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## Executive summary

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The Netherlands has a good cervical cancer screening programme. Nevertheless, there are ways in which cervical cancer prevention might be improved. A new test method is available, for example; participation amongst women in certain subgroups could be increased and follow-up for screen-positive women could also be improved. In this report, the Health Council reviews developments in this field and gives advice on reshaping of the screening programme.

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### **Cervical cancer and the associated screening programme**

In the Netherlands, more than 700 women a year develop cervical cancer: 2 per cent of all new cancer cases in women. More than half of the women in question are less than fifty years old. The average five-year survival rate in the Netherlands is 67 per cent. Each year, between 200 and 250 women in our country die of cervical cancer. Without a screening programme, the figures would be at least 2 times higher.

It is estimated that, in 2005, cervical cancer cost the Dutch health care system 55 million euros. In 2008, the cost of screening for the disease was 30 million euro.

### *Disease causation*

Cervical cancer is caused by infection with a high-risk genotype of the human papilloma virus (hrHPV), which is transmitted by sexual contact. During the course of their lives, most women (and men) will have at least one hrHPV infection. The virus is most common in the young. The large majority of infections clear spontaneously and do not lead to the development of any cellular or tissue abnormalities. However, the longer an infection persists, the greater the likelihood that changes will take place in the epithelial cells and that the precursor of cervical cancer – cervical intraepithelial neoplasia (CIN) – will develop. Because it takes about fifteen years for cervical cancer to develop and manifest itself, the disease is an ideal ‘candidate’ for screening.

### *Screening*

If treatment is provided when CIN is detected, it is possible to prevent cancer. Furthermore, invasive cervical cancer can usually be treated effectively if detected early. In the Netherlands, therefore, women between the ages of thirty and sixty are invited to undergo screening once every five years. This involves having a so-called ‘Pap smear test’ at the GP’s surgery. Smear taking is typically performed by the practice assistant and the collected sample is analysed at a pathology laboratory. The analysis technique employed is cytological; in other words, it consists of microscopic study of the sampled cells. If the cells exhibit mild abnormalities, the woman is advised to undergo two follow-up tests. If serious abnormalities are suspected, the woman is immediately referred to a gynaecologist for diagnostic examination (colposcopy, biopsy) and, if appropriate, treatment.

By comparison with the approach taken in most other countries, the Netherlands’ cervical cancer screening programme is low-key but effective. Under the Dutch system, a woman may undergo seven smear tests, whereas her counterparts in some countries may be tested more than fifty times. Despite the relative infrequency of the testing, cervical cancer is less common in the Netherlands than in most other countries.

### *Weaknesses of the current arrangements*

Research has shown that the sensitivity of cytological screening for the detection of high-grade CIN or cervical cancer increases as the age of the subject increases. Consequently, cytology is least efficacious for the group that can potentially

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derive the most prolonged benefit from effective screening, namely young women. Furthermore, cytological screening is not a particularly effective means of detecting the precursors of adenocarcinomas, which account for about 20 per cent of cervical cancer cases.

Another drawback of cytological screening is that it lacks high specificity. Relative to the number of cervical cancer cases prevented, a large number of abnormalities are detected which would never lead to cancer.

Participation rates in the existing programme are also suboptimal. For a long time, attendance has been about 66 per cent. Ultimately, five-year coverage in the eligible target population reached 79 per cent in 2008; the difference being due to smear-taking outside the screening programme. More than half of the women who develop cervical cancer have not attended for screening, or their attendance has been sporadic. Increasing participation is therefore the best way of maximising the programme's public health benefit. Participation is low amongst younger women, women of non-western origin, women of lower socio-economic status or women who live in cities.

Follow-up compliance also requires improvement. Screen-positive women are expected to make an appointment for follow-up testing themselves. Recent research has shown that a quarter of women diagnosed with cervical cancer have experienced a long delay between their first abnormal smear test and their ultimate diagnosis, despite the existing fail safe system (a reminder sent to the non-attendees' GPs).

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## **New techniques**

### *HPV vaccination*

In 2009, the Netherlands started vaccinating girls against human papilloma virus (HPV), the virus that causes cervical cancer. Nevertheless, screening remains very important. It is needed first to provide continued protection of the existing target group (women who have not been vaccinated). It will be another forty years before the youngest cohort of unvaccinated women reach the age at which participation in the screening programme ends. Second, screening is needed because vaccination has only just started, meaning that many women are not yet protected. It will last at least fifteen years before the first women vaccinated in adolescence reach the programme entry age. Third, the vaccine has been aimed to protect against the two high-risk types of HPV (HPV16 and 18) which

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together cause about 70 per cent of all cervical cancers. Hence, administration of the existing vaccines cannot prevent all cervical cancer. Moreover, by no means all members of the target group submit to vaccination.

### *Liquid-based cytology*

Liquid-based cytology (LBC) was developed as an alternative for the conventional Pap test. The technique increases the quality of the sample and has practical advantages. However, LBC is not demonstrably more sensitive than conventional cytology, and it has the disadvantage of increasing the number of false positives. The technique is also more expensive and not a solution for the weaknesses of conventional cytology in the existing screening programme. Moreover, the quality of cervical smears is already high in the Netherlands (1 to 2 per cent 'unsatisfactory'), meaning that the added value provided by the new technique is modest. LBC is already widely used in the Netherlands as a primary screening method, but the Committee takes the view that the technique's adoption is neither evidence-based nor cost-effective.

### *Computer-aided screening*

LBC makes it possible to semi-automate the screening process. However, recent research in the UK found that computer-aided screening was associated with significantly reduced sensitivity, combined with uncertainty over cost-effectiveness.

### *HrHPV test*

Because there is a very strong causal relationship between persistent hrHPV infection and the development of cervical cancer, tests have been developed, which can detect HPV DNA. This enables all high-risk genotypes of the virus to be detected. Numerous studies have shown that hrHPV screening is a considerably more sensitive method of detecting cervical lesions than cytology. Experimental studies have shown that hrHPV screening leads to the earlier detection of and better protection against the disease. The long-term risk of high-grade CIN or cervical cancer is considerably lower following a negative hrHPV test than following negative cytology.

Although hrHPV screening is more sensitive, it is also less specific. This means that more women need follow-up examinations. The life-time risk of being referred for colposcopy increases from 3.3 to 3.5 per cent.

## *Self-sampling*

Another new development is the availability of self-sampling kits, which enable women to take their own smear tests at home. Offering self sampling of cervico-vaginal material for hrHPV testing to women who did not attend regular screening proved to be an effective method of increasing coverage in a screening programme. The added value of offering self-sampling as an alternative for a physician-taken smear to women invited for regular screening is unknown.

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### **Recommendations: screening programme reform**

#### **1**      *HrHPV testing*

The Committee recommends that hrHPV testing should replace cytology as the primary screening method. HrHPV testing affords better protection against cervical cancer than cytology. A switch would have no practical consequences for subjects, from whom samples would be collected by smear taking as before.

It is of crucial importance that the hrHPV test is clinically valid and reliable: various tests are available, which differ in terms of test performance. What matters is not that the chosen test is capable of detecting all hrHPV infections, but that it detects only those hrHPV infections that are associated with high-grade CIN or cancer. In June 2010, the Netherlands Pathology Society published guidelines for hrHPV test requirements and validation.

#### **2**      *Cytology triage*

With a view to ensuring high quality, the Committee regards triage – the sorting and selection of women whose hrHPV test results are positive – as an essential element of the screening process. To prevent unnecessary colposcopy referrals, hrHPV-positive women should not be offered colposcopy immediately but should be further stratified by means of triage testing and repeat testing. It is appropriate to use cytology for this purpose. This does not involve the subject making another visit to the GP, because either the sample used for the hrHPV test can be re-used for cytology, or a cervical smear has already been made when a scrape for screening was taken (co-collection). If cytological abnormalities ( $\geq$ BMD) are observed, immediate referral should follow for diagnosis and, where appropriate, treatment. If no abnormalities are observed in triage, the subject should be offered follow-up testing (cytology) at six months.

### 3 *Screening frequency*

The implementation of hrHPV testing leads to earlier detection of CIN3+ lesions. This permits an extension of the screening interval. The Committee believes that the lifetime number of screening tests should be reduced from seven to five. It is proposed that, for women between the ages of thirty and forty, the interval should remain five years; thereafter, it should increase to ten years. Hence, women would be tested at the ages of thirty, thirty-five, forty, fifty and sixty. Thirty is still regarded by the Committee as the right age for beginning cervical screening. The screening of younger women leads to a high proportion of false positive results, overdiagnosis and unnecessary treatment. Nor does the Committee see any reason to extend screening to women over the age of sixty. However, it is advisable that, if a woman's hrHPV test result at the age of forty, fifty or sixty is positive, but no abnormalities are detected in cytological triage at baseline and after six months, the woman should be re-screened after five years.

### 4 *Promoting participation*

In order to promote participation, particularly amongst subgroups whose members are currently less likely to participate, such as young or ethnic minority women, the Committee recommends first that the screening organisations should involve more GPs in the call and recall system. The response rate is highest when the GP issues the (re)invitation; the next best approach is when the GP sends a reminder to women not responding to the initial invitation (sent by the screening organisation). It is preferable that the invitation letter should include a pre-fixed, modifiable appointment. The interval before a woman who does not respond is sent a reminder should be reduced from six months to roughly six weeks.

Finally, the Committee recommends that, after three to six months, a device for self collection of cervico-vaginal material should be sent to women who do not attend regular screening. The used test kit can be sent by mail to the laboratory for hrHPV testing. This safety net plan requires careful introduction and evaluation. The Committee has taken the position that at present women who would otherwise have attended for testing are inclined to ignore their invitations and simply wait for the self sampling kit. If such behaviour became established, it may impact negatively on the efficiency and effectiveness of the screening programme: some studies have found that false positives are more common in the context of self sampling than when hrHPV tests are performed on samples taken by doctors and practice assistants.

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It is not clear whether there is any advantage in offering self sampling kits to the entire target group (as opposed to non-respondents only), so that women may choose to test themselves at home, rather than go to their GPs. The Committee advises conducting a regional trial with a view to establishing whether this approach is preferable to the programme design described above in terms of participation, yield of high-grade lesions and cost-effectiveness.

#### 5 *Follow-up compliance*

In order to make the screening programme more effective, compliance to follow-up should be increased. The Committee recommends that the screening organizations be involved in contacting women if follow up is needed. Offering pre-fixed, changeable appointments is expected to increase attendance.

#### 6 *Cost-effectiveness*

Modelling indicates that the programme design described above may be expected to prevent 75 more cases of cervical cancer and eighteen more deaths from cervical cancer than the existing programme design, without increasing the cost.

#### 7 *Implementation*

The Committee recognises that the introduction of its proposed programme design will have significant implications. The recommended changes would certainly impact on the forty-plus laboratories involved in sample analysis (a few of which focus primarily on cervical cytology). Furthermore, particularly in the first five years after the introduction of hrHPV screening, there would be more colposcopy referrals and more follow up testing of women after six months. However, the changes may be expected to have health benefits in the form of the reduced incidence of cervical cancer and false negative test results.