Cancer- Warts ‘n All

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What is Human Papillomavirus

- Human Papillomavirus (HPV) is a Double Stranded DNA virus
- Up to four out of five sexually active men and women will become infected with at least one genital HPV type in their lifetime\(^2,3\)

VLPs: breakthrough to HPV vaccine
HPV Infection

- Over 90% of HPV infections are cleared naturally by immune system
- Cancer is a rare outcome of infection
- HPV infection is detected during Pap tests as abnormal cervical cells
  - Surrogate marker of infection
- If detected early, treatment is highly curative
HPV transmission

- Mainly sexually transmitted
  - Other modes
- Most infections asymptomatic
- Most infections clear within 2 years, 98% within 5 years
- Condom effectiveness – compliance, competence, timing
### Rate of Acquisition of HPV Infection Following Sexual Debut, in Virgins

<table>
<thead>
<tr>
<th></th>
<th>24 Months</th>
<th>56 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Denmark</strong></td>
<td>35.4%</td>
<td>-</td>
</tr>
<tr>
<td>(S.K. Kjaer et al. 2001)</td>
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<tr>
<td><strong>US</strong></td>
<td>40.0%</td>
<td>70.0%</td>
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<tr>
<td>(L. Koutsky 2001 / 3)</td>
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</tbody>
</table>
HPV Types

- More than 100 types of HPV identified in humans\(^1\)
- More than 40 types infect the anogenital mucosa\(^1\)
  - **High risk** HPV types (e.g. 16, 18)
  - Responsible for majority of high grade pre-cancerous lesions and virtually all cervical cancers\(^2,3\)
  - Sufficient evidence for causality of HPV 16 in following cancers:
    - Vulva & vagina
    - Anus
    - Penile
    - Oropharynx\(^4\)

• **Low risk** HPV types (eg. 6, 11) rarely undergo malignant transformation however cause significant morbidity and disease:
  
  – Genital warts
  
  – Low grade cervical, vaginal and vulval abnormalities

  – Recurrent respiratory papillomatosis

Burden of HPV Disease

HPV Type | Women | Men
--- | --- | ---
16 / 18 | • 70% of cervical cancer\(^1\)  
• 50% of CIN 2/3\(^2\)  
• 25% of CIN 1\(^3\)  
• Most anal cancers\(^4\)  
• ~50% of vaginal and vulval cancers\(^7\)  
• 10% of CIN 1\(^3\)  
• >90% of genital warts\(^5\)  
• Recurrent respiratory papillomatosis (RRP)\(^6\) | • Most anal cancers\(^4\)  
• Potential prevention of infection  
(reduced transmission to women)  

6 / 11  

CIN = Cervical Intra-epithelial Neoplasia  
RRP = Recurrent Respiratory Papillomatosis.  
% Associated with Certain HPV Types

Cancer Type

- Cervical
- Vagina
- Vulvar
- Penile
- Anal
- Oropharynx
- Larynx and digestive Tract

*Includes cancer and intraepithelial neoplasia

New Cases Estimated in 2006, United States

- Cervical: ~100,000
- Vagina: ~50,000
- Vulvar: ~20,000
- Penile: ~10,000
- Anal: ~35,000
- Oropharynx: ~20,000
- Larynx and digestive Tract: ~5,000
HPV is a Potent Carcinogen causing Multiple Related Cancers in Men and Women

Annual number of new cancer cases calculated based on crude incidence rates from IARC database (1998-2002) and population estimate Eurostat 2008; estimate Globocan 2008 for cervical cancer; published HPV prevalence rates were applied (for Europe, when available) Genital warts estimates based on incidence rates in UK, HPA 2007. Source: Giuliano, Oral presentation, EUROGIN 2011
Infection to abnormality

- HPV infects basal epithelium
  - Minor skin abrasions
- Replicates its DNA in dividing cells
- Normally, cells rising from basal epithelium
  - Cease division and differentiate
- In cervical HPV lesions, cells rising from base continue to divide
  - i.e. cells proliferate, not differentiate
    - (“poorly differentiated” is not good)
HPV to Cancer

- HPV necessary but not sufficient cause for cervical cancer
  - Persistent infection with oncogenic type
  - 4-6 independent causal events to induce malignancy
Risk factors for cervical cancer

- Lifetime no of sexual partners
- Young age at onset of sexual activity
- Smoking
- Immune suppression by disease, drugs, pregnancy
- Inflammatory STIs

(Svare et al 2002)
Cervical Cancer

- Second most common cause of death in women worldwide, preceded only by breast cancer
- Worldwide prevalence: >2 million cases
- Approximately 510,000 new cases each year and an estimated 288,000 deaths (particularly developing countries)
- Preventable and curable in >95% of patients if detected early
Cervical Cancer (2)

Australia

- I.R. 2002 6.9/100 000
- 735 deaths (2002)
- Projected incidence n=461 by 2011 (AIHW)
- Aboriginal mortality 6x higher
- 15 000 HSIL results 2002-3 (NOT cancer)
- Strikes young women, with an average age of first diagnosis of 53 years compared to breast cancer (60 years) and lung cancer (69 years)
HPV DNA found in 99.7% of all cervical cancers

Walboomers et al, J Pathology 1999

HPV is a necessary cause for invasive cervical cancer
Cervical Screening

- Since introduction of routine screening in Australia:
  - Incidence of cervical cancer halved over past decade
- Two yearly screening for females aged 18-69 years
- Involves visualisation of cervix with a speculum and taking a sample of cervical cells
National Cervical Screening Program

Ref: 1. Screening to Prevent Cervical Cancer 2005 NHMRC
Pap Tests

- Pap tests pick up abnormalities before they become cancerous

- Low grade abnormalities (LSIL) require more frequent follow up and re-screening
  - ~15,000 low grade abnormalities (2006)

- High grade abnormalities (HSIL) require surgical treatment (cone biopsy, LEEP)
  - Procedures may affect ability to carry pregnancy to term
  - ~14,500 high grade abnormalities (2006)

- Psychosocial consequences
- Role of HPV testing
Burden of Disease in Screened Women

- Due to success of screening, burden shifted to screened women
- Every day, 40 Australian women undergo surgery to remove affected part of cervix
- 80% of these women < 40 years old

![Rate of high-grade abnormalities per 1000 women screened vs. age](chart)

Ref: AIHW-AACR 2003
Cervical Cancer

- Treatment consists of:
  - Surgery
    - hysterectomy (partial, complete or radical)
  - Radiation
  - Chemotherapy
Vaginal Intraepithelial Neoplasia (VaIN)

- Main predisposing factor for VaIN is likely exposure to HPV
- Average age of women with VaIN: 40–60 years
- True incidence unknown, but lower than for CIN
- VaIN is often asymptomatic and difficult to diagnose.
- While untreated VaIN can spontaneously regress, there is a potential for VaIN to progress to invasive vaginal cancer.
Vulvar Intraepithelial Neoplasia (VIN)

- Incidence of VIN is increasing in the United States and worldwide.
- Mean age of women with VIN is decreasing.
- Symptoms occur and may be present for a long time prior to diagnosis (median of 1 year).
- HPV 16 appears to be the dominant HPV type associated with high-grade VIN.
  - Majority of VIN 1 cases are associated with HPV types 6 and 11.
  - HPV 6, 11, 16, or 18 can be found in VIN 2 or 3.
<table>
<thead>
<tr>
<th>Year</th>
<th>No. new cases</th>
<th>Anal canal cancers and Age Standardised Rates</th>
<th>Year</th>
<th>No. new cases</th>
<th>Anal canal cancers and Age Standardised Rates</th>
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</thead>
<tbody>
<tr>
<td>1983</td>
<td>97</td>
<td>0.6</td>
<td>1993</td>
<td>159</td>
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<td></td>
<td>0.9</td>
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<td></td>
<td>0.9</td>
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<td>1984</td>
<td>121</td>
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<td>1994</td>
<td>180</td>
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<tr>
<td>1985</td>
<td>142</td>
<td>0.9</td>
<td>1995</td>
<td>187</td>
<td></td>
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<td></td>
<td>1.0</td>
<td></td>
<td></td>
<td>1.0</td>
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<tr>
<td>1986</td>
<td>120</td>
<td>0.8</td>
<td>1996</td>
<td>206</td>
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<td></td>
<td>1.1</td>
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<tr>
<td>1987</td>
<td>126</td>
<td>0.8</td>
<td>1997</td>
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<td>1.0</td>
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<tr>
<td>1988</td>
<td>150</td>
<td>0.9</td>
<td>1998</td>
<td>213</td>
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<td></td>
<td>1.1</td>
<td></td>
<td></td>
<td>1.1</td>
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<tr>
<td>1989</td>
<td>133</td>
<td>0.8</td>
<td>1999</td>
<td>250</td>
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<td></td>
<td>1.3</td>
<td></td>
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<td>1.3</td>
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</tr>
<tr>
<td>1990</td>
<td>170</td>
<td>1.0</td>
<td>2000</td>
<td>227</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.2</td>
<td></td>
<td></td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>1991</td>
<td>161</td>
<td>0.9</td>
<td>2001</td>
<td>225</td>
<td></td>
</tr>
</tbody>
</table>
ANAL CANCER: RISK FACTORS

- Receptive anal sex in men
- HIV
- History of STD’s: GC, CT, HSV2
- History of genital warts
- Current cigarette smoking
- ≥10 sexual partners
- Female sex
  - History of cervical, vulvar or vaginal cancer
  - Immunosuppression after solid organ transplantation
  - Long term use of corticosteroids
  - HPV 16 and 18 responsible for 90% of all cancers

WARTS

- Genital warts are the commonest STI
- 75% of people are exposed
  - 1% have warts
  - 15% subclinical disease
- Estimated lifetime risk of developing genital warts ~10%
Burden of Genital Warts

- Each year in Australia it is estimated there are approximately 44,000 new cases of genital warts\(^1\)
  - 34,000 managed by GPs
  - 10,000 managed by sexual health clinics
- Total of 120,000 medical visits
- Estimated annual cost $12.35 million
- Psychosocial impact of genital warts is similar to that of HSIL\(^2\)

Warts

- 6 and 11 cause 90% of genital warts
- Some evidence for auto inoculation
- Multicentric infection occurs
- Median time from infection to warts is 3 months but can be much longer
- Most clear virus in 12-24 months
- Condoms?
Preventing HPV infection

- The ‘common cold’ of STIs
- Reduce risk
  - Limit the number of sexual partners
  - Use condoms
  - STI screening
  - Don’t smoke
- New vaccines
What New Vaccines?

- Gardasil (Merck/CSL) for HPV types 6, 11, 16 and 18
- Cervarix (GSK) types 16 and 18
- Both vaccines 100% against persistent infection types 16 and 18
- Other types associated with cancer
  - 31, 33, 35, 39, 45, 51-53, 55, 56, 58, 59, 66, 68
  - Cross protection issue
- Gardasil reduces genital warts by >90%
Efficacy in Sexually Active Women

- While the most effective time to vaccinate with GARDASIL is prior to exposure to HPV there is some clinical benefit in vaccinating those already sexually active\(^1\)
- Clinical trial subjects were ~20,000 mostly sexually active women, 16 to 26 years
- Women infected with vaccine HPV types prior to vaccination were protected from clinical disease due to remaining vaccine HPV types\(^1\)

1. GARDASIL Product Information 2011.
GARDASIL Prophylactic Efficacy
Females 16 to 26 years

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>GARDASIL™</th>
<th>Placebo</th>
<th>Efficacy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN 2/3 or AIS*</td>
<td>2/8,493</td>
<td>112/8,464</td>
<td>98 %</td>
<td>94-100</td>
</tr>
<tr>
<td>VIN 2/3*</td>
<td>0/7,772</td>
<td>10/7,744</td>
<td>100 %</td>
<td>56-100</td>
</tr>
<tr>
<td>VaIN 2/3*</td>
<td>0/7,772</td>
<td>9/7,744</td>
<td>100 %</td>
<td>50-100</td>
</tr>
<tr>
<td>CIN or AIS#</td>
<td>9/7,865</td>
<td>225/7,865</td>
<td>96 %</td>
<td>92-98</td>
</tr>
<tr>
<td>Genital Warts^</td>
<td>2/6,932</td>
<td>189/6,856</td>
<td>99 %</td>
<td>96-100</td>
</tr>
</tbody>
</table>

*Due to HPV 16 or 18
# Due to HPV 6,11,16 or 18
^Due to HPV 6 or 11

Primary efficacy results with combined database of efficacy studies in per-protocol population.
Mean duration of follow up 4, 3, 3 and 3 years for Protocol 005, Protocol 007, FUTURE I and FUTURE II respectively.
GARDASIL Product Information 2011.
Efficacy in Women Aged 24 – 45 Years, Seropositive and DNA Negative at Baseline (post hoc analysis)

- Subjects with evidence of prior infection that had resolved by vaccination onset were protected from reacquisition or recurrence of infection leading to clinical disease

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>GARDASIL Cases</th>
<th>Placebo Cases</th>
<th>Observed Efficacy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 6/11/16/18 – Related Persistent Infection, CIN or EGL</td>
<td>5/506</td>
<td>15/513</td>
<td>66.9 %</td>
<td>4, 91</td>
</tr>
</tbody>
</table>

CIN = Cervical Intra-epithelial Neoplasia. EGL = External Genital Lesions.

Castellsague et al, 2011; Median follow up period 4 years
Proportion of women of free vaccine eligible age with genital warts, by resident status, 2004-2010

- Resident women
  - Pre-vaccine period: p-trend=0.84
  - Vaccine period: p-trend<0.001
- Non-resident women
  - Pre-vaccine period: p-trend=0.96
  - Vaccine period: p-trend=0.06

-25% and -73% decrease in proportions.
Proportion of men with genital warts, by gender of sexual partners, 2004-2010

-35%

Heterosexual men
Men who have sex with men

p-trend=0.35
p-trend=0.03
p-trend<0.001
p-trend=0.19
Impact on Cervical Abnormalities in Victoria: An Ecological Study

- Analysis of trends in cervical abnormalities from Victorian Cervical Cytology Registry between 2003 and 2009
- Compared incidence of histopathologically defined high-grade cervical abnormalities (HGAs) and low-grade cytological abnormalities (LGAs) in five age groups before and after the vaccination programme began
- After vaccination program introduction:
  - Decrease in incidence of HGAs by 0.38% (95% CI: 0.61 to 0.16, p=0.003) in females less than 18 years
  - No similar decline for LGAs or older age groups
- First report of decrease in incidence of HGAs within 3 years of vaccination program
- Important to note this is ecological study - data not currently linked to vaccination status

Brotherton et al, 2011
### Efficacy Against HPV 6/11/16/18 Anal Disease

#### Per Protocol Efficacy Population

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>GARDASIL (N=194)</th>
<th>Placebo (N=208)</th>
<th>Observed Efficacy</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 6/11/16/18 - Related AIN</td>
<td>5</td>
<td>24</td>
<td>77.5 %</td>
<td>(39.6, 93.3)</td>
</tr>
<tr>
<td>HPV 6/11/16/18 - Related AIN 2/3</td>
<td>3</td>
<td>13</td>
<td>74.9 %</td>
<td>(8.8, 95.4)</td>
</tr>
</tbody>
</table>

Palefsky *et al*., 2011; Mean follow up time 2.2 years.
Who should have the vaccine?

- **Age?**
  - Prophylactic so pre infection is best
  - Higher immunogenicity in young
  - Compliance – 3 doses
  - Logistics

- **Men**
Women Remain at Risk for Acquiring HPV Infection Throughout Their Lifetime

Prevalence of HPV Infection by Age

# HPV Seroprevalence

## Table 3. Seropositivity for combinations of human papillomavirus (HPV) types in the female population, by age group.

<table>
<thead>
<tr>
<th>Age group</th>
<th>No. of samples tested</th>
<th>Proportion positive, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HPV types 16 or 18</td>
</tr>
<tr>
<td>0–9 years</td>
<td>128</td>
<td>0.0 (0.0–2.8)</td>
</tr>
<tr>
<td>10–14 years</td>
<td>95</td>
<td>2.1 (0.3–7.4)</td>
</tr>
<tr>
<td>15–19 years</td>
<td>142</td>
<td>10.6 (6.0–16.8)</td>
</tr>
<tr>
<td>20–29 years</td>
<td>247</td>
<td>18.2 (13.6–23.6)</td>
</tr>
<tr>
<td>30–39 years</td>
<td>313</td>
<td>26.8 (22.0–32.1)</td>
</tr>
<tr>
<td>40–49 years</td>
<td>288</td>
<td>23.3 (18.5–28.6)</td>
</tr>
<tr>
<td>50–59 years</td>
<td>158</td>
<td>15.8 (10.5–22.5)</td>
</tr>
<tr>
<td>60–69 years</td>
<td>152</td>
<td>11.8 (7.2–18.1)</td>
</tr>
<tr>
<td>All\textsuperscript{a}</td>
<td>1523</td>
<td>15.2 (13.5–16.9)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Weighted population total, with estimates weighted by age distribution of the 2005 Australian midyear population estimates from the Australian Bureau of Statistics.
Table 4. Seropositivity for combinations of human papillomavirus (HPV) types in the male population, by age group.

<table>
<thead>
<tr>
<th>Age group</th>
<th>No. of samples tested</th>
<th>Proportion positive, % (95% CI)</th>
<th>HPV types 16 or 18</th>
<th>HPV types 6 or 11</th>
<th>Any HPV type 6, 11, 16, or 18</th>
<th>HPV type 16 and 18</th>
<th>All HPV types</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–9 years</td>
<td>148</td>
<td>0.0 (0.0–2.5)</td>
<td>0.0 (0.0–2.5)</td>
<td>0.0 (0.0–2.5)</td>
<td>0.0 (0.0–2.5)</td>
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<td>0.0 (0.0–2.5)</td>
</tr>
<tr>
<td>10–14 years</td>
<td>119</td>
<td>0.0 (0.0–3.1)</td>
<td>0.0 (0.0–3.1)</td>
<td>0.0 (0.0–3.1)</td>
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<td>0.0 (0.0–3.1)</td>
<td>0.0 (0.0–3.1)</td>
</tr>
<tr>
<td>15–19 years</td>
<td>165</td>
<td>1.2 (0.1–4.3)</td>
<td>1.2 (0.1–4.3)</td>
<td>2.4 (0.7–6.1)</td>
<td>0.0 (0.0–2.2)</td>
<td>0.0 (0.0–2.2)</td>
<td>0.0 (0.0–2.2)</td>
</tr>
<tr>
<td>20–29 years</td>
<td>209</td>
<td>8.6 (5.2–13.3)</td>
<td>13.4 (9.1–18.8)</td>
<td>19.1 (14.0–25.1)</td>
<td>0.5 (0.0–2.6)</td>
<td>0.0 (0.0–1.7)</td>
<td>0.0 (0.0–1.7)</td>
</tr>
<tr>
<td>30–39 years</td>
<td>172</td>
<td>15.1 (10.1–21.4)</td>
<td>17.4 (12.1–24.0)</td>
<td>27.3 (20.8–34.6)</td>
<td>2.3 (0.6–5.8)</td>
<td>0.6 (0.0–3.2)</td>
<td>0.6 (0.0–3.2)</td>
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<tr>
<td>40–49 years</td>
<td>143</td>
<td>18.2 (12.2–25.5)</td>
<td>20.3 (14.0–27.8)</td>
<td>31.5 (24.0–39.8)</td>
<td>3.5 (1.1–8.0)</td>
<td>2.1 (0.4–6.0)</td>
<td>2.1 (0.4–6.0)</td>
</tr>
<tr>
<td>50–59 years</td>
<td>147</td>
<td>19.0 (13.0–26.3)</td>
<td>15.6 (10.2–22.5)</td>
<td>25.9 (19.0–33.7)</td>
<td>3.4 (1.1–7.8)</td>
<td>1.4 (0.2–4.8)</td>
<td>1.4 (0.2–4.8)</td>
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<tr>
<td>60–69 years</td>
<td>144</td>
<td>8.3 (4.4–14.1)</td>
<td>11.8 (7.0–18.2)</td>
<td>18.8 (12.7–26.1)</td>
<td>2.1 (0.4–6.0)</td>
<td>0.0 (0.0–2.5)</td>
<td>0.0 (0.0–2.5)</td>
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<tr>
<td>Alla</td>
<td>1247</td>
<td>10.1 (8.4–11.9)</td>
<td>11.4 (9.6–13.3)</td>
<td>17.8 (15.7–20.0)</td>
<td>1.7 (0.9–2.4)</td>
<td>0.6 (0.1–1.1)</td>
<td>0.6 (0.1–1.1)</td>
</tr>
</tbody>
</table>

a Weighted population total, with estimates weighted by age distribution of the 2005 Australian midyear population estimates from the Australian Bureau of Statistics.
Impact In Women Who Have Undergone Definitive Therapy

- A **retrospective post-hoc analysis** showed that women vaccinated with GARDASIL who were diagnosed and treated for HPV related disease (cervical, vulvar and vaginal intra-epithelial neoplasia and genital warts) were less likely to develop subsequent HPV related disease.

| Reduction in HPV related disease irrespective of causal HPV type | 35.2% (95% CI 13.8-51.8) - 46.2% (95% CI 22.5-63.2) |
| Reduction in HPV related disease related to HPV 6, 11, 16 or 18 | 64.4% (95% CI 41.6-79.3) - 79.1% (95% CI 49.4-92.8) |

- Note: GARDASIL is not a therapeutic treatment for HPV disease.

Joura et al, 2012; Average follow up period 1.2 to 1.3 years.
Long Term Protection

- GARDASIL efficacy against HPV 6/11/16/18 cervical dysplasia and genital warts is 100% (95% CI: 12,100) at 5 years\(^1,2\)
- Efficacy of HPV 16 component of GARDASIL against HPV 16 related CIN is 100% (95% CI: 47,100) at a mean of 8.5 years follow up\(^3\)
- Importantly, GARDASIL has demonstrated immune memory, the hallmark of long term protection\(^4\)

Long Term Follow Up: Nordic Registry

- Registry based study in countries with centralised cervical screening infrastructure
- To evaluate long term effectiveness, immunogenicity and safety
- Long term follow up study in ~5,000 women aged 16 through 26 years who participated in FUTURE II
- Planned follow up of 10 to 14 years
- From this registry, GARDASIL shows a trend of continued protection in women who were vaccinated up to 7 years previously:
  - No breakthrough cases of HPV 16/18-related CIN2 or worse although follow-up time in person-years is still insufficient to make a definitive statement regarding effectiveness
  - GARDASIL continues to be generally safe and well tolerated up to 7 years following vaccination

Vaccine coverage

School-based program
◆ 80-85% received dose 1 nationally.
◆ 87% of those completed the course.
◆ most successful adolescent vaccination program in Australia’s history.
◆ NEW FOR BOYS 2013
  ➡ Year 8, 9 nad 10 this year as a catchup
  ➡ Thereafter year 8 with girls

Community-based program
Is it Safe?

- Virus Like Particles
  - No Viral DNA
- No more than usual local side effects
- Fainting
- Anaphylaxis 1:3.2 million doses
- Not recommended in pregnancy

Would I vaccinate my children?
- Girls/ Boys

Would I vaccinate my wife?
GARDASIL Safety

Pregnancy & Lactation

- Category B2 - Not recommended for use in pregnancy
- In clinical trials, 3,620 women reported at least one pregnancy
- Proportion of pregnancies with adverse outcomes were analysed
- No evidence to suggest that GARDASIL adversely affects pregnancy outcomes
- May be administered to lactating women

Adverse Events

- In clinical trials, adverse events included:
- Mostly mild to moderate injection site reactions including pain, swelling, erythema
- Fever
Issues to Consider

- Low level awareness of HPV/cervical cancer link
- Attitudes and beliefs
  - Professionals, parents and kids, young adults
- Recommend for the older patient?
  - Case by case
  - Assess risk
Will women still need Pap smears?

- Yes
- Protection is genotype specific
- Population level effects 2040
- Duration of vaccine efficacy not clear
- Cancer is a very uncommon result of HPV infection in developed countries with good screening