Human papillomavirus vaccines

Suzanne M. Garland

Director of Microbiological Research,
Director of Clinical Microbiology and Infectious Diseases,
The Royal Women’s Hospital,
Senior Consultant Microbiology, Royal Children’s Hospital
Honorary Research Fellow, Murdoch Childrens Research Institute,
Professor, Department of Obstetrics, Gynaecology, University of Melbourne, Victoria, Australia.

Inaugural and Past President of AOGIN (Asia Oceania research organization on Genital Infections and Neoplasia)
A trip down memory lane: infectious diseases in women's & babies' health

• group B streptococcus [GBS]
  - early epidemiology [1979], intervention strategies EONGBS¹-³

• Genital mycoplasmas
  - role of bacteriuria by *Ureaplasma urealyticum* & *Gardnerella vaginalis*
    in adverse pregnancy outcomes [1983-1884]⁴
  - bacterial vaginosis
  - *M. genitalium* [molecular diagnostic assays, resistance markers]

• *Chlamydia trachomatis*
  - self collected sampling, PCR, STI epidemiology⁵-⁶
  - sexual health [MSHC]

The prevalence of CT in 2015 did not differ significantly from that reported for 2016 (P = 0.47).

Total number of female patients: 19,148
Total number of *Chlamydia trachomatis* (CT) positives: 613 (3.1%)
a trip down memory lane:
infectious diseases in women's & babies' health

- Probiotics and neonatal sepsis prevention
  - 54% absolute reduction in necrotising enterocolitis
  
- innovation and information technology (YFHI)
  - preventative medicine, innovations for change

- human papillomavirus (HPV)
  - vaccine efficacy, effectiveness & impact at the population level

University Women's College 1961
• Of the estimated **12.7 million** new cancers worldwide each year in males and females, **610,000 (~5%)** are attributable to HPV\(^1\)

• Annually, **HPV-related cancers** represent ~**10%** of all new cancers in females worldwide and ~**14%** in females in developing-world regions\(^1,2\)
New estimates worldwide cervical cancer age-standardized incidence rates: GLOBOCAN 2012

85% of countries cervical cancer ranks among the 3 most frequent cancers among younger women (15–44 years age)
COVERAGE
Global Progress in HPV Vaccination

National programs
Pilot programs

Cervical Cancer Action, September 2014
Girls 9-13 years

- HPV vaccination
  From 10 years old and onward

Health education and services, for example:
- Sexual health education tailored to the age group
- Providing contraceptive counseling and services including condoms
- Prevent tobacco use and support cessation*

Women > 30 years of age
 Screening and treatment
- “screen and treat” with low cost technology VIA followed by cryotherapy
- HPV testing for high risk HPV types (e.g. types 16, 18 and others)

All women as needed
 Treatment of invasive cancer at any age
- Ablative surgery
- Radiotherapy
- Chemotherapy

Comprehensive approach: Programmatic interventions over the life course to prevent HPV infection and cervical cancer
Estimated percentage of cancers attributable to HPV

Australian health policy for HPV immunisation

- **2006 (Nov)** Commonwealth Government announced that it would fund the cervical cancer vaccine, 4vHPV vaccine GARDASIL®, for girls and women aged 12 to 26 years from 2007

- **2007 (April)** school based program
  - girls 12 - 13 years (ongoing and as a 3 dose regimen) α first year of high school
  - girls 13 - 18 years (catch-up)

  **GP based (July 2007)**
  - young women 18 - 26 years (catch-up) December 2009
  - girls 12 - 18 years who missed doses at school

- **2013 (February)** **gender neutral approach**: Ongoing school-based HPV program for boys
  - 12-13 year old boys (ongoing and as a 3 dose regimen)
  - 14-15-year-olds catch-up to December 2014
Because of high coverage:

- Outcomes with ↓ in vaccine-related HPV 6/11/16/18 of 77%¹
- Herd protection 86% and cross protection 58% for 31,33 45²
- Genital warts 93% ³,⁴↓
- histologically proven high grade abnormalities (HGA) ⁵-⁷

-<20 years 57% ⁴,⁵
-20-24 years 25% ⁶

3. Fairley et al. Sexual Health 2010;7:325-7
The key objectives are:

1. Program monitoring- vaccine safety, coverage

2. Infection monitoring- prevalence in the general male and female population (HPV genotype/antibody)

3. Monitoring of non-cancer disease endpoints- GW, RRP, cervical abnormalities (prevalence and genotype)

4. Monitoring cancer endpoints- incidence/mortality, cancer (anogenital and oropharyngeal)
HPV-associated outcomes

Early Outcomes (Years)
- HPV Prevalence
- Genital warts

Mid Outcomes (Years to Decades)
- CIN/Precancers

Late Outcomes (Decades)
- HPV-associated cancers
PREVACCINE Genoprevalence: baseline data

**WHINURS**: women attending for routine Pap smear from 2005-2007: invited
- HPV DNA testing on their Paps
- (2500 18-40 year olds [1500 nonindigenous, 1000 indigenous] & 500 40+ year old nonindigenous)

- prevalence of HPV DNA overall & by HPV genotypes identified & stratified by age group, region (metropolitan, rural, remote) and Pap prediction (+/-biopsy) 34 sites

---

Vaccine Impact in Population (VIP) Study

- Repeat cross sectional study - HPV prevalence was compared with the 18 - 24 year old pre-vaccine WHINURS cohort from 2005-2007.
- Study recruitment period was 2010-2012.
- Estimating HPV prevalence in 1,058 women aged 18-24 presenting for a Pap test at 6 FPC in Victoria, NSW and WA.
- Between 2007-2009, these women would have been aged 13 - 21 at the time of vaccination.
Australian HPV genoprevalence reduction following national vaccination programme + cross protection

**HPV prevalence and herd protection following Australian national vaccination program: final results**

- Any, HR, and vaccine-targeted HPV types: reduced in all groups receiving vaccination
- Reduction in vaccine-targeted HPV types in unvaccinated women suggests herd protection

**Crude HPV prevalence according to study group & vaccination status**

- Any HPV type
- High-risk HPV types
- Vaccine-targeted HPV types

*P* < 0.05 when compared to prevaccine-implementation group.

Preliminary VIP-Indigenous results

Not yet published

Investigators: Saulo, McGregor, Tabrizi, Phillips, Luey, Oliver, Skinner, Stewart, Liu, Brotherton, Kaldor, Garland. unpublished
National HPV Genotype Prevalence Survey (HPV-GPS)

- HPV genotyping
- HPV Vaccination status
- Demographics (including locality)
- Sexual activity and partners
- Test acceptability
HPV prevalence in females

Unpublished data
HPV prevalence in heterosexual males

Unpublished data
Proportion of Australian-born females with genital warts, by age group (2004–2011)\(^1\)

![Graph showing the proportion of Australian-born females with genital warts, by age group (2004–2011) with a qHPV vaccine introduced in 2007. The graph shows a decrease in genital wart diagnosis percentages across different age groups and years, with significant trends indicated by \(P_{\text{trend}} < 0.001\).](image)

\(^1\) Ali H et al. BMJ. 2013;346:f2032.
Proportion of Australian-born heterosexual males with GWs, by age group (2004–2011)

Significant decline ($P_{\text{trend}} < 0.001$) in proportion of males diagnosed with GWs at first visit during the qHPV vaccination period

$qHPV$ vaccine introduced

<table>
<thead>
<tr>
<th>Year</th>
<th>&lt;21 Years (n=3,982)</th>
<th>21–30 Years (n=15,147)</th>
<th>&gt;30 Years (n=13,647)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>8.1%</td>
<td>16.2%</td>
<td>16.2%</td>
</tr>
<tr>
<td>2005</td>
<td>12.3%</td>
<td>15.7%</td>
<td>16.2%</td>
</tr>
<tr>
<td>2006</td>
<td>13.7%</td>
<td>15.4%</td>
<td>15.3%</td>
</tr>
<tr>
<td>2007</td>
<td>15.2%</td>
<td>11.5%</td>
<td>15.3%</td>
</tr>
<tr>
<td>2008</td>
<td>12.5%</td>
<td>12.5%</td>
<td>15.3%</td>
</tr>
<tr>
<td>2009</td>
<td>10.8%</td>
<td>12.2%</td>
<td>15.3%</td>
</tr>
<tr>
<td>2010</td>
<td>8.5%</td>
<td>11.3%</td>
<td>15.3%</td>
</tr>
<tr>
<td>2011</td>
<td>7.2%</td>
<td>10.1%</td>
<td>15.3%</td>
</tr>
</tbody>
</table>

*Significant decline ($P_{\text{trend}} < 0.001$) in proportion of males diagnosed with GWs at first visit during the vaccination period.

Trends in HGAs in women <18 years old in Victoria, Australia, before and after introduction of qHPV vaccine (2003-2010)\(^1\)

Significant decrease in HGA incidence in women age <18 years occurred during the qHPV vaccination period, by 2009 (\(P=0.003\))

HGA=high-grade cytological abnormality; qHPV=quadrivalent human papillomavirus vaccine

\(^1\) Brotherton JM et al, Early effect of the HPV vaccination programme on cervical abnormalities in Victoria, Australia: an ecological study, 2085-2092, 2011, Lancet
Reduction in cervical abnormalities due to Australian national vaccination program: results

Risk of cervical abnormalities for vaccinated and unvaccinated women (histological abnormalities)

*Error bars represent 95% confidence interval.
†All high-grade histology is defined as CIN2, CIN3, AIS, and mixed CIN3/AIS. AIS=adenocarcinoma in situ; CIN=cervical intraepithelial neoplasia.

HPV vaccination coverage among females

**Sub Study A) Population Cohort (1500 18-25 year olds)**

- Estimate prevalence of vaccine-type HPV infections
- Current demographic and clinical correlates of genital HPV infection, HPV vaccination uptake and cervical screening uptake
- Vaccine type replacement and/cross protection

**Sub Study B) Biopsy Cohort (500 CIN3* biopsies)**

- Estimate proportion of CIN3 biopsies that contain vaccine-type HPV DNA in a sample of young women (<30 years) in Victoria

*CIN3: Cervical Intraepithelial Neoplasia, Grade 3*
VACCINE STUDY substudy A
Vaginal Swab (n=737)

Unpublished data

Multiple HPV genotypes is common with >20% of CIN3 biopsies.

Each individual lesion has been associated with only a single HPV genotype.

Lesion specific method of laser-capture microdissection and PCR within each high-grade cervical lesion with multiple HPV infections.
Laser Capture Microdissection (LCM)

IR Laser
(melts thermoplastic cap onto sample for capture)

PEN Membrane

LCM Cap

Glass Slide

Tissue Section
(Cutting and Ablation of Tissue)

UV Laser

Photo courtesy of Arcturus Biosciences

SEM image of bottom of wetted LCM cap with captured cells

Unpublished data
Australian Cervical Cancer typing study (ACCTS)-Interim Data

Unpublished data
Status of HPV vaccination programs worldwide

Unpublished data
Challenges in policy implementation & future plans

- **Communication**
  - anti-vaccine groups
  - AE

- **Changes in practice**
  - ? dosing
  - ? nonavalent vaccine
  - impact on cervical cytology screening Renew [May 1st, 2017]

- **Ongoing surveillance**
  - safety, coverage,
  - Infection monitoring - genoprevalence, IgG
  - non-cancer disease endpoints CIN3, GWs, RRP,
  - HPV related cancer endpoints (incidence/mortality: anogenital, oropharyngeal)

- **HPV FASTER** (vaccination of indigenous ATSI & CALD)

ATSI: Aboriginal and Torres Strait Islanders
CALD: culturally and linguistically diverse, including refugees
Impact of not having a strategy

Pre- & post-suspension of proactive recommendation

- Estimation of uptake rates in the primary target age-group (Junior high school, 1st grade)
- Approximately 8% based on the volume of vaccines shipment

Uptake rates
2010-2012 2013, June

Estimated uptake rates based on the volume of vaccines shipment

Recently, below 1%
safety of HPV vaccines has been reviewed by multiple medical authorities, regulatory agencies globally & by health authorities in many individual countries: all endorse them as safe and effective

250,000 women die every year of cervical cancers caused by HPV

IPVS urges national regulatory authorities in countries where HPV vaccination is not currently available to implement HPV vaccination in girls & women as soon as possible & to strongly consider vaccination of boys & men
In a real world setting, vaccination with qHPV vaccine results in reduction in ...
- vaccine related HPV infection
- vaccine related HPV disease - genital warts, abnormal Pap smears, CIN2+ [precursor cancer]

Consistent reassuring safety profile: endorsement government

Ongoing surveillance

HPV DNA assays for primary screening
- QA programme RCPA/RWH molecular Microbiology laboratory
Among medical interventions, **VACCINATION** has the highest impact on health!

Drop in death rate for diseases prevented or treated with innovative medicines 1965-1999

### Infectious Diseases
- Polio, measles, Hib, HVB, Hib etc
- >97%

### Rheumatic fever and rheumatic heart disease
- 75%

### Hypertensive heart disease
- 67%

### Ulcer of stomach and duodenum
- 61%

### Ischemic heart disease
- 41%

*Source: EFPIA 1999 – 2002*
Acknowledgement

- MSHC: Marcus Chen, Kit Fairley, Rebecca Wigan, Catriona Bradshaw
- SSHC: Anna McNulty
- University of Melbourne: Jane Hocking, Hennie Williams
- Kirby: John Kaldor, Basil Donovan; Dina Saulo, Skye McGregor, Marlene Kong, Andrew Grulich, Jeff Jin, Mary Poynton, Matthew Law, David Regan
- University of Sydney: Rachel Skinner, Richard Hillman
- VCS: Julia Brotherton, Jennifer Nguyen, Michael Malloy, Marion Saville
- Family planning Victoria and NSW: Kathy McNamee, Deborah Bateson, Mary Stewart, Mandy Johnson
- Royal Women’s Hospital: Dorothy Machalek, Amy Peach, Alyssa Cornall, Sam Phillips, Marin Poljak Sepehr Tabri,zi
Thank-you

Women’s Centre for Infectious Diseases
Acknowledgements: the VACCINE study team

- CIs: Suzanne Garland, Sepehr Tabrizi, Jan Pyman, Marion Saville, C. David Wrede, Elisa Young, Yasmin Jayasinghe, Dorota Gertig, Jeffrey Tan, John Wark, Marian Pitts
- Sarah Osborne, Alyssa Cornall, Houda Abdo, Angela Hurley, Melissa Yow, Adele Rivers, Emma Callegari, Fiona Tan, Tania Tabone, Eileen Tan, Elizabeth McKinnon, Margaret Nguyen
- Funded by the Victorian Cancer Agency