HPV vaccine – a global tour

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Disclosure

I am a really big fan of HPV vaccine
What I will talk about

• What has happened since HPV vaccines were licenced?
  – How effective has it been?
  – How safe is it?
• Boys
• FAQs
• Anti HPV movement – the case of Ireland
Available HPV vaccines - June 2017

- 4vHPV (GARDASIL®)
  Licensed in 2006
  > 55 million subjects vaccinated

- 2vHPV (CERVARIX®)
  Licensed in 2007
  > 19 million subjects vaccinated

- 9vHPV (GARDASIL®9)
  Licensed in 2014
  ~10 million doses distributed

- Total doses distributed: 85 million doses
80 countries (41%) introduced to national programme for girls and 11 (6%) for boys too.
Immunogenicity – superior immune response to vaccine compared with natural infection

**HPV natural infection**
- Seroconversion 8-12m
- 70-80% seroconvert with low affinity and avidity
- Weak response directed at L1 protein
- Few men seroconvert and Ab not protective
- Limited protection against reinfection
- Lesions usually lead to CMI and clearance

**HPV vaccination**
- Seroconversion rapid and peaks 2w after booster dose
- Almost 100% seroconvert
- Polyclonal, broad, potent, sustained
- Long-lived plasma cells
- Memory cells
- One dose effective, two better
How effective has the HPV vaccine been so far?

Polona J. Maver, Mario Poljak, Progress in prophylactic human papillomavirus (HPV) vaccination in 2016: A literature review. Vaccine, Volume 36, Issue 36, 2018
Important definitions

Vaccine effectiveness =

– impact of the vaccine in the general population. Vaccinated compared with unvaccinated

Not the same as vaccine efficacy

– Healthy people assigned at random in a controlled environment (RCT)

Measured and calculated slightly differently

Effectiveness is what happens in the real world
In Sweden high grade cervical lesions declined by 75% in vaccinated

- 75% effective in girls vaccinated under 17y
- Less effective when given at older age because already infected
  - 46% in 17-19y
  - 22% 20-29y

Number of people = 1,333,691 aged 13-29

In Japan the reduction of high grade lesions was 69% among women in their 20’s.

Sadly the programme in Japan was interrupted early on and coverage is just 1%.

Early indication of effectiveness in the USA - where coverage is low

Reduction in HPV 16/18-associated high grade cervical lesions following HPV vaccine introduction in the United States – 2008–2012 ☆

Fig. 2. HPV 16/18 attribution to CIN2+ lesions among women age-eligible for vaccination, by year and vaccination status. Abbreviations: CIN2+: cervical intraepithelial neoplasia grades 2, 3 and adenocarcinoma in situ (AIS). aVaccinated includes women vaccinated >30 days before trigger test (screening test that led to CIN2+ diagnosis).
Cervical screening outcomes in Denmark: Decline in risk for high grade lesions

Impact of HPV vaccination programmes on genital warts
In Denmark rates of genital warts have plummeted in younger people.

Australia have almost eliminated genital warts among women
NZ: New cases of genital warts have dived since the introduction of HPV programme. 4000 > 1000

Genital warts case counts NZ Sexual Health and Family Planning Clinics 2006-2014

Data from ESR Annual Surveillance Report: Sexually Transmitted Infections In NZ 2014 +personal communication Dr Jill Sherwood +quarterly reports
Impact of HPV vaccination programmes on HPV infection prevalence
Prevalence of HPV4 types reduced by 64% among US females 14-19

Analysis of HPV DNA in cervicovaginal specimens from females 14-34y in cross sectional survey pre and post vaccine era

- 14-19y: 11.5% to 4.3% HPV4 types, ↓64%
- 20-24y: 18.5% to 12.1% HPV4 types, ↓34%
- Older: No change in HPV4 types

Prevalence of HPV4 types reduced by >90% among vaccinated US females

Analysis of samples of sexually experienced women in a community health setting before and after vaccine introduction

- **Vaccinated women**: 90.8% decline in HPV4 types
- **Unvaccinated women**: 32.3% decline in HPV4 types
- **All women**: 75% decline in HPV4 types

In US vaccine virus types declined 90.8% in vaccinated females

- ↓90.8% among vaccinated women
- ↓32.3% among unvaccinated women (herd immunity)
- ↓75% among all women

HPV9 offers modest additional protection against some cancers

<table>
<thead>
<tr>
<th></th>
<th>HPV4</th>
<th>HPV9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical Cancer</td>
<td>70%</td>
<td>90%</td>
</tr>
<tr>
<td>AIS</td>
<td>95%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>CIN 2/3</td>
<td>50%</td>
<td>75 - 85%</td>
</tr>
<tr>
<td>CIN 1</td>
<td>30 - 35%</td>
<td>50 – 60%</td>
</tr>
<tr>
<td>Vulval cancer</td>
<td>70 - 75%</td>
<td>85 – 90%</td>
</tr>
<tr>
<td>VIN 2/3</td>
<td>80 - 85%</td>
<td>90 - 95%</td>
</tr>
<tr>
<td>Vaginal cancer</td>
<td>65%</td>
<td>80 – 85%</td>
</tr>
<tr>
<td>VaIN 2/3</td>
<td>60 - 65%</td>
<td>75 – 85%</td>
</tr>
<tr>
<td>Anal cancer</td>
<td>85 - 90%</td>
<td>90 – 100%</td>
</tr>
<tr>
<td>AIN 2/3</td>
<td>80 - 85%</td>
<td>85 – 90%</td>
</tr>
<tr>
<td>Penile cancer</td>
<td>75 - 85%</td>
<td>85%</td>
</tr>
<tr>
<td>PIN 2/3</td>
<td>80%</td>
<td>90%</td>
</tr>
</tbody>
</table>

Key points on effectiveness

- Significant declines in cervical disease now observed multi-nationally
- Significant declines in genital warts indicate elimination possible
- Significant declines in vaccine-type virus in the community
  - Herd immunity effect evident

The significant impact of this vaccine was evident 8 years after introduction – it works!
Blokes
Evidence for males more limited but encouraging

Rarer outcomes in males and smaller studies than for females.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital warts</td>
<td>89.4 – 100%</td>
</tr>
<tr>
<td>Anal intraepithelial neoplasia 2</td>
<td>75.8 (-16.9-97.5)</td>
</tr>
<tr>
<td>Anal intraepithelial neoplasia 3</td>
<td>63.7 (~103 to 96.4%)</td>
</tr>
<tr>
<td>Anal cancer</td>
<td>No cases</td>
</tr>
<tr>
<td>Penile, perineal, perianal neoplasia 2-3</td>
<td>1 case in unvaccinated</td>
</tr>
<tr>
<td>Penile, perineal, perianal cancer</td>
<td>No cases</td>
</tr>
</tbody>
</table>

FAQs about use
What if a woman has evidence of prior exposure to same vaccine type?

- Systematic review in 2017 no evidence but small effects possible

How much cross protection is there?

- HPV2 and HPV4 vaccines provide some level of cross-protection against hrHPV types other than 16 and 18, mainly types 31, 33 and 45.
- These 3 are associated with 13% cervical cancers.

Can we expect to see serotype replacement

• Unlikely
  – No competition (infection with multiple types)
  – Currently no evidence for serotype replacement.

How long is protection expected to last for?

• For HPV4, using a 3-dose schedule, no breakthrough cases of cervical/genital disease related to HPV types 6, 11, 16, and 18 have been observed among vaccinated pre-adolescents and adolescents during 10 years of follow-up.
• First principals support decades to life
• Males: up to 11.5 years post dose 1 - effective and immunogenic

Grading of scientific evidence – table VII: Duration of protection conferred by HPV vaccination in immunocompetent females. Available at http://www.who.int/immunization/position_papers/hpv_grad_duration_immunocompetent.pdf
Stephen Goldstone, Anna Giuliano, Joel Palefsky, Alain Luxembourg, and on behalf of the V501-020 study teamLong-term effectiveness and immunogenicity of quadrivalent HPV vaccine in young men: 10-year end-of study analysis
Journal of Clinical Oncology 2018 36:15_suppl, 1553-1553
How safe is HPV vaccine?

A: extremely safe
First came the HPV4 pivotal trials to 2006 – vaccine very safe

- Safety evaluated in placebo-controlled double blind trials in 22 countries
  - Placebo aluminium adjuvant OR saline
  - 11,778 vaccinated/9686 unvaccinated

- Local & systemic events
  - Detailed diary card 14 days
  - Long term follow up >800 days

- Safety during pregnancy
Observational studies

Passive and active surveillance
Post licensure studies to 2016 - most compare outcomes in vaccinated with unvaccinated

Outcomes include autoimmune, neurological, blood clots, CNS, CRPS, other specified conditions...

<table>
<thead>
<tr>
<th>System or review (country)</th>
<th>Year of Publication</th>
<th>Number of doses evaluated</th>
<th>Description</th>
<th>Methods</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAERS (US)</td>
<td>2009</td>
<td>N/A</td>
<td>Summary of 12,424 VAERS reports following 4 HPV between 2006–2008</td>
<td>Spontaneous reporting; data mining for disproportionality reporting</td>
<td>Disproportional reporting of syncope and VTE</td>
</tr>
<tr>
<td>Vaccine Safety Datalink (US)</td>
<td>2011</td>
<td>600,558</td>
<td>Large database used for active surveillance and research; safety assessment of 9 prespecified health outcomes among females vaccinated recipients aged 9–26 years</td>
<td>Cohort design with weekly sequential analyses of electronic medical data</td>
<td>No statistically significant increase in risk for the outcomes monitored; non-significant elevated risk detected for VTE</td>
</tr>
<tr>
<td>Institute of Medicine review (US)</td>
<td>2011</td>
<td>N/A</td>
<td>Review of 4 HPV safety data</td>
<td>Review of published studies, case reports, and surveillance systems</td>
<td>No evidence to support association among 12 outcomes; anaphylaxis causally associated with 4 HPV vaccine-associated serious adverse events</td>
</tr>
<tr>
<td>Post-marketing commitment to FDA (US)</td>
<td>2012</td>
<td>346,972</td>
<td>General safety, VTE, neurologic, death</td>
<td>General surveillance following active use of vaccine in the US</td>
<td>Proportional reporting observed; no new concerns for serious adverse events</td>
</tr>
<tr>
<td>VAERS (US)</td>
<td>2013</td>
<td>N/A</td>
<td>Review of 25,176 VAERS reports following 4 HPV between 2006–2014</td>
<td>Review of published studies, case reports, and surveillance systems</td>
<td>No disproportionate reporting observed; no new concerns</td>
</tr>
<tr>
<td>Register-based cohort study (Denmark and Sweden)</td>
<td>2013</td>
<td>696,420</td>
<td>Autoimmune, Neurologic, VTE</td>
<td>Assessment of autoimmune outcomes following 4 HPV among 211 cases and 875 controls aged 14–26 years</td>
<td>No increased risk for combined endpoint of six autoimmune disorders</td>
</tr>
<tr>
<td>VAERS (US)</td>
<td>2014</td>
<td>N/A</td>
<td>Review of 25,176 VAERS reports following 4 HPV between 2006–2014</td>
<td>Spontaneous reporting; data mining for disproportionality reporting</td>
<td>No disproportionate reporting observed; no new concerns</td>
</tr>
<tr>
<td>Pharmacoepidemiologic General Research Extension (France)</td>
<td>2014</td>
<td>N/A</td>
<td>Assessment of 6 different autoimmune outcomes following 4 HPV among 2014 cases and 875 controls aged 14–26 years</td>
<td>Case-control study with recruitment of cases and controls through registries</td>
<td>No increased risk for combined endpoint of six autoimmune disorders</td>
</tr>
<tr>
<td>Register-based cohort study (Denmark)</td>
<td>2014</td>
<td>500,345</td>
<td>Assessment of VTE following 4 HPV among women aged 10–17 years</td>
<td>Self-controlled case series using national patient registers</td>
<td>No increased risk for VTE</td>
</tr>
<tr>
<td>System or review (country)</td>
<td>Year of Publication</td>
<td>Number of doses evaluated</td>
<td>Description</td>
<td>Methods</td>
<td>Findings</td>
</tr>
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<td>---------------------------</td>
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<td>----------</td>
</tr>
<tr>
<td>Register-based cohort study [Denmark and Sweden]</td>
<td>2015</td>
<td>1,924,581</td>
<td>Assessment of multiple sclerosis and other demyelinating diseases of the central nervous system among females aged 10–44 years</td>
<td>Cohort design using data linked to national registers</td>
<td>No association with the development of multiple sclerosis and other demyelinating diseases</td>
</tr>
<tr>
<td>Vaccine Safety Datalink (US)</td>
<td>2015</td>
<td>1,240,000</td>
<td>VTE</td>
<td>Self-controlled case series; cases confirmed by medical record review</td>
<td>No increase risk for VTE</td>
</tr>
<tr>
<td>Sentinel System (US)</td>
<td>2015</td>
<td>1,240,000</td>
<td>VTE</td>
<td>Self-controlled risk interval design; cases confirmed by medical record review</td>
<td>No increased risk for VTE</td>
</tr>
<tr>
<td>VAERS (US)</td>
<td>2015</td>
<td>N/A</td>
<td>Neurologic</td>
<td>Review of 21 CRPS-related VAERS reports following 4vHPV between 2006 and 2015</td>
<td>Spontaneous reporting; clinical review of CRPS cases</td>
</tr>
<tr>
<td>Post-marketing commitment to FDA (US)</td>
<td>2015</td>
<td>N/A</td>
<td>Pregnancy</td>
<td>Review of 4,919 reports of pregnancy following 4vHPV between 2006–2012</td>
<td>Voluntary reporting to pregnancy registry</td>
</tr>
<tr>
<td>VAERS (US)</td>
<td>2015</td>
<td>N/A</td>
<td>Pregnancy</td>
<td>Review of 147 VAERS pregnancy reports following 4vHPV between 2006 and 2013</td>
<td>Spontaneous reporting; data mining for disproportion reporting</td>
</tr>
<tr>
<td>Vaccine Safety Datalink (US)</td>
<td>2016</td>
<td>1,355,535</td>
<td>Death</td>
<td>Case-centered method; medical record review</td>
<td>Evaluation of deaths among individuals aged 9–26 years</td>
</tr>
</tbody>
</table>

**Abbreviations**
- CRPS: Chronic Regional Pain Syndrome
- FDA: Food and Drug Administration
- HIV: Human Immunodeficiency Virus
- 4vHPV: Quadrivalent Human Papillomavirus vaccine
- VAERS: Vaccine Adverse Event Reporting System
- VTE: Venous thromboembolism

**Sources**
Previous 7 GACVS* reviews found no signals of concern

*WHO Global Advisory Committee on Vaccine Safety

- **2007**: Pre and post data; 2007 no issues of concern identified, 2008 report of anaphylaxis from Australia, 2009 syncope added to label of one product; data on inadvertent use in pregnant women limited but no issues identified.

- **2008**: 2013 Cases of chronic pain reported from Japan; no similar signal from other countries. 2013 Cases of multiple sclerosis reported from France, but no increase in risk seen in multiple studies.

- **2009**: 2014 No evidence of harm from aluminium or DNA fragments in vaccines.

- **2014**: 2013 No issues of concern identified.
Activities and conclusions from December 2015

- Review of data on association between HPV and autoimmune diseases
  - No overall association, weak signal for GBS (H1N1?)
  - Additional epidemiological studies found no signal

- Proposed safety signals from VigiBase
  - Committee proposed a closer role for GACVS in VigiBase signalling

- POTS and CRPS discussed
  - Available evidence, including EMA review found no indication for an association.
    The committee also acknowledged that the perceived associations continue to disrupt vaccine programmes.
  - Denmark planning additional study
2016 - 2017 challenges for building trust, risk communication, limiting impact on vaccine uptake

• Nordic Cochrane
• EMA
• Over 30 further publications proposing immunological mechanisms for HPV vaccine induction of purported autoimmune conditions, case reports, case series
Reviewed in 2017 by GACVS

- A systematic review (GRADE)
  - All SAEs, medically sig conditions, NOCD, deaths
  - 75,697
  - Very high level of evidence
- UK self controlled case-series, VAERS and VSD
  - GBS
  - 10.4 million doses, 60 million doses, 2.7 million administered
- Denmark and Sweden
  - Autoimmunity
  - >3 million 18-44
  - Unmasking of celiac disease
- Cohort study from Denmark
  - 540,805 pregnancies
- VSD
  - >92,000 pregnancies
- New data from Japan
  - Nationwide epidemiological survey
Primary Ovarian Insufficiency and Adolescent Vaccination

• Cohort of 199,078 patients
• No elevated risk of POI after HPV, Tdap, flu, or MenACWY
GACVS Subcommittee on Immunization Anxiety Reactions Related to AEFI

- Syncope related to fear, anxiety
- Can occur in clusters (mass hysteria)
- Social media amplification
- *define *recognise *prevent *manage *communicate *research
Summary of safety data after 270 million doses

No serious safety issues*, high level of evidence

* Except anaphylaxis
But...
### Reported HPV coverage rates

**Selected years in two time periods**

<table>
<thead>
<tr>
<th>Country</th>
<th>2006-2013</th>
<th>2014 ff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaysia</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Rwanda</td>
<td>85</td>
<td>90</td>
</tr>
<tr>
<td>Bhutan</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>Mexico</td>
<td>65</td>
<td>75</td>
</tr>
<tr>
<td>England</td>
<td>60</td>
<td>70</td>
</tr>
<tr>
<td>Norway</td>
<td>70</td>
<td>80</td>
</tr>
<tr>
<td>Australia</td>
<td>55</td>
<td>75</td>
</tr>
<tr>
<td>Chile</td>
<td>65</td>
<td>75</td>
</tr>
<tr>
<td>South Africa</td>
<td>50</td>
<td>60</td>
</tr>
<tr>
<td>Denmark</td>
<td>45</td>
<td>60</td>
</tr>
<tr>
<td>Argentina</td>
<td>50</td>
<td>65</td>
</tr>
<tr>
<td>Austria</td>
<td>50</td>
<td>65</td>
</tr>
<tr>
<td>Latvia</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>USA</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>Colombia</td>
<td>20</td>
<td>30</td>
</tr>
</tbody>
</table>

Source: Brotherton et al. 2016
Ireland
Familiar story

- Lobby groups established in 2015
- Strong social media platform
- Emotive, misinformation
- Facilitated by media
Coverage plunged from ~85% to 50%
Irish Immunisation Office fight back - 2016

- Established a steering group of concerned organisations
- Encourage all key stakeholders to actively promote vaccine
- Focus groups on parent attitudes
- Established liaisons with education, parent, political, etc.
- Revised print and online materials
- Comprehensive training programme for health professionals

HPV Vaccination Alliance
launched 2017

• >35 diverse organisations collaborating to present facts
• Signed a contract pledging commitment to raise awareness of HPV vaccine
• Unvaccinated girls offered vaccine again
Decline in uptake from 89.7% to 50%. 2017-18 uptake 61.7%

<table>
<thead>
<tr>
<th>Academic year</th>
<th>First dose</th>
<th>Second dose</th>
<th>Third dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-11</td>
<td>84.0</td>
<td>87.9</td>
<td>81.9</td>
</tr>
<tr>
<td>2011-12</td>
<td>87.9</td>
<td>87.0</td>
<td>85.5</td>
</tr>
<tr>
<td>2012-13</td>
<td>87.0</td>
<td>86.3</td>
<td>84.2</td>
</tr>
<tr>
<td>2013-14</td>
<td>89.3</td>
<td>88.2</td>
<td>84.9</td>
</tr>
<tr>
<td>2014-15</td>
<td>89.7</td>
<td>86.9</td>
<td></td>
</tr>
<tr>
<td>2015-16</td>
<td>82.4</td>
<td>72.3</td>
<td></td>
</tr>
<tr>
<td>2016-17</td>
<td>50.0</td>
<td>51.0</td>
<td></td>
</tr>
<tr>
<td>2017-18*</td>
<td>55.8</td>
<td>61.7</td>
<td></td>
</tr>
</tbody>
</table>


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Powerful cross sectorial alliances led to rapid improvement in uptake

➢ Support
➢ Teamwork
➢ Communication
➢ Trust
➢ Motivation
➢ Inspiration
➢ SUCCESS

Questions/discussion?
Recent bits from NZ on pertussis vaccine in pregnancy
NZ cohort study using data-linking: No safety concerns

350,041 women contributed pregnancy person-time from 2009–2013. Restricted cohort of 68,550 women eligible to receive funded Tdap vaccination antenatally from 28 to 38 weeks gestation during 2013, 8,178 (11.9%) received Tdap vaccine and 60,372 (88.1%) did not.

<table>
<thead>
<tr>
<th>Decreased risk</th>
<th>No effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>• pre-eclampsia with severe features, antenatal bleeding, preterm labour, premature rupture of membranes, pre-term delivery, hyperemesis gravidarum, urinary tract infections, rhesus isoimmunisation, other fetal problems, placenta previa, and false labour</td>
<td>• gestational hypertension, pre-eclampsia, gestational diabetes mellitus, fetal growth restriction, placental abruption, chorioamnionitis, premature rupture of membranes, labour dysfunction, first-stage labour dysfunction, second-stage labour dysfunction, fetal distress, post-partum haemorrhage, maternal fever during labour, C-section delivery, maternal sepsis, maternal fever after labour, anaemia, neurologic disorders and hyperemesis gravidarum.</td>
</tr>
<tr>
<td>• moderate to late preterm birth, low birth weight and small for gestational age (SGA)</td>
<td>• stillbirth, infant Apgar score at 5 minutes after birth, microcephaly, asphyxia, sepsis or infection, hypoxic ischemic encephalopathy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Increased risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• lactation disorders and perineal laceration during delivery</td>
</tr>
<tr>
<td>• ankyloglossia and neonatal erythema toxicum</td>
</tr>
</tbody>
</table>

Current area of uncertainty – blunting and finding the ‘sweet spot’

Birth

Infant antibody

Infant age in weeks

Maternal antibody

Too early for vaccination

Ideal time for vaccination

Too late for vaccination

Infant antibody

Infection risk