Chapter 8
Recommendations for public health implementation and further research

Introduction

Much of the evidence to be generated on the long-term effectiveness of modified or new screening modalities, in terms of reduction in the incidence of invasive disease, will come from evaluation of the results of organized population-based programmes. Modifications of screening modalities in existing screening programmes therefore need to be introduced in a way that will facilitate rigorous evaluation of long-term effectiveness. This is best achieved by incorporating randomization.

This requirement is particularly relevant for cervical cancer screening, where much of the evidence for programme modifications comes from short-term end-points (e.g., cross-sectional rates of histological diagnosis of CIN 3) and cost considerations.

For the reasons above, this section presents recommendations for public health implementation and further research combined.

General

1. Two major determinants of the effectiveness of public health screening programmes are high coverage of the target population and quality of the total screening process including the primary screening test and follow-up of those positive. Research is needed on methods (i) to improve coverage, especially among deprived populations, and (ii) for continuing quality assurance, whatever the screening modality in operation.
2. Once an organized system is in place, opportunistic (or unscheduled) screening should be discouraged.
3. New developments in screening technology can be evaluated in short-term or cross-sectional studies using surrogate markers of efficacy such as sensitivity and specificity for a histological diagnosis of CIN 3, compared with screening tests known to reduce cervical cancer incidence such as high-quality conventional cytology. The design of such short-term studies is most efficient if the same women undergo both the new and the established test.
4. For longer-term assessment of efficacy in terms of absolute sensitivity or incidence of invasive cancer, a design in which women are allocated to different modalities is required. For example, comparison might be between HPV testing only versus cytology, cytology versus HPV testing plus cytology or visual inspection with acetic acid (VIA) versus cytology. Collection of material for retrospective analysis of another modality is an acceptable study design.
5. The adoption of a new screening modality in a population-based screening programme should depend upon the local cost environment, expertise and facilities. Considerations include the capacity both for the primary screening test and for management of screen-detected lesions. Any such implementation should be based on population-based studies.
6. All screening will have associated negative effects. These include psychosocial, biological and economic effects of the screening episode. Research is needed to minimize the impact of each of these components. In particular for cervical screening, research is needed into the possible negative effects of overtreatment of screen-detected lesions. In all comprehensive assessments and comparisons, full account needs to be taken of the potential harmful consequences of screening.
7. HIV-positive women have a higher prevalence of HPV infection and cervical cancer and its precursors of all degrees of severity. These women may therefore benefit from more frequent screening than HIV-negative women. Whether

screening should begin at a younger age in HIV-positive women is unclear and requires study.

Conventional cytology

The issues identified by the Working Group for implementation of conventional cytology were the ages at which screening should start and might stop, and the possibility of adopting different screening frequencies at different ages.

1. There is minimal benefit and substantial harm in screening below age 25. Organized programmes should not include women aged less than 25 years in their target populations.
2. Women who have always tested negative in an organized screening programme should cease screening once they attain the age of 65, as there is little benefit of screening to women over the age of 65 who have had at least two negative tests in the last 10 years. Research is needed to determine whether screening can cease earlier.
3. For women over age 50, a five-year screening interval is considered appropriate. For women aged 25–49, a three-year rather than a five-year interval might be considered in countries with the necessary resources. Annual screening is not recommended at any age.
4. Implementation of the preceding three recommendations needs continuing long-term evaluation in terms of invasive cervical cancer incidence and mortality.
5. In countries with limited resources, solutions other than those recommended above are likely to be required. However, screening should always be introduced after an informed strategic analysis within the context of the national (or regional) cancer control programme, and only after the necessary resources and facilities to permit high-quality screening, efficient diagnosis and management of detected abnormalities are secured.
6. New screening policies developed in accordance with the previous recommendation should usually be piloted in a feasibility (demonstration) project in a defined area with a defined population, preferably with a population-based cancer registry. In the absence of such a registry, an information system that includes data on the cases of clinically invasive cancer that occur in the population can be used.

New developments in cytological screening

1. Large, randomized controlled clinical trials comparing the performance of LBC and conventional cytology need to be conducted by laboratories in which the techniques are well established.
2. Implementation of liquid-based cytology and automation-assisted screening in organized screening programmes needs to be based on cost and local feasibility. It is imperative that the introduction of each new modality is accompanied by long-term evaluation of impact on invasive cancer and continuing quality assurance and monitoring. The age and screening interval for conventional cytology should also apply here.
3. New modifications to these modalities are frequently proposed. Each such modification needs rigorous evaluation in short-term assessments of relative sensitivity and specificity for histologically diagnosed CIN 3 compared to the current standard, as well as economic and logistic evaluations before implementation.

HPV testing

If a country, on reviewing the available evidence, decides to introduce HPV testing as a primary screening modality, it must consider local circumstances, including the acceptability of the test. Introduction would be facilitated by the availability of low-cost public-domain HPV tests. Implementation should be preceded by demonstration projects. Large-scale implementation needs to be designed so as to allow rigorous long-term evaluation.

1. It is likely that the same reduction in incidence of invasive disease could be achieved with a longer screening interval using HPV testing as a screening test than the intervals recommended above for cytological screening. It is expected that evidence supporting a longer interval may emerge from properly designed public health screening programmes in which HPV testing has been incorporated.
2. The optimal ages for starting and stopping HPV screening require further research. Age-specific population rates of HPV positivity and cancer incidence should be based on samples for immediate (reflex) cytology testing. Cohort studies and demonstration projects are appropriate for this research. At present, commencing HPV-based screening at ages below 30 years is not recommended.
3. The management of women who are HPV-positive but negative on cytology is of vital importance to avoid overtreatment, particularly in younger women, in whom transient infections are common. Research is required to identify secondary biomarkers, whether cellular or viral, which are accurate predictors of persistence of viral infection and/or progression of cervical lesions.

4. In countries that lack expertise for high-quality conventional cytology which adopt HPV testing as a primary screening test, long-term follow-up studies should be conducted of the effectiveness of HPV testing followed by colposcopy without cytology in women who test positive.
5. Efficient implementation of HPV screening requires research into HPV as a viral infection as well as a screening test. Aspects to be studied include: (i) factors, both individual and social, determining transmission and susceptibility; (ii) factors influencing age-specific rates of infection, reinfection, duration and natural history of infection in the relevant populations (these studies need to be by type and variant of HPV and, in particular, need to consider older women, for whom relatively little information currently exists); (iii) the consequences of using a test for a sexually transmitted agent as a primary screening test in terms of behavioural and psychosocial impact; and (iv) the natural history of HPV infection in males, including risk factors for persistence and transmission as well as the social impact of knowledge of HPV infection status in men and women.
6. Health professionals and the population at large must be educated on HPV and its connections with cervical cancer and screening programmes.
7. HPV testing systems need to be standardized and specification requirements for test performance need to be defined.
8. New commercial testing systems need rigorous evaluation and validation before being adopted by the public health system.

Visual inspection

1. The evidence on visual inspection with application of acetic acid (VIA) or with Lugol's iodine (VILI) was considered not yet sufficient for it to be recommended for adoption as the primary screening test in a public health programme. The size and quality of studies currently in progress should provide definitive evidence on the impact of a single test on the cumulative incidence of both invasive cancer and advanced disease. Future research will be required to assess the impact of repeated testing using a variety of intervals. The validity of the test is highly dependent on the training and skills of those performing the test. Research is needed to establish quality assurance markers for visual inspection.
2. Studies in other settings are needed to confirm the performance of VILI.
3. Studies are required to improve the specificity of criteria in order to increase the positive predictive value of "screen and treat" policies, and so reduce the false positive rate.

Colposcopy

1. Colposcopy is less accurate than is commonly believed and improving colposcopy depends upon improved training and assuring quality control of existing services. Basic clinical research in relation to improved visual diagnosis and use of tissue sampling techniques should be encouraged.
2 Studies are required to improve the specificity of colposcopic criteria to increase the positive predictive value of "see and treat" policies, and so reduce the false positive rate.