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THE HEALTH PROFESSIONAL'S HPV HANDBOOK 3

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HPV HANDBOOK

3: HPV AND CERVICAL CANCER: PUBLIC HEALTH PERSPECTIVES

Editors-in-Chief
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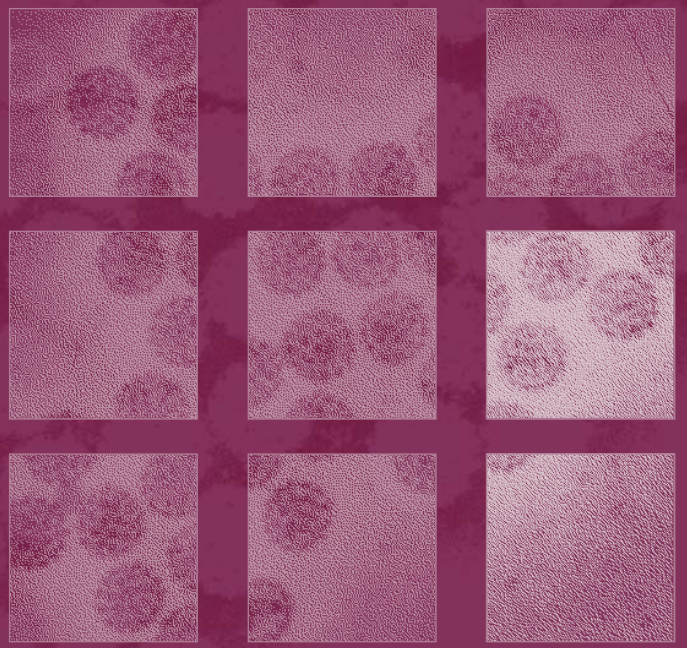

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Introduction to the HPV Handbook series

These compact, illustrated handbooks are concise but comprehensive resources that introduce medical students, general medical practitioners and gynaecologists to the significance of the human papillomaviruses in the etiology of cervical cancer. All chapters are fully referenced and written by experts in the field.

Handbook 1: *Human Papillomavirus and Cervical Cancer*, introduces the human papillomaviruses that are responsible for genital warts or cervical cancer. The chapters review virus structure, the epidemiology of HPV, the latest advances in HPV vaccination and new markers for cervical disease.

Handbook 2: *Current Evidence-based Applications*, describes the implications of implementing HPV testing for the management of women with various degrees of dysplasia, and discusses HPV testing for post-treatment follow-up. It also provides an overview of the current status of HPV testing as a tool for cervical cancer screening.

Handbook 3: *HPV and Cervical Cancer: Public Health Perspectives*, examines the benefits and drawbacks of cervical cytology and HPV testing as part of an organized screening programme to prevent cervical cancer.

1. Cervical cytology as a screening test

Ahti Anttila, Pekka Nieminen and Matti Hakama

- Cervical cancer screening based on the Pap smear test is the only method for which there exists direct evidence to show consequent substantial reductions in cervical cancer incidence and mortality
- Population-based screening programmes require large, complex administrative structures that must be highly efficient in order to ensure satisfactory performance
- Resolution of suspicious or borderline cytological results may only marginally improve the overall effectiveness of a programme
- Reliable quality control, together with continual patient monitoring and feedback to cytology laboratories, are essential and can support reduction in screening intervals, while maintaining high clinical specificity and good staff motivation
- The performance of the screening programme – not the screening test – is paramount

Introduction

Appropriately organized cervical cancer screening based on cervical cytology (the Pap smear test) markedly reduces both cervical cancer incidence and mortality.[1–3] Finland has one of the lowest rates of cervical cancer incidence in Europe and has documented decreases of almost 75% in its incidence and 90% in mortality rate since the introduction of a national Pap smear-based cervical cancer screening programme in the early 1970s.[4–10]

Rationale of cytology-based screening for cervical cancer

Within a public health context, the objective of screening is the identification of disease while in a preclinical state, so that its further development (and therefore consequent mortality) can be reduced. Screening should be regarded as public health policy, in that it is applied to populations rather than individual patients, although, in practice, the distinction between screening and case-finding is sometimes difficult to make, because the detection of a preclinical cancer may occur either within the population-based screening programme or in normal clinical practice.

The key elements influencing the success of population-based screening (see box) all need to be optimized for a programme to operate effectively,[1,2,11,12] and deficiency in one or more of these factors might explain the suboptimal performance of cervical cancer screening in some European countries.

The performance of the screening test: the Pap smear

When considering the performance of the test, it is important to recognize that a Pap smear result is not unambiguously positive or negative, and its performance is dependent on the subjective

Key elements of cervical cancer screening

- Population coverage of all social classes
- Target age range
- Compliance
- Screening interval
- Sample taking and handling
- Cytological analysis and reporting of results
- Patient follow-up and treatment of pre-cancerous lesions
- Quality control and audit procedures that cover all aspects of the programme, from invitation to post-treatment follow-up

judgement of the individuals who are interpreting the tests, as well as the selection of the particular cut-off points that are used to define a positive or negative result.

It has been estimated that the sensitivity of Pap smears can range from 50% to 70%.[13–15] Consequently, approximately 30–50% of histologically confirmed pre-cancerous lesions would not be detected by a single Pap smear. However, the sensitivity of the Pap smear for the detection of high-grade lesions is greater than that for low-grade lesions. Conversely, the Pap smear is less sensitive for the detection of adenocarcinoma than for squamous cell carcinoma.[7,16]

The specificity of the Pap smear test usually ranges from 95% to 99.5%, this variation being largely dependent on whether the cut-off for a positive test result is set at the need for follow-up or the need for immediate treatment (i.e. referral to colposcopy for high-grade disease). Using the need for immediate treatment as the threshold, the specificity of the Pap smear within the Finnish cervical cancer screening programme is high. In Finland, the overall frequency of referral for colposcopy or other confirmatory investigations is <1% of women screened. A clearly positive finding of high-grade cytology

requiring referral is found in only 0.6–0.8% of the screening population,[17] and histology will confirm pre-cancerous or cancerous lesions in approximately 50% of these cases. Approximately 85–90% of all pre-cancerous or cancerous lesions treated within the programme present as high-grade lesions. Pap smears also identify about 6% of women with a suspicious or borderline cytological finding. These women are managed by having a repeat Pap smear every 6 months, with referral to colposcopy if indicated, or by returning to routine screening after three negative Pap smear results. Using this triage protocol, only a small percentage of women with suspicious or borderline results will be referred to colposcopy within one screening round of the programme. About 10–15% of all pre-cancerous or cancerous lesions identified in the programme are detected in this group. Even though women with suspicious or borderline smears are at higher than average risk of contracting cervical cancer later in their lives, the probability of high-grade disease remains small, and is $<1\%$ within 15 years after the screening visit.[18] Suspicious or borderline cytological results thus increase the overall effectiveness of the screening programme in Finland only marginally.

The performance of the screening programme

Screening programmes can effectively reduce incidence and mortality of invasive disease because between 5 and 15 years are needed for a pre-cancerous lesion to develop into invasive disease if left untreated[19] and a substantial proportion of pre-cancerous lesions will regress spontaneously without intervention.[20–22] Disease missed by a Pap smear in one screening round, therefore, may be picked up in the next whilst still treatable; otherwise the disease may regress totally and pose no health risk to the individual. Thus, the performance of a screening programme can be substantially different from that of a screening test and, for public-health decisions, the sensitivity and specificity of the programme is more relevant than the performance of a single Pap smear *per se* (Table 1).

Table 1 Sensitivity and specificity of a screening programme:[12] programme sensitivity = (*a* + *g*)/M and programme specificity = (*d* + *f* + *j* + *l* + *s*)/N

Screening		Confirmation		Target population	
Attendance	Test	Attendance	Test	Disease	Healthy
Yes	Positive	Yes	Positive	*a*	*b*
Yes	Positive	Yes	Negative	*c*	*d*
Yes	Positive	No	Not available	*e*	*f*
Yes	Negative	Yes	Positive	*g*	*h*
Yes	Negative	Yes	Negative	*i*	*j*
Yes	Negative	No	Not available	*k*	*l*
No	Not available	No	Not available	*r*	*s*
			Total	M	N

Implementation of cervical cancer screening programmes in Europe

Despite recommendations from the European Commission that all European Union states should implement organized cervical cancer screening programmes, there are wide variations in screening policy between and within the countries of the European Union.[23] Screening may be included (1) within an organized programme; (2) as an organized programme mixed with opportunistic screening; (3) as fully opportunistic screening; or, alternatively, there may be no screening at all. The screening policies of the European Union member countries are compared in Table 2, but because there have been few properly conducted analyses of the effects of these programmes, we are reliant on estimates that may not reflect the true situation in these countries.

In most European countries, other than Finland, the estimated decrease in disease-incidence or mortality rates ranges from 10% to 65%,[24] suggesting that there are substantially smaller effects on the risk of invasive disease than might be expected on the basis of observations at the individual level[1] (or at the population level, in the case of Finland). The average age-standardized rates for disease incidence and mortality were 16.8 and 6.1 (per 100 000 woman-years), respectively, in Europe in 1995,[25] but the range of rates show there is substantial variation in these figures: 5–40 (for disease-incidence rates)

Table 2 Policies of cervical cancer screening by country or region in the European Union[26]

	Age range (years)	Interval (years)	Smears (lifetime number per woman	Proportion of population subjected to formal programme (%)
Country				
Belgium	25–64	3	14	58
Denmark	23–59	3	13	90
Finland	30–60	5	7	100
France	25–65	3.5	14	< 5
Germany	≥ 20	1	50+	90
Ireland	25–60	5	8	–
Italy	25–64	3	14	13
The Netherlands	30–60	5	7	100
Sweden	20–59	3	14	100
England, UK	20–64	3 or 5	10–16	100
Region				
Olympia, Greece	25–64	3	14	88
Mid-region, Portugal	20–64	3	16	100
C.y. Léon, Spain	25–65	3	14	86

and 1.5–14 (for mortality rates), as shown in Figure 1. The highest rates may be partly the consequence of differences in background risk or registration and diagnostic criteria, but the data signify substantial failures in the implementation of cervical cancer screening policies.[27]

Data supporting the value of organized cervical cancer screening comes from those countries where such programmes have been effectively implemented. After the introduction of the Pap smear in the early 1940s, it was not until the late 1950s/1960s that cytological screening became widespread. One of the first large-scale organized screening programmes was initiated in 1949 in British Columbia, Canada, and its lifetime coverage increased to 85% from 1970 onwards,[28,29] during a period when the age-specific incidence rate of squamous cell carcinoma of the cervix decreased by 78% in women over 20 years of age and the corresponding mortality rate decreased by 72%.

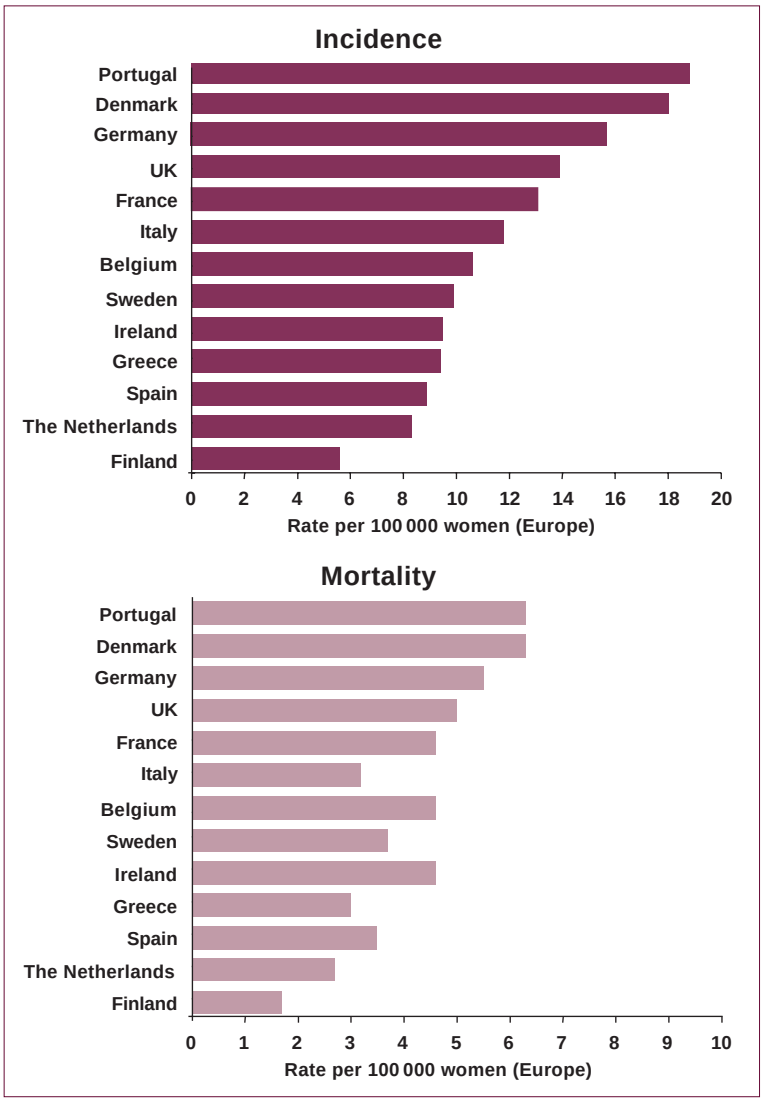

Figure 1 Incidence and mortality rates of cervical cancer in European countries in 1995; data adjusted for age to the European standard population and countries ordered by incidence rate. (Modified from Bray *et al*. 2002)

The effect of population-based organized cervical cancer screening has been well demonstrated in Nordic countries.[5,6] In Finland (population 5 million), organized screening for cervical cancer was initiated in the early 1970s and was accompanied by progressive decreases of 80% in both the age-adjusted disease-incidence and mortality rates for cervical cancer, by the early 1990s.[7] Similar decreases in disease incidence and mortality were evident in Iceland following the introduction of organized screening. In contrast, during the same period in Norway – where cervical cancer screening operated on an opportunistic basis – the incidence and mortality rates showed smaller decreases of about 30%. Similarly, in Sweden and Denmark, where regional coverage of organized programmes is incomplete, decreases in cervical cancer incidence rates of 52–56% have been reported.[24]

In the UK, cervical cancer screening became more widespread in the early 1960s,[30] but there was no associated clear decrease in cervical cancer incidence between 1960 and 1986, from an analysis of data for all ages combined.[31] However, there was a decline in the registered disease-incidence and mortality rates among the target population of 35–54-year-old women. After 1988, following the introduction of a computerized call–recall system, new quality standards and new guidelines for the follow-up of women with abnormal smears, coverage increased rapidly to approximately 80% of the target population (women 20–69 years old). The incidence of invasive cervical cancer decreased by 35% during 1991–1993, compared with the expected incidence based on the age- and district-specific trends in the period from 1971 to 1990,[32] and the age-standardized mortality from cervical cancer decreased by 39% between 1987 and 1997.[33] There was even a larger decrease in mortality among women <55 years of age.[34]

Protective effect of the Pap smear

Historical cohort studies that have compared the observed and expected incidences of cervical cancer cases or deaths in screened populations indicate that the protective effect of a negative Pap smear

exceeds 90%, and decreases only marginally over a period of up to 3 years[1,35] (Table 3). Moreover, in Finnish women 30–59 years old, the cumulative cervical cancer risk was 1 in 100 before organized screening was introduced, and declined to 1 in 300 among those screened during 1963–1971.[4,36] A later cohort study which followed cervical cancer incidence within the Finnish programme showed an approximate 50% decrease in risk among those with a single negative smear, which increased to about 80% when the entire 5-year follow-up period was included in the analysis.[10] Several case–control studies in cervical cancer have reported relative risks of 0.16–0.76 for women who have participated in screening, compared with women who have never been screened (reviewed by Zappa and Ciatto 2000).[36]

Table 3 Protective effect of Pap smear screening for cervical cancer after a negative smear (in women aged 35–64 years)[1]

Interval between screenings (years)	Number of smears between 35–64 years	Reduction in cumulative disease incidence (%)
1	30	93
2	15	92
3	10	91
5	6	84
10	3	64

A case–control study in Finland compared the effect of organized screening with opportunistic screening on cervical cancer incidence.[37] The relative risk for cervical cancer was 0.25 among the women participating exclusively in the organized programme, and 0.57 among those screened opportunistically, where both groups were compared to women who had never been screened. However, most women had participated in both the organized as well as the opportunistic screening modalities and the relative risk for this group was 0.27, which indicates that the additional opportunistic Pap smears offered little, if any, benefit to the women involved.

Summary

- Pap smear-based cervical cancer screening programmes can reduce cervical cancer incidence and mortality rates by 80% or more, when implemented via well-organized national programmes
- Across Europe, improving the coverage and compliance among women in the age groups with the highest incidence of cervical cancer is likely to be the single most important factor for reducing cervical cancer
- An organized call–recall system, using personal invitations, is the key to increasing coverage
- Increasing the emphasis on quality assurance and the diagnostic validity of Pap smear screening can improve the performance and effectiveness of screening programmes
- Any weak component in a screening programme will affect performance, and an ineffective programme is not to be regarded as proof of the inefficiency of Pap smear-based screening for cervical cancer
- Whilst the implementation of new technologies may provide benefits, the advantages gained should not be compromised by replacing the Pap smear with a new test within an ineffective screening programme

References

1. No author given. IARC Working Group on cervical cancer screening, in Hakama M, Day NE, Miller AB (eds): Screening for Cancer of the Uterine Cervix. Lyon, IARC Scientific Publication, 1986
2. Coleman D, Day N, Douglas G *et al*. European Guidelines for Quality Assurance in Cervical Cancer Screening. Europe against cancer programme. *Eur J Cancer* 1993;29A Suppl 4:S1–38
3. Advisory Committee on Cancer Prevention in the European Union. Recommendations on cancer screening in the European Union. *Eur J Cancer* 2000;36:1473–8
4. Hakama M, Rasanen-Virtanen U. Effect of a mass screening program on the risk of cervical cancer. *Am J Epidemiol* 1976;103:512–7
5. Hakama M. Trends in the incidence of cervical cancer in the Nordic countries, in Magnus K (ed): Trends in cancer incidence. Causes and practical implications. New York, Hemisphere Publishing Corporation, 1982, pp 279–92
6. Laara E, Day NE, Hakama M. Trends in mortality from cervical cancer in the Nordic countries: association with organised screening programmes. *Lancet* 1987;1:1247–9
7. Nieminen P, Kallio M, Hakama M. The effect of mass screening on incidence and mortality of squamous and adenocarcinoma of cervix uteri. *Obstet Gynecol* 1995;85:1017–21
8. Anttila A, Pukkala E, Soderman B *et al*. Effect of organised screening on cervical cancer incidence and mortality in Finland, 1963–1995: recent increase in cervical cancer incidence. *Int J Cancer* 1999;83:59–65
9. Nieminen P, Kallio M, Anttila A, Hakama M. Organised vs. spontaneous Pap-smear screening for cervical cancer: A case-control study. *Int J Cancer* 1999;83:55–8
10. Viikki M, Pukkala E, Hakama M. Risk of cervical cancer after a negative Pap smear. *J Med Screen* 1999;6:103–7
11. Hakama M, Chamberlain J, Day NE *et al*. Evaluation of screening programmes for gynaecological cancer. *Br J Cancer* 1985;52:669–73
12. Hakama M. Screening, in Holland WW, Detels R, Knox G (eds): Oxford textbook of public health (ed 2). Oxford, New York, Toronto, Oxford University Press, 1991
13. Koss LG. The Papanicolaou test for cervical cancer detection. A triumph and a tragedy. *JAMA* 1989;261:737–43

14. Canadian Co-ordinating Office for Health Technology Assessment Assessment of techniques for cervical cancer screening. CCOHTA Report 2E. 1997,1–33

15. Agency for Health Care Policy and Research Evaluation of cervical cytology. Technology Assessment Report No. 5. (Available at http://www.ahcpr.gov/clinic/tp/cervtp.htm). Agency for Health Care Policy and Research, 1999

16. Sigurdsson K. Quality assurance in cervical cancer screening: the Icelandic experience 1964–1993. *Eur J Cancer* 1995;31A:728–34

17. Anttila A, Nieminen P. Cervical cancer screening programme in Finland. *Eur J Cancer* 2000;36:2209–14

18. Viikki M, Pukkala E, Hakama M. Risk of cervical cancer subsequent to a positive screening cytology: follow-up study in Finland. *Acta Obstet Gynecol Scand* 2000;79:576–9

19. Syrjanen KJ. Spontaneous evolution of intraepithelial lesions according to the grade and type of the implicated human papillomavirus (HPV). *Eur J Obstet Gynecol Reprod Biol* 1996;65:45–53

20. Fidler HK, Boyes DA, Worth AJ. Cervical cancer detection in British Columbia. A progress report. *J Obstet Gynaecol Br Commonw* 1968;75:392–404

21. Luthra UK, Prabhakar AK, Seth P *et a*l. Natural history of precancerous and early cancerous lesions of the uterine cervix. *Acta Cytol* 1987;31:226–34

22. Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gyn Path* 1993;12:186–92

23. Linos A, Riza E, Ballegooijen M. Introduction. Cervical cancer screening. *Eur J Cancer* 2000;36:2175–6

24. Antilla A, Laara E. Cervix cancer: geographical considerations, in Sankila R, Demaret E, Hakama M, *et al* (eds): Evaluation and monitoring of screening programmes. Brussels – Luxembourg, European Commission, Europe Against Cancer Programme, 2000, pp 77–97

25. Bray F, Sankila R, Ferlay J, Parkin DM. Estimates of cancer incidence and mortality in Europe in 1995. *Eur J Cancer* 2002;38:99–166

26. van Ballegooijen M, van den Akker-van Marle E, Patnick J *et al*. Overview of important cervical cancer screening process values in European Union (EU) countries, and tentative predictions of the corresponding effectiveness and cost-effectiveness. *Eur J Cancer* 2000;36:2177–88

27. Miller AB. The (in)efficiency of cervical screening in Europe. *Eur J Cancer* 2002;38:321–6

28. Boyes DA, Worth AJ, Anderson GH. Experience with cervical screening in British Columbia. *Gynecol Oncol* 1981;12:S143–55

29. Anderson GH, Boyes DA, Benedet JL *et al*. Organisation and results of the cervical cytology screening programme in British Columbia, 1955-85. *Br Med J (Clin Res Ed)* 1988;296:975–8

30. Parkin DM, Nguyen_Dinh X, Day NE. The impact of screening on the incidence of cervical cancer in England and Wales. *Br J of Obs Gyn* 1985;92:150–7

31. Fouquet R, Gage H. Role of screening in reducing invasive cervical cancer registrations in England. *J Med Screen* 1996;3:90–6

32. Gibson L, Spiegelhalter DJ, Camilleri_Ferrante C, Day NE. Trends in invasive cervical cancer incidence in East Anglia from 1971 to 1993. *J Med Screen* 1997;4:44–8

33. Quinn M, Babb P, Jones J, Allen E. Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. *BMJ* 1999;318:904–8

34. Sasieni P, Adams J. Effect of screening on cervical cancer mortality in England and Wales: analysis of trends with an age period cohort model. *BMJ* 1999;318:1244–5

35. Lynge E. Cohort studies evaluating cervical cancer, in Sankila R, Demaret E, Hakama M, *et al* (eds): Evaluation and monitoring of screening programmes. Brussels – Luxembourg, European Commission, Europe Against Cancer Programme, 2000, pp 119–31

36. Zappa M, Ciatto S. Cervix cancer: case control studies, in Sankila R, Demaret E, Hakama M, *et al* (eds): Evaluation and monitoring of screening programmes. Brussels – Luxembourg, European Commission, Europe Against Cancer Programme, 2000, pp 99–118

37. Nieminen P, Kallio M, Anttila A, Hakama M. Organised vs. spontaneous Pap-smear screening for cervical cancer: A case-control study. *Int J Cancer* 1999;83:55–8

2. HPV testing as a screening test: the case for

Chris JLM Meijer and Peter JF Snijders

- HPV testing is most informative in women >30 years of age
  - HPV testing in women <25 years is not cost-effective
- HPV testing is useful for the triage of women with borderline and mild dyskaryosis (BMD)
- The 4% of women with normal cytology who test positive for high-risk (HR) HPV genotypes may be followed up at yearly intervals
- The 96% of women with normal cytology who test negative for HR HPV genotypes may be followed up at prolonged intervals (e.g. 8–10 years)
- The addition of HPV testing to cytology testing has many potential advantages for population-based screening programmes

Introduction

In order to understand the rationale and advantages of HR HPV testing as a tool for cervical cancer screening, the following factors must be considered:

- The natural history of an HPV infection (Figure 1)
- HPV genotypes:
  - Around 18 HR genotypes which cause persistent infection that is strongly associated with the development of invasive carcinoma have been identified; clinical HPV testing detects the 13–14 most common HR types
- The age of the woman when tested:
  - In women <25 years of age, most HPV infections are short-lived and will not proceed to carcinoma
  - In women <30 years of age, a positive HR test may indicate persistent infection and a higher risk of disease
- HR HPV-positive BMD smears identify women at risk
- The presence of HR HPV in women with normal smears identifies a group that will need frequent follow-up

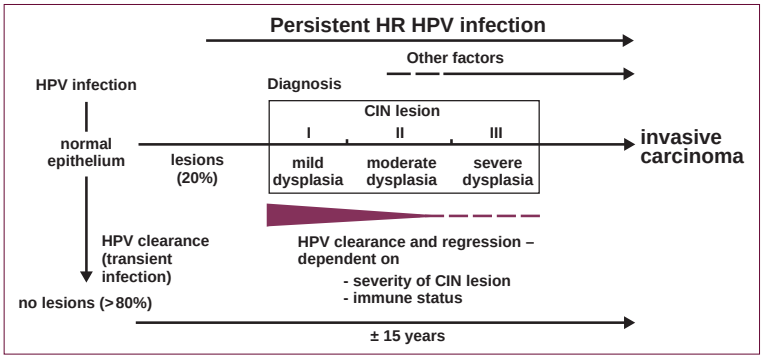

Figure 1 Relationship between HR HPV infection and the pathogenesis of cervical cancer

The role of HPV testing in young women

Cross-sectional studies of infection in relation to age show a peak prevalence of HR HPV infection of about 12% at 20–25 years, which decreases to about 4% in women >35 years of age.[1] These HPV peak prevalence figures indicate that primary HPV infections occur in sexually active women. In women >30 years of age, these are more likely to be persistent HPV infections that cannot be cleared, rather than primary infections acquired at a later age.[2] Consequently, testing for HR HPV in women aged <30 years, in order to assess their risk of developing CIN 3 or cervical cancer, is of little use, because the HPV infections will clear spontaneously in the great majority of cases. However, it is in the subset of women >30 years of age who test positive for HR HPV that the probability of having or developing a progressive CIN lesion is much higher.

Studies by Woodman *et al*. 1992 and Koutsky *et al*. 2001 of young women (around 20 years of age) confirm that the majority of these HPV infections resolve, and the associated cervical lesions (CIN 1 and CIN 2, though rarely CIN 3) regress.[3,4] Moreover, cervical cancer in Western countries is rare in younger women (<30 years) and accounts for less than 5% of the total.[5] It is also relevant to consider whether HR HPV testing should be performed at all in women <25 years of age, as is now common practice in the US and UK. In The Netherlands, the annual incidence of cervical cancer among its 6 million inhabitants is 770 cases, with 235 mortalities each year. In women <25 years of age, cervical cancer was found in only a total of four, four, and two cases in 1996, 1997, and 1998, respectively, indicating that screening for cervical cancer in this age group is not cost-effective. The disease incidence among women 25–30 years of age is currently about 5%, so this age group is also excluded from The Netherlands population-based screening programme.

HPV and triage of women with borderline and mild dyskaryosis

We conducted a prospective study in Middelburg, Zeeland, in the Netherlands, in which women with BMD were tested for HR HPV.[6] Median follow-up in this study was 2 years (range 1.5–4 years). Prevalent CIN 3 lesions were found only in the HR HPV-positive group. Moreover, during follow-up, CIN 3 lesions developed only in women who had tested HR HPV-positive at baseline.

Other studies have reported identical findings – i.e. that there is no development of CIN 3 lesions in women who tested HR HPV-negative or who cleared their high-risk HPV infection[7,8] (Table 1). These results strongly support a strategy whereby HR HPV-positive women with BMD would be directly referred for colposcopy-directed biopsy, while their HR HPV-negative counterparts are referred back to the normal screening programme. Estimates suggest that this policy would reduce referrals from 50% (after two smears, 6 months apart) to 40% (no repeat testing required) and would therefore be very cost-effective. However, these triage studies have thus far been carried out only in a small number of women. Therefore, more conclusive evidence is required from population-based screening programmes, before HR HPV testing plus cytology is able to replace cytology alone as the principal screening tool for cervical cancer. Such studies are underway, at the time of writing, in the UK and the Netherlands.

Table 1 Risk assessment in mild and moderate dyskaryosis: all figures are cumulative incidences (%), with ranges in parentheses[8]

Follow-up (months)	Cytological regression		End histology CIN 3		Clinical progression	
Mild dyskarosis						
3	7.6	(1.1–14.1)	1.5	(0–4.5)	–	–
6	20.6	(10.4–30.8)	3.0	(0–7.2)	–	–
9	28.8	(17.3–40.3)	6.3	(0.2–12.4)	3.3	(0–7.9)
Moderate dyskarosis						
3	11.8	(2.8–20.8)	–	–	–	–
6	17.8	(7.0–28.6)	4.0	(0–9.6)	–	–
9	24.4	(12.1–36.7)	8.1	(0.3–15.9)	3.3	(0–7.9)

The role of HR HPV testing in women >30 years of age with normal cytology

Rozendaal *et al*. 2000 have shown that women who are HR HPV-positive are 116 times more at risk of developing CIN 3, compared with women who test HR HPV-negative.[9] Moreover, they reported that 4% of the women participating in a population-based screening programme (aged 35–55 years in 1992) had tested positive for HR HPV. After 4 years, 8% of the women who had initially tested HR HPV-positive developed CIN 3, indicating that HR HPV-positive women with normal cytology should be followed up more intensively (i.e. yearly). However, because cervical cancer takes more than 12 years to develop, HR HPV-negative women with normal cytology could have an extended screening interval of 8–10 years, instead of 5 years, which is the current interval in The Netherlands.[10] If the screening interval were to be extended in this way (i.e. for 96% of the women participating in the screening programme), cost-savings would undoubtedly be made, but this would be offset by the increased follow-up of the 4% of HR HPV-positive women with normal cytology, which would increase costs. Data from recent studies and preliminary observations in our ongoing population-based trial (in women aged 30–60 years) suggest, however, that only those women with a relatively high viral load (as determined by a real time PCR assay) require intensive follow-up. These are the women who are likely to develop CIN 3.[11–13] A defined viral load threshold is therefore likely to reduce further the number of HR HPV-positive women with normal cytology who would require follow-up.[12]

Cervical cancer screening by HR HPV testing followed by cytology in HR HPV-positive cases

Should HPV testing be used exclusively, instead of cytology for cervical cancer screening? Since cytology detects the few cases (approximately 1.5%) of CIN 3 that test HR HPV-negative, clinicians are reluctant to rely on a single test that could potentially miss a few

CIN 3 lesions or perhaps even cases of cervical cancer. Currently, HR HPV testing would be unacceptable as a primary screening method for cervical cancer in the absence of evidence that HR HPV-negative CIN 3 lesions would regress, or at least not progress to cervical cancer. However, such evidence is difficult to obtain, for ethical reasons. Preliminary modelling studies have shown that the anticipated reduction in mortality from cervical cancer that would result from HR HPV testing once every 5 years would be at least as high as that from a cervical smear test once every 3 years. However, as previously stated, until data from population-based screening studies with combined cytology and HR HPV testing are able to show that HR HPV-negative CIN 3 lesions will regress, screening by HR HPV testing alone will not be considered. In addition, a single HR HPV test is unable to determine whether the infection is new or long-standing. This is an important consideration, because it is the persistent HPV infections that give rise to CIN 3.

Advantages of adding HPV testing to cytology testing for population-based screening programmes

- Adding HPV to cytology testing improves the negative predictive value from 96–97% to >99%[14]
- Women with BMD could be referred directly, on the basis of the presence of HR HPV, because high-grade lesions (≥CIN 3) are found only in HR HPV-positive women[7,8,15]
  - Referrals would reduce by 10%
  - There would be less need for repeat smears at 6 and 18 months
- Only those women with normal cytology who are also HR HPV-positive (4% of the screened population) are at risk of CIN 3/cervical carcinoma within 4 years, and require annual assessment by cytology and HR HPV testing
  - HR HPV-negative women with normal cytology (96% of the screened population) could be assessed every 8–10 years

Cervical cancer screening by a combination of cytology and HR HPV testing

Screening studies in countries such as Costa Rica, Mexico and China, where HR HPV is highly prevalent, show that combined HPV and cytology testing is successful with very few false-negative results (and a high negative predictive value) for CIN 3 and cervical cancer, high sensitivities and a somewhat lower specificity for high-grade cervical lesions. However, these studies were not carried out in a population-based screening programme setting.

HPV testing to confirm cure

HR HPV testing may be very effective in the post-operative follow-up of women who have had cervical lesions (discussed elsewhere in this handbook series). As with other applications, HPV testing, as the sole test, can provide reassurance that a woman is free of disease, because of its powerful negative predictive value.[16–19] However, data indicate that a consistently better negative predictive value is achieved when HPV testing is combined with cytology.[20]

HPV testing to detect adenocarcinoma

Screening by a combination of HR HPV testing and cytology may improve the detection of adenocarcinomas. In the Netherlands, 15% of cervical carcinomas are adenocarcinomas. From 1989 to 1998, the estimated annual percentage change in incidence was a decrease of 1.6% for cervical squamous cancer, whereas it was an increase of 0.7% for adenocarcinomas, indicating the failure of cytology to decrease the incidence of this disease. However, as HR HPV DNA is present in approximately 94% of the adenocarcinomas and 100% of the adenocarcinomas *in situ*,[21] testing for HR HPV has the potential to lower the incidence of adenocarcinomas.

Conclusions

All the currently available data indicate that population-based cervical cancer screening by HR HPV testing in combination with cytology is at least as effective as screening by cytology alone, provided that this policy is applied to women >30 years of age. Using such a screening policy would be cost-effective in a population-based screening programme, because of the associated extended screening interval for HR HPV-negative women with normal cytology, and the expected reduction in the number of referrals to the gynaecologist and the number of repeat smears needed for women with BMD.

Summary

- HPV testing is currently not accepted as a primary screening method for cervical cancer
- HPV testing has a very powerful negative predictive value, and is cost-effective when used as an adjunct to cytology
- HPV testing alone can provide reassurance that a woman is free of disease
- There is a role for HPV testing in post-operative follow-up
- HPV testing is more effective than cytology in detecting cervical adenocarcinomas and their precursors

References

1. Jacobs MV, Walboomers JM, Snijders PJ *et al*. Distribution of 37 mucosotropic HPV types in women with cytologically normal cervical smears: the age-related patterns for high-risk and low-risk types. *Int J Cancer* 2000;87:221–7
2. Ho GY, Bierman R, Beardsley L *et al*. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med* 1998;338:423–8
3. Koutsky LA, Holmes KK, Critchlow CW *et al*. A cohort study of the risk of cervical intraepithelial neoplasia grade 2 or 3 in relation to papillomavirus infection. *N Engl J Med* 1992;327:1272–8
4. Woodman CB, Collins S, Winter H *et al*. Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. *Lancet* 2001;357:1831–6
5. Bulk S, Visser O, Rozendaal L *et al*. Incidence and survival rate of women with cervical cancer in the Greater Amsterdam area. *Br J Cancer* 2003;89:834–9
6. Zielinski GD, Snijders PJ, Rozendaal L *et al*. High-risk HPV testing in women with borderline and mild dyskaryosis: long-term follow-up data and clinical relevance. *J Pathol* 2001;195:300–6
7. Clavel C, Masure M, Bory JP *et al*. Human papillomavirus testing in primary screening for the detection of high-grade cervical lesions: a study of 7932 women. *Br J Cancer* 2001;84:1616–23
8. Nobbenhuis MA, Meijer CJ, van den Brule AJ *et al*. Addition of high-risk HPV testing improves the current guidelines on follow-up after treatment for cervical intraepithelial neoplasia. *Br J Cancer* 2001;84:796–801
9. Rozendaal L, Westerga J, van der Linden JC *et al*. PCR based high risk HPV testing is superior to neural network based screening for predicting incident CIN III in women with normal cytology and borderline changes. *J Clin Pathol* 2000;53:606–11
10. Wallin KL, Wiklund F, Angstrom T *et al*. Type-specific persistence of human papillomavirus DNA before the development of invasive cervical cancer. *N Engl J Med* 1999;341:1633–8
11. van Duin M, Snijders PJ, Schrijnemakers HF *et al*. Human papillomavirus 16 load in normal and abnormal cervical scrapes: an indicator of CIN II/III and viral clearance. *Int J Cancer* 2002;98:590–5

12. Snijders PJ, van den Brule AJ, Meijer CJ. The clinical relevance of human papillomavirus testing: relationship between analytical and clinical sensitivity. *J Pathol* 2003;201:1–6

13. Josefsson AM, Magnusson PK, Ylitalo N *et al*. Viral load of human papilloma virus 16 as a determinant for development of cervical carcinoma in situ: a nested case-control study. *Lancet* 2000;355:2189–93

14. Lorincz AT, Richart RM. Human papillomavirus DNA testing as an adjunct to cytology in cervical screening programs. *Arch Pathol Lab Med* 2003;127:959–68

15. Zielinski GD, Snijders PJ, Rozendaal L *et al*. HPV presence precedes abnormal cytology in women developing cervical cancer and signals false negative smears. *Br J Cancer* 2001;85:398–404

16. Jain S, Tseng CJ, Horng SG *et al*. Negative predictive value of human papillomavirus test following conization of the cervix uteri. *Gynecol Oncol* 2001;82:177–80

17. Kucera E, Sliutz G, Czerwenka K *et al*. Is high-risk human papillomavirus infection associated with cervical intraepithelial neoplasia eliminated after conization by large-loop excision of the transformation zone? *Eur J Obstet, Gynecol Reprod Biol* 2001;100:72–06

18. Lin CT, Tseng CJ, Lai CH *et al*. Value of human papillomavirus deoxyribonucleic acid testing after conization in the prediction of residual disease in the subsequent hysterectomy specimen. *Am J Obstet Gynecol* 2001;184:940–5

19. Kanamori Y, Kigawa J, Minagawa Y *et al*. Residual disease and presence of human papillomavirus after conization. *Oncology* 1998;55:517–20

20. Nobbenhuis MA, Meijer CJ, van den Brule AJ *et al*. Addition of high-risk HPV testing improves the current guidelines on follow-up after treatment for cervical intraepithelial neoplasia. *Br J Cancer* 2001;84:796–801

21. Zielinski GD, Snijders PJ, Rozendaal L *et al*. The presence of high-risk HPV combined with specific p53 and p16INK4a expression patterns points to high-risk HPV as the main causative agent for adenocarcinoma in situ and adenocarcinoma of the cervix. *J Pathol* 2003;201:535–43

3. HPV testing as a screening test: the case against

Anthony B Miller

- Due to the transient nature of most HPV infections, HPV-positivity is not correlated with a disease state in the majority of women, and so is of little use as a marker in women <25 years of age
- HPV testing, if used as primary screening, would result in many women being sent for further testing who would subsequently prove to have normal or only mildly abnormal cytology
- This might incur unnecessary investigational costs and induce anxiety in women who test positive
- Many abnormal lesions will subsequently regress
- There are multiple opportunities to detect abnormalities using cytology-based testing, because of the slow natural history of invasive carcinoma

Introduction

HPV is one of the most common sexually transmitted infections. In the majority of women, these HPV infections are asymptomatic and regress spontaneously.[1–3] However, some intraepithelial lesions – especially those caused by high-risk (HR) HPV types – will persist and, after a long preclinical period, develop into cervical cancer.

Cervical cancer is the second most common cancer in women, but it has become more manageable in developed countries because of the success of cytology-based screening. The use of the Pap smear alone has resulted in a significant reduction in the incidence and mortality of the disease over the last two decades.[4–6]

Investigators have demonstrated that HR HPV testing is able to identify women with CIN 3, the highest-grade precursor of cervical cancer, and that only cases of CIN 3 with HR HPV infection are at risk for disease progression.[7] It has been proposed, therefore, that screening programmes for cervical cancer could be made more effective by changing from the Pap test to HPV testing for primary screening. The potential pitfalls of such an approach are explored in this chapter.

Transient nature and regression of HPV lesions

Many of the cervical abnormalities (CIN 1 and CIN 2) detected by cytology are likely to regress without treatment (Figure 1).[6,8] As such, the most effective screening strategy would identify only those lesions with a high probability of progression, and for which treatment would be warranted. Conversely, screening strategies that simply identify all cervical abnormalities, without regard to progressive potential, would lead to unnecessary treatments, increased patient anxiety and increased use of healthcare resources, particularly if treatment is given immediately to those in whom low-grade disease has been detected.[6] The evidence reviewed here suggests that HPV testing is particularly prone to the indiscriminate detection of cervical lesions, and that the implementation of HPV screening would be accompanied by all of the problems outlined above.

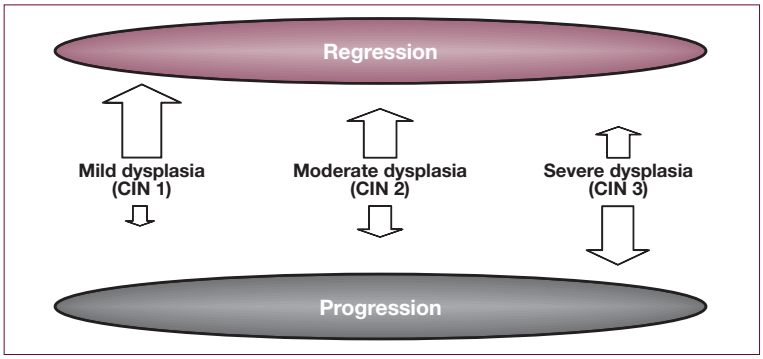

Figure 1 Mild and moderate dysplasias are more likely to regress than to progress

Melkert *et al*. 1993 reported a higher prevalence of HPV infection in women aged <35 years than in older women, and concluded that most of these infections must be transient.[9] Transience was confirmed by Jacobs *et al*. 2000, who also found a decreasing HPV prevalence with increasing age in cytologically negative women. These authors suggested that at least 70% of HPV infections are cleared spontaneously.[3] Other data from Zielinski *et al*. 2001 indicate that infection with HPV precedes the development of cytologic abnormalities,[10] while an earlier study by Remmink *et al*. 1995 suggested that only women who were infected with HR HPV types were likely to have cervical disease, and that the disease was likely to progress only in women with persistent infections.[11]

More specific information on the early natural history of HPV infections was obtained by Ho *et al*. 1998, who prospectively followed 608 US college students; these authors estimated that 43% of such women would have acquired an HPV infection after 3 years.[2] In their study, increased risk of infection was associated with young age, Afro-Caribbean origin, many sexual partners, alcohol and tobacco use. The median duration of infection was 8 months. Of those who acquired an HR HPV infection, 37% had an abnormal smear. The authors suggested that because of the transitory nature of most of the infections, such women should be managed conservatively.

Similar magnitudes of risk were reported by other US investigators. Koutsky *et al*. 1992 reported a cumulative risk of 28% for CIN 2 or 3, at 2 years, in those women who were initially HPV-positive, compared with 3% for those who were HPV-negative.[12] The risk of developing CIN 2 or 3 was highest for those women infected with HPV 16 or HPV 18.

Woodman *et al*. 2001 confirmed the transitory nature of most HPV infections in young women, and also showed that cytology may identify abnormalities after a remarkably short period from the first evidence of HPV infection.[13]

Sensitivity of the Pap smear

Sensitivity

Sensitivity: the probability that a test will be positive, given that the individual being tested has the disease

The low correlation between positive HPV testing and abnormal cytology seen in studies of women in whom HPV tests of Pap smear samples have been carried out, is almost certainly due to the HPV test detecting mainly non-progressive lesions.[14,15] Although more samples indicative of women at risk can be recognized by HPV testing, the corresponding Pap smear will often demonstrate normal or mildly abnormal cytology. For ideal programme planning, a test should be accurate enough to distinguish between lesions that will progress and lesions that will regress. Despite the low sensitivity of Pap smear testing – around only 50% in some studies[14–16] – evidence from organized cytology-based screening programmes indicates that cytology is equally as likely as HPV testing to detect lesions that progress. This hypothesis is supported by the success of a 5-yearly screening programme in Finland.[17]

Specificity issues

Specificity

Specificity: the probability that a test will be negative, given that the individual being tested does not have the disease

The specificity of HPV testing is almost invariably found to be lower than that of cytology, especially in younger women.[18] Reducing the number of false-positive results during screening is particularly important, as they introduce unnecessary investigational costs and induce anxiety in women. Indeed, it has long been recognized that focusing on high sensitivity, to the detriment of low specificity, is a poor strategy for public health purposes. Under circumstances where the disease has a long natural history and involves regression, and where repeat testing at least every 3 to 5 years is generally envisaged, undue emphasis on high sensitivity at the expense of specificity would be a serious error.

Overview

For women >35 (or preferably >40) years of age with cytologically negative smears, HPV testing may prove valuable in confirming that they have no evidence of infection with an oncogenic HPV virus. Under such circumstances, it is probable that repeat screening would be unnecessary for at least 5 and probably 10 years. An important requirement would be that such women should remain in a stable relationship and that neither they nor their partner should acquire a new HPV infection, otherwise their risk of developing progressive CIN would relapse to the same level as that for a woman aged 35 years who is HR HPV-positive.

Simply testing for HPV infection, when the great majority of infections are transient, makes little sense. Testing for the consequences of such infection (i.e. CIN) with cytology is more logical, but only if a conservative approach to management is followed. Therefore,

surveillance should be initiated for women with cytologic evidence of borderline or atypical smears (ASCUS: atypical squamous cells of undetermined significance) and CIN 1. Time is on the clinician's side, and it is perfectly safe to repeat smears at 6-month intervals for up to 2 years if there is no evidence of cytologic progression. In the majority of cases, regression will occur and referral to colposcopy with unnecessary treatment is avoided. Even those women identified as having cytologic evidence of CIN 2 could be followed up by 6-monthly smears on at least two occasions, because the majority of these lesions will also regress.[6] HPV testing in these circumstances (triage) is able to reveal those with HR HPV infections, but will not help to determine which cases will progress or regress, so triage with HPV tests is of no help in determining which lesions need to be treated.

Summary

- Screening for HPV infection, if performed at the appropriate age, may identify women with a low risk of cervical cancer if they test negative, but cannot help identify the minority who have a high risk of progression; alternative tests which measure host susceptibility to HPV oncogenicity may supplement or replace HPV detection
- HPV testing, even if contemplated, should not begin until women reach 30 (and preferably 35) years of age
- HPV testing may be of value in confirming that women aged >35 years with cytologically negative smears have no evidence of infection with an oncogenic HPV virus
- Because the majority of infections are transient, merely testing for HPV infection would be illogical, whereas testing for the consequences of such infection (CIN) with cytology, and then adopting a conservative approach to management, would be more valid
- In the light of our current understanding of the causes and natural history of cervical cancer, a radical change in approach is needed, in order to make the most appropriate use of the new technology of HPV testing

References

1. Sellors JW, Karwalajtys TL, Kaczorowski J *et al*. Incidence, clearance and predictors of human papillomavirus infection in women. CMAJ 2003;168:421–5
2. Ho GY, Bierman R, Beardsley L *et al*. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med* 1998;338:423–8
3. Jacobs MV, Walboomers JM, Snijders PJ *et al*. Distribution of 37 mucosotropic HPV types in women with cytologically normal cervical smears: the age-related patterns for high-risk and low-risk types. *Int J Cancer* 2000;87:221–7
4. Eddy DM. Secondary prevention of cancer: an overview. *Bull World Health Organ* 1986;64:421–8
5. Hristova L, Hakama M. Effect of screening for cancer in the Nordic countries on deaths, cost and quality of life up to the year 2017. *Acta Oncol* 1997;36 Suppl 9:1–60
6. Holowaty P, Miller AB, Rohan T, To T. Natural history of dysplasia of the uterine cervix. *J Natl Cancer Inst* 1999;91:252–8
7. Nobbenhuis MA, Walboomers JM, Helmerhorst TJ *et al*. Relation of human papillomavirus status to cervical lesions and consequences for cervical-cancer screening: a prospective study. *Lancet* 1999;354:20–5
8. Duggan MA, McGregor SE, Stuart GC *et al*. The natural history of CIN I lesions. *Eur J Gynaecol Oncol* 1998;19:338–44
9. Melkert PW, Hopman E, van den Brule AJ *et al*. Prevalence of HPV in cytomorphologically normal cervical smears, as determined by the polymerase chain reaction, is age-dependent. *Int J Cancer* 1993;53:919–23
10. Zielinski GD, Snijders PJ, Rozendaal L *et al*. HPV presence precedes abnormal cytology in women developing cervical cancer and signals false negative smears. *Br J Cancer* 2001;85:398–404
11. Remmink AJ, Walboomers JM, Helmerhorst TJ *et al*. The presence of persistent high-risk HPV genotypes in dysplastic cervical lesions is associated with progressive disease: natural history up to 36 months. *Int J Cancer* 1995;61:306–11
12. Koutsky LA, Holmes KK, Critchlow CW *et al*. A cohort study of the risk of cervical intraepithelial neoplasia grade 2 or 3 in relation to papillomavirus infection. *N Engl J Med* 1992;327:1272–8

13. Woodman CB, Collins S, Winter H *et al*. Natural history of cervical human papillomavirus infection in young women: a longitudinal cohort study. *Lancet* 2001;357:1831–6

14. Fahey MT, Irwig L, Macaskill P. Meta-analysis of Pap test accuracy. *Am J Epidemiol* 1995;141:680–9

15. Agency for Health Care Policy and Research Evaluation of cervical cytology. Technology Assessment Report No. 5. (Available at http://www.ahcpr.gov/clinic/tp/cervtp.htm). Agency for Health Care Policy and Research, 1999

16. Nanda K, McCrory DC, Myers ER *et al*. Accuracy of the Papanicolaou test in screening for and follow-up of cervical cytologic abnormalities: a systematic review. *Ann Intern Med* 2000;132:810–9

17. Anttila A, Nieminen P. Cervical cancer screening programme in Finland. Eur *J Cancer* 2000;36:2209–14

18. Ratnam S, Franco EL, Ferenczy A. Human papillomavirus testing for primary screening of cervical cancer precursors. *Cancer Epidemiol Biomarkers Prev* 2000;9:945–51

4. Cervical cancer screening: a public health issue

Julietta Patnick and Dik Habbema

- Organized screening programmes apply to populations, rather than individuals
- Thousands of women will require follow-up after a positive test, with further diagnostic procedures, and often treatment, in order to prevent a single case of cervical cancer
- Increasing the number of smears offered during a woman's lifetime improves programme sensitivity but diminishes cost-effectiveness
- Adjustment of any part of the programme can influence the performance of the whole
- HPV testing has an exceptionally high negative predictive value and may allow some women to be screened less frequently

Introduction

Cervical screening has substantially reduced the incidence of cervical cancer when it has been implemented in conjunction with adequate administrative structures and quality-control procedures. The Pap smear was first introduced in the mid-20th century, so early policies for cytology-based cervical screening were not rigorously defined, in contrast to the current situation, where randomized controlled trials are required before the introduction of a new screening technology. Nevertheless, the effectiveness of the Pap smear has been demonstrated by observing and evaluating the effect of these organized screening programmes on their target populations.[1,2]

The screening process

Organized screening programmes apply to populations, rather than individuals. Consequently, they require large, complex administrative organizations and well-defined protocols, to ensure that the total population is covered and that all receive the appropriate care. The screening programme will oversee the entire process, from the initial identification of individuals to be screened, through testing, to their return to the routine screening population if no disease has been identified. In this case, the programme will also detect and treat cases of cervical intraepithelial neoplasia (CIN) and oversee the start of the treatment pathway for those women with dyskaryosis or cancer.

Organized cervical screening commences with the identification of the individual and the issuing of an invitation or an appointment for testing. A typical screening algorithm is shown in Figure 1. At each stage, the administrative centre must be notified about treatment and surveillance outcomes, so that a patient's return to the routine recall schedule can be programmed appropriately. The costs of a screening programme include surveillance, testing, treatment and administration.

The effectiveness of a screening programme in controlling disease is directly dependent on the proportion of the population screened.[2–4] The most cost-effective way of maximizing coverage is through an

organized, systematic programme, rather than by opportunistic methods.[5] Programmes that are organized on a public health basis are also more likely to reach 'underserved' women than are services that rely on a woman's own initiative or on her relationship with her physician. Comprehensive coverage of the population is desirable because non-attenders are a high-risk group; the incidence of cancer is known to be disproportionately higher in women who either attend irregularly or do not attend for screening at all. Increasing the population coverage is a good use of resources where it is able to supplement the implementation of new screening technologies, or even obviate their introduction.

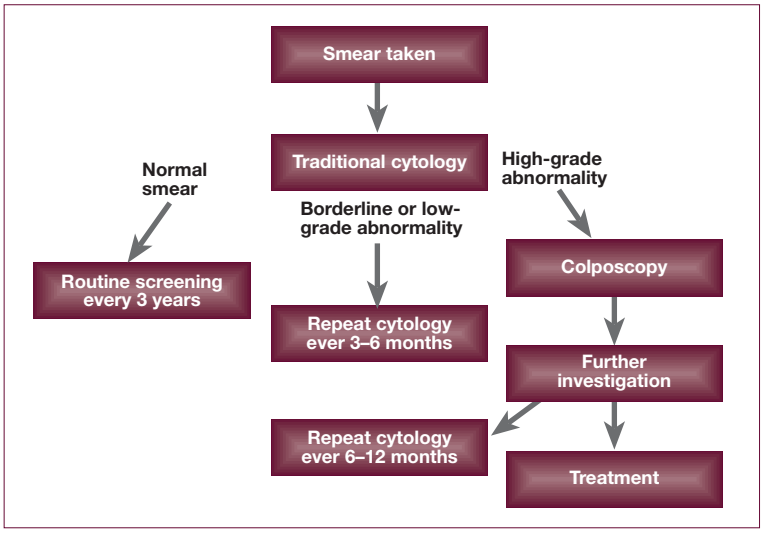

Figure 1 Screening algorithm using traditional cytology

Cervical cancer screening programmes aim to prevent invasive disease by detecting and treating CIN, the precursor condition. However, CIN can regress spontaneously, persist or progress to become invasive cancer,[6] and it is difficult to predict which individuals with CIN would go on to develop invasive cancer or die from their disease if it was left untreated. Many low-grade abnormalities could

simply be observed periodically over time before any action would need to be taken. This would increase the complexity of the screening process, because within a public health programme dealing with a population, the screening interval has to be tailored to an individual woman's medical history.

Balancing the benefits and drawbacks of cervical screening

The small burdens imposed on the many women screened have to be balanced against the potentially large benefits for the few in whom disease is detected (Figure 2). This is particularly important in cervical cancer screening because of the relatively low lifetime risk of developing this disease, compared with more common cancers, such as breast or colorectal cancer.[7] Thousands of women have to be followed up after a positive test with further diagnostic procedures, and eventually treatment, in order to prevent a single woman from developing cervical cancer.

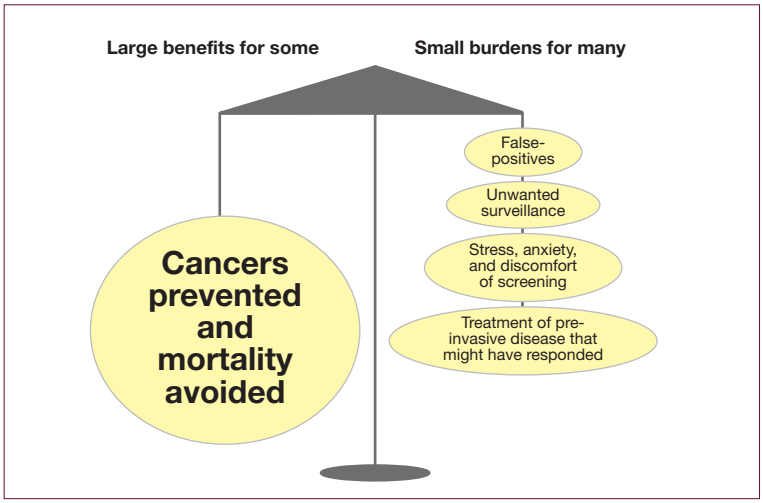

Figure 2 Balancing the benefits and costs of cervical cancer screening

The psychological costs of screening – particularly the anxiety caused when an abnormality is reported – should not be overlooked. Because of the prevalence of the negative effects of screening, the number of quality-adjusted life years (QALYs) saved by a screening programme will be considerably lower than the number of life years saved.

With greater public awareness, quality-of-life issues are becoming increasingly important in public health policy formulation. The sensitivity and specificity of the techniques used directly influence the effectiveness of the overall screening programme. Sensitivity is determined by the probability that disease (a pre-invasive lesion) will be detected, and specificity by the probability that women without disease will have a negative test result. Both measures should be considered in the context of the entire screening programme. For example, following the discovery of a recent false-negative smear, a cytologist might refer more (normal) women to colposcopy. Similarly, a colposcopist who observes predominantly normal samples would tend to report those at the extreme end of the normal spectrum as abnormal, thereby lowering the threshold of reporting.

The diagnostic testing component of cervical screening

The Pap smear has been very effective in reducing the incidence of cervical cancer, and up to 80% of cervical cancers can be prevented by a Pap-based screening programme.

However, the sensitivity of an individual cytology smear is known to vary widely between settings, and has an average value of 58%.[8] This discrepancy highlights the difference between the performance of an individual screening test and that of the programme as a whole. In an analysis in which sensitivity was calculated for a cytology smear, including the follow-up of positive smears ('positive screening episode'), the sensitivity was 80% for CIN or carcinoma *in situ* (CIS).[9] The transition from HPV infection to high-grade dyskaryosis is slow, so there are several opportunities for a pre-invasive lesion to be detected

in a woman being screened, and the sensitivity of a cytology-based screening programme will be much higher than the sensitivity of an individual cytology smear.

Key features of a successful Pap-based testing programme

- High proportion of the population participating
- Adequate frequency of testing
- Effective administrative and quality-control procedures to ensure accurate reporting of tests
- Appropriate follow-up and treatment of the population where required

The sensitivity of a screening programme is a function of the sensitivity of the test used and the frequency of its administration. A comparison of different screening policies shows that the cost-effectiveness of a programme is highly dependent upon the frequency of screening.[7] Simulations that compare these parameters under realistic assumptions of population coverage indicate that a decrease in the interval between subsequent Pap tests reduces cost-effectiveness.[7] The incremental cost of reducing a 5-year screening interval to a 4-year one is $35 000 per life year saved; similarly, reducing a 4-year interval to a 3-year one costs $56 000 and for intervals below 3 years, the cost-effectiveness ratio deteriorates even more rapidly, and the sensitivity benefit is marginal. This trend is related to the number of false-positive results reported in each screening round, and becomes more pronounced if QALYs are used.

Thus, increasing the number of smears offered during a woman's lifetime, whilst increasing the sensitivity of the programme, diminishes cost-effectiveness.

The cost estimates above are calculated on the basis of initiating screening at the age of 25 years; in general, beginning screening at an earlier age should be discouraged, because of the relationship

between HPV prevalence, disease incidence, and age. The peak prevalence of HPV infection occurs between the ages of 18 and 25 years. Most infections are transient, and the average transition time from HPV infection to the development of cervical cancer is 13 years. Extrapolation from these data indicates that most cases of cervical cancer occur after 25 years of age, in close agreement with observations in most Western populations, where cervical cancer is rare in younger women. In conclusion, therefore, screening young women is not a cost-effective public health strategy.

Implications of liquid-based cytology for screening programmes

The introduction of liquid-based cytology (LBC) techniques may improve the performance of cervical cancer screening.[10] In a recent systematic review, the estimated mean sensitivity of LBC was 16% higher than that of the Pap test,[11] although the evidence on LBC performance is not yet convincing, because the trials undertaken to date all have weakness in study design. However, even if the 16% figure for improved sensitivity is accurate, the cost-efficiency of screening with LBC would only be better than that for Pap smear screening if the additional costs per LBC preparation could be reduced to $2.[11] Importantly, this estimate is for a screening policy with a 5-year interval and seven lifetime invitations. In many Western countries, the screening policy is more intensive, and the incremental contribution of LBC to the effectiveness of screening is lower; this is because false-negative cases from one screening round have a higher chance of being detected during subsequent screening rounds whilst there is probably still sufficient time for the disease to be successfully treated. In addition, the higher sensitivity of LBC may be associated with a lower specificity. If so, a higher proportion of screened women would be kept under cytological surveillance, or referred for colposcopy, and only a small proportion of them would derive a health benefit, whereas the remainder would have to endure a period of increased anxiety and discomfort. Such factors need full consideration before the implementation of the technology.

Implications of computer-based slide analysis for screening programmes

Computer-based automated screening of cytology slides is under development. The first system for conventional smears (PAPNET) is no longer available, and the closely related 'Autopap' primary screening system has recently been adapted for use with LBC slides. There is no substantial difference between the performance of this system and manual screening.[12] However, the cost-effectiveness of automatic screening is less favourable, unless the costs of the automatic screening device can be substantially reduced. Conversely, working with an automated system may contribute positively to the motivation of cytology laboratory staff, since monotonous screening of large numbers of negative smears will be greatly reduced. Such an effect may offset concerns about cost-effectiveness.

The use of HPV testing within cervical screening

HPV testing may be of benefit within cervical screening programmes in three different capacities. Triage is already in place in some countries,[13,14] whilst primary screening and test of cure are the subject of intensive research.

HPV testing as triage

HPV testing can be readily incorporated into screening, in addition to cytology, particularly in LBC, which provides residual fluid containing cervical cells for further analysis. Furthermore, HPV testing does not require women to be recalled for further sampling.

A major component of cervical screening is the visit to the clinic for speculum examination; once this has been undertaken, the most accurate test possible should be applied. However, whilst additional disease would undoubtedly be detected, if present, being aware of the presence of HPV infection would not be clinically useful in cytology-

Key risk factors for residual disease

- As a triage test for women with atypical squamous cells of undetermined significance (ASCUS) or borderline cytology results
  - Women testing positive for HR HPV are referred to colposcopy
  - Women testing negative for HR HPV are followed up 1 year later or returned to the routine follow-up pool
- As a primary screening test, either instead of cytology or as an adjunct to cytology
- As a test for cure, following treatment for CIN, instead of cytological surveillance

negative women and could be an ongoing source of stress. The potential marginal benefits of additional cancer prevention would, therefore, need to be balanced against, firstly, the additional costs of two screening tests rather than one; secondly, the resultant increased referrals; and, thirdly, the stress for the women involved.

HPV testing for the triage of women with atypical squamous cells of undetermined significance (ASCUS) or borderline cytology has already been adopted by screening programmes in some countries and by individual clinicians in others, on the basis of work from the ASCUS/Low-Grade Squamous Intraepithelial Lesions Triage Study (ALTS) group, in the US (see box).[13–15] HPV testing identified those women with equivocal cytology who were at highest risk of having underlying cervical lesions of a more serious nature, and those who were at virtually no risk.

The ALTS study results demonstrate that the cost-effectiveness of HPV-based triage is highly dependent on the precise cytological category being triaged and the characteristics of the cytology system used. In Europe, there are many cytology classification systems in use, but few of them have a direct correlate of the 'ASCUS' category of the Bethesda system classification. Furthermore, even where the

Key features of the ALTS study

- Large, multicentre, randomized trial that has produced credible data
- HPV testing and a single repeat Pap smear each referred a similar number of women with ASCUS to colposcopy
  - This use of HPV testing may be cost-effective
- >80% of women with low-grade squamous intraepithelial lesions (LSIL) were HPV-positive
  - HPV testing would not be valuable for LSIL triage because too many women would be referred to colposcopy

Bethesda system is used, a 'European' ASCUS will not necessarily be the same as an 'American' ASCUS. Therefore, unless clinicians in a particular country are confident that they have a direct correlate of the ASCUS classification used in the ALTS trial, it is not valid to adopt the results of this study for public health purposes without re-validating the protocol within their own system. For example, at the time of writing, pilot implementation is being undertaken in the NHS in England and will be subject to a thorough evaluation before further implementation is considered.

The value of HPV testing may lie in its high negative predictive value, since it has been demonstrated that women who are HPV-negative are at low risk of having underlying cervical cancer, even if their cytology test shows a borderline abnormality. In the ALTS study, the negative predictive value of HPV testing was found to be 99.5% and, largely on the basis of these results, the American Society for Colposcopy and Cervical Pathology has issued recommendations that ASCUS-positive, HPV-negative women can be returned to routine recall (after 1 year, under the American system). Within such a system, therefore, HPV-based triage offers two important advantages: women can be returned to routine screening without a lengthy period of heightened surveillance (with the resultant anxiety that this entails), and women who test HPV-positive may be referred to colposcopy sooner than might otherwise have been the case.

HPV testing as primary screening

Testing for HR HPV types as primary screening has been the subject of research trials in many countries. A positive HR HPV test has a much higher sensitivity than cytology for the detection of CIN 2 or worse.[16] However, the majority of women who test positive for HR HPV do not have clinically relevant cervical dyskaryosis, and the clinical relevance of a single positive test is as yet uncertain. HPV is a sexually transmitted infection (STI) and, in common with other STIs, has a peak prevalence between the ages of 18 and 25 years. Nevertheless, few women in this age group develop cervical abnormalities, let alone cancer, and many of them are never even aware that they have harboured the virus.

Persistence of the infection has been shown to be a requirement for the development of CIN and cervical cancer[17] but, as yet, there is no way of determining, from a single HPV test, whether the infection is newly acquired or long-standing, which would therefore place the woman at higher risk. Both viral load and viral typing are now being examined to assess whether they can be used as surrogate markers for persistence or for the likelihood of persistence but the currently available data are unconvincing. Other markers that may augment or replace HPV testing are also being investigated.

If HPV testing is adopted as the primary screening test, the problem of poor specificity might be resolved using cytology to triage positive specimens. Cytology screeners are scarce in many parts of the world. Whereas there might be unwillingless to switch completely to HPV testing for primary screening, because of poor specificity and a reluctance to lose scarce cytological skills, the use of cytology as triage might increase specificity and optimize the available cytology skills.

The studies published to date on HPV as primary screening have concentrated on the performance of a single HPV test, in comparison with a single Pap smear, and have not examined the use of HPV testing within the context of a screening programme, with an evaluation of its impact on the programme as a whole. Furthermore, only a few studies

have assessed the cost benefits achieved from the introduction of HPV testing, and these rely on estimates derived from modelling. The results of such studies are highly dependent on the assumptions that underpin the models used. In 1997, van Ballegooijen *et al*. examined the cost-effectiveness of primary screening after inclusion of a HPV test, using both favourable and unfavourable variants of the interval between HR HPV persistence and the development of high grade cervical lesions, consistent with the evidence then available.[18] These authors concluded that the cost-effectiveness of including HPV testing could range from favourable to poor.[18]

As with triage applications, the advantage of HPV testing for population screening may not lie in its positive predictive value, which is very low, but in its negative predictive value, which is very high. Furthermore, preliminary data now indicate that this unprecedented negative predictive value may hold for 5 years or more. If this finding is confirmed, it would be possible to screen women at less frequent intervals, or even withdraw them from screening altogether, or earlier than would otherwise be possible. The expenditure saved from a non-screening policy would contribute to, if not cover entirely, the costs needed to pay for the HPV test. The savings might also provide for more frequent screening of those women who are HR HPV-positive and, therefore, more likely to be at risk of developing invasive cervical cancer. However, since HPV infection is very common amongst younger women, it may prove appropriate to have different strategies for cervical screening in women of different ages, with HPV testing being reserved for those over the age of 30 or 35 years.

HPV testing to confirm cure

HPV testing has also been proposed for the follow-up of women who have been treated for CIN. These women often undergo increased cytological surveillance for a lengthy period of time. In the UK, annual cytology testing is performed for 5–10 years after the conclusion of treatment, and is organized as part of the national cervical screening programme. The negative predictive value of a HR HPV test is so high that it should be possible to return women who test negative after

treatment to routine screening much sooner than is currently the norm. This application of HPV testing is currently under active investigation in several countries.

Summary

- The inclusion of HPV testing in cervical screening programmes is a promising option
  - Knowledge of a woman's HPV status may add to her anxiety, particularly given the sexual mode of transmission of the virus
  - However, the great potential of HPV testing for reducing anxiety – either by returning her to 'normal' status, or by allowing doctors to proceed more decisively with her management – may at least balance this out
- The ultimate equation to be resolved, when comparing a programme that uses some form of HPV testing with the currently successful cytology-based programmes, is the relationship between sensitivity and specificity, financial costs and savings, and psychological effects

References

1. Hakama M, Louhivuori K. A screening programme for cervical cancer that worked. *Cancer Surv* 1988;7:403–16
2. Laara E, Day NE, Hakama M. Trends in mortality from cervical cancer in the Nordic countries: association with organised screening programmes. *Lancet* 1987;1:1247–9
3. Day NE. Screening for cancer of the cervix. *J Epidemiol Community Health* 1989;43:103–6
4. Day NE. The epidemiological policy basis for evaluating different screening policies, in Hakama M, Day NE, Miller AB (eds): Screening for Cancer of the Uterine Cervix. Lyon, IARC Scientific Publication, 1986
5. Schaffer P, Anthony S, Allemand H. Would a higher frequency of smear tests lead to the prevention of cervical cancer, in Monsonegro J (ed): Papillomavirus in Human Pathology, Challenges of Modern Medicine. Paris, Ares-Serona Symposia Publications, 1995
6. Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gynecol Pathol* 1993;12:186–92
7. van den Akker-van Marle ME, van Ballegooijen M, van Oortmarssen GJ *et al*. Cost-effectiveness of cervical cancer screening: comparison of screening policies. *J Natl Cancer Inst* 2002;94:193–204
8. Fahey MT, Irwig L, Macaskill P. Meta-analysis of Pap test accuracy. *Am J Epidemiol* 1995;141:680–9
9. van Oortmarssen GJ, Habbema JD. Duration of preclinical cervical cancer and reduction in incidence of invasive cancer following negative pap smears. *Int J Epidemiol* 1995;24:300–7
10. Payne N, Chilcott J, McGoogan E. Liquid-based cytology in cervical screening: a rapid and systematic review. *Health Technol Assess* 2000;4:1–73
11. Meerding WJ, van Ballegooijen M, Habbema JDF. Performance and cost-effectiveness of liquid based cytology. *Histopathology* 2002;41 (Suppl 2):494–505
12. Doornewaard H, van der Schouw YT, van der Graaf Y *et al*. Observer variation in cytologic grading for cervical dysplasia of Papanicolaou smears with the PAPNET testing system. *Cancer* 1999;87:178–83

13. Solomon D, Schiffman M, Tarone R. Comparison of three management strategies for patients with atypical squamous cells of undetermined significance: baseline results from a randomized trial. *J Natl Cancer Inst* 2001;93:293–9

14. Manos MM, Kinney WK, Hurley LB *et al*. Identifying women with cervical neoplasia: using human papillomavirus DNA testing for equivocal Papanicolaou results. *JAMA* 1999;281:1605–10

15. ALTS Group. Human papillomavirus testing for triage of women with cytologic evidence of low-grade squamous intraepithelial lesions: baseline data from a randomized trial. The Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesions Triage Study (ALTS) Group. *J Natl Cancer Inst* 2000;92:397–402

16. Cuzick J, Sasieni P, Davies P *et al*. A systematic review of the role of human papillomavirus testing within a cervical screening programme. *Health Technol Assess* 1999;3:i-iv,1–196

17. Bosch FX, Lorincz A, Munoz N *et al*. The causal relation between human papillomavirus and cervical cancer. *J Clin Pathol* 2002;55:244–65

18. van Ballegooijen M, van den Akker-van Marle ME, Warmerdam PG *et al*. Present evidence on the value of HPV testing for cervical cancer screening: a model-based exploration of the (cost-)effectiveness. *Br J Cancer* 1997;76:651–7

5. The potential public health impact of vaccines against human papillomavirus

Ruanne V Barnabas and Geoffrey P Garnett

- Candidate HPV vaccines to protect against cervical cancer are progressing rapidly through efficacy trials
- The potential epidemiological impact of a HPV vaccine can be estimated using a mathematical model
- Modelling the population dynamics of infectious disease can explore the potential consequences of new technologies
- Extensive vaccine coverage is required to combat widespread infection
- Modelling results can help to specify clinical trial endpoints

Introduction

Public health measures to prevent cervical cancer (CC) currently rely on early detection and excision of precancerous lesions. The recent identification of oncogenic HPV infections as a necessary cause of CC has provided new directions for research. Vehicles have been developed to present HPV antigens to the immune system, and candidate vaccines are progressing rapidly through efficacy trials. However, HPV and CC epidemiology is complex, and decisions about the use of HPV vaccines are challenging. Here we review vaccine development, and illustrate the potential epidemiological impact of an HPV vaccine using a mathematical model.

HPV vaccine development

Candidate HPV vaccines have the potential to control infection, decrease the burden of screening for HPV infections, and of their treatment, and at the same time reduce CC incidence.[1,2]

Types of HPV vaccine

- Prophylactic vaccines that aim to induce virion neutralizing antibodies to prevent new HPV infection
- Therapeutic vaccines that aim to stimulate lesion regression through cell-mediated immune mechanisms
- Chimeric vaccines that attempt to combine the properties of prophylactic and therapeutic vaccines

Modelling the epidemiological impact of vaccines

Mathematical models describing the population dynamics of infectious disease can explore the potential consequences of new technologies that alter the epidemiology of an infection (Figure 1).[3–7]

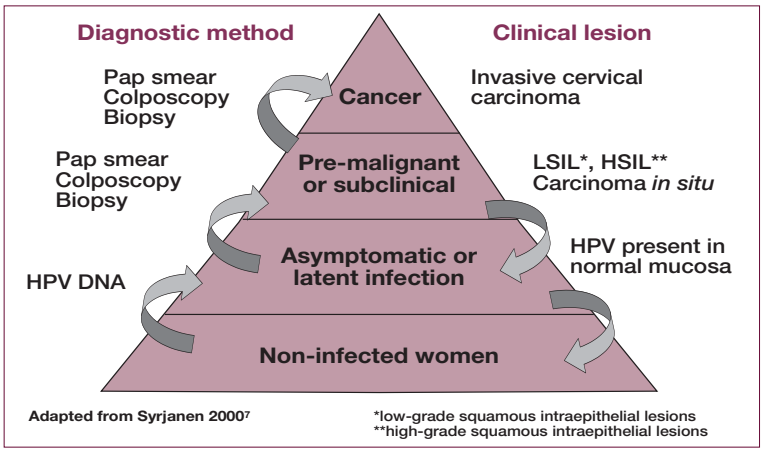

Figure 1 HPV infection and cervical cancer (CC) at population level

Simple theory has identified a critical fraction of the population that needs to be effectively vaccinated to eliminate infection (p_c), which increases as the basic reproductive number of infection (R_0) – the number of new infections caused by one infectious individual in an entirely susceptible population – increases: ($p_c=1-(1/R_0)$). If an infection is widespread, more coverage (the percentage of the target population vaccinated) is required for elimination. Attempts to eliminate HPV, a sexually transmitted infection (STI), are hampered by high-risk reservoirs where infection can persist. It is more appropriate, therefore, to attempt to reduce the endemic prevalence of infection (p). Here, the mechanism that causes vaccine failure when efficacy is below 100% is of crucial importance. The level of protection provided by a vaccine (measured as efficacy) in a trial can reflect a variety of biological effects, and this may be illustrated by considering two extremes of protection (see box).

The relationship between prevalence, take, and degree of protection for a vaccine against an infection in a homogeneous population with a reproductive number of 10 is shown in Figure 2. If the vaccine provides 'take' type protection, there is a linear decrease in the prevalence of infection as efficacy (see box) increases, whereas if it provides 'degree' type protection, there is a non-linear decrease.

Spectrum of protection afforded by a vaccine[8]

Take

Vaccine may protect a fraction of recipients against all challenges

$$p = 1 - \frac{1}{R_0} - V_t \cdot e_t$$

Degree

Vaccine may protect all recipients against a fraction of challenges

$$p = 1 - \frac{1}{R_0 \cdot (1 - V_d \cdot e_d)}$$

P = endemic prevalence of infection
V_t = coverage with a vaccine providing total protection with a take efficacy e_t
V_d = coverage with a vaccine providing degree protection with efficacy e_d

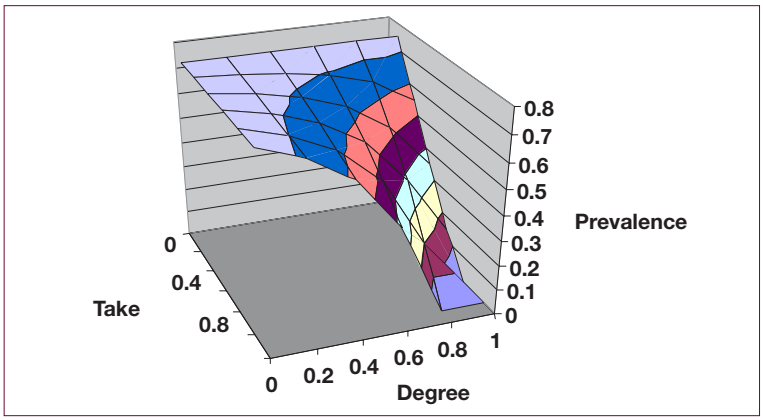

Figure 2 The impact of vaccination, according to simple theory

If a vaccine protects a fraction of recipients against a fraction of challenges, then its impact is a combination of the two types.[9] These solutions apply to vaccines when the pattern of risk is the same for everyone. Where there is behavioural heterogeneity, as for STIs, the reduction in incidence and prevalence of infection is initially rapid, and then slows as unprevented infections remain evident in a small, highly sexually active population.[10]

Vaccine efficacy and effectiveness

- Efficacy: measures how well an intervention can work under ideal conditions, such as a vaccine trial
- Effectiveness: measures the impact of an intervention under more realistic conditions: for example, in an immunization programme that does not vaccinate 100% of the target population

HPV clinical vaccine trials should provide data on the 'efficacy' of the vaccine, but how this factor relates to take, degree and also duration of protection may be unclear. However, the very high seroconversion rate in early clinical trials, together with the high level of protection in animal models, suggests that there could be a high take against the particular viral types included in the vaccine.

Model definition

To advance from simple theory, we developed a compartmental, deterministic model and applied it to the question of whether women and men, or women only, should be vaccinated (see box on page 66).

For both squamous intraepithelial lesions (SIL) and CC, at high vaccination coverage, the additional benefit achieved by vaccinating men as well as women is small. For men, the HPV vaccine would carry the risks of immunization but little benefit, although the inclusion of low-risk HPV types 6 and[11] would potentially decrease the incidence of genital warts. 11 There may also be immunological reasons why immunization should be confined to women: if breakthrough infections do occur among vaccinated women, mucosal antibodies coating the shed virus may neutralize the virus and stop transmission to susceptible men, thus reducing the need for men to be vaccinated (J Schiller, personal communication). If vaccination of men carries little benefit, then resources could be conserved and public strategies should concentrate on vaccinating women only.

Should men also be vaccinated? Model integrating HPV-progress-to-disease-with-age and HPV transmission

Model assumptions

- Based on developing country demographics
- Population growth rate of 3% annually
- Individuals are either vaccinated at 15 years of age or remain susceptible to HPV infection
- Sexual activity begins at 15 years of age
- Population was stratified according to age (0–85 years) and sexual activity class (i = 1, 2…4), defined according to the rate of sexual partner change

Conclusions

Male vaccination would:

- Protect women
- Protect homosexual men
- Expose heterosexual men to risks associated with vaccination, while only a minority might benefit from prevention of low-incidence HPV anogenital and head/neck cancers
- Produce small benefits in HSIL and CC reduction
- Be most effective at low vaccine overall coverage

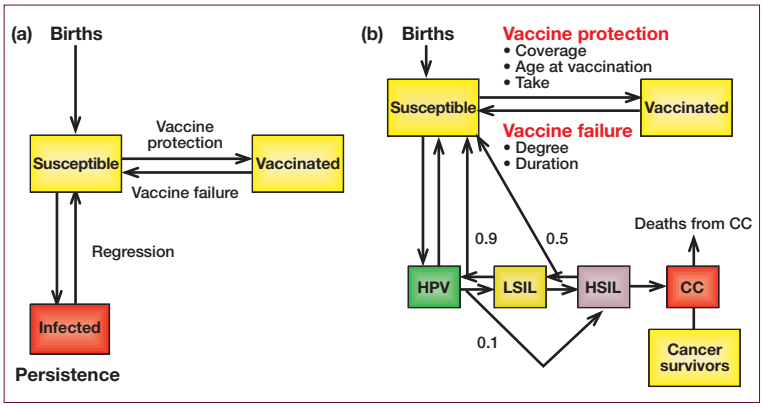

Figure 3 Modelling the natural history of infection in (a) men and (b) women

The model description of infection and disease in men and women is illustrated in Figure 3.

Men may either be susceptible, infected with HPV or protected by vaccination. After infection in women, there are several possible progressive outcomes: HPV latent or asymptomatic infection; low-grade squamous intraepithelial lesions (LSIL: mild dysplasia) and high-grade squamous intraepithelial lesions (HSIL: moderate to severe dysplasia). A fourth outcome is CC, and the fifth is CC survivors (CS). Of the asymptomatic HPV infections that progress, 10% move directly to HSIL, rather than through LSIL, representing rapidly progressive infection.[12] At each stage of infection, for men and women, HPV can regress, persist or progress.

The vaccine is assumed to have an ideal efficacy of 100%, and lifetime duration, with only the coverage varying. In an alternative model, coverage is assumed to be 100% and the variation included in the model represents altered efficacy. Complete protection is a reasonable initial assumption because virus-like particles (VLPs) have been shown to induce approximately 40-fold higher neutralizing antibody titres than natural infection[13] and provide close to 100% protection in animal studies against homologous papillomavirus challenges.[14] Also, the initial results of a US vaccine trial indicate that this Merck vaccine has 100% efficacy.[15] Over time, Phase IV clinical trials should provide more accurate data on the duration of vaccine protection. Although HPV virion antibodies persist after natural infection,[16] it is unclear whether antibody levels are sufficient to protect against reinfection.

Parameters used for HPV regression and progression in the model were derived from several studies,[12] and progression and regression rates were converted to transition probabilities (Table 1).[17]

The model captures the pattern of infection and disease with age, as it uses partial differential equations to describe changes with respect to age and time. In the current analysis, the rate of transition from one compartment to the next is independent of the time spent in each compartment. While the 'time since HPV infection' appears to be closely correlated with progression, in the case of persistent infections that are more likely to progress to high-grade lesions than transient

HPV infection, the model does not take account of the duration of asymptomatic or low-grade disease before progression.[18] However, young women more commonly have transient infections, whereas women >35 years of age are more likely to have persistent ones, age-dependent transition rates are different for those younger and older than 30 or 35 years (Table 1).

Table 1 Transition probabilities and incidence rates of HPV infection.[12] Incidence rates were converted to probabilities in the model (see Figure 2)

Parameter description	Parameter value
Asymptomatic HPV progression rate to SIL	0.2/36 months
Proportion of asymptomatic HPV progressing directly to HSIL	0.1
Asymptomatic HPV regression rate to susceptible	
15–29 years	0.6/18 months
≥30 years	0.15/18 months
LSIL progression rate to HSIL	
15–34 years	0.1/72 months
≥35 years	0.35/72 months
LSIL regression rate to asymptomatic or susceptible	
15–34 years	0.65/72 months
≥35 years	0.4/72 months
Proportion of LSIL regressing to susceptible	0.9
HSIL progression rate to invasive cancer (stage 1)	0.4/120 months
HSIL regression rate to LSIL or susceptible	0.35/72 months
Proportion of HSIL reverting to susceptible	0.5

HSIL: high-grade squamous intraepithelial lesions; LSIL: low-grade squamous intraepithelial lesions

Progression and regression rates probably change gradually with age, rather than instantly as described in the model. Hopefully, the longitudinal studies currently in progress will shed light on infection dynamics over time[19,20] and allow more detailed age-specific regression and progression rates to be incorporated in theoretical analyses.

Susceptible men and women are infected at an age and sexual activity-specific rate per year: the force of infection (λ). This per-susceptible risk of acquiring infection is a function of the rate of sexual partner acquisition; the pattern of mixing between sexual partners according to sexual activity; the fraction of these partners infected; and the likelihood per sexual partnership that HPV is transmitted from an infected to a susceptible partner. The methods used are similar to those previously used in modelling HIV transmission dynamics.[21,22] The transmission probability was estimated to be 0.036 for susceptible women with infectious male partners and 0.031 for susceptible men with infectious women.

Model results for HSIL and CC

The model age-specific prevalence for asymptomatic HPV infection, LSIL, HSIL and CC in an unvaccinated, unscreened population is shown in Figure 4.

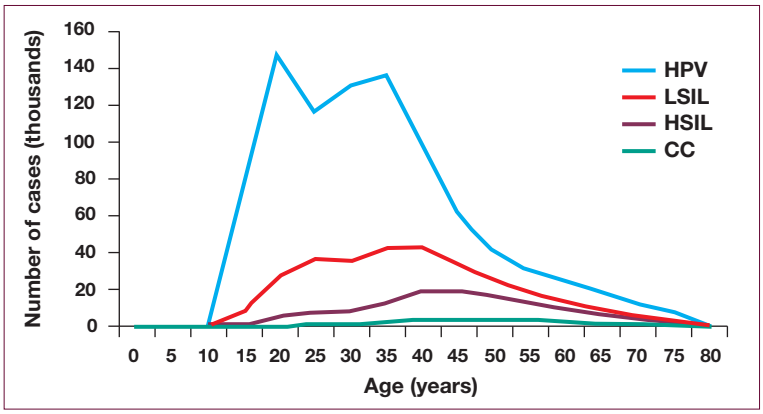

Figure 4 Age-specific prevalence of HPV, LSIL, HSIL and CC at model equilibrium. (Total number of women in the population = 14 million)

The highest prevalence of HPV is evident in 15–25-year-olds, and a second peak occurs, due to the different regression rates used for those women >35 years old (Table 1). As disease progresses, the peak

incidence age of LSIL and HSIL shifts to older women, and the peak age for CC is 50 years.

The impact on CC of vaccinating men and women at different coverage is modelled in Figure 5 for those HPV types included in the vaccine. The dynamics of HPV evolve slowly and monotonically to a new stable prevalence as successive cohorts of susceptibles are vaccinated. At the lower vaccine coverage of 30%, vaccinating both men and women decreases the incidence of CC by a further 32%, compared with vaccinating women alone, but there are long time-delays (>90 years) before reductions are realized. At high vaccine coverage (80%), vaccinating both women and men has a marginal increased benefit over vaccinating women only.[23] Vaccinating 80% of the population or 80% of women reduces the incidence of CC from 45 cases to <1 case per 100 000 women after 60 years. After vaccinating 80% of women and men, CC incidence reaches equilibrium 5 years earlier than vaccinating women only. However, since a vaccine will not protect against all high risk (HR) HPV types, the CC incidence will certainly be higher after vaccination than is shown here.

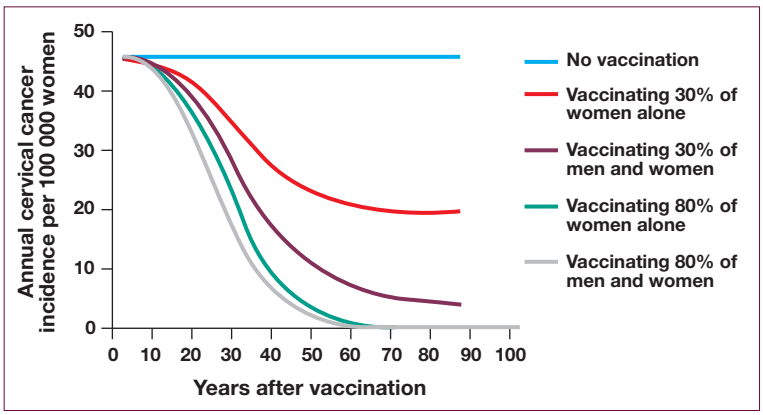

Figure 5 The effect of vaccination on the incidence of cervical cancer over time

Interpreting the model results

Major simplifying assumptions of model

- The vaccine is assumed to either work and protect individuals from all HPV types or fail to protect the vaccinated individuals. There is the potential for transient infection with vaccine types in vaccine recipients or infection with non-vaccine types. The model will overestimate the impact of vaccination
- The model considers the broad range of HPV types as a single pathogen; repeated infections appear possible because individuals return to the susceptible population on recovery, whereas, biologically, repeated infections occur because of infection with different types, because of type-specific immunity

The simplified model represents a vaccine covering the broad range of HPV types (see box). In theory, a multivalent vaccine could potentially cover as much as 80% of oncogenic types,[2] but there will always be a limit to this coverage. Removing viral types through vaccination could potentially allow other viral types to take their place, a possibility that requires research. In a worst-case scenario, the removal of benign types could release pathogenic viral types. More realistically, new pathogenic viral types could replace the most frequent pathogenic forms, if cross-immunity between types is present; if cross-immunity acts in a frequency dependent manner to suppress some viral types; and if the vaccine does not offer the same cross-protection.

A multivalent HPV vaccine could easily cover the handful or so of the most prevalent oncogenic HPV types, and further tailoring could make a vaccine region-specific for a particular geographic area.[2] It is possible that HPV types not covered by the vaccine would fill the ecological niche created by immunization, and screening would have to continue to monitor changes in the dominant HPV types. The consequences of vaccination depend on any changes seen in

dominant HPV types; an increase in the incidence of benign HPV infections may necessitate screening, but not treatment, whilst an increase in HR HPV types not included in the vaccine would require ongoing screening, treatment and follow-up of pre-cancerous lesions.

The effect of varying vaccine coverage on the incidence of CC over time is modelled in Figure 6. Vaccine coverage of at least 66% is needed to decrease CC incidence substantially. With a vaccine coverage of 66%, incidence of CC decreases by 80% after 40 years. In addition to the long pre-malignant lag-phase, a sustained vaccine programme over decades at a high coverage would be prudent because HPV can be maintained in the population at low levels by a small number of people with high sexual activity.[10] Also due to the many HR HPV types, HPV control, rather than elimination or eradication, should be the first goal of vaccine programmes.

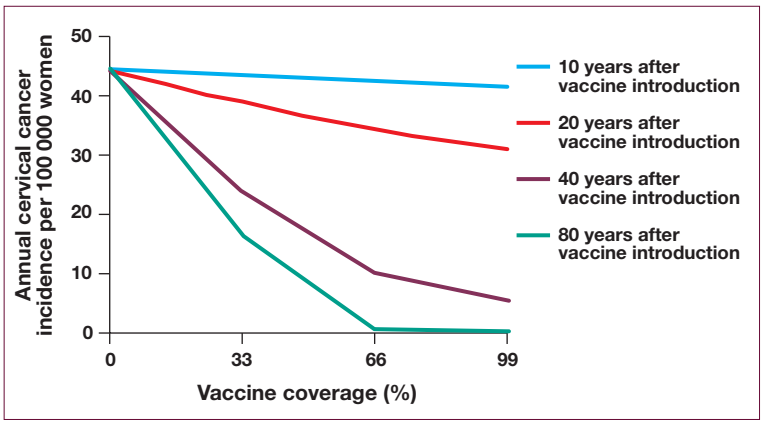

Figure 6 The effect of varying vaccine coverage on CC incidence

Following the introduction of vaccination, a lag-phase occurs until the full benefits of decreased disease incidence are realized; this interval is around 60 years for CC and 40 years for SIL. Although catch up vaccination has the potential to accelerate these benefits, decision makers would have to ensure the longevity of HPV immunization

programmes to ensure all benefits are realized, because the effects of vaccination on women already exposed to HPV infection are not yet known. Adding therapeutic properties to a prophylactic vaccine could make it a more attractive option to decision makers, because some short-term gains would be possible. These considerations highlight the importance of identifying suitable clinical trial endpoints.

Implications for clinical trial endpoints

Table 2 summarizes the efficacy trials for prophylactic vaccines that are currently planned (2004).

Table 2 Current stage of candidate HPV vaccine development

Vaccine type (prophylactic or therapeutic)	Group	Antigen(s)	Adjuvant	Safety and immuno-genicity trial results (Phase I–II)	Clinical trial endpoints (Phase III–IV)
Prophylactic VLP	GSK	L1 HPV 16 & 18	Alum-based	Ongoing	Planned
Prophylactic VLP	Merck	L1 HPV 16 & 18	Alum	Ongoing	In Phase III • Genital warts related to HPV 6/11 • CIN 1 related to HPV 6/11/16/18 • CIN 2/3 related to HPV 16/18
Prophylactic VLP	NCI	L1 HPV 16	No adjuvant	Ongoing	Planned (Costa Rica) • Persistent cervical HPV 16 DNA • HPV 16 positive LSIL (CIN 1)

The choice of clinical endpoints for vaccine efficacy trials is an important issue. Because clinical trials cannot ethically consider CC as a trial endpoint, other stages in disease pathogenesis, such as persistent HPV infection or SIL, should be used as surrogate endpoints of vaccine efficacy.[2] However, using HSIL or LSIL as endpoints is

problematic. While 30% of women with persistent oncogenic HPV infections were observed to develop cervical dysplasia, only 5–8% of those women developed HSIL.[18] Few cases of HSIL develop into CC, so if HSIL were used as an endpoint, large, extended clinical trials would be required, and a possibly effective prophylactic vaccine would be beyond the reach of women who could have benefited from it. Using LSIL as an endpoint could introduce significant inter-observer and inter-laboratory variation and, since LSIL can resolve spontaneously, vaccine efficacy might not be accurately recorded. As shown in Table 2, another endpoint is persistent HR HPV DNA-positivity, as this can be reliably and consistently determined and is a necessary step in disease pathogenesis.

Figure 7 shows the modelled impact of vaccination on LSIL, HSIL and CC on the HPV types vaccinated against over the first 25 years. The decrease in type-specific LSIL is earlier and of greater magnitude, compared with HSIL. Thus, the model results support the use of type-specific LSIL as a trial endpoint, because it is a surrogate for the decrease in CC incidence that follows the LSIL incidence decrease. The introduction of an HPV vaccine based on reduction in type-specific LSIL has the potential to save lives because the time-interval before a reduction in HSIL would be many more years.

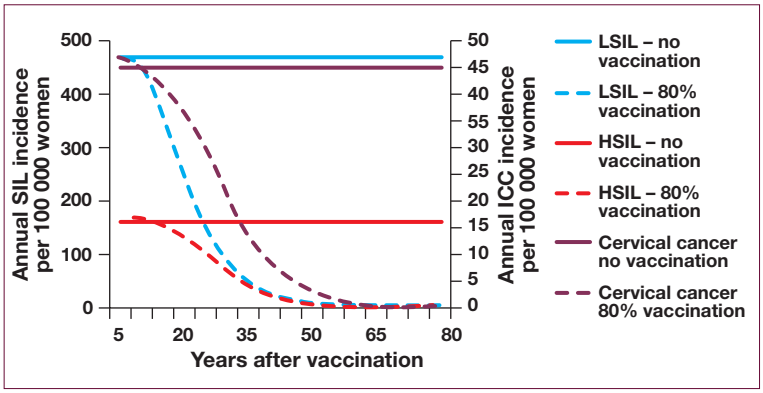

Figure 7 The effect of vaccination on the incidence of LSIL, HSIL and CC: implications for trial endpoints

Permission for vaccine licensing would ensue, if it were demonstrated that HPV vaccines can prevent steps in CC pathogenesis.[2] The introduction of vaccination programmes with promising, though incomplete, evidence of efficacy has a precedent: in the UK, meningococcal vaccination was introduced early because of the substantial potential benefits, in terms of lives saved.[24] However, early licensing of HPV vaccines carries with it the responsibility of long-term follow-up of initial trials, to determine the duration of protection from incident infection; to confirm the expected protection against high-grade dysplasia; and to provide sufficient safety data to evaluate the incidence of rare adverse events. Whilst the results of HPV vaccination may not be immediate or medium-term, the benefits are potentially large.

Cost and purpose of a HPV vaccine

Where screening to prevent CC is adequate, it should be maintained, both to 'mop up' cases of infection and subsequent progression amongst those unvaccinated or unprotected, and to cover the remaining pathogenic HPV types not included within the vaccine. Cost is likely to become a major issue, since the regions that are most in need of HPV vaccines are those where screening is ineffective, because they are typically those least able to afford such healthcare measures. Current VLP vaccine production methods are expensive and are tailored to parenteral administration. An oral vaccine may be more cost-effective[25] and easier and safer to administer.

Decreasing the incidence of HPV infection and cervical dysplasia could result in some savings in the developed world, where screening and intervention programmes are costly.[26] However, HPV vaccination may provide the greatest benefit in the developing world, where resources for screening are scarce.

Summary

- HPV control, rather than elimination or eradication, should be the first goal of vaccine programmes
- Modelling results indicate that:
  - Vaccination of men as well as women has little benefit in reducing CC incidence compared to vaccinating women alone
  - Vaccine coverage of at least 66% is needed to decrease CC incidence substantially
  - A lag-phase of about 60 years and 40 years occurs from the introduction of vaccination until the full benefits of a decreased incidence of CC and LSIL, respectively, are realized
  - Introduction of an HPV vaccine for the purpose of reducing type-specific LSIL has the potential to save lives

References

1. Lehtinen M, Paavonen J. Efficacy of preventive human papillomavirus vaccination. *Int J STD AIDS* 2001;12:771–6
2. Lehtinen M, Dillner J. Preventive human papillomavirus vaccination. *Sex Transm Infect* 2002;78:4–6
3. Anderson RM, May RM. Directly transmitted infections diseases: control by vaccination. *Science* 1982;215:1053–60
4. Anderson RM, Garnett GP. Low-efficacy HIV vaccines: potential for community-based intervention programmes. *Lancet* 1996;348:1010–3
5. Anderson RM, Grenfell BT. Quantitative investigations of different vaccination policies for the control of congenital rubella syndrome (CRS) in the United Kingdom. *J Hyg (Lond)* 1986;96:305–33
6. Gay NJ, Hesketh LM, Morgan-Capner P, Miller E. Interpretation of serological surveillance data for measles using mathematical models: implications for vaccine strategy. *Epidemiol Infect* 1995;115:139–56
7. Syrjänen KJ, Syrjänen S Papillomavirus infections in human pathology. Chichester, Wiley, 2000
8. Smith PG, Rodrigues LC, Fine PE. Assessment of the protective efficacy of vaccines against common diseases using case-control and cohort studies. *Int J Epidemiol* 1984;13:87–93
9. Longini IM, Jr., Hudgens MG, Halloran ME, Sagatelian K. A Markov model for measuring vaccine efficacy for both susceptibility to infection and reduction in infectiousness for prophylactic HIV vaccines. *Stat Med* 1999;18:53–68
10. Garnett G. The influence of behavioural heterogeneity on the population level impact of potential prophylactic HIV-1 Vaccines. *J R Stat Soc* 1998;161:209–25
11. Schiller JT, Lowy DR. Papillomavirus-like particle based vaccines: cervical cancer and beyond. *Expert Opin Biol Ther* 2001;1:571–81
12. Myers ER, McCrory DC, Nanda K *et al*. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. *Am J Epidemiol* 2000;151:1158–71
13. Harro CD, Pang YY, Roden RB *et al*. Safety and immunogenicity trial in adult volunteers of a human papillomavirus 16 L1 virus-like particle vaccine. *J Natl Cancer Inst* 2001;93:284–92

14. Schiller JT, Hidesheim A. Developing HPV virus-like particle vaccines to prevent cervical cancer: a progress report. *J Clin Virol* 2000;19:67–74

15. Koutsky LA, Ault KA, Wheeler CM *et al*. A controlled trial of a human papillomavirus type 16 vaccine. *N Engl J Med* 2002;347:1645–51

16. af Geijersstam V, Kibur M, Wang Z *et al*. Stability over time of serum antibody levels to human papillomavirus type 16. *J Infect Dis* 1998;177:1710–4

17. Miller DK, Homan SM. Determining transition probabilities: confusion and suggestions. *Med Decis Making* 1994;14:52–8

18. Schlecht NF, Kulaga S, Robitaille J *et al*. Persistent human papillomavirus infection as a predictor of cervical intraepithelial neoplasia. *JAMA* 2001;286:3106–14

19. Munoz N. Human papillomavirus and cancer: the epidemiological evidence. J Clin Virol 2000;19:1–5

20. Franco EL, Villa LL, Sobrinho JP *et al*. Epidemiology of acquisition and clearance of cervical human papillomavirus infection in women from a high-risk area for cervical cancer. *J Infect Dis* 1999;180:1415–23

21. Garnett GP, Anderson RM. Factors controlling the spread of HIV in heterosexual communities in developing countries: patterns of mixing between different age and sexual activity classes. *Philos Trans R Soc Lond B Biol Sci* 1993;342:137–59

22. Garnett GP, Anderson RM. Balancing sexual partnerships in an age and activity stratified model of HIV transmission in heterosexual populations. *IMA J Math Appl Med Biol* 1994;11:161–92

23. Hughes JP, Garnett GP, Koutsky L. The theoretical population-level impact of a prophylactic human papilloma virus vaccine. *Epidemiology* 2002;13:631–9

24. Miller E, Salisbury D, Ramsay M. Planning, registration, and implementation of an immunisation campaign against meningococcal serogroup C disease in the UK: a success story. *Vaccine* 2001;20 Suppl 1:S58–67

25. Gerber S, Lane C, Brown DM *et al*. Human papillomavirus virus-like particles are efficient oral immunogens when coadministered with Escherichia coli heat-labile enterotoxin mutant R192G or CpG DNA. Journal of Virology 2001;75:4752–60

26. Follen M, Richards-Kortum R. Emerging technologies and cervical cancer. *J Natl Cancer Inst* 2000;92:363–5

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