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The challenges of organising cervical screening programmes in the 15 old member states of the European Union

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ABSTRACT

Cervical cancer incidence and mortality can be reduced substantially by organised cytological screening at 3 to 5 year intervals, as was demonstrated in the Nordic countries, the United Kingdom, the Netherlands and parts of Italy. Opportunistic screening, often proposed at yearly schedules, has also reduced the burden of cervical cancer in some, but not all, of the other old member states (belonging to the European Union since 1995) but at a cost that is several times greater. Well organised screening programmes have the potential to achieve greater participation of the target population at regular intervals, equity of access and high quality.

Despite the consistent evidence that organised screening is more efficient than non-organised screening, and in spite of the Cancer Screening Recommendations of the European Council, health authorities of eight old member states (Austria, Belgium, France, Germany, Greece, Luxembourg, Portugal and Spain) have not yet started national organised implementation of screening for cervical cancer. A decision was made by the Irish government to extend their pilot programme nationally while new regional programmes commenced in Portugal and Spain.

Introduction of new methods of prevention, such as HPV screening and prophylactic HPV vaccination, can reduce the burden further, but this will require a high level of organisation with particular attention needed for the maximisation of population coverage, compliance with evidence-based guidelines, monitoring of data enabling continued evaluation and improvement of the preventive programmes.

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1. Introduction

Among all malignant tumours, cervical cancer is the one which can be most effectively controlled by screening. Detec-

tion of cytological abnormalities by microscopic examination of Pap smears, and subsequent treatment of women with high-grade cervical intraepithelial neoplasia (CIN), avoids the development of cancer.¹ In 1986, the high effectiveness

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of cervical cancer screening using Pap smears was established through the expert review of case-control and cohort studies as well as by comparisons between areas or periods with different population coverage.² Further evidence has been generated from more recent studies,^{3–6} confirming the conclusion that well organised cytological screening, every 3 to 5 years in the age range 35–64 years reduces the incidence of cervical cancer by 80% or more among screened women.⁷

In 1993, when the European Union (EU) comprised 12 member states (Belgium, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Denmark, Portugal, Spain and the United Kingdom), the first edition of the European Guidelines for Cervical Cancer Screening was published in this journal.⁸ Two years later, Austria, Finland and Sweden joined the Union. In the 1990s, cytological screening was well organised in only a few countries, such as the Nordic countries, the United Kingdom, the Netherlands and parts of Italy.⁹ In the other countries, screening was mainly opportunistic, depending on the initiative of the individual woman or her doctor. The first edition of the European Guidelines for Quality Assurance in Cervical Cancer Screening established the principles of organised screening. It was pivotal in initiating some new pilot projects in Europe and pioneering in launching the concept of quality assurance.¹⁰ Nevertheless, the 1993 version has had limited impact on opportunistic screening in countries with a 'liberal' health care system.¹¹ In 2003, the national ministers of health of all member states endorsed the European Council Recommendation on Cancer Screening and proposed that screening for breast, colorectal and cervical cancer should be offered only in organised settings.¹² In 2008, the European guidelines were updated in a 2nd edition, which corroborated the principles of organised screening and assessed the level of evidence regarding the effectiveness of new methods of cervical cancer prevention.¹³

In the current paper we demonstrate that well organised screening programmes have a greater impact than opportunistic screening because they have the potential to achieve greater participation of the target population at regular intervals, equity of access and high quality. In the second part, we discuss the challenges for health authorities and health professionals in implementing recommendations to organise screening where it is not yet standard. The current paper is restricted to screening in the 15 old member states of the EU in 1995, with some relevant references to Iceland and Norway, which are not EU members. Cervical cancer prevention in the new member states, where the burden of cervical cancer is of a higher order of magnitude,^{14,15} is discussed separately.¹⁶

2. Evidence indicating greater effectiveness and efficiency of organised versus non-organised screening

2.1. Trends in Nordic countries

Trend analyses in Denmark, Finland, Iceland, Norway and Sweden have revealed a strong correlation between the decline in the burden of cervical cancer and the geographical extent and the population coverage of organised cytological screening.¹⁷ In Norway, with only 5% of the population cov-

ered by organised screening, the cumulative mortality rates (0–74 years) fell by only 10% between the late 1950s and the early 1980s, whereas in Finland and Iceland, with nationwide implementation of organised screening, the reduction was 50% and 80%, respectively.¹⁷

In Finland, where a high level of organisation was reached (targeting women in the age range 30–60 years, screening interval of 5 years, 70% attendance, 98% invitational coverage), age-standardised incidence and mortality dropped by approximately 80%, between the start of the programme in 1963 and the 1990s.¹⁸ A case-control study, comparing screening histories in women with and without cervical cancer in the Helsinki area, showed that the age-adjusted odds ratios (reflecting the relative risk of getting invasive cancer compared to non-screened women) were 0.25 (confidence interval [CI]: 0.13–0.48) for women participating exclusively in organised screening, 0.57 (CI: 0.30–1.06) for women participating in opportunistic screening only and 0.27 (CI: 0.15–0.49) for those attending both types of screening.¹⁹ These results indicate that the decrease in incidence of invasive cervical cancer was mainly due to the organised mass screening programme.

In Denmark, cervical cancer screening is organised at a county level. In 1962, the first county set up a pilot screening programme, followed, in subsequent years, by several other counties. However, 30 years passed before screening was organised over the whole territory.²⁰ Incidence rates of cervical cancer were significantly higher in counties that started organised programmes later (after 1980) compared to those that had started earlier (1980 or before). In one county, the organised programme was interrupted between 1982 and 1994 resulting in a significant increase in the incidence of and mortality from cervical cancer. It was shown that contrasts in the burden of cervical cancer were mainly explained by differences in organised screening coverage.²⁰

In 1995, Norway set up a national centralised system based on the integration of spontaneous and organised activities and comprising obligatory registration of all screen tests carried out in the organised, as well as in the opportunistic, setting. The 3-year coverage in the 25–67 year age group in the period 2001–2004 increased by about 7% compared to the period 1992–1995.²¹ At the same time, the consumption of smears decreased by 7%. Also, the increase in coverage was accompanied by a decrease in the average number of yearly smears used (533,000 versus 494,000) and reached more older and high-risk women. Consequently, the incidence of invasive squamous cervical cancer, which was stable over the first half of the 1990s, dropped and was 22% lower in 1999–2000 compared to the 2-year period preceding the introduction of the programme.²¹

2.2. United Kingdom, Netherlands and Italy

Although cervical cancer screening in England and Wales started in 1964, it failed to achieve sufficient screening coverage and adequate follow-up of women with cytological lesions for over 20 years. The recognition that the incidence and even the mortality was rising among young cohorts²² prompted health authorities to set up a national screening programme in 1988, involving financial incentives for general practitioners reaching 80% coverage and mandatory quality

assurance procedures.²³ The screening coverage rose from 42% in 1988 to 85% in 1994, and the incidence of invasive disease rapidly decreased by 35%.^{24,25}

The Dutch nationwide screening programme started in 1989 for women aged 35–54 years with screening at 3 year intervals. Evaluation revealed suboptimal performance and, in 1996, the programme was restructured. It concerned the management and financing of the programme, organisation, target age ranges (30–60 years), a longer screening interval (5-years), follow-up of abnormal results, and evaluation.²⁶ As a result, the coverage increased substantially (currently around 80%) and the follow-up compliance among screen-positive women improved as well. Also, side effects of screening were reduced by a decrease of the test positivity rate from over 10% to approximately 2%.²⁷ In spite of the longer screening interval and the lower percentage of women under follow-up, no increased incidence of interval cancer was noted and the incidence of cervical cancer was maintained at a very low rate.^{28–30}

In Italy, it was shown that through organised screening the incidence of cervical cancer can be reduced further in areas with pre-existing opportunistic screening.³¹

2.3. Opportunistic screening in other countries

In Austria, Belgium, France, Germany and Luxemburg, a substantial reduction in cervical cancer mortality has been observed.^{32–35} In these countries, screening is mainly opportunistic, with the exception of a few isolated locally organised programmes. Opportunistic screening is characterised by too frequent testing, often performed by gynaecologists, and low coverage among older women, in socio-economically disadvantaged and high-risk categories, heterogeneous quality, uncontrolled introduction of new technologies and a poor level of monitoring.^{16,11,36–38} All these elements result in poor cost-effectiveness.

For instance, in Belgium, approximately 1.2 million cervical samples are taken each year, whereas approximately 900,000 screening samples would be sufficient to cover the whole target population, if the recommended policy (one smear every 3 years for women in the 25–64 year age range) was adhered to.³⁹ In Germany, the quality of cytological screening has been reported to be poor, partially due to inadequate collection using cotton tip applicators, with low sensitivity for detection of high-grade CIN (less than 45% in certain settings).^{40,41} In Germany, Luxemburg and Austria, yearly screening is still the official policy, despite evidence of its low cost-effectiveness.³⁶

In Ireland, Spain and Portugal, increased mortality has been reported, which is explained most plausibly by the absence of a population-based screening programme or the low quality and coverage of present opportunistic screening.^{32,42,43}

2.4. Cost-effectiveness of different screening policies

Fig. 1 shows the efficient cost-effectiveness frontier of optimal starting ages, number of scheduled examinations, and screening intervals, including cost-effectiveness of different screening policies in use in several old member states in the 1990s.³⁶ The costs and number of life-years gained were com-

puted assuming 100% participation of the target population, absence of excess Pap smears, average sensitivity and natural history parameters.³⁶ When moving toward a more intensive policy (starting at a younger age and ending at an older age with a shorter interval), the incremental cost-effectiveness ratio increased because the incremental effects rapidly diminish. Screening policies from Finland and the Netherlands were remarkably close to the efficient frontier. Screening every year starting at young adult age without an upper age limit, as recommended in Austria, Germany and Luxemburg (>50 smears/lifetime), yielded a rather small additional gain in life years but at a cost that was dramatically high (Fig. 1). The costs per percentage reduction of life-years lost due to cervical cancer estimated for the German screening policy (yearly intervals, 50 smears per lifetime) were approximately five times greater than for the Finnish or Dutch policy (5-yearly screening).⁴⁴

3. Imperfections of organised programmes

Organised screening is more effective than non-organised screening but is not free from imperfections and achieved effects are not permanent if attention wanes. However, an intrinsic characteristic of organised screening is that imperfections come to the fore more easily and can be corrected in due time.

In England, since the year 2000, overall screening attendance has remained at a high level (80% screened <5 years ago, in the age group 25–64 years) but a continuing slow but steady fall-off has been observed among women under 50.⁴⁵ Similarly, in the Netherlands, the coverage among women in the youngest target age (30–34 years) has ceased to improve since 1999 and is currently lagging behind other age groups by about 10%.¹⁶ Moreover, screening coverage is still lower in areas with low socioeconomic status, resulting in higher incidence rates of cervical cancer and more advanced staging at diagnosis.⁴⁶ In a Finnish area, poor performance observed in a cytology laboratory, characterised by low detection rates of cytological lesions, was accompanied by an increased incidence in the rate of cervical cancer.⁴⁷ In Denmark and Italy, where preventive health care is the responsibility of counties or provinces, extension of well organised screening has been slow.^{20,48} A nationwide audit in Sweden detected regional differences in terminology and coding that hampered the straightforward pooling of data and highlighted the need for uniform methods of data collection.⁶

4. Challenges for the future

Despite evidence indicating greater effectiveness and cost-effectiveness of organised screening and in spite of the European Council Recommendation,¹² detection of cervical cancer precursors remains mainly opportunistic in eight of the 15 old member states. It should be considered as a compelling responsibility for national or regional health authorities of these countries to set up organised programmes preferably extending over the whole country in agreement with current European Guidelines for Quality Assurance for Cervical Cancer Screening.¹³ Stakeholders and health professionals must understand that organised screening is not a question of

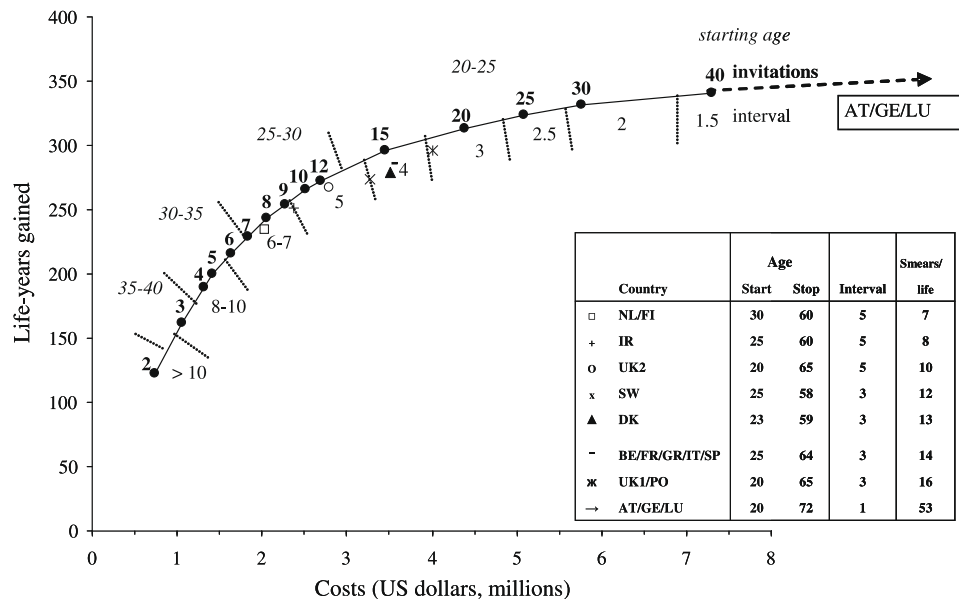


Fig. 1 – Schematic representation of the simulated efficient frontier showing the location of optimal starting ages, number of scheduled examinations, and screening intervals, including a comparison of the costs and effects for screening policies used in countries with a cervical screening programme or a programme recommended in national guidelines. The starting age ranges (in years), number of invitations and screening intervals (in years) are indicated above, on, or under the curve, respectively. The estimated life-years gained (per 1,000,000 screened women) and costs are shown for nine screening policies in place in EU member states in the 1990s (AT = Austria, BE = Belgium, DK = Denmark, FI = Finland, FR = France, GE = Germany, GR = Greece, IR = Ireland, IT = Italy, LU = Luxembourg, NL = The Netherlands, PO = Portugal, SW = Sweden, SP = Spain, and UK = United Kingdom) using a discount rate for costs and effects of 3% (adopted from Van den Akker et al.³⁶).

economy to save resources for the public treasury but is, first of all, a question of optimising the effectiveness and minimising the adverse effects.

4.1. Roll-out of pilot projects or local programmes to national implementation

In Denmark, since 1996, and in Sweden, since 1977, all counties are covered by an organised programme.^{20,49} In Italy, geographical coverage is rising progressively with 69% of the target population currently covered by an invitational system.⁴⁸

Interesting pilot projects of organised screening have been set up over the past decades, for instance, in Bas-Rhin and Isère (France), the five Flemish provinces (Belgium),^{50,51} in Vorarlberg (Austria)⁵² and in Ormylia (Greece).⁵³ These local initiatives were more or less successful, but were never able to manage all the stages of an organised screening programme and were never extended to the national level. In the Bas-Rhin programme, all smears are recorded and under quality control whether the woman was invited or not. Three-yearly coverage in the 25–64 year age group reaches 71% (10% above the estimated coverage for the whole of France) and compliance to colposcopy is over 84%. Unfortunately, over-screening is still significant because health authorities do not limit reimbursement of unnecessary smears.⁵⁴ In France, national implementation of organised screening according to European guidelines, as successfully implemented in Bas-Rhin, has been proposed on several occasions without success. This was repeated very recently at a workshop organised at the Institut National du Cancer, by a

group of national and European experts (Paris, 25 September 2008). The decision whether to implement this recommendation or not and the choice between cytology and HPV-based screening now rests in the hands of the French National Health Authority.

It is encouraging to note that the Irish Cervical Screening Programme Phase I which commenced in 2000, in Limerick, has been extended nationally since 1 September 2008.¹⁶ A contract for the provision of smear taking services was issued directly to doctors in primary care settings. The Programme has signed a contract with Quest Diagnostics USA for the provision of cytology services to ensure volume capacity and turnaround time in an accredited facility. Colposcopy services are an integral part of the Irish programme. It is also encouraging to observe emerging pilot programmes in Spain and Portugal.¹⁶ For regional screening programmes, it is crucial to evaluate the technical quality and population coverage, and to modify the programme appropriately before roll-out at the national level is considered.

4.2. Integration of data collection from opportunistic screening activities

In countries with organised screening systems, a substantial volume of opportunistic screening may co-exist with organised activities and this also consumes public resources. Screening could be further improved by extending data collection and evaluation procedures to include opportunistic screening activities such as is currently conceptualised in Sweden and Norway.

4.3. Homogenisation of screening throughout the whole state or region

In countries with decentralised responsibilities for preventive health care, the definition of screening policies, implementation of screening guidelines, data collection and evaluation should be homogenised. Funding should be made available to create a permanent team of highly skilled screening specialists to support health authorities and professionals workers involved in screening at the intermediate or local level. Such a team of specialists could also contribute to the training of health workers, establishing contacts with scientific societies, centralisation of data collection, analysis and statistical interpretation, organisation of the feedback at the peripheral level, scientific reporting, information to public and health authorities and coordination of screening activities.

As highlighted in the Swedish audit, and as a requirement for national and international comparison, it is of major importance to use common terminology and to develop uniform monitoring systems for screening and follow-up.⁶ European guidelines allow proper national terminology systems which as a minimum should be perfectly translatable into the widely used *Bethesda System*⁵⁵ for reporting of cervical cytology. Information systems should be adapted whenever a new screening or triage method, such as HPV testing, is introduced. Regional screening programmes should use unique identifiers and procedures for data exchange between regions to allow completeness of data and to enable linkages between screening, follow-up and cancer registries.

4.4. Reaching older women

In organised screening, invitations cease at an upper age limit (59–65 years in the old 15 member states of the EU). It has been proposed that regularly screened women, aged 50 years or older, with successive negative cytology results have a very low-risk of cervical cancer precursors later in life and could be safely discharged from further screening.^{56–58} This proposition has been challenged by recent data from the Netherlands showing that cumulative incidence of invasive cancer after three consecutive negative smears was similar in younger (30–44 years) and older women (45–54 years).⁵⁹ However, unscreened or insufficiently screened older women are still at considerable risk and could benefit from screening beyond the target age range.⁶ Moreover, older women treated for high-grade CIN have a higher rate of recurrence or residual disease than younger women.⁶⁰ Women with a history of CIN treatment, in general, are at risk for subsequent cervical cancer that is 2–4 times higher than in the general population and this increased risk further rises by age at diagnosis.^{61,62} A negative HPV at the age of 50 years or older or after treatment of CIN has been proposed as a criterion for ceasing screening or relaxing follow-up. Nevertheless, data are conflicting.^{63,64} More research is needed regarding the choice of the age limit to stop screening, taking into account the screening and treatment history, the remaining healthy-life expectancy, the age-specific incidence of cervical cancer as well as age- and stage-specific survival.

4.5. Monitoring of performance

In order to be able to identify and act on problems, screening should be organised in such a way that the process, the impact, the side effects and the costs can be evaluated (invitation of the target population, response to invitation, overall attendance [organised + opportunistic], results of screen tests, proportion of unsatisfactory tests, compliance to follow-up or management according to guidelines, occurrence of interval cancers and auditing of all registered cancers).⁶⁵ Such a comprehensive evaluation requires population-wide individual linkages of routinely collected data, screening tests (laboratory results), follow-up (histology, treatment), cancer registry and mortality. Given evidence on obstetrical morbidity associated with prior surgical therapy of CIN, it is recommended to link treatment with maternity files.⁶⁶ Health authorities should create the legal and administrative framework, and services involved in data collection and processing must include adequate safeguards to preserve data safety and privacy. Where HPV vaccination is introduced (which should, preferentially, also be organised), vaccination registries linkable with the aforementioned data files must be set up as well.

A particularly interesting evaluation tool is the audit of screening histories of patients with cervical cancer selected from the cancer registry and matched with controls free of cancer, using a case-control study design.^{3,6} Such case-control studies can be made even more informative by examining archived cervical cytology samples, allowing distinctions between screening and management errors. Cervical cytology biobank-based research is also a powerful tool to evaluate future screening methods and to answer pending questions on HPV vaccination (cross-protection, type replacement, duration of protection).^{67,68} For instance, HPV testing using material scraped from stored smears of cancer cases and non-cancer controls could answer the question of whether interval cancers (previously Pap smear negative) could have been picked up by HPV screening.⁶⁷

4.6. Structural funding favouring the organised approach

Health authorities and services defining tariff rates should direct public funding to the organised, quality-controlled, evidence-based and surveyed screening activities. The key to the success of the English programme involving payment of an additional fee for GPs reaching 80% coverage of their clients seems to be an effective template. Payment per individual screening act, independent of the screening interval or age, favours over-screening, which is cost-ineffective from an economical point of view but also results in over-diagnosis and over-treatment with associated adverse effects.^{66,69} In Sweden, women not recently screened are invited to have a smear taken by a midwife. A visit to a doctor for a screening test is five times more expensive. In Stockholm, organised screening was free until 2003. Introduction of a fee (14€) resulted in a decline of attendance of 23%. When, in 2004, reimbursement for spontaneous screening visits to doctors was abolished and, in 2005, organised screening was rendered free again, attendance to organised screening rose to previous levels.⁷⁰ In the Netherlands, the issue of over-screening was

addressed in the national GP guidelines for cervical screening by abolishing payments for non-programme primary smears and by introducing special forms attached to the individual screening invitation, based on which payments are made (and not otherwise). However, in France, propositions to reduce payment for over-screening were not accepted by gynaecologists and lobbying from professional groups impeded resource reallocation favouring organised screening.⁷¹

4.7. EU added value to improved cervical cancer screening in the member states

The EU should offer a forum for discussion and exchange of experiences among national and regional experts who are mandated to manage or evaluate screening programmes. The EU should also continue to support international data collection using standardised aggregated datasets allowing calculation of comparable performance indicators as conceptualised within the European Network for Information of Cancer Epidemiology.⁶⁵ The EU could organise or at least actively support international efforts to assess and pool evidence of efficacy and effectiveness of new methods of cancer prevention.⁷² Unbiased international systematic reviews of evidence are an important source in keeping guidelines updated. Finally, the EU should continue publishing guidelines taking into account actualised scientific evidence, cost-effectiveness and affordability.¹³

4.8. Introduction of new methods of cervical cancer prevention

European guidelines, updated according to evidence available in early 2007, recognised the clinical utility for high-risk HPV testing in the triage of women with atypical squamous cells of undetermined significance (ASCUS) and in the follow-up of women treated for high-grade CIN.^{13,73,74} For a discussion of new evidence from randomised trials comparing HPV- and cytology-based screening, the triage of HPV-positive women, use of HPV self-sampling to reach non-participants at high-risk of cervical cancer, HPV vaccination and adaptation of screening policies for vaccinated cohorts, we refer to other sources.^{72,75,76} It must be stressed that new strategies of cervical cancer prevention must be evaluated thoroughly before introduction, preferentially in an organised setting. Updated and evidence-based European guidelines on HPV screening and vaccination are currently being worked out and these should be ready by 2010. When new methods are introduced, information systems should be adapted accordingly, integrating all screening, triage and management data and allowing appropriate invitation of women (possibly at longer intervals), follow-up of screen positive subjects and evaluation of the modified policies.

5. Conclusions

The major take-home message for policy makers is that screening must be well organised with optimal screening coverage and follow-up of women with a positive screening test. The quality of screening should be assured and monitored at each stage of the screening process.

Achieving a high coverage for HPV vaccination is expected to reduce the burden of disease substantially which will require modification of screening policies, in the mid- to long-term. Meanwhile, cervical screening will need to be continued without change.

Conflict of interest statement

None declared.

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