Derby Gynaecological Cancer & DELTA Centre

Gynaecological Oncology Symposium

24th February 2017

Derby Teaching Hospitals NHS
NHS Foundation Trust

HPV, cervical cancer & vaccination programme

Mr Summi Abdul

Consultant Gynaecological Oncologist

Laparoscopic & Robotic surgeon

Taking pride in caring

SURGICAL TRAINING NETWORK

Objectives

1. Human Papilloma Virus

2. Burden of disease caused by HPV

3. Vaccination programme

Human Papillomavirus (HPV)

- Small DS DNA virus
- >100 types
- Around 40 HPV types target genital tract in women and men

Classified into:

- High-risk (oncogenic) types
  - 16, 18, 58, 33, 45, 31, 52, 35 (worldwide)
- Low-risk HPV types
  - 6, 11, 42, 43, 44

Visual of HPV Virus

L1- Major capsid protein
L2- Minor protein

Human Papillomaviruses

> 100 types of HPV

40 Anogenital types:

>90% warts

Low Risk **6, 6,11, , 42, 43, 44, 54, 61**

Anogenital warts

High risk 16, 16,18, 33, 45, 31, 52, 35

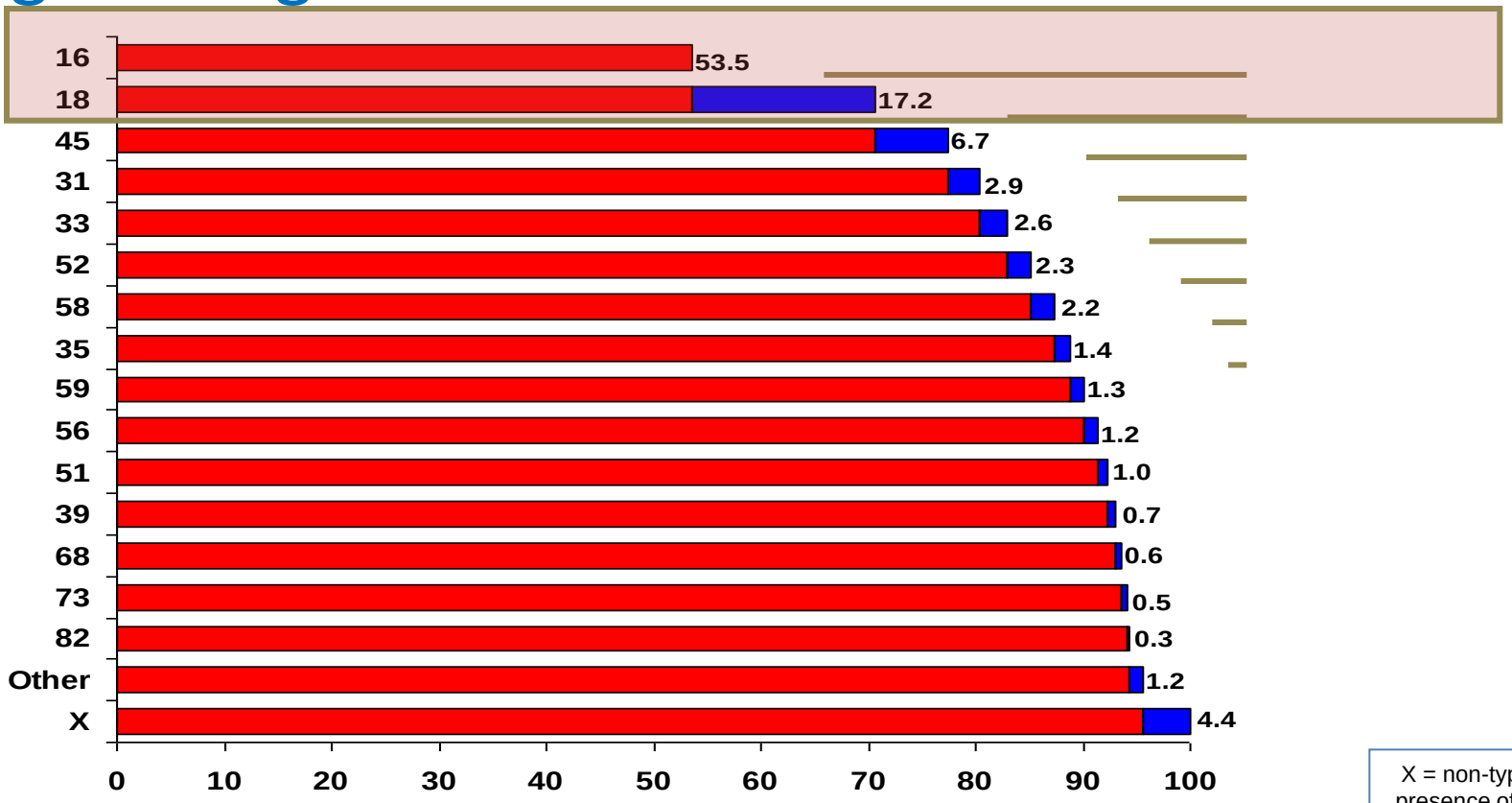
Cervical neoplasia

70% cervical cancer

DELTA Centre
Derby Endoscopic & Laparoscopic Training & Academic Centre

Derby Teaching Hospitals NHS
NHS Foundation Trust

HPV types in cervical cancer – global figures



X = non-typeable types in the presence of multiple infections

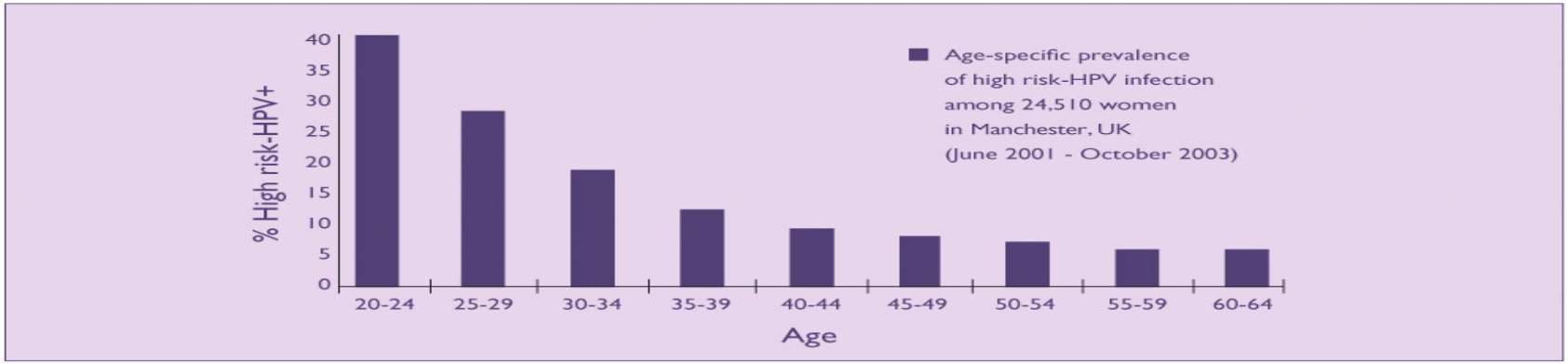
Cervical cancer cases attributed to the most frequent HPV genotypes (%)

Taking pride in caring

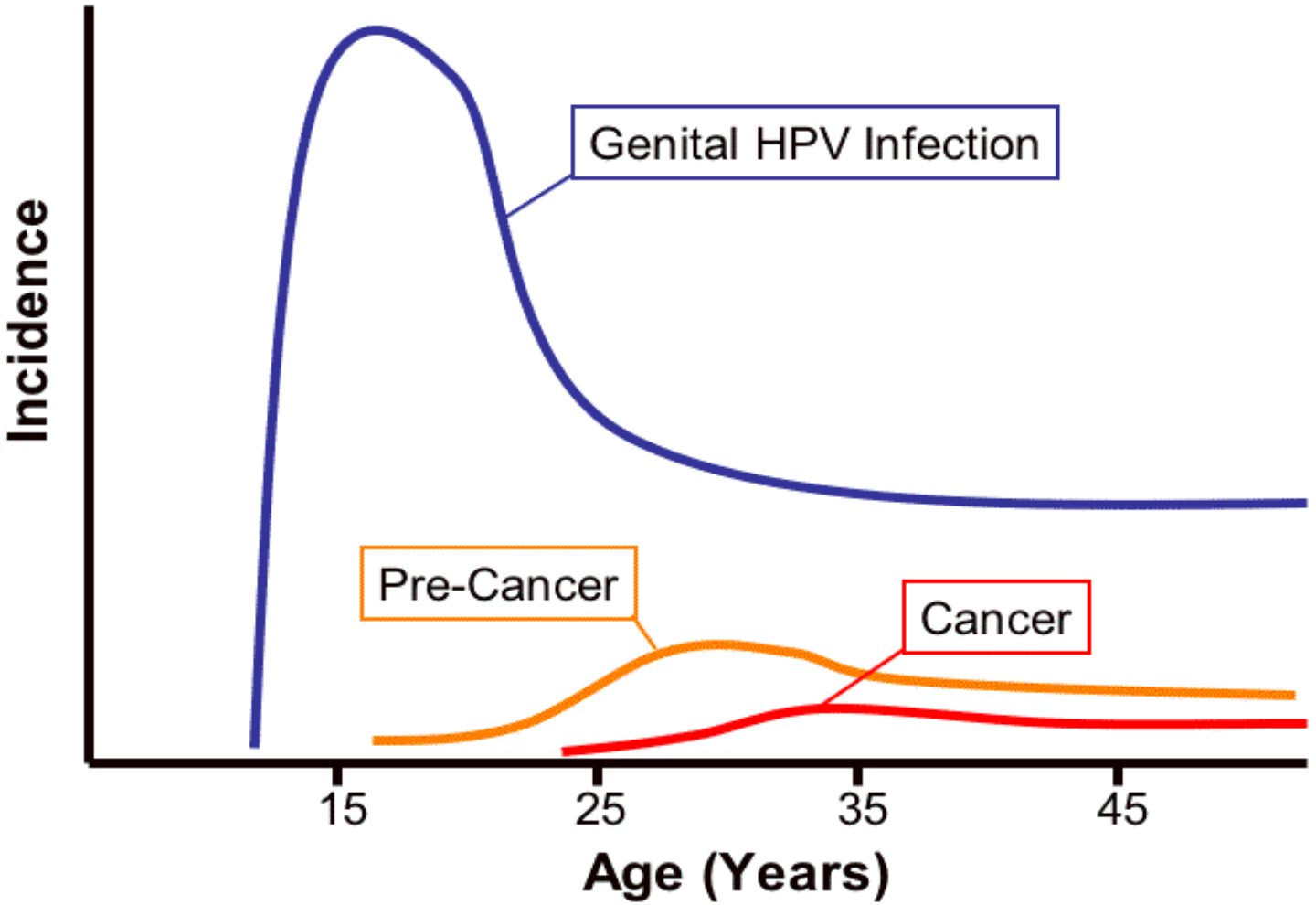
Munoz N *et al*. Int J Cancer 2004; 111: 278-285

HPV infection

- Very common infection - up to 75% of sexually active women will be infected with HPV at some point in their lives
- Easily transmitted through close sexual contact
- Acquisition can occur via skin to skin contact in the genital area,
  - Oncogenic HPV types found in 50 - 75% of HPV infections
- Most (over 90%) HPV infections are transient, asymptomatic and cleared by the immune system

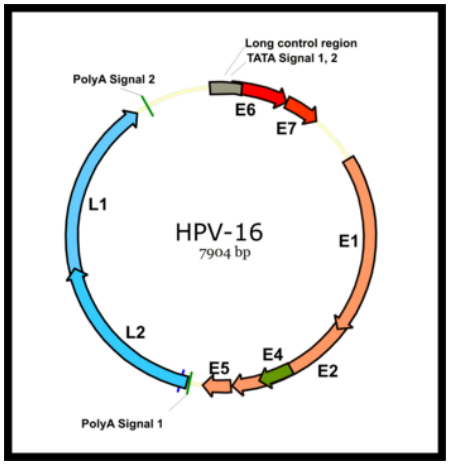


Incidence of cervical cancer & precursors



Integration of Viral Genome & carcinogenesis.

- HPV genome has 6 early proteins E1,E2 and E4-7.
- E6,7- encode virus onco-proteins.
- Late proteins L1,L2 facilitate viral DNA entry into cell.
- Viral genome integrated into host cell genome
- E6 binds to p53,E7 to pRb leading to uncontrolled cell proliferation

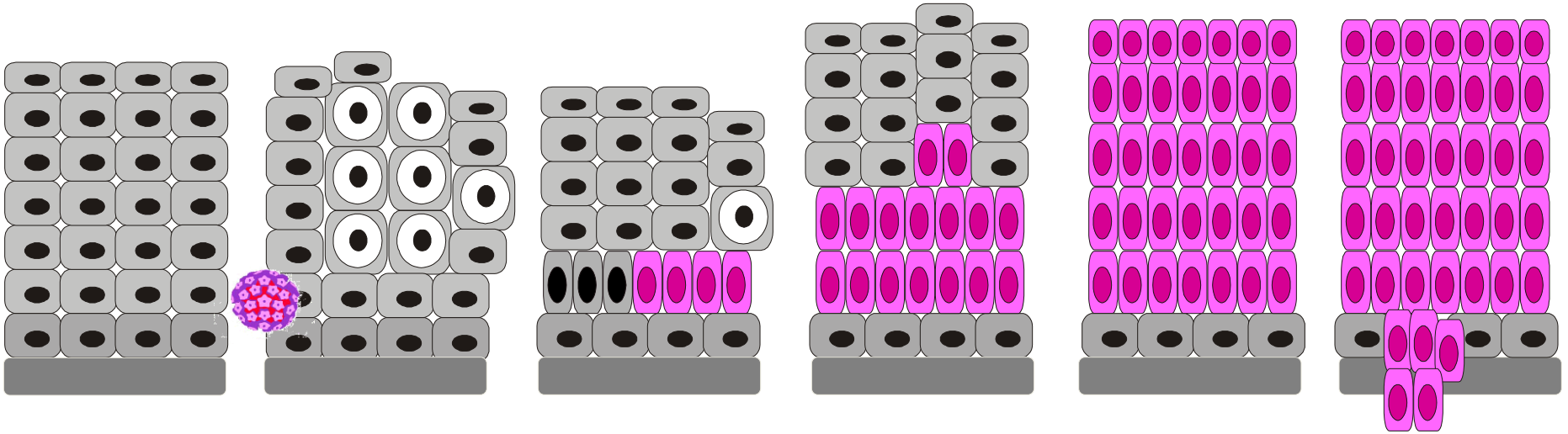


DELTA Centre
Derby Endoscopic & Laparoscopic Training & Academic Centre

Derby Teaching Hospitals NHS
NHS Foundation Trust

Disease progression

Time ····· **Months** ····· **Years**

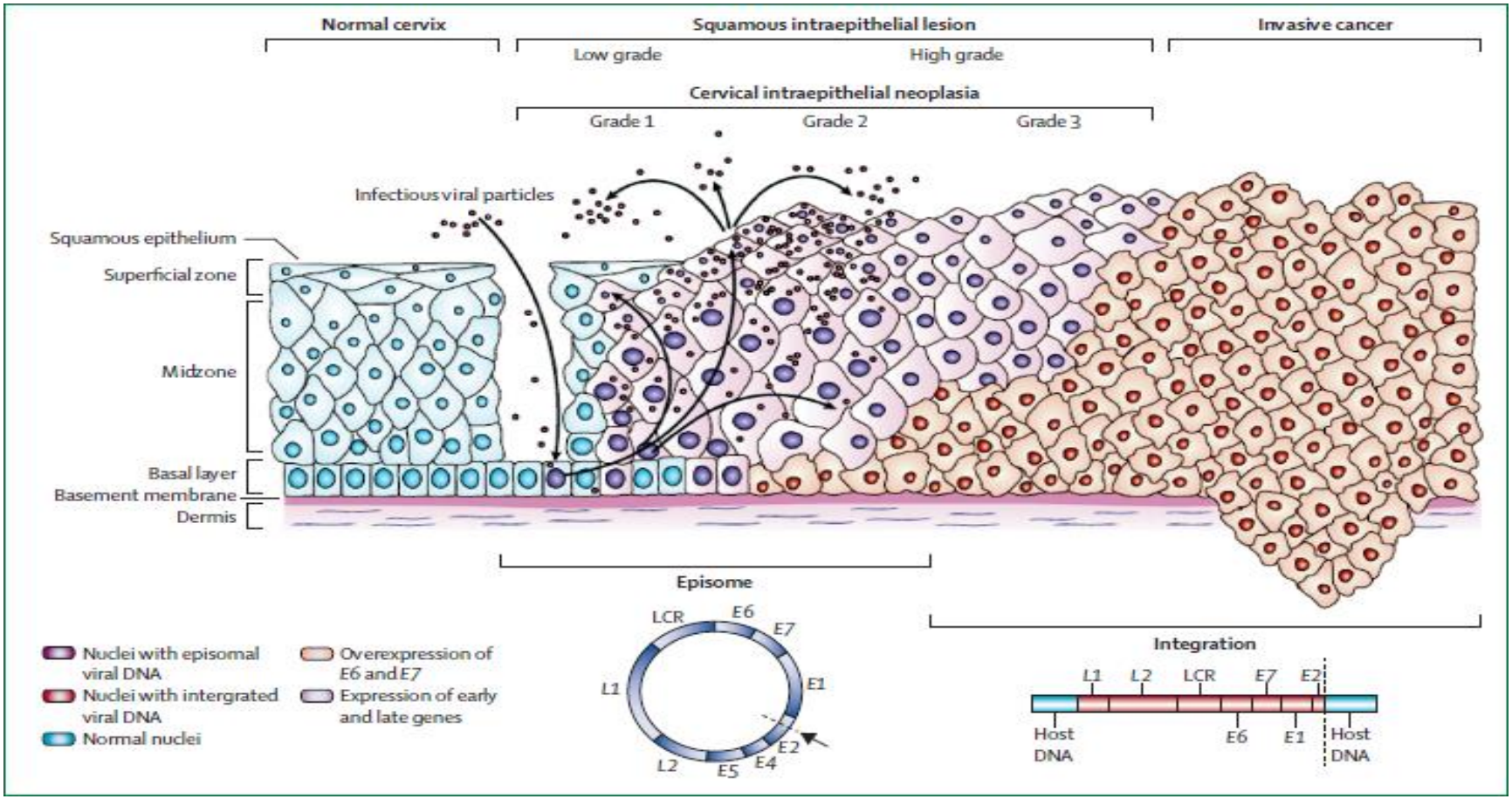


Normal epithelium | **HPV infection; koilocytosis** | **CIN I** | **CIN II** | **CIN III** | **Invasive cervical cancer**

CIN I 57% CIN II 43% CIN III 32%
Approx. likelihood of regression

Taking pride in caring

Burd EM. *Clin Microbiol Rev* 2003; 16: 1–17.
Ostor AG. Int J Gynecol Pathol 1993; 12(2): 186-192.
Solomon D *et al*. *JAMA* 2002; 287: 2114–9.


Normal cervix
Squamous intraepithelial lesion
Low grade
High grade
Invasive cancer
Cervical intraepithelial neoplasia
Grade 1
Grade 2
Grade 3
Infectious viral particles
Squamous epithelium
Superficial zone
Midzone
Basal layer
Basement membrane
Dermis
Episome
LCR
E6
E7
E1
E2
E4
E5
L2
L1
Integration
L1
L2
LCR
E7
E2
Host DNA
E6
E1
Host DNA
Nuclei with episomal viral DNA
Nuclei with intergrated viral DNA
Normal nuclei
Overexpression of E6 and E7
Expression of early and late genes

HPV-related neoplastic disease

- Genital tract disease
  - Cervical and vaginal cancers and precursor lesions
- Perineal disease
  - Vulval, penile and anal cancers and precursor lesions
  - Multifocal disease
- Skin, oesophageal and URT cancer

1. Wieland U and Pfister H. Papillomaviruses in human pathology: Epidemiology, pathogenesis and oncogenic role. In: Gross, Barrasso Eds. Human papilloma virus: A clinical atlas. Ullstein Mosby; 1997. p1–18.

HPV-related neoplastic disease

		DEVELOPED COUNTRIES		DEVELOPING COUNTRIES	
Site	Attributable to HPV (%)	Total Cancers	Attributable to HPV	Total Cancers	Attributable to HPV
Cervix	100	83 400	83 400	409 400	409 400
Anus	90	14 500	13 100	15 900	14 300
Vulva/Vagina	40	18 300	7 300	21 700	8 700
Penis	40	5 200	2 100	21 100	8 400
Mouth	≥3	91 200	2 700	183 100	5 500
Oropharynx	≥12	24 400	2900	27 700	3 300
Other	0	4 779 100	0	5 148 600	0
All sites		5 016 100	111 500	5 827 500	449 600

HPV-related neoplastic disease

		DEVELOPED COUNTRIES		DEVELOPING COUNTRIES	
Site	Attributable to HPV (%)	Total Cancers	Attributable to HPV	Total Cancers	Attributable to HPV
Cervix	100	83 400	83 400	409 400	409 400
Anus	90	14 500	13 100	15 900	14 300
Vulva/Vagina	40	18 300	7 300	21 700	8 700
Penis	40	5 200	2 100	21 100	8 400
Mouth	≥3	91 200	2 700	183 100	5 500
Oropharynx	≥12	24 400	2900	27 700	3 300
Other	0	4 779 100	0	5 148 600	0
All sites		5 016 100	111 500	5 827 500	449 600

5% OF ALL CANCERS

Strength of Association

RR	Carcinogenic Agent
> 500	HRHPV-DNA and cervical cancer - Philippines, Costa Rica, Bangkok
50-100	HBsAg and liver - Taiwan, Greece
20	HCV and liver cancer - Italy
10	Cigarette smoking and lung cancer

Prevention of Cervical Cancer

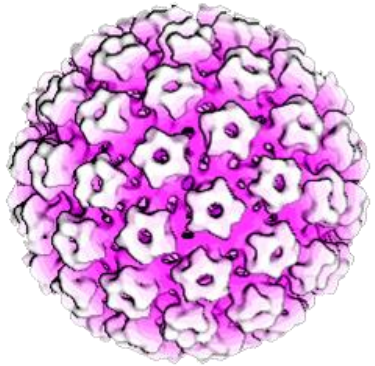
- Cervical cancer is a *preventable* disease

- *Primary* prevention:
  - Education
  - HPV vaccination

- *Secondary* prevention:
  - Treatment of precancerous lesions- screening programme

Prophylactic vaccines - Virus Like Particles (VLPs)

- Recombinant L1 structural protein



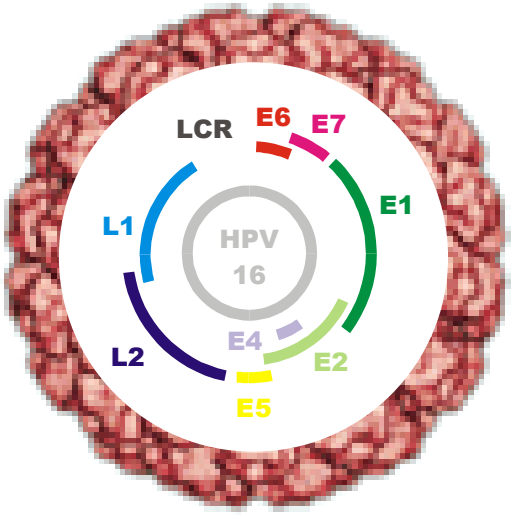
Resemble intact viruses - no DNA

Self-assemble into Virus Like Particles

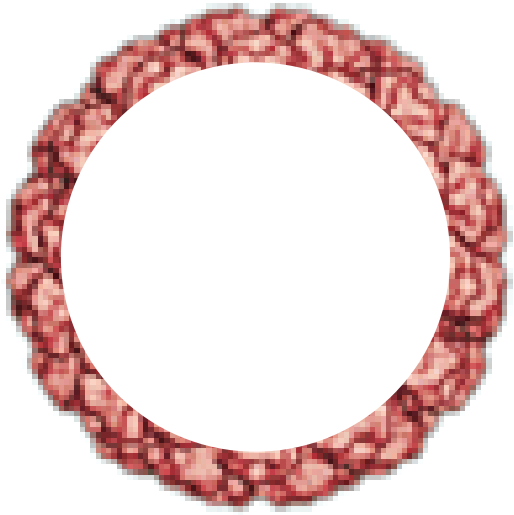
Non infectious

- Immunogenic - Neutralizing Antibodies

Virus Like Particles



HPV Virion



Virus Like Particle

VLP Vaccines

- Merck quadrivalent vaccine HPV 16/18/6/11 (licensed Sept 06)

  - No exposure- 98% efficacy (95% CI(86-100)
  - Prior exposure/ active HPV 44% efficacy (95%CI(26-58)

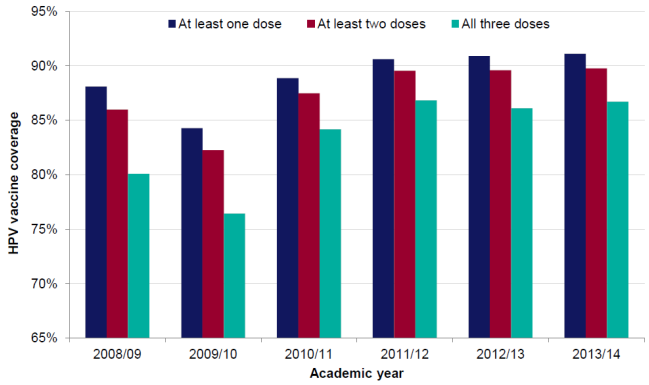
- GSK bivalent vaccine HPV 16/18 (licensed July 2007)

  - No prior exposure - 93% efficacy (95%CI(80-98)
  - Evidence of Cross protection i.e HPV 31/33

Key questions:

- Acceptability
  - Varies 15-80%
- Uptake
  - 85-90%
- Booster requirements?
  - No evidence as yet

Figure 2. Routine HPV vaccine coverage in Year 8 girls (aged 12-13 years) in England, assessed at the end of academic years 2008/09 to 2013/14



Combined HPV vaccination & screening Advantages

- Reduction of
  - Abnormal cytology & pre-invasive disease (CIN2/3)
  - Colposcopy workload
  - Morbidity of screening
  - Psychological morbidity
  - Incidence, morbidity & mortality of cervical cancer
- Other benefits: Reduction of:
  - Ano-genital neoplasia
  - Head and neck cancers

Therapeutic vaccines

- In clinical development!!
- Targeting E6/E7 + others
- Issues:
  - Difficult to measure immune responses after vaccination
  - Broad immunotherapies seem to have toxic effects where effective outpatient treatment has relatively few
  - Does a boosted immune response equate to a defence at the level of the basement membrane

UK HPV vaccination programme

Gardasil®

- Quadravalent vaccine.
- Vaccination of choice: Sept 2012
- Protects against HPV types 16,18, 6 and 11
- Chosen due to action again ano-genital warts. Previously Cervarix
- Immunity for at least 7 years

Vaccine effectiveness

- Uninfected women - 99% effective -preventing CIN - HPV types 16 and 18
- Some cross-protective against other high-risk HPV types.
- Will save the lives of around 400 women each year- UK.

Vaccine side effects

- Localised stinging sensation, and redness
- less commonly reported side effects are
  - slight temperature, sickness, dizziness, diarrhoea and muscle aches.
- Anaphylaxis - extremely rare.
- Few contra-indications

Vaccine schedule and administration

- Schedule changed from 2014 for Gardasil®: by IM injection upper arm
  - 1st dose
  - 2nd dose at least 6 month after 1st dose (And with 2 years)

- Further information (http://www.dh.gov.uk/greenbook).

DELTA Centre
Derby Endoscopic & Laparoscopic Training & Academic Centre

Derby Teaching Hospitals NHS
NHS Foundation Trust

The HPV routine and catch-up vaccination schedule for girls and young women in England, starting from September 2008

	School year 7	School year 8	School year 9	School year 10	School year 11	School year 12	Girls aged 17-18 (school year 13)
08/09							
09/10							
10/11							
11/12 Onwards							

Routine programme for Year 8 girls

Catch-up programme for older girls

Taking pride in caring

HPV coverage

Figure 2. Routine HPV vaccine coverage in Year 8 girls (aged 12-13 years) in England, assessed at the end of academic years 2008/09 to 2013/14

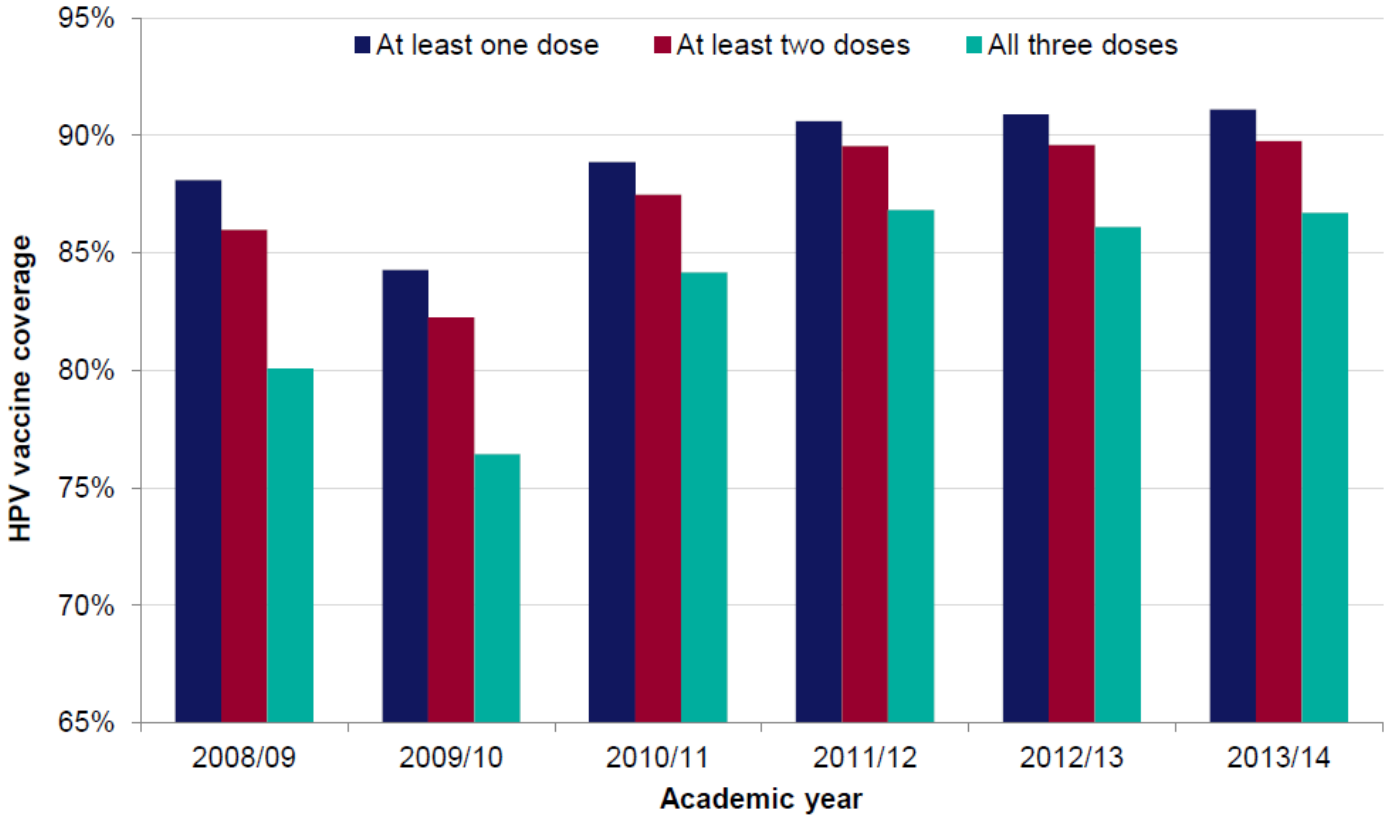
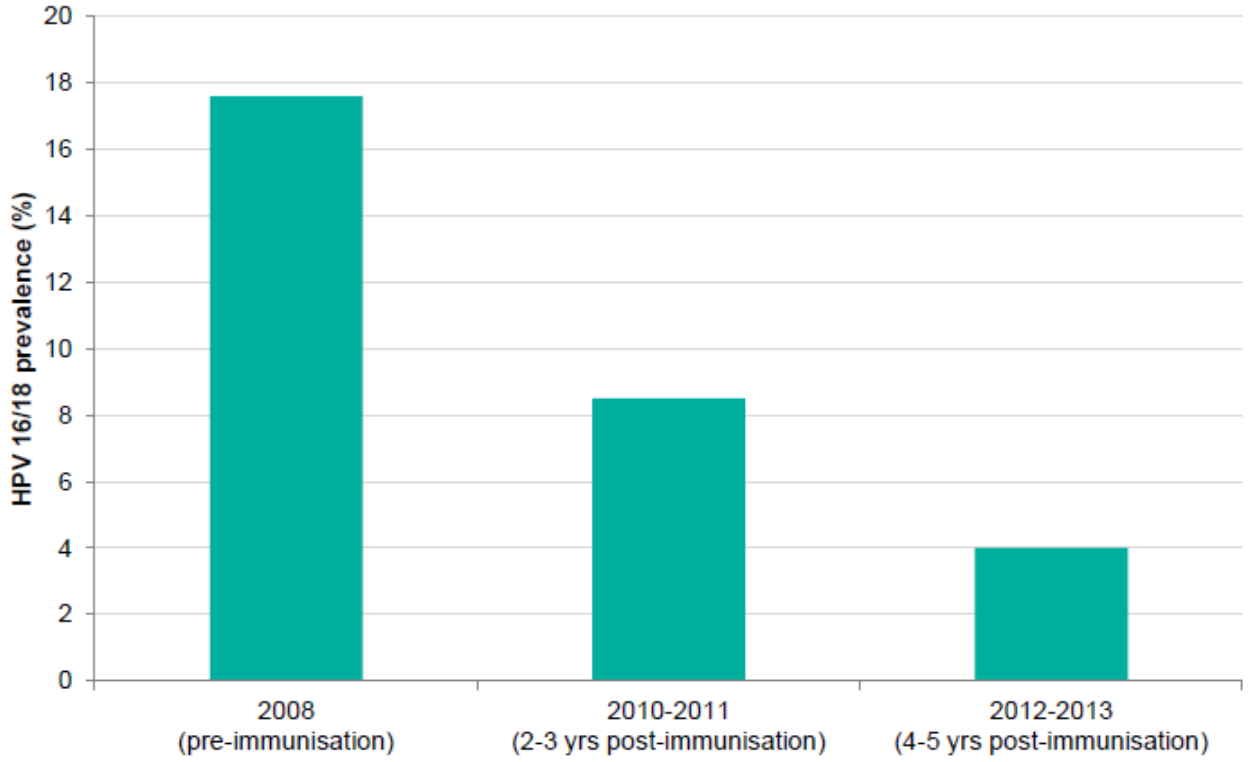


Figure 4. Proportion of routine cohort HPV doses given in different locations, England, 2008/09 to 2013/14

Figure 9. Prevalence of HPV16/18 in a survey of 16-18 year old sexually active young females in England in 2008 (before the immunisation programme) and in 2010-11 and 2012-13 (after)



Vaccination of boys and young women 18 and over

- Vaccination of boys is not cost-effective (unless vaccine costs decrease or high coverage in girls cannot be achieved)

- The vaccination of girls will reduce HPV infections in boys by a herd immunity effect.
- In Australia – genital warts rate reduced by 73% in women and 44% in unvaccinated males

- Those aged 18 and over NOT offered vaccine

Summary

- HPV is the main cause of cervical cancer
- HPV infection is associated with a range of perineal neoplastic diseases
- HPV vaccination started autumn 2008 and has had good uptake with Gardasil
- Women MUST still continue in the cervical Cervical screening programme!!

Any Questions