CERVICAL CANCER SCREENING IN RESOURCE-POOR SETTINGS

EVIDENCE FROM NICARAGUA AND KENYA

Doctoral Thesis submitted to the Faculty of Medicine and Health Sciences by Patricia Claeys

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STRUCTURE

Preface ........................................................................................................................................................................ 1
I. Introduction .................................................................................................................................................................. 3
1. Magnitude of the problem ......................................................................................................................................... 4
2. Aetiology and natural history ..................................................................................................................................... 7
3. Pathogenesis ............................................................................................................................................................ 9
4. Classification .......................................................................................................................................................... 10
5. Risk factors ............................................................................................................................................................ 11
6. Aim and rationale for screening ............................................................................................................................ 12
7. Screening tests ........................................................................................................................................................ 13
8. Vaccine development .............................................................................................................................................. 15
9. Management of cervical dysplasia .......................................................................................................................... 16
10. Is screening for cervical cancer effective ? ............................................................................................................. 17
11. General principles of cervical cancer screening .................................................................................................. 19
12. Cost effectiveness of cervical cancer screening .................................................................................................. 21
13. Issues in cervical cancer screening in Developing Countries .................................................................................. 24
14. Reference list ........................................................................................................................................................ 28
II. Objectives and methodology .................................................................................................................................... 35
1. General objective ...................................................................................................................................................... 37
2. Specific objectives ..................................................................................................................................................... 37
3. Study sites and study development .......................................................................................................................... 38
4. Study design including data collection .................................................................................................................... 40
5. Dissemination of results .......................................................................................................................................... 42
III. Results .................................................................................................................................................................... 45
III-1. Prevalence and risk factors of cervical neoplasia in Nicaragua ............................................................................ 45
III-2. Determinants of cervical cancer screening in a poor area ..................................................................................... 55
III-3. Successful involvement of community health workers in the promotion of cervical cancer screening ................. 69
III-4. Performance of screening tests .......................................................................................................................... 83
III-4-1. Performance of screening tests in research conditions .................................................................................... 83
III-4-2. Performance of the acetic acid test in field conditions ...................................................................................... 99
III-4-3. Improving quality of cytology ......................................................................................................................... 111
III-5. Decentralising diagnosis and treatment ............................................................................................................. 121
III-6. Integration of cervical screening in family planning clinics .................................................................................. 131
IV. Discussion .................................................................................................................................................................. 141
1. Contribution of this work to the field ........................................................................................................................ 143
2. Relevance of cervical cancer screening programmes in low resource settings ....................................................... 144
3. Strategies to reach high-risk groups for screening .................................................................................................. 145
4. Selection of a screening test in resource-poor settings ............................................................................................. 146
5. Options for service delivery ...................................................................................................................................... 148
6. Overall conclusions ................................................................................................................................................. 149
7. Reference list ........................................................................................................................................................ 151
V. Executive summary ...................................................................................................................................................... 153
1. Context and objectives .............................................................................................................................................. 155
2. Results ..................................................................................................................................................................... 155
3. Discussion and conclusions ..................................................................................................................................... 158
VI. Samenvatting ............................................................................................................................................................. 159
1. Achtergrond en objectieven ....................................................................................................................................... 161
2. Resultaten .................................................................................................................................................................. 162
3. Discussie en conclusies ............................................................................................................................................ 165
VII. Abbreviations .......................................................................................................................................................... 167
Acknowledgements ...................................................................................................................................................... 171
During nearly ten years’ residence in Nicaragua in the period 1985-1994, I participated, in the health centre, in the examination of thousands of women for early detection of cervical cancer. Despite the active collaboration of many healthcare workers, each year a number of women of the village died from the disease. As a clinician I did not question this. At most, I was a bit surprised that the Papanicolau smears were always reported as being normal.

Later, studying for my masters in public health, I started understanding why our attempts to prevent women developing cervical cancer were unsuccessful. And when - almost by coincidence - I started working as a researcher, I decided to study this in more depth. If cervical cancer is a disease that can be prevented, why are there nearly 500 000 new cases reported per year?

And why do the majority of these women live in developing countries? Is it possible and feasible to detect and to manage cervical cancer in time in resource-poor settings? And how? The operational research presented in this work tries to formulate a number of answers to these questions. It is an undertaking that is carried out with many others and that is certainly not finished, the problems being too extensive and too diverse. But I dare to hope that the work presented here contributes to the efforts to improve the reproductive health of women, especially in developing countries.
I. INTRODUCTION
1. **Magnitude of the problem**

Worldwide, cervical cancer is the seventh most prevalent cancer and in women the second in frequency. The most recent compilation of data\textsuperscript{1} indicates that an estimated 470 000 new cases occur annually among women worldwide, responsible for 9.9% of all cancers. Eighty percent of these cases occur in developing countries. Since 1985, it has given way its place as the leading cancer in developing countries to breast cancer, but in several areas, including sub-Saharan Africa, Central America, South-central Asia and Melanesia, it is still the main cancer in women (figures 1 and 3)\textsuperscript{1,2}. Central America has the highest estimated crude incidence rate in the world: 31.7 per 100 000 women, compared to 15.7 worldwide (table 1). In all regions, there is a sharp increase of the incidence rate after the onset of sexual activity, but cervical cancer is rare before the age of 30 (figure 2)\textsuperscript{1}.

Cervical cancer is responsible for more than 230 000 deaths annually (Globocan database, 2000)\textsuperscript{1}. In developing countries, it is the leading cause of cancer mortality in women. The average age-adjusted mortality rate is twice as high in developing as in developed countries (9.8 compared to 4.1 per 100 000 women). In Eastern Africa, the mortality is as high as 24.2, in Central America and the Caribbean 17.0 per 100 000 women\textsuperscript{1,3}.

For each death from cancer of the cervix, it has been estimated that on average 17 potential years of life before 70 years of age are lost. This means that worldwide, about 3.4 million women-years of life before 70 years of age are lost annually due to the existence of the problem of cervical cancer\textsuperscript{4}.

Cervical cancer deserves special attention as, on a global scale, it might be the most preventable major form of cancer\textsuperscript{5}.

![Figure 1: Worldwide incidence rate of cervical cancer, per 100 000\textsuperscript{1}]
Table 1. Estimated crude rates (CR) and age-standardized rates (ASR) of cervical cancer incidence and mortality by region, (per 100 000)\(^1\)

<table>
<thead>
<tr>
<th>REGION</th>
<th>INCIDENCE CR</th>
<th>INCIDENCE ASR</th>
<th>MORTALITY CR</th>
<th>MORTALITY ASR</th>
</tr>
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<tbody>
<tr>
<td>Eastern Africa</td>
<td>24.4</td>
<td>44.3</td>
<td>12.8</td>
<td>24.2</td>
</tr>
<tr>
<td>Middle Africa</td>
<td>14.4</td>
<td>25.1</td>
<td>7.9</td>
<td>14.2</td>
</tr>
<tr>
<td>Northern Africa</td>
<td>12.2</td>
<td>16.8</td>
<td>6.4</td>
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</tr>
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<td>Southern Africa</td>
<td>23.2</td>
<td>30.3</td>
<td>12.2</td>
<td>16.5</td>
</tr>
<tr>
<td>Western Africa</td>
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<td>20.3</td>
<td>6.4</td>
<td>10.9</td>
</tr>
<tr>
<td>Caribbean</td>
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<td>35.8</td>
<td>16.4</td>
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</tr>
<tr>
<td>Central America</td>
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<td>40.3</td>
<td>12.8</td>
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<tr>
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<td>30.9</td>
<td>10.7</td>
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</tr>
<tr>
<td>North America</td>
<td>9.5</td>
<td>7.9</td>
<td>4.5</td>
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</tr>
<tr>
<td>Eastern Asia</td>
<td>7.1</td>
<td>6.4</td>
<td>3.5</td>
<td>3.2</td>
</tr>
<tr>
<td>South Eastern Asia</td>
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<td>18.3</td>
<td>7.9</td>
<td>9.6</td>
</tr>
<tr>
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<td>14.9</td>
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<tr>
<td>Western Asia</td>
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<td>4.8</td>
<td>1.9</td>
<td>2.5</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>21.9</td>
<td>16.8</td>
<td>9.4</td>
<td>6.2</td>
</tr>
<tr>
<td>Northern Europe</td>
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<td>9.8</td>
<td>5.4</td>
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</tr>
<tr>
<td>Southern Europe</td>
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<td>10.2</td>
<td>6.2</td>
<td>4.0</td>
</tr>
<tr>
<td>Western Europe</td>
<td>14.2</td>
<td>10.4</td>
<td>6.6</td>
<td>3.7</td>
</tr>
<tr>
<td>Australia/New Zealand</td>
<td>9.4</td>
<td>7.7</td>
<td>3.8</td>
<td>2.7</td>
</tr>
<tr>
<td>Melanesia</td>
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<td>23.8</td>
</tr>
<tr>
<td>Polynesia</td>
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<td>29.0</td>
<td>11.6</td>
<td>15.2</td>
</tr>
<tr>
<td>DEVELOPED COUNTRIES</td>
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<td>11.3</td>
<td>6.4</td>
<td>4.1</td>
</tr>
<tr>
<td>DEVELOPING COUNTRIES</td>
<td>15.8</td>
<td>18.7</td>
<td>8.1</td>
<td>9.8</td>
</tr>
<tr>
<td>ALL AREAS</td>
<td>15.7</td>
<td>16.1</td>
<td>7.8</td>
<td>8.0</td>
</tr>
</tbody>
</table>

Figure 2: Cervical cancer incidence rate in different regions and age-groups\(^1\)
Figure 3: Estimated incidence of cervical cancer in less and more developed regions.
2. Aetiology and natural history

Epidemiological studies have shown a strong association between human papillomavirus (HPV) and cervical neoplasia and its precursors. In November 1991, a consensus was reached during a meeting of the World Health Organization (WHO)/International Agency for Research on Cancer (IARC) that there was compelling evidence that HPV has a causal role in the disease. This association is independent of other risk factors and consistent in several countries. HPV infection is now recognized to be the central causal factor in invasive cervical cancer worldwide. An overall HPV prevalence of 99.7% among cervical cancers worldwide has been reported and HPV-negative cervical carcinoma appears to be extremely uncommon, if it exists at all. Human papillomaviruses are classified according to their oncogenic potential, but the clinical classification of HPV types into either high- or low risk groups is still not completely clear. Distinction is made between 1) “low-risk” (LR) HPV types, weakly associated with cervical cancer or pre-cancer (types 6, 11, 34, 40, 42, 43, 44, 54, 55, 70, 74) and 2) “high-risk” (HR) or “cancer associated” HPV types, associated with high grade squamous intra-epithelial lesions (HSIL) and invasive cancer (mainly types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82). HPV 26, 53 and 66 can probably also be considered high-risk.

Cervical HPV infection is a very common sexually transmitted infection (STI), and can be found in 5-50% of women of reproductive age. The prevalence is highest in sexually active young women, but rapidly declines with age.

There is limited evidence that HPV could be acquired by modes other than sexual contact, including vertical transmission.

Most of the HPV infections are transient, and are probably of little significance. A positive HPV test, especially in young women, rarely represents disease that could, if unrecognised, progress to cervical cancer. However, even if it is unclear which factors intervene in establishing a chronic carrier state, it is recognized that persistent infection increases the risk for the development of squamous intra-epithelial lesions’ (SIL) of the cervix. These SIL have 3 options for further development: 1) regression, 2) persistence and 3) progression to the next higher step in the sequence. The traditional paradigm is that cervical cancer progresses as a continuum from low-grade lesions through intermediate stages (high-grade lesions) into invasive cancer. This is supported by epidemiological data, showing that the distribution curves of different grades of dysplasia and of invasive cancer have virtually the same shape as a function of age, but with peak rates of precancerous cervical lesions, such as carcinoma in situ (CIS) and cervical intraepithelial neoplasia (CIN) occurring one to two decades before peak rates of invasive cancer.

The risk for regression and progression is dependent on the grade of dysplasia, type and viral load of HPV infection age, persistence, and concurrent HIV infection.

* Several classifications exist for reporting pre-cancerous lesions of the cervix. The original classification used by Papanicolaou, has been replaced by a descriptive one (using the dysplasia terminology), and later by the CIN (cervical intraepithelial neoplasia) classification. Since 1988, the Bethesda classification (using the terminology SIL or squamous intraepithelial lesion) has been introduced. More information on the changes in terminology can be found in subchapter 4, page l-9 and in table 3, page l-10.
The average duration of progression of HSIL to invasive cancer is about 10 years. Modelling showed that new lesions in women under 34 years regress in 84% of cases opposed to 40% in older women.

Most authors agree that mild and moderate dysplasia are more likely to regress than to progress. Low grade SIL are common, and mostly represent the usually benign cytopathologic signs of (transient) HPV infection. They are more and more considered as an epidemiological exposure or a "risk factor" for cervical cancer. Still, women with LSIL are at a more than 16-fold increased relative risk of developing HSIL and invasive cancer than women with normal cytological diagnosis.

Data on the natural history of severe dysplasia are scarce, as these lesions are normally treated. However, the cohort study of cervical cancer screening in British Columbia showed that regression is part of the natural history of both dysplasia and carcinoma in situ, and that the probability of progression of carcinoma in situ to invasive stages increases with age. Yet it is agreed universally that CIN III is a true cancer precursor and that these patients need to be treated. Composite data from a critical review performed by Ostör in 1993 are reflected in table 2. The data reflect a summary of data obtained in cohort studies on the natural history of cervical intraepithelial neoplasia since 1950. These data have to be interpreted with caution, as they are subject to several biases. The first is that the diagnosis of lesions in most of the studies is biopsy-based. Yet, once a lesion has been biopsied, its natural history has been interfered with, as the biopsy itself might be curative by removing small lesions.

Another important bias is that most studies lack long-term follow-up, truncating the true biologic course of the disease. The progression rate of CIN3 to invasion in particular may be higher than stated as most series have been titrated to an end point of carcinoma in situ (for ethical reasons), longer follow-up possible yielding a higher figure.

Despite recent increases of the disease in women under 35 years in developed countries, invasive cervical cancer is rare under age 25. For both developed and developing countries, the incidence increases with age up to 35, where it remains fairly stable till age 60 or over, after which it may decline.

<table>
<thead>
<tr>
<th>Grade of dysplasia</th>
<th>Likelihood of Progression to invasion (%)</th>
<th>Likelihood of Progression to CIS (%)</th>
<th>Likelihood of Regression to normal (%)</th>
<th>Likelihood of Persistence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN I</td>
<td>1</td>
<td>11</td>
<td>57</td>
<td>32</td>
</tr>
<tr>
<td>CIN II</td>
<td>5</td>
<td>22</td>
<td>43</td>
<td>35</td>
</tr>
<tr>
<td>CIN III</td>
<td>&gt;12</td>
<td></td>
<td>32</td>
<td>&lt;56</td>
</tr>
</tbody>
</table>
3. Pathogenesis

A minority of women exposed to HPV will develop persistent infection, probably as a result of an inadequate immune response. Persistent infections with high-risk HPV may progress to HSIL and invasive cancer and cofactors (such as smoking and oral contraceptive use) may play a role in this progression. Viral deoxyribonucleic acid (DNA) in malignant cells differs from viral DNA in a benign HPV infection, as it is integrated into the host DNA (figure 4). By the over-expression of certain early proteins and the interaction between these and the host proteins, this DNA is intimately involved in the transformation to malignancy. Two viral proteins, E6 and E7, bind to and inhibit two key cellular anti-oncogenes, p53 and retinoblastoma protein (Rb).

![Figure 4: Stepwise progression of high risk HPV-induced lesions](image)

Nearly 90% of invasive cervical cancers are squamous cell carcinomas (SCC). SCC almost always arises in the anatomic region of the cervix known as the transformation zone, which is the interface between the squamous epithelium of the lower genital tract (vagina and exocervix) and the columnar epithelium of the endocervix and endometrium. When the columnar epithelial cells are exposed to the acidic environment of the vagina (process that starts following puberty), they transform to squamous epithelium. This transformation process is known as metaplasia. When metaplastic cells are exposed to cancer-inducing factors, this physiological process is altered, resulting in atypical metaplastic epithelium. Squamous metaplasia of the cervical columnar epithelium may play a role in promoting integration or expression of the HPV E7 locus in the transformed cell, explaining why women at highest risk for cervix cancer are those exposed to HPV during the dynamic periods of metaplasia: early adolescence and first pregnancy. HPV infection induces changes in differentiated keratinocytes known as koilocytosis. This may proceed further to cellular atypia (CIN or dysplasia) or spontaneously return to normal epithelium. Based on the degree of epithelial differentiation, the precursors of invasive squamous intraepithelial disease can be divided in four categories: mild dysplasia; moderate dysplasia, severe dysplasia and carcinoma in situ. The progression from CIS to invasive cervical cancer (ICC) is marked by the invasion of abnormal cells into the inner cervical tissue. From early ICC, the cancer may spread to the surrounding pelvic tissues, and finally to more distant parts of the body. The chance of surviving cervical cancer is directly related to the stage at which the disease is diagnosed. Women with cancer detected in the pre-invasive and even in the in-situ stages, have a 5-year survival rate of essentially 100%.
4. Classification

The earliest terminology related to cytological nomenclature was described in 1954, by Papanicolaou, the discoverer of the exfoliate cytology. He classified the cytological findings in five groups, from Class I (absence of atypical or abnormal cells) to Class V (cytology conclusive for malignancy)\textsuperscript{54}. This classification received criticism, and was replaced by a widely recognized histological and cytological classification, recommended by the World Health Organization. A third classification used the generic term of CIN instead of the two terms “dysplasia” and “carcinoma in situ”. This classification has been adopted by many people \textsuperscript{48}. However, the variable and in some instances ambiguous use of this terminology, resulted in confusion about the clinical implications of the report. In 1988, a workshop was convened by the National Cancer Institute, resulting in the adoption of a uniform reporting system for cervical and vaginal cytology: the Bethesda System. The Bethesda classification addresses the lack of consistency in subclassifying dysplasia, CIN or other epithelial abnormalities of the cervix that form a morphological continuum of precursors to squamous cell carcinoma. As a result, only two terms were introduced: “low grade squamous intraepithelial lesion or LSIL” and “high-grade squamous intraepithelial lesion or HSIL”. Cellular changes associated with HPV are classified as LSIL. Furthermore, the use of the term “atypical squamous cells” is limited to those cases with cytological findings of undetermined significance or ASCUS \textsuperscript{55,56}. One of the three major components for interpretive reporting specified by the Bethesda System is that it directly addresses specimen adequacy, a source of false-negative Papanicolau smears. The inter-and intra-observer reproducibility of these guidelines has proven to be satisfactory \textsuperscript{57}. In 2001, another workshop was convened in Bethesda to evaluate and update the Bethesda System terminology. The 2001 Bethesda Classification differs in several fundamental ways with regard to reporting equivocal results. “Atypical squamous cells” are now qualified as of “undetermined significance” ASC-US or “cannot exclude HSIL” ASC-H. The classification of glandular abnormalities has also been revised, but the tiered LSIL-HSIL terminology remains unchanged \textsuperscript{58}. An overview of changes in cytological nomenclature is given in table 3.

<table>
<thead>
<tr>
<th>DESCRIBTIVE CLASSIFICATION</th>
<th>CIN CLASSIFICATION</th>
<th>BETHESDA 1988</th>
<th>BETHESDA 2001</th>
</tr>
</thead>
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<td>Atypia</td>
<td>Atypia</td>
<td>ASCUS</td>
<td>ASC-US</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ASC-H</td>
</tr>
<tr>
<td>Koilocytosis</td>
<td>Flat condyloma</td>
<td>LSIL</td>
<td>LSIL</td>
</tr>
<tr>
<td>Mild dysplasia</td>
<td>CIN grade I</td>
<td>LSIL</td>
<td>LSIL</td>
</tr>
<tr>
<td>Moderate dysplasia</td>
<td>CIN grade II</td>
<td>HSIL</td>
<td>HSIL</td>
</tr>
<tr>
<td>Severe dysplasia</td>
<td>CIN grade III</td>
<td>HSIL</td>
<td>HSIL</td>
</tr>
<tr>
<td>CIS</td>
<td>CIN grade III</td>
<td>HSIL</td>
<td>HSIL</td>
</tr>
</tbody>
</table>
5. Risk factors

Risk factors for cervical cancer include socio-demographic factors, including sexual activity (lifetime number of sex partners, early age at first intercourse, frequency of sexual encounters) age and parity, as well as factors related to health behaviour such as smoking, use of oral contraceptives, nutrition and regular screening.\(^{59;60}\)

Some of these factors are now recognized to be proxies for exposure to HPV. HPV itself is no longer considered a risk factor, but a causal factor for cervical neoplasia, as HPV is present in virtually all cervical cancers. This implies that HPV is the highest worldwide attributable fraction so far reported for a specific cause of any major human cancer.\(^{16}\) The most important determinant of risk of HPV infection is age, and most studies show a sharp decrease in prevalence after age 30. This decrease seems to be independent of sexual activity.\(^{34;59;61}\) HPV however, is not a sufficient cause, and cofactors have a role in the persistence of HPV infection and occasionally in the progress to cervical neoplasia and ultimately invasive cancer.\(^{62}\) Determinants of persistent HPV infection of \(\geq 6\) months include older age, infection with multiple types of HPV, infection with a high-risk type at the previous visit and a high viral burden in subsequent samples.\(^{32;34;37}\)

Pooled analysis of data of several case-control studies recently showed that parity and long-term use of oral contraceptives are probably cofactors increasing the risk for cervical cancer in HPV positive women. A direct association was found between the number of full-term pregnancies and the risk of squamous-cell cancer. Long-term use of oral contraceptives (\(\geq 5\) years) increased the risk of cervical cancer by up to four-fold in women who were HPV positive. The risk did not vary by time since first or last use. Among the controls, multiparous women and those who had taken oral contraceptives were not more likely than the others to be carriers of HPV DNA, indicating that oral contraceptives do not enhance the acquisition of persistence of HPV infection, but rather promote progression to CIN and invasive disease.\(^{62-64}\)

Immunosuppression is another recognized risk factor, and there is a clear association between HIV infection, HPV infection and SIL. Yet, it is unclear whether HIV immunosuppression is a cofactor for progression, or if it mainly increases the prevalence and persistence of HPV.\(^{46}\)

**Male factor**

Recently, it has been shown that male circumcision is associated with a reduced risk of penile HPV infection and, in the case of men with a history of multiple sexual partners, a reduced risk of cervical cancer in their current female partners.\(^{65}\)
6. Aim and rationale for screening

Screening is a public health initiative based on two assumptions:

1. Prevention is better than cure
2. Early diagnosis may allow treatment to be instituted while the primary pathologic process is still reversible.

Screening tests are relatively simple procedures that separate well persons from those with a high probability of having the disease under study. They are not intended to be diagnostic, but to identify people who need a formal workup.

In 1968, Wilson and Jungner published a list of the prerequisites for successful screening. Their criteria relate to the disease, the test and the provision of services to deal with test results.

**Disease**

1. The condition sought should be an important health problem
2. There should be a recognizable latent or early symptomatic stage
3. The natural history of the condition should be adequately understood
4. There should be an accepted treatment for patients with the disease
5. Treatment at the pre-symptomatic, borderline stage of the disease should favourably influence long-term course and prognosis.

**Test**

1. The test should be cheap, specific, sensitive, and risk free
2. The test should be acceptable to the population
3. The cost of screening should be economically balanced with the expenditure of medical care as a whole

**Services**

1. Facilities for treatment and diagnosis should be available
2. There should be an agreed policy on whom to treat as patients
3. Case-finding should be a continuing process and not a once and for all project

Applying these criteria to cervical cancer, it is easy to understand why so many efforts have been put in the development of adequate screening tools. Cervical cancer seems to be the ideal disease for application of screening principles. The long transit time from early cervical atypia to invasive cancer provides an opportunity to identify precursors at a stage where safe and affordable treatment is available. Whereas the prognosis of symptomatic, invasive disease is poor, treatment of pre-invasive lesions is highly effective. The aim of screening for cervical cancer is to identify and treat pre-invasive lesions, thus preventing the progression to invasive cancer. Unarguably, there is a rationale to screen for cervical cancer. Yet the effectiveness of screening programmes will depend highly on which (and how) tests are used, which women are screened and how screening programmes are organized. This will be discussed in the next chapters.
7. Screening tests

At this moment, no single screening method exists that is highly sensitive, highly specific, affordable and practical. It has long been thought that the Pap smear was the “ideal” screening tool, but several studies have shown that the sensitivity of conventional cytology is limited. Moreover, screening programmes based on cytology face operational problems and are expensive. Newer methodologies, developed to increase the sensitivity, also increase the cost. Sensitivity can be increased by combination of methods, but mainly at the expense of specificity. Visual screening methods, developed to be used in resource poor settings, are sensitive, but lack specificity, and result in a high referral rate. Two-step models (using one method after another) increase the specificity, but reduce the sensitivity considerably. Hereunder, we give a short overview of the existing conventional and adjuvant screening tools.

7.1 Cytology

Exfoliated cytology, or the so-called Papanicolaou test (Pap-smear) was the first introduced screening test and is still the most widespread.

The test is highly specific, especially with regard to HSIL and cancers, with reported specificities ranging from 86 to 100%, even in low resource settings. But the sensitivity is negatively influenced by inadequate sample collection and errors in screening and interpretation of the smears, and high false negative rates have been reported, ranging from 13 to 70% as shown in a meta-analysis of well controlled studies 68.

In Western countries, growing concern about the medicolegal liability has led to the development of automated systems to increase the sensitivity of the Pap smear.

The AutoPAP300 QC System and PapNet system are examples of computerised instrumentation for the analysis of cytological preparations. They allow consistent, non-fatiguing, high-quality review of cytological smears and are mainly used to rescreen the previous (manually) screened Papanicolau smear to identify potentially false-negative results 69;70.

The sensitivity of cytology can also be improved by the use of liquid-based, thin-layer cytology in primary screening. Liquid based cytology not only improves the amount of cells transferred for evaluation, it also presents cells on slides in an automated fashion, making it easier for the cytotechnologist to interpret. A meta-analysis of prospective studies comparing liquid based cytology with conventional Pap smears, concluded that liquid-based cervical cytology improves sample adequacy and leads to improved diagnosis of both LSIL and HSIL 71. Other results suggest that the specificity of liquid based cytology is slightly lower than that of conventional cytology 72.

In developing countries, screening based on cytology is not only hampered by the low sensitivity of the test, but mainly by logistic problems and lack of resources. The high cost of both computerised cytology and liquid based cytology make them unsuitable for low resource settings.
7.2 HPV testing

The exploration of HPV testing as an adjunct or primary screening tool is the result of the growing understanding of the etiologic role of HPV in cervical carcinogenesis and advances in the technologies for HPV detection. Screening for high-risk types of HPV can be done using DNA-based tests, as polymerase chain reaction (PCR) techniques or Hybrid Capture microtitre assays (HC II, Digene). Studies showed HPV testing to be more sensitive than conventional Pap testing for high-grade lesions and cancer, but less specific. Especially in young women, where transient infections are common, the test has a limited significance for predicting (pre)-cancer. The use of HPV as a primary screening tool can be considered in women aged 30-35 or over, as the persistence of HPV in an older population is an indication of increased cervical cancer risk. There is also growing consensus that HPV testing is useful for the ‘triage’ of women with ASCUS lesions and for the follow-up of women with LSIL.

7.3 Colposcopy

The most recognized form of visual inspection is the colposcopy, using a magnifying device with built-in light sources which allows magnification of the tissue up to 60 times. After the application of acetic acid, the colposcopist visualises the cervix looking for abnormal findings within the transformation zone. Colposcopy is normally used as a reference test, to help the diagnosis of cervical lesions and to identify areas that should be biopsied. It is also used to help visualising the cervix during treatment. Colposcopy has been suggested as a screening tool for cervical cancer, but it has not proven to be successful for this purpose. It is rather expensive, it requires high trained personnel and the specificity is low as it is difficult to differentiate immature metaplasia from dysplasia. Yet, it is frequently used as a complement of a gynaecological examination in most Latin countries and in Germany.

7.4 Naked eye Visual Inspection with Acetic Acid (VIA)

VIA is considered in the context of general approaches to cervical cancer prevention in developing countries. After “washing” the cervix with 3-5% acetic acid (vinegar), it is illuminated with a lamp and visualised with the naked eye. A difference is sought between negative (no acetowhite lesions) and positive (presence of acetowhite lesions). The advantages of VIA are the simplicity and the low cost of the test; there is no need for equipment nor for high qualified personnel to perform the test. Several studies have been conducted to assess the accuracy of VIA in low resource settings. Most studies show that, compared to Pap smear, the sensitivity of VIA is equal or even higher, but the specificity is considerably lower. VIA as a primary screening tool seems to be an alternative for Pap smear in resource-poor settings, especially when cytology services are inexistent, but concerns have raised about the low specificity, resulting in a high referral rate, and the lack of standardisation. The number of false positives could be reduced by the sequential use of VIA followed by HPV testing, but this test is expensive and not widely available. Moreover, most studies have been done in research settings, and there is still need to assess the accuracy of VIA when used as a routine screening test in normal field conditions.
7.5 Cervicography

With this technique, high-quality colposcopic-type photographs of the cervix are taken by paraprofessional personnel in the field and interpreted by experts. Cervicography is limited by its dependence on an expert, trained evaluator to interpret cervigrams 84. The ability to detect pre-malignant cervical lesions is highly dependent on the training and experience of the assessors. Moreover, cervicography seems to have a high sensitivity for low-grade lesions, but sensitivity and specificity for HSIL are lower than with conventional Pap smear. It can be considered as a complementary test to cytology, but its use as a primary screening tool is limited 85.

7.6 Polarprobe

Polarprobe is still an experimental, new electronic method of cervical screening, using electrical and optical techniques to distinguish between malignant and non-malignant tissues. The principle is that precancerous and cancerous cervical tissue reflects the light and the voltage in different and characteristic ways and that these response signals can be relayed to a notebook-sized computer. The advantages are the short and safe procedure (20 sec) and instant diagnosis. Preliminary results on the accuracy of the test are promising 69.

7.7 Moving towards newer tests

One of the major disadvantages of the current existing screening tests is their disability to discriminate between lesions that will progress and those that do not. To overcome the disadvantages of the current tests, a test is required that indicates that an oncogenic HPV virus has already enhanced genetic instability and rendered infected cells susceptible to transformation, facilitating the development of cancer. In other words: a test for HPV that indicates the virus will exert its oncogenic potential in that particular woman. Miller suggests that this probably means we should transfer our attention from the agent, to the host 86.

8. Vaccine development

Whereas screening for pre-invasive disease has been the only strategy to prevent cervical cancer for several decennia, strong efforts are currently being made for development of prophylactic vaccines against high-risk HPV types.

For developing countries, vaccination may be the only possibility to significantly reduce the incidence of cervical cancer. But also in developed countries, considerable gains at both individual and societal level would be obtained if a significant proportion of cervical cancer and its precursors could be prevented by vaccination 87.

The first results of the clinical efficacy (phase III trial) of a prophylactic HPV-16 virus-like-particle vaccine have recently been published. The vaccine showed to have an efficacy for prevention of persistent HPV-16 infection of 100% (95% CI 90-100). The incidence of persistent HPV-16 infection was 3.8 per 100 women-years at risk in the placebo group and 0 per 100 women-years at risk in the vaccine group, after a median follow up of 17.4 months after completing the vaccination regime 88. Whereas these results are very promising, there is no doubt that screening for cervical cancer will have to continue for at least a couple of decades. First of all, the
available results report on a monovalent HPV-16 vaccine. Whereas HPV-16 is responsible for 50% of squamous cell carcinomas of the cervix, the other half are associated with a variety of types. From a public health perspective, a vaccine that prevents infection with a broad spectrum of HPV types will be necessary. Multivalent vaccines are still being evaluated. Second, the duration of protection of the vaccines remains to be determined. Third, it has to be proven that immunisation with HPV vaccines significantly reduces the incidence of cervical cancer. It has been calculated that it will take 15-20 years of registry based follow up to judge whether a vaccine which covers two thirds of the oncogenic HPV types protects against CIN III and invasive cervical cancer. And the question remains if and how screening services will have to exist once vaccines will be available at population level, as there will always be people who are not vaccinated and might be at risk for developing cervical dysplasia and cancer.

9. Management of cervical dysplasia

Successful treatment of lesions detected by screening is one of the major prerequisites for successful screening. Depending on the lesion, the resources available and the setting, several treatment modalities are available: excisional methods, ablation and expectant management or follow-up. There is now growing evidence that cervical cancer precursors can be treated safely and efficaciously on an outpatient basis. Inpatient methods as hysterectomy, though highly effective, should be reserved for micro-invasive and invasive cancers and for those cases or settings where outpatient methods cannot be provided. In general, biopsy-confirmed LSIL can be regularly followed up by cytology, and should only be treated in case of progression. If regular follow-up cannot be guaranteed, treatment with an ablative form of therapy is the best option. HSIL should preferably be treated with the loop electrosurgical excision procedure (LEEP) in order to have a specimen for histological analysis.

9.1 Ablative forms of therapy

Pre-invasive disease can be destroyed using electrocautery, cryotherapy or laser ablation. The three methods have similar cure rates, with recurrence rates of 13-19%. For all methods, the effectiveness is affected by the size of the lesion and by the age of the patient. Laser ablation is consistently more effective for the treatment of large lesions than the other methods. All these techniques can be provided on an outpatient basis. Their main disadvantage is the absence of a tissue specimen, making a histological evaluation impossible.

The advantages of cryotherapy are that it is reliable, easy to use, and relatively inexpensive. There is no need for electrical power, it can be performed during pregnancy and there are few complications. Moreover, it has the potential to improve the immune response by leaving a large dead viral load of HPV within the disrupted cells. Disadvantages include presence of watery vaginal discharge during 10 to 12 days, and, in some resource poor settings, problems to purchase the N2O or CO2 needed.

Laser ablation allows the precise destruction of cervical lesions under local anaesthesia, without the inconvenience of associated vaginal discharge. However,
the equipment is very expensive, a smoke evacuating system is needed, and in nearly 5% complications as cervical bleeding do occur 91.

Electrocautery, mostly used to treat benign chronic cervicitis and erosions, can successfully be used to destroy cervical lesions. Side effects include pain, uterine cramping and bleeding and an increased risk of cervical stenosis. As it does require electrical power, it might not be useful in settings where electricity is not or rarely available 91.

9.2 Excisional methods

The performance of a cone biopsy is a highly effective way of treating pre-invasive diseases and early stages of invasive cancer. The procedure is well known by gynaecologists and special equipment is not required. Yet, it is a surgical procedure requiring inpatient treatment and general or spinal anaesthesia. Potential side effects and complications include bleeding, cervical stenosis, spontaneous second trimester abortion, obstructed labour and infection 92.

The loop electrosurgical excision procedure (LEEP) technique, also known under the name large loop excision of the transformation zone (LLETZ), is a method of outpatient excisional biopsy and treatment used to remove the entire transformation zone by slowly moving a loop electrode across the cervix. The cervix is further coagulated using a ball-type electrode. It allows diagnostic sampling and treatment in the same visit, and by the removal of suspicious tissue, a histological sample is produced, so that the presence of invasive disease can be ruled out 93,94. Side effects include peri-operative and postoperative bleeding (up to 9% of cases), but this may be reduced to 2% by the use of Monsel’s paste (ferric subsulfate solution). Infection (2%) and stenosis (1%) are other major side effects. The cure rate for CIN3/CIS is around 95%.

9.3 Expectant management (follow-up)

There has been much debate on the need of treating LSIL, but it is now recognised that most LSIL, especially in young women, represent a self-limited HPV infection 34. As most LSIL will either not progress or will regress spontaneously, treating all LSIL will result in considerable overtreatment. Moreover, the time to progress to invasive cancer is sufficiently long to allow detection of progressive lesions during follow-up 40. This approach can only be used if regular follow-up can be guaranteed.

10. Is screening for cervical cancer effective?

Screening for cervical cancer was introduced without evaluation via randomised trials, but indirect evidence on the effectiveness is available from three types of studies. A first group are the correlation studies. In these studies, a time trend or a geographical difference in incidence or mortality is related to the existence of a screening programme 5. This was shown for British Columbia and for the US, where large screening programmes introduced in the late 1940s-1950s, resulted in a reduction of cervical cancer mortality. This decline was strongly correlated with the screening intensity 40,95. Yet, as falling mortality rates preceded the introduction of screening in these countries, it is difficult to measure the contribution of the screening itself 96,97. A second group, existing in comparisons among the Nordic
countries, provides more credible evidence on the effectiveness of screening to reduce the incidence and mortality from cervical cancer. In Iceland and Finland, organized mass screening programmes resulted in a marked reduction in cervical cancer incidence and mortality between 1965 and 1982. These rates had been stable and even increasing before the start of the programme. In Norway, where an organised programme was not introduced nationally, the risk continued to increase until the mid-1970s.

Third, case-control studies provided more direct evidence for an effect of screening by relating cancer risk to screening activity at an individual level. Several studies have shown that women attending screening programmes have a lower risk of developing invasive cancer than the non-attenders, and the relative protection is estimated to be as high as 10-15 fold, and still estimated at five fold 3-4 years after the last negative smear. A 90% protective effect can be achieved at individual level. While the experience from the Nordic countries indicates that organized programmes can achieve a 60-80% protective effect at population level in the targeted age groups, not all screening programmes have shown to be effective at population level.

Data from the United Kingdom (UK) showed the failure of an organized programme to have a major impact on the incidence and mortality from the disease, though recent data suggest a beneficial effect of the national screening programme relaunched in 1988. Population screening done in Belgium between 1965 and 1980 failed to have any impact on morbidity and mortality trends for cervical cancer. It cannot be excluded that changing risk factors for cervical cancer in the population and more accurate registration have had a role in the reported incidence of cases in those countries. Yet, it is known from the Finnish data that the smears from an organised programme have the greatest impact, while the spontaneous (or opportunistic) smears taken outside the programme have little impact, largely because they are taken too frequently from the same, younger age group. In the UK, the programme failed to reach the women most at risk, as it covered mainly young women from better social classes. In Belgium, most of the screening is on opportunistic basis, while the evaluation of an organized programme in the province East Flanders showed that older women and women with poor screening history were significantly better reached than through spontaneous screening.

There is thus evidence that cervical cancer screening programmes can be, but are not always effective. In the next chapter, a summary is given of the key issues to take into account in the organisation of a cervical cancer screening programme. Addressing these key issues is a major challenge for developing countries.

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It can be argued that a negative screening test does not provide protection. After all, it is treatment of lesions detected by a positive test that has a protective effect. In the literature, the concept of relative protection of a negative test is commonly used to indicate the low risk of having and/or developing disease when a screening test is negative.
11. General principles of cervical cancer screening

The effectiveness of a cervical cancer screening programme is determined by the proportion of progressive lesions that are successfully detected and treated.

This proportion is dependant on 4 determinants: 1) attendance rate, 2) attendance pattern, 3) sensitivity and specificity of the test and 4) correct management of screen-detected lesions. Programmes should also be organised in such a way that they are patient friendly and cost-effective.

11.1 Attendance rate and attendance pattern (Table 4)

As cervical cancer mainly develops in women who have never been screened, screening the unscreened population, even once in lifetime, is the most clinically effective and cost-effective method to reduce the incidence of cervical cancer. One of the main problems associated with screening programmes is that the women at greatest risk of disease are the ones most likely to fail to accept an invitation for screening. The best-known risk group are women aged 45 or more, as they have a higher incidence of disease. Strategies that encourage these women to attend for screening need to be developed and the highest priority of all screening programmes should be to ensure an adequate coverage of women at higher risk.

Table 4. Reduction in the cumulative incidence of invasive cervical cancer over the age range 35-64 years, with different proportions of the population screened and different frequencies of screening

<table>
<thead>
<tr>
<th>Frequency of screening</th>
<th>Proportion screened</th>
<th>Percentage reduction in cumulative incidence</th>
<th>Number of tests per women</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>20%</td>
<td>19*</td>
<td>6</td>
</tr>
<tr>
<td>2 years</td>
<td>30%</td>
<td>28</td>
<td>4.5</td>
</tr>
<tr>
<td>3 years</td>
<td>40%</td>
<td>37</td>
<td>4</td>
</tr>
<tr>
<td>5 years</td>
<td>50%</td>
<td>42</td>
<td>3</td>
</tr>
<tr>
<td>10 years</td>
<td>80%</td>
<td>51</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Organized programmes have shown to be more effective than opportunistic screening, because they reach more women from the risk groups and they can ensure a higher quality of the screening test. Yet, some studies have shown that this is not always the case, resulting in opportunistic screening to be at least as effective as organised screening in some countries. The main reason for total or partial failure of many programmes, is that they take too frequently smears from the same, younger age group, while they do not reach older women, who are at higher risk.

11.2 Adequacy of the screening test

Inadequate smears have an important impact on the outcome of a cervical cancer screening programme. Women with false negative smears are equivocally reassured, false positive smears cause anxiety for patients recalled, discourage future screening and add to an already not inconsiderable cost as unnecessary follow-up exams have to be provided. The sub-optimal sensitivity of a single
cervical smear can be improved by quality control of specimen collection and of the laboratory interpretation of the smear.\(^{110}\)

### 11.3 Follow-up

Reports have estimated that 30% to 50% of women with abnormal screens are lost to follow-up.\(^{112}\) There can be lost to follow-up at different stages of the management of screen positives: 1) in the diagnostic work-up (confirm screening, colposcopy, biopsy...) and 2) in those confirmed as true-positives who never get treated. Particularly in developing countries, a large fraction of women diagnosed positive after screening cannot afford to pay for the treatment, and never present for treatment. A prerequisite of any screening system is that a highly efficient mechanism is in place to deal with women with positive test results.\(^{96}\)

To optimise the cost-effectiveness of a screening programme, over-screening of low risk groups and unnecessary follow-up and treatment of lesions that would spontaneously regress, has to be avoided. There is still a lot of debate on the optimal starting age, screening interval and age to stop screening.\(^{86}\)

### 11.4 Starting age

As cervical cancer is in many respects a sexually transmitted disease, many cervical cancer screening programmes recommend to start screening from the onset of sexual activity.\(^{36}\) Yet, there are several arguments against introducing screening at young age: 1) the transient nature of most HPV infections, 2) the long pre-invasive phase of dysplasia, 3) the potential harm that can result from overdiagnosis and overtreatment and 4) the associated cost.\(^{113}\)

Invasive cervical cancer is rare under age 25 and it is assumed that progressive lesions in young women are fast growing and have a lower probability of being detected by regular screening.\(^{114}\) Screening under age 25 is thus mainly a waste of resources, as the high prevalence of LSIL detected will most probably spontaneously regress, and the probability of detecting those lesions that will progress is low. There is no doubt that the maximum age-related benefit is related from starting screening at the age of 35 years.\(^{48}\) There are also arguments in favour of starting screening earlier: the greater perceived value of a young life than an older one and the increase in sexual activity at a younger age. Results of existing programmes have shown that there might be some benefit in starting screening at 30 years, but little or no gain is observed in screening the 25-29 age groups, and screening earlier should be discouraged.\(^{86}\)

### 11.5 Screening interval

The calculation of the optimal screening interval is based on the risk women with a negative smear have to develop invasive cancer in the screening interval. An international collaborative investigation has shown that screening intervals of 1, 2 and 3 years result nearly in the same risk reduction, and that even 5 years is an acceptable screening interval (Table 5). Many countries have changed their policies from annual screening for all sexually active women, towards tri-or five annual screening. Because of the false-negative rate of Pap smears, many programmes recommend to start with annual screening and to provide less frequent screening after two or three consecutive normal smears.\(^{36}\)
Table 5. Reduction in the cumulative rate of invasive cervical cancer over the age range 35-64 years, with different frequencies of screening

<table>
<thead>
<tr>
<th>Frequency of screening</th>
<th>Percentage reduction in cumulative incidence</th>
<th>Number of tests per women</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>93.3</td>
<td>30</td>
</tr>
<tr>
<td>2 years</td>
<td>93.3</td>
<td>15</td>
</tr>
<tr>
<td>3 years</td>
<td>91.4</td>
<td>10</td>
</tr>
<tr>
<td>5 years</td>
<td>83.9</td>
<td>6</td>
</tr>
<tr>
<td>10 years</td>
<td>64.2</td>
<td>3</td>
</tr>
</tbody>
</table>

11.6 Age to stop screening

There is sufficient evidence that screening can cease at 65 years for women who have a history of regular (at least two) negative smears. However, older women who have never been screened or who have lapsed from screening should be actively recruited.

12. Cost effectiveness of cervical cancer screening

Cost-effectiveness analyses of cervical cancer screening strategies are usually performed using mathematical simulation models. These models combine information about the natural history of the disease and performance of screening and treatment with other relevant demographic and epidemiological characteristics of the population under study. They also provide insight into the relative importance of different components of the screening process and investigate how cost-effectiveness ratios will change if values of key parameters are changed.

In Europe, the Department of Public Health and Social Medicine of Erasmus University, Rotterdam, has been actively involved in cost-effectiveness analyses based on modelling. Studies on economic aspects of cervical cancer screening in developing countries are being implemented by Jeanne Mandelblatt (Georgetown University School of Medicine, Lombardi Cancer Center, Washington) and Sue Goldie (Department of Health Policy and Management, Harvard School of Public Health, Boston), amongst others. In general, these analyses show that organized screening programmes are more efficient, mainly because they reach the older, less affluent and minority groups better than spontaneous screening. The cost-effectiveness of screening improves when screening efforts are focused on women older than 25 years of age. Yearly screening intervals are inefficient, because of the cost of the large number of screening tests needed and the cost of treating lesions that would have regressed spontaneously.

In the Netherlands, 5 ‘efficient’ organized programmes were identified, with screening intervals ranging from 2 to 8 years, starting age from 26 to 39 and age to stop screening from 64 to 71. The total cost of an organized screening programme (including screening, diagnosis and treatment) varied between 524 million DFL and 1,367 million DFL (compared to 271 million DFL when no screening was performed). Spontaneous screening was estimated to cost 638 million DFL. The
costs of screening were by far the most important part of the total costs, especially for more intensive screening programmes. Costs of diagnosis and treatment were relatively small. Savings, to be expected on terminal treatment, were modest.

With an attendance rate of 65%, the number of life years gained varied between 13,300 when 7 smears were performed in a lifetime to 20,100 when 16 smears were performed. The costs per life-year gained oscillated between 24,300 DFL and 36,500 DFL.\textsuperscript{118-120}

The benefits and costs of different screening tests (VIA, HPV DNA testing and Pap smears) were calculated using a population-based model of Thailand, as an example of a less-developed country. Forty-two combinations of seven different screening strategies performed at varying intervals were evaluated. Compared to absence of screening, all screening strategies and intervals reduced incidence and mortality at costs ranging from $121 to $6,720 per life-year saved. The most cost-effective strategy was screening women aged 35-55 years every 5 years with VIA and with immediate treatment ($517 per life-year saved). In this model, Pap smear was considered to be cost-effective if a sensitivity of 80% and a follow-up compliance of 90% were achieved\textsuperscript{121}.

A cost-effectiveness analysis using a mathematical model and a hypothetical cohort of previously unscreened 30-year-old black South African women included several screening tests (VIA, Pap, HPV) and screening strategies. The strategies were analysed as a single lifetime screen at age 35 years, and compared with no screening. HPV testing followed by treatment of screen-positive women reduced the cancer incidence with 27% at a cost of 39$ per life-year saved. VIA with immediate treatment reduced the cancer incidence with 26% and was less costly than no screening. Performing screening twice per lifetime (at ages 35 and 40 or at 40 and 45) could be done for less than $20 per life-year saved. Cytology reduced the cancer incidence with 19% at a cost of 81$ per life-year saved\textsuperscript{122}.

Whereas these models provide useful information on the application of different screening strategies in well-defined populations, they have to be interpreted cautiously. Models are only as good as the assumptions built into them\textsuperscript{116}, and many parameters related to the natural history of cervical cancer are estimates. However, they are useful for public health decision making as they simultaneously consider different components and alternatives, difficult to implement in demonstration or intervention studies.

The cost-effectiveness of Pap screening in Vietnam was assessed using decision analytic methods. Outcomes measured included life expectancy, cervical cancer carcinoma incidence, cost per women and cost-effectiveness.

The authors calculated that the cost of establishing a nationwide 5-year interval Pap screening programme in Vietnam would be less than $148,000 annually during the first 10 years (assumed necessary to develop the programme). This would be lower if only high-risk geographic areas were targeted. Maintenance costs would average less than $0.092 annually per woman in the target screening population. Assuming 70% programme participation, the cervical cancer incidence would decrease from 26 per 100,000 to 14.8 per 100,000 and the cost-effectiveness was calculated at $725 per discounted life-year\textsuperscript{123}.
Goldie has calculated the discounted lifetime costs and clinical benefits (expressed as reduction in the lifetime risk of cancer) of different screening strategies performed at different screening intervals (figure 5). The cost-effectiveness of moving from one screening strategy to a more costly alternative is represented by the difference in cost divided by the difference in cancer incidence reduction associated with the two strategies. For each strategy, the cost-effectiveness ratio is shown. The figure illustrates the global inequity in cervical cancer control worldwide. When a benefit-cost ratio is employed instead of a cost-effectiveness ratio, the incremental benefits for a fixed amount of money can be calculated. In the US, 15 weeks of average life expectancy would be gained per $50,000. In South-Africa, this would be 1,000 years.¹¹⁷

Figure 5: Costs and benefits of cervical cancer screening¹¹⁷
13. Issues in cervical cancer screening in Developing Countries

In most developing countries, cervical cancer screening is not widespread, with few countries offering comprehensive screening services. Where they exist, they are faced with following problems:\textsuperscript{92,124-134}:

13.1 **Inexistent or poor design of screening programmes**

Screening programmes might be inexistent, as in many African countries, where screening services are not offered through the public sector. In Nairobi, Kenya, a pilot screening programme conducted in the mid-90’s, showed the feasibility of screening women for cervical cancer in the City Commission family planning clinics\textsuperscript{135}. In this country, screening is still integrated in FP services.

In other countries, and this is specially the case in Latin America, national screening programmes are designed by specialists, who tend to maximise the target population and screening interval. Despite limited resources, priorities are not adequately set. Many countries still have guidelines that promote yearly screening for all sexually active women. As an example, in Costa Rica and Mexico, where national screening programmes exist, all sexually active women are encouraged to have annually cytology smears\textsuperscript{128}. It is estimated that in India, four time more women could be screened if the age range for screening would change from 20-65 years to 35-55, and the screening interval would be increased from 2-3 years to 5-10 years\textsuperscript{126}.

13.2 **Low screening coverage**

Most programmes are not successful at achieving broad coverage. Most cervical cancer screening programmes in developing countries reach only a small fraction of the population, usually young urban women. This is the result of a lack of knowledge and awareness of the most-at risk population, as well as of the lack of accessible and acceptable screening services. As an example, private family planning clinics in Indonesia, Kenya, Thailand and Uganda offer cervical cancer screening services to their clients, generally in urban areas and for a fee\textsuperscript{136}. A study on the knowledge and attitudes of patients with invasive cervical cancer in Tanzania showed that both patients and controls had low levels of knowledge of basic symptoms of cancer of the cervix\textsuperscript{137}. Despite the existence of a cervical cancer screening programme, in Mexico, only 10-15\% of women 35-64 years old are screened\textsuperscript{131}.

13.3 **Lack of equipment and supplies**

As most programmes are cytology-based, equipment and supplies for taking, processing and reading Pap smears is needed. These supplies are often missing.

Some countries (such as Honduras and Zimbabwe) have earmarked a portion of their external funds to purchase essential equipment and supplies, such as gynaecological examination tables and instruments\textsuperscript{124}. 

24
13.4 Inadequate training

Nursing and medical schools and doctors are often not trained in the technique of Pap smear taking. In the Dominican Republic, there is no provision in medical or nursing schools for training in cervical screening\textsuperscript{136}.

Medical doctors lack knowledge on the natural history of cervical cancer, and the diagnosis and management of precancerous disease is not always foreseen in the curriculum of gynaecologists.

13.5 Limited laboratory facilities and lack of cytologists

Cytology laboratories might be available only at large teaching hospitals, making transport and timely processing of smears difficult. In other countries, services are decentralised, and cytologists do not read enough smears to guarantee high standard of reading. Mechanisms for adequate quality control are often lacking. Training of cytologists is another problem developing countries face. As an example, in India (1995), there were about 200 cytotechnicians. Even if all women would be screened only once in lifetime, the country would need four times more of them\textsuperscript{132}.

In Kenya, lack of cytotechnologists was identified as a major problem in the 90s\textsuperscript{138}. Through a collaborative effort between the University of Antwerp and the University of Nairobi, a Masters training in Clinical Cytology started in 1995. This “Training of Trainers” course, open for students from Eastern Africa, consists of a two-year programme, including cytology, histology, pathology, statistics, organisation of health structures and organisation of the laboratory. To date, 11 students have finished their training, of whom 6 have successfully submitted their Masters Thesis and received a Masters in Clinical Cytology. This course, a unicum for the region, has now been adopted in the curriculum of the University of Nairobi. (Prof E Van Marck, Dr Hugo De Vuyst, personal communication).

13.6 Loss-to-follow up of patients with abnormal smears

Many patients never come back to pick up the smear result, and, especially in urban areas, it might be difficult to trace patients with an abnormal smear. As a result, many patients never receive adequate follow-up. Inadequate follow-up is a factor contributing to reduced programme impact in a variety of countries such as Brazil, India, Indonesia, Lesotho, and Nigeria\textsuperscript{136}. In Kenya, a baseline-assessment showed that drop out of patients, long waiting lists for treatment and costs of treatment contributed to the poor follow-up of screen-positive patients\textsuperscript{139}.

13.7 Lack of diagnostic services

Colposcopy clinics might be inexistent, or only available at referral hospitals and in private clinics, and thus inaccessible for many women. As a result, final diagnosis and subsequent treatment is delayed, or women are treated on the basis of a screening test without confirmatory diagnosis. In Kenya, a second Pap smear is often used to confirm diagnosis\textsuperscript{136}.

13.8 Non-selective treatment

In many countries, all grades of cervical lesions are treated. This can be defended in some settings, as follow-up of women with LSIL can be difficult, but few or no attempts are done to propose follow-up instead of treatment.
13.9 **Reliance on highly trained medical personnel**

Treatment for pre-invasive disease is mainly provided by gynaecologists, and in some countries, even by oncologists. This limits accessibility to treatment, which is mainly restricted to tertiary hospitals in the capital. This has also negative consequences on follow-up.

13.10 **Reliance on in-patient treatment**

Precancerous lesions of the cervix are mainly treated in the hospital, by cone biopsy and even hysterectomy, and outpatient treatment modalities are often not available. This results in over-treatment of many women, and a high cost of treatment. Hysterectomy is widely used to treat SIL in all regions, except Latin America, where cone biopsy is used more widely than other methods. Larger differences exist among regions regarding cryotherapy and loop excision (Figure 6).[91]

![Figure 6: Type of CIN treatment being used by region (1995) ![](image)

*Other includes cautery/electrocoagulation diathermy, laser, and cold coagulation.*

In 1998, a meeting was organized on the prevention and control of cervical cancer in the East and Southern Africa Region. Representatives of each country presented the challenges cervical cancer programmes were faced to in their country. An overview of these findings is presented in Table 6. A situational analysis for diagnosis and treatment of cervical cancer in Tanzania showed that basic equipment for cytology-based cervical cancer was available at all health care facilities, but that the screening was inadequate at all levels of the health care system. Nurses were hardly utilised for screening, and treatment facilities for precancerous lesions were inadequate or non-existing. There was also a lack of organised institutional or national policy guidelines on cervical cancer screening in the country.[141]
<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>PROBLEMS IDENTIFIED</th>
</tr>
</thead>
</table>
| Botswana  | Staff shortages (lack of trained health personnel)  
Lack of cervical cancer protocols                                                                                                                                 |
| Eritrea   | No policy regarding cervical cancer  
Lack of trained cytotechnologists  
Lack of public awareness regarding prevention                                                                                                                                 |
| Ethiopia  | No policy nor guidelines  
Weak infrastructure                                                                                                                                 |
| Kenya     | Screening limited to more urban areas  
Follow-up of abnormal results  
Low public awareness  
Shortages of equipment and supplies  
Lack of trained personnel  
Few diagnostic centres with long waiting lists                                                                                                                                 |
| Lesotho   | Follow-up erratic  
Staff shortages  
No treatment facilities                                                                                                                                 |
| Malawi    | Problem not incorporated into the National Health Programme  
No screening performed on a widespread basis  
Surgery only mode of treatment available  
Lack of knowledge of population                                                                                                                                 |
| Mozambique| No nationwide cervical cancer screening programme  
Current services only available to middle-and upper-class women                                                                                                                                 |
| Rwanda    | No cervical cancer screening programme  
Pap smears only in one referral hospital  
Limited access to health care                                                                                                                                 |
| South Africa | Human resource disparities between rural/urban and public/private  
Underutilisation of resources associated with opportunistic screening  
Cost and availability of transport                                                                                                                                 |
| Tanzania  | Opportunistic screening  
No colposcopy services  
Only few patients can be treated (present with late stage of disease)                                                                                                                                 |
| Uganda    | Lack of policy guidelines  
Screening inadequate at all levels of health care  
70% of public health care facilities are equipped for Pap smears, but they are not being performed  
Lack of trained personnel                                                                                                                                 |
| Zambia    | Lack of trained cytologists and pathologists  
Lack of diagnostic and treatment options for SIL                                                                                                                                 |
| Zimbabwe  | Pap smears only for a small number of urban women  
Women present with late-stage cancer                                                                                                                                 |
14. Reference list


II.

OBJECTIVES AND METHODOLOGY
1. **General objective**

The general objective of this work is to assess the feasibility, acceptability and effectiveness of strategies for cervical cancer screening and management in resource-poor settings.

2. **Specific objectives**

1. To collect baseline-information for the set up of a cervical cancer screening programme, adapted to the needs of the population. As this programme was to be started in Rivas, Nicaragua, we were particularly interested in:
   b. Analysing issues and determinants of cervical cancer screening in the population of Rivas, as an example of a resource-poor setting.

2. To devise strategies for encouraging women at risk to attend for screening. As low coverage of a screening programme is a major issue, the effect on the attendance rate of a proactive approach inviting women of a well-defined target population, was to be assessed.

3. To define which screening tests are suitable in field conditions and how the quality of current tests can be improved. Poor quality of cytology being another major issue in resource-poor settings, we want to assess how the quality of cytology could be improved and whether other tests could be valuable alternatives. Of particular interest is the assessment of visual inspection with acetic acid, which has been promoted as a low cost and highly sensitive test.

4. To assess the effect of decentralising diagnosis and treatment. In developing countries, services for treating patients with pre-invasive disease of the cervix are mainly available at the referral level. This results in a high drop out of screen positive patients who never reach the referral hospital. Yet these services can easily be provided on an outpatient basis, integrated in gynaecological services. We want to assess how feasible it is to set up an outpatient clinic for the management of precancerous lesions of the cervix at regional level. We also want to know whether these services are acceptable for the population and whether high quality of service delivery can be achieved.

5. To describe the advantages and disadvantages of different strategies of service delivery. Whereas the previous objectives focus on public services, alternative services are available where cervical cancer screening can be provided. In Kenya, cervical cancer screening is mainly provided through family planning clinics. The suitability of integrating cervical cancer screening in these clinics is to be assessed.
3. Study sites and study development

Most of the data used for this work have been collected in Nicaragua, within the framework of two research projects funded through the Flemish Interuniversity Council (Project numbers AEIN1998PR204 and AEIN2000PR219, respectively). Data on integration of cervical cancer screening in family planning clinics and on the performance of screening tests in research conditions, were collected in Nairobi, Kenya. The first study was performed on data of the Family Planning Association of Kenya (FPAK), with headquarters in Nairobi, and the second in Ribeiro Clinic, one of the FPAK clinics in Nairobi (Figure 1).

In Nicaragua, the first project started in 1998 and was a study on prevalence and risk factors for sexually transmitted infections (STI) and cervical cancer. Sexually active women of all ages, attending the women’s health programme in the public health centres of three districts (capital Managua, the southern district Rivas and the northern district Matagalpa, see figure 2) and in one centre of the national health centre in Managua were invited to participate in this study.

The second, an action-research project on the integration of cervical cancer screening services in primary health care, started in 2000 and is still on-going. This community-based intervention programme aims at increasing the cervical cancer screening coverage of women most at risk, and is implemented in Rivas, Southern Nicaragua. This district has a population of 153 000 inhabitants, and is divided in six geographically different health areas: Tola, San Juan del Sur/Cardenas, Rivas, San Jorge/Buenos Aires, Belen/Potosi and Isla de Omotepe (Figure 3).
In all areas, cervical cancer screening was previously done within the public health sector on an opportunistic basis. No organized programme was in place, and no efforts were made to reach the population at risk. Conventional cytology was used as a screening test and all smears were read by the cytologist at Rivas Hospital.

Nicaragua and Kenya were chosen as study-sites because of the high prevalence of cervical disease in both countries. In Nicaragua, the first study was implemented in several sites, to have a more general idea of the prevalence of disease in women attending different health centres. The intervention programme was implemented in the district of Rivas, mainly because of two reasons. The first is that the researcher was familiar with this region, which facilitated contacts with health personnel and access to data. The second was the existence of a community-based organization with a network of health promoters. In Kenya, a colposcopy clinic was set up within a clinic of FPAK, as this clinic gave access to a population of sexually active women for whom a gynaecological examination was part of clinical routine clinical examination.

The intervention, aiming at improving the effectiveness of the existing programme, was composed of several elements:

1. A population-based survey to obtain baseline information on the determinants of cervical cancer screening in Rivas.

2. Promotion of cervical cancer screening through personal invitation of a well-defined target group (women aged 30 or more who had never been screened or who had not been screened within the last 3 years). Volunteer health promoters were involved to invite the women.

3. Interventions to improve quality of cytology: training of cytologist, medical doctors and nurses; provision of supplies and adequate forms.

4. Training in and utilisation of VIA as an alternative screening test

5. Decentralisation of diagnosis and treatment of pre-invasive cervical disease to district level.

The population-based survey was conducted in April 2000. In July 2000, the cytologist of Rivas hospital, responsible for reading all Pap smears of the district,
received an additional training course on cytology in the Bertha Calderon Hospital in Managua.

Due to logistical constraints, different components of the intervention started in a stepwise fashion in the 6 different geographical areas of the district. In September 2000 and May 2001, training courses on VIA including a refresher training module in correct sampling of Pap smears, were organized for the health staff of Tola, San Juan del Sur and Rivas. From October 2000 on, all health centres and health posts, as well as the hospital and one NGO clinic located in these areas were able to use VIA as a screening test. In these clinics, women of the target population were concurrently screened with both conventional cytology and the VIA test. New Pap forms, including data on personal history, clinical exam and reporting following the Bethesda classification were introduced in all centres.

Community health promoters were involved as a strategy to improve the coverage of the programme. Training of volunteer health promoters and subsequent invitation of women of the target population, started in Tola in October 2000, in San Juan del Sur in May 2001 and in Rivas in May 2002. In the 3 other areas, none of the components had started by the end of December 2002.

A referral colposcopy clinic for diagnosis and treatment of cervical dysplasia started functioning in the district hospital in October 2000. The clinic was later (June 2001) transferred to a local NGO, after unsuccessful attempts to provide regular services within the hospital. Colposcopies, cryotherapy and LEEP excision are performed by a gynaecologist of the Universidad Nacional Autónoma de Nicaragua (UNAN)-Managua, who provides the services on a weekly basis. Patients with invasive cancer are referred to the Bertha Calderon Hospital in Managua. After staging, they are treated with surgery and/or radiotherapy in the National Centre for Radiotherapy.

4. Study design including data collection

Observational studies, including surveys, and cross-sectional designs have been used, as well as routinely collected data. Several studies were implemented to reach the defined objectives. These studies were approved by the ethical committee of the UNAN-Managua, for the studies implemented in Nicaragua and by the National Ethical Review Committee of Kenyatta National Hospital, Nairobi, for the studies implemented in Kenya.

1. The prevalence of cervical neoplasia in Nicaragua was assessed as part of a cross-sectional study on prevalence and risk factors of sexually transmitted infections in women’s health clinics. From April 1999 to May 2000, sexually active women of all ages, attending the women’s health clinics in different regions, were interviewed and examined for STI, HIV and cervical neoplasia, using the Papanicolau-test as a screening test. Smears were taken by a study doctor (gynaecologist) and read by a pathologist at the referral laboratory in Managua. Special Pap forms including data on screening history were used for data collection. Details can be found in chapter III.1.

2. To obtain baseline information on screening status and determinants of cervical cancer screening in Rivas district, a survey was conducted in April 2000. The
study design is a face-to-face interview survey in a population-based proportional stratified two-stage cluster sample of adolescents and adults. Stratification criteria were geographical area and urban or rural setting. Primary sampling units were neighbourhoods and secondary sampling units were individual adolescents aged 15 years and older, and adults. The interview was carried out using a structured questionnaire. The 26 interviewers included members of the communities as well as medical students from the UNAN-Managua. Details on sample frame, selection of neighbourhoods and individuals as well as on the instruments and the procedure used for this survey, are highlighted in chapter III.2.

3. The effect of community health promotion on the uptake of cervical cancer screening by the defined target group, was assessed through a descriptive study on the number of health promoters trained, women invited and women attending screening centres. The number of screening tests provided in the intervention and non-intervention areas in Rivas district were compared, and this for different age groups. A historical comparison was made with the year prior to the intervention. Data on coverage were obtained through extrapolation of data to 36 months, 3 years being considered an adequate screening interval. The effect of service delivery on the uptake was also assessed in this study. The number of invitations provided to health promoters was registered by the NGO responsible for training. Health promoters were asked to notify the number of women invited. Women returned the invitation letters to the peripheral health centres when they attended for screening. The total number of screening tests done was assessed through collection of the Pap forms at the cytology laboratory. More details are found in chapter III.3.

4. The sensitivity and specificity of VIA as an alternative screening test for use in resource-poor settings, was assessed through a cross-sectional study among family planning attenders in Nairobi, Kenya. Women, aged 25-55 and attending a family planning clinic in Nairobi between January 1998 and July 2000, were invited to participate in the study as well as a small number of women referred to the same facility. Different screening tests for the detection of cervical cancer and pre-cancer were compared for their applicability in low resource settings. These tests included Pap smear, VIA, HPV testing and cervicography. The 'gold standard' was histology on colposcopy directed biopsies, performed on all women. The detailed study methodology is to found in chapter III.4-1.

5. The performance of VIA when used in field conditions as a screening test for cervical cancer, was assessed in Rivas, Nicaragua. Women who attended the programme in one of the areas where VIA was performed, were concurrently screened with VIA and Pap smear. Women with either positive test result were referred for colposcopy and biopsy when indicated. The performance of VIA was compared to Pap smear. Data were retrieved from the VIA, Pap, cytology and biopsy forms, designed for the purpose of this study (chapter III.4-2).

6. The improvement in quality of the conventional cytology was looked at in Rivas district, Nicaragua. Detection rates for cervical disease before and after training of the cytologist were compared as well as detection rates in the areas where health staff had and had not received training in correct sampling techniques. Routine collection of cytology data was used for this purpose. (chapter III.4-3).
7. A descriptive study design was used to assess the effect of decentralising diagnosis and treatment. Data on patients attending the colposcopy clinic in Rivas, Nicaragua, were routinely registered. Mean time to diagnosis and outpatient treatment as well as proportion of patients that benefit from outpatient treatment and attend follow-up have been used as indicators (chapter III.5.).

8. The suitability of integrating cervical cancer in family planning clinics was assessed in Nairobi, Kenya. A survey was done on clients visiting the clinics of the Family Planning Association of Kenya. Client characteristics, age, screening status and Pap smear results were registered. In-depth interviews were held with a limited number of staff and clients, through exit interviews. Results of Pap smears taken in 1999 were retrieved from the central handling system. A trained nurse was responsible for the surveys with clients and health providers. More detailed data on age, parity and contraceptive use of women with abnormal smears were collected from data at the cytology department. Further details can be found in chapter III.6.

Details on data-entry and analysis, including statistical tests, are included in the different chapters.

5. Dissemination of results

In Nicaragua, data dissemination was done through the organization of workshops at the end of each of the studies. Researchers, health workers and policy makers attended these workshops. In Kenya, results were locally disseminated during the Retreat Conference, held in Nairobi in January 2002 and 2003. Results were also made available through presentations in International Conferences: the 4th Eurogin Conference, Paris 2000; the 18th HPV Conference, Barcelona 2001; the 5th Eurogin Conference, Paris 2003.
The following papers have been published or submitted for publication:


III. RESULTS

III-1. PREVALENCE AND RISK FACTORS OF CERVICAL NEOPLASIA IN NICARAGUA
PREVALENCE AND RISK FACTORS OF SEXUALLY TRANSMITTED INFECTIONS AND CERVICAL NEOPLASIA IN WOMEN'S HEALTH CLINICS IN NICARAGUA

P Claeys, C Gonzalez, M Gonzalez, L Van Renterghem, M Temmerman

Sexually Transmitted Infections 2002; 78: 204-207

Abstract

Objectives
To determine the prevalence and risk factors of sexual transmitted infections (STI), HIV and cervical neoplasia in women attending women's health clinics in Nicaragua, and to assess the potential impact of screening for these diseases.

Study design
Consecutive women attending women’s health clinics in different regions were interviewed and examined for STI, HIV and cervical neoplasia.

Results
Whereas only 30.4% of the 1185 participating women attended the clinics because of STI-related complaints, 77.0% reported STI-related symptoms after probing. Clinical cervicitis was diagnosed in 32.8%, Chlamydia Trachomatis in 4.1%, gonorrhoea in 0.4%, trichomoniasis in 10.2%. Antibodies for syphilis were found in 0.7%, for hepatitis B in 3.7% and none were HIV seropositive. The STI prevalence was 21.8% in women attending with complaints, 17.3% in symptomatic women after probing and 14.8% in asymptomatic women. Abnormal Papanicolaou (Pap) smears were found in 7.7%, with high-risk human papillomavirus (HPV) types in almost 60%. Male promiscuity was associated with high-grade squamous intraepithelial lesions (HSIL) and reported former screening was not shown to be protective. Young age and being employed were risk factors for C.trachomatis.

Conclusion
Nearly one out of five women attending women's health clinics in Nicaragua did have a STI, and one out of 13 a precancerous lesion of the cervix. These clinics provide an opportunity to improve the reproductive health of women by probing for STI symptoms, especially in young women, and by offering cervical screening to casual attendees. Of concern is the high rate of cervical lesions in women with a screening history, underlining the need for proper quality control.
Introduction

In developing countries, sexually transmitted infections (STI) and HIV are endemic and cervical cancer prevalence high. It has been suggested that integrating STI management and early detection of cervical dysplasia in broader reproductive health services, can improve women's health\textsuperscript{1}. In Nicaragua, these services are offered in the health centres through the so-called “consulta integral a la mujer”. Little is known on the burden of disease of women attending this programme. In this study, we wanted to assess the prevalence and risk factors of STI, HIV and cervical neoplasia in this population and evaluate the potential impact of screening for STI and cervical cancer.

Material and methods

Study population and data collection

From April 1999 to May 2000, sexually active women of all ages, attending the women's health programme in the public health centres of three districts (capital Managua, the Southern district Rivas and the Northern district Matagalpa) and in one centre of the national health service in Managua were invited to participate in the study. Consecutive women attending the consultation were included after giving verbal consent. History was taken, a gynaecological examination was done, samples for laboratory analysis and for Papanicolaou (Pap) smears were obtained.

Blood sera were tested for syphilis using the Macro-Vue RPR Card Test (Becton Dickinson, MD, USA). Reactive sera were diluted and quantified. A rapid plasma regain (RPR) test $\geq 1/4$ was considered indicative for syphilis. Testing for HIV-1 and HIV-2 was done by a third generation enzyme immunoassay (EIA) Plus (Abbott, Abbott Park, USA), positive tests were confirmed by western blot assay. An enzyme linked immunosorinent assay (ELISA) test (Human, Wiesbaden, Germany) was used to detect antibodies to Hepatitis B Virus core antigen (anti HBc) and a second generation radioimmunoassay (LSU-ICMRT Version 2) to detect hepatitis B surface antigen (HbsAg) for establishing active infections.

Trichomonas vaginalis and candida species were diagnosed either on wet mount or by Gram stain. Bacterial vaginosis (BV) was diagnosed using the Nugent score\textsuperscript{2}.

Cervical samples were obtained for Gram staining and culture of Neisseria gonorrhoeae

in Thayer-Martin medium (Merck, Darmstadt, Germany) and in chocolate blood agar medium (Difco, Detroit, MI, USA). Polymerase chain reaction (PCR) (Amplisorc, Roche Diagnostics, Ontario, Canada) was used for the detection of Chlamydia trachomatis at the Ghent University.

PCR tests for N gonorrhoeae were done to confirm gonorrhoea in women with a Gram stain suggestive of intracellular diplococci and a negative culture, as well as in 80, randomly chosen, negative samples. Patients were considered as having gonorrhoea if either the culture or PCR was positive. Human papilloma virus (HPV) detection was done on endocervical swabs of women with an abnormal Pap smear. Samples identified as HPV positive were genotyped with the Inno-Lipa HPV
prototype research assay (DDL, Delft, The Netherlands), as described previously\(^3\). HPV amplimers, which do not hybridise to any probe, were assigned HPV genotype X. According to their oncogenic potential, HPV viruses were classified as high or low risk\(^4\). Pap smears were read using the Bethesda Classification.

Patients were asked to return for the laboratory results after 2 weeks. All women with a clinical or laboratory diagnosis suggestive of an STI or with cervical dysplasia were counselled and treated free of charge.

**Data analysis**

The data were entered in Epi-info (version 6.0) and analysed using SPSS version 10 for Windows (SPSS, Inc., Chicago, IL, USA). Univariate analysis was done using Pearson’s \(\chi^2\) test, odds ratio and 95% confidence intervals (CI) and/or Fischer’s exact test and multivariate analysis using the logistic regression (enter model).

**Results**

**Demographic data**

A total of 1185 women were included in the study, of whom 80% lived in urban areas and 81.0% were married. The mean age was 32.3 years (range 13-72) and 47.3% were housewives. The monthly family income was less than 125 US$ in 69.3% of the families.

**Sexual, reproductive and screening history**

The mean parity was 3.3 and 22% had had at least one abortion. Sexual relations started at a mean of 17.9 years (range 8-35). Only 2.1% reported more than one partner in the last 3 months, but 46% believed their husband or boyfriend had extramarital sex. More than 16% had ever used condoms, in 2.8% on a regular basis and in 1.6% for contraceptive purposes.

Seventy six percent of women had a Pap test done in lifetime and 47% within the last 3 years. Only 1.2% reported a history of an abnormal Pap result.

**STI-related symptoms, signs and prevalence**

Women attended the clinic for a variety of reasons, including 360 (30.4%) for STI-related complaints, 67 (5.7%) for pregnancy control, 272 (23.0%) for family planning and 486 (40.7%) for regular check-ups including Pap smear taking. After probing for STI-related symptoms, 552 (67.0%) of the women attending for other reasons, admitted having problems. The most reported symptoms were vaginal discharge (58.1%), abdominal pain (35.1%), pruritus (27.7%) and dyspareunia (19.8%). They had a duration of less than 1 week in only 7.2%; dyspareunia and abdominal pain were the longest supported symptoms. Previous treatment with antibiotics was reported in 13.5%. A clinical diagnosis of cervicitis and of pelvic inflammatory disease (PID) was made in, respectively, 32.8% and 6.4% of the women. More than 18% of the patients had an STI, though no HIV was detected. An additional 35.7% of woman had a non-STI reproductive tract infection, including candidiasis (19.1%) and bacterial vaginosis (30.5%). *T. vaginosis* was commonly associated with other pathogens, in 43% with BV, and in 10% with *C. albicans*. An overview of clinical and laboratory diagnosis is given in Table 1.
**Table 1. Clinical diagnosis and laboratory results**

<table>
<thead>
<tr>
<th></th>
<th>Total population (n=1185) (%)</th>
<th>STI related complaints (n=360) (%)</th>
<th>Symptoms after probing (n=552) (%)</th>
<th>Asymptomatic (n=273) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical exam</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>380 (32.1)</td>
<td>89 (24.7)</td>
<td>148 (26.8)</td>
<td>143 (52.4)</td>
</tr>
<tr>
<td>GUD</td>
<td>4 (0.3)</td>
<td>2 (0.6)</td>
<td>2 (0.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Condylomata</td>
<td>14 (1.2)</td>
<td>9 (2.5)</td>
<td>4 (0.7)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>593 (50.1)</td>
<td>195 (54.2)</td>
<td>299 (54.2)</td>
<td>99 (36.4)</td>
</tr>
<tr>
<td>Cervicitis</td>
<td>389 (32.8)</td>
<td>129 (35.8)</td>
<td>200 (36.2)</td>
<td>60 (22.0)</td>
</tr>
<tr>
<td>PID</td>
<td>76 (6.4)</td>
<td>38 (10.6)</td>
<td>38 (6.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T. vaginalis</td>
<td>119/1175 (10.1)</td>
<td>41/357 (11.5)</td>
<td>55/547 (10.2)</td>
<td>23/271 (8.5)</td>
</tr>
<tr>
<td>C. trachomatis</td>
<td>40/969 (4.1)</td>
<td>16/292 (5.5)</td>
<td>21/461 (4.6)</td>
<td>3/264 (1.4)</td>
</tr>
<tr>
<td>N. gonorrhoeae</td>
<td>5/1162 (0.4)</td>
<td>3/354 (0.8)</td>
<td>2/544 (0.4)</td>
<td>0/0</td>
</tr>
<tr>
<td>GUD</td>
<td>4/1180 (0.3)</td>
<td>2/359 (0.6)</td>
<td>2/554 (0.4)</td>
<td>0/0</td>
</tr>
<tr>
<td>Condylomata</td>
<td>14/1182 (1.2)</td>
<td>9/360 (2.5)</td>
<td>4/552 (0.7)</td>
<td>1/272 (0.4)</td>
</tr>
<tr>
<td>HIV antibodies</td>
<td>0/1158 (0)</td>
<td>0/356 (0)</td>
<td>0/540 (0)</td>
<td>0/262 (0)</td>
</tr>
<tr>
<td>HbsAg</td>
<td>4/1180 (0.3)</td>
<td>1/359 (0.3)</td>
<td>1/549 (0.2)</td>
<td>2/272 (0.7)</td>
</tr>
<tr>
<td>HBc antibodies</td>
<td>43/1179 (3.7)</td>
<td>15/358 (4.2)</td>
<td>14/549 (2.6)</td>
<td>14/270 (5.2)</td>
</tr>
<tr>
<td>RPR &gt;=1/4</td>
<td>8/1185 (0.7)</td>
<td>5/360 (1.4)</td>
<td>3/552 (0.5)</td>
<td>3/273 (0)</td>
</tr>
<tr>
<td>At least one STI</td>
<td>213/1175 (18.5)</td>
<td>78/357 (21.8)</td>
<td>95/548 (17.3)</td>
<td>40/270 (14.8)</td>
</tr>
<tr>
<td><strong>Non-STI RTI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida species</td>
<td>222/1175 (18.5)</td>
<td>74/357 (20.7)</td>
<td>107/547 (19.6)</td>
<td>43/271 (15.9)</td>
</tr>
<tr>
<td>Bacterial vaginosis</td>
<td>359/1176 (19.1)</td>
<td>132/358 (36.9)</td>
<td>155/547 (28.3)</td>
<td>72/271 (26.6)</td>
</tr>
</tbody>
</table>

**Cervical neoplasia and HPV**

Ninety (7.7%) patients had an abnormal Pap result, including 40 (3.4%) atypical squamous cells of undetermined significance (ASCUS), 35 (3.0%) low-grade squamous intraepithelial lesions (LSIL), 12 (1.0%) high-grade squamous intraepithelial lesions (HSIL) and three (0.3%) invasive cancer. Of those, only 31 (34.4%) came to the clinic for Pap smear taking. All patients diagnosed with invasive cancer attended the clinic for screening reasons, but 75% HSIL were diagnosed in casual attenders. Of the 15 patients with a HSIL or invasive cancer, 13 (86.6%) were previously screened, six of them within the last 12 months and six within the last three years. None of them reported an abnormal result on their last Pap smear.

HPV tests were done on 72 patients with abnormal Pap smears (Table 2). High-risk HPV were present in 54.6% of ASCUS lesions, 62.0% of LSIL and 70% of HSIL. Multiple infections were found in 19 (26.4%) patients. One patient with a LSIL was infected with seven different types and another with six. High-risk HPV types related to HPV 16 were most prevalent in any of the lesions.
Table 2: HPV types

| Pap       | No HPV detected | Single infections | Multiple Infections |  
|-----------|-----------------|-------------------|---------------------|-----------------|
|           | n (%)           | Low-risk or not specified HPV n (%) | High-risk HPV n (%) | Only low-risk HPV n (%) | Presence of high-risk HPV n (%) |
| ASCUS (n=33) | 10 (30.3) | 4 (12.1) | 12 (36.4) | 1 (3.0) | 6 (18.2) |
| LSIL (n=29) | 4 (13.8) | 7 (24.1) | 9 (31.0) | 0 (0) | 9 (31.0) |
| HSIL (n=10) | 2 (20.0) | 1 (10.0) | 4 (40.0) | 0 (0) | 3 (30.0) |
| TOTAL (n=72) | 16 (22.2) | 12 (16.7) | 25 (34.7) | 1 (1.4) | 18 (25.0) |

Low-risk HPV: 6, 11, 34, 40, 42, 43, 44, 53, 54, 70, 74
High-risk HPV: 16, 18, 31, 33, 39, 45, 51, 52, 56, 58, 59, 66, 68

Determinants of STI and cervical neoplasia

In univariate analysis, age < 30 years, being single, being employed, pregnancy and STI-related symptoms were associated with *C. trachomatis* infection. No significant associations were found with number of partners, age at first sexual relations, reason for attending the clinic, duration of symptoms and clinical diagnosis of cervicitis. In multivariate analysis, only age < 30, being employed and having STI-related symptoms remained significant, with adjusted odds ratios (AOR) of 5.2 (95% CI 2.2 to 12.0), 2.4 (95% CI 1.1 to 5.0) and 3.3 (95% CI 1.0 to 10.9) respectively. Fifty percent of *C. trachomatis* cases could be found in the group of symptomatic, employed women younger than 30 years old. In this group, the prevalence was 11.3%.

Genital ulcers and/or warts were associated with past condom use: AOR 4.1 (95% CI 1.4 to 11.8).

In univariate analysis, HSIL or invasive cancer on current Pap smear was associated with age >= 30 years (OR 3.35, 95% CI 0.94 to 11.94), having more than three children (OR 5.0, 95% CI 1.6 to 15.8) and reporting non-monogamous partners (OR 11.9, 95% CI 1.5 to 93.4). In multivariate analysis, only the latter remained significant with an AOR of 11.3 (95% CI 1.4 to 82.0). Reporting a normal Pap smear within the past 3 years was not shown to be protective (OR 2.5, 95% CI 0.7 to 8.8).

Discussion

In this study population, none of the patients was infected with HIV. This is in line with the UNAIDS estimated prevalence rate of 0.1% in Nicaraguan women. However, our data show that the potential for an HIV epidemic exists. Nearly one out of five of this low to middle class, low risk population was found to have an STI. The prevalence of genital ulcer disease and of gonorrhoea was low in our group whereas the prevalence of *C. trachomatis* was 4.1% and of *T. vaginalis* 10.1%. Condom use was very low, though half of the women believed that their husband or boyfriend had extramarital sex. Even if women might have few possibilities to
negotiate sexual and reproductive practices, appropriate health education could increase the reported condom use among women, as shown in a HIV/AIDS programme set up in Managua in 1991-26.

A high prevalence of abnormal smears was found in this population, mainly mild lesions. In women with ASCUS lesions, HPV testing has been suggested as a triage to identify those women most at risk of having an underlying HSIL. In many low resource countries this test is not as widely available as to allow common use. In our study we detected high-risk HPV types in more than 50% of ASCUS lesions, indicating that, in the absence of HPV testing, ASCUS lesions should always be further investigated.

As shown in other studies7, only a few classic risk factors were significantly associated with genital infections. This might be explained by the importance of male risk behaviour, which is not addressed in this survey. The prevalence of C. trachomatis in women younger than 30 years is nearly six times higher than in older women. Similar data were found in a study of 863 clinic attendees in three regions in Nicaragua8. The higher prevalence in working women could be due to a more liberal sexual behaviour in this group. This was not confirmed by the reported sexual history but, within the culture of machismo, it might be difficult for a woman to mention the number of sexual partners9. Another possibility is that these women do have more promiscuous partners.

Genital ulcer disease and genital warts were significant associated with past condom use. We found similar results in studies from Kenya and Azerbaijan7,10. However, other researchers showed that consistent condom use significantly reduced the risk of acquiring genital warts11. This might indicate that in our studied populations, condom use is irregular or that condoms are a surrogate for more risky sexual behaviour, either by the woman or by her partner.

Probably as a result of the small number of cases, the classic risk factors for HSIL and cervical cancer could not be found in our study, with the exception of promiscuous male behaviour. Contrary to what is widely accepted, previous screening was not shown to have a protective effect in this population. The poor quality of Pap smears might be the main reason for this. Whereas it has been mentioned that screening programs in Latin America should have a wider coverage in order to reduce cervical cancer in these countries12, this should be preceded by measures to guarantee the quality of the screening if results are to be reached.

As half of the HSIL and invasive cancers were detected in casual clinic attendees, our data further show the importance of inviting these women to the programme, especially if they are more than 30 years old. On the same line, health providers should ask women for STI related symptoms, and pay special attention to the possibility of C. trachomatis infections in young women. If the quality of the services were further guaranteed, these simple measures would contribute to more comprehensive care in women’s health clinics. To have a substantial impact on women’s health, it is necessary to link these clinics with referral level where diagnostic procedures as colposcopy and biopsy and outpatient treatment of dysplastic lesions can be provided. The district hospital or larger health centres might be excellent sites to provide this care.
Acknowledgements

The authors thank the staff of the health centres and clinics involved in the study, whose collaboration made this work possible.

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Reference list


III-2.
DETERMINANTS OF CERVICAL CANCER SCREENING IN A POOR AREA
DETERMINANTS OF CERVICAL CANCER SCREENING IN A POOR AREA: RESULTS OF A POPULATION BASED SURVEY IN RIVAS, NICARAGUA

P Claeys, C Gonzalez, M Gonzalez, H Page, R E Bello, M Temmerman

Tropical Medicine and International Health 2002, 7 (11) 935-941

Summary

Objective

To obtain baseline information for designing a community-based intervention programme aimed at increasing the cervical cancer screening coverage of women most at risk.

Methods

A population-based survey, using proportional stratified two-stage cluster sampling in Rivas, one of the 16 Departments of Nicaragua. The individuals selected were interviewed at home by one of 26 interviewers, using a structured questionnaire. The questionnaire was designed to elicit (1) knowledge, attitudes and practices concerning sexual and reproductive health and behaviour, (2) risk factors for cervical cancer and (3) the use of health and cervical cancer screening services.

Results

A total of 612 men and 634 women participated in the survey. Of the women who had been sexually active at least 3 years, only 41.1% had undergone screening within that period and were considered adequately screened. Correlates of inadequate screening status included low educational level, exclusive use of public health facilities and lack of knowledge about prevention and symptoms of cervical cancer. Negligence, absence of medical problems, fear, lack of knowledge and economic reasons were the main reasons given for not being screened. Reluctance to be screened in the future was related to lack of knowledge of the disease, inadequate screening status, older age and low educational level.

Conclusions

The current screening programme is not effective in reaching the majority of the population. Complementary activities such as education and information, as well as a more pro-active approach to invite women for screening are necessary.
Introduction

Each year, an estimated 371,000 new cases of invasive cervical cancer occur worldwide, representing nearly 10% of all cancers in women. In 1990, the estimated age standardized incidence rate in Central America was 44.4/100,000, which is the highest in the world and three times higher than in the industrialized world.

Cervical cancer is among the few cancers that can be prevented. In Western countries, the decline in cervical cancer incidence and mortality has been attributed to extensive screening programmes. However, in most developing countries, cervical cancer screening is not widespread, and comprehensive screening services are rare. Current screening programmes face obstacles such as inadequate equipment and supplies, inadequate provider training, limited cytology services and difficulties in patient follow-up and treatment. As a substantial proportion of women at risk has never been screened, low coverage is the most important deficiency.

In Nicaragua, screening services are provided through the public health system, where Papanicolaou (Pap) smear taking is integrated into the women’s health clinics. Screening is opportunistic: women attending the services and requesting a Pap smear are screened, whatever their age or date of last screening. Private practitioners and non-governmental organization (NGO) clinics also offer cervical cancer screening services. Despite improved access to health services since the 1980s, fertility surveys have shown that only 35% of the women have had at least one Pap smear by the age of 35.

We wanted to obtain baseline information for designing a community-based intervention programme to increase the cervical cancer screening coverage of women at risk. The first step in this process was the description of the population in terms of both demographic and socio-economic status and reproductive and sexual behaviour. We also examined the perceptions of both men and women regarding cervical cancer and screening. To establish determinants of cervical cancer screening, we distinguished between the current screening status and the intention to be screened in the future. In order to design feasible interventions, information on the perception and use of health services was collected. As community volunteers and outreach personnel can successfully increase the coverage of cervical cancer screening programmes, we assessed the extent to which the population was aware of the existence and role of brigadistas de salud.

Methodology

Study design and sampling

The study design is a face-to-face interview survey in a population-based proportional stratified two-stage cluster sample of adolescents and adults. The total population was the population of the Department of Rivas, one of the 16 Departments of Nicaragua, with 153,000 inhabitants. Stratification criteria were geographical area and urban or rural setting. Primary sampling units were neighbourhoods and secondary sampling units were individual adolescents aged 15 years and older, and adults.
The sample frame for the first stage was developed using data from the 1995 electoral survey, which includes the entire population aged 16 or over, living in Rivas at that time. The Department was first divided into six geographical areas, each with an urban and a rural zone, resulting in 12 strata. We then listed the number of neighbourhoods and inhabitants in each stratum, taking into account an estimated 15% population increase. The planned sample size was set at 1200: 600 men and 600 women, 300 urban and 300 rural, respectively. The number of people to be interviewed in each stratum was proportional to the size of the stratum.

Two neighbourhoods were then randomly selected in each stratum, with the exception of urban Rivas, where three neighbourhoods were included, and urban Tola, where only one was included because of the size of the respective strata. We censused the total population of those neighbourhoods by house-to-house visits. All men and women aged 15 years and older were listed. The individuals to be interviewed, proportional in number to the size of the neighbourhood and including an additional 7-8% to allow for non-response in the form of refusals, were then selected randomly. For each neighbourhood, a randomly selected reserve list of 20% of the sample size was made to substitute for subjects who could not be located.

**Instruments**

The interview was held using a structured questionnaire. The questionnaire was designed to characterize people in terms of knowledge, attitudes and practices concerning sexual and reproductive health, reproductive and sexual behaviour, risk factors for cervical cancer, and use of health services in general and of cervical cancer screening services in particular.

The questionnaire included questions assessing knowledge and preferences concerning Pap testing. Women were asked extensively about their history, current use and intention to use cervical cancer screening services. Men were asked about their attitudes towards and preferences concerning screening services. Barriers and facilitating factors for cervical cancer screening were identified using both closed and semi-open questions.

These data were completed by questions on demographics, socio-economic status, knowledge and practices concerning family planning, STD services and AIDS.

**Procedure**

The 26 interviewers (20 females, six males) consisted of members of the various communities with at least secondary education level, and medical students from the Universidad Nacional de Nicaragua. All received a 1-day training in the correct use of the questionnaire. All the persons selected were visited at home and interviewed individually. If absent, they were visited again, and if not found then, replaced by other subjects. Participants were asked about their willingness to participate at the start of the questionnaire to get informed consent. Ethical approval for the study was obtained from the ethical committee of the Universidad Nacional Autónoma de Nicaragua, Managua.

**Analysis**

Data were entered in Epi-info version 6.04.b, and analysed with SPSS 9.0 for Windows (SPSS Inc., Chicago, IL, USA).
Proportions were compared using the chi-square test and mean values by the Student’s t-test. The association between current screening status and intention to be screened, respectively, and independent variables (including socio-demographic characteristics, accessibility and use of health services, knowledge of cervical cancer and screening history) was assessed in univariate analysis using the chi-square test, and summarized with odds ratios (OR) and their respective 95% confidence intervals (CI). For this purpose, various continuous variables (age, income, distance from health centre) were grouped in categories. To adjust for multiple determinants of current screening status and intention to be screened, multivariate logistic regression using a forward stepwise model was performed. Only determinants significant in univariate analysis were included in the model, and in the same form. All tests of hypothesis were two-tailed with a type I error rate fixed at 5%.

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**Results**

A total of 1298 people, 646 men and 652 women, were selected for the interview and visited by the interviewers between 3 and 15 April 2000. Of those selected, 239 men and 127 women were not at home during the first visit and were visited a second time. Seventy-six (12%) men and 43 (6%) women could not be located and were replaced by subjects from the reserve list. Thirty-four men and 18 women refused to answer the questionnaire (5% and 3%, respectively, of those present), resulting in 612 men and 634 women participating in the survey.

**Characteristics of the population**

The mean age of the interviewee population was 35.5 years (range 15-90). Nearly 18% was younger than 19 years. Half of the population lived in rural areas. About 59.8% of men and 57.6% of women were married or living with a partner. The educational level was similar for men and women, 12.2% being illiterate and 5.3% having a higher education. About 42% of men were farmers and 73.4% of the women housewives. Two-thirds of the families had an income of < 1000 Cordoba per month (75 US$). The mean parity of the women was 4.1 (SD 3.3, range 0-16) and more than half had at least three children. Nearly 40% of women and 79.6% of men had had more than one sexual partner. Just under half of the women believed their partner to be faithful, but only 3.3% of the men admitted having more than one sexual partner at the time of the interview. Adolescent boys were more likely than their female counterparts to be sexual active by the age of 18, but they were less likely to have a stable relationship and children. An overview of the reproductive and sexual behaviour is given in Table 1. The reports were independent of the sex of the interviewers.
Table 1. Characteristics of the population

<table>
<thead>
<tr>
<th></th>
<th>MEN</th>
<th>WOMEN</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total population (n=1246)</strong></td>
<td>n = 612</td>
<td>n = 634</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>35.6 (17.5)</td>
<td>35.3 (16.6)</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Sexual experience</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>546 (89.2)</td>
<td>532 (83.9)</td>
<td>0.006</td>
</tr>
<tr>
<td>No</td>
<td>66 (10.8)</td>
<td>102 (16.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Sexually active population (n=1078)</strong></td>
<td>n = 546</td>
<td>n = 532</td>
<td></td>
</tr>
<tr>
<td>Mean starting age (years)</td>
<td>15.8 (3.0)</td>
<td>17.7 (3.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Number of sex partners lifetime</strong> a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.00</td>
<td>100 (20.4)</td>
<td>323 (61.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2-10</td>
<td>262 (53.6)</td>
<td>199 (37.8)</td>
<td></td>
</tr>
<tr>
<td>&gt; 10</td>
<td>127 (26.0)</td>
<td>4 (0.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Having children</strong> b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With one partner</td>
<td>246 (67.6)</td>
<td>344 (70.8)</td>
<td>0.316</td>
</tr>
<tr>
<td>With different partners</td>
<td>118 (32.4)</td>
<td>142 (29.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Trust partner to be faithful</strong> c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>271 (81.6)</td>
<td>159 (46.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No</td>
<td>61 (18.4)</td>
<td>181 (53.2)</td>
<td></td>
</tr>
<tr>
<td><strong>Adolescents 15-18 years (n=220)</strong></td>
<td>n = 115</td>
<td>n = 105</td>
<td></td>
</tr>
<tr>
<td><strong>Civil status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>104 (90.4)</td>
<td>80 (76.2)</td>
<td>0.004</td>
</tr>
<tr>
<td>Married/accompanied</td>
<td>11 (9.6)</td>
<td>25 (23.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Sexual experience</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>64 (55.7)</td>
<td>39 (37.1)</td>
<td>0.006</td>
</tr>
<tr>
<td>No</td>
<td>51 (44.3)</td>
<td>66 (62.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Having children</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7 (6.1)</td>
<td>21 (20.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>No</td>
<td>108 (93.9)</td>
<td>84 (80.0)</td>
<td></td>
</tr>
</tbody>
</table>

a Fifty-seven missing values in men, six in women.
b Analysis limited to 377 men and 490 women reporting children, 13 missing values in men, four in women.
c Analysis limited to 341 men and 344 women living in stable relationship, nine missing values in men, four in women.

**Accessibility, perception and use of health services**

Nearly 80% of the population had access to a public health facility within 5 km or one accessible within less than half an hour. This was more than 95% in urban areas and 60.5% for rural people. Four-fifths of the population reported having attended a public health service the last time they had health problems, mainly because the public services were nearby and cheap. Nearly 20% of people in urban and less than 10% of people in rural areas attended private practitioners, mainly because of a perceived higher quality of service delivery. There were no major
differences in the perception between males and females, or between different age categories.

Questioned about community health workers, only 36.7% of the population knew that there was a *brigadista de salud* in their neighbourhood or community. Health promoters were better known in rural than in urban areas: 42.6% vs. 30.8% (*P* < 0.001).

**Perception and practices regarding cervical cancer screening**

Only 433 women (68.3%) and 348 men (56.9%) said they knew some basic facts about cervical cancer, yet 94.3% and 89.2%, respectively, knew that women could be examined to detect the illness. Women more often than men (59.1% vs. 44.4%, *P* < 0.001) referred to the Pap test as a means of preventing cervical cancer. Only 19.6% of women and 14% of men could give at least one symptom of cervical cancer. Symptoms most cited were abdominal pain (13.2%), bleeding (9.1%) and vaginal discharge (2.6%).

As more than 50% of responders without sexual experience (mainly adolescents) were not able to reply to the questions, we limited the analysis of attitudes to cervical screening to the 546 men and 532 women who were sexually active.

In general, people were favourable towards screening: 89.2% of men and 80.3% of women thought it was good for women to be screened. Nearly 80% of both sexes considered the medical doctor best placed to perform the screening and significantly more women than men preferred a female health worker (70.3% vs. 38.5%, *P* < 0.001). For 25% of men and 56.4% of women the screening should preferably be offered through private services, but one quarter of men and 37.2% of women were not able or willing to pay 10 Cordoba (0.75 US$) for a Pap smear.

Screening practices and predictors of inadequate screening status

Because we considered women to be adequately screened if they had a screening test within the last 3 years, we limited this analysis to the 489 women who had been sexually active at least 3 years. Of these women, 201 (41.1%) were adequately screened and 288 (58.9%) inadequately; of them, 205 (41.9%) had never been screened and the remaining 83 (17.0%) had had their last Pap smears more than 3 years ago.

Of the women screened, 57.8% had the test performed in a public centre, 34.5% in the private sector and the rest in NGO clinics. Several variables related to socio-demographic status, accessibility and use of health services, and knowledge were significantly related to screening status. In multivariate analysis, predictors of inadequate screening were low educational level, exclusive use of public health services and lack of knowledge (Table 2). The reasons given for not being screened were negligence (23.6%), absence of medical problems (22.1%), fear of the examination (21.1%), ignorance (15.1%) and economic reasons (8%). Less than 10% declared that they had been unwilling to undergo screening tests.
Table 2. Determinants of inadequate screening status

<table>
<thead>
<tr>
<th>Socio-demographic variables</th>
<th>Proportion of women inadequately screened</th>
<th>OR (95% CI)</th>
<th>AOR (95% CI)c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=489)b (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Area</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>urban</td>
<td>126/232 (54.3)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>rural</td>
<td>162/257 (63.0)</td>
<td>1.44 (1.00-2.06)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤45 years</td>
<td>179/336 (53.3)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&gt;45 years</td>
<td>109/153 (71.2)</td>
<td>2.17 (1.44-3.28)</td>
<td></td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ secondary level</td>
<td>63/142 (44.4)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>≤ primary level</td>
<td>220/341 (64.5)</td>
<td>2.28 (1.53-3.40)</td>
<td>1.74 (1.07-2.83)</td>
</tr>
<tr>
<td>Income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1000 Cordoba (&gt; 75 $)</td>
<td>37/87 (42.5)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>≤1000 Cordoba (≤ 75 $)</td>
<td>143/241 (59.3)</td>
<td>1.97 (1.20-3.24)</td>
<td></td>
</tr>
<tr>
<td>Accessability and use of health services</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distance from health facility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5km</td>
<td>204/373 (54.7)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&gt;5 km</td>
<td>81/113 (71.7)</td>
<td>2.10 (1.33-3.32)</td>
<td></td>
</tr>
<tr>
<td>Use of private services</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sometimes/ever</td>
<td>32/71 (45.1)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>never</td>
<td>252/413 (61.0)</td>
<td>1.91 (1.15-3.17)</td>
<td>1.95 (1.03-3.68)</td>
</tr>
<tr>
<td>Knowledge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Knows cervical cancer can be prevented</td>
<td>230/419 (54.9)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>57/69 (82.6)</td>
<td>3.90 (2.03-7.49)</td>
<td>2.42 (1.09-5.37)</td>
</tr>
<tr>
<td>Able to mention at least one symptom</td>
<td>51/113 (45.1)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>237/376 (63.0)</td>
<td>2.07 (1.35-3.17)</td>
<td>1.79 (1.06-3.03)</td>
</tr>
</tbody>
</table>

a Analysis limited to women at least 3 years sexual active
b Missing values: 6 for educational level, 161 for income, 3 for distance, 5 for use of private services, 1 for knowledge on prevention
c Logistic regression using forward stepwise model, adjusting for all variables included in univariate analysis. Only educational level, use of private services and factors related to knowledge were withheld in the equation. OR: Odds Ratio; AOR: Adjusted Odds Ratio; CI: Confidence Interval

Determinants of future screening planning

This analysis is limited to the 483 women who were sexually active for at least 3 years, excluding those who had a hysterectomy.

A total of 135 (28.0%) women expressed reluctance to future screening. Nearly half of the women never screened were unwilling to attend screening programmes in the future.

In univariate analysis, age > 45 years, lower educational level, monthly income < 1000 Cordoba, ignorance of symptoms and prevention of cervical cancer, and inadequate screening status were significantly related to unwillingness to be screened in the future. In multivariate analysis, including all significant variables, the main determinants of unwillingness to be screened in the future were lack of
knowledge, inadequate screening status, age > 45 years and low educational level, with adjusted odds ratios of 4.96 (CI 2.41-10.05); 5.13 (CI 2.033-11.30); 4.12 (CI 2.18-7.80) and 2.89 (CI 1.28-6.52), respectively.

Nearly half of the women attributed their reluctance to absence of medical problems; fear of the test, lack of knowledge, advanced age and economic problems accounted for the other half.

## Discussion

Previous data collected in Nicaragua have shown a relatively high prevalence of dysplasia, with abnormal smears found in 7.7% of patients attending health services\(^8\). The aim of the current survey was to collect data on determinants of cervical cancer screening, applicable to the population living in a district preparing for an improved screening programme. The face-to-face interview was chosen to give people the opportunity to express themselves in a confidential way. In practice, it was often impossible to interview people in private. Men as well as women were often surrounded by family and friends, and this could have biased some of the answers, especially in relation to sexual behaviour. This was mainly reflected in non-response to some of the questions. However, as the collected data are in line with the results from other surveys, we are confident that the information received is representative for the population.

The high incidence and mortality rates of cervical cancer in Latin America are ascribed to both the high frequency of risk factors for the disease and low screening coverage\(^9\). Studies in the region identified multiple sex partners (of both men and woman) and early age at first intercourse as the main risk factors, as well as high parity, low socio-economic status and low educational level\(^10,11\). In the population under study here, several of these risk factors are present, and people inadequately screened are most likely to be exposed to these factors.

Early age at first sexual intercourse is, as in most Latin American countries, most pronounced in men. Reported sexual activity started at a mean age of 15-16 years in boys, two years earlier than in girls. These results coincide with other published national data\(^12,13\). Fifteen years seems to be a strong normative age for sexual initiation in boys; these relations are often casual or with a sex worker\(^14\). Men are also more promiscuous than women. Women are well aware of the promiscuous behaviour of their spouses; more than half suspect their partner of having other contacts. This social pattern of initiation and male promiscuity may be an important factor in the transmission of human papillomavirus.

As cervical cancer screening programmes are offered within health services, it is important that these services are used by the target population. Therefore, they have to be affordable, accessible, and considered appropriate by the women they serve\(^15\). Within our survey, we assessed some of these aspects. In general, geographical accessibility did not seem to be a major problem, as only 20% of the population live more than 5 km from a health facility. Most people think well of the public health sector, which they use for convenience, as the services are nearby and cheap. Private services are perceived as providing services of higher quality, but only a minority have the means to use them. This is reflected in the use of private facilities for screening: more than half of the women consider private services
optimal for Pap tests, yet only one-third had the Pap test performed in a private clinic.

High coverage of women at risk of cervical cancer is a key element in achieving a successful screening programme\textsuperscript{16}. To attend the programme, people have to be aware both of the disease and of the means of early detection and prevention. Whereas most of the interviewed people knew cervical cancer could be detected, only 50\% referred to the Pap test as a means to prevent it and < 20\% were able to mention at least one symptom. A substantial part of the population still lacks sufficient knowledge about cervical cancer in general and the existing means to prevent it. We identified this gap in knowledge as one of the most important determinant of inadequate screening status.

Men are less knowledgeable than women, but they seem to have a more positive attitude towards screening. This should be exploited by targeting not only women but also men in education and information campaigns. As men have an important decision-making role in the family, they can help motivate their partner to attend the programme.

In general, the coverage of the current screening programme is low: 58\% of women sexually active for at least 3 years had had a Pap test, but only 41\% had had a test within the last three years and can be considered as adequately screened. This coverage is similar to neighbouring Honduras, but in Costa Rica coverage of 83.5\% has been reported\textsuperscript{17}. Costa Rica however, has an overall higher economic status and a highly developed health system delivering care to most inhabitants\textsuperscript{18}.

Of even more concern is that nearly one-third of the target population is reluctant to attend screening programmes in the future. This is especially the case for women inadequately screened, the population most at risk for cervical cancer.

Lack of knowledge and factors related to low socio-economic status and educational level were the main barriers to screening, which is consistent with reports from other countries\textsuperscript{19-21}. Most of the perceived barriers such as fear of the test, negligence, and the believe that screening is unnecessary in the absence of symptoms, could be overcome by providing correct information to women and by inviting them directly in order to motivate them. Educational messages should focus on the preventive nature of a Pap smear, to counter the idea that medical care is only necessary in the presence of symptoms.

Although many seem to be willing to pay for a Pap test, availability of screening services free of charge is important for reaching people for whom financial problems are an obstacle to screening. Where possible, screening services should be provided by female health workers, as two thirds of the women prefer a female health worker.
Conclusions

This survey provides useful information for the design of a screening programme adapted to the needs of the population. The current programme, based on opportunistic screening, is not effective in reaching the majority of the population. Complementary activities, including education and information of both men and women, are necessary, as well as a more pro-active approach to invite women to attend the programme. At least in rural areas, where they are best known and most active, the community health workers can be involved.

To ensure affordability, services should be integrated in existing public primary health care centres, or provided free of charge or at low cost by NGO's, and preferably provided by female health workers.

Acknowledgements

The authors thank the students of the UNAN and the volunteer interviewers, whose collaboration made this work possible. This study was supported by the Belgian Development Co-operation through the Flemish Interuniversity Council.


III-3.
SUCCESSFUL INVOLVEMENT OF COMMUNITY HEALTH WORKERS IN THE PROMOTION OF CERVICAL CANCER SCREENING
SUCCESSFUL INVOLVEMENT OF COMMUNITY HEALTH WORKERS IN THE PROMOTION OF CERVICAL CANCER SCREENING

P Claeys, C Gonzalez, RE Bello, M Gonzalez, M Temmerman

Submitted to Social Science and Medicine, 2003

Abstract

Low coverage of cervical cancer screening is the most important deficiency of cervical cancer screening programmes. This study was conducted in Rivas, Nicaragua to assess whether volunteer community health workers (CHW) can increase the uptake of cervical cancer screening. An improved screening programme, specifically aimed at women older than 30 years without a previous history of being screened or not screened in the last three years, was started in a step-by-step process in the different areas of the district. In the intervention areas, CHW invited resident women of the target population to participate. Cervical cancer screening was provided in the public health centres, in two NGO clinics and through outreach activities. In the non-intervention area, the existing programme based on opportunistic screening in the health centres was continued. A total of 142 CHW were trained. In total, they were given 3,630 invitation letters and visited 3,214 women, of whom 1,765 were screened for cervical disease. Compared to the non-intervention area, a significantly higher number of Pap smears were done in the intervention area, and a significant higher proportion of Pap smears were provided to the target population. One third of the target population were screened in NGO clinics and 15% through mobile interventions. The results show that CHW can be –at least temporary- successful in improving the coverage of cervical cancer screening. Their effectiveness depends on the capacity of the organisation responsible for training, supervision and follow-up of cervical cancer screening activities, and on the willingness of the health system to effectively reach the population. Service provision by NGOs can be an important help.

Introduction

In most developing countries, the provision of comprehensive and effective cervical cancer screening is rare. Current screening programmes face many obstacles and low coverage is an important problem.

In Nicaragua, cervical cancer screening is offered in both the public and private health sectors. The guidelines of the national cervical cancer control programme (CCCP) that previously recommended annual cytological screening for all sexually active women, have recently been changed. The new guidelines focus on women aged 25 and older, and recommend less frequent screening after three consecutive normal Pap smears, without defining clearly the screening interval. In 2000, we implemented a population-based survey in the District of Rivas, assessing the knowledge, attitudes and practices (KAP) of the women regarding reproductive health, including their cervical cancer screening history. Forty-one percent of
women had been screened within the last 3 years. In women aged 30 and older, 39% had never been screened and another 22% had not had a Papanicolaou (Pap) test in the last three years and these women were considered inadequately screened. Of those screened, more than one third had their Pap test taken in private clinics. Moreover, 63% of the women never screened and 21% of the women inadequately screened expressed their unwillingness to attend screening programmes in the future. These results indicate that the national cervical cancer screening programme was not effective in reaching those women most at risk for cervical cancer, and that a more pro-active approach would be necessary to reach them.

In Nicaragua, as in other countries, volunteer community health workers (CHW) have played an important role in extending health care to the communities. The “promotores” and “brigadistas populares de salud” were formed during the Sandinista Revolution in the eighties in order to increase community participation in health care provision. In the 90s, the “Movimiento Comunal Nicaraguense”, responsible for the development of the CHW network during the revolution, tried to consolidate its activities as a non-governmental organisation (NGO). Community health participation through the network of CHW and empirical midwives was further considered an important element of the health reform starting in 1994.

We present results of this current study in order to assess whether community volunteers can be successfully deployed in order to improve the utilization of cervical cancer screening, particularly in high-risk populations.

**Methodology**

**Description of the intervention**

An improved CCCP was designed in order to be implemented in the District of Rivas, one of the 16 Districts of Nicaragua, with 153,000 inhabitants. This programme includes training and involvement of volunteer health promoters, training of nurses in the provision of Pap-smears, quality control of cytology, and the decentralisation of diagnosis and treatment of precancerous cervical disease to the district level. Training of health promoters was done by the local NGO “Servicios Medicos Comunales (SMC)”, which have their head office in San Juan del Sur, District of Rivas. The training and supervision of nurses and cytologists was provided by the Universidad Nacional Autónoma de Nicaragua (UNAN-Managua). Colposcopy and outpatient treatment of cervical dysplasia was organised in the clinic of SMC, after unsuccessful attempts to have a colposcopy clinic opened in the district hospital. Despite initial interest, several meetings and training of one of the gynaecologists in outpatient management of cervical lesions, neither place nor time was made available to attend patients in the hospital. The provision of new cervical cancer screening and treatment services with little profit was probably of little interest for the gynaecologists, who generally provide clinical care to patients with precancerous lesions in their private practices.

The new cervical cancer screening programme was established to target women aged 30 and older who had never been screened or who have not been screened within the last 3 years. This target group was chosen based on recommendations of the World Health Organization on the use of available resources in a cost-effective manner. In order to be consistent with the national policy to screen all women who
spontaneously attend cervical cancer screening programs, no woman was turned away from obtaining services, irrespective of the time of her last Pap smear.

Due to logistical constraints, the programme started in a stepwise fashion in the 6 different geographical areas of the district. It was started in Tola in October 2000, in San Juan del Sur in May 2001 and in Rivas in May 2002, and was, for the purpose of this study, completed in December of 2002. In total, the intervention areas covered a female population of 42,000 of whom 9,430 were older than 30 years.

In these areas, health promoters living in the different neighbourhoods were contacted and asked to participate in the training sessions that consisted of a series of consecutive monthly workshops. Following topics were included: 1) General knowledge of the cervical cancer programme, and the rationale for focusing screening on women at the highest risk of disease, 2) communication techniques, 3) mapping communities, 4) registration system, and 5) leadership. These workshops lasted one day and were organized at sub-area level to guarantee high attendance rates of health promoters. At the end of each workshop, health promoters received invitation letters to be given to women in the target population living in their neighbourhood. They also received leaflets with information for the general population. The promoters were asked to visit the women, give information on cervical cancer and screening opportunities and to invite them to participate in the cytological screening programme. In the intervention areas, cytological screening was provided through the women’s health programme at the public health centre. In San Juan del Sur and Rivas, screening was also provided through two NGO clinics.

A number of field visits were organized, particularly in Tola, during which Pap smears were taken in or outside the health centre, by external staff.

In the 3 other areas, the so-called “non-intervention areas” the existing CCCP continued to be provided in the public health centres during the study-period. In these areas, the new programme started in January 2003.

Both intervention and non-intervention sites provided screening free of charge. During the study period, screening was also provided through private practitioners and a family planning clinic (“Profamilia”). It was not possible to collect data at this level.

**Data collection and analysis**

The NGO responsible for training registered the number of invitations provided to health promoters. All promoters registered the number of women visited and of invitations provided to the population. The invitation letters were collected on a monthly basis from the health services where screening was provided.

The increase in the number of Pap smears provided was calculated by comparing the average number provided during the intervention months with the average in the year prior to the intervention (October 1999-September 2000). For data collected during the intervention months, a comparison of the proportion of smears taken in the target population was made between intervention and non-intervention areas. Data on geographical screening area as well as on age, screening history and Pap results of clients during the study-period, were obtained on Pap forms completed at the cytology laboratory. For data collected one year prior
to the intervention, historical data were obtained through revision of the cytology records. These include screening site, age of clients and Pap results, but not previous screening history.

As a screening interval of 3 years results nearly in the same risk reduction as an interval of 1 or 2 years\(^6\), we considered that women were covered by the programme if they were screened within a three years period. An estimate of the coverage of the population living in the intervention and non-intervention areas was calculated by extrapolating the average number of Pap smears taken during the intervention months to 36 months. Non-published population data for Rivas, available in the Ministry of Health, was used to calculate the number of women in different age groups. Results of the KAP study\(^2\) regarding the percentage of women not screened or inadequately screened were applied to this population.

Data were entered in Epi-info version 6.04.0, and analysed with SPSS 11.0 for Windows (SPSS Inc, Chicago, IL, USA). Proportions were compared using the chi-square test

**Definitions**

Target population: Women aged 30 or more without cytological screening history or who have not been screened within the last three years (inadequately screened).

Intervention area: The 3 areas where the intervention takes place, from the start of the intervention in that particular area until the end of December 2002. Tola was considered an intervention area for 27 months, San Juan del Sur for 20 and Rivas for 8 months, respectively.

Non-intervention area: The 3 areas where the intervention did not start during the study period. Data from these areas are taken into account for the total duration of 27 months.

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**Results**

**Women invited by health promoters attending screening centres**

From October 2000 to September 2002, 142 CHW were trained as part of the programme. A total of 47 workshops was organized, at irregular intervals varying from 1 to 6 months. Health promoters attended an average of 7 workshops, but this varied by geographical site. A total of 3,630 invitations to be provided to the women of their neighbourhood, were given to the health promoters. The promoters visited 3,214 (88.5%) women and handed over 2,750 (76%) letters. Finally, 1,765 (48.6%) invited women visited the screening centres. An overview per area is given in table 1.
Table 1. Women invited by health promoters and response rate*

<table>
<thead>
<tr>
<th></th>
<th>TOLA Total</th>
<th>TOLA mean/ promoter</th>
<th>San Juan del Sur Total</th>
<th>San Juan del Sur mean/ promoter</th>
<th>RIVAS Total</th>
<th>RIVAS mean/ promoter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nb of health promoters</td>
<td>41</td>
<td></td>
<td>71</td>
<td></td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Nb of workshops organized/attended</td>
<td>15</td>
<td>7</td>
<td>27</td>
<td>10</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Nb of invitations given to promoters</td>
<td>1,550</td>
<td>38</td>
<td>1,780</td>
<td>25</td>
<td>300</td>
<td>10</td>
</tr>
<tr>
<td>Nb of women visited</td>
<td>1,389</td>
<td>34</td>
<td></td>
<td>1,525</td>
<td>300</td>
<td>10</td>
</tr>
<tr>
<td>Nb of invitations handed over to women</td>
<td>1,247</td>
<td>30</td>
<td>1,263</td>
<td>18</td>
<td>240</td>
<td>8</td>
</tr>
<tr>
<td>Nb of invitation letters received in screening centres</td>
<td>785</td>
<td>19</td>
<td>830</td>
<td>12</td>
<td>150</td>
<td>5</td>
</tr>
</tbody>
</table>

* These results were obtained during 27 study-months in Tola, 20 in San Juan del Sur and 8 in Rivas

Average number of Pap smears provided in intervention and non-intervention sites

Compared to the monthly average prior to the intervention, there was an increase in the average number of Pap smears and of Pap smears in women aged 30 and older in both areas. In the intervention area, the total number of Pap smears increased from an average of 141 per month to 194 (an increase of 38%) and the number of Pap smears taken in women aged 30 and older from 62 to 121 (increase of 95%). In the non-intervention area, the total number increased from 114 to 140 (increase of 23%) and for women aged 30 and older from 60 to 86 (increase of 43%). The differences in increase between intervention and non-intervention area were statistically significant for both groups with p values < 0.001.

Compared to the non-intervention area, the intervention area had a significantly higher proportion of Pap smears provided to the target population (39% versus 21%, p<0.001), particularly among women inadequately screened in the past (24% versus 12%, p=0.003) (see table 2).

Table 2. Percentage of Pap smears in target population, intervention and non-intervention area

<table>
<thead>
<tr>
<th></th>
<th>Intervention area</th>
<th>Non-intervention area</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of all Pap (average nb per intervention-month) **</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pap in women &gt;=30 years old</td>
<td>62% (121)</td>
<td>61% (86)</td>
<td>p=0.81</td>
</tr>
<tr>
<td>Pap in target population*</td>
<td>39% (76)</td>
<td>21% (29)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Pap in women &gt;= 30 years old and inadequately screened</td>
<td>12% (16)</td>
<td></td>
<td>p=0.003</td>
</tr>
<tr>
<td>Pap in women &gt;=30 years old and never screened</td>
<td>9% (13)</td>
<td></td>
<td>p=0.124</td>
</tr>
</tbody>
</table>

* Target population: women aged >= 30 years and never screened or not screened within the last three years
** Intervention months: 27 months in Tola, 20 in San Juan del Sur, 8 in Rivas
Coverage of the population

Accepting a screening interval of 3 years to be adequate and extrapolating the data of the intervention period to 36 months, cytological coverage is significantly better in the intervention area for all groups, except for women 15-29 years of age.

In the intervention area, 52% of all women aged 30 or older would have had a Pap smear, compared to 41% in the non-intervention area (p=0.016). Women who were inadequately screened in the past appear to most benefit from the intervention: 85% of them would have been screened in a three years interval, compared to 34% in the non-intervention area (p<0.001). The coverage for women not screened in the past would nearly be twice as high: 31% versus 16%, p=0.017 (table 3).

| Table 3. Coverage of population living in intervention and non-intervention areas* |
|------------------------------------------|------------------------------------------|------------------------------------------|------------------------------------------|
|                                         | Intervention area                        |                                         | Non-intervention area                     |
|                                         | Total |Average to be screened monthly |Average screened monthly | % of population covered by programme | Total |Average to be screened monthly |Average screened monthly | % of population covered by programme | p-value |
| Female population >=15 years old        | 25,584 |711 |214 |30% |22,152 |615 |150 |24%° |0.016 |
| Female population 15-29 years old       | 16,154 |449 |78 |17% |13,987 |389 |57 |15% |0.427 |
| Female population >=30 years old        | 9,430 |262 |136 |52% |8,165 |227 |93 |41%° |0.016 |
| Target population                       | 5,724 |159 |80 |50% |4,956 |138 |31 |23%° |0.000 |
| Fem pop >=30 years, inadeq.screened(22%)| 2,075 |58 |49 |85% |1,796 |50 |17 |34%° |0.000 |
| Fem pop >=30 years, not screened (38.7%)| 3,649 |101 |31 |31% |3,160 |88 |14 |16%° |0.017 |

* Accepting an adequate screening interval of 3 years, and extrapolating data to 36 months. These data also take into account the women covered by a PAP smear taken in the public hospital.
* p value <0.05

Attendance of different screening sites in the intervention areas

Whereas the public health centres account for 66% of all Pap smears taken in the intervention area, only 53% of the target population attended a public centre. Nearly one third went to one of the NGO clinics and 15% were reached through mobile interventions (figure 1). In Tola, 22% of all Pap smears and 31% of Pap smears in target population were provided during outreach activities organized in 9 communities.

In San Juan del Sur, only 1 outreach activity was organized. Here, 51% of all Pap smears and 64% of smears in target population were taken in the NGO clinic. In Rivas, no mobile interventions were carried out, and 43% of Pap smears in the target population were taken in the NGO clinic.
Figure 1: Proportional utilisation of health facilities by target and non-target population attending the screening programme

Impact of screening promotion during the time of the intervention

The effect of the promotion was different from one area to another. In Tola, where the intervention started, little effect was seen during the first months. There was a small increase in the attendance rate at the end of the first year, and a peak at the end of the second year, when the outreach activities started. In Rivas, a short peak was observed after the start of the training and mobilisation of health promoters. In San Juan del Sur, a sharp increase in the number of target populations attending the programme was observed during nearly 6 months, followed by a plateau phase (figure 2).

Figure 2: Number of Pap taken in target population in relation to the time of the intervention
Legend: 1: start involvement health promoters in Tola
2: start involvement health promoters in San Juan del Sur
3: start involvement health promoters in Rivas
4: start outreach activities in Tola
Discussion

Whereas worldwide many efforts are ongoing to improve the quality and reliability of screening tests, less is done to improve the coverage of screening programmes despite evidence from Nordic countries showing that coverage is a critical factor for success. In countries where organized programmes are in place, the coverage rate is around 80-90%, compared to 20-40% when screening is opportunistic. In these countries, unscreened women represent a significant problem.

Several strategies have been developed—with variable success—to encourage women to attend screening programmes. These include mass-media campaigns, invitations by letters and/or appointments of mobile units, promotion by health visitors, and deployment of nurses and general practitioners. Many of these strategies are of little value in low resource settings, with a large part of the population living in rural areas and difficult to reach by modern media. A person considered trustworthy by the population could have the possibility to effectively reach these people in their community. In this study, we assessed if volunteer community workers can be deployed successfully for this purpose.

Our results show that the CHW that worked on this project were not only willing to visit the women of their neighbourhoods, they were also able to invite a well-defined target group and to motivate at least half of the women they visited to attend the cytological screening programme. The impact was particularly high in women who had already been screened in the past, but not within the last three years. The estimated coverage of 85% is consistent with the willingness of these women to be regularly screened. Data from a KAP survey at the start of the program showed that only one fifth of women surveyed were not willing to be screened in the future. As shown in the non-intervention area, only 34% of women surveyed attend the programme spontaneously. The visit of the health promoter appeared to motivate women to proactively seek screening.

Women with no history of screening were less likely to attend the screening programme, and the response rate in this group was notably lower. Compared to the non-intervention area, health promoters were able to increase the uptake of screening in this group by 50%. However, despite this increase, only one third of this population would have been screened at the end of the three years intervention. Similar response rates in this group have been reported by other authors.

The results on coverage are estimates and subject to bias. Data provided on cytological screening coverage were obtained through extrapolation of collected data to 36 months and the intervention period was not equally for the different sites. These data could be over-estimated as it is to be expected that the effect of health promotion would decrease with time. They can also be under-estimated as no data are available on the women who attended private practitioners. The KAP study revealed that more than one third of women ever screened had their smear taken in private clinics and perceived the quality of these clinics as being higher than in the public centres. It is thus probable that a notable number of women have received cytological screening in a private clinic and were not accounted for in this analysis.

Comparisons between intervention and non-intervention areas are also subject to a spill-over effect. All areas lie within the same district, and non-intervention
communities were aware of the ongoing activities in the other areas. This might explain an increase in the number of smears taken in the non-intervention areas. It might have also led to an overestimation of the coverage rates of cytological screening in the absence of any intervention.

It is difficult to separate the effect of health promotion and health providers’ attitude through this study design. The response rate of the target population depends not only on the dedication of the health promoters and the willingness of the people to attend the programme, but also on the perception of quality of the health services. In May 2002, a survey of health promoters was conducted, in order to have more insight in existing barriers to cytological screening, particularly in Tola, where response rates were lower than expected. In this survey, factors related to the organization of the health centres and the poor relationship between communities and public centres may represented important problems for the lack of cytological screening. Additional problems include distrust of the population in the public health centres, closed centres, lack of health personnel to screen patients, nurses not willing to attend patients coming for screening, and lack of privacy in the health centres. These problems are characteristic for public services in the country. Although the Ministry of Health is the main provider of health services, its capacity to recruit, train and employ health personnel has been severely diminished during the past few years, and it is showing a low capacity to enforce health personnel planning. In response to this need, nine site visits were organized whereby external staff screened the women who had been invited by the health promoters. Nearly one third of the cytological smears of the target population in Tola were taken during these visits. In San Juan del Sur and Rivas, a high proportion of women preferred to attend the two NGO screening sites (64% and 43%, respectively). This is remarkably high, as in the same areas, four public health centres and seven health posts exist. This suggests again that women prefer quality of services to geographical accessibility, especially for sensitive issues as gynaecological examinations.

In all sites, a seasonal pattern is observed in the response rate to a screening programme. The attendance rate is highest during the winter months (June-September), and decreases around Christmas and Easter when health centres are traditionally closed. In the intervention area, the attendance rate is different by geographical site, but the peak response does not last longer than 6 months in any of the study areas. This might be due to a consequence of the nature of the health promoter network in Nicaragua. The ‘brigadistas’ found their origin under the Sandinista government, during which the health system was nationalized, creating a centralized and vertical rather than a community-based and horizontal organizational structure. During that period, the brigadistas had a predominant role in the highly successful single-day health campaigns. It is still controversial if during that period, the basis of popular participation was set, or if it failed in fostering long-term commitment to community participation in health. Nowadays, the health promoters still deploy the same methods to mobilise populations to attend the screening and other programmes. These highly motivated and committed people employ their enthusiasm to reach the people of their communities and neighbourhoods. However, their role as volunteers is limited and in the specific context of Nicaragua, they would probably perform best in motivating women to attend punctual screening campaigns.
Involving health promoters, even if they are volunteers, does have a cost. There is a need for training, supervision and follow-up of their activities. They need an organisation or an institution that provides the framework in which they can function. Nevertheless, CHW have an important role. At the ‘interface’ between the formal health care system and the community, they bridge the gap between health needs and provision. It is across this bridge that primary health care may advance\textsuperscript{18}. From that perspective, they can only be successfully deployed in cervical cancer screening and other programmes, when there is a willingness of the health system to effectively reach the population. Even in the revolutionary Nicaragua of the 80s, when community participation was high on the agenda, a kind of popular/professional “struggle” was noticed, which was carried out in daily processes of both confrontation and negotiation\textsuperscript{17}. Now that the network of CHW is not longer supported by the government, but by NGOs, these tensions are more perceptible. An example is that patients, referred by the CHW to the health centres, are not always attended to, despite commitments of the Ministry of Health to do so. In order not to disappoint the communities, the NGOs tend to provide the full range of services themselves. In our programme, the success of the health promotion was also owed to the active service provision by the NGO, both at clinic and community level. Though this is a successful strategy to respond to an existing demand, efforts to face the public health sector with the needs of the population should go on. Health promoters should be better prepared to envisage this confrontation. If real community participation is to be sought, health promoters should not only be prepared to motivate and convince their communities, but also to negotiate with health providers. Besides training in leadership and communication skills, supporting agencies should prepare them to be spokespersons of their communities, transmitting to the service providers what the communities really want and pressuring the ministry of health into putting its policies in practice.

Acknowledgements

The authors thank the community health promoters, whose collaboration made this work possible.

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Reference list

III-4.

PERFORMANCE OF SCREENING TESTS

III-4-1.

PERFORMANCE OF SCREENING TESTS IN RESEARCH CONDITIONS
Comparing Pap smear, visual inspection, human papillomavirus DNA-PCR testing and cervicography in Kenya

H De Vuyst, P Claeys, S Njiru, L Muchiri, S Steyaert, P De Sutter, E Van Marck, J Bwayo, and M Temmerman

Submitted to Obstetrics and Gynaecology

Abstract

Objectives
To compare the performance of Pap smear screening, visual inspection of the cervix with acetic acid (VIA), detection of high risk HPV (HR HPV) and cervicography for the detection of cervical (pre-)cancer.

Methods
A cross-sectional study was carried out among family planning attenders in Nairobi, Kenya. The “Gold standard” was histology on colposcopy directed biopsies, performed on all women.

Results
Six hundred fifty-three women were included. LSIL, HSIL and invasive cancer were detected in respectively 8.3%, 8.3% and 0.9% of the study population. Sensitivity (to detect HSIL or more) and specificity (to exclude any SIL) were for Pap smear 83.3% (95% CI [71.5, 91.7]) and 94.6% (95% CI [92.3, 96.4]), respectively; for VIA 73.3% (95% CI [60.3, 83.9]) and 80.0% (95% CI [76.3, 83.3]); for HR HPV 94.4% (95% CI [84.6, 98.8]) and 73.9% (95% CI [69.4, 78.1]); and for cervicography 74.5% (95% CI [59.7, 86.1]) and 89.9% (95% CI [86.5, 92.6]). Positive (proportion any SIL among positive tests) and negative (proportion normal or LSIL among negative tests) predictive values were for Pap smear 73.3% and 98.1% respectively; for VIA 39.0% and 96.6%; for HR HPV 44.0% and 99.1% and for cervicography 55.8% and 97.1%.

Conclusions
Pap smear performed excellent, knowing that it was done at a cytology training facility. Other screening tests performed adequately compared to Pap smear, including VIA as the cheapest test, and requiring the least technical support. However, more operational studies are needed to assess its performance in field conditions.
Introduction

Screening for cervical lesions has been successful in the industrialized world. Incidences of cervical cancer have been reduced with up to 80% in countries with rigorous screening programs for cervical cancer and pre-cancer\textsuperscript{1,2}. The success of these programs can largely be attributed to the use of the Papanicolaou (Pap) smear\textsuperscript{3}. In the developing world however, incidences of cervical cancer remain high. In sub-Saharan Africa, especially, incidence rates have been recorded of 67.2 per 100,000 in Harare, Zimbabwe\textsuperscript{4} and 44.1 per 100,000 in Uganda\textsuperscript{5} compared to 13.4 in a Western country like France\textsuperscript{6}. The lack of organized screening and treatment programs for cervical cancer is certainly one of the reasons. One of the other reasons could be the high prevalence and different pathogenicity of the human papillomavirus (HPV)\textsuperscript{7,8}. The aim of cervical cancer screening programs is: (1) to detect pre-cancerous lesions that can be treated relatively easily with outpatient methods and (2) to detect early invasive cervical cancer that still has a fair chance of successful surgical treatment. Success of screening programs are largely dependent on the coverage of the population at risk and the quality of the screening test\textsuperscript{9}. To date Pap smear is the only widely accepted and validated screening test. However, several reports have described its poor performance especially in low resource settings\textsuperscript{10,11}. Reasons for this are the high technological and training requirements for the test. Constant quality assurance and refreshment training for the cytotechnologists is mandatory. Hence, alternative screening methods are being evaluated for their usefulness in these settings. An alternative test should have an acceptable sensitivity and specificity and should be easy to implement on a large scale at a low cost. In this paper, we report on the performance of visual inspection with acetic acid (VIA), HPV PCR testing and cervicography, compared to Pap smear.

Materials and methods

Participants

Between January 1998 and July 2000, women aged 25 – 55 attending a family planning clinic in Nairobi, Kenya, were invited to participate in the study. In addition, a small number of women was referred to the same facility for further investigations because of cervical lesions (clinical or abnormal Pap smears). The study was approved by the National Ethical Review Committee of Kenyatta National Hospital, Nairobi, Kenya.

Study design

We conducted a cross-sectional screening study for cervical lesions in a group of family planning clients. Different screening tests for the detection of cervical cancer and pre-cancer were compared for their applicability in low resource settings (Pap smear, visual inspection with acetic acid (VIA), HPV testing and cervicography).
Clinical examinations and sample taking

The staff consisted of a study nurse, trained in the technique of VIA with a pictorial atlas for visual inspection of the cervix, projected images of cervices and hands-on training, and two medical doctors trained in colposcopy.

At the first visit (V1), patients were invited for a Pap smear, VIA and cervicography and were requested to come for a follow-up visit after 3 weeks. A signed informed consent was obtained from all participants. At the second visit (V2), the results were communicated to the patient and a routine gynaecological examination was performed again including VIA and colposcopy on all women. If either Pap smear, VIA(V2) or colposcopy were positive, a biopsy and/or endocervical curettage was obtained.

Laboratory tests

Exfoliative cervical cells were obtained using a cervex brush (Rovers Medical Devices, Oss, The Netherlands). One smear was made on a glass slide for staining according to the Papanicolaou method. The brush was then submerged and stirred in 10 ml phosphate buffered saline (PBS) and frozen at –20 degrees Celsius. Samples were shipped to the Laboratory of Virology, Ghent University Hospital, Belgium for HPV DNA extraction, detection and genotyping, which was performed as described earlier.

Pap smears and cervical biopsies were processed and analysed at the Department of Human Pathology, University of Nairobi, Kenya according to the Bethesda 1991 classification. Quality control was done on all the histology specimens at the Department of Pathology, University of Antwerp, Belgium. For final data analysis, the histology results of the Antwerp University were used.

Cervicographies were assessed at the department of gynaecology, Free University of Brussels, Belgium, by a senior staff member colposcopist and accredited cervicography evaluator (PDS).

Scientists performing the biological assays were blinded to the clinical diagnoses.

Definitions

A Pap smear was considered positive in case of LSIL or more severe lesions. VIA was considered positive in case of a distinct acetowhite lesion that was perceived different from (normal) metaplasia or cervicitis. The colposcopic examination was also considered positive for a colposcopic impression of LSIL or more. Any positive result on biopsy was taken as the final positive diagnosis, hereafter called “reference test”. If biopsy was negative, or in case there was no indication for biopsy, the reference test was considered negative. We combined the Pap smear with two visual tests in order to enhance the sensitivity of the screening test hence reducing the possibility of missing true positive cases to a minimum. Lesions on the reference test are reported as ‘cases’. Two cut-offs were compared for HPV testing. Samples which were positive for any HPV type were compared with samples positive for only high risk (HR) oncogenic types.

Cervicographies were protocolled using the criteria as described in Table 1. All grades higher then P0 were considered as positive test result.
Table 1. Cervicography protocol

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>Negative, transformation zone visible</td>
</tr>
<tr>
<td>N2</td>
<td>Negative, transformation zone not visible</td>
</tr>
<tr>
<td>A1</td>
<td>Atypical inside transformation zone</td>
</tr>
<tr>
<td>A2</td>
<td>Atypical outside transformation zone</td>
</tr>
<tr>
<td>P0</td>
<td>Positive exclusion*</td>
</tr>
<tr>
<td>P1a</td>
<td>Positive doubtful; lesion disappearing in canal</td>
</tr>
<tr>
<td>P1b</td>
<td>Positive compatible with low grade lesion</td>
</tr>
<tr>
<td>P2</td>
<td>Positive compatible with high grade lesion</td>
</tr>
<tr>
<td>P3</td>
<td>Positive compatible with cancer</td>
</tr>
<tr>
<td>TD</td>
<td>Technically defective</td>
</tr>
</tbody>
</table>

* Probable normal variant; appearance warrants colposcopy to exclude significant diseases.

Statistical analysis

Data were entered in Epi-info (CDC, USA; WHO, Geneva) and analysed in SPSS 10.0.5 for windows (SPSS, Chicago, IL, USA). Comparisons of categorical variables were made using Pearson’s X² and Fisher’s exact tests. Means of continuous variables were compared using independent-Samples T-Test. Exact binominal 95% CIs were calculated for sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NVP).

Results

Characteristics of the study population

Of the 816 women presenting at Visit 1, 653 attended the clinic for visit 2 and were included in the study. The majority (548, 83.9%) were women who attended the clinic for family planning services (random group). Another 105 women were referred because of previous abnormal Pap smear or clinical reasons.

Table 2 compares risk factors for cervical (pre-)cancer between the random and the referred group. The referred women indeed scored higher on most classical risk factors for cervical dysplasia (younger mean age at first sexual intercourse, less monogamous marriage, more single, more frequently more than one regular partner and more frequently more than four lifetime sexual partners). No significant differences were detected between the group presenting for V1 and the group attending for V2 (data not shown).
Table 2. Comparison of risk factors for cervical (pre-)cancer between the random and referred group.

<table>
<thead>
<tr>
<th></th>
<th>Random (N = 548)</th>
<th>Referred (N = 105)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>35.8</td>
<td>34.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean Parity</td>
<td>2.9</td>
<td>2.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Mean Age first sex</td>
<td>19.4</td>
<td>18.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Monogamous marriage</td>
<td>76.2%</td>
<td>64.4%</td>
<td>0.02</td>
</tr>
<tr>
<td>Single</td>
<td>12.7%</td>
<td>24.4%</td>
<td>0.004</td>
</tr>
<tr>
<td>More than 1 regular partner</td>
<td>0.8%</td>
<td>4.5%</td>
<td>0.006</td>
</tr>
<tr>
<td>Lifetime partners =&gt;4</td>
<td>21.2%</td>
<td>28.8%</td>
<td>0.09</td>
</tr>
<tr>
<td>HIV prevalence</td>
<td>11.3%</td>
<td>29.8%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Detection of SIL and Carcinoma

A total of 114 lesions were found on the biopsy reference test. Table 3 shows the number of LSIL, HSIL and invasive squamous cell carcinoma found in the random and the referred group. Lesions were more prevalent in the referred group. For assessment of the performance of the different screening tests, results from both groups are combined.

Table 3. Prevalence of SIL and cancer in the random and referred group.

<table>
<thead>
<tr>
<th></th>
<th>Random (548) N (%)</th>
<th>Referred (105) N (%)</th>
<th>Total (653) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSIL</td>
<td>34 (6.2%)</td>
<td>20 (19.0%)</td>
<td>54 (8.3%)</td>
</tr>
<tr>
<td>HSIL</td>
<td>30 (5.5%)</td>
<td>24 (22.9%)</td>
<td>54 (8.3%)</td>
</tr>
<tr>
<td>Inv. squamous cell carcinoma</td>
<td>1 (0.2%)</td>
<td>5 (4.8%)</td>
<td>6 (0.9%)</td>
</tr>
</tbody>
</table>

A biopsy result was missing in 20 cases of positive VIA (V2) and negative colposcopy and in 6 cases with positive VIA and colposcopy suggestive of LSIL.

All 26 cases had a negative Pap smear. We kept these cases in the dataset and consider them negative on the reference test. Deleting these cases from the analysis would introduce a considerable bias, as the majority of the deleted cases represent false positive VIA examinations.
**Performance of Pap smear screening**

Of the 653 Pap smears, 629 were “satisfactory for evaluation” (99.1%) (table 4). 16.1% of the smears were abnormal (LSIL or more). All 6 cases of invasive squamous cell cancer on the reference test were detected (5 correctly as invasive squamous cell cancer on Pap smear screening, one case as HSIL). Of the 54 cases of HSIL, 44 (81.5%) were diagnosed on Pap smear as LSIL or more. Similarly, 27 (50.0%) of the 54 cases of LSIL, were detected. Of the abnormal Pap smears, 26.7% yielded a normal reference test.

**Table 4. Results screening tests compared to biopsy results.**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>BIOPSY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Pap</td>
<td>Unsatisf</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>451</td>
</tr>
<tr>
<td></td>
<td>ASCUS</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>LSIL</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>HSIL</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Inv Ca</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>539</td>
</tr>
<tr>
<td>VIA</td>
<td>Negative</td>
<td>431</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>108</td>
</tr>
<tr>
<td></td>
<td></td>
<td>539</td>
</tr>
<tr>
<td>HPV</td>
<td>Neg</td>
<td>246</td>
</tr>
<tr>
<td></td>
<td>Pos</td>
<td>168</td>
</tr>
<tr>
<td></td>
<td>HPV excl.LR*</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>HPV HR†</td>
<td>108</td>
</tr>
<tr>
<td></td>
<td>HPV X‡</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>414</td>
</tr>
<tr>
<td>Cervicogr</td>
<td>Tech def</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Neg</td>
<td>353</td>
</tr>
<tr>
<td></td>
<td>Atypical</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Atyp/colp§</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Lgrade</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Hgrade</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Cancer</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>413</td>
</tr>
</tbody>
</table>

*Samples with exclusively LR HPV types
† Samples containing HR HPV types
‡ Samples with an unknown HPV type
§ Atypical cervicographies where colposcopy is warranted
**Performance of VIA examination**

Hundred and seventy-seven VIA examinations were positive at visit 1 (27.1%). Four of the invasive squamous cell cancers were diagnosed (66.7%), 40 (74.1%) of the HSIL cases and 25 (46.3%) of the LSIL cases. Hundred and eight (61%) positive VIA tests were normal on the reference test.

**Performance of HPV testing**

Five hundred sixteen HPV PCR test results were available. Hundred twenty had no HPV sample taken, as this was dependent on the availability of the PBS sampling medium at the clinic, that had to be prepared freshly on a regular basis. Four HPV tests had a borderline (unequivocal) result and 13 were indeterminate. These cases were also excluded from the analysis.

In this group we found all 6 cases of invasive cancer, 48 HSIL and 48 LSIL. Two hundred fifty-six (49.6%) women had a positive HPV test, 193 (37.4%) were infected with a high risk (HR) HPV type. All invasive cancers were infected with a HR HPV type. Forty-six (95.8%) of the HSIL cases had a positive HPV test, 45 (93.8%) had a HR HPV type. Thirty-six (75.0%) of the women with LSIL were HPV positive, 34 (70.9%) were infected with a HR HPV type. Hundred sixty-eight (65.6%) women with HPV were normal on the reference test, compared to 108 (56.0%) of the women with HR HPV.

**Performance of cervicography**

A total of 523 cervicographies were taken in this group. Fifteen were technically defective. In the group of the 508 assessable cervicographies were 5 invasive cancers, 39 HSIL and 47 LSIL. Ninety-five of the cervicographies (18.7%) were positive. All the invasive cancers were diagnosed, 30 (76.9%) of the HSIL and 18 (38.3%) LSIL. Forty-two (44.2%) of the women with a positive cervicography were normal on the reference test.

**Comparison of the four screening tests**

Table 5 compares the four screening tests. We compared their ability to detect HSIL or invasive squamous cell cancer (sensitivity). Also important was the ability to correctly exclude disease (specificity). We compared the tests in their ability to exclude any SIL or cancer.

The Pap smear in our setting performed with a sensitivity and specificity of 83.3% (95% CI [71.5 , 91.7]) and 94.6% (95% CI [92.3 , 96.4]), respectively. The highest sensitivity was found in HPV testing (any type), 96.3% (95% CI [87.3 , 99.5]). However, the rate of false positives was considerably high yielding a specificity of 59.4% (95% CI [54.5 , 64.2]). Considering only HR HPV results as positive test results did not change the sensitivity significantly (94.4% (95% CI [84.6 , 98.8])), but increased the specificity considerably (73.9% (95% CI [69.4 , 78.1])). VIA scored with a sensitivity and specificity of respectively 73.3% (95% CI [60.3 , 83.9]) and 80.0% (95% CI [76.3 , 83.3]) and cervicography with respectively 74.5% (95% CI [59.7 , 86.1]) and 89.9% (95% CI [86.5 , 92.6]).
Table 5. Sensitivity, specificity, positive predictive value and negative predictive value of the screening tests.

<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Cut-off disease:</th>
<th>Rate of pos test in women with disease *</th>
<th>Rate of neg test in women who have no disease†</th>
<th>Rate of women with disease in the positive test results‡</th>
<th>Rate of women without disease in the negative test results§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap smear</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSIL + Ca</td>
<td>50/60 (83.3%)</td>
<td>514/569 (90.3%)</td>
<td>50/105 (47.6%)</td>
<td>514/524 (98.1%)</td>
<td></td>
</tr>
<tr>
<td>LSIL + HSIL + Ca</td>
<td>77/113(68.1%)</td>
<td>488/516 (94.6%)</td>
<td>77/105 (73.3%)</td>
<td>488/524 (93.1 %)</td>
<td></td>
</tr>
<tr>
<td>VIA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSIL + Ca</td>
<td>44/60 (73.3)</td>
<td>460/593 (77.6)</td>
<td>44/177 (24.9)</td>
<td>460/476 (96.6)</td>
<td></td>
</tr>
<tr>
<td>LSIL + HSIL + Ca</td>
<td>69/114 (60.5)</td>
<td>431/539 (80.0)</td>
<td>69/177 (39.0)</td>
<td>431/476 (90.5)</td>
<td></td>
</tr>
<tr>
<td>HPV Pos</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSIL + Ca</td>
<td>52/54 (96.3%)</td>
<td>258/462 (55.8%)</td>
<td>52/256 (20.3%)</td>
<td>258/260 (99.2%)</td>
<td></td>
</tr>
<tr>
<td>LSIL + HSIL + Ca</td>
<td>88/102 (86.3%)</td>
<td>246/414 (59.4%)</td>
<td>88/256 (34.4%)</td>
<td>246/260 (94.6%)</td>
<td></td>
</tr>
<tr>
<td>HPV HR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSIL + Ca</td>
<td>51/54 (94.4%)</td>
<td>320/462 (69.3%)</td>
<td>51/193 (26.4%)</td>
<td>320/323 (99.1%)</td>
<td></td>
</tr>
<tr>
<td>LSIL + HSIL + Ca</td>
<td>85/102 (83.3%)</td>
<td>306/414 (73.9%)</td>
<td>85/193 (44.0%)</td>
<td>306/323 (94.7%)</td>
<td></td>
</tr>
<tr>
<td>Cervicography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSIL + Ca</td>
<td>35/47 (74.5%)</td>
<td>401/461 (87.0%)</td>
<td>35/95 (36.8%)</td>
<td>401/413 (97.1%)</td>
<td></td>
</tr>
<tr>
<td>LSIL + HSIL + Ca</td>
<td>53/95 (55.8%)</td>
<td>371/413 (89.9%)</td>
<td>53/95 (55.8%)</td>
<td>371/413 (89.9%)</td>
<td></td>
</tr>
</tbody>
</table>

*Approximates sensitivity of the test
† Approximates specificity of the test
‡ Approximates positive predictive value
§ Approximates negative predictive value
+ Unsatisfactory Pap smear results are considered negative for this assessment

The positive predictive value (PPV) of a test (true positive cases/total positive test results) reflects the ability of the test to avoid false-positive cases. The proportion of false-positive diagnoses is 1-PPV. This would be the proportion of over-treated women (number of incorrectly treated women/total number of treatments) in case treatment would be decided on a positive screening test without confirmatory colposcopy. Over-treatment would be worst when using HPV testing (any type) (65.6% (95% CI [59.5, 71.4])), least if using Pap smear testing (26.7% (95% CI [18.5,
VIA would cause an over-treatment of 61.0% (95% CI [53.4, 68.2]) and cervicography 44.2% (95% CI [34.0, 54.8]).

Figure 1 describes the proportion of women treated in the study population, if treatment would be decided on all positive primary screening tests results, without prior confirmation on colposcopy. Indeed, treatment after HPV testing would result in the highest over-treatment (32.6% (95% CI [28.5, 36.8]) of the population incorrectly over-treated). Similarly, Pap smear would only over-treat 4.3% (95% CI [2.9, 6.1]), VIA 16.5% (95% CI [13.8, 19.6]) and cervicography 8.3% (95% CI [6.0, 11.0]).

<table>
<thead>
<tr>
<th>forums</th>
<th>% women over-treated without disease</th>
<th>% women correctly treated with LSIL</th>
<th>% women correctly treated with HSIL</th>
<th>% women under-treated with Inv Ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap smear</td>
<td>4.30%</td>
<td>4.10%</td>
<td>6.70%</td>
<td>0.90%</td>
</tr>
<tr>
<td>VIA</td>
<td>16.50%</td>
<td>3.80%</td>
<td>6.10%</td>
<td>0.60%</td>
</tr>
<tr>
<td>HPV</td>
<td>32.60%</td>
<td>7.00%</td>
<td>8.90%</td>
<td>1.10%</td>
</tr>
<tr>
<td>HPV HR</td>
<td>20.90%</td>
<td>6.60%</td>
<td>8.70%</td>
<td>1.20%</td>
</tr>
<tr>
<td>Cervicography</td>
<td>8.30%</td>
<td>3.50%</td>
<td>5.90%</td>
<td>1.00%</td>
</tr>
</tbody>
</table>

Discussion

This study was designed to compare the performance of different screening methods for the detection of HSIL and invasive cervical cancer in poor regions. Alternative methods are compared to the conventional cytology smear. This is a clinic-based population with a small proportion of referred women who fairly contributed to the high number of (pre-) cancerous lesions. The higher number of cases assisted in the assessment of sensitivity and specificity. However, it biases the reporting of PPV and NVP. Therefore, these latter variables should be considered with caution, when extrapolated to a general population.

Our Pap smear performed superior with a good sensitivity and an excellent specificity. We realize that this test was performed at a referral and training centre,
and that these results cannot be generalized straight away for other cytology labs in the region. A meta-analysis on Pap test accuracy reported ranges for sensitivity and specificity of respectively 11 to 99% and 14 to 97% 16. Indeed, in a similar study in Zimbabwe, Pap smear performed with a sensitivity and specificity of respectively 44.3% and 64.1% 10. Another study from a resource-poor setting (South Africa) reports respectively 19.3% and 99.3% for the detection of any SIL 11.

The presence of persistent HR HPV is highly prognostic for the development of cervical neoplasia 17. Therefore, it is not surprising that HR HPV PCR testing revealed to be highly sensitive in the detection of HSIL and invasive cancer. Very few cases of HSIL or cancer were missed. However, a minority of all incident HR HPV infections are persistent and the progression to HSIL or worse takes a long time. Therefore, the presence of HR HPV gives an indication to which women are at a higher risk for developing a cervical neoplasia, rather than identifying them. This reflects in the high rate of false-positive cases (low specificity). Most studies reporting on the use of HPV testing for cervical cancer screening report on the use of the Digene HPV Hybrid Capture II test. It detects 13 HR HPV types and 5 LR HPV types. This test performs with a slightly lower sensitivity and higher specificity, compared to our test, respectively 88.4% and 81.9% in South Africa 18, 88.4% and 89% in Costa Rica 19, 81% and 62% in Zimbabwe 20 and 95% and 85% in and older women (35 – 45 years) in China 21. The high cost and the low specificity of the test are currently important impediments. However, it has the potential to be used as a sole method for primary screening in women over thirty years old, as HPV infection is more often persistent in older women 22. We should also consider the fact that we assessed the performance of this test in a population with high prevalence of HIV (14.1%). HPV is more prevalent in such a population 23, 24. However, the correlation of HPV with SIL and cervical cancer is lower in HIV seropositive women 25. This means that the specificity of HPV testing will be lower in populations with high HIV-1 prevalence 26.

Visual screening techniques are being evaluated more intensely since the last decade, especially the “unaided” techniques without magnification devices. They are at low cost and require no technological back-up. The two visual screening methods, VIA and cervicography score with an almost identical sensitivity. Cervicography however was significantly more specific. The sensitivity and specificity of VIA was similar to other recent reports (respectively 71.0 and 74.3% in China 21, 76.6 and 64.1% in Zimbabwe 10, 67.4 and 84.9% in South Africa 27). One study from India reported superior results (90.1% sensitivity and 92.2% specificity) 28. Not all women underwent colposcopy in the two latter studies, whereby verification-bias could not be excluded.

It is not easy to compare the performance of cervicography in our study to others, because of the use of different thresholds or the possible presence of verification bias 11, 15, 29-31. Two studies provide sensitivity and specificity of respectively 54.5% and 97.2% 31 and 49.3% and 95.0% 15 for the detection of HSIL or cancer. A study from South Africa reports sensitivity and specificity of respectively 41.8% and 78.8% for detection of any SIL 11. Our study reports a higher sensitivity with a comparable specificity compared to those studies mentioned above.

The use of colposcopy and colposcopy-directed biopsy to confirm a positive test result on the primary screening test is widespread and recommended policy in the industrialized world. The rationale is to filter out the false positive cases and also to
confirm the stage of the neoplasia. This policy is very hard to implement in poor-resource countries. Colposcopy facilities are costly and require highly trained medical personnel. The prospect of having one test that is sensitive enough to be used for screening, and at the same time be specific enough to direct the treatment is appealing. Inevitably, a number of false-positive cases would be treated unnecessarily. How harmful this policy is also depends on the treatment modality. Loop electro-excision procedure (LEEP) and cryotherapy have very few side-effects (mostly perioperative bleeding (3-8%) and cervical stenosis (1%) for LEEP, profuse watery discharge for 4 – 6 weeks for cryotherapy). The treatments destroy the transformation zone and could be considered preventive for later development of SIL. In the fifties, postpartum cryotherapy was common practice in the USA for this reason. These considerations might make over-treatment acceptable if limited. However, HIV seropositive women shed the HIV virus more intensely in the first weeks after treatment, making them more infectious in case of unprotected sexual intercourse. This is certainly an aspect to consider carefully when weighing this option in regions with high HIV prevalence. Pap smear would cause very little over-treatment of the population, which would be very acceptable. Cervicography is also quite specific with a limited over-treatment. VIA and testing for HPV HR would cause a higher and similar over-treatment of 21% or less. The lack of screening programs in developing countries is largely due to the cost of those programs, which have to compete with other health interventions. Our study did not evaluate cost-effectiveness of the different strategies, but one study showed that VIA was a cost-saving strategy in South Africa, compared to HPV HR testing and cytology.

We conclude that Pap smear has the advantage of being very specific, HPV testing is very sensitive. Cervicography and VIA are comparable and score in between. However, in the perspective of the need for a simple and widely applicable screening test for cervical (pre-)cancer in resource-poor countries, our study contributes to the growing evidence of the effectiveness of VIA as a primary screening tool.

Acknowledgments

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III-4-2.
PERFORMANCE OF THE ACETIC ACID TEST
IN FIELD CONDITIONS
PERFORMANCE OF THE ACETIC ACID TEST WHEN USED IN FIELD CONDITIONS AS A SCREENING TEST FOR CERVICAL CANCER

P Claeys, H De Vuyst, C Gonzalez, A Garcia, RE Bello, M Temmerman

Tropical Medicine and International Health, 2003, 8 (8): 704-709

Executive summary

Objectives

To assess if visual inspection with acetic acid (VIA) is a useful alternative screening test for cervical cancer, when used in a resource-poor setting with an existing cytology-based screening programme.

Methods

Women living in Rivas District, Nicaragua, who attended the programme, were concurrently screened with VIA and Papanicolau (Pap) smear. Screening was performed by health providers who had received training in VIA and a refresher course in cytology. Women testing positive for either of the result were referred for colposcopy and biopsy when indicated. The performance of VIA was compared with Pap smear, calculating the relative true and false positive rate (RELTPR and RELFPR), and for a high threshold on biopsy (cervical intraepithelial neoplasia grade 2 or a higher grade). We determined the trade-off between both tests by calculating the ratio of extra false positives detected through extra true positives (EFP:ETP ratio).

Results

A total of 1076 patients were screened. Nearly 33% had a positive screening test. On biopsy, 7.6% had a low-grade intraepithelial lesion, 4.5% a high-grade intraepithelial lesion (HSIL) and 0.5% invasive cancer. The RELTPR (VIA to Pap) was 1.96, the RELFPR 5.02 and the EFP:ETP ratio 8.04. VIA detected twice as much HSIL and invasive cancers as the Pap smear. Yet, for every extra diagnosis, eight extra false positives had to be examined at the referral level.

Conclusions

The VIA spectacularly increases the number of HSIL and invasive cancer detected. The high FPR is a concern for the organization of the referral level. There is a need to establish uniform criteria on test positivity and to further improve the performance in field conditions.
Introduction

During the last decade, the problem of cervical cancer has received renewed interest. The decrease in cervical cancer prevalence in most of the developed countries is attributed to the success of cytology-based cervical cancer screening programmes, hardly observed in many developing countries. The cost and the operational problems related to cytology-based programmes result in the lack of quality screening programmes in resource-poor settings. This has attracted the attention of policy makers, health professionals and researchers, and led to the development of alternative approaches to improve the success of screening programmes. One of the new screening tools is visual inspection of the cervix with acetic acid (VIA).

This cheap technique involves the application of 3-5% acetic acid (household vinegar) on the cervix followed by inspection of the cervix 2 minutes later, under illumination, for the presence of acetowhite areas. A number of studies report test sensitivity for high-grade squamous intraepithelial lesions (HSIL) varying between 70% and 76%, with a specificity of 64.1%--79%. Yet, most of these promising results have been obtained in research settings, with specially trained research staff or health providers performing the test under adequate supervision.

The performance of VIA was desired to be assessed when used in field conditions, particularly as an adequate alternative in a setting where a screening programme based on Papanicolau (Pap) smear already exists.

Methodology

This study is part of a larger study on integration of cervical cancer screening services in primary health care in the District of Rivas, in Southern Nicaragua. The study was approved by the Ethical Board of the Universidad Nacional Autónoma de Nicaragua.

Within this project, women aged 30 years or older who had never been screened, or who had not been screened for the past 3 years (the so-called target population) were invited by community health workers to attend the programme. In line with the national policy, women who attended spontaneously were also screened, irrespective of the time of their last Pap smear.

Within this project, the local cytologist responsible for reading all the Pap smears taken in Rivas District within the public health system (2,000-4,000 annually) received a refresher-training course in July 2000.

In September 2000 and May 2001, seven medical doctors and 26 nurses from six health centres, 13 health posts, one non-governmental organization (NGO) clinic, and the gynaecology consultation of the district hospital were trained. The training consisted of 1 day theoretical sessions on clinical and epidemiological aspects of cervical (pre-) cancer, the technique of VIA and a refreshment module on Pap smear sampling. A full day was spent on VIA training, using a pictorial atlas developed at the International Centre for Reproductive Health, Ghent University (not published) and a teaching set of projected 35 mm photographic slides of cervixes images after application of acetic acid (cervicograms). Each participant then received 1 day of
supervised practical training on women attending the clinics for cervical screening. The trainees received a 1-day refresher workshop 6 months after the initial training, using a teaching slide set and practice sessions.

A positive result on visual inspection was defined as an opaque white or grey lesion with well-defined borders, located close to the squamo-columnar junction.

The Pap smears were classified according to the 1991 Bethesda Classification ⁹, and considered positive when at least atypical squamous cells of unknown origin (ASCUS) were reported. In order to keep the reporting uniform throughout the study period, no adaptation was made to the 2001 Bethesda Classification¹⁰.

The two screening tests were performed on all women of the target population attending the health facilities for screening purposes. Other women were screened by Pap smear, with or without VIA test. A Pap smear was obtained using Ayre’s spatula and spray fixative for cytodiagnosis (Labofix, Labonord, Villeneuve d’Ascq, France), and after Pap staining, read by the cytologist of the district hospital in Rivas. All positive Pap smears and 10% of negative smears were revised by a pathologist from the Bertha Calderon Hospital, a referral hospital in Managua. Conventional cytology (dry slides) was used at both levels.

Immediately after the Pap smear, the health providers applied 5% acetic acid to the cervix, and recorded the findings 2 minutes later, using a simple household torch as a light source.

Women testing positive on either screening test were referred to the colposcopy clinic. Colposcopies were offered at the NGO clinic in San Juan del Sur, one of the areas of the district. Referred patients were asked to attend the clinic as soon as possible, without previous appointment. The clinic was open every Saturday and colposcopy and outpatient treatment of pre-invasive disease were free of charge.

The referral test involved colposcopy and a biopsy if indicated. Colposcopies and subsequent biopsies were performed by a trained gynaecologist. Biopsies were examined at the Bertha Calderon Hospital by a local pathologist. All biopsies were independently reviewed by a pathologist from Ghent University. This pathologist was blinded for the first result. The overall inter-observer agreement of the biopsies was 66%. Discordant biopsies were investigated by both pathologists, using a binocular training microscope with two heads. The consensus diagnosis was taken as the final result.

Statistical analysis

As only those women testing positive on either VIA or Pap smear were further investigated, hence, introducing verification bias, we used specific statistical methods¹¹,¹² to assess the accuracy of the VIA compared to the conventional Pap smear as currently used in Nicaragua.

Our data were represented using the sample scheme developed by Schatzkin. As the referral test is not applied to patients who tested negative on both screening test, sensitivity and specificity cannot be calculated. Yet, information about the relative true positive rate (RELTPR) and the relative false positive rate (RELFPFR) of both tests is available (Table 1): the RELTPR of Test 2 (VIA) compared to Test 1 (Pap) = (a+b)/(a+c); the RELFPFR of Test 2 (VIA) compared to Test 1 (Pap) = (A+B)/(A+C).
Table 1 Sample scheme used (Schatzkin et al.1987)

<table>
<thead>
<tr>
<th></th>
<th>Diseased</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test1 +</td>
<td>Test1 -</td>
<td>Total</td>
<td>Test1 +</td>
<td>Test1 -</td>
<td>Total</td>
</tr>
<tr>
<td>Test2 +</td>
<td>a</td>
<td>b</td>
<td>a+b</td>
<td>A</td>
<td>B</td>
<td>A+B</td>
</tr>
<tr>
<td>Test2 -</td>
<td>c</td>
<td>[d]</td>
<td>C+[d]</td>
<td>C</td>
<td>[D]</td>
<td>C+[D]</td>
</tr>
<tr>
<td></td>
<td>a+c</td>
<td>b+[d]</td>
<td>[n]</td>
<td>A+C</td>
<td>B+[D]</td>
<td>[N]</td>
</tr>
</tbody>
</table>

*Value in brackets indicates unknown values.

We used McNemar’s test, with the usual correction for continuity, to test for a statistically significant difference in the sensitivities and specificities between the two tests, even when the sensitivity and the specificity of the tests cannot be established, as the test compares only the discordant cells within each of the diseased and non-diseased groups: $X^2 = (|b-c|-1)^2 / b+c$ and $X^2 = (|B-C|-1)^2 / B+C$, respectively.12 We further determined the trade-off between VIA and Pap smear by calculating the ratio of extra false positives (EFPs) to extra true positives (ETPs) detected. According to Chock et al.11 this EFP:ETP ratio equals $\frac{(A+B)-(A+C)/(a+b)-(a+c)}{B-C}/(b-c)^2 + (B-C)/(B-C)^2$. The performance of VIA was compared with the Pap test using a high threshold for the referral test: cervical intraepithelial neoplasia (CIN) grade 2 or higher, on biopsy.

The effect of the number of tests done on the test result was assessed in univariate analysis, calculating a $P$ value for the difference in the false positive rate (FPR) between providers having used the test at least 100 times and the others. The FPR is subject to verification bias as no biopsy was performed on VIA positive patients with negative colposcopy, but we assume the bias to be equal in both the groups.

Results

Visual inspection was used as a screening tool by six of seven (85.7%) trained medical doctors and by 14 of 26 (53.8%) trained nurses. It was implemented in all health centres, in the NGO clinic, in four of 13 (30.8%) health posts and for a few months in the gynaecology consultation of the district hospital.

Between September 2000 and July 2002, 1080 patients underwent visual inspection. Of them 572 (53.0%) were seen in the health centres, 362 (33.5%) in the NGO clinic, 133 (12.3%) in the health posts and 13 (1.2%) in the hospital.

Medical doctors performed 580 (53.7%) of the tests and nurses 500 (46.3%). A total of 977 (90.5%) women were aged 30 or older. Of them, 381 had never been screened and 432 had not been screened in the last 3 years, resulting in 813 (75.3%) patients belonging to the defined target population.

The 1076 patients who had both a Pap test and a visual inspection were included for further analysis on the test performance.
Patients had a mean age of 39.8 years (range 16-86), a mean parity of 5.6 (range 0-25) and started their sexual life at a mean age of 17.4 years (range 11-35). Only 7.5% were smokers.

Overall, 352 patients (32.7%) had a positive screening test: 47 (4.4%) tested positive on both VIA and Pap smear, 275 (25.5%) had a positive visual inspection only, and 30 (2.8%) only a positive cytology. Of the screen positive patients, 290 (82.4%) were assessed at the colposcopy clinic, where colposcopy and biopsy was performed. Seventeen patients with two negative screening tests underwent additional colposcopies, because they had cervical polyps. Five patients (0.5%) had a histological diagnosis of invasive cancer, 46 (4.5%) of CIN2/CIN3 and 77 (7.6%) of CIN1 and human papilloma virus (Table 2).

### Table 2. Distribution of histological results by outcome of screening tests

<table>
<thead>
<tr>
<th>VIA</th>
<th>PAP</th>
<th>N</th>
<th>Did not attend</th>
<th>Colpo</th>
<th>Colpo</th>
<th>Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>colposcopy</td>
<td>performed</td>
<td>normal</td>
<td>no dysplasia</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>47</td>
<td>4 (8.5%)</td>
<td>43</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>275°</td>
<td>(18.9%)</td>
<td>223</td>
<td>112</td>
<td>33</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>30</td>
<td>6 (20.0%)</td>
<td>24</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>724°°</td>
<td>-</td>
<td>17*</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>1076</td>
<td>62**</td>
<td>307</td>
<td>131</td>
<td>48</td>
</tr>
</tbody>
</table>

| VIA: Visual inspection with acetic acid. CIN: cervical intra-epithelial laesion. HPV: Human Papilloma Virus |
| ° Including 4 patients with no diagnosis on Pap smear because of bad quality |
| °° Including 2 patients with no diagnosis on Pap smear because of bad quality |
| * Patients referred to colposcopies for other reasons, mainly because of presence of polyps |
| ** Patients excluded from analysis on comparison of the two tests |

Of 51 patients diagnosed as CIN2 and more on biopsy, 17 were positive on both screening tests, whereas 28 had a positive VIA test only and six a positive Pap smear only. Of 256 patients with a negative referral test, 26 were both Pap en VIA positive, 195 had a positive VIA test only and 18 a positive Pap smear only.

The RELTPR of VIA compared with Pap smear was 1.96 (45 : 23), $P < 0.001$. The RELFPR was 5.02 (221: 44), $P < 0.001$. The EFP:ETP ratio was 8.05 (95% CI : 4.68-13.86).

The FPR of VIA was 82.8%. The FPR decreased with experience: it was 86.8% for health providers who used the test less than 100 times, compared to 76.8% when used at least 100 times ($P = 0.04$). These rates were similar for nurses and for doctors (Table 3).
Table 3. Performance of visual inspection in relation to experience*

<table>
<thead>
<tr>
<th>Number</th>
<th>VIA Result</th>
<th>Final Result</th>
<th>False Positive Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VIA</td>
<td>Neg &gt;=HSIL</td>
<td>Overall</td>
</tr>
<tr>
<td>&gt;=100</td>
<td>NEG</td>
<td>282 (74.0%)</td>
<td>76/99 (76.8%)</td>
</tr>
<tr>
<td></td>
<td>POS</td>
<td>99 (26.0%)</td>
<td>76/99 (76.8%)</td>
</tr>
<tr>
<td>5-99</td>
<td>NEG</td>
<td>446 (74.7%)</td>
<td>76/99 (76.8%)</td>
</tr>
<tr>
<td></td>
<td>POS</td>
<td>151 (25.3%)</td>
<td>76/99 (76.8%)</td>
</tr>
</tbody>
</table>

VIA: visual inspection with acetic acid; HSIL: high-grade intraepithelial lesion

* The cases where final results were not available were excluded from the analysis:
In group >=100: four (14.8%) VIA negative and 23 (84.6%) VIA positive
In-group 5-99: six (15.4%) VIA negative and 33 (84.6%) VIA positive
And 32 VIA carried out by various health providers during training sessions.

Time between screening and diagnosis was significantly shorter for visual inspection than for Pap smear. For 206 patients with a positive VIA and a negative Pap smear, mean time to colposcopy was 17.5 days (95% CI 14.3-20.8, median 10) compared to 68.9 days (95% CI 47.5-90.3, median 54) for 23 patients who had a positive Pap but a negative VIA and 36.2 days (95% CI 24.8-47.5, median 30) for 42 patients with both tests positive (P < 0.001).

Discussion

Despite the fact that cytology-based screening programmes for cervical cancer have been introduced in most countries of South and Central America since the 1970s, they have had very limited success. Low screening coverage and inappropriate collection and reading of Pap smears and limitations in the accuracy of this test have been shown to be important reasons for the observed ineffectiveness of these programmes.

Our study shows that, despite additional training in correct sampling and reading of Pap smears, the detection rate for dysplasia was only 4.7% in a high-risk population. Earlier data, whereby Pap smears were taken by one single gynaecologist in a general population in Nicaragua, showed a detection rate for abnormal smears of 7.7%. Quality control data revealed that sampling (including lack of endocervical cells and poor fixation) rather than misclassification was the main problem. Yet, compared with the centres where personnel was not trained, the detection rate was three times higher and the number of inadequate samples halved, indicating that the training had had an effect on the quality of the Pap smears (data not shown in this paper). Even though the performance was improved, the Pap test only detected 47 of the 138 lesions, missing nearly half of the HSIL and more than half of the invasive cancers. Conversely, through visual inspection, twice as many pre-malignant lesions of the cervix were detected. This result was obtained after a very short training, without further supervision and by a variety of health providers using the test. This confirms VIA to be a cheap test, easy to perform and
with a high sensitivity\textsuperscript{15}. Our study further showed that the performance increases with experience, as reflected by a decrease in the false positive rate. The study design does not allow an assessment of the false negative rate, as no gold standard was applied to all people with a negative test. Yet, this might be less important as the main problem of VIA is the low specificity\textsuperscript{16}.

Other advantages of visual inspection include the shorter delay in referral and final diagnosis, which is crucial for compliance and timely treatment.

Unfortunately, this does not mean that the ideal screening test for cervical cancer screening has been found. Comparing the test performance of VIA to Pap smear reflects a common situation where one test has a higher true positive rate than the other at the expense of having a higher FPR\textsuperscript{11}. Whereas VIA is known to have a higher sensitivity than Pap smear, its specificity is substantially lower. This results in a high number of women needing unnecessary confirmatory investigation. Normal diagnostic procedures consist in colposcopy and biopsy, which are performed at the referral level. The practical impact of this trade-off is shown by the EFP:ETP ratio for VIA compared with Pap smear. This ratio was 8.05, indicating that for every extra case of at least a CIN2 on histology, eight extra false positives had to be attended at the referral level.

The increase in both ETPR and EFPR has a serious impact on the organization of the referral level. In our setting, the detection of more than twice as many lesions through the use of VIA meant quadrupling the number of patients referred to colposcopy, and a doubling of the number of patients needing treatment for high-grade lesions or invasive cancer. Using the Pap smear as a primary screening tool, only 77 women would have been referred, 24 low-grade intraepithelial lesions (LSIL) followed-up, 21 HSIL and 2 cancers treated. In absolute terms, VIA meant a surplus of 245 (of whom 199 attended) referrals to the colposcopy clinic, of 41 extra LSIL needing close follow-up, of 19 extra HSIL and three extra invasive cancers needing specialized treatment, and this for 1080 women screened over a period of nearly two years.

If visual inspection were to be used as a common screening test, an easily accessible colposcopy clinic would have to be set up at the level of the district hospital. Gynaecologists would have to be trained in colposcopy and outpatient treatment modalities and accept to examine many false positive patients. However, the increase in workload could be countered by focusing the screening-programme on older women and increasing the screening-interval to 3 years. This would reduce the total number of tests provided and increase the cost-effectiveness of the programme.

Recently, it was shown, using a population-based simulation model that VIA, with immediate treatment when abnormalities were found, would be the most cost-effective approach in Thailand if the test was applied at 5-years intervals in women aged 35-55. In the model, treatment consisted of cryotherapy provided at community site and referral for hospital evaluation when a suspected invasive cancer is revealed by the test. However, the authors comment that, depending on resources, test performance and compliance with screening and follow-up, several other options are viable alternatives\textsuperscript{17}. In Nicaragua, as in most of the Latin American countries, where screening and referral systems, as well as large number of professionals exist, a see and treat approach can hardly be defended. In our study, only 45 of the 266 (16.9\%) women with a positive VIA test had a lesion that
needed immediate treatment (high-grade dysplasia or more). The others would have been unnecessarily over-treated. Moreover, compliance with referral was very good: 82% of referred women attended the colposcopy clinic, which is much higher than the estimated 50% of the model used in the previous study. This high compliance rate might have been influenced by the organization of the programme, including the invitation of women of the target population and the provision of diagnosis and treatment free of charge. Yet, health promotion to increase the uptake of a screening programme and the (geographical and financial) accessibility of diagnostic and treatment services should be taken into account in the design of all screening programmes. From an operational point of view, it is also easier and more feasible to provide treatment at the referral level, than it would be to make cryotherapy available in all primary health centres where screening is currently provided.

It might be too early to advocate widespread use of visual inspection as a screening test. Our study, as most of the studies on VIA, focuses on one single test, and no information is available on test performance when the test is repeated. It cannot be excluded that the results are positively influenced by the motivation of the health workers who used the test, as half of the nurses did not use it and no information is available on their performance. Yet, these nurses neither performed Pap smears, so most probably they were assigned to other programmes during the study period.

There is an urgent need to establish uniform criteria on test positivity and on definitions to evaluate test performance\(^7\). Our criteria resulted in nearly 30% tests reported as positive. Other authors report 24-25% positive tests\(^6\)\(^-\)\(^8\). Using the same criteria in a research setting in Kenya, more than 27% of the tests were positive (H. De Vuyst, personal communication).

VIA is a promising test and further field-testing to increase its performance is surely needed. Now that more results are available on its effectiveness, standardization and methods for quality control are highly required.

Meanwhile, efforts should be targeted into further improving the existing cytology-based programme. Measures to increase coverage\(^1\)\(^8\) need to be complemented by additional in-depth training of health professionals for correct sampling of Pap smears and further exploring VIA as an alternative screening test.

In conclusion, our study shows that VIA when applied on a larger scale spectacularly increases the number of CIN and invasive cancer detected in a general, but inadequately screened, population. However, the relatively high FPR remains an important concern for the organization of the referral level.

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**Acknowledgements**

The authors thank the health providers of the public health centres in Rivas and of the NGO clinic of Servicios Medicos Comunales whose collaboration made this work possible. This study was supported by the Belgian Development Co-operation through the Flemish Interuniversity Council.
Reference list

III-4-3.

IMPROVING QUALITY OF CYTOLOGY
IMPROVING QUALITY OF CYTOLOGY

Introduction

Poor quality of cytology is a major issue in the provision of cervical cancer screening programmes in developing countries. Low screening coverage as well as inappropriate collection and reading of Pap smears and limitations in the accuracy of this test have been shown to be important reasons for the observed ineffectiveness of these programmes. The implementation of quality control programmes to obtain, fix, stain, transport and diagnose smears, has been described as one of the strategies to improve the efficiency of these programmes. In Rivas, prior to the introduction of an improved cervical cancer screening programme, an assessment was made of the existing programme. Several limitations of this programme were identified:

1. Insufficient training of health personnel, as revealed by a survey done amongst health providers to assess their training level and needs for further training. Fifty-eight persons, including 14 medical doctors, 20 nurses and 24 auxiliary nurses, filled out a questionnaire. Fifty percent of doctors, 40% of nurses and 33% of auxiliary nurses acknowledged not having been trained in the collection of specimen. Six doctors, 8 nurses and 3 auxiliary nurses, had been trained as part of their professional training and the others had benefit from additional workshops organised by the Ministry of Health or by a family planning NGO. All of the participants declared welcoming training initiatives.

2. Whereas all health centres had equipment and supplies to provide screening services, the quality was not guaranteed. Standardized forms for reporting were not available, and Pap smears were sent to the laboratory wrapped in a piece of paper mentioning the name of the patient, the age, and in some cases the obstetrical and screening history. Extended tip Ayre spatulae were not available and cotton swabs were used for smear taking. The slides, which had been stored in warm depots for prolonged time had lost their transparency and had a white shine. In the health posts, Pap smears were taken without using a torch or lamp and fixation spray was not available.

3. There was one cytologist at district level, responsible for reading all the smears taken in the public health centres and hospitals of the district. The number of smears increased from year to year: 938 in 1996, 1470 in 1997, 2383 in 1998, 3327 in 1999 and 2886 in 2000 (January-September, before the start of the intervention). The cytologist received no supervision, there was no quality control and she did not have to report the results of her work to any higher structure. The number of Pap smears reported as being positive was extremely low: less than 0.6%. A review of 58 slides read as negative in 1999, and selected by chance, were revised at the reference laboratory in Managua. Of the 58, 55 were confirmed to be negative, and 3 smears were reported as ASCUS. Specimen adequacy was assessed using the Bethesda guidelines. Of the 58 smears, 17 were qualified as “satisfactory”, 17 as “unsatisfactory” and 24 as “limited”. Main problems were fixation and staining of the smears, resulting in artefacts that made correct interpretation of the smears difficult.
4. No information system for reporting was available. Health centres registered the names of the patients, and sometimes the age and the community, in a book, which was signed by the cytologist when the smears were handed over. In some health centres, the results were annotated. The cytologist had a book where she registered, by year, the names of the patients, the health centre, and the Pap smear result.

Within the framework of the cervical cancer screening programme, efforts were made to improve the quality of the cytology, both at primary health care level as at the cytology laboratory.

**Methodology**

In July 2000, the cytologist of the Rivas hospital, responsible for reading all the Pap smears of the district, received a refresher course on cytology in Managua. The course had a duration of three weeks. It was organized by the pathology department of the Bertha Calderon Hospital (third level clinic), in collaboration with the Instituto Dexeus de España. The course focused on quality aspects of conventional cytology, including definitions and criteria for specimen adequacy. Emphasis was given to the use of the Bethesda system for reporting cervical and vaginal cytologic diagnosis. The course included theoretical seminars and practical exercises on existing slides.

Conventional cytology (dry slides) was used and Pap smears classified according to the 1991 Bethesda Classification ³, and considered positive when at least ASCUS was reported. This classification was used during the whole study period and, in order to guarantee uniformity, no adaptation was made to the 2001 Bethesda Classification ⁴.

In September 2000, a refreshment training module in correct sampling was integrated in the training course on cervical pathology and screening modalities. This course was organized for the health staff in three of the six areas of Rivas district. Seven medical doctors and 26 nurses from 6 health centres, 13 health posts, 1 NGO clinic, and the gynaecology consultation of the district hospital attended the course. The “trained” areas were also provided with the necessary supplies to allow good quality of specimen: Ayre's spatulae with extended tip, torches, spray fixative for cytodiagnosis (Labofix, Labonord, Villeneuve d'Ascq, France), laminae. In the three other areas, training and provision of supplies started in January 2003.

Since the start of the programme in September 2000, new Pap forms have been introduced. These forms facilitated a descriptive diagnosis based on the Bethesda classification, and include an assessment of the specimen adequacy as well clinical and epidemiological data. These forms were only introduced in those areas where staff had received the refresher training module.

All specimen taken at the peripheral centres were sent to the District Hospital in Rivas and read by one cytologist. Internal quality control mechanisms were installed in September 2000. Since then, all positive Pap smears were looked at by a pathologist in Managua. This quality control has been set up as a continuous training mechanism. Every week, a meeting is organized between the cytologist and
a pathologist of the referral hospital, and all specimen diagnosed as having epithelial cell abnormalities were looked at. The diagnosis of the pathologist was taken as the final result. Ten percent of the negative smears were also re-examined.

In August 2002, an external quality control was performed by a pathologist from Ghent University. Concern had raised because of the high number of patients with biopsy proven lesions (detected through VIA) and negative Pap smears. The pathologist reviewed all, initially diagnosed as negative, smears of patients with a positive biopsy.

Information on Pap smear results before the start of the programme was obtained by revising the cytology register at the cytology department of the district hospital. Since the start of the intervention, all original Pap forms have been collected and entered in epi-info. Information on the age of clients attending the programme one year prior to the intervention has been obtained by review of the cytology registers at health centre level. These registers only include name, age and community. Pap results are not registered in a systematic way at that level.

**Results**

During the intervention period, from October 2000 to the end of December 2002, a total number of 9004 Pap smears were collected. All of them were reviewed by the cytologist in Rivas district. Of them, 8750 (97.2%) were classified as normal, 83 (1.0%) as ASCUS/AGUS, 74 (0.8%) as LSIL, 89 (1.0%) as HSIL and 8 (0.1%) as invasive cancer.

Comparing to the years before the intervention (1996-September 2000), the overall detection rate increased by a factor 4.5 (from 0.6% to 2.8%). For LSIL, the increase was fourfold and for HSIL fivefold. Yet, no difference in the detection rate of invasive cancer was observed (table 1).

<table>
<thead>
<tr>
<th>Report</th>
<th>TRAINING AREA</th>
<th>NON TRAINING AREA</th>
<th>OVERALL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>before* n=6464 (%)</td>
<td>since** n=5523 (%)</td>
<td>before* n=451 (%)</td>
</tr>
<tr>
<td>Normal</td>
<td>6427 (99.42)</td>
<td>5317 (96.27)</td>
<td>4516 (99.45)</td>
</tr>
<tr>
<td>ASCUS/AGUS</td>
<td>2 (0.03)</td>
<td>65 (1.18)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>LSIL</td>
<td>16 (0.25)</td>
<td>64 (1.16)</td>
<td>8 (0.18)</td>
</tr>
<tr>
<td>HSIL</td>
<td>14 (0.22)</td>
<td>72 (1.30)</td>
<td>11 (0.24)</td>
</tr>
<tr>
<td>Invasive cancer</td>
<td>5 (0.08)</td>
<td>5 (0.09)</td>
<td>6 (0.13)</td>
</tr>
</tbody>
</table>

*before: January 1996-September 2000
**since: October 2000 – December 2002

During the intervention period, significantly more clients were aged 30 and more than during the year prior to the intervention (October 1999-September 2000): 58.6% versus 50.7%, respectively; p<0.0001) (table 2). In this age group, significantly more specimen were reported to be abnormal than in women younger
than 30 years old (3.4% versus 2.1%, respectively; p<0.0001) (table 3). There was no
difference in the proportion of abnormal smears between the women never and ever
screened: 3.0% and 2.7% respectively, p= 0.52 (table 4).

Table 2. Distribution of Pap smears per age group, before and since start intervention

<table>
<thead>
<tr>
<th></th>
<th>TRAINING AREA</th>
<th></th>
<th>NON TRAINING AREA</th>
<th></th>
<th>OVERALL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>year before*</td>
<td>since**</td>
<td>year before*</td>
<td>since**</td>
<td>year before*</td>
<td>since**</td>
</tr>
<tr>
<td>n= 2073</td>
<td>n= 5553 (%)</td>
<td></td>
<td>n= 1370 (%)</td>
<td>n= 3518 (%)</td>
<td>n= 3443 (%)</td>
<td>n= 9071 (%)</td>
</tr>
</tbody>
</table>

Pap in women >=30 years old
1028 (49.6) 3380 (60.9) 718 (52.4) 1933 (54.9) 1746 (50.7) 5313 (58.6)

Pap in women < 30 years old
1045 (50.4) 2173 (39.1) 652 (47.6) 1585 (45.1) 1697 (49.3) 3758 (41.4)

year before*: October 1999-September 2000
since**: October 2000-December 2002

Table 3. Cytology results in function of age

<table>
<thead>
<tr>
<th>Report</th>
<th>TRAINING AREA</th>
<th></th>
<th>NON TRAINING AREA</th>
<th></th>
<th>OVERALL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>age &lt;30 (%)</td>
<td>age &gt;=30 (%)</td>
<td>age &lt;30 (%)</td>
<td>age &gt;=30 (%)</td>
<td>age &lt;30 (%)</td>
<td>age &gt;=30 (%)</td>
</tr>
<tr>
<td>Normal</td>
<td>2104 (97.2)</td>
<td>3213 (95.8)</td>
<td>1555 (98.9)</td>
<td>1878 (98.4)</td>
<td>3659 (97.9)</td>
<td>5091 (96.6)</td>
</tr>
<tr>
<td>ASCUS/AGUS</td>
<td>21 (1.0)</td>
<td>44 (1.3)</td>
<td>3 (0.2)</td>
<td>15 (0.8)</td>
<td>24 (0.6)</td>
<td>59 (1.1)</td>
</tr>
<tr>
<td>LGSIL</td>
<td>27 (1.2)</td>
<td>37 (1.1)</td>
<td>6 (0.4)</td>
<td>4 (0.2)</td>
<td>33 (0.9)</td>
<td>41 (0.8)</td>
</tr>
<tr>
<td>HGSIL</td>
<td>14 (0.6)</td>
<td>58 (1.7)</td>
<td>9 (0.6)</td>
<td>8 (0.4)</td>
<td>23 (0.6)</td>
<td>66 (1.3)</td>
</tr>
<tr>
<td>Invasive cancer</td>
<td>0 (0)</td>
<td>5 (0.1)</td>
<td>0 (0)</td>
<td>3 (0.2)</td>
<td>0 (0)</td>
<td>8 (0.2)</td>
</tr>
</tbody>
</table>

Table 4. Cytology results in function of Pap history

<table>
<thead>
<tr>
<th>Report</th>
<th>TRAINING AREA</th>
<th></th>
<th>NON TRAINING AREA</th>
<th></th>
<th>OVERALL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ever screened</td>
<td>never screened</td>
<td>ever screened</td>
<td>never screened</td>
<td>ever screened</td>
<td>never screened</td>
</tr>
<tr>
<td></td>
<td>n= 3640 (%)</td>
<td>n= 1686 (%)</td>
<td>n= 2384 (%)</td>
<td>n= 847 (%)</td>
<td>n= 6024 (%)</td>
<td>n= 2533 (%)</td>
</tr>
<tr>
<td>Normal</td>
<td>3506 (96.3)</td>
<td>1624 (96.4)</td>
<td>2357 (98.9)</td>
<td>835 (98.5)</td>
<td>5863 (97.3)</td>
<td>2459 (97.0)</td>
</tr>
<tr>
<td>ASCUS/AGUS</td>
<td>39 (1.1)</td>
<td>25 (1.5)</td>
<td>13 (0.5)</td>
<td>3 (0.4)</td>
<td>52 (0.9)</td>
<td>28 (1.1)</td>
</tr>
<tr>
<td>LGSIL</td>
<td>44 (1.2)</td>
<td>16 (0.9)</td>
<td>4 (0.2)</td>
<td>3 (0.4)</td>
<td>48 (0.8)</td>
<td>19 (0.8)</td>
</tr>
<tr>
<td>HGSIL</td>
<td>49 (1.3)</td>
<td>19 (1.1)</td>
<td>10 (0.4)</td>
<td>4 (0.5)</td>
<td>59 (1.0)</td>
<td>23 (0.9)</td>
</tr>
<tr>
<td>Invasive cancer</td>
<td>2 (0.1)</td>
<td>2 (0.1)</td>
<td>0 (0)</td>
<td>2 (0.2)</td>
<td>2 (0.03)</td>
<td>4 (0.2)</td>
</tr>
</tbody>
</table>
As can be observed in Table 1, the number of abnormal Pap smears was higher in the training area than in the areas where health staff had not been trained: 3.7% versus 1.4% (p<0.0001). The difference was consistent in strata of different age groups and with different screening history (Table 2 and 3) and the positive association between training of health staff and abnormal Pap results remained highly significant after adjusting for age and history of Pap smear (p<0.0001).

A total number of 84 specimen out of 9071 (0.9%) were reported unsatisfactory for evaluation: 47/3518 (1.3%) in the area where staff had not received additional training and 37/5553 (0.7%) in the area where staff were trained. In the latter, a further 17.4% of smears were reported as being limited for evaluation, mainly due to absence of an adequate endocervical/transformation zone component or due to fixation problems (table 5). As only the new Pap forms included reporting of the limitations of quality of the specimen following the Bethesda guidelines, this information is not available for the areas where staff was not trained.

Table 5. Reported specimen adequacy in areas with trained staff

<table>
<thead>
<tr>
<th></th>
<th>n=5256 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satisfactory for evaluation</td>
<td>4305 (81.9)</td>
</tr>
<tr>
<td>Satisfactory but limited: lack of an endocervical/transformation zone component</td>
<td>444 (8.5)</td>
</tr>
<tr>
<td>Satisfactory but limited by poor fixation</td>
<td>357 (6.8)</td>
</tr>
<tr>
<td>Satisfactory but limited for other reasons</td>
<td>113 (2.1)</td>
</tr>
<tr>
<td>Unsatisfactory for evaluation</td>
<td>37 (0.7)</td>
</tr>
</tbody>
</table>

Follow-up data of colposcopy and biopsy when indicated were available for 176 patients with an abnormal smear. Of the 52 patients with a cytology report of ASCUS/AGUS, 5 (9.6%) had a histology compatible with a HSIL and 4 (7.7%) had an invasive cancer. Of the 55 with a cytology report of LSIL, 11 (20.0%) had a high-grade lesion. Of the 65 with a HSIL, 45 (69.2%) were confirmed and 4 (6.2%) had invasive cancer. An overview of these results is to be found in table 6.

Table 6. Follow-up (FU) data* for patients with abnormal Pap smear

<table>
<thead>
<tr>
<th>Pap RESULT</th>
<th>FU</th>
<th>COLPOSOCPY</th>
<th>BIOPSY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Yes</td>
<td>NEG</td>
</tr>
<tr>
<td>ASCUS/AGUS</td>
<td>83</td>
<td>52</td>
<td>21</td>
</tr>
<tr>
<td>LSIL</td>
<td>74</td>
<td>55</td>
<td>6</td>
</tr>
<tr>
<td>HSIL</td>
<td>89</td>
<td>65</td>
<td>4</td>
</tr>
<tr>
<td>INVASIVE CA</td>
<td>8</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>TOTAL</td>
<td>254</td>
<td>176</td>
<td>31</td>
</tr>
</tbody>
</table>

An external pathologist reviewed 37 specimen which were diagnosed as negative by the cytologist, but had a positive biopsy. Only 16 (42.1%) were considered satisfactory for evaluation and ten were diagnosed as totally unsatisfactory. In 14
specimen, the negative diagnosis was confirmed, while 10 had an ASCUS and 3 a LSIL (table 7).

Table 7. Quality control of 37 negative Pap smears of patients with positive biopsy

<table>
<thead>
<tr>
<th>BIOPSY RESULT</th>
<th>N</th>
<th>Specimen adequacy</th>
<th>QUALITY CONTROL</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive cancer</td>
<td>2</td>
<td>1 Limited for evaluation</td>
<td>ASCUS</td>
<td></td>
</tr>
<tr>
<td>1 Unsatisfactory for evaluation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN3</td>
<td>5</td>
<td>3 Limited for evaluation, lack of endocervical cells</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>2 Adequate</td>
<td></td>
<td></td>
<td>ASCUS</td>
<td></td>
</tr>
<tr>
<td>CIN2</td>
<td>13</td>
<td>2 Adequate</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>5 Adequate</td>
<td></td>
<td></td>
<td>ASCUS</td>
<td></td>
</tr>
<tr>
<td>4 Limited for evaluation, lack of endocervical cells</td>
<td></td>
<td></td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>1 Limited for evaluation, lack of endocervical cells</td>
<td></td>
<td></td>
<td>LGSIL</td>
<td></td>
</tr>
<tr>
<td>1 Unsatisfactory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN1</td>
<td>13</td>
<td>2 Adequate</td>
<td>ASCUS</td>
<td></td>
</tr>
<tr>
<td>2 Adequate</td>
<td></td>
<td></td>
<td>LGSIL</td>
<td></td>
</tr>
<tr>
<td>6 Unsatisfactory for evaluation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Adequate</td>
<td></td>
<td></td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>HPV</td>
<td>4</td>
<td>2 Limited for evaluation, lack of endocervical cells</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>2 Unsatisfactory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In the report the pathologist stated “that in most cases an explanation was found for the discrepancy between the cytological diagnosis and the histology. Poor quality of sampling was the main reason for inadequate diagnosis. In a few cases, the presence of so-called “small, blue and mean cells” was erroneously reported as negative. This is a known cause of false negative Pap smears.”

He further considered “the educational level and knowledge of both the cytologist at district hospital and the pathologist at the referral level, to be very good and conform to international standards.”

**Discussion**

Whereas the collected data only provide indirect information on the quality of the cytology, strong arguments exist in favour of an improved quality of the cytology since the start of the intervention.

A first observation is the substantial increase (450%) in the number of abnormal smears (from less than 0.6% to 2.8%). This increase might be influenced by: 1) an
improved quality of the Pap smear, resulting in a reduction of the number of false negatives (increased sensitivity), 2) an increase in the number of false positives (decreased specificity) and 3) an increase in the number of lesions in the examined population, due to a shift towards a higher risk population.

Our data support the argument that there is an increased sensitivity as a result of improved quality of the Pap smear:

1. Earlier data, whereby Pap smears were taken by one single gynaecologist in a general population in Nicaragua showed a detection rate of 7.7%. In coherence with these data, 0.6% abnormal Pap smears would be totally unacceptable and 2.8% would still be an underestimation.

2. Even if there might be an increase in the false positive rates, biopsy results show that 74.4% of the abnormal Pap smears are “true positive results”. If all positive specimen prior to the intervention were “true positives” (which is unlikely), there would still be a more than threefold increase in true positive rate (2.10% versus 0.6%).

3. The increase in smear positivity cannot only be explained by a shift towards a higher risk population. Women aged 30 and older are at higher risk, but the increase in the proportion of this high-risk group in the screening population (7.9%) cannot explain the increase in positive smears. Moreover, the overall prevalence of abnormal smears in women younger than 30 (2.1%) is still 3.5 times higher than the overall prevalence before the intervention. Previous screening did not show to have an effect on smear result.

Our data further show that training of health providers in correct sampling had a positive effect on quality of Pap smears. In the areas where staff had received a refresher training course, the proportion of inadequate smears was only half as high as in the other areas. The proportion of positive smears was more as double as high and the positive association between training of health staff and abnormal Pap results remained highly significant after adjusting for age and history of Pap smear.

The improved quality of the work performed by the cytologist can be deduced from the increase in abnormal Pap smears in the areas where staff had not been trained.

Yet, our data also show that the overall quality was still far of satisfying high standards.

In the areas where staff had been trained in correct sampling, more than 17% of specimen were reported as “limited for evaluation”. Lack of endocervical cells and poor fixation were the main problems. In the same areas, the use of visual inspection with acetic acid as a screening test showed to be twice as sensitive as Pap smear in the detection of high-grade laesions. The external quality control of false negative smears confirmed that sampling errors rather than detection errors were the main problem. This is in line with other reports showing a false negative rate for Pap smear of at least 20%, half of the failures being due to inadequate specimens.

The additional training and supervision of the cytologist surely had a positive effect on quality of reading, but the training provided to health care workers might have been insufficient to ensure high quality of sampling. As not all health providers had
been trained, a number of smears might also have been taken by non–trained personnel.

Yet, it is the question if it is possible to reduce the sampling false negative smears in a poor-resource setting. It has been suggested that using improved sampling devices, such as the endocervical cytobrush, could reduce sampling errors. Yet, a meta-analysis found that there were no substantial differences in the yield of cytologic abnormalities between the extended tip spatula, the classic Ayre spatula combined with the Cytobrush or cotton swab, or the Cervex brush. Based on this analysis, changing the sampling device would not result in a reduction of sampling error. The use of liquid-based cytology Papanicolaou testing instead of conventional smears seems to reduce sampling errors, but these tests are not accessible for the population attending health centres in Nicaragua, where screening services are provided free of charge. If more in-depth training will improve the quality of sampling, will be shown by future results, as in February 2003, a new training course for all health staff of the district has been organized.

The need for adequate follow-up of all positive Pap smears, including ASCUS/AGUS and LSIL, as shown in earlier studies, has been confirmed by our data. Of these Pap reports, 17 and 20 percent, respectively, harboured a high-grade lesion or an invasive cancer. Where colposcopy is available, colposcopic examination of all patients with a positive cytology should be the norm.

In conclusion, our intervention has been successful in improving the quality of the cytology. Yet, the low detection rate of Pap smear when compared to alternative screening techniques as VIA, is a concern. Further efforts are needed to ensure that specimen are adequate for interpretation. This includes training and supervision of the health care workers on a regular basis. The cytologist can play an important role in this training, using the collected specimen as training material.

Reference list

III-5. DECENTRALISING DIAGNOSIS AND TREATMENT
DECENTRALISING DIAGNOSIS AND TREATMENT

Introduction

The incidence rate of cervical cancer in Central-America is 44.4/100,000, which is the highest in the world and three times higher than in the industrialized world\(^1\). In Nicaragua, 49 cases of cervical cancer are diagnosed weekly and cervical cancer is since several years the first cause of cancer-related mortality in women. The mortality is not declining despite the existence of a national screening programme. Because of the magnitude of the problem, the Health Ministry has developed guidelines for early detection and management of cervical cancer. Access to screening and diagnostic services has been highlighted as one of the key strategies to reduce the burden of cervical cancer in the country\(^2\). Yet, reliable diagnostic services are only available at the referral level in Managua. As the management of cervical neoplasia is not included in the curriculum of gynaecology training, most gynaecologists are not able to perform colposcopies or to use outpatient technologies to treat cervical dysplasia. In the district hospitals, the necessary equipment for outpatient management is neither available. This results in overtreatment of cervical dysplasia, as gynaecologists resort easily to hysterectomy. Alternatively, patients with a positive screening test are sent to the oncology department of the referral Bertha Calderon hospital in Managua. This hospital provides good quality services, but waiting periods of 3-6 months for the first visit are common, as the services are seriously overcrowded (personal communication). To make the cervical cancer programme effective, there is not only a need to screen more at-risk women, but also to improve access to effective diagnostic and treatment methods and appropriate follow-up protocols \(^3\). Pre-invasive disease is preferentially treated on an outpatient basis, as this is more patient-friendly and more cost-effective as hysterectomy. The treatment modalities that are of particular interest for developing countries because of their effectiveness, lack of side-effects, simplicity and low cost, are cryotherapy and loop electrosurgical excision procedure (LEEP) \(^4\).

Cryotherapy has an overall effectiveness of 80-90%, its effectiveness being affected by the severity and size of the lesion\(^4\). LEEP has also shown to be easy to use, acceptable to women, and relatively inexpensive\(^5\). Its advantage over destructive techniques is that it removes rather than destroys suspect tissue, thus producing a histological sample for pathologic review\(^4,6\). This is of particular interest in patients with HSIL, to rule out invasive disease. The overall success rate for treatment of cervical dysplasia is 95%. Women with incomplete excision need long term colposcopy and cytological follow up\(^7\).

In the district of Rivas, Nicaragua, an improved cervical cancer screening programme started in September 2000 in three of the six geographical areas. Decentralized management of cervical dysplasia was part of that programme. In particular, we wanted to assess: 1) the feasibility of setting up an outpatient clinic for management of cervical dysplasia in the district; 2) the attendance and follow-up rate of patients; 3) the quality of treatment compared to international standards.
Methodology

The design consisted in the organization of a colposcopy clinic in the district of Rivas. Amongst the staff, one gynaecologist with a previous training in colposcopy was identified to receive additional training in the outpatient management of cervical dysplasia. This practical training was provided in Belgium in August 2000.

The necessary equipment for diagnosis and treatment (colposcope, cryotherapy and LEEP unit) was provided to the hospital and the colposcopy clinic would be opened on a weekly basis. Staff from the Universidad Nacional Autónoma de Nicaragua (UNAN-Managua) assisted the hospital staff during the first months.

Patients attending one of the health centres of the intervention were referred to the colposcopy clinic when they had a positive screening test (VIA positive and/or a Pap smear with at least ASCUS). The patients could attend the clinic without previous appointments and free of charge. The clinic also attended patients referred from other centres (non-intervention area, private practitioners, NGO clinics...), but these data have not been collected in a systematic way.

The management guidelines used are to be found in figure 1. It was foreseen that the trained gynaecologist(s) would gradually train all the other gynaecologists working in the hospital.

*Except in the case of a PAP smear reporting HSIL or invasive cancer. In this case, an endocervical curettage is done, and further management depends on the result.

° Follow-up visits at two weeks, 6 months, 1 year and 2 years after treatment.
Colposcopy was done using a SUNCO Optostar colposcope. Colposcopy was performed after the application of 4% acetic acid to the cervix. Colposcopically abnormal-appearing areas were biopsied and the specimen were sent for histopathologic examination at the Bertha Calderon Hospital in Managua, were they were read by a pathologist.

Cryotherapy was performed without anaesthesia and using double-freeze technique. For this technique, the cervix is frozen for three minutes, thawed for five minutes, and refrozen for another three minutes so that an ice ball extended 5 mm beyond the lesion and transformation zone. The Wallach LL100 Cryo Multitip Freezer was used (Wallach Surgical Devices Inc, Orange, CT). Liquid nitrogen was used as refrigerant.

LEEP was performed with an Erbotom ICC-200 electrosurgical unit (ERBE Elektromedizin GmbH, Tübingen) and usually done under local anaesthesia. Different loop electrodes were used, depending on the size of the lesion. A ball-type electrode was used to coagulate the raw area of the cervix after excision.

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**Results**

The colposcopy clinic started functioning at the district hospital in October 2000.

Two months later, the trained doctor felt ill and left the clinic. From December 2000 to February 2001, the clinic was opened on an irregular basis by a volunteer gynaecologist from outside the district. In March 2001, two gynaecologists (one from the district hospital and one from the Universidad Nacional de Nicaragua, UNAN-Managua) received a three weeks training in colposcopy, cryotherapy and LEEP excision by a specialist in Managua. During a couple of months, colposcopy and outpatient treatment was provided to all patients attending the colposcopy clinic, but the treatment depended mainly on the presence of the gynaecologist from the UNAN-Managua. The trained gynaecologist from the hospital could not provide services on a regular basis because of other duties. Despite several meetings with the hospital direction and head of department, no commitment was obtained for the provision of services within the hospital.

In June 2001, the clinic was transferred to Servicios Medicos Comunales, a NGO clinic located in San Juan del Sur, one of the areas of the district. From then on, the clinic opened every Saturday (except holidays). Colposcopies and treatment were provided by the gynaecologist from the UNAN-Managua.

From January 1st, 2001 until December, 31st, 2002 a total number of 5329 patients were screened in the intervention area. Of them, 539 (10.1%) were referred for colposcopy: 335 with a positive VIA test, 152 with a positive Pap test, 25 VIA and Pap positive, and 27 because of other reasons. By the end of March 2003, 440 (81.6%) of them had attended the colposcopy clinic. The attendance rate was similar for people living in different geographical screening areas and for the different screening tests (Table 1 and 2).
Table 1: Colposcopy attendance rate in function of screening area

<table>
<thead>
<tr>
<th>HEALTH UNIT</th>
<th>N</th>
<th>COLPOSCOPY REALIZED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>no</td>
</tr>
<tr>
<td>Tola</td>
<td>194</td>
<td>43 (22.2%)</td>
</tr>
<tr>
<td>Rivas</td>
<td>86</td>
<td>14 (16.3%)</td>
</tr>
<tr>
<td>SJS-Cardenas</td>
<td>228</td>
<td>36 (15.8%)</td>
</tr>
<tr>
<td>Hospital</td>
<td>31</td>
<td>6 (19.3%)</td>
</tr>
<tr>
<td></td>
<td>539</td>
<td>99 (18.4%)</td>
</tr>
</tbody>
</table>

Table 2: Colposcopy attendance rate in function of indication for colposcopy

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>N</th>
<th>COLPOSCOPY REALIZED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>no</td>
</tr>
<tr>
<td>VIA pos</td>
<td>335</td>
<td>58 (17.3%)</td>
</tr>
<tr>
<td>Pap pos</td>
<td>152</td>
<td>30 (19.7%)</td>
</tr>
<tr>
<td>VIA and Pap pos</td>
<td>25</td>
<td>4 (16.0%)</td>
</tr>
<tr>
<td>Other</td>
<td>27</td>
<td>7 (25.9%)</td>
</tr>
<tr>
<td></td>
<td>539</td>
<td>99 (18.4%)</td>
</tr>
</tbody>
</table>

The mean time to colposcopy was 31.3 days (range 0-270). This was 27.8 days for people living in the San Juan del Sur area, 33.5 for the patients of Tola and 36.1 for those living in Rivas (p= 0.15 and 0.12, respectively).

Time between screening and diagnosis was significantly shorter for visual inspection than for Pap smear: a mean of 19.3 days when referred for positive VIA test versus 57.6 days when referred for positive Pap smear (p<0.001)

Of the 440 colposcopies performed for diagnostic reasons, 155 (35.2%) were normal. The results of the 282 biopsies taken when the colposcopy showed whatever lesion and the respective treatment are shown in table 3. In 3 patients no biopsy was taken because of pregnancy.

Table 3: Biopsy results and treatment provided

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N</th>
<th>none</th>
<th>lost to fu</th>
<th>cryo</th>
<th>leep</th>
<th>referred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervicitis</td>
<td>52</td>
<td>50</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV-CIN1</td>
<td>127</td>
<td>15</td>
<td>110</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CIN2-CIN3</td>
<td>86</td>
<td>8</td>
<td>9</td>
<td>58</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Invasive CA</td>
<td>12</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Polyps</td>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>282</td>
<td>55</td>
<td>23</td>
<td>121</td>
<td>59</td>
<td>24</td>
</tr>
</tbody>
</table>
The mean age of patients with confirmed LSIL was 35.8 years (range 17-70). Of them, 87.4% received outpatient treatment, nearly always cryotherapy, while 11.8% were lost to follow up, and 0.8% referred.

The mean age of patients with confirmed HSIL was 40.3 years (range 20-74). Of them, 77.9% were treated at the outpatient clinic, mainly with LEEP, 9.3% were lost to follow up and 12.8% were referred.

Patients with invasive disease had a mean age of 53.3 years (range 34-86). All were referred to the district hospital in Rivas or to the women’s clinic in Managua. No follow up data are available of these patients.

No complications of cryotherapy were reported. In the patients having had a LEEP excision, 10% had complications: bleeding in 4 cases and a postoperative pelvic inflammatory disease (PID) in one.

Of the histological specimen, 48 had free margins, 10 had margins with residual disease and in one case the margins could not be evaluated. One specimen showed invasive disease.

Outpatient treatment was provided in a mean time of 70.90 days after screening (range 0-375) and in 34.5 days after colposcopy (range 0-318). Time between diagnostic colposcopy and treatment was 32.8 days for patients of San Juan del Sur, versus 28.9 for patients living in Tola and 36.6 for those living in Rivas (p= 0.6 and 0.7, respectively).

All patients treated with LEEP came for a follow-up visit at two weeks, 95% were seen at 6 weeks and 83% attended the 6 months visit. At follow-up, a colposcopy was performed and a Pap smear taken.

Of patients treated with cryotherapy, 80% attended the 6 weeks follow-up and 64% the six months follow-up.

Results on treatment outcome will be available when more follow-up data become available.

**Discussion**

Whereas we succeeded in decentralising diagnostic and treatment procedures to the district level, we were not successful in installing the colposcopy clinic at the district hospital. A number of factors might explain the lack of interest at that level. The first is that the public health sector is still suffering from a hierarchical structure, whereby local directors are not used to start new services themselves. Yet, it was somehow surprising that the gynaecologists did not show major interest in running a colposcopy clinic in the hospital. As management of cervical dysplasia is not integrated into the curriculum of gynaecologists, we had expected that most of them would be willing to receive a postgraduate training and to put it in practice. But they assigned only one (of the 5 gynaecologists present) for training. This doctor, who was also vice-director of the hospital, was finally not in a position to run the clinic, because of other duties.

All other gynaecologists had a private practice in the city and spent less than 50% of their time in the hospital. Hospital services being free of charge, or at low cost, no major revenues were to be expected from integrating a diagnostic and treatment
clinic at that level. Gynaecologists seemed more interested in managing patients with dysplasia in their private practices, even if none of them had the necessary equipment for diagnosis and outpatient treatment. We have anecdotic evidence of two young patients diagnosed with a LSIL at our clinic, and who were treated with hysterectomy by one of the private practitioners.

Integrating the diagnostic services into a NGO clinic rather than a public hospital did not affect the acceptability as shown by the high attendance rate (more than 80%). Geographical accessibility did neither seem a major problem, as similar attendance rates were observed for women living in different geographical areas. Only 10% of patients did not return for treatment after diagnosis. As mentioned before, this high compliance rate might have been influenced by the organisation of the programme, including the personal invitation of women of the target population and the provision of diagnosis and treatment free of charge and without previous appointment.

An average time to diagnosis of one month, and for treatment of two months, is also highly acceptable compared to the average waiting times at the Bertha Calderon Hospital.

The clinic was able to provide adequate treatment to nearly all patients with confirmed LSIL and to 80% of patients with HSIL. Treating LSIL might be controversial, as LSIL do have a high spontaneous remission rate. For those who progress, the time for progression is sufficiently long to allow for an adequate follow-up. This avoids overtreatment, as only those patients who persist or progress should be treated. The problem with this approach is that only highly compliant and reliable patients can be considered for follow-up. In our setting, we preferred to treat all patients with LSIL. Firstly, because our programme targeted older women. It has been shown that in women aged 34 and more, new lesions are less likely to regress than in younger ones. Secondly, because we were unsure about the compliance of women in attending follow up visits if not treated. Our data show that after treatment, only two thirds attended the six months follow-up visit.

The follow-up rate of patients treated for HSIL was substantially higher. This can be due to the treatment procedure (as LEEP is more drastically, the disease could be perceived as more seriously) or to a higher insistence of the service provider.

There is surely a need to follow up patients with HSIL after treatment, and especially those with incomplete excision. These women have a significantly higher risk of recurrent CIN (RR >8) and the time to recurrence is significantly shorter.

In our clinic, 17% of histology specimen had positive margins. This proportion, as well as the complication rates are similar to published data, indicating an acceptable quality of the surgery provided.

This classic approach of screening, diagnosis and treatment has a number of inconveniences. The first is that, even with a high acceptability rate, a number of patients do not attend the referral level. Through informal interviews with nurses we know that a number of those patients had a repeat Pap smear, others went to private practitioners, and at least two patients were treated in neighbouring Costa Rica. Yet, a number of patients were lost to follow up and did not receive adequate management. To avoid lost to follow up between screening, diagnosis and treatment, a single-visit approach with VIA and immediate cryotherapy has been
proposed. This has been shown to be safe, acceptable and feasible in rural Thailand\textsuperscript{14}. The disadvantage of this method is considerable overtreatment as well as the lack of diagnosis, whereby invasive disease could be overlooked at. The efficiency of this method should still be established, and it is unlikely that it would be acceptable in Nicaragua, where professional health staff exists and pathology laboratories are already in place.

Lost-to-follow up after diagnosis could be avoided by a ‘see and treat’ policy at the colposcopy clinic. Patients having a positive colposcopy result could be immediately treated. This approach is now standard in a number of countries, at least for patients with colposcopic appearances of CIN3 lesions\textsuperscript{15}. The treatment with LEEP of suspected CIN3 on colposcopy minimizes overtreatment and reduces workload\textsuperscript{16}. In our setting, the gynaecologist felt it difficult to put this in practice within the current set-up. As most patients were from rural areas, patients attending for LEEP were seen before the onset of the consultation. This gave the patients time to rest before travelling home, which could take several hours. Only in a few cases the ‘see and test’ approach was implemented.

A major issue related to integrating patient management within a NGO clinic is the cost. Until now, services have been provided free of charge. As a high number of colposcopies were performed for research objectives, it was decided not to charge for any of the diagnostic or treatment procedures. To make the service sustainable, there will surely be a need to introduce a user’s fee. Fees of existing services in other NGO clinics and in the Bertha Calderon Hospital could be used as guideline. Through the introduction of a waiver’s system, financial barriers can be avoided. NGOs are very well placed for this, and do have experience with similar systems in other programmes.

\section*{Conclusions}

Our study showed that it is perfectly feasible to decentralise outpatient management of cervical dysplasia to district level. We did not succeed in integrating these services into the public district hospital, but the provision of services in a NGO clinic showed to be a suitable alternative. The services were highly acceptable and accessible as shown by the high attendance and follow-up rate of patients. The quality of treatment provided was conform to international standards. The clinic could be better organised in order to allow for a see-and-treat approach whereby the number of visits could be limited. There is also a need to start thinking of mechanisms to enhance sustainability.
Reference list

III-6.
INTEGRATION OF CERVICAL SCREENING IN FAMILY PLANNING CLINICS
Abstract

Objective
To assess the suitability of cervical cancer screening in family planning (FP) clinics and the relevance for women’s health.

Methods: A survey was done on clients visiting the clinics of the Family Planning Association of Kenya (FPAK). Client characteristics, age, screening status and Pap smear results were registered. In-depth interviews were held with a limited number of staff and clients.

Results
In 1999, 38 052 clients visited FPAK clinics, 43.5% were younger than 30 years old. More than 10 000 cervical smears were taken. A total of 4.5% of the smears were abnormal, including 1.5% high-grade squamous intraepithelial lesions (HSIL) and 0.2% invasive cancers. The clinics were well prepared to provide high quality screening services. Patients and staff had a positive view on screening.

Conclusions
Providing cervical cancer screening in FP clinics is beneficial for the clients but is unlikely to have an impact on the epidemiology of cervical cancer morbidity as FP services reach only a small percentage of the women who are most at risk. Measures to reach more and older women could assure a larger impact.

Introduction
Cervical cancer is responsible for more than 234 000 deaths per year. Its prevention remains an issue in low resource settings1. Screening programs resulted in a dramatic decrease of cervical cancer morbidity and mortality in Western countries2. Most developing countries have not introduced cervical screening programs, because of limited resources and competing health priorities. Where these programs do exist, problems have been reported with coverage, logistics, maintenance of equipment, training and follow-up3.

In high-risk sub-Saharan African countries, screening for cervical cancer is not done in a routine way, although it can be provided on demand in certain settings4. In Kenya, where the incidence of cervical cancer is estimated at 45/100 000, only 6% of women presenting with invasive cancer at Kenyatta National Hospital have a history of previous screening5. In this country, cervical cancer screening is mainly offered through family planning (FP) clinics. With this assessment, we found out...
how suitable FP clinics are for providing screening and what the relevance is of this screening for women’s health and cervical cancer morbidity.

Methodology

The assessment was done in clinics of the Family Planning Association of Kenya (FPAK). Data were collected from November 1999 until February 2000. Information on the clinics, the organization of the screening services, the perceived problems, the attitudes towards screening and the influence of the screening program on the workload of the staff was obtained through interviews with key persons at FPAK headquarters, including the Program Manager, the lab technologist in charge and the Senior Program Officer for service delivery. Data on client characteristics were obtained through a review of 791 files. These files were selected through systematic random sampling of women attending seven of the 14 FPAK clinics in 1999. In four of these clinics interviews were conducted. Two urban clinics (Ribeiro, Phoenix) and two rural clinics (Meru and Kisii) were selected. There, four female head nurses, eight other service providers (including two males) and 84 randomly chosen patients were interviewed through exit interviews. Results of Papanicolau (Pap) smears taken in 1999 were retrieved from the central data handling system of FPAK. More detailed data on age, parity and contraceptive use of all women with abnormal Pap smears were collected from records at the cytology department. This was also done for a random sample of 981 of the 10 335 women who had normal smear results during that same year. To assess the age distribution of women from whom a Pap smear was taken, the data from women with a normal smear were weighted with a factor 10.535.

Results

Description of the family planning clinics and clients

FPAK is a local Non Governmental Organization (NGO) with a countrywide network of 14 clinics, distributed over eight urban and six rural communities. FPAK clinics are typical examples of the evolution of family planning clinics from previously being distributors of FP methods to currently having developed into women’s health clinics, providing a wide range of services, including cervical cancer screening. In 1999, 38 052 clients of whom 5135 new clients, visited the FPAK clinics, on average three times a year. The mean age of the clients was 31.0 years (median 30) of age, with respectively 43.5% younger than 30 and 10.5% older than 39 years of age. The main reasons for attending the clinic were family planning services and cervical cancer screening (Table 1).
Table 1. Characteristics of clients attending the family planning clinics

<table>
<thead>
<tr>
<th>Age group (n=791)*</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25</td>
<td>125 (15.8)</td>
</tr>
<tr>
<td>25-29</td>
<td>219 (27.7)</td>
</tr>
<tr>
<td>30-34</td>
<td>239 (30.2)</td>
</tr>
<tr>
<td>35-39</td>
<td>125 (15.8)</td>
</tr>
<tr>
<td>≥ 40</td>
<td>83 (10.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reasons for attending (n=788)*</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FP services</td>
<td>592 (75.2)</td>
</tr>
<tr>
<td>Pap smear</td>
<td>124 (15.7)</td>
</tr>
<tr>
<td>Curative services</td>
<td>7 (0.9)</td>
</tr>
<tr>
<td>Counseling</td>
<td>42 (5.3)</td>
</tr>
<tr>
<td>Antenatal clinic</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Infertility management</td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Other reasons</td>
<td>16 (2.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Current use of Family planning (n=789)*</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>126 (16.0)</td>
</tr>
<tr>
<td>Norplant</td>
<td>75 (9.5)</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>178 (22.8)</td>
</tr>
<tr>
<td>Depo-Provera</td>
<td>253 (32.1)</td>
</tr>
<tr>
<td>Intrauterine Device</td>
<td>97 (12.3)</td>
</tr>
<tr>
<td>Tubal ligation</td>
<td>41 (5.1)</td>
</tr>
<tr>
<td>Vasectomy</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Condoms</td>
<td>10 (1.3)</td>
</tr>
<tr>
<td>Foaming tablets</td>
<td>5 (0.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Professional status (n=82)*</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employed</td>
<td>51 (62.2)</td>
</tr>
<tr>
<td>Housewife</td>
<td>29 (35.4)</td>
</tr>
<tr>
<td>Student</td>
<td>2 (2.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Educational level (n=84)*</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>21 (25.0)</td>
</tr>
<tr>
<td>Secondary</td>
<td>33 (39.3)</td>
</tr>
<tr>
<td>Higher level</td>
<td>30 (35.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Personal monthly income (n=80)*</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>31 (38.7)</td>
</tr>
<tr>
<td>1-5000 KSH</td>
<td>16 (20.0)</td>
</tr>
<tr>
<td>&gt; 5000 KSH</td>
<td>33 (41.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Screening status (n=84)*</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequately screened</td>
<td>42 (50.0)</td>
</tr>
<tr>
<td>Screened &gt; 3 years ago</td>
<td>8 (9.5)</td>
</tr>
<tr>
<td>Never screened</td>
<td>34 (40.5)</td>
</tr>
</tbody>
</table>

* Data obtained through revision of files
* Data obtained through interviews with clients
Organization of the screening services

The policy at FP AK is to perform a Pap smear on a yearly basis on all clients. Screening services are available in all the FP AK clinics. They are all fully equipped and dispose of the necessary supplies to do Pap smears. All smears are sent to the central laboratory in Nairobi, which is at a maximum distance of 500 Km. There they are processed and read by two cyto technologists and one cytopathologist. The transport of slides as well as results is done by courier services, which reach any place in the country within 1 day. All results are stored in a computerized information management system. On average, the clinics receive the results within 2-4 weeks.

All clinics have trained nurses, who take an average of 10 Pap smears a week (range 4-37). Promotion for cervical cancer screening is done through posters in the waiting room, through personal communication of providers to clients, and to some extent by the community-based distributors (CBD) of FP methods in rural and slum areas.

Pap smears are usually not free of charge. Interviewed patients paid on average 200 KSH (range 0-300), depending on the location and the socio-economic level of the patient. This user’s fee, which is considered high by 16.3% of the women, does not cover the total screening cost (e.g. the kits are donated).

When a dysplasia is diagnosed, patients are referred to medical doctors in public or private hospitals. No information is available on patient compliance or on the number of patients actually treated.

Prevalence and characteristics of women with dysplasia

In 1999, 10 830 Pap smears were done and processed, half of them in women of 25-34 years of age and nearly 36% in women younger than 30 years old. The mean age of the women was 32.9 years of age (median 32). The quality of smear taking was good: only 0.38% was reported as unsatisfactory. A total of 4.5% of smears were abnormal: 2.8% showed low-grade squamous intraepithelial lesions (LSIL), 1.5% high-grade squamous intraepithelial lesions (HSIL) and 0.2% invasive cancer. The prevalence rate of HSIL was 0.7% for women younger than 30 years of age, 1.7% for women between 30 and 35 years of age and more than 2% for women 36 years of age or older. The prevalence rate of cervical cancer was 10 times higher in women of 40 years of age or older, compared to the other age groups (Table 2).

<table>
<thead>
<tr>
<th>Age group</th>
<th>Total N (%)</th>
<th>Normal (%)</th>
<th>LSIL (%)</th>
<th>HSIL (%)</th>
<th>Invasive cancer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16-24</td>
<td>1263 (11.7)</td>
<td>1,222 (96.7)</td>
<td>35 (2.8)</td>
<td>5 (0.4)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>25-29</td>
<td>2632 (24.2)</td>
<td>2,539 (96.5)</td>
<td>69 (2.6)</td>
<td>24 (0.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>30-34</td>
<td>2896 (26.7)</td>
<td>2,760 (95.3)</td>
<td>83 (2.9)</td>
<td>50 (1.7)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>35-39</td>
<td>2109 (19.5)</td>
<td>1,991 (94.4)</td>
<td>73 (3.5)</td>
<td>44 (2.1)</td>
<td>1 (0.0)</td>
</tr>
<tr>
<td>&gt;=40</td>
<td>1930 (17.9)</td>
<td>1,823 (94.5)</td>
<td>43 (2.2)</td>
<td>43 (2.2)</td>
<td>21 (1.1)</td>
</tr>
<tr>
<td>Total</td>
<td>10,830 (100)</td>
<td>10,335 (95.5)</td>
<td>303 (2.8)</td>
<td>166 (1.5)</td>
<td>26 (0.2)</td>
</tr>
</tbody>
</table>

a LSIL: low-grade squamous intraepithelial lesion; b HSIL: high-grade squamous intraepithelial lesion

136
Women with HSIL and invasive cancer were significantly older and had significantly more children than women with normal Pap results, but the age and parity of women with LSIL did not differ from women with normal Pap smears (Table 3).

Table 3. Age and parity of women in function of Pap result

<table>
<thead>
<tr>
<th></th>
<th>Mean age</th>
<th>P-valuea</th>
<th>Mean parity</th>
<th>P-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Pap (n=981)</td>
<td>32.82</td>
<td>2.82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LSIL (n=303)</td>
<td>32.98</td>
<td>0.762</td>
<td>2.83</td>
<td>0.921</td>
</tr>
<tr>
<td>HSIL (n=166)</td>
<td>36.18</td>
<td>&lt;0.0001</td>
<td>3.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Invasive cancer (n=26)</td>
<td>51.73</td>
<td>&lt;0.0001</td>
<td>6.04</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Note: Pap: Papanicolaou smear; LSIL: low-grade squamous intraepithelial lesion, HSIL: high-grade squamous intraepithelial lesion

a Compared to normal Pap smears

Screening status and barriers to screening

All interviewed nurses declared to promote annual Pap smears to all their clients, independent of the age or screening history of the woman. Fifty percent of the interviewed patients declared not to have been screened in the last 3 years. Women of 30 years of age and older were screened significantly more than women younger than 30 years of age; 36/48 (75%) and 14/36 (38.9%) respectively (P = 0.01).

Of the women ever screened, 96% of them had their Pap test done in a FPAK clinic. The main reasons mentioned for this choice were quality of service delivery and comprehensive approach.

Service providers considered lack of awareness and knowledge, as the main barrier to screening. This was confirmed by the clients’ interviews. Sixteen out of 34 (47%) women mentioned lack of awareness as the reason for not being screened, 10 (23.5%) implied negligence, 4 (11.8%) had economic reasons and the others said absence of medical problems and fear of the test result motivated their conduct.

Twenty four out of 47 (51.1%) women with an income of ≤ 5000 KSH had never been screened compared with eight of 33 (24.2%) of those with an income of 5000 KSH and more (OR=3.26, 95% CI 1.22-8.69). After adjusting for age, educational status and employment, low income remained a risk factor for absence of screening, (AOR 2.82; 95% CI 1.02-7.81).
Discussion

From a programmatic point of view, offering cervical cancer screening in MCH/FP services seems to be a waste of resources, as older women, most at risk for cervical cancer, are poorly covered by these services. Some people argue that in developing countries, cervical cancer occurs at an earlier age, so screening should start earlier. Two studies on invasive cervical cancer in Kenya showed the mean age of the patients to be 42 and 47 years of age, respectively. In our study population, the mean age of invasive disease is nearly 52 years of age, but HSIL present at a mean age of 36 years of age. The timely detection and treatment of this precursor stage should be the aim of all screening programs. The maximum age-related benefit is obtained by starting the screening at the age of 35. The mean age of the FPAK clients was 31 and more than half of the clients were 30 years of age or older, thus being a suitable population for cervical cancer screening. Under the age of 25, only 0.4% of FP attendees were diagnosed with HSIL, but the prevalence was four to five times higher for women aged 30 and more. This supports the thesis that screening young women should be discouraged. Screening services can be made more efficient by starting screening at 30 years, and by increasing the screening interval to 3 years, as the additional benefit gained by screening more frequently is very small.

The integration of cervical cancer screening services within FP clinics is in line with the concept of reproductive health services as endorsed by the Cairo Conference of 1994. During the last decades, family planning clinics worldwide have broadened the scope of their services, evolving from “providers of contraceptives” to “women’s health clinics”, providing a broad range of preventive and curative services. FP clinics have access to a population of sexually active women. They have the necessary infrastructure, trained personnel and the logistics to provide services of good quality. As gynecological examinations are routine clinical practice in FP clinics, the screening of women at risk for cervical cancer is an opportunity not to be missed. Our assessment of FPAK outlines additional advantages of these clinics such as their good reputation, their geographical accessibility, their equipped laboratories, and their highly motivated staff.

An additional element advocating for the screening of FP attendees is the suggested association between oral contraceptives and cervical cancer. A pooled analysis of eight case-control studies showed that the risk of cervical cancer increased threefold in HPV positive women who had been using oral contraceptives for 5 years or longer. Amongst the FPAK clients, 22.6% used oral contraceptives. In our assessment, we did not gather information about the duration of use, but the regular screening of all FP attendees aged 30 and older guarantees that the group of long-term users is surely not missed.

Linking cervical cancer screening to contraceptive use does, however, contain risks and limitations. The first is that potential FP users might be deterred from using contraceptives. This could particularly be the case if a pelvic examination is required prior to provision of hormonal contraception. The reinforcement of the perception that hormonal contraceptive methods are dangerous could further discourage women from using them. As a result, the access to highly effective contraceptive methods might be reduced and women’s overall health risks increased. A group of women who might adopt this approach are women served by
CBD, as they do not attend the clinics regularly. The CBD network can, however, also be used as a very efficient means of promoting cervical cancer awareness and screening in the communities. They are excellent mediators for health promotion and have access to those women who do not easily attend reproductive health services, especially older women and women from lower socio-economic classes.

Another risk is that cervical cancer is perceived as related to reproduction and therefore that screening activities stop after menopause sets in. Both service providers and clinic attendees would then focus on over-screening young and sexually active women, while the older, most at risk population is not reached. This does not seem the case in FPAK clinics, as older women were significantly more screened than younger ones. The age distribution of the clients does, however, indicate that women do not attend FP clinics regularly after menopause. One could overcome this problem by reinforcing the focus of the educational messages in the clinics on screening at older age. The organization of well women’s consultations, where women can attend for whatever reproductive health related issue, is an additional option.

A third limitation is related to the nature of family planning clinics in general. As NGO clinics, their services have to be sustainable, and user’s fees have proven an important barrier for the poorest population. Our data show that the women attending FPAK clinics are not representative for the overall population of Kenya. In this group of middle-class, high-educated women, economic problems were still mentioned as the main barrier to screening by one out of six women who had not been screened in the past. It is difficult to strike the balance between safeguarding quality and financial accessibility. Here again, outreach activities can be a means of reaching underserved populations, who could be exempted of user’s fees.

In conclusion, our assessment has shown that cervical cancer screening based on Pap smear tests can be perfectly integrated in FP clinics. This impacts positively on clients’ health as women with precancerous lesions are treated timely and others are reassured. It is unlikely, however, that there is an epidemiological impact on morbidity due to cervical cancer as FP services reach only a small percentage of the women most at risk. The impact could be improved by organizing information and education sessions on cervical cancer, by providing screening services as part of the community outreach activities and by taking initiatives to reduce financial barriers. A more rational organization of screening, concentrating on women of 30 years of age and older and on a tri-annual basis can further reduce the costs.
Reference list


IV.
DISCUSSION
1. Contribution of this work to the field

Cervical cancer deserves special attention in national cancer control programmes, particularly in developing countries. In these countries, it is the leading cause of cancer mortality in women, and the mortality rate is twice as high as in developed countries. Moreover, it is one of the few cancers that can be prevented through early detection and treatment of the precursor stages.

Exfoliated cytology, introduced by Papanicolau in the forties, is still the most widespread screening test. Screening programmes based on cytology have proven to be effective in several countries. The interest for new screening tests results from a double concern. In developed countries, there is concern about high false negative rates and medico-legal liability. Developing countries face logistic problems and lack of resources to ensure high-quality cytology-based screening programmes. This led to the development of a range of new screening tests. Moreover, the identification of human papillomavirus (HPV) as an etiological factor, has provided more insight in the pathogenesis of the disease. Whereas HPV testing as a screening tool is limited by the high prevalence of transient infections, progress is being made in the development of vaccines, which might become available within the next decade. As currently developed vaccines are only useful for women who are not yet infected, cervical cancer screening will still be needed for one generation, at least.

The effectiveness of a cervical cancer screening programme depends on the attendance rate and pattern, the sensitivity of the test used, and the correct management of detected lesions. In developing countries, low screening coverage, poor reliability of cytology and lack of access to diagnostic and treatment services have been reported as important problems.

The work presented in this thesis contributes to a better understanding of factors jeopardizing the implementation of successful screening programmes in resource poor settings. It also describes and assesses a number of strategies to improve the feasibility, acceptability and effectiveness of cervical cancer control programmes. As the research was limited to two well-defined geographical areas, the problems discussed and the strategies proposed are not necessarily valid for all resource poor countries. Given the specificities of each country (and within each country, of different areas, e.g. urban versus rural), cervical cancer screening programmes, adapted to the local situation, have to be designed at national level. We hope that the results of our studies will contribute to the design of those programmes, providing evidence on the effectiveness of interventions when applied in a particular field.

First, we assessed the prevalence of cervical cancer precursors in women attending public health centres in order to document the magnitude of the problem in Nicaragua. Baseline-information for the design of a community-based intervention programme aiming at increasing the cervical cancer screening coverage of women most at risk was obtained through an evaluation of the current screening programme and an assessment of the screening status and the determinants for screening of the population in Rivas district, Nicaragua. The results showed that the existing cervical cancer screening programme, based on opportunistic screening of women attending health centres, had a low coverage and low detection rate of
In the newly implemented intervention programme, involvement of volunteer community health promoters was found to be a successful strategy to increase the uptake of the screening programme. Clients attended the public screening centres, but preferred NGO clinics and on-site clinics when offered as an alternative. Efforts to improve the quality of the cytology-based programme were effective, but the detection rate of the cytology remained low. Visual inspection with acetic acid (VIA), an alternative screening test for cervical cancer, assessed in both research and field conditions, showed to be highly sensitive but at the expense of low specificity and high referral rate. Decentralisation of diagnosis and treatment to district level resulted in high attendance and follow-up rates, but implementation within the public health sector was not successful. Finally, some thought was given to other strategies for service provision, particularly to the integration of screening services in family planning clinics.

In the light of the above, we want to discuss more in-depth following issues:

1. Relevance of introducing cervical cancer screening programmes in resource poor settings
2. Strategies to reach high-risk groups for screening
3. Selection of a screening test in resource poor settings
4. Options for service delivery

2. Relevance of cervical cancer screening programmes in low resource settings

As highlighted above, cervical cancer, being the leading cause of cancer mortality in women of developing countries, deserves special attention in the national cancer control programmes of these countries. In western countries, it has been shown that programmes of early detection and treatment of cervical cancer precursors are effective in reducing cervical cancer incidence and mortality. Until effective HPV vaccines become widely available, screening will remain a necessary means to control cervical cancer.

Yet, the relevance of setting up cervical cancer screening programmes has to be weighted against the need of responding to other competing health problems. Even if cervical cancer is one of the most prevalent cancers, especially in developing countries, it remains a rare disease. Worldwide, only 1% of total mortality in women is caused by cervical cancer. In Africa, HIV/AIDS causes 35 times more deaths, malaria and respiratory infections 15 times more and measles 7 times more. When health resources are scarce, governments may decide not to invest in cervical cancer prevention. In countries where treatment facilities for advanced disease are not available, introducing cervical cancer screening implies serious investments, as services for screening and for treatment have to be put in place. In countries with high prevalence of disease, screening can be cost-effective as shown by a study carried out in South Africa. Assuming a 2 percent CIN prevalence and a 50 percent CIN progression rate, it was calculated that a programme approach that did not attempt to screen women, but focused on treating women with symptomatic,
invasive disease, would cost over 80% more than a screening programme using public-sector providers. When a new screening programme is set up, more disease will be detected and the cost-effectiveness will be higher. In countries where cervical cancer prevalence is low, and women are regularly screened, the situation might be quite different. A study carried out in the Netherlands showed that the potential savings from a mass screening programme (resulting in a reduction in both advanced disease and mortality) would compensate only 10% of the costs of screening.

Mainly due to lack of resources, cervical cancer screening programmes are rare in developing countries. In the few developing countries where a programme has been introduced, a substantial reduction in the incidence and mortality from cervical cancer has yet to be observed. In these countries, ongoing programmes, based on western models, lack effectiveness as previously discussed.

In countries were no organized screening programmes exist, these programmes should only be started when resources are available to guarantee service delivery for screening and treatment, at least of pre-invasive disease. It has to be taken into account that all strategies of detection and treatment, even the single visit approach with immediate treatment of all VIA positive women, need considerable resources. When no resources are made available for organized screening programmes, services can always be made available through private and/or NGO clinics (e.g. in family planning clinics). As shown in our results however, this might be beneficial for the women using the services, but will have little impact on cervical cancer prevalence and mortality in the country, unless special efforts are made to reach high coverage, particularly in elder women. From a reproductive health perspective though, not providing cervical cancer screening to women attending women’s health clinics (e.g. gynaecology consultation, family planning services) would be a missed opportunity. In these clinics, screening should be provided as an essential element of the package of reproductive health services offered to the client in a comprehensive approach. In order to improve the cost-effectiveness and to avoid overscreening and overtreatment of low risk, mainly young, women, the screening should be provided following previously developed guidelines.

In countries where ineffective screening programmes exist, the impact can be increased by a number of simple measures to improve coverage, quality of screening and access to treatment. This can be done by re-orientation of the available programme resources towards less frequent screening of the population most at risk, introduction of supervision mechanisms and decentralisation of treatment.

3. Strategies to reach high-risk groups for screening

Whereas several risk factors for cervical cancer have been identified, many of these factors (e.g. multiple sexual partners, early onset of sexual activity) are of little value in selecting women for screening. The most important risk factor for determining the priority group for screening is age. As invasive cervical cancer is rare in young women, and difficult to prevent in this age-group, it is widely accepted that screening programmes should not start before the age of 30. Women never screened are at higher risk, and it is known that the relative protection of a
negative screening test decreases strongly after 3-5 years. Not surprisingly, organized screening programmes with a call- and recall system have shown to be the most effective in reducing cervical cancer prevalence. These programmes (all in developed countries) reach a high coverage of the target population. In developing countries, these programmes are hardly realizable. In our study, we involved community health workers in inviting women of their neighbourhood to participate in the programme. Our results showed that this approach was very successful for women who had previously expressed willingness to be screened in the future, but limited for other women. This is worrisome, as most of these women belonged to the group who had never been screened before. Health promotion and personal invitation as such, were not sufficient to ensure screening uptake: only half of the women invited finally participated in the screening programme. Moreover, the effect was limited in time, and the involvement of health promoters required substantial training and supervision. Results were considerably better when screening opportunities were available outside the public sector. This indicates the need to organize screening in coordination with all stakeholders: the women themselves, public health sector, private practitioners and NGOs as well as the people at the interface between the health sector and the communities (e.g. health promoters). The organization of programmes as a collaborative effort, will also have a positive impact on the sustainability. NGOs are well placed to maintain networks of community health workers. To compensate for the cost of the screening test, small user’s fees can be introduced. This cost can be very low if visual inspection is used as a test. Screening should ideally be provided on a regular basis, but even the provision of a single test in a women’s lifetime, appropriately timed, can reduce the incidence of invasive cervical cancer.

The results indicate that health promotion and a pro-active approach to reach women of a defined target population are necessary, but are not sufficient to improve the coverage of a screening programme. They have to be complemented by measures to improve service delivery and to provide services that are adapted to the needs of the population.

4. Selection of a screening test in resource-poor settings

4.1 Cytology

There is growing evidence that cytology is not an ideal test to be used in a resource poor setting. The low sensitivity of the test and the logistic constraints related to the implementation of cytology-based programmes hamper the effectiveness. We showed that poor quality of cytology remains a major issue, even with training and supervision mechanisms. Yet, in settings where cytology-based programmes are in place, efforts to improve the quality should continue. The question remains whether other screening tests are a valuable alternative. We should be careful in promoting new approaches that increase sensitivity if this is at the expense of specificity.

* As mentioned in the introduction, the concept of relative protection of a negative test is commonly used to indicate the low risk of having and/or developing disease when a screening test is negative.
4.2 Visual inspection with acetic acid

The most promising screening test for use in resource-poor settings is VIA, as the test has a low cost and is easy to perform\textsuperscript{12}. Our results confirm previous studies showing a high sensitivity, but relatively low specificity of this test. We also documented a number of operational problems related to the referral of a high number of false positives to diagnostic services. A strategy based on VIA at the screen level, followed by colposcopy/biopsy at the referral level seems difficult to realize in resource poor settings. After all, most of the gains at screening level would be lost due to the cost and logistical problems related to attending to a high number of healthy patients at the referral level.

Another major issue in assessing VIA as a screening tool is that knowledge on the effectiveness when used in screening programmes is still lacking. For cytology-based programmes, it is known that the relative protection and the effect on cervical cancer incidence increase when the test is repeated at regular intervals (in most countries established at 3-5 years)\textsuperscript{6}. As disease progression is slow, repeated cytology is effective in the prevention of invasive cervical cancer, in spite of the poor sensitivity of a single test. Yet, no information is available on VIA test results when the test is repeated at regular intervals. As VIA has a poor specificity, it would be particularly interesting to examine whether the specificity can be improved by repeating the test.

4.3 Combining VIA with cytology

There seem to be two interesting applications for VIA in resource poor settings. The first is the use of VIA as a primary screening test, followed by conventional cytology when the primary test is positive. Published data have shown that this results in a loss of sensitivity (from 75% to 58%), but also in a eightfold reduction of the number of false positives needing further management\textsuperscript{13}. We expect the sensitivity of this approach to increase when the tests are repeated at regular intervals. Moreover, the quality of the Pap smear could improve, as fewer tests would have to be done, and a higher number of true positives could be presented to the cytologists. This strategy would be particularly interesting in sites where poor performing cytology programmes exist.

4.4 Combining VIA with immediate treatment

The second is the use in a single-visit approach combining VIA and immediate cryotherapy of all screen positives. Mathematical models show that this strategy, used as a single lifetime screen at age 35 in a South African previously unscreened population, is one of the most cost-effective, compared to absence of screening\textsuperscript{14}. A demonstration-intervention project in rural Thailand further illustrates the safety, acceptability and feasibility of this approach\textsuperscript{7}. Further assessment of the effectiveness is necessary before this strategy can be advocated for wide-scale use. Moreover, the feasibility of the approach in other settings needs to be assessed. The overall VIA test-positive rate in the Thailand study was 13.3%\textsuperscript{7}. This is only one third of the rate in our study implemented in Nicaragua\textsuperscript{15}. Moreover, logistic problems related to making cryotherapy available at screen level could be a major issue.
4.5 HPV as a primary screening tool

The use of HPV as a primary screening tool is still under discussion, even in western countries. Yet there is growing evidence that HPV should be used in conjunction with cytology for women > 30 years\textsuperscript{16-18}. Strategies based on HPV screening could be cost-effective compared to other screening tools\textsuperscript{19;20}. Self-collection of samples for HPV testing seems attractive\textsuperscript{21}, but the implementation of HPV-based screening programmes in resource-poor settings is limited. The test is expensive and needs adequate laboratory support, which is not available in many settings. Research is undergoing on the development of low-cost rapid HPV tests for field-testing (by the Programme for Appropriate Technology in Health, PATH; personal communication). If such tests could be developed, this could be an alternative test for primary screening, at least for women aged 30 and older, where transient HPV infections are less prevalent\textsuperscript{18}.

5. Options for service delivery

When a specific disease control programme exists, there are several options for service delivery. An important decision to be made is whether implementation belongs in a vertical setting or if the health activities of that programme will be integrated within a horizontal, multifunctional health service\textsuperscript{22}. Our results show that there are several arguments in favour of integrating cervical cancer screening in basic health services.

In our first study, we demonstrated that many women (including older), attended the primary health care clinics on a regular basis. Hence, not offering screening services in these clinics would be a missed opportunity\textsuperscript{23}. The population-based survey further demonstrated that geographical and financial accessibility were the main reasons for using public primary health care centres in Nicaragua. The same survey revealed that people were concerned about the quality of these services, and that up to one third of women screened in the past had the test performed in private clinics\textsuperscript{24}. Our intervention, partially based on integration of improved screening services in primary health care centres, had variable results. In nearly all the larger health centres, health staff was keen to provide screening, and quality screening was provided. In the smaller rural health posts, health staff did not show interest in providing screening, despite having attended the training sessions. Lack of motivation seemed the major reason for this, as the workload at that level is low. This might indicate that integrating cervical cancer screening up to the lowest level of health care (here the health posts), is not the best option. To provide quality services, a minimum of training, supervision, experience (independent of the screening test used) and confidentiality is needed. Larger health structures might be better placed to provide this kind of services. Populations living in remote areas could be reached through site visits to the communities. To optimise the attendance rate, health promoters or village health workers can be involved in inviting the target population.

Whereas opportunistic or voluntary screening is mainly provided through private services, organised programmes could also make use of these services. Co-operation between public and private sector is a must in a systemic view of health service provision and in avoiding expensive and useless duplications\textsuperscript{24}. Moreover, where
several service delivery points exist, clients have the possibility to be screened in the setting best adapted to their individual needs. Collection of information in these clinics would allow monitoring of the real coverage of the population.

Within both private and public services, cervical cancer screening can be provided as an isolated service, but preferentially integrated within comprehensive reproductive health services. Beyond the epidemiological perspective of decreasing morbidity and mortality, screening is then as a measure to improve the reproductive health of the women seeking health care.

In most settings, specialized clinics seem the most appropriate for the management and follow-up of cervical dysplasia, which can be provided on an outpatient basis at district level.

A strategy based on see-and-treat without diagnosis could be totally implemented at primary care level, limiting the need for referral to suspected cases of invasive disease\(^7\). Yet local research groups should check this strategy for its effectiveness and repeatability in realistic service delivery settings before implementing it in the field.

At all levels of care, adequate referral mechanisms have to be set up for patients with invasive disease. Treatment facilities have to be available and accessible, including access to surgery, radiotherapy and palliative care\(^{25}\).

### 6. Overall conclusions

#### 6.1 Conclusions from the current work

Cervical cancer screening programmes are relevant in low resource settings, but means have to be made available to ensure an effective programme. In addition to the development of guidelines at national level and measures to reach a high coverage of the population most at risk, screening, diagnosis and treatment facilities have to be foreseen, as well as adequate mechanisms for supervision and quality control. The choice of screening test, screening strategy and service delivery will depend on the local situation and existing health structures. Whatever option is chosen, it is of crucial importance that mechanisms are set up to guarantee high quality of service delivery. This includes promotion of the programme and provision of adequate information to the women. It also involves training, supervision and quality control to ensure reliable test results. Women need to be informed about their test results, and should have access to diagnostic and treatment facilities. Referral mechanisms should be in place to ensure an adequate follow-up of women who need care at a higher level.

An organized programme, where screening is provided by both public and private services, set within the health structures and complemented by outreach activities, seems the best option. Treatment of pre-invasive disease can be decentralized to district level; whereas specialized services to treat advanced cancer should be available at national level.

If the resources or the political willingness to set up a programme fulfilling all the above criteria are not present, it might be wiser to invest in the solution of other health problems. In all countries however, limited services can be made available to
women attending women’s health clinics, if quality of screening and access to treatment can be guaranteed. Even when screening is provided on an opportunistic basis, guidelines have to be developed and to be used in order to optimise the use of resources and to maximize the benefit for the women.

6.2 Future prospects

At international level, interest in HPV-related research is growing. One of the major questions to be addressed is why HPV, a commonly sexually transmitted agent, gives rise to cervical cancer in only a few women. Studies on local immunity and the interaction between host and infectious agent are trying to provide more insight into the pathogenesis of the infection. At the same time, research on the development and introduction of HPV vaccines is now a priority. Biomedical research in this field is complemented by epidemiological studies on HPV prevalence and types in different populations and subgroups, and by operational research on how to implement the vaccine programme.

The search for alternative screening tests and/or improvement of existing tests will continue to be important in the next decade. So far, no single test has been identified with a high sensitivity, high specificity and low cost that can be used easily in resource-poor settings.

In Kenya, operational research on the implementation of a screening programme is still ongoing in Mombasa. Research on the interaction between HPV and HIV and treatment modalities for HIV-positive patients deserves special attention.

In Nicaragua, priority will now be given to the further development of the demonstration-intervention project in Rivas, and to the dissemination of the results at national level. Special attention will be given to further analysis of existing data. Based on our results, recommendations will be formulated to the Ministry of Health for greater cost-effectiveness, better quality and higher coverage of the existing programme. At the UNAN-Managua, efforts are ongoing to include the diagnosis and management of cervical pre-cancer in the curriculum of gynaecologists, and to give more attention to the topic of cervical cancer in the curriculum of nurses and medical doctors.

Worldwide, programme managers and service providers would benefit from clear guidelines on the screening and management of cervical (pre)-cancer. These guidelines should be evidence-based and include recommendations for the different levels of care. During the coming months, we will assist the World Health Organization in the elaboration of guidelines, making use of the literature review performed during the last years and of the evidence collected by several research projects, including our field data from Nicaragua and Kenya.
7. Reference list

15. Claes, P., De Vuyst, H., Gonzalez, C., Garcia, A., Bello, RE., and Temmerman, M. Performance of the acetic acid test when used in field conditions as a screening test for cervical cancer. Trop Med Int Health 2003:5-941;
V. EXECUTIVE SUMMARY
1. Context and objectives

1.1 Problem definition

Worldwide, cervical cancer is the second most prevalent cancer in women. Of the almost 500,000 new cases a year, 80% occur in developing countries. Human papillomaviruses (HPV), especially the high-risk types, are the central causal factor. Most HPV infections are transient, but a minority persist, increasing the risk of development of squamous intra-epithelial lesions (SIL) of the cervix. Cervical cancer is thought to progress as a continuum from low-grade lesions (LSIL) through high-grade lesions (HSIL) to invasive cancer, but at all stages, regression to normal is possible. The long transit time to invasive cancer and the possibility of treating precursor stages effectively provide an opportunity for screening. Cytology-based screening programmes have been shown to be effective in several Western countries. In many developing countries however, they are inexistent or inefficiently designed. The most important problems are the poor quality and the low coverage of screening, and the inaccessibility of treatment.

1.2 Objectives of the study

The general objective of our work was to assess the feasibility, acceptability and effectiveness of strategies for cervical cancer screening and management in resource-poor settings, based on evidence from Nicaragua and Kenya. These countries were chosen because of their high prevalence of cervical cancer, and the existing links with partner institutes, which made the research possible.

We were particularly interested in 1) devising strategies that encourage women at risk to attend for screening, 2) defining which screening tests are suitable in field conditions and how the quality can be improved, 3) assessing the effect of decentralising treatment of precancerous lesions and 4) assessing alternative strategies for service delivery.

1.3 Data

In Nicaragua, results were analysed from an action-research project on the integration of cervical cancer screening in primary health care, set up in one district (Rivas). In Nairobi, data were collected in family planning clinics.

Prior to the set up of the screening programme in Nicaragua, baseline information was collected in order to adapt the programme to the needs of the population. We were particularly interested in assessing the prevalence and risk factors of cervical cancer in the country, and in analysing problems related to and determinants of cervical cancer screening in the population of Rivas.

2. Results

2.1 Increasing the coverage of screening

The prevalence of cervical neoplasia in Nicaragua was assessed as part of a cross-sectional study on prevalence and risk factors of sexually transmitted infections (STI) in women’s health clinics. A total of 1,185 sexually active women, attending the women’s health clinics in different regions, were interviewed and...
examined for STI, HIV and cervical neoplasia. One out of 13 women attending the clinics had an abnormal Pap smear, with high-risk HPV types in almost 60%. Male promiscuity was associated with HSIL and reported former screening did not show to be protective. The high rate of cervical lesions in women with a screening history underlined the need for proper quality control.

To obtain baseline information on screening status and determinants of cervical cancer screening in Rivas district, a population-based face-to-face interview survey was conducted amongst 1,246 adult women, men and adolescents. Only 41.1% of the surveyed women reported having being screened for cervical cancer in the last three years. Inadequate screening status was correlated with low educational level, exclusive use of public health facilities and lack of knowledge about prevention and symptoms of cervical cancer. Reluctance to be screened in the future was related to lack of knowledge of the disease, inadequate screening status, older age and low educational level. These results showed that the ongoing screening programme, based on opportunistic screening, was not effective in reaching the majority of the population. Complementary activities such as education and information as well as a more pro-active approach to invite women for screening were thought to be necessary to reach the women most at risk.

A strategy to encourage women at risk to attend for screening was further implemented and assessed. Volunteer community promoters were trained to invite all women aged 30 and older in their neighbourhood, who had never been screened or not screened for the past three years (the so-called target population). The intervention was implemented in three of the six geographical different areas of Rivas, Nicaragua. Compared to the non-intervention area, a significant increase in the number of Pap smears was observed in the intervention area (38% versus 23%, p<0.001), and a significant higher proportion of Pap smears was provided to the target population (39% versus 21%, p<0.001). One third of the target population were screened in NGO clinics and 15% through mobile interventions. The results showed that community health workers can be, at least temporarily, successful in improving the coverage of cervical cancer screening. Factors for success include the level of training, supervision and follow-up of the health promoters, and the willingness of the health system to reach the population effectively. Service provision by NGOs is an important help.

2.2 The choice of suitable screening tests

The test performance of visual inspection with acetic acid (VIA) was first looked at in a research setting, as part of a cross-sectional study on the performance of several screening tests for the detection of cervical (pre-)cancer. The study was implemented among family planning attenders in Nairobi, Kenya. The “gold standard” was colposcopy and histology on colposcopy directed biopsies, performed on all women with an abnormal colposcopy. Pap smears were shown to have a sensitivity (to detect HSIL or more) and a specificity of 83.3% (95% CI 71.5-91.7) and 94.6% (95% CI 92.3-96.4) respectively. For VIA this was 73.3% (95% CI 84.6-98.8) and 80.0% (95% CI 76.3-83.3), for high-risk HPV 94.4% (95% CI 84.6-98.8) and 73.9% (95% CI 69.4-78.1), and for cervicography 74.5% (95% CI 59.7-86.1) and 89.9% (95% CI 86.5-92.6). We were particularly interested in the test results of VIA, recently promoted as an alternative screening tool for use in a resource constrained context. The Pap test had a good performance in this research setting, where the swabs were collected by highly qualified personnel and the reading was
done in a cytology training facility. VIA, the cheapest test and the one requiring the least technical support performed adequately compared to the Pap smear.

The performance of VIA in field conditions as a screening test for cervical (pre-) cancer was assessed in Rivas, Nicaragua. A total of 1,076 women were screened concurrently with VIA and Pap smear. Nearly 33% had a positive screening test (4.4% positive on both VIA and Pap, 25.5% positive VIA only and 2.8% abnormal Pap only). All women with either positive test result were referred for colposcopy and a biopsy was performed when indicated. On biopsy, 7.6% had a low-grade intraepithelial lesion, 4.5% a high-grade intraepithelial lesion and 0.5% invasive cancer. Compared to the Pap smear, twice as many HSIL and invasive cancers were detected through VIA. The high detection rate was, however, at the expense of a high rate of false positives: for every extra diagnosis of at least a HSIL, eight extra false positives were referred to the colposcopy clinic. This high false positive rate means an extra burden for the referral level, which has to be taken into account in the organisation of screening programmes using VIA as a screening test.

The improvement in quality of conventional cytology was also looked at in Rivas district, Nicaragua. An assessment of the quality of the cytology, prior to the introduction of our project, showed that health personnel was insufficiently trained in correct sampling and that the quality of the supplies was poor. One cytologist, hosted at the district hospital, was responsible for reading the smears, without supervision or quality control. The overall detection rate for dysplasia was extremely low: less than 0.6% was reported to be abnormal. Training of the cytologist and the health staff responsible for collection of specimen resulted in a more than fourfold increase in the prevalence of abnormal Pap smears (2.8%). Several data supported the argument that this increase was, at least partially, due to an increased detection rate of lesions as a result of improved quality. Even with an improvement in quality, however, the detection rate of Pap smear was still lower than for VIA, as shown above.

### 2.3 Strategies for effective service provision

A descriptive study design was used to assess the effect of decentralising diagnosis and treatment. More than 80% of the patients referred for a positive screen test attended the clinic, in average after 31.3 days (range 0-270). Outpatient treatment was provided to 88% of patients with low-grade lesions (using cryotherapy) and to 80% of patients with high-grade lesions (using LEEP technique), in average 34.5 days after colposcopy. All patients treated with LEEP came for a follow-up visit at two weeks, and more than 80% attended the 6 months visit. In 10%, complications were reported, including bleeding and infection. Patients with invasive disease were referred to the women’s hospital in Managua, for further assessment and treatment. The study showed that it was feasible to decentralise outpatient management of cervical dysplasia to district level. We did not succeed in integrating these services into the public district hospital, as originally planned, but the provision of services in a NGO clinic showed to be a suitable alternative. The services were highly acceptable and accessible as shown by the high attendance and follow-up rate of patients.

The suitability of integrating cervical cancer screening in family planning clinics was assessed in the clinics of the Family Planning Association of Kenya. Study results showed that the clinics were well prepared to provide high quality
screening services and that patients as well as staff had a positive view on screening. Nearly 10,000 Pap smears are taken on an annual basis, 36% in women younger than 36 years old. Of the 4.5% reported as abnormal, 1.5% are HSIL and 0.2% invasive cancers. Provision of cervical cancer screening in family planning clinics seems to be beneficial for the clients, but the impact on the epidemiology of cervical cancer morbidity is expected to be low, as family planning services reach only a small percentage of the women who are most at risk. Measures to reach more and older women could assure a larger impact.

3. Discussion and conclusions

Our results show first that involvement of volunteer community health promoters can be a successful strategy to increase the uptake of a screening programme. Clients attended the public screening centres, but preferred NGO clinics and on-site clinics when offered as an alternative. Secondly, efforts to improve the quality of the cytology-based programme were effective, but the detection rate for precancerous lesions through cytology remained low. Visual inspection with acetic acid, an alternative screening test for cervical cancer, assessed in both research and field conditions, was shown to be highly sensitive but at the expense of low specificity and a high referral rate. Thirdly, decentralisation of diagnosis and treatment to district level resulted in high attendance and follow-up rates, but implementation within the public health sector was not successful. Finally, some thought was given to other strategies for service provision, particularly to the integration of screening services in family planning clinics.

Cervical cancer screening programmes are relevant in low resource settings, but means have to be made available to ensure an effective programme. In addition to the development of guidelines at national level and measures to reach a high coverage of the population most at risk, screening, diagnosis and treatment facilities have to be foreseen, as well as adequate mechanisms for supervision and quality control. The choice of screening test, screening strategy and service delivery will depend on the local situation and existing health structures. An organized programme, where screening is provided by public and private services, within the health structures and complemented by outreach activities, seems the best option. Treatment of pre-invasive disease, can be decentralized to district level, whereas third level care facilities should be available at national level to treat advanced cancer.

If the resources or the political willingness to set up a programme fulfilling all the above criteria are not present, it might be wiser to invest in other health problems. In all countries however, limited services can be made available to women attending women’s health clinics, if high quality of screening and accessibility to treatment can be guaranteed. Even when screening is provided on an opportunistic basis, guidelines have to be developed and to be used in order to optimise the use of resources and to maximize the benefit for the women.
VI.
SAMENVATTING
1. Achtergrond en objectieven

1.1 Definitie van het probleem

Baarmoederhalskanker is de tweede meest prevalentie kanker in vrouwen. Jaarlijks worden er bijna 500.000 nieuwe gevallen geteld, waarvan 80% in ontwikkelingslanden. Humaan papillomavirussen (HPV), vooral de hoog-risico types, zijn de belangrijkste causale factor. De meeste HPV infecties zijn voorbijgaand, maar een minderheid persisteert en is verantwoordelijk voor de ontwikkeling van squameuze intra-epitheliale letsels (SIL) van de baarmoederhals.

De ontwikkeling van baarmoederhalskanker moet gezien worden als een continu proces, beginnend bij laaggradige letsels (LSIL) over hooggradige letsels (HSIL) tot invasief carcinoom. Alle letsels kunnen echter ook regresseren, en deze regessiekans is hoger naarmate het letsel minder sterk gevorderd is. Doordat de ontwikkeling tot carcinoom een traagverlopend proces is en de voorstadia herkend en behandeld kunnen worden, kan baarmoederhalskanker voorkomen worden door vroegtijdige opsporing. Opsporingsprogramma’s, gebaseerd op regelmatige afname van een baarmoederhalsuitstrijkje, zijn effectief gebleken in verschillende Westerse landen. In veel ontwikkelingslanden zijn ze echter niet bestaand of inefficiënt. De belangrijkste problemen bij het organiseren van vroegtijdige opsporing in deze landen zijn de ondermaatse kwaliteit van de gezondheidsvoorzieningen, de lage couverture van de screening en de afwezigheid van toegankelijke behandelingsmethodes.

1.2 Objectieven van de studie

De algemene doelstelling van dit werk is na te gaan welke strategieën voor vroegtijdige opsporing en behandeling van baarmoederhalskanker uitvoerbaar, aanvaardbaar en effectief zijn in ontwikkelingslanden, en dit gebaseerd op data uit Nicaragua en Kenia. Deze landen werden gekozen wegens hun relatief hoge prevalentie van baarmoederhalskanker en de reeds bestaande samenwerking met partnerinstellingen, die dit onderzoek mogelijk maakte.

In het bijzonder willen we nagaan 1) hoe vrouwen met een hoger risico beter bereikt kunnen worden, 2) welke opsporingsmethodes bruikbaar zijn in landen met weinig middelen en hoe de kwaliteit van bestaande testen kan verbeterd worden, 3) of de behandeling van precancereuze letsels gedecentraliseerd kan worden en 4) in welke diensten screening kan aangeboden worden.

1.3 Data

De gegevens van Nicaragua zijn het resultaat van een actie-onderzoeksproject over integratie van opsporing van baarmoederhalskanker in de eerste-lijns gezondheidszorg. Dit programma werd opgezet in één district, namelijk Rivas. Data uit Kenia werden verzameld in centra voor gezinsplanning in Nairobi.

Vóór het screeningsprogramma werd opgezet in Nicaragua, werd baseline informatie verzameld om het programma zo goed mogelijk af te stemmen op de noden van de bevolking. We wilden meer informatie verzamelen over de prevalentie van-, en risicofactoren voor cervixkanker in het land, en weten hoeveel en welke vrouwen reeds gescreeend waren in Rivas.
2. Resultaten

2.1 Deelname aan een opsporingsprogramma

De prevalentie van baarmoederhalsletsel in Nicaragua werd berekend als onderdeel van een cross-sectionele studie over prevalentie en risicofactoren van seksueel overdraagbare aandoeningen (SOA) bij vrouwen die op consultatie kwamen in de vrouwenklinieken. Een totaal van 1.185 seksueel actieve vrouwen werd ondervraagd en onderzocht voor SOA, HIV en cervixdysplasie. Eén op dertien vrouwen had een abnormaal uitstrijkje, en hoog-risico HPV types waren aanwezig in bijna 60% van deze letsels. Mannelijke promiscuïteit bleek een risicofactor voor HSIL. De hoge prevalentie van letsels bij vrouwen die een uitstrijkje hadden laten nemen in het verleden (maar met een negatief test resultaat), wijst op de nood aan kwaliteitsverbetering van de screening.

In Rivas werd verder een bevolkingsstudie georganiseerd om meer gegevens te verkrijgen over de determinanten van screening in deze bevolking. Persoonlijke interviews werden gehouden bij 1.246 volwassen vrouwen, mannen en adolescenten. Van de vrouwen bleek slechts 41,1% een uitstrijkje gehad te hebben in de laatste drie jaar. Lage screeningsstatus was gecorreleerd met laag studieniveau, exclusief gebruik van de publieke gezondheidssector en gebrekkige kennis over preventie en symptomen van baarmoederhalskanker. Uit het onderzoek bleek verder dat 28% van de vrouwen weigerachtig stond tegenover toekomstige screening; dit waren vooral oudere vrouwen, met een lagere scholingsniveau, een gebrekkige kennis omtrent de ziekte en een onvoldoende screening in het verleden.

Deze resultaten toonden dat het bestaande opsporingsprogramma, gebaseerd op vrijwillige (zo genaamde opportunistische) screening, er niet in slaagde de meerderheid van de bevolking te bereiken. Bijkomende activiteiten als vorming en informatie, alsook een meer actieve benadering om vrouwen te overtuigen zich te laten onderzoeken, bleken noodzakelijk om de risicogroepen te bereiken.

Een strategie om vrouwen te motiveren aan een opsporingsprogramma deel te nemen, werd verder uitgevoerd en geëvalueerd. Een groep vrijwillige gezondheidspromotoren werd gevormd en opgeleid. Er werd hen gevraagd alle vrouwen uit hun omgeving van 30 jaar of ouder en nog nooit gescreened of niet onderzocht in de laatste drie jaar, uit te nodigen om aan het programma deel te nemen. De interventie werd uitgevoerd in drie van de zes verschillende geografische deelgebieden van Rivas, om zo de resultaten te kunnen vergelijken. In de gebieden waar de interventie plaats vond, werd een toename van 38% in het aantal uitstrijkjes vastgesteld, in vergelijking met het jaar vóór de interventie. De toename in de controlegebieden was 23%, mogelijks door een spill-over effect. Dit verschil was statistisch significant (p<0,001). In de interventiegebieden werden ook significante meer uitstrijkjes genomen bij vrouwen ouder dan 30 (39% van alle uitstrijkjes tegenover 21% in de controlegebieden, p<0,001). Eén derde van de doelgroep werd gescreean in gezondheidscentra van niet gouvernementele organisaties (NGOs) en 15% via mobiele eenheden. Deze resultaten tonen aan dat vrijwillige gezondheidswerkers een -op zijn minst tijdelijke- bijdrage kunnen leveren om de couverture van een opsporingsprogramma te verbeteren. Hiervoor is wel voldoende vorming, supervisie en opvolging noodzakelijk, en moet er voldoende
wil zijn om de bevolking te bereiken. Dienstverlening via NGOs bleek belangrijk om het aanbod te verhogen.

2.2 Screeningsmethodes

De tweede doelstelling van het onderzoek was vooral gericht op het verbeteren van de screeningsmethode zelf, gezien de logistieke en andere problemen verbonden aan het uitstrijkje volgens Papanicolaou. De waarde van visuele inspectie met azijnzuur (VIA) als alternatieve test voor gebruik in lage loonlanden, werd geëvalueerd via een cross-sectionele studie in ideale testomstandigheden. De resultaten zijn onderdeel van een bredere studie over screeningstests voor de opsporing van baarmoederhalskanker, uitgevoerd in een gezinsplanningskliniek in Nairobi, Kenia. Colposcopie en histologie van colposcopie-geleide biopsies, toegepast op alle vrouwen met een positief colposcopie resultaat, werd hierbij gebruikt als “gouden standaard”.

Voor de detectie van HSIL of meer, had het klassieke uitstrijkje een gevoeligheid van 83,3% (95% CI 71,5-91,7) en een specificiteit van 94,6% (95% CI 92,3-96,4). Voor VIA was dit 73,3% (95% CI 84,6-98,8) en 80,0% (95% CI 76,3-83,3), voor hoogrisico HPV 94,4% (95% CI 84,6-98,8) en 73,9% (95% CI 69,4-78,1) en voor cervicografie 74,5% (95% CI 59,7-86,1) en 89,9% (95% CI 86,5-92,6). De resultaten van de Pap test bleken uitzonderlijk goed in dit onderzoek. Dit was mede te wijten aan de hoge kwaliteit van zowel de afname (die gebeurde door hoog gekwalificeerd personeel) als de lezing (die gebeurde aan de universiteit). De testresultaten van VIA, de goedkoopste test die ook het minst technische ondersteuning vereist, waren bevredigend in vergelijking met de Pap test.

De resultaten van visuele inspectie, gebruikt in operationele omstandigheden, werden verder geanalyseerd in Rivas, Nicaragua.

Een totaal van 1.076 vrouwen werden gelijktijdig gescreend met VIA en Pap uitstrijkje. Bijna 33% had een positieve screening test (4,4% hadden één positieve VIA één een abnormale Pap, 25,5% hadden enkel een positieve VIA en 2,8% enkel een abnormale Pap). Alle vrouwen die minstens één abnormale test hadden werden verwezen voor colposcopie en een biopsie werd uitgevoerd indien aangewezen. De biopsies toonden aan dat 7,6% een LSIL had; 4,5% een HSIL en 0,5% een invasief carcinoom. De visuele inspectie detecteerde tweeëmaal meer HSIL en invasieve carcinomen dan het Pap uitstrijkje. Deze hoge gevoeligheid was echter ten koste van een hoger aantal vals positieve: voor iedere extra diagnose van een HSIL of een invasief carcinoom, werden acht extra vals positieve gevallen doorverwezen naar de colposcopie kliniek. Dit betekent een zware belasting voor het refereerniveau, waarmee rekening moet gehouden worden indien screeningsprogramma’s opgezet worden op basis van visuele inspectie.

In Rivas bekeken we ook of de kwaliteit van de conventionele cytologie kon verbeterd worden. Een evaluatie van de kwaliteit, uitgevoerd bij de aanvang van het programma, leerde dat het gezondheidspersoneel onvoldoende gevormd was in de afnametechniek voor Pap uitstrijkjes en dat de materialen voor afname van slechte kwaliteit waren. Één cytologe, werkzaam in het districtshospitaal, stond in voor de lezing. Ze kreeg hierbij geen supervisie en er was geen kwaliteitscontrole ingebouwd. De detectiegrootte voor dysplasie was dan ook extreem laag: minder dan 0,6% van de uitstrijkjes werd als abnormaal gerapporteerd. Via bijkomende vorming van de cytologe en het gezondheidspersoneel, steeg de prevalentie van
abnormale uitstrijkjes tot 2,8%. Verschillende data ondersteunen het argument dat deze stijging -op zijn minst gedeeltelijk- te wijten was aan een verbeterde kwaliteit van de afname en de lezing. Echter, wanneer we deze resultaten vergelijken met de VIA, blijkt de gevoeligheid van het Pap uitstrijkje nog altijd veel lager, zoals hierboven aangetoond.

2.3 Strategiën voor effectieve dienstverlening

Het derde luik van het onderzoek richt zich op diagnose en behandeling. Een descriptieve studie werd uitgevoerd om het effect van de decentralisatie van diagnose en behandeling te meten. De resultaten tonen aan dat meer dan 80% van de patiënten die gerefereerd werden voor een positieve opsporingstest, daadwerkelijk naar de colposcopie kliniek kwamen, gemiddeld na 31,3 dagen (0 - 270). Acht en tachtig procent van de patiënten met een LSIL werden ambulant behandeld (met cryotherapie), alsook 80% van de patiënten met HSIL (met de LEEP techniek), gemiddeld 34,5 dagen na de colposcopie.Alle patiënten die een LEEP kregen kwamen na 2 weken op controle, en meer dan 80% ook na 6 maand. In 10% waren er verwikkelingen, waaronder bloeding en infectie. Vrouwen met invasief carcinoom werden verwezen naar de vrouwenkliniek in Managua voor verdere evaluatie en behandeling. Onze studieresultaten tonen aan dat het mogelijk is om patiënten met cervicale dysplasie ambulant te behandelen op districtsniveau. We slaagden er echter niet in deze diensten te integreren in het openbaar ziekenhuis, zoals aanvankelijk gepland. De dienstverlening gebeurde via een NGO kliniek, wat een volwaardig alternatief bleek. Dat de diensten zowel toegankelijk als aanvaardbaar waren, bleek uit het hoge aantal doorverwezen patiënten dat naar de kliniek kwam, zowel voor diagnose, behandeling als controle.

In de centra van de Associatie voor Gezinsplanning in Kenia, keken we na of het aangewezen was opsporing van baarmoederhalskanker te integreren in de contraceptie consultatie. De resultaten toonden aan dat de condities in deze centra goed waren om hoge kwaliteitsscreening te verzekeren. Zowel de zorgverleners als de patiënten hadden een positieve kijk op screening. In de verschillende klinieken werden ongeveer 10.000 uitstrijkjes genomen per jaar, waarvan 36% in vrouwen jonger dan 30 jaar. Van de 4,5% uitstrijkjes die als abnormaal geprotocolleerd werden, waren er 1,5% HSIL en 0,2% invasieve kankers. Het screenen van vrouwen in centra voor gezinsplanning, komt ten goede aan deze vrouwen, maar heeft weinig impact op de algemene morbiditeit te wijten aan baarmoederhalskanker in een land. Daarvoor bereiken deze centra te weinig vrouwen uit de hoogste risicogroepen. Speciale maatregelen zouden echter kunnen genomen worden om meer, en vooral oudere, vrouwen te bereiken.
3. **Discussie en conclusies**

Samengevat tonen onze resultaten dat vrijwillige basisgezondheidswerkers met succes konden ingezet worden om de deelname aan een screeningsprogramma te vergroten. De patiënten lieten zich screenen in openbare centra, maar verkozen NGO klinieken en plaatselijke centra wanneer dit als een alternatief werd aangeboden. De kwaliteit van de cytologie als screeningstest kon verbeterd worden, maar de gevoeligheid van conventionele cytologie bleef laag in operationele omstandigheden. De alternatieve VIA test, uitgetest in zowel ideale testomstandigheden als op het veld, bleek opmerkelijk gevoeliger maar veel minder specifiek, waardoor veel patiënten moesten doorverwezen worden voor verdere diagnose.

Decentralisatie van diagnose en behandeling op districtsniveau maakte deze diensten bereikbaar voor de bevolking, maar we slaagden er niet in ze aan te bieden in de openbare gezondheidssector in Nicaragua. Tenslotte gaven we aandacht aan andere strategieën voor dienstverlening, in het bijzonder aan de integratie van screening in centra voor gezinsplanning.

Als besluit, denken wij dat vroegtijdig opsporing van baarmoederhalskanker relevant is in lage-loonlanden, op voorwaarde dat voldoende middelen ter beschikking worden gesteld om de effectiviteit van het programma te verzekeren. Dit houdt de ontwikkeling van nationale richtlijnen in, maatregelen om de hoogrisico bevolking te bereiken, integratie van screening in bestaande diensten, oprichting van centra voor diagnose en behandeling, en adequate mechanismen voor supervisie en kwaliteitscontrole. De keuze van de screeningstest, de strategie en de dienstverlening, is afhankelijk van de lokale situatie en de aanwezige structuren van gezondheidszorg. Een georganiseerd programma, waarbij screening zowel in bestaande openbare als private diensten wordt aangeboden, aangevuld door terreinbezoeken, lijkt de beste optie. Behandeling van precancereuze letselso kan aangeboden worden op districtsniveau, maar gespecialiseerde diensten moeten voorhanden zijn op nationaal niveau om gevorderde letselso te behandelen.

Wanneer de middelen en de politieke bereidheid niet voorhanden zijn om een programma op te zetten dat aan de hierboven vermelde criteria voldoet, kan het verstandiger zijn te investeren in andere gezondheidsproblemen. Toch kunnen in alle landen beperkte diensten worden aangeboden aan patiënten die vrouwenklinieken bezoeken, mits de kwaliteit van de screening en de toegankelijkheid van de behandeling verzekerd worden. Ook als de opsporing gebeurt op een vrijwillige basis, moeten er richtlijnen bestaan om het gebruik van middelen te optimiseren en een maximum effect te bereiken.
VII.
ABBREVIATIONS
ABBREVIATIONS

AGUS  Atypical glandular cells of undetermined significance
AOR  Adjusted odds ratio
ASC-US  Atypical squamous cells of undetermined significance
ASC-H  Atypical squamous cells, cannot exclude high grade squamous intraepithelial lesion (HSIL)
ASR  Age standardized rate
BV  Bacterial vaginosis
CBD  Community-based distributor
CCCP  Cervical cancer control programme
CHW  Community health worker
CI  Confidence interval
CIN  Cervical intraepithelial neoplasia
CIS  Carcinoma in situ
CR  Crude rate
DNA  Deoxyribonucleic acid
EFP  Extra false positives
ETP  Extra true positives
FP  Family planning
FPAK  Family Planning Association of Kenya
HC  Hybrid Capture
HIV  Human immunodeficiency virus
HPV  Human papillomavirus
HR  High risk
HSIL  High-grade squamous intraepithelial lesion
IARC  International Agency for Research on Cancer
ICC  Invasive cervical cancer
KAP  Knowledge, attitudes and practices
LEEP  Loop electrosurgical excision procedure
LLETZ  Large loop excision of the transformation zone
LR  Low risk
LSIL  Low-grade squamous intraepithelial lesions
MCH  Maternal and child health
NGO  Non-Governmental Organization
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<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>NPV</td>
<td>Negative Predictive Value</td>
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<tr>
<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>Pap</td>
<td>Papanicolaou</td>
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<tr>
<td>PATH</td>
<td>Programme for Appropriate Technology in Health</td>
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<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
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<tr>
<td>PID</td>
<td>Pelvic Inflammatory Disease</td>
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<tr>
<td>PPV</td>
<td>Positive Predictive Value</td>
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<tr>
<td>Rb</td>
<td>Retinoblastoma protein</td>
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<tr>
<td>RELFPR</td>
<td>Relative false positive rate</td>
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<tr>
<td>RELTPR</td>
<td>Relative true positive rate</td>
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<tr>
<td>RPR</td>
<td>Rapid plasma reagin</td>
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<tr>
<td>SCC</td>
<td>Squamous cell carcinoma</td>
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<td>SIL</td>
<td>Squamous intraepithelial lesion</td>
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<tr>
<td>SMC</td>
<td>Servicios Medicos Comunales</td>
</tr>
<tr>
<td>STD</td>
<td>Sexually transmitted disease</td>
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<tr>
<td>STI</td>
<td>Sexually transmitted infection</td>
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<tr>
<td>UNAN</td>
<td>Universidad Nacional Autónoma de Nicaragua</td>
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<tr>
<td>VIA</td>
<td>Visual inspection with acetic acid</td>
</tr>
<tr>
<td>VLIR</td>
<td>Flemish Interuniversity Council (Vlaamse Interuniversitaire Raad)</td>
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<td>WHO</td>
<td>World Health Organization</td>
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