Human papillomavirus and vaccination for cervical cancer

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VIRUSES AND CANCER

• Responsible for around 15% of the global burden of cancer
  - Hepatitis B and C with liver cancer
  - Epstein-Barr virus with Burkitt’s lymphoma
  - The human T-cell lymphotropic virus (HTLV1) with adult T-cell leukaemia
  - Human herpesvirus type 8 (HHV-8) with Kaposi’s sarcoma
  - Human papillomavirus (HPV) with cervical and other anogenital cancers (1982)
HUMAN PAPILLOMA VIRUSES

- 8000-base pair, double-stranded, circular DNA viruses
  - 8 genes: 6 early (viral replication) & 2 late (capsid formation)
- ~150 related types, of those ~40 infect the genital mucosa
  - 15 classified as oncogenic or high-risk (HR) associated with cancer
  - Low-risk (LR) associated with benign genital warts
- Varying carcinogenicity related to expression of E6 and E7 oncoproteins
  - HPV16 and HPV18 are the most oncogenic

Schiffman et al. JNCI 2012
HPV IS A COMMON VIRUS

• HPV is the most common sexually transmitted agent worldwide

• Easily transmitted through skin-to-skin contact; mostly through genital contact/intercourse
  - Estimated 20-40% probability of male to female transmission per coital act
    - Higher than other viral STIs (i.e. HSV-2; 1 in 1000) but similar to bacterial STIs such as chlamydia (20%) and gonorrhea (50%)

• Infections are mostly asymptomatic and clears on their own

Schiffman et al. JNCI 2012
Burchell et al. CEBP 2012
NATURAL HISTORY

Risk factors:
- Age at first intercourse, number of sexual partners, condom use
- Smoking
- Multiparity
- HPV genotype

Correlates of exposure to HPV:
- 90% within 2 years
- HPV16/18: 40% absolute risk of developing high-grade cervical lesions
- 1 in 80 progress to invasive cancer

HPV16/18: 40% absolute risk of developing high-grade cervical lesions

80% exposed

10% persistence

Natural history model:
- Normal
- Infection
- HPV infection
- Regression
- Precancer
- Invasion
- Cancer

90% within 2 years

Wentzensen et al. CEBP 2014; McCredie Lancet Oncol. 2008
Persistent infection with HR-HPV plays a central role in a number of malignancies.

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Proportion HPV-Associated</th>
<th>Proportion of HPV-Associated Attributable to HPV16/18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>100%</td>
<td>70%</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>35%</td>
<td>89%</td>
</tr>
<tr>
<td>Anus</td>
<td>90%</td>
<td>92%</td>
</tr>
<tr>
<td>Vulva</td>
<td>40%</td>
<td>80%</td>
</tr>
<tr>
<td>Vagina</td>
<td>40%</td>
<td>80%</td>
</tr>
<tr>
<td>Penis</td>
<td>40%</td>
<td>63%</td>
</tr>
</tbody>
</table>
Annual number of cancers caused by HPV worldwide

- Cervix: 530,000
- Vagina: 9,000
- Penis: 11,000
- Vulva: 12,000
- Oropharynx: 17,000
- Anus: 11,000
  - Male: 4,400
  - Female: 13,000
GLOBAL ESTIMATES OF CERVICAL CANCER INCIDENCE AND MORTALITY (2012)

- Preventable disease related to disparities, mostly socioeconomic, in access to adequate healthcare
- ~84% of cases occur in less developed regions of the world

*a Number of cases shown in black text; number of deaths shown in red text.*

GLOBOCAN 2012
Organised cervical screening program since 1991

The Papanicolaou test (Pap test or smear) used to detect potentially pre-cancerous and cancerous HPV related changes

Biennial Pap test for 18-69 year olds
- 2-year participation at 58%
- 5-year participation at 83%
IMPACT OF ORGANISED SCREENING IN AUSTRALIA

Number per 100,000 females


Organised screening

Opportunistic screening

AIHW Australian Cancer Incidence and Mortality Books (Jan 2015)
• 14th most common cancer in women
• Populations at highest risk:
  – New migrants from countries with no organised screening
  – Lapsed screeners or women who never screen
    – 80% of new cervical cancer cases
  – Aboriginal and Torres Strait Islander women
    – 2X higher incidence
    – 4X higher mortality
PROPHYLACTIC HPV VACCINES

Ian Frazer AC

- 1991-2005 Developed the first vaccine for HPV (Gardasil)

“God’s gift to women”
(Weekend Australian, March 2006)
PROPHYLACTIC HPV VACCINES

Gardasil
Quadrivalent
(HPV6/11/16/18)

Cervarix:
Bivalent (HPV16/18)

Gardasil-9:
9-valent
(HPV6/11/16/18/31/33/45/52/58)

70% of cervical and 90% other HPV-related cancers + 90% of genital warts
(Gardasil)

90% of cervical and other HPV-related cancers + genital warts
Prophylactic HPV vaccine programs constitute major worldwide public-health initiatives

- Implemented in >60 countries; School/clinic based delivery models
• First country to implement national funded HPV vaccination program - April 2007

• Routine school based vaccination, with initial two year catch-up phase
  - 1st year of high school, usual age 12-13

• Quadrivalent HPV vaccine
  - Three doses: 0, 2 and 6 months
TIMELINE

- Community-based program targeting females ≤26 (2007)
- School-based program targeting 12–18 year old females (2008-2009)
- School-based program continued, targeting 12–13 year old females in first year high school (2010-2011)
- School-based program targeting 12–15 year old males (2012-2013)
VACCINE COHORTS TO 2017

PRE-VACCINE COHORTS

Catch-up - female

VACCINE COHORTS

School - females

School - males

Calendar year

Age, years

THE REGISTER

- Established to support the HPV vaccination program
- Records information about HPV vaccine doses administered in Australia
  - Mandatory reporting of doses administered in schools
  - Voluntary reporting of doses administered in the community
National vaccination coverage for females, by age in years and dose, in mid 2009

National three dose vaccination coverage (%) for girls 15 years of age in 2011 through 2014, and males age 15 years in 2014, by state/territory

- Relatively stable coverage (>70%) is being achieved over time.
- Some variation in coverage by jurisdiction suggesting more effective delivery in some states/territories than others

<table>
<thead>
<tr>
<th>Year</th>
<th>ACT</th>
<th>NSW</th>
<th>NT</th>
<th>Qld</th>
<th>SA</th>
<th>Tas.</th>
<th>Vic.</th>
<th>WA</th>
<th>Aust.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>74.2</td>
<td>74.5</td>
<td>87.0</td>
<td>72.4</td>
<td>68.0</td>
<td>66.5</td>
<td>76.5</td>
<td>64.6</td>
<td>72.9</td>
</tr>
<tr>
<td>2012</td>
<td>74.4</td>
<td>71.0</td>
<td>84.5</td>
<td>69.4</td>
<td>71.0</td>
<td>64.7</td>
<td>74.2</td>
<td>70.1</td>
<td>71.4</td>
</tr>
<tr>
<td>2013</td>
<td>74.0</td>
<td>68.6</td>
<td>81.4</td>
<td>71.0</td>
<td>72.4</td>
<td>64.1</td>
<td>75.2</td>
<td>71.2</td>
<td>71.4</td>
</tr>
<tr>
<td>2014</td>
<td>70.0</td>
<td>69.8</td>
<td>77.3</td>
<td>70.5</td>
<td>70.1</td>
<td>67.7</td>
<td>77.4</td>
<td>76.0</td>
<td>73.4</td>
</tr>
<tr>
<td>2014 males*</td>
<td>64.2</td>
<td>56.9</td>
<td>55.4</td>
<td>61.1</td>
<td>63.3</td>
<td>55.1</td>
<td>67.8</td>
<td>61.0</td>
<td>61.4</td>
</tr>
</tbody>
</table>
COVERAGE DATA

Equity in vaccination versus screening

National HPV Vaccination Program by socioeconomic status, Victoria

National Cervical Screening Program by socioeconomic status, Victoria

www.hpvregister.org.au/research/coverage-data
REAL WORLD IMPACT OF VACCINATION

- Program currently in its 11th year
- Impact monitoring is challenging because expected reductions in cancer will take decades to be realised
- Important to monitor changes in early endpoints
Impact on HPV infection in young women shortly after sexual debut

- Before and after HPV prevalence surveys
- Young women presenting for cervical cancer screening
- Baseline survey conducted in pre-vaccine cohorts
- Subsequent surveys conducted in vaccine-eligible cohorts using same recruitment and testing methodologies
- Extent of impact can be quantified
Cervical HPV prevalence in Australia

- Two cross-sectional studies, 1 before (2005-2007) and 1 after (2010-2012) vaccine introduction
- Women age 18-24 years at public family clinics undergoing routine Pap test
- HPV detection by Pap test specimens
HPV INFECTIONS AMONG 18-24 YEAR OLD WOMEN ATTENDING CERVICAL SCREENING

Tabrizi et al. Lancet ID 2014

Prevaccine (n=202)
Post vaccine (n=1058)
HPV INFECTIONS AMONG 18-24 YEAR OLD WOMEN ATTENDING CERVICAL SCREENING

Tabrizi et al Lancet ID 2014
# HPV Infections Among 18-24 Year Old Women Attending Cervical Screening

<table>
<thead>
<tr>
<th>Vaccine-target HPV types 6, 11,16, 18</th>
<th>Crude Rate of HPV Prevalence</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ratio</td>
<td></td>
</tr>
<tr>
<td>Prevaccine implementation</td>
<td>1.0</td>
<td>--</td>
</tr>
<tr>
<td>Postvaccine implementation</td>
<td>0.23 (0.17-0.31)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>0.65 (0.44-0.97)</td>
<td>0.0370</td>
</tr>
<tr>
<td>Partial or unconfirmed</td>
<td>0.26 (0.17-0.39)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Vaccinated</td>
<td>0.08 (0.04-0.15)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Tabrizi et al Lancet ID 2014
**IMPACT MONITORING**

**Impact on genital warts**

- Ecological trends over time
- Routinely collected hospital admissions data and sexual health sentinel surveillance networks
TRENDS IN GENITAL WARTS

Proportion of Australian-born women diagnosed with genital warts at sexual health clinics

Ali H et al. BMJ 2013
Proportion of Australian-born heterosexual men diagnosed with genital warts at sexual health clinics

Ali H et al. BMJ 2013
Admissions involving diagnosis of genital warts per 100,000 population by socioeconomic status and age group, in females

TRENDS IN GENITAL WARTS
TRENDS IN GENITAL WARTS

Admissions involving diagnosis of genital warts per 100,000 population by socioeconomic status and age group, in males

Males aged 10–19 years were excluded due to the small number of admissions.
Impact on cervical pre-cancerous abnormalities

- Ecological trends over time
- Routinely collected data on screen detected abnormalities reported to State/territory based Pap registries
TRENDS IN SCREEN DETECTED ABNORMALITIES

Early effects on cervical abnormalities in Victoria, Australia

TRENDS IN SCREEN DETECTED ABNORMALITIES

Trends in prevalence rates of high-grade cervical abnormalities diagnosed in Victorian women, by age group, 2000-2014

Future linkage to the vaccination register will allow for determination of association between receipt of vaccine and disease status

Brotherton JM, et al. MJA. 2016
WHAT ABOUT INDIGENOUS POPULATIONS?

• High rates of STIs among Aboriginal and Torres Strait Islander populations

• Continue to experience health disadvantage and have poorer outcomes

• Lower participation rates in screening programs

• Vaccination program has the potential to substantially improve health outcomes

• Lack of national data on HPV vaccine uptake
  – Estimated 15% lower completion rates in Indigenous adolescents based on limited data*

*NCIRS National HPV Vaccination Program Evaluation Report 2014
## TRENDS IN GENITAL WARTS

Genital warts admission rates per 100,000 population among Indigenous females

<table>
<thead>
<tr>
<th>Sex, Age Group, Subanalysis</th>
<th>Admission Rate, No./100 000, Mean</th>
<th>Overall Reduction From Jul 2006–Jun 2007 to Jul 2010–Jun 2011</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before NHVP&lt;sup&gt;a&lt;/sup&gt;</td>
<td>After NHVP&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Percentage (95% CI)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15–24 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indigenous</td>
<td>82.7</td>
<td>22.7</td>
<td>86.7 (76.0–92.7)</td>
</tr>
<tr>
<td>Non-Indigenous&lt;sup&gt;c&lt;/sup&gt;</td>
<td>73.8</td>
<td>24.9</td>
<td>76.1 (71.6–79.9)</td>
</tr>
<tr>
<td>18–26 y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>84.8</td>
<td>32.1</td>
<td>72.7 (67.0–77.5)</td>
</tr>
<tr>
<td>Unrelated to cervical</td>
<td>64.9</td>
<td>24.3</td>
<td>75.7 (69.6–80.6)</td>
</tr>
</tbody>
</table>

Fall in genital warts admissions has been comparable for Indigenous and non-Indigenous females

Smith et al. JID. 2016
Proportion of women diagnosed with genital warts at sexual health clinics, by Indigenous status

A. Under 21 years of age

B. 21–30 years of age

C. Over 30 years of age

Ali et al. MJA. 2017
SUMMARY

• HPV vaccination has been a great success for Australia.

• Substantial fall in early disease endpoints in vaccine eligible cohorts, where the real-world data closely replicates clinical trial findings.

• Very substantial reductions also evident among young Indigenous women.
  - Potential benefit even greater than for non-Indigenous.

• Likely to translate to significant reductions in HPV associated cancers in the future.

• **Need to address the global inequalities in cervical cancer burden.**
WHAT IS NEXT FOR THE VACCINE PROGRAM?

• A two dose 9-valent HPV vaccination schedule is effective and will likely replace the three dose quadrivalent schedule in the near future

• Ongoing surveillance will be critical
• **Program monitoring:** vaccine safety, coverage

• **Infection monitoring:** prevalence in the general male and female populations (genotype/antibody)

• **Monitoring of non-cancer disease endpoints:** GW, RRP, cervical abnormalities (prevalence and genotype)

• **Monitoring cancer endpoints:** incidence, mortality, cancer (anogenital and oropharyngeal)
Table 1. Summary of Publications Reporting the Impact and Effectiveness of Quadrivalent Human Papillomavirus Vaccination Programs in 9 Countries

<table>
<thead>
<tr>
<th>Country (No. of Included Publications) and HPV Vaccination Program</th>
<th>Genital Warts</th>
<th>HPV Infection</th>
<th>Cervical Cytological Abnormalities</th>
<th>Cervical Histological Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia (18 publications)</td>
<td>10</td>
<td>3</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Belgium (2 publications)</td>
<td>1</td>
<td>1</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
</tr>
<tr>
<td>• End of 2008: reimbursement extended to age 18 y</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
</tr>
<tr>
<td>• Since 2010/2011: school-based, girls aged 12–13 y</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
</tr>
<tr>
<td>Canada (3 publications)</td>
<td>1</td>
<td>. . . . . .</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Denmark (8 publications)</td>
<td>5</td>
<td>. . . . . .</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>• Since 2009: females aged 12 y, free</td>
<td>Sande 2014 [A39]</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
</tr>
<tr>
<td>• August 2012: 2nd catch-up, females aged ≤27 y old</td>
<td>Blomberg 2015 [A45]</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
</tr>
<tr>
<td>• Initially: recommended for females ≥14 y old with no prior sexual intercourse or within 1st year following sexual debut</td>
<td>Judlin 2015 [A32]</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
</tr>
<tr>
<td>• Since September 2012: recommended in females aged 11–14 y, with catch-up for females 15–19 y</td>
<td>Juddin 2015 [A32]</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
</tr>
<tr>
<td>Germany (2 publications)</td>
<td>1</td>
<td>1</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
</tr>
<tr>
<td>New Zealand (2 publications)</td>
<td>2</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
</tr>
<tr>
<td>• September 2006: vaccine available</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
</tr>
<tr>
<td>Sweden (5 publications)</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>• Since 2012: organized, publicly funded school-based vaccination of females aged 10–12 y with catch-up for females 13–18 y</td>
<td>Leval 2012 [A33]</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
</tr>
<tr>
<td>•umber 2015 [A10]</td>
<td>Leval 2012 [A33]</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
<td>. . . . . .</td>
</tr>
<tr>
<td>United States (17 publications)</td>
<td>4</td>
<td>9</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>
THANK YOU!

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