NCPTS

HPV and Cervical Cancer

Margaret Sage
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Topics

1. HPV Infection and carcinogenesis
2. HPV and Invasive cervical cancer in New Zealand
3. Using High-risk HPV Testing
4. Cancer prevention using HPV vaccines

HPV and Cervical Cancer

- hrHPV infection necessary but not sufficient in cervical carcinogenesis. Cancer is still a rare outcome of hrHPV infection.
  - Estimated prevalence of genital HPV infection = 326 million adult women worldwide.
  - Annual incidence of new cases of cervical cancer = 530,000 worldwide
- Progression to cancer is generally slow
  - Modal age of first infection with hrHPV is between 15 and 25 years.
  - Modal age of invasive cervical cancer in unscreened women is 35-50 years (differs geographically)

HPV subtypes

- Only some HPV genotypes associated with cervical cancer
- HPV 16 is the most common and highest risk subtype.
  Present in 55% SCC, 48% endocervical AdenoCa

- HPV 18 present in 12% of SCC,
  and 36% endocervical AdenoCa
  HPV 45, 31, 33 in 4-5% for invasive cancer, any type

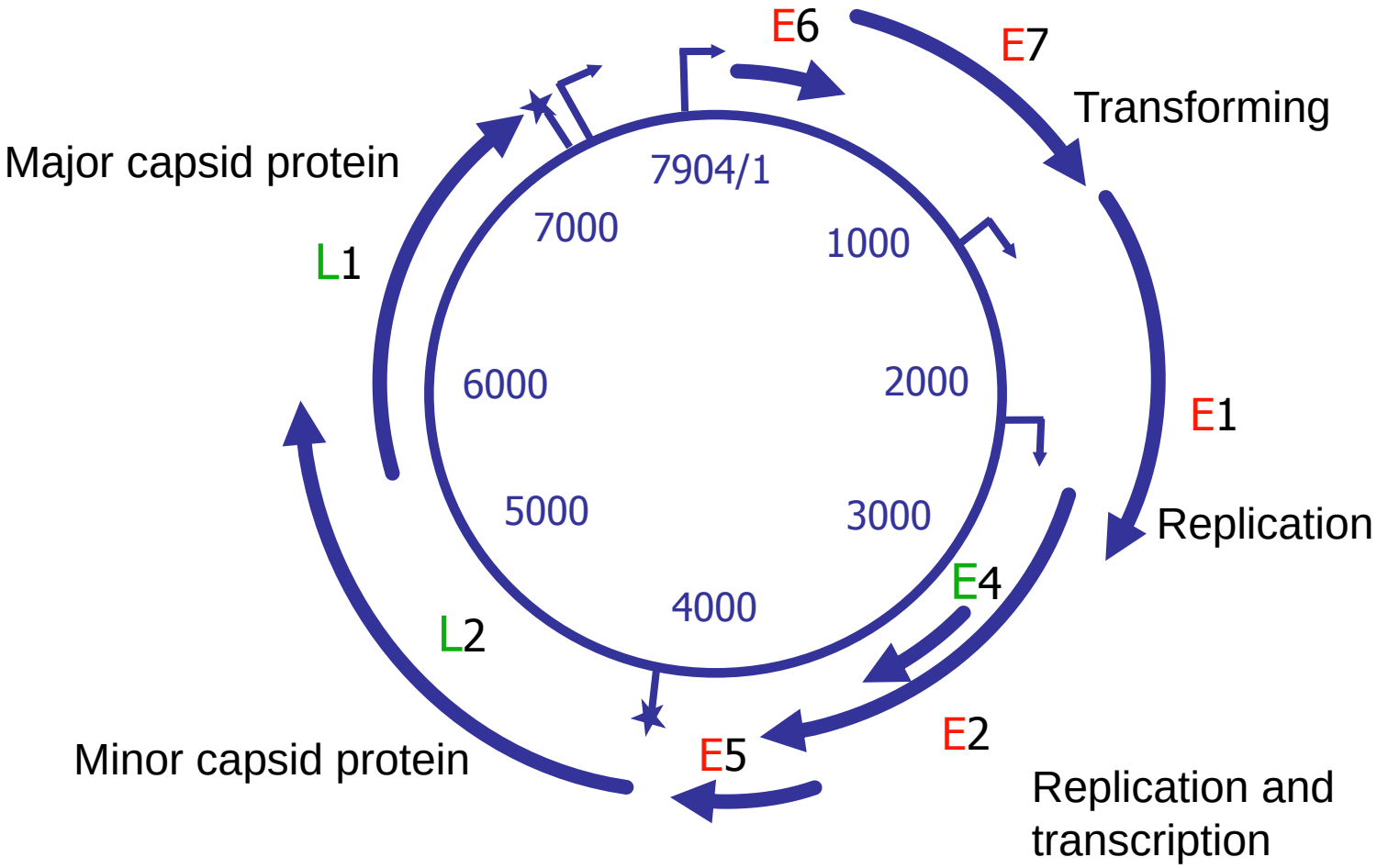
- "Progression to disease" rates also vary.
  HPV 16 is associated with high progression rates.

HPV Virology

Small double-stranded DNA viruses

- More than 100 genotypes, classified by DNA sequences.
- Cutaneous and Mucosotropic: Low-risk e.g. HPV 6,11
  Moderate-high risk e.g.16,18,45 and 31
  Varying oncogenic potential: HPV 16 the worst
- Virus can replicate only in the nucleus of an infected cell.
  - does so as a circular structure independent of the host DNA
  - large numbers of infectious virions produced as the cell matures
  - Viral protein E4 binds to and disrupts the cytoplasmic keratin network of the infected cell, producing the koilocyte
  - Desquamation of the cell releases large numbers of potentially infectious virion particles

THE HPV GENOME
is divided into Late and Early regions



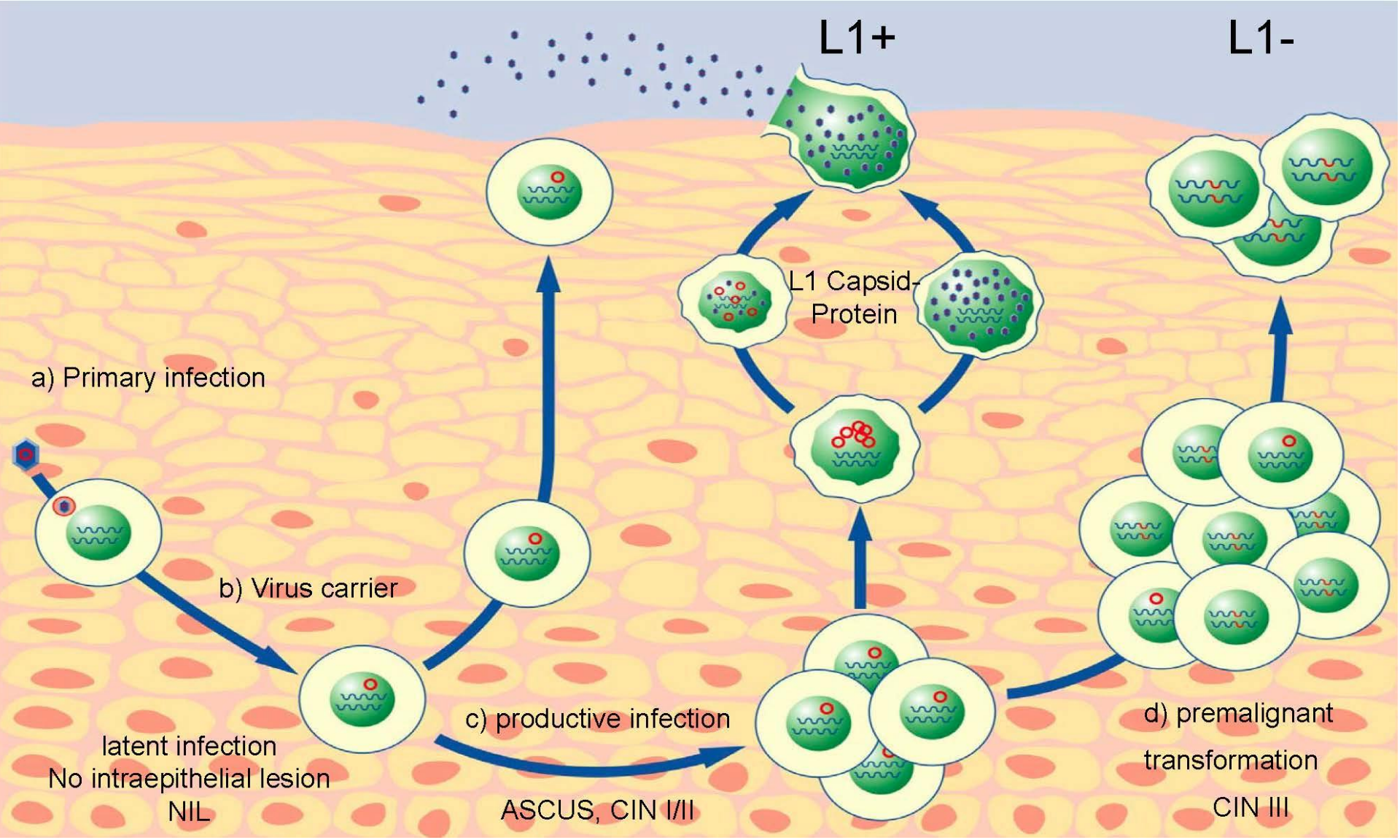
HPV Infection

- HPV infection is a very common usually transient sexually transmitted infection.
- Prevalence very high in women under 30 years of age. HPV testing in women under 30 years is of little value

  80% of sexually active adults are likely to be infected during their lifetime.
- 98% of infections resolve spontaneously in 3-5 years, most in 2-3 years. Resolution depends on host immunity.
- The 2% of women in whom high-risk HPV infection persists after 5 years, are the group at significant risk for developing cervical cancer. Persistent HPV infection in women over 30 years is associated with increasing risk of high-grade disease.

HPV Infection: clinical aspects

- Almost always sexually transmitted
- Probability of transmission is greater than 50% following unprotected sexual intercourse with a person with a productive anogenital infection
- Enters through microabrasions in skin/mucosa
- Acute infection occurs 6-12 weeks later. Can be totally asymptomatic
- HPV can be detected by molecular techniques before the acute infection is apparent
- LSIL is the morphological correlate of a productive HPV infection

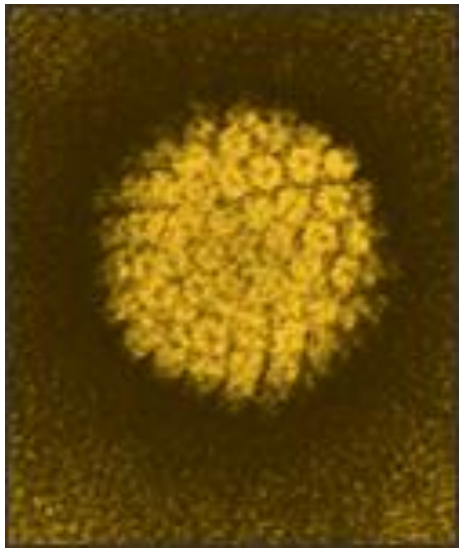


"Human Papillomavirus and Related Diseases From Bench to Bedside A Diagnostic and Preventive Perspective"

Ed: Davy Vanden Broeck, ISBN 978-953-51-1072-9, Published: April 30, 2013 © The Author(s).

Chpt 4:HPV L1 Detection as a Prognostic Marker for Management of HPV High Risk Positive Abnormal Pap Smears (Ralf Hilfrich)

HPV in pathogenesis of cancer



Electron micrograph of the Human Papillomavirus

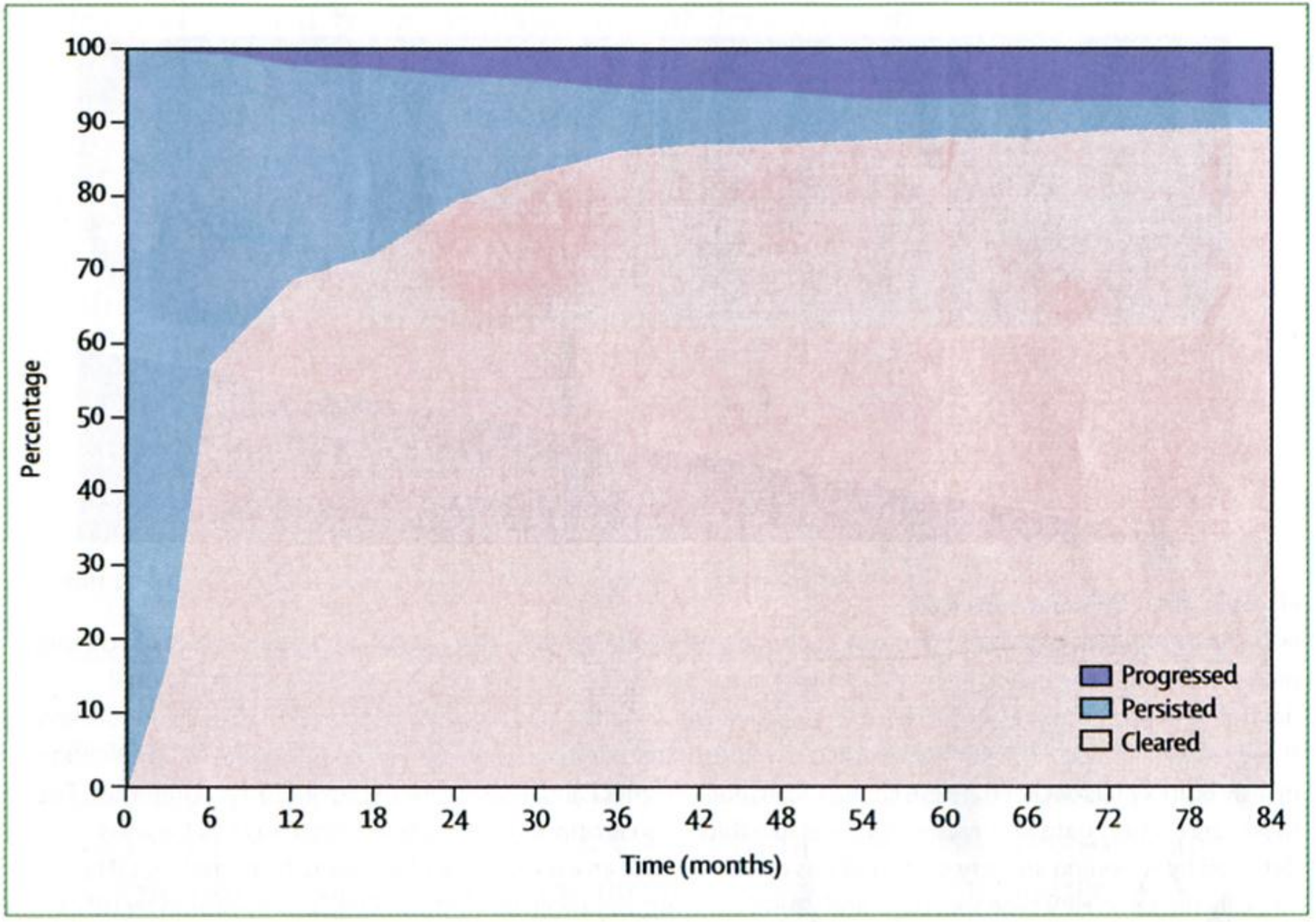
- Protein products of two viral genes bind to host regulatory proteins with tumour suppressor functions

  E6 binds to and degrades p53

  E7 binds to and inactivates rb

- this prevents the arrest of cell division that occurs when epithelial cells differentiate

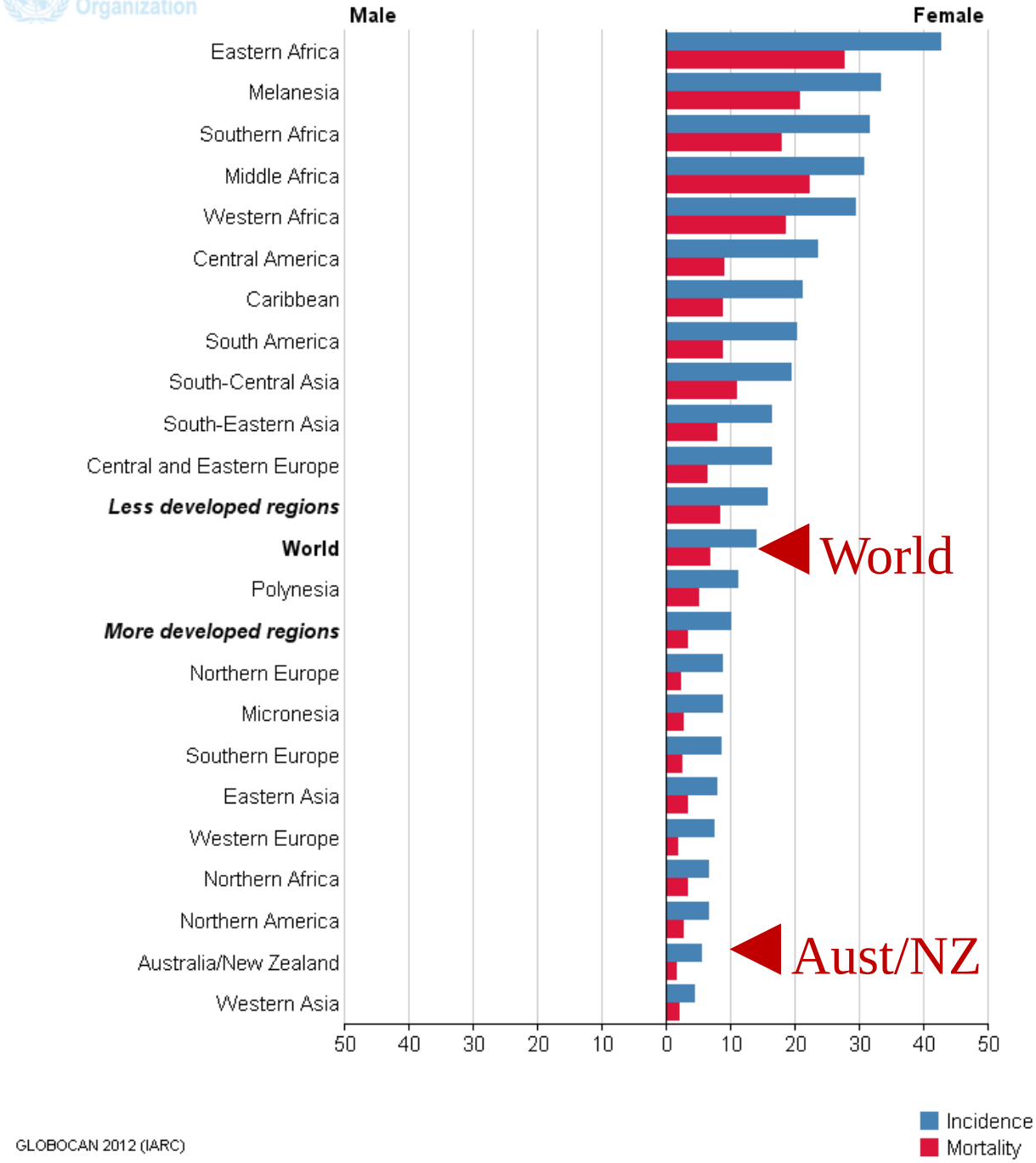
- In a proportion of persistent infections, the usually circular viral DNA becomes integrated by becoming inserted into the host DNA
- After integration, E6 and E7 can be over-expressed causing host squamous cells to proliferate in a disorderly way resulting in HSIL lesions
- the HSIL cells are then at risk of acquiring further genetic errors which increase the risk of malignant transformation
- possible promoters include smoking, other virus infections, and random mutation.



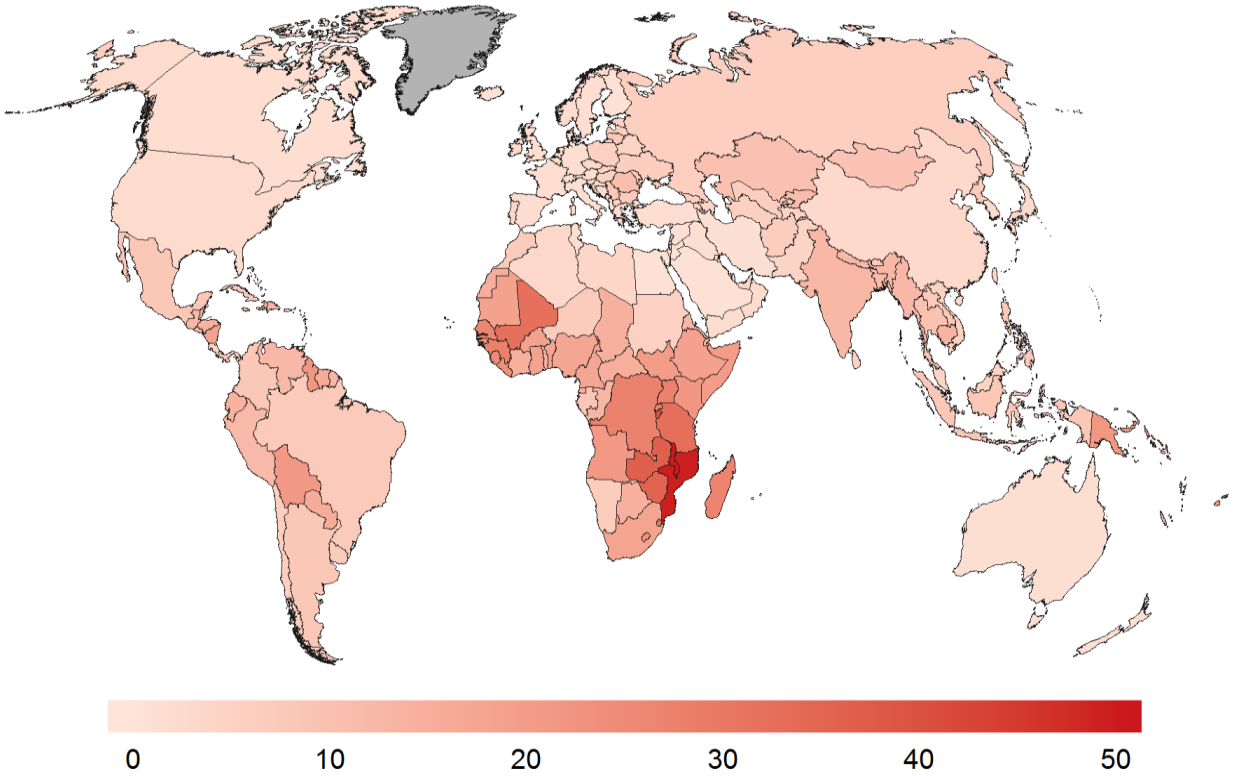
Typical pattern of clearance, persistence and progression of high-risk HPV infections with time

Incidence and Mortality Cervical Cancer by Region

Globocan 2012



Estimated Cervical Cancer Mortality Worldwide in 2012



ASR mortality per 100,000

GLOBOCAN 2012

NCSP achievements

- Our NCSP is one of the most successful cervical screening programmes in the world.

Incidence and Mortality Rates* Cervical Cancer 2012

	Incidence	*Mortality*
1. Finland	4.3	1.0
2. New Zealand	5.3	1.4
3. Australia	5.5	1.6
United States	6.6	2.2
United Kingdom	7.1	1.8
……		
Zambia	58.0	19.9
Papua New Guinea	34.5	21.7

**per 100,000 women (age standardized)*

Ref: GLOBOCAN

Incidence and Mortality by Cancer type for NZ women 2012

Cervical cancer in New Zealand:
12th in incidence
15th in mortality

	Incidence	Mortality
Breast	**96.9**	17.7
Colorectal	37.0	14.8
Melanoma	33.8	3.6
Lung	26.9	**19.7**
Uterine Body	16.2	3.2
Non-Hodgkin Lymphoma	9.4	3.2
Ovary	8.0	4.8
Leukaemia	7.7	4.0
Thyroid	7.9	0.4
Kidney	5.2	1.6
Pancreas	7.2	5.8
→ **Uterine Cervix**	**6.3**	**1.8**

NZ Cancer Registry

ASR (W)

Type distribution of human papillomavirus among adult women diagnosed with invasive cervical cancer (stage 1b or higher) in New Zealand

Peter Sykes, Kusuma Gopala, Ai Ling Tan, Diane Kenwright, Simone Petrich, Arico Molijn, and Jing Chen

BMC Infectious Diseases 2014,14:374

- Women ≥18 years of age with ICC FIGO stage 1b or higher diagnosed 2004 - 2010 from five NZ hospitals
- Stored paraffin embedded cervical specimens were used, with consent.
- Cervical specimens underwent histopathological review and assays were performed for HPV genotyping

Results: HPV Positivity

227 Invasive cancer cases

159 (70%) = squamous cell carcinoma (SCC)

61 (27%) = adenocarcinoma (ADC)

7 (3%) = adenosquamous carcinoma (ASC)

HPV was detected in 88.5%

93.1% = SCC

77.9% = ADC/ASC

Results: HPV subtypes

For the 227 ICC cases, HPV 16 and 18 were the most frequent

HPV 16 = 51% : 56% of SCC 40% of ADC/ASC
HPV 18 = 21% : 15% of SCC 35% of ADC/ASC

For the 201 HPV positive cases

HPV 16 + 18 = 81.1%

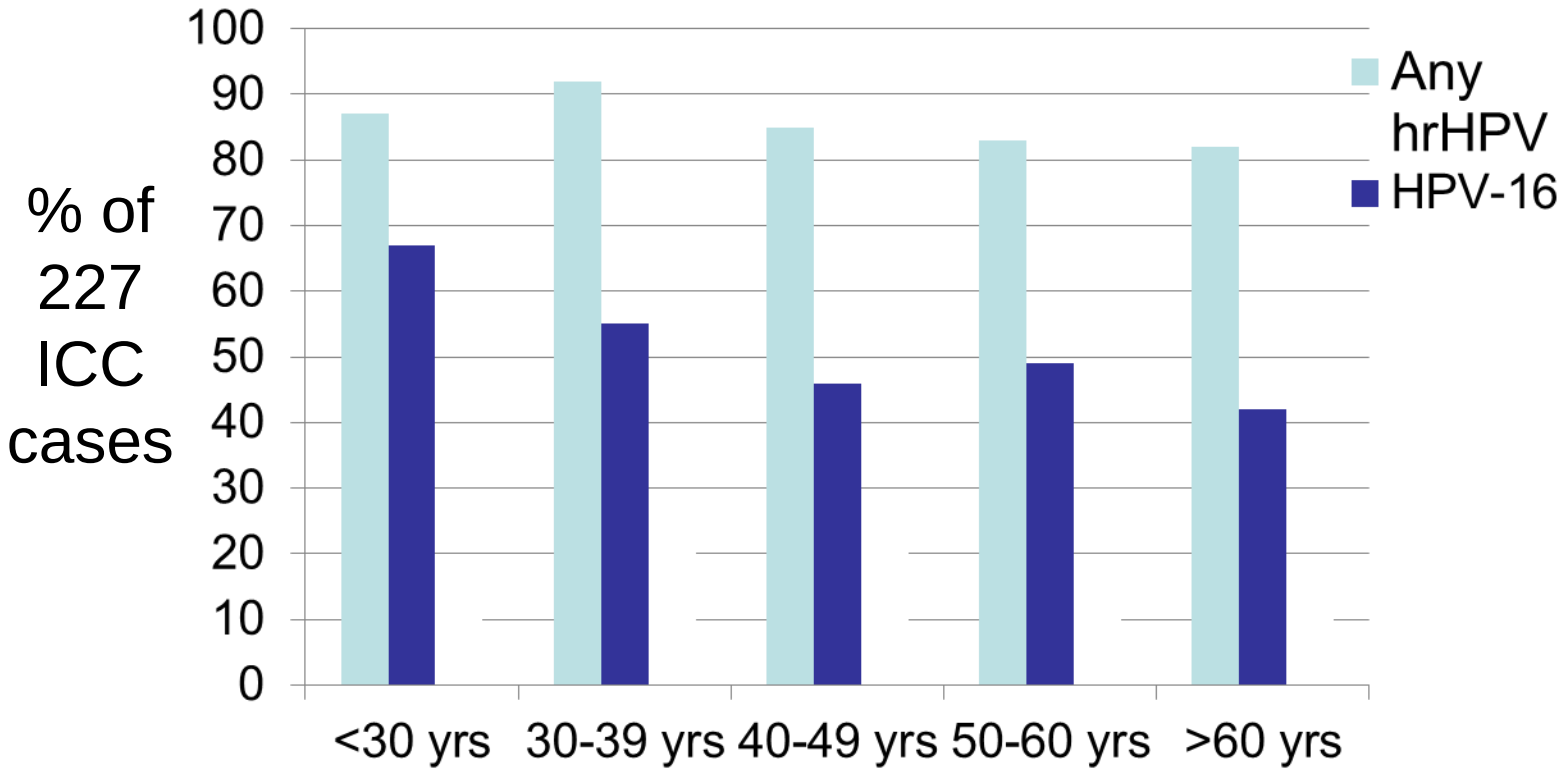
Frequent non-16/18 types: 31, 45, 52, 59 and 33

Two low-risk HPV types (11,70) = one SCC each

Multiple subtypes

5.5% had multiple subtypes present (Both SCC and ADC/ASC)

Prevalence of hrHPV subtypes by age



- The prevalence of any HPV type: highest in women 30-39 yrs
- HPV-16: more frequent in younger women

Results: Ethnicity

- 15% of the women (n=34) with invasive cervical carcinoma were of Maori ethnicity
- There was no significant association between ethnicity and either HPV detection rate or histological cancer type or stage of disease at diagnosis
- Subtype prevalence was similar:
  - HPV 16: 58.8% Maori 49.7% non-Maori
  - HPV 18: 11.8% Maori 22.3% non-Maori
  - Minor variations in non-16/18 subtype distribution

International Comparison

HPV infection and subtype distribution rates are comparable with other international studies

Type-specific oncogenic human papillomavirus infection in high grade cervical disease in New Zealand

Leonardo Simonella, Hazel Lewis, Megan Smith, Harold Neal, Collette Bromhead and Karen Canfell

BMC Infectious Diseases 2013, 13:114

Aim: to measure the pre-vaccination prevalence of HrHPV in 20-69 yrs women with high-grade squamous and glandular lesions

594 women 20-69 years from NCSP-Register 2009-2011

Group 1: histologically confirmed CIN2/3 or AIS

Group 2: possible or definite high-grade squamous or glandular cytology reports

LBC specimens were genotypes for 37 HPV subtypes

Results

Group 1: Histologically confirmed lesions

356 women = CIN2/3 6 women = AIS/glandular dysplasia

Any hrHPV infection: 95% HPV 16/18: 60%

Most common subtypes: 16 (51.2%) 52 (18.9%) 31 (17.1%) 18 (12.1%)

Group 2: 594 Women with possible or definite HG cytology

Any hrHPV infection: 87% HPV 16/18: 53%

Most common subtypes: 16 (44.1%) 52 (16.8%) 31 (15.2%)

Highest relative prevalence of HPV 16/18 in confirmed CIN3 was seen in women 20-29 years of age

International comparisons

- The prevalence of HPV 16 in CIN2/3 was broadly consistent with that in Australia and Europe (about 50%) but higher than that reported for North America, Asia and South/Central America (about 40%)

- The prevalence of HPV 18 in CIN2/3 was broadly consistent with Australia and North America but higher as that reported for Asia, Europe and South/Central America

- The prevalence of HPV 52 was higher than that reported from other regions

hrHPV Testing
Detection of high-risk HPV types

- hrHPV Tests are positive if any of the selected High-risk HPV subtypes are present

  c.f. specific genotyping - identifies specific subtype(s) present

- Hybrid-Capture 2 (Digene): was initially the standard test used in research-based clinical trials.

  DNA-RNA hybrid capture technique for 13 subtypes

  HPV 16, 18,31,33,35,39,45,51,52,56,58,59 and 68

- Two PCR-based amplification methods in use in NZ:

  Cobas 4800 (Roche)

  Abbott Realtime

hrHPV Testing in practice

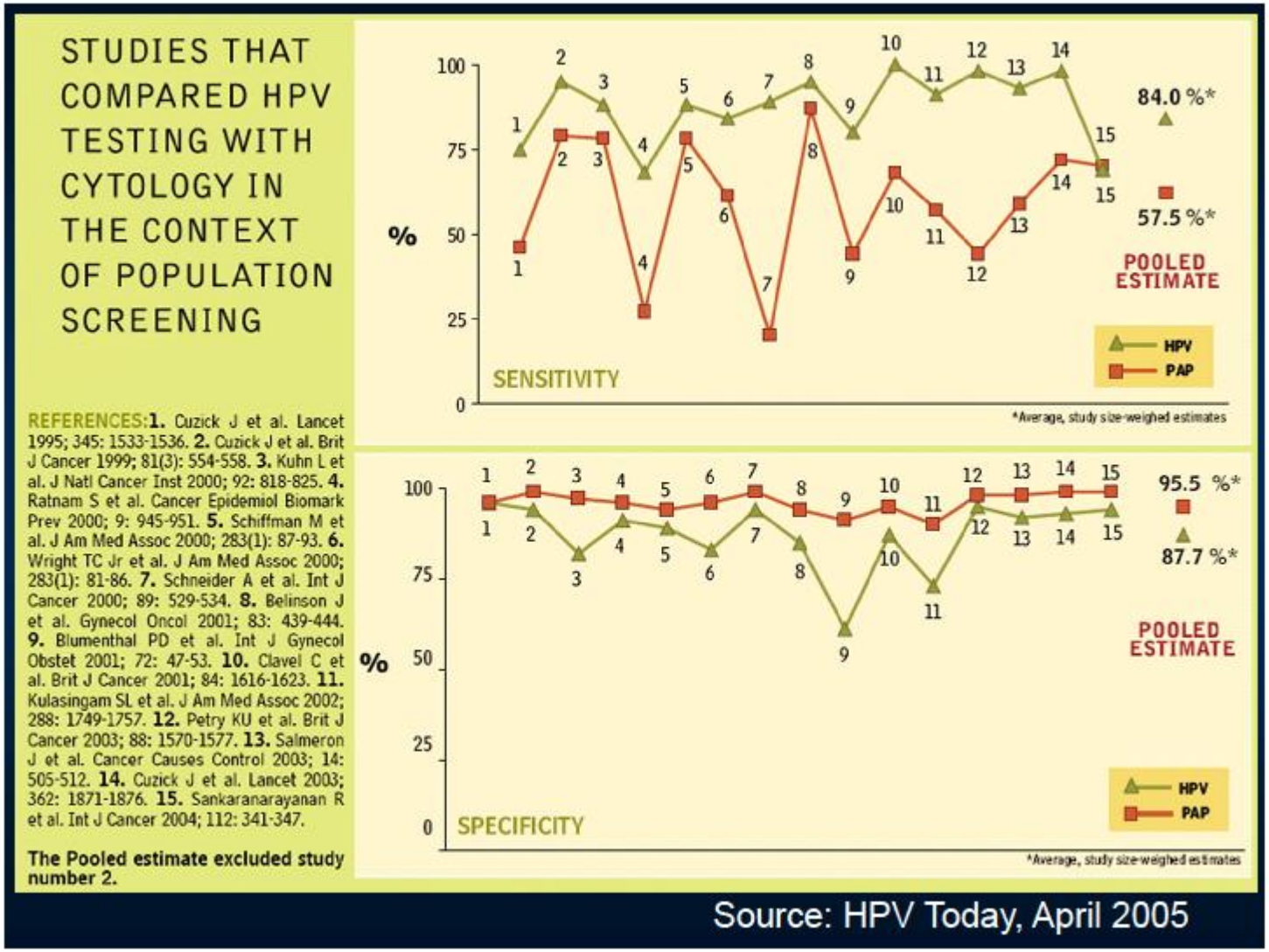
- High negative predictive value: 99%
- More sensitive than cytology for detecting high-grade disease.
  - At any given time, 8-10% of women who are cytology negative, are positive for HrHPV

But

- Not so specific i.e. false positive rate about 5%
- Cytology is more specific
- Potential for patient anxiety if HPV positive

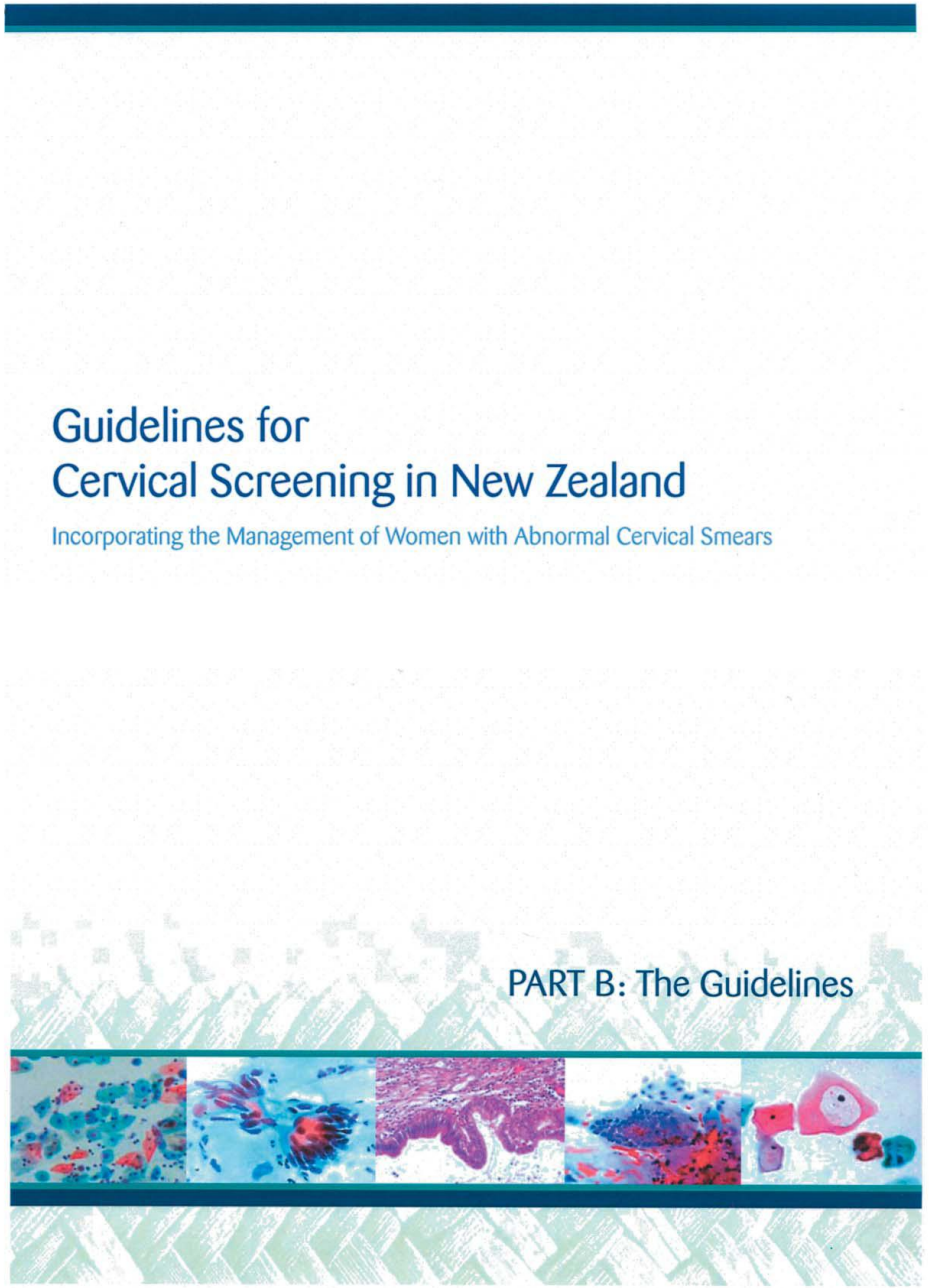
- Can perform hrHPV tests on fluid in LBC vials

HPV Testing compared with Cytology



NCSP Guidelines
29 Sept 2008

- HPV Testing was introduced on **1 October 2009** with NCSP funding for selected clinical situations



Current use of HrHPV Testing in New Zealand

1. Triage of ASC-US and LSIL in women 30+ years of age.

   If hrHPV positive, refer for colposcopy

   If hrHPV negative, repeat cytology in 12 months

2. Test of cure after treatment of high-grade lesions

   Return to 3-yearly screening after two paired [Cytology+ HrHPV Test] results taken 12 months apart, if all four results are negative

3. Histo-cyto-colp discordance: specialist testing

1. Triage of ASCUS

- For women age 30 years or older who
  - Have ASC-US or LSIL cytology and
  - Have not had an abnormal cytology or cervical histology result in the previous 5 years
- The laboratory automatically adds on a reflex hrHPV test with must be reported with the cytology result in one report
- The hrHPV result is reported as *Detected* if any one of the 14 hrHPV subtypes is present.
  - laboratories also now report if HPV subtype 16 or 18 is specifically identified. The remaining subtypes are reported together as “other”

Triage of ASC-US: management

- Women (30+ yrs, no prior abnormality within 5 yrs, ASC-US/LSIL cytology) who are hrHPV test positive (*Detected*) are referred for colpscopy
- Those who are negative for hrHPV (*Not detected*) have repeat cytology in 12 months and are referred for colposcopy if there is any abnormal cytology result.

2. Test of cure

- Women successfully treated for high-grade disease remain at greater risk of subsequent lesions for at least 10 years
- Successful local treatment of CIN is followed by the disappearance of HPV positivity: Viral clearance may take 12 months
- Need two paired “cyto plus hrHPV” tests, 12 months apart. If all four tests are negative they return to three yearly screening
- HPV testing is more sensitive than cytology for detecting residual or recurrent CIN after treatment
- Women who return to “hrHPV negative” status can return to a normal screening interval as they are at no greater risk of subsequent disease than the normal population

3. Post colposcopy management of discordant cases

- High-grade or possible high-grade cytology cases with negative or low-grade disease at colposcopy are a management problem as lesions can be missed at colposcopy
- hrHPV testing may be used to exclude the likelihood of disease. Helpful if negative.
- In practice, any hrHPV tests ordered by colposcopists are funded.

HPV Vaccines

- Can't grow HPV in vitro but in the 1990's Papilloma virus-like particles (VLP's) produced by recombinant DNA technology
  - non-infectious HPV viral capsid particles which induce neutralising antibodies in humans
  - a major advance - an effective anti-cancer vaccine

- In clinical trials immunisation shown to protect previously uninfected young women against HPV infection and against the development of premalignant lesions with very high level of protection

Clinical Trials

- HPV Virus-like particles shown to be safe and immunogenic in man
- induce specific antibodies at titres considerably higher than seen with natural infections
- Immunisation: protects previously uninfected young women against HPV infection and the development of premalignant lesions with very high level of protection
- duration of protection stable for at least 7+ years
- If woman is already infected with one HPV type, the vaccine still provides a high level of protection against other HPV types in the vaccine
- may also provide some protection against progression of disease, even if already infected
- Excellent safety record

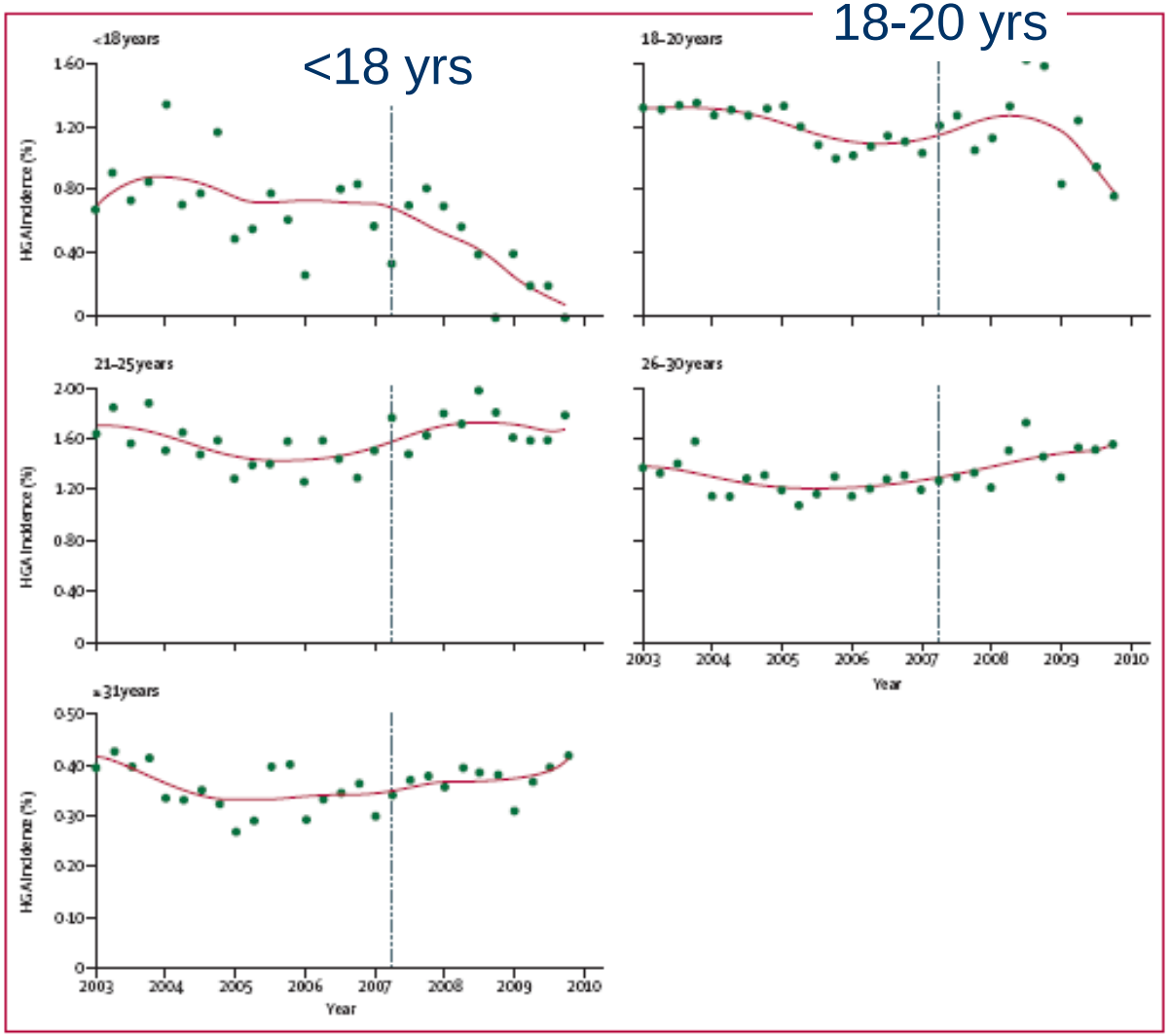
Immunisation

- A primary disease prevention strategy
- at best, could prevent 70% of cancers in countries with no screening programme: cost-effective option for some countries
- Big advantage with universal vaccination is that the whole population receives it, including women who don't go on to have cervical smears
- Cost is currently prohibitive for countries that need it most. The Gates Foundation and others are funding programmes in some developing countries

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

Lancet 2011; 377: 2085–92
Julia M L Brotherton et al

HG Rates against year
2003 – 2010
by age group



Incidence of high-grade cervical abnormalities, by age group

Impact of immunisation on cervical screening

- Significant disease reduction

  HPV 16+18: 66% of cervical cancers, 50% HSIL, 25% LSIL

  HPV 6+11 causes 90% of cases of genital warts

  – impact on cancer mortality only seen 15 - 20 years after widespread vaccination, although pre-invasive disease reduction will happen earlier

- Cervical screening will need to continue because:
  – Vaccines protect against 70% of invasive cancers i.e. not all HPV types and subtypes may change
  – Many women already infected
  – Not all women will be vaccinated/receive all three doses

Cervical screening will need to change after widespread vaccination

FUTURE CERVICAL CANCER PREVENTION STRATEGY

Primary prevention:

HPV immunisation

Secondary Prevention:

hrHPV Testing followed by cervical cytology if positive

Concluding Comments

- Cervical screening is undergoing a time of major change
- HPV testing has already refined the way women in specific clinical groups are managed
- The roles of HPV testing and cervical cytology in screening will change in 2018
- HPV vaccination will reduce the incidence of HPV infection and HPV-related disease: this will reduce the number of abnormal smears and the number of smears taken