addition, not all federal states have a cancer registry. Existing registries gather information about incidence, mortality and survival by age split. Registries do not contain information about the screening test, results, and follow-up (with the exception of some pilot-projects). Information on the performance of screening programme is not available for the entire country and is generally extrapolated from the individual states.
Statutory health insurance programmes and private insurances cover the costs of the screening examination as well as any diagnostic follow-up or treatment of abnormalities detected by screening. Most women are covered by insurances (more than 95% of the population), mainly through statutory insurances (90% statutory and 10% private).
Pap smear is the tool for primary screening and parts of the subsequent management of abnormal findings is left at the discretion of the screener. A significant drop of incidence and mortality with 65 and 60% respectively has been seen since the 1970s (Figure 5).
Head for cluster 4 was Poland. Screening system is not well organised and there are limited guidelines for screening tests and the invitation system is opportunistic. Free cervical cancer screening is offered to each woman attending a gynaecology visit with the possibility of benefit from a higher level of diagnosis in case of positive primary screening. However, the standard technique, e.g. colposcopy, is not sufficiently used and new techniques are not available. There is an insufficient quality assurance system with respect to collection, preparation, stor-

age, and analysis of cytology slides. Mortality and morbidity are under-registered and underestimated in the national cancer registry. There is no screening registry for cervical cancer in place. Opportunistic screening in private practices is significant, although there is no monitoring of processes and results.

A national breast and cervical cancer screening programme was developed in 1999. Some screening guidelines have been defined (e.g. age, primary test, financing of screening, type of tests to be used for primary screening), and implementation of the programme is largely up to each region/city and up to each physician. A national programme "against cancer act" is under finalisation and implementation should start in 2006. Under this act, new guidelines will be set out for cervical cancer with the establishment of one national centre which will coordinate and monitor the activities of 16 regional centres, quality assurance of cytodiagnosis and wide introduction of cervical cancer management techniques.

Women between 25 and 59 years are screened on a yearly basis. Size of the target population is 9.8 million. It is planned to extend the age limit to 64 years, which would increase the size of the target population to 10.6 million women. The frequency will be extended to every three years. At the moment, no proactive recruitment is in place and women are proposed to be screened opportunistically during a visit to their gynaecologist. From 2006 on it is planned to send an invitation letter to each woman.

There is a national cancer registry in place since 1997; each physician has to report the age of the patient, type of neoplasm, and type of treatment. No specific information about cervical cancer is available and no registration of the number of screening tests, test results, and patient follow-up is recorded. There will be a national registry for cervical cancer, implemented and managed by the Ministry of Health.

Tests within screening programmes are free for women and financed by their obligatory social security (covering more than 90% of the population). The programme is either financed by the city if organised by the city, or financed by the sickness funds. Screening can also be done in private practice, although the women have to carry the full costs. The future screening programme will be financed by a special budget from the Ministry of Health.

Pap smear is the primary screening tool. There are some guidelines for the management of abnormal Pap smear results in place. In future, the screening algorithm of the ASCCP guidelines will be used. Poland displays one of the highest cervical cancer incidence and mortality rates. In the European Union and on the data available, there seems to have been a reduction of incidence of 55% and of mortality of 30% over the last three decades (Figure 6).

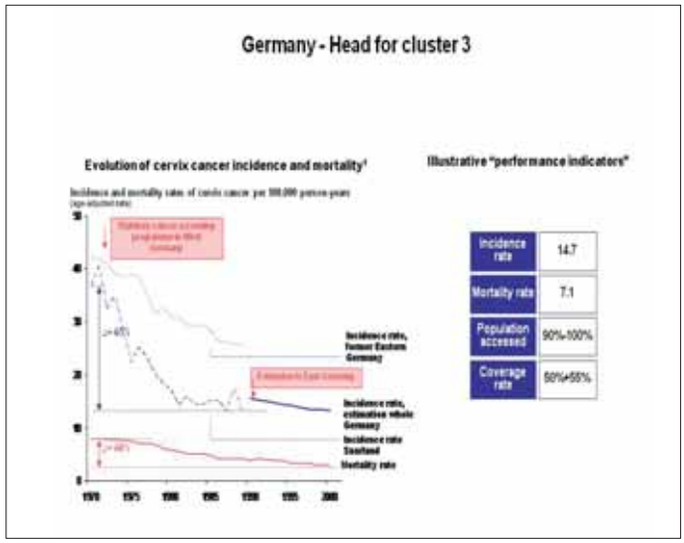

Figure 5. Assessment of the outcome of the current cervical cancer screening programme in Germany, representing Cluster 3

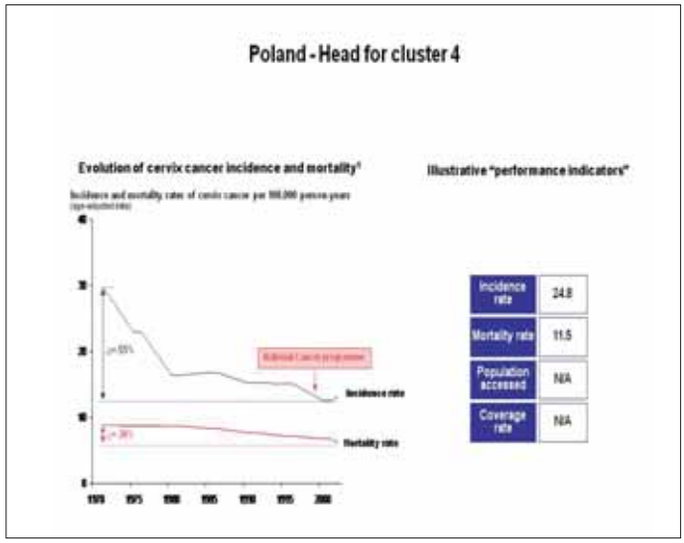

Figure 6. Assessment of the outcome of the current cervical cancer screening programme in Poland, representing Cluster 4

Discussion

The present study shows that European countries can be grouped on the basis of current practice of cervical cancer screening. Countries from clusters 1 and 2 have well established cervical screening programmes and gather relevant epidemiological information on cervical cancer prevention. Although nationally organised screening programmes exist in cluster 1 but not cluster 2, the outcomes of cervical screening for cervical cancer incidence and mortality in countries of these clusters is similar, keeping in mind that reports on decreasing incidence and mortality rates are only reliable for countries in cluster 1 and Denmark. Thus, existence of a nationally organized programme is not the only pre-requisite for successful implementation of cervical screening, although it may influence efficiency. Countries from clusters 3 and 4 (except Denmark) have less developed national or local cervical screening programmes and are characterized by a higher disease burden.

In the majority of European countries, there is a willingness on the part of health authorities to provide cervical cancer prevention. The extent and effectiveness of current prevention is variable. Cervical cancer screening can be highly effective in those

countries where there are highly organised programmes. It is estimated, and shown in practice (e.g. in Finland), that full implementation of such programmes has reduced the number of deaths from cervical cancer by 80% (9). Effectiveness of screening depends on the organisation, i.e. coverage, frequency and test performance which are governed by local guidelines.

In the prevention of cervical cancer, vaccination represents the primary prevention strategy whereas screening provides a secondary means of prevention, and thus an integrated approach should optimize the effect. This approach has been advocated by numerous public health bodies including WHO (10, 11). Different incidence and mortality rates could impact the design of an HPV vaccination strategy throughout European countries.

Furthermore, the impact of the HPV vaccination can be monitored through cervical screening programmes and existing registries. Continued cervical screening programmes, where they exist, are important for monitoring the impact of vaccination, and providing protection for cervical cancer associated with HPV types for which there is no protection or cross-protection offered by vaccination. Currently, there is no evidence of significant therapeutic benefit of vaccination in women with an established HPV infection. Therefore, it is important that women who are vaccinated are informed of the necessity to continue to comply fully with screening recommendations, and to ensure compliance with the screening programmes and current screening practices.

Vaccination has the potential to reduce the economic and social burden associated with screening and follow-up procedures. As a result of mass vaccination of women against HPV-16/18, the number of HPV-16 and 18 infections in the population should decline, as well as the numbers of lesions and cancer associated with these types. It is predicted that a vaccine which prevents 75% of persistent HPV-16/18 infections could reduce HPV-16/18 related cervical cancer cases by 70-83% with effects also on HSIL and LSIL (10). This will result in a reduction in abnormal smears and in follow-up colposcopy treatment. Therefore, an overall decrease is expected in terms of the cost of screening programmes, as it is foreseen that vaccination could ultimately allow delayed entry into screening programmes, an increase in the required intervals between screening visits, and a reduction in the need for follow-up colposcopy and treatment.

There is also the potential for a vaccination programme to achieve a high-level of coverage among women who do not participate in regular screening. To ensure broad coverage vaccination requires suitable information on HPV and cervical cancer for potential vaccinees and their parents. The major drawbacks of the vaccine can be the risk of lower attendance rates due to false security among the vaccinated women and lower positive predictive value of screening leading to increased cost of screening. Besides, antibody persistence and protection against persistent HPV infection have been shown for up to 5 years, but further studies are necessary to evaluate the duration of protection (7).

The validity of the assumption that countries which successfully implement a nationally organized screening and better health care organization might be successful in implementing an effective vaccination programme is supported by evidence from measles immunization in Europe. With regard to measles, the countries from cluster 1 belong to those with a good control of measles resulting in a low incidence, while the head of cluster 3, i.e. Germany, belongs to the European countries with the highest measles incidence (12). Policymakers should be aware of the benefit of good screening programmes before implementing HPV vaccination and also need to be aware of the success and limitations of the current practice for the prevention of cervical cancer in the country groups in order to ensure that all women may benefit from HPV-vaccination.

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European Cervical Cancer Prevention Board

List of 24 opinion leaders in 12 countries, which are the members of the CCPB:

Belgium: Dr. Marc Arbyn, Prof. Frank van Ranst; Czech Republic: Prof. Roman Prymula; Finland: Dr. Dan Apter, Dr. Pekka Nieminen, Prof. Jorma Paavonen; France: Dr. Josef Monsonego; Prof. Catherine Weil-Olivier; Germany: Prof. Ulrich Schenk; Prof. Heinz Schmitt; Prof. Achim Schneider; Hungary: Dr. Peter Bosze; Italy: Dr. Fausto Boselli; Prof. Gioia Montanari; The Netherlands: Prof. Theo Helmerhorst; Dr. Marjolein Van Ballegooijen; Poland: Dr. Jacek Luczak; Dr. Marek Spaczyński; Russia: Prof. Vera Prilepslaya; Prof. Svetlana Rogovskaya; Spain: Dr. Juan Picazo; Dr. Luis Puig; UK: Dr. Ian Duncan; Prof. Julian Peto

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