

HPV surveillance in the vaccine era



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History to HPV vaccination



- 493,000 cases of cervical cancer worldwide
- 70% of cervical cancers associated with HPV 16 and 18 and potentially can be prevented by vaccination
- Quadrivalent vaccine first licensed 2006 (HPV types 6, 11, 16, 18)
- Bivalent vaccine first licensed in 2007 (HPV types 16, 18)
- HPV vaccines licensed in over 100 countries
- HPV immunisation programme in UK started September 2008 using bivalent vaccine
- 27 countries now include HPV in immunisation schedule*

History cont.



April 2009, WHO recommended “*that routine HPV vaccination should be included in national programs*” provided that¹:

- Prevention of cervical cancer and other HPV related disease is a public health priority
- Vaccine introduction is feasible
- Sustainable financing can be secured
- Cost-effectiveness of vaccination strategies is considered

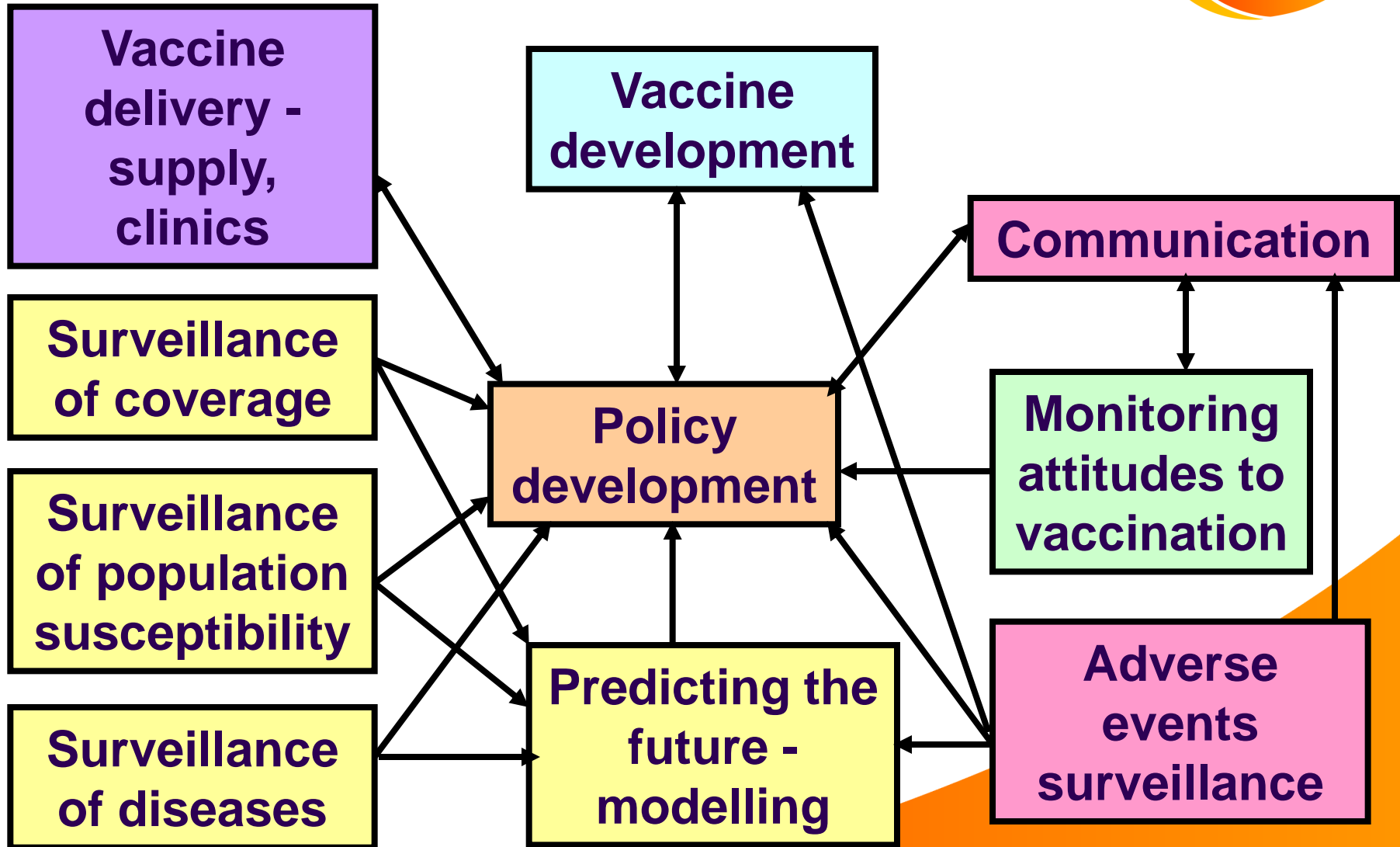
¹WHO : Wkly Epidemiol. Rec. 2009. 15(84):117-132



Why conduct any HPV surveillance in the vaccine era?

- **Ensure vaccine effectiveness when used in the general population**
- **To feed back into vaccination policy**
- **To feed into policy on wider cervical cancer prevention**
- **To show that vaccines are effective against cervical cancer endpoints**

Components of vaccination programmes



Overview of monitoring programme



Focus on 6 key outcomes:

1. Coverage
2. Vaccine Safety
3. Impact of HPV vaccine
 - a. Impact on HPV infections
 - b. Impact on anogenital warts and RRP
 - c. Impact on pre-cancerous cervical lesions (CIN2/3, AIS)
 - d. Impact on cervical cancer

Vaccine Effectiveness

Herd immunity

Changes in frequency of non-vaccine types (cross protection, type-replacement)

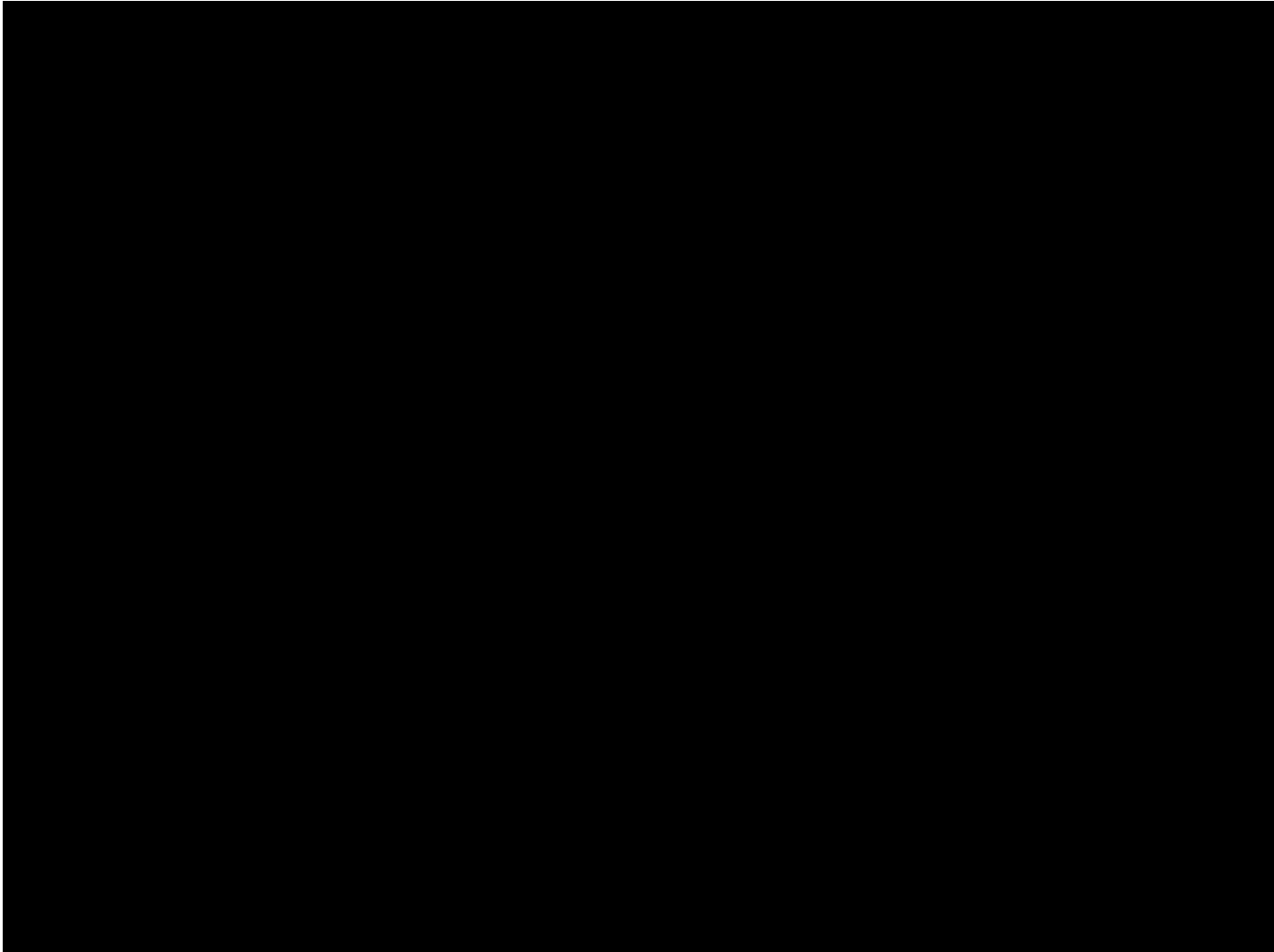
Vaccine failures' characteristics

1. Coverage



- **Complete and accurate vaccine coverage needed to interpret data on impact of vaccine**
- **Denominator used should be the total national population recommended for vaccination**
- **Coverage by age and dose**
- **Due to target age groups countries may need to set up new systems to collect data (Australia) or modify and expand existing systems (UK, USA)**

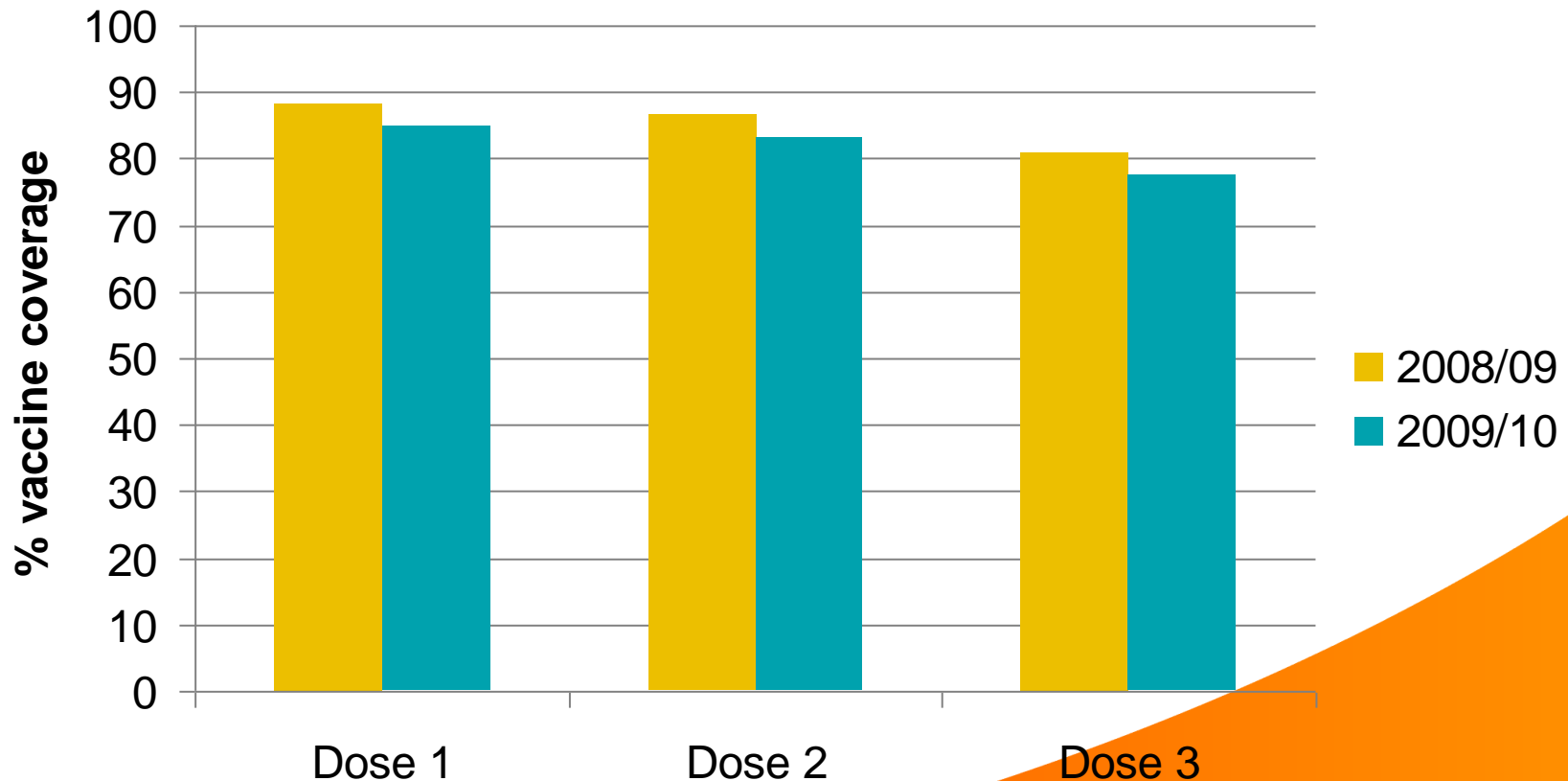
National HPV media campaign



1. Coverage



Annual UK HPV vaccine coverage for females aged 12-13 years



1. Coverage

HPV seroprevalence surveys

- Coverage data will be supplemented and validated by seroprevalence surveys
 - Pragmatic classification of natural infection vs vaccine coverage
 - Surveys of general population and high-risk groups
 - General population: Existing collection of residual blood samples (hospital); potential to extend to blood donors
 - High-risk population: Residual blood samples from GUM clinic attenders¹
 - Baseline studies in 2007/082
 - Natural infection (given seroconversion rates) in males & females
 - Repeat surveys in 2010 onwards
1. Unlinked Anonymous Survey of Genitourinary Medicine Clinic Attendees (UA GUM Survey) webpage on www.hpa.org.uk: http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1202115496235?p=1201094588821
 2. Jit M *et al* Prevalence of human papillomavirus antibodies in young female subjects in England Br J Cancer 2007; 97:989-91

2. Vaccine Safety



- **No evidence of safety concerns in clinical trials**
- **Need post-licensure monitoring to detect rarer adverse events**
- **Countries often have established systems for other vaccines (Vaccine Adverse Event Reporting System – USA, Yellow card scheme – UK)**
- **No safety concerns to date**



Additional safety initiatives

Two additional safety initiatives:

- i) Background rate of autoimmune disorders (HPA and MHRA)**
- ii) Vaccination in pregnancy registry (HPA)**

BACKGROUND RATE OF AUTOIMMUNE DISORDERS

E Miller, J Stowe & N Andrews

P Bryan & L Wise, Medicine and Healthcare products Regulatory Agency (MHRA)

A Hall & S Thomas, London School of Hygiene and Tropical Medicine (LSHTM)

Aim: To predict consultation and referral rates for disorders of interest expected by chance in the post vaccination periods in young women

Methods:

- 1. General Practice Research Database (GPRD)**
 - 12 to 20y females with a disorder of interest**
 - April 1992 to December 2007**
- 2. Disorders of interest: possible immune-mediated or unknown aetiology**

Similar to US study: Siegrist CA, et al. Human papilloma virus immunization in adolescent and young adults: a cohort study to illustrate what events might be mistaken for adverse reactions. *Pediatr Infect Dis J.* 2007



Additional safety initiatives

Two additional safety initiatives:

- i) Background rate of autoimmune disorders (HPA and MHRA)**
- ii) Vaccination in pregnancy registry (HPA)**

VACCINATION IN PREGNANCY REGISTRY

H Campbell & E Miller

Aim: To compile additional information on women immunised in pregnancy and on their pregnancy outcomes

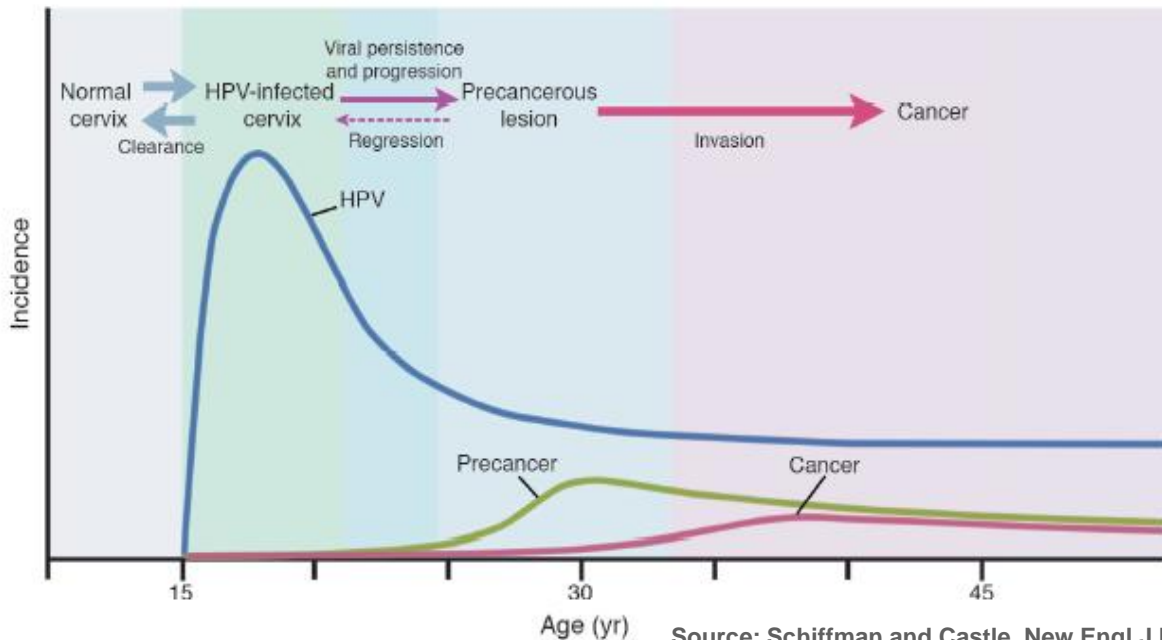
Methods:

- 1. Self, or healthcare professional, reported**
- 2. Up to 3 follow up questionnaires via GP:**
 - i. at initial report**
 - ii. ~8 weeks after estimated delivery date**
 - iii. one year after birth of child**

Vaccination in pregnancy webpage on www.hpa.org.uk:
<http://www.hpa.org.uk/webw/HPAweb&Page&HPAwebAutoListName/Page/1221202947595?p=1221202947595>

3. Impact of HPV vaccine

- a) HPV infections
- b) HPV disease - Anogenital warts and Recurrent respiratory papillomatosis (RRP)
- c) HPV disease - Pre-cancerous cervical lesions
- d) HPV disease - Cervical Cancer



Source: Schiffman and Castle, New Engl J Med 353;20:2101-2104, 2005

3a. Impact on HPV infections

- Offers the first measurable outcome to monitor the impact of the immunisation programme
- Vaccine **effectiveness**: Impact on HPV 16/18 and other HPV infections (**cross protection**) can be measured by comparison of:
 - Vaccinated Vs unvaccinated individuals
 - Targeted birth cohorts Vs baseline data
- **Herd immunity** effects can be investigated by comparison of:
 - Unvaccinated individuals in targeted cohorts Vs baseline data
 - Age groups older than vaccine target cohorts Vs baseline data
- **Challenges**
 - Access to appropriate samples from this population
 - Individual vaccination history

3a. Impact on HPV infections

Example: HPV infections in young women undergoing chlamydia screening in England.

Study design:

- Unlinked, anonymous survey using opportunistic samples (residual vulva-vaginal swabs)
- Collected from women 16-24y participating in the National Chlamydia Screening Programme
- Type-specific HPV testing using in-house luminex-based assay
- Baseline data obtained in 2008
- Repeat annually from 2010

Outcomes:

- Vaccine effectiveness
- Herd immunity
- Cross protection and other changes in frequency of non-vaccine HPV types (type-replacement)
- Vaccine failure

Challenges:

- Not population-based
- Obtaining individual HPV vaccination records
- Changes in HPV testing method between baseline and post-immunisation surveys

3b. Impact on anogenital warts and RRP

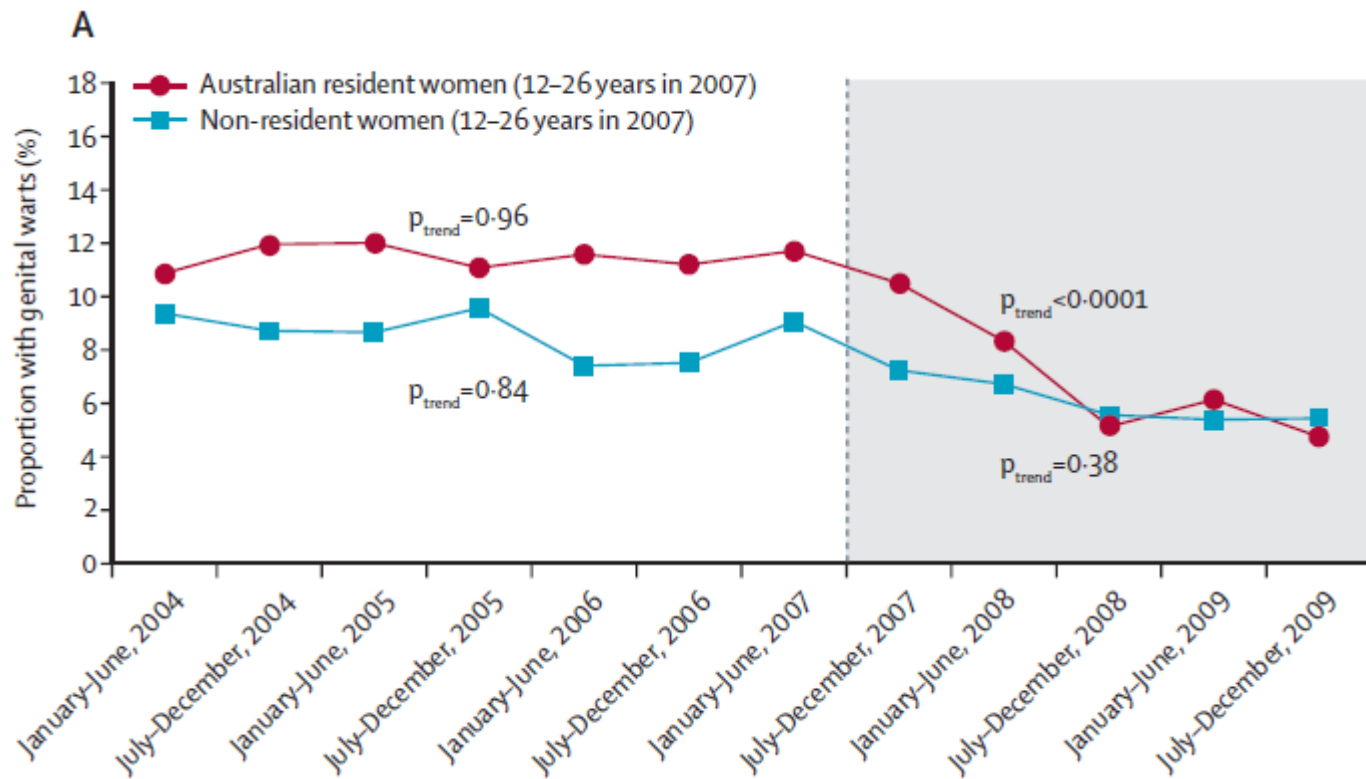


- **Only in countries using quadrivalent vaccine**
- **Genital warts develop months after HPV infection**
- **Decreases in incidence should be an early impact**
- **Challenges**
 - Lack of pre-existing national surveillance for genital warts or RRP
 - Distinguishing between recurrent and incident warts
- **Establish sentinel surveillance in sexual health clinics**

3b. Impact on anogenital warts



Example: Surveillance of genital warts diagnoses in sexual health clinics in Australia



3c. Impact on pre-cancerous cervical lesions (CIN2/3, AIS)



- **End points used in clinical trials**
- **Only detected as result of cervical cancer screening**
- **Challenges**
 - Countries without established cervical screening programmes
 - Precursors not routinely monitored
 - Changes to screening practices will have an impact (bias)
 - Changes in population attending screening
 - Quality assurance in cytology
 - Obtaining vaccination status

3c. Impact on pre-cancerous cervical lesions (CIN2/3, AIS)

Example: Monitoring the effects of vaccination on cancer precursors CIN2+ in Scotland

Study design:

- Population: Young (20-24y) women attending for colposcopy following 'abnormal' cervical screen
- 500 samples every other year until 2020, collected from all colposcopy centres across Scotland.
- Sample: Part of diagnostic colposcopy biopsy, CIN2+
- HPV testing using Multimetrix HPV Genotyping Assay, with reflex HPV Inno-LiPA HPV Genotyping Extra assay for HPV Negative samples.

Outcomes:

- Vaccine effectiveness against HPV 16/18 in cancer precursors.
- Vaccine effectiveness against non-16/18 infections (i.e. cross-protection, type replacement) in cancer precursors.

Challenges:

- Non-attenders at cervical screening

3d. Impact on cervical cancer



- **Prevention of cervical cancer is primary aim of HPV vaccination programmes**
- **Requires a cancer registry**
- **Ideally need to determine HPV genotype of cervical cancers**
- **Challenges**
 - Linkage between cancer register and vaccination history



General Challenges to HPV monitoring

- **Funding**
- **Different age cohort to normal immunisation programmes**
- **Variety in implementation strategies**
- **Long interval to primary endpoint of interest**
- **Retaining and linking to vaccination history**
- **Accessing populations for interim measures**
- **Changes to diagnostic and screening practices**
- **May not be feasible in many settings**

WHO and ECDC recommendations



WHO

- **Vaccine coverage by age and dose**
- **Cervical cancer**
- **HPV infection (not for all countries)**

ECDC

- **Vaccine coverage**
- **Adverse events following immunisation**
- **Sentinel surveillance of impact on precancer lesions**

Summary



- **Countries have a variety of implementation strategies and different vaccines**
- **A variety of surveillance systems are in the process of being set-up in a number of countries**
 - **Systems developed for early monitoring (1st 5 years)**
 - **Impact on cervical disease outcomes 10-20 years away**
- **Modification of existing systems and establishing new systems**
- **Both population level and sentinel surveillance**
- **Good coverage data and long-term individual vaccination records critical for the monitoring programme**
- **No correct or single approach**