Evaluating vaccine effectiveness using registry data: an example of data linkage between the Victorian Cervical Cytology Registry and the National HPV Vaccination Register.

Assoc Prof Dorota Gertig
Medical Director, Victorian Cervical Cytology Registry

Or…. A tale of two registries

Victorian Cervical Cytology Registry (VCCR)

and the

National HPV Vaccination Program Register (NHVPR)

Operated by VCS Inc.
Outline

- HPV vaccination program
- The Victorian Cervical Cytology Registry
- Ecologic analysis of VCCR data
- The National HPV Vaccination Program Register
- Data linkage of VCCR and NHVPR

Where it all began...

Australian of the Year 2006

Professor Ian Frazer
Professor Ian Frazer founded and leads the University of Queensland's Centre for Immunology and cancer research. For 20 years he has been researching the link between papilloma viruses and cancer, seeking ways to treat these viruses in order to reduce the incidence of cancer. Ian has now developed vaccines to prevent and to treat cervical cancer, which affects 500,000 women each year. A vaccine based on his research has shown in worldwide trials to prevent papilloma virus infection and reduce Pap smear abnormalities by 90%. It has the potential to virtually eradicate cervical cancer within a generation. Expected to be on the market within a year, this vaccine will revolutionise women's health across the globe. Ian embodies Australian know-how, determination and innovation.

Scientists are reporting the second most common forms of cancer in women, writes Christopher Jay.

HPV 16 and 18 are the most frequent types detected and account for 80% of cervical cancers in Australia. However, other less common types can also cause cancer. New vaccines are now available for some of these types.

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NCIRS

5 most frequently detected HPV types cervical cancer

<table>
<thead>
<tr>
<th>TYPE</th>
<th>PERCENTAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 16</td>
<td>51.0%</td>
</tr>
<tr>
<td>HPV 18</td>
<td>16.3%</td>
</tr>
<tr>
<td>HPV 31</td>
<td>3.9%</td>
</tr>
<tr>
<td>HPV 33</td>
<td>3.8%</td>
</tr>
<tr>
<td>HPV 39</td>
<td>2.3%</td>
</tr>
<tr>
<td>HPV 45</td>
<td>4.6%</td>
</tr>
<tr>
<td>HPV 73</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

Clifford HPV 16+18=67.3%  Australia HPV 16+18=80.1%
One small jab, but a giant leap for womankind

Ruth Pollard
Health Reporter

The world’s first vaccine against cervical cancer was launched yesterday, with its creator, Jan Fraser, administering the first dose and declaring it a significant step towards combating the disease to the history books.

But the vaccine, which is licensed for women and girls aged from nine to 26, is not yet available on the government-funded Pharmaceutical Benefits Scheme.

Those who want the vaccine will have to pay $450 for the three shots – a cost that is prohibitive to many families, Professor Fraser acknowledged.

He is keen for the vaccine to be added to the Government’s immunisation scheme, saying “this is a vaccine designed to prevent a rather nasty cancer which clearly works”.

The Sydney Morning Herald 29 Aug 06

Towards an HPV Vaccination Program

→ Oct 2006 - ATAGI endorses Working Party Report and post-submission

→ Nov 2006 – PBAC considers Gardasil®

PBS committee rejects cervical vaccine funding

A new cervical cancer vaccine has been refused Federal Government funding under the Pharmaceutical Benefits Scheme (PBS).

It is understood the Pharmaceutical Benefits Advisory Committee (PBAC) rejected the application for a number of reasons.

The committee was concerned there was not enough information about how long the vaccine remains effective, or about its long-term effects.

The committee also found the vaccine was not cost effective at the price proposed by the pharmaceutical company CSL.

→ HUGE PUBLIC OUTCRY!!

Roughead E et al, Health Policy 2008
Senators urges review of cervical cancer vaccine decision

Liberal Senator Jeanie Ferris has urged the Pharmaceutical Benefits Advisory Committee to review its decision to refuse to subsidise a new cervical cancer vaccine.

The Committee said an application from the pharmaceutical company CSL lacked information about the effectiveness of the vaccine and whether boosters would be needed.

Towards an HPV Vaccination Program

→ 29 November 2006 – Australian Government announces Program

→ 1 April 2007 – Program start!

• Target population 2.4 million

• Cost $537 million over 4 years, including $100 million for program implementation (eg education campaign and HPV register)
The National HPV Vaccination Program

- 12-18 year old ♀ school based program
- 18-26 year old ♀ through GPs/primary care
- 2 year catch up program 2007-2009, then ongoing cohort of 12-13 year old females
- 2007-2009 target population ~ 2.4 million
- Funded by federal government, delivered by States and Territories
- Quadrivalent vaccine Gardasil used
- National HPV Vaccination Program Register established

Australia is in a unique situation to monitor vaccine effectiveness

- Comprehensive state-based Pap test registers (n=8)
- High participation in screening
- Young age at starting screening 18 years, every 2 years
- Timely information on cytology and histology
- Early adopter of national HPV vaccination program
  - 12-13 year old girls, extensive catch-up to age 26
- Overlaps with screening cohort
- National HPV vaccination program register established
- High coverage achieved
The Australian Setting: screening

- National Cervical Screening Program
  - Established 1991
  - Biennial Pap screening for women aged 18-69
  - Participation 20-69yrs: 2yr 61%, 3yr 74%, 5 yr 87%
  - 70%/55% reduction in incidence and mortality
  - Program supported by State based Pap test Registers
- VCCR established 1989
Age-standardised mortality from cervical cancer in women aged 20-69 years in Australia and the United Kingdom (England and Wales)

*Rates per 100,000 women. Although data are shown for England and Wales, annual age-standardised mortality rates for the UK were within 3% of those for England and Wales in each year for which data were available.

Canfell K et al MJA 2007

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**UK screening programme**

- “Cancer of the cervix: Death by incompetence” Lancet 1985

At the time screening in UK was opportunistic, not organized

“Blocks to effective action were neither scientific nor technical, but administrative”

“Recall system ... was ineffective”

“System could not link one smear with another to tell us how many women had been screened..”

“Denominators... were estimated by measuring the thickness of heaps of paper with a ruler (pressed down to compensate for paperclips)”
Victorian Cervical Cytology Registry

- Operates under Victorian Cancer Act
- Sends reminders to women due for a Pap test (250,000 per year, 13,000 phone calls)
- Follows up abnormal Pap test results (about 8000 per year by q’re, phone call and letter)
- Statistics and research
- Provide history links for Pap tests to laboratories
- Quality assurance data for laboratories
- Critical for monitoring and evaluation

How does the register operate?

- Safety net function
- Opt-off register (all tests sent to the VCCR unless a woman objects), about 2% opt-off rate
- Women go on VCCR when they have their first Pap test
- No invitations sent (using a population register as in the UK)
- Incoming tests matched with women on the VCCR
- Screening history sent to lab for reporting of smear
- Coded result sent back to VCCR (within a week or so)
- Histology and HPV tests received from labs

- Part of clinical management pathway and underpins screening program
VCCR database

- Denominator for participation from ABS
- Laboratory performance measures
- Colposcopy QA
- Screening histories to laboratories
- Reminders (recall)
- Follow-up
- Data/Evaluation/Research Program requirements
- Standard reports plus BI tool

GP/Nurses take Pap test and inform women about VCCR

Laboratories (Demographic data, Cytology, HPV, Histology)

Cancer Registry

Colposcopy data Questionnaires

History links
Reminder and Follow up functions

- Reminders sent to women as a back up to practitioner systems – once the test is overdue
- According to national policy, algorithm based on NHMRC guidelines
- Follow up of abnormal results where there is no record of colposcopy or treatment
- All lists and actions generated and diarised by CIS

VCCR Reports

**Statistical reports**
- Annual statistical report
- Evaluation of Nurse Pap smears
- Quarterly statistical reports
- VCCR Quality report
- Research collaborations

**Reports to laboratories**
- Performance Standards data
- Monthly histology/cytology reports
- Laboratory statistics – reporting profile
Follow up outcomes of Pap test results of high grade (including possible HG) and worse within 6 to 9 months of the index Pap episode

Only 3.9% of women with significant abnormalities didn’t have evidence of further investigation within a 6 to 9 month period (3rd Qtr 2013)
Aim (Brotherton et al Lancet 2011)

• To determine if there has been any change in the incidence of screen detected cervical abnormalities since the 4vHPV (HPV types 9,11,16,18) vaccination program

• Low grade cytological abnormalities
  • Up to 30% HPV 16,18 detected

• High grade histological abnormalities
  • 50% + HPV16 or 18 detected

AIS/CIN2+ histopathology: Victoria 2003-2009 by age

- Apparent decline in youngest age groups
- Under 18 yo HGA incidence declined from 0.85% in 2006 to 0.22% in 2009
- IRR 1.14 decline in incidence was 14% greater after commencement of vaccination

Conclusions

- HPV vaccination may already be reducing AIS/CIN2+ incidence in Australia
- Ecological analysis limits interpretation
- More data (and more time!) are needed to fully assess these emerging trends
- Data linkage between the HPV vaccination register and cytology registers is needed to assess LGA and HGA incidence by vaccination status

Source: Cervical Screening in Australia 2011-2012, AIHW
Decline in genital warts

- 8 public sexual health services
- New Australian born patients only 2004-2011 - first visit to clinic. N=85,770
- No prior history of genital warts.

Males <21 years 81.8% decline post vaccination
Males 21-30 yrs 51.1% decline post vaccination

Comencement of NHVPR

[Diagram showing timeline with years 2006 to 2010]
HPV Vaccination Register
Key Functions

- Record vaccination doses and key demographic information
- Provide system to support completion of 3 dose vaccination schedule i.e. reports, statements
- Managed processes of vaccination program (GP incentive payments)
- Telephone information service
- Generate data to monitor and evaluate participation rates of the HPV vaccination program
- Inform women if booster doses are required
- Eventually link with Pap Test & Cancer registries to assess vaccination impact on Cervical Cancer.
- Separate from ACIR (Childhood Immunisation Register)
- Consent obtained at vaccination

HPV Register web portal
www.hpvregister.org.au

- Query database for a consumer’s vaccination status
- Enter and submit vaccination records
- Manage batches of notification records
- Lodge requests to change consumer or provider information
- Access reports on incomplete dosage, and statistical reports
- Manage on line user accounts and sub accounts
Data input: School vaccination program

- School data are uploaded from local level
- Different consent forms, common data fields
- Variety of protocols for data flow and capture depending on systems in place at the jurisdictional level
Data input: GP program

- GP’s notify the HPV Register directly (except NT and Qld)
- Invitations mailed out to register and complete registration form (if payment or access required)
- Methods of notification
  - Mailed/faxed notification forms and reports from practice management software
  - Other format (as directed by AGPN website eg excel spreadsheet word template)
  - Batch upload from central database in Qld and NT

HPV register outputs

Completion statements
  - mailed directly upon notification of 3 doses

History statements and reminder letters
  - Configurable by jurisdiction
  - to indicate incomplete vaccination

Overdue dose reports
  - lists to indicate details of incomplete dose schedules

De-identified data - Statistical reports
  - numbers of notifications, vaccination completion rates and vaccination numbers by: Health regions, LGA, provider type, consumer, age, school
Aims:
- to compare detection rates of cervical pre-cancer among vaccinated and unvaccinated women in the school age cohort
- Evaluate vaccine effectiveness at the population level

De-identified data linkage between the Victorian Pap test registry and HPV vaccination register

Addresses issues of previous ecologic analysis
Methods - linkage

- VCCR – Victorian women age eligible for vaccination (DOB after 1 July 1962)
- NHVPR- Australian women vax prior to 1 Jan 2012
- De-identified in same way, random number generated per record, then linkage unit generated 22 linkage keys using combinations of variables eg letters name, perturbed dob, parts Medicare no. Best 16 linkage keys used to link.
- Custodian and HREC approval

Methods

- Retrospective cohort analysis between April 1, 2007 and 31 December 2011
- Average 4.8 years of followup
- Women were 17 years or younger in 2007 and had a Pap test recorded during the study period
- Censored at outcome of interest, date of death, hysterectomy or end of study period
- Proportional hazards regression
- Outcomes: CIN1, CIN2, CIN3+/AIS, low and high-grade cytology
- Vaccination status treated as time varying covariate
- Adjusted for age, SES, geographic area
### Summary of descriptive characteristics of cohort

<table>
<thead>
<tr>
<th></th>
<th>Unvaccinated</th>
<th>Vaccinated, Any dose</th>
<th>Vaccinated, 1 dose</th>
<th>Vaccinated, 2 doses</th>
<th>Completely vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>14,085</td>
<td>24,871</td>
<td>1,422</td>
<td>2,268</td>
<td>21,151</td>
</tr>
<tr>
<td><strong>Mean age in 2007</strong></td>
<td>16.1 (± 1.0)</td>
<td>16.0 (± 1.0)</td>
<td>16.0 (± 1.0)</td>
<td>16.0 (± 1.0)</td>
<td>16.0 (± 1.0)</td>
</tr>
<tr>
<td><strong>Remoteness area</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major cities</td>
<td>10,019 (71.8%)</td>
<td>16,608 (66.8%)</td>
<td>955 (67.2%)</td>
<td>1,477 (65.1%)</td>
<td>14,154 (67.0%)</td>
</tr>
<tr>
<td>Inner regional</td>
<td>3,250 (23.3%)</td>
<td>6,858 (27.6%)</td>
<td>383 (26.9%)</td>
<td>642 (28.3%)</td>
<td>5,826 (27.6%)</td>
</tr>
<tr>
<td>Outer regional</td>
<td>681 (4.9%)</td>
<td>1,380 (5.6%)</td>
<td>83 (5.8%)</td>
<td>147 (6.5%)</td>
<td>1,149 (5.4%)</td>
</tr>
<tr>
<td>Remote</td>
<td>6 (0.0%)</td>
<td>14 (0.1%)</td>
<td>1 (0.1%)</td>
<td>2 (0.1%)</td>
<td>11 (0.1%)</td>
</tr>
<tr>
<td><strong>Age at first screen (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 to 17</td>
<td>2,831 (20.1%)</td>
<td>4,840 (19.5%)</td>
<td>436 (30.7%)</td>
<td>624 (27.5%)</td>
<td>3,775 (17.8%)</td>
</tr>
<tr>
<td>18+</td>
<td>11,149 (79.2%)</td>
<td>19,917 (80.1%)</td>
<td>973 (68.4%)</td>
<td>1,614 (71.2%)</td>
<td>17,305 (81.8%)</td>
</tr>
</tbody>
</table>

### Rate of cervical abnormalities for vaccinated and unvaccinated women

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rate</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histological abnormalities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any high grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>6.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Vax (any dose)</td>
<td>4.8</td>
<td>0.72 (0.58-0.91)</td>
</tr>
<tr>
<td>Vax (complete)</td>
<td>4.1</td>
<td>0.61 (0.48-0.78)</td>
</tr>
<tr>
<td>CIN3/AIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>2.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Vax (any dose)</td>
<td>1.9</td>
<td>0.64 (0.45-0.90)</td>
</tr>
<tr>
<td>Vaccinated (complete)</td>
<td>1.5</td>
<td>0.53 (0.36-0.77)</td>
</tr>
<tr>
<td>CIN2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>4.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Vax (any dose)</td>
<td>3.2</td>
<td>0.78 (0.59-1.03)</td>
</tr>
<tr>
<td>Vax complete</td>
<td>2.9</td>
<td>0.70 (0.52-0.94)</td>
</tr>
<tr>
<td>CIN1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>7.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Vax (any dose)</td>
<td>6.5</td>
<td>0.83 (0.68-1.02)</td>
</tr>
<tr>
<td>Vax complete</td>
<td>6.3</td>
<td>0.82 (0.66-1.01)</td>
</tr>
</tbody>
</table>

*Adjusted Rate per 1,000 person-years.
Rate of cervical abnormalities for vaccinated (any dose) and unvaccinated women

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. women-doses</th>
<th>Rate*</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytological abnormalities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-grade cytology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>15,192</td>
<td>15.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Vaccinated (adjusted)</td>
<td>27,179</td>
<td>11.9</td>
<td>0.75 (0.65 to 0.87)</td>
</tr>
<tr>
<td>Low-grade cytology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>15,192</td>
<td>125.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Vaccinated (adjusted)</td>
<td>27,179</td>
<td>95.3</td>
<td>0.76 (0.72 to 0.80)</td>
</tr>
</tbody>
</table>

*Adjusted rate per 1,000 person-years

Gertig et al BMC Medicine 2013

Cervical abnormality rates by vaccinated status

High-grade histology per 1,000 woman years, by age in 2007

ON 3/4 histology per 1,000 woman years, by age in 2007

ON 2 histology per 1,000 woman years, by age in 2007

ON 1 histology per 1,000 woman years, by age in 2007

Gertig et al BMC Medicine 2013
Summary of linkage analysis

- This was the first report of population level impact of quadrivalent vaccine in a school based cohort 12-13 yo and 14-18yo catch up, 5 years after implementation
- Vaccine effectiveness was 47.5% for CIN3/AIS histological outcomes for completed vaccine course, comparable to vaccine efficacy trials
- Greatest impact was observed for women youngest at time of vaccine program implementation

Footnotes: All high grade histology defined as CIN2, CIN3, AIS, and mixed CIN3/AIS. Vaccine effectiveness defined as (1- adjusted hazard rate) x 100. Age in 2007 years.

Gertig et al BMC Medicine 2013
Limitations of present Pap test registry system

- Cross border issues
- Different legislation, different databases make it difficult to implement timely policy changes
- Need to modernise to include SMS/email reminders, invitations and greater electronic transmission of data
- Variation in procedures at jurisdictional level

The future...

- May 2014, Renewal of cervical screening program recommends major changes to cervical screening
- HPV test will be primary screening test 25 years, exit test at 74 years
- 5 yearly screening interval
- Major registry changes will be required to support and evaluate the new program
- National Cervical screening register? Would include link to NHVPR for vaccination status
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