



The role of Pap and HPV test in new era of cervical cancer screening

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DISCLOSURES

- Speaker bureau BD Diagnostics Europe
- Speaker Bureau BD Diagnostics Asia-Pacific
- Speaker bureau Source Bioscience plc
- Medical advisory board Zilico Ltd

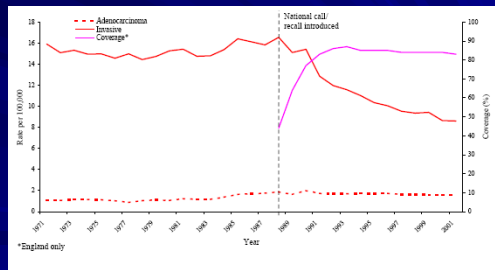
Cancer of the Cervix: Death by Incompetence

The most successful programmes:

- 'are organised as public health cancer control programmes, specifically directed towards a reduction of mortality'
- 'call the age groups at greatest and most immediate risk (30+) and keep on trying. Concentrate first upon women who have never had a smear at all. They use population registers'
- 'someone is in charge...and can be held to account'

Lancet 1985; ii: 363-364

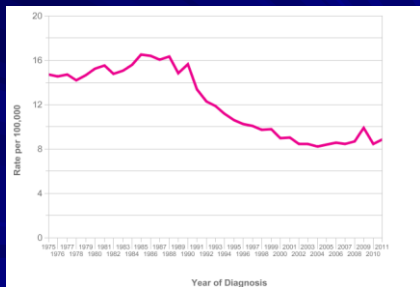
Age-standardised incidence of invasive cervical cancer (total) and adenocarcinoma of the cervix. England and Wales 1971-2001



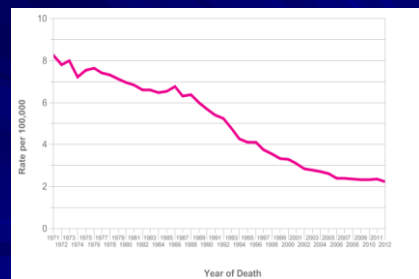
*England only

Cancer Trends: Office for National Statistics

Cervical Cancer, European Age-Standardised Incidence Rates, Great Britain, 1975-2011



Cervical Cancer, European Age-Standardised Mortality Rates, UK, 1971-2012



Cervical Screening in England and Wales after 1988

- Screening saves at least 1100 and up to 4000 lives per annum
- Impact on both squamous cell carcinoma and adenocarcinoma
- Annual deaths below 1000 per annum
- 78.3% eligible women screened every 5 years:
 - 71.5% women aged 25-49 every 3 years
 - 77.5% women aged 50-64 every 5 years

Peto et al. *Lancet* 2004; 364: 249
Sasieni. *Lancet* 2001; 357:1490

Liquid Based Cytology: Likely Benefits

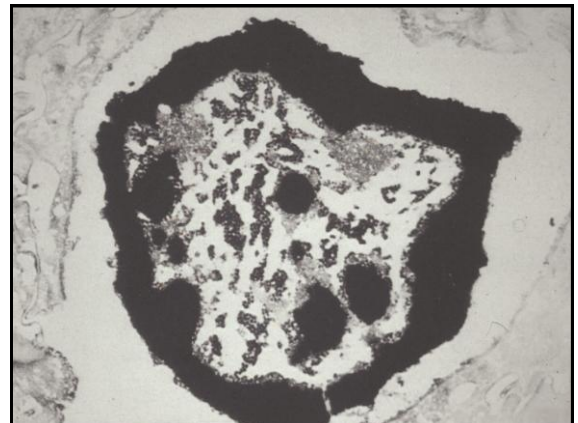
- Reduced inadequate rate
- Improved sensitivity and specificity
- Improved productivity ~25-30%
- Ancillary testing
- Optimised platform for semi-automation

1 Guidance

- 1.1 It is recommended that liquid-based cytology (LBC) is used as the primary means of processing samples in the cervical screening programme in England and Wales.
- 1.2 There is currently insufficient evidence to recommend one LBC product over another. The NHS Cervical Screening Programme and Cervical Screening Wales may wish to consider evaluating further the different products as the method is introduced.

www.nice.org.uk/Docref.asp?d=82877

Technology Appraisal 69
October 2005



Epidemiologic classification of HPV

High risk types: high grade CIN and cancer

16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82

Low risk types: low grade CIN and condyloma

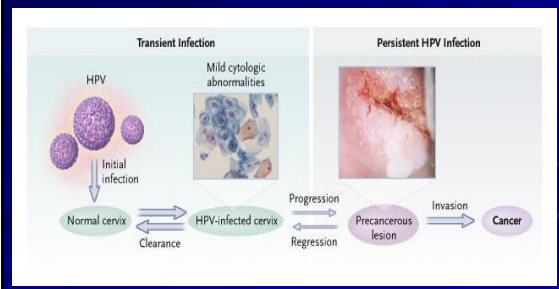
6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, CP6108

Probable high risk types

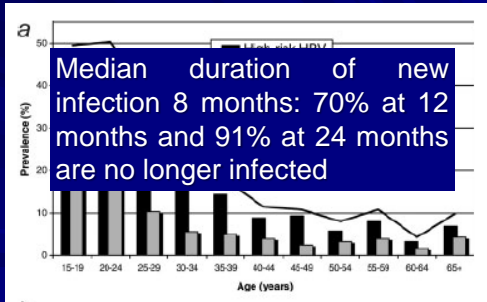
26, 53, 66

Munoz et al. *NEJM* 2003; 348: 518

The natural history of HPV infection and cervical cancer



Age specific prevalence HPV



HPV Testing in Cervical Screening

- Positive predictive value high risk HPV test is very low
- Negative predictive value high risk HPV test is very high
- Low long term risk of CIN 3+ in high risk HPV negative women

Kitchener et al. Eur J Cancer 2011; 47: 864
Ellstrom BMJ 2014; 348: g130

HPV testing in secondary prevention of cervical cancer

- Triage of women with equivocal (ASC) or low grade (LSIL) cytological abnormalities
- Prediction of therapeutic outcome after treatment of CIN (**Test of cure - ToC**)
- Primary screening for cervical cancer and pre-cancer

Arbyn et al. Vaccine 2012; 30S: F89

Triage of women with equivocal (ASC) or low grade (LSIL) cytological abnormalities

Test	Cytology	Sensitivity	Specificity
HC2	ASCUS	↑	↔
Abbott RT PCR Papillocheck® Cervista®	ASCUS	↑	↔
APTIMA®	ASCUS	↑	↑
HC2	LSIL	↑	↓
APTIMA®	LSIL	↑	↔

Arbyn et al. Vaccine 2012; 30S: F88

Prediction of therapeutic outcome after treatment of CIN

- HPV testing detects residual or recurrent high-grade CIN *more quickly*, with *higher sensitivity* and *not lower specificity* than follow up cytology
- Combined HPV and cytology screening produces further small gain in sensitivity but considerable loss of specificity if positive by either test referred for colposcopy

Arbyn et al. Vaccine 2012; 30S: F88

Primary screening for cervical cancer and pre-cancer

- Women aged 30+ yrs hrHPV negative at enrolment have a significantly lower cumulative incidence of CIN3+ compared to women cytology negative at enrolment
- Small difference in cumulative risk of CIN3+ for cytology and HPV negative women versus only HPV negative women

Arbyn et al. Vaccine 2012; 30S: F88

Primary screening for cervical cancer and pre-cancer

- HC2, GP5+/6+ PCR, cobas® 4000 PCR and Real Time PCR validated for primary screening
- Loss in specificity compensated by algorithms involving reflex cytology and/or HPV genotyping for HPV 16/18

Arbyn et al. Vaccine 2012; 30S: F88

HPV triage in NHS LBC pilot

- HPV triage is feasible
- It is acceptable to women
- May lead to increased detection of CIN2+
- It accelerates the diagnosis of high-grade CIN
- It avoids the need for repeated cytology
- It is cost effective in terms of quality and of life years saved

Legood. BMJ 2006; 332: 79-83
Moss. BMJ 2006; 332: 83-85

- Currently women treated for CIN 2 or worse are followed by annual sampling for at least 10 years before returning to routine screening
- Women treated for CIN 3 should continue surveillance beyond the age limit of regular screening

NHSCSP Publication 20, 2004

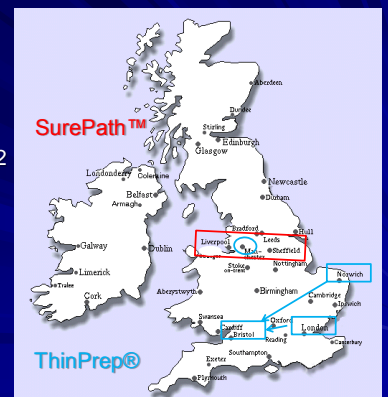
Strander et al. BMJ 2007; 370: 1764

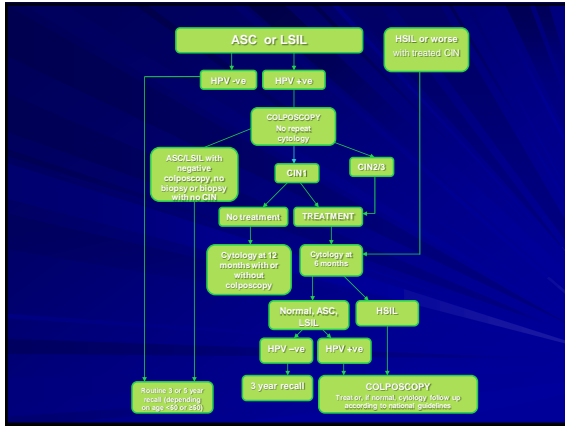
Sentinel Site Study

A person employed to keep watch for some anticipated event

Hybrid Capture 2

RLU>2





Sentinel Site Triage Results

- HPV positive rates
 - ASC 53.7% (range 34.8% - 73.3%)
 - LSIL 83.9% (range 73.4% - 91.6%)
 - Low grade overall **64.4%**
- PPV HPV +ve for CIN 2+ 16.3% (9.3 – 21.1%)
- PPV HPV +ve for CIN 3+ 6.1% (2.5 – 11.5%)

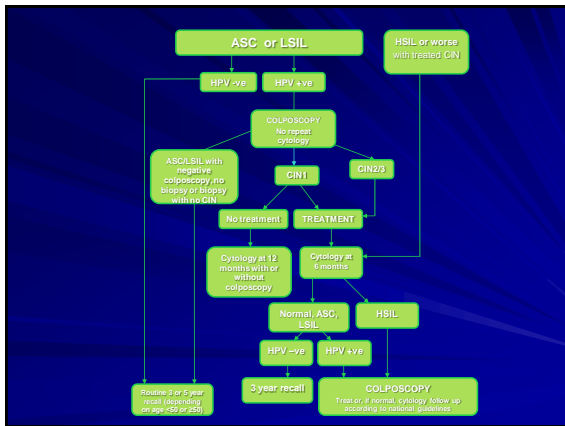
Kelly et al. British Journal of Cancer 2011; 105: 983-988

Sentinel Site Test of Cure Results

- 78% HPV & cytology negative at 6 months and could revert to normal recall

Detection of CIN in ToC

PPV	CIN 2+	CIN 3+
HSIL	13.6%	8.5%
Normal/ASC/LSIL and HPV +ve	2.9%	0.4%



Cytology/HPV +ve and Colp -ve

- Cumulative incidence CIN 2+ after 3 years = 4.4% (1.2% normal screened population)
- Cumulative incidence CIN 3+ after 3 years = 2.4% (0.7% normal screened population)
- No cases of invasive disease

Kelly et al. BJOG 2012; 119: 20

Advantages of HPV Triage and ToC

- Detection of high-grade CIN leading to earlier treatment and early discharge
- Early return of women with low-grade cytology and HR-HPV negative to routine recall
- Early return of women treated for CIN who were cytology negative and HR-HPV negative to routine recall.

Figure 1 A woman with CIN 3, (a) with and (b) without HPV triage and test of cure

(a) HPV triage and test of cure	(b) Standard treatment
<ul style="list-style-type: none"> ▪ Routine screen ▪ Borderline cytology, HPV+ ▪ Colposcopy at 8 weeks from date of test ▪ CIN3 detected ▪ Treated with LLETZ ▪ Test of cure at 6 months, negative ▪ 3 year recall ▪ Time for whole episode: 9 months 	<ul style="list-style-type: none"> ▪ Routine screen ▪ Borderline cytology ▪ Repeat at 6 months, borderline cytology ▪ Repeat at 6 months, borderline cytology ▪ Colposcopy 14 -18 months from date of initial test ▪ CIN 3 detected ▪ Treated with LLETZ ▪ Annual follow up for 10 years ▪ Time for whole episode: 12 years

HPV Triage and Test of Cure: Implementation Guidance. NHSCSP. July 2011

What will be the impact of HPV testing on national cytology workload and laboratory practice?

Impact on National Workload

Combined effect HPV triage & test of cure

HPV triage	175,000 fewer tests
Test of cure	428,000 fewer tests
Total	603,000 fewer tests

**Total cost saving of €26 million/year
= 13% saving**

Impact of HPV triage on cytology reporting practice

- Will it make screening staff lazy?
 - Why worry about whether abnormality is ASC or LSIL or thoroughly check to exclude HSIL when management will be decided by the HPV test?
- Must be careful NOT to over use HPV testing.
 - A significant proportion of young women will test HPV positive whether they have disease or not
 - Adds cost
 - Decreases specificity
 - Impacts on colposcopy clinic workloads
 - Creates unnecessary anxiety in women

Impact of HPV triage on cytology reporting practice

- Will it alter reporting parameters?
 - In past, if unsure but favouring high grade (ASC-H), guidance was to code as HSIL (moderate) and refer to colposcopy
 - With HPV testing more benefit is gained by coding as ASC and requesting an HPV test
- What are the main benefits in reporting?
 - Minimal changes in poor attendees
 - Atrophic samples
 - Hyperchromatic crowded cell groups (HCCGs)

Impact of HPV triage and ToC 5 years on

- Overall reduced workload – impact on screening sensitivities
- Fewer abnormal slides impacting on consultant/AP* reporting numbers
- Established protocol
 - Simplified management decisions
 - Improved laboratory workflow

*Advanced biomedical scientist practitioner

Main Challenges for Laboratories

- Impact on morale of staff
- Understanding protocols
- Access to appropriate follow up information
- **Clinical liaison with gynaecologists**

Impact on colposcopy

- Colposcopy DNA (no show) Rates
 - Reduced from approximately 20 to 10%
 - Repeated across the NHSCSP could avoid approximately 17,600 missed appointments per year

Are all HPV testing platforms the same?

- TP/HC2 = 54%
- SP/Abbott = 80%
- TP/HC2 = 56%
- SP/Roche = 55.7%
- TP/HC2 = 55.5%
- SP/Roche = 72.3%
- TP/Roche = 69.4%

Changing platforms overall

Cytology	% Test positive HC II	% Test positive Cobas-4800
Negative	12.4	26.4
ASC/AGC	77.0	69.4
LSIL	94.2	89.6
OVERALL	40.1	54.0

Changing platforms in ToC

	HC II	Roche Cobas-4800
Median age	30 (18-66)	29 (20-68)
Negative cytology	95.1%	96.6%
Negative HR HPV +ve	13.5%	26.1%
Low grade HR HPV +ve	1.5%	3.69%
Significant disease (CIN 2+)	3.14%	2.53%

Innema et al. Cytopathology 2014 (in press)

Primary HPV Screening



Estimating the long-term impact of a prophylactic human papillomavirus 16/18 vaccine on the burden of cervical cancer in the UK

- 100% coverage of a 12-year old cohort of girls would lead to:
 - 75000 fewer abnormal cytology tests
 - 442000 fewer cytology tests including follow up tests

Estimates most sensitive to age of vaccination and coverage

Kohli et al. Br J Cancer 2007; 96: 143

Estimating the long-term impact of a prophylactic human papillomavirus 16/18 vaccine on the burden of cervical cancer in the UK

- 100% coverage of a 12-year old cohort of girls would lead to:
 - 66% reduction in prevalence of CIN 2/3
 - 76% reduction in cervical cancer deaths
 - 25% reduction in abnormal cytology tests
 - 33% reduction in diagnostic tests and CIN treatments

Results sensitive to increase in vaccination age and coverage

Kohli et al. Br J Cancer 2007; 96: 143

Predicted impact of vaccination against human papillomavirus 16/18 on cancer incidence and cervical abnormalities in women aged 20-29 in England

- Assuming 80% coverage:
 - 63% reduction in invasive cancer
 - 51% reduction in CIN 3
 - 27% reduction in cytological abnormalities by age 30

Cuzick et al. Br J Cancer 2010; 102: 933

Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study

Julia M L Brotherton, Masha Fridman, Cathryn L May, Genevieve Chappell, A Marion Sewell, Dorota M Gertig

After introduction of the HPV vaccine, progressive decrease (by 0.38%) in the incidence of high grade cervical abnormality in girls younger than 18 years and significantly different to the linear increase in incidence prior to the vaccine introduction

No similar temporal decline for low grade abnormality or in older age groups

Brotherton et al. Lancet 2011; 377: 2085

The near disappearance of genital warts in young women 4 years after commencing a national human papillomavirus (HPV) vaccination programme

Read et al. Sex Transm Infect 2011; 87: 544

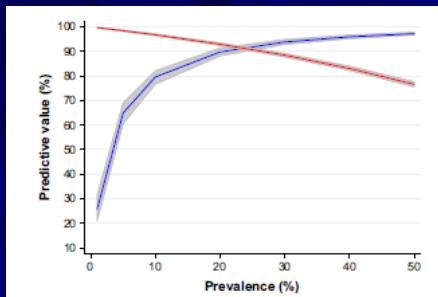


Figure 1. Influence of variations in the prevalence of cervical lesions on the positive predictive value (PPV, blue line) and negative predictive value (NPV, red line) of cytology as a primary screening test. A constant 70% sensitivity and 98% specificity are assumed for the test. The gray bands represent 95% and 98% specificity.

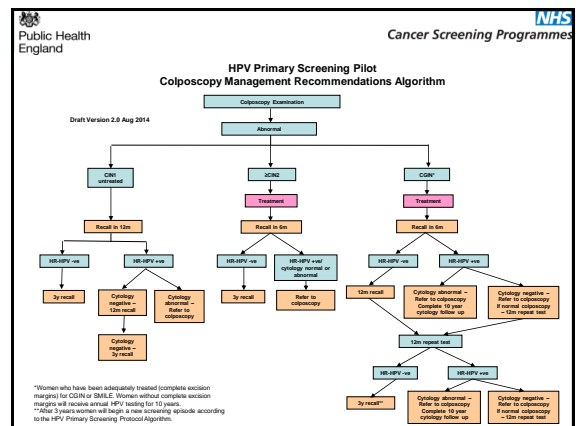
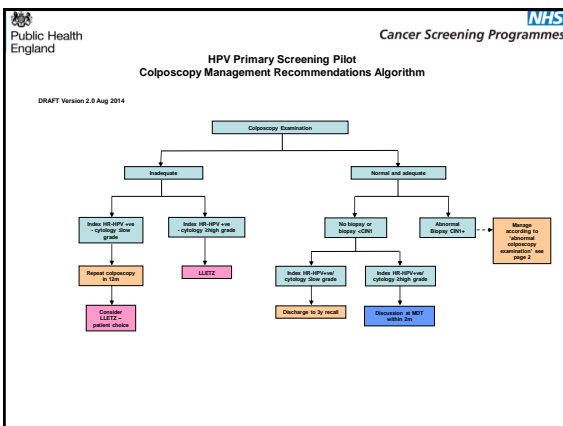
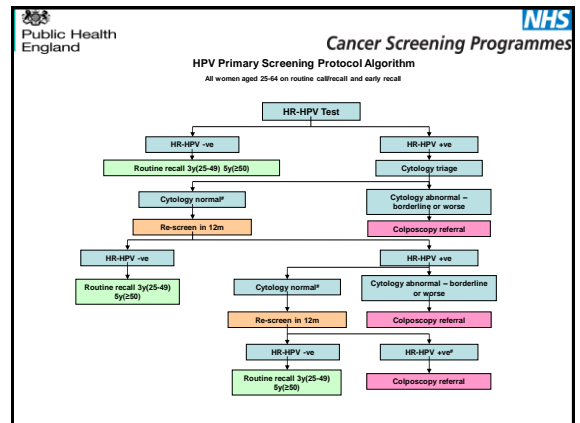
Franco et al. Arch Med Res 2009, 40: 478

Is cytology the best way to screen a vaccinated population?

- HPV testing in primary screening
 - Greater sensitivity but slightly lower specificity than cytology
 - Highly standardised and validated assay system – maintain performance characteristics under low prevalence conditions
 - Monitor the epidemiology of HPV infection
 - Incidence of HPV infection in vaccinated women

Sentinel Site Conversion

	Proportion of Workload	Primary HPV tests
Bristol	33%	20,000
Liverpool	33%	15,000
Manchester	40%	47,000
Norwich	20%	11,500
Northwick Park	25%	20,000
Sheffield	33%	35,000
TOTAL		148,500



Primary HPV Screening in Sheffield

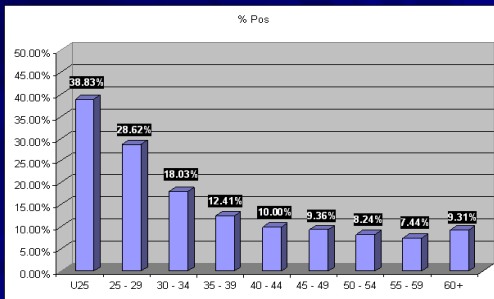
– End April 2014

- 30,063 samples HPV tested
 - 82.78% HPV -ve
 - 16.32% HPV +ve
 - 0.9% HPV test unreliable
- 4,906 cytology slides assessed
 - 71.2% no abnormality – repeat 12 months
 - 27.8% abnormal cytology – refer to colp

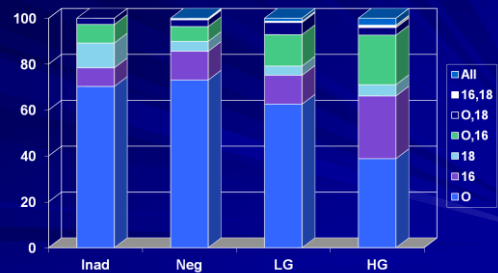
HPV Positive Cytology Breakdown

Cytology Grade	Number	%
Inadequate	46	0.94%
Negative	3493	71.20%
Low Grade	882	17.98%
High Grade	383	9.86%
Non-cervical cancer	1	0.02%
Total	4906	100.00%

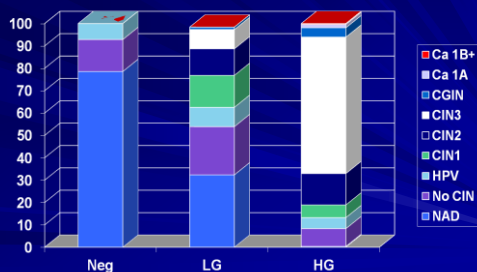
Sheffield HPV prevalence



HPV Type by Cytology (%)



Histology – HPV +ve/cytology (%)



Sheffield Story > First Year

- HPV positive/cytology negative repeat test at 12 months
- 361 of 563 women (64.1%) still HPV positive
- Persistent HPV 16 +/- 18 referred for colposcopy

Cytology grade in women with persistent HPV positive test

Cytology Grade	Number	%
Unsatisfactory	7	1.9
Negative	279	77.3
LSIL	57	15.8
HSIL	18	5
Total	361	100.00

Risks of HPV Primary Screening

- Will miss some CIN and cancer
- ARTISTIC data – 10.9% CIN II and 4.3% CIN III, and 3 cancers were HPV negative
- Magee Hospital - 17% of 454 women had negative HPV test within 3 years of diagnosis of cervical cancer
- CAP Study 2012 – 25% women had negative HPV test 1 to 5 years prior to diagnosis of cervical cancer

Cuzick et al. Int J Cancer 2006;119:1099-101
Obstet Gynecol 2010; 116:76-84
J Lower Genital Tract Disease 2010; 14: 247A, 255A

However

- Cytology also misses cervical disease
- Of women with cervical cancer
 - 20% aged 20 - 49 had a negative test within 3.5 years of diagnosis
 - 28% aged 50 - 64 had a negative test within 5.5 years of diagnosis (NHSCSP 2012).

SUMMARY

- **HPV triage** will result in
 - An increased colposcopy and biopsy workload initially
 - A cheaper, more effective and speedier service for women with low grade abnormality
 - A sustained reduction in cytology workload

SUMMARY

- **HPV test of cure** will result in
 - A sustained reduction in cytology workload

SUMMARY

- **HPV vaccination** will progressively decrease the prevalence of HPV-related cervical disease and related cytological and histological abnormalities
- Cytology based screening will become less sensitive and specific and replaced by HPV primary screening

