Should cost-effectiveness inform HPV vaccine introduction?
Outline

- Why is cost-effectiveness important in HPV vaccine introduction and implementation
- Cost-effectiveness models for decision-making
- Budget impact for scaling up
- [https://www.youtube.com/watch?v=lm2E0skxZI4&index=10&list=WL](https://www.youtube.com/watch?v=lm2E0skxZI4&index=10&list=WL)
Why economic evaluation?

- The ultimate objective of economic evaluation is to improve decisions about the allocation of health care resources
  - By carefully assessing the costs and benefits of the services, it can help determine which services should be given priority over other potential uses of resources
- When resources are scarce, choosing to do one activity means that you have fewer resources to do another activity
  - This concept of trade-offs is implicit in economic decision-making
  - Economic evaluation provides a systematic framework to consider these trade-offs
Key questions addressed by economic evaluation

- Is this health procedure, service or programme worth doing compared with the other things we could be doing?

- Prior/complementary questions not addressed:
  - Can it work (efficacy)
  - Does it work (effectiveness)
  - Is it reaching those who need it (accessibility)
What is cost-effectiveness analysis?

- CEA always involves comparison of at least two options with the same goal
- So many questions...
  - Should planners provide the HPV vaccination to school girls?
  - Should the Prevention of Mother to Child Transmission protocol be changed to include more effective but more costly drugs?
  - Should doctors or nurses provide antiretroviral treatment services?
  - Should that new expensive drug be included in the tertiary hospital drug list?
- Who should do what, to whom, with what health care resources, and with relation to the other uses of these health care resources
In 2007, UCT designed a study to investigate if a cervical prevention programme which includes an HPV vaccine is more cost-effective than the current strategy in South Africa.

We developed a Markov state transition model to describe the screening and management of cervical disease within the South African context.

We estimated and compared the cost-effectiveness of two strategies: screening only and vaccination followed by screening, defined as cost per life year saved and cost per quality adjusted life year gained (QALY).
A number of base-case assumptions for screening, treatment and vaccination were made.

To reflect the uncertainty inherent in the analysis, a number of one-way sensitivity analyses were undertaken on the following parameters:

- Screening tests (VIA and HPV DNA test)
- Vaccine (price, efficacy, delivery options)
- Discounting (different discount rates)
- Mortality rates from other causes (excluding HIV-related mortality)
Study findings

- Adding a vaccine to the current screening programme to prevent HPV related diseases can potentially be a cost-effective strategy (Sinanovic et al 2009)
- ICER per QALY gained US $1,078 from the societal perspective and US $1,460 per QALY gained from the provider perspective
- Findings were sensitive to discount rate, vaccine price and increases in mortality from HIV/AIDS
Decision-making rules

- **Is it cost-effective?**
  - Yes, if GDP per capita of US $5,724 is used as a threshold
  - Comparable with studies on the cost-effectiveness in South Africa:
    - cervical cancer screening (Goldie et al 2005)
    - ART interventions (Cleary et al 2006)

- **Is it affordable?**
  - Not, at the current vaccine price
  - Possibly, if the vaccine price were to be reduced by 60%
Thresholds

- Threshold = societal value of living longer and healthier lives
  - Explicit policy in some countries
  - No threshold policy in SA (or much of developing world)
  - WHO
    - ICER < 2*GDP per capita “very cost effective”
    - ICER < 3*GDP per capita “cost effective”
- Because it is a societal value, it differs depending on the burden of disease, severity, characteristics of the population in need, etc.
- Key point is that more money is needed to treat the same number of patients
- Implicit assumptions
  - The budget is flexible or can be reallocated (but if this is the case, what are the losses of reallocating the budget from its current use?)
  - It is not a problem if fewer patients receive the treatment
What conclusions can we make?

- Adding a vaccine to the current screening programme to prevent cervical cancer in South Africa can potentially be a cost-effective policy option.
- The threshold analysis indicated that a price reduction of 60% or more would make the vaccine plus screening strategy more cost-effective than the screening only strategy.
- However, even if the price is reduced, and given the size of the population in need, two questions remain:
  - is the HPV vaccine introduction still affordable and sustainable?
  - should the vaccine introduction be publicly funded?
Next step: Budget impact analysis

- Budget impact analysis (BIA) estimates the financial consequences of adoption of a new health care intervention within a specific health care setting given the limited resources
- Likely to be considerable because of the larger size of the population eligible for vaccination
- In 2010, UCT developed an expenditure-based model to estimate costs associated with different levels of coverage for vaccination and screening
Cost per capita of integrated preventative programme at different vaccine prices
Programme costs as a share of public spending on health using different vaccine prices

<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>50% price reduction</th>
<th>70% price reduction</th>
<th>90% price reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost per vaccinated girl, 2010 Rand</td>
<td>4 129</td>
<td>1 710</td>
<td>1 196</td>
<td>573</td>
</tr>
<tr>
<td>Number of girls age 10-12, 2010</td>
<td>1 502 191</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of girls with 70% coverage</td>
<td>1 051 534</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total population, 2010</td>
<td>49 147 177</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public spending per capita, 2010</td>
<td>1 819</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total vaccination costs (billions), 2010 Rand</td>
<td>4.34</td>
<td>1.81</td>
<td>1.23</td>
<td>0.66</td>
</tr>
<tr>
<td>Total screening costs (billions), 2010 Rand</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Total costs of the integrated programme (billions), 2010 Rand</td>
<td>4.35</td>
<td>1.82</td>
<td>1.24</td>
<td>0.67</td>
</tr>
<tr>
<td>Total costs as % public spending on health</td>
<td>4.86%</td>
<td>2.03%</td>
<td>1.38%</td>
<td>0.75%</td>
</tr>
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</table>
The findings suggest that the extra costs of scaling up the preventive programmes for cervical cancer range from R9.77 to R88.51 per capita, depending on the vaccine price and vaccine type.

Although the estimated investments are not large in absolute terms, they represent an additional 4.86% of total public spending on health.

If the vaccine price is reduced by 90%, this spending would be 0.75% - much less of a burden on the health budget but still a sizable amount, considering competing priorities and the small margin that South Africa has for reallocation in the short term from their own resources.
The aim of economic evaluations of health care programmes is to serve as an aid to decision making and to affect policy making.

Decision criteria of economic evaluation techniques offer an indispensable basis for priority setting (especially in pursuit of efficiency goals).

Where possible, implementation of health care intervention policies should be preceded by economic evaluations.

Whilst CEA may help assigning priority to interventions, BIA is useful in assessing their affordability and sustainability.

Values and political considerations will determine final decision.
Implementation of HPV vaccination
Key lessons from across the globe: Australia

Assoc Prof Julia Brotherton
Medical Director, Public Health Physician
National HPV Vaccination Program Register
Medical Director, Registries and Research, VCS

Honorary Principal Fellow
School of Population and Global Health
University of Melbourne
Overview

First country to implement national funded HPV vaccination program- April 2007

Very large scale: 12-26 years females

1. Use champions for the vaccine to engage the community
2. Political will is key
3. Cancer prevention is a powerful motivator
4. School programs can provide effective delivery for young adolescents
5. A vaccine register is effective infrastructure to improve coverage and evaluate program impact
6. There will be AEFI: be prepared
1. Value of vaccine champions

A local hero is born…
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.


- “God’s gift to women” (Weekend Australian, March 2006)
- 2nd most trusted Australian, 2008 survey
2. Political will is key

Deal closer on vaccine for cervical cancer

After a flood of demands for a rethink, including from Liberal female senators, Mr Howard said yesterday he wanted to see the "wonderful drug available and [for] the mass immunisation campaign to start as soon as possible". Mr Howard – whose wife, Janette, has survived cervical cancer – said he would discuss the matter further with the Minister for Health, Tony Abbott, “to see if there is any way that it [the immunisation program] might be started, say, halfway through next year”.

National HPV Vaccination Program Register
3. Focus on cancer prevention

At last there’s some good news about cancer.


Cervical cancer is the second most common cancer in women worldwide and is almost always caused by the human papilloma virus (HPV). The good news is that a new vaccine, developed in Australia, was approved by the US Food and Drug Administration that is 95% effective.

The Australian Government is making the cervical cancer vaccine available free to all females aged 13 to 26 under the National HPV Vaccination Program. For girls, the program starts in April 2007. A consent form will be sent home shortly for parents to fill in and return.

For women who have already been vaccinated against HPV, five annual Pap tests and five annual cervical cancer tests will be available from your GP or wastewater screening clinic from July.

The vaccine does not prevent all cervical cancers, so regular Pap tests are still essential. But a free cervical cancer test will still be given to women.

Help protect your daughter from cervical cancer. Sign the consent form.

For more information:
National Immunisation Hotline 1800 671 811
australia.gov.au/cervicalcancer

With your permission we can stop the spread of HPV.
For more information contact us at:
australia.gov.au/HPV

School-based HPV vaccination program for males and females

Say yes to protecting everyone from HPV-related cancers

National HPV Vaccination Program Register
4. School programs work


Under notified by 10-20%*
4. School programs work

• Overcome access barriers for parents
• Equity of access*
  – Have a strategy for those not in school and missed doses
• Very reliant on working relationship between education and health sectors
• Improving processes and familiarity over time**
  – Coverage now 87/85/79% for 14 yr old females in 2015
  – Coverage now 82/79/73% for 14 yr old males in 2015

5. Role of vaccine registers

National (Australia) HPV 3 dose vaccination coverage for females turning 15 years of age in 2015

Source: www.hpvregister.org.au/research/coverage-data
## History Statement Responses - example

<table>
<thead>
<tr>
<th>History Statements</th>
<th>No. of Females</th>
<th>%</th>
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<tbody>
<tr>
<td>Statements Sent</td>
<td>8272</td>
<td>100%</td>
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<tr>
<td>Response - Updated Records</td>
<td>3292</td>
<td>39.8%</td>
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</table>

<table>
<thead>
<tr>
<th>Response Outcome</th>
<th>No. of Notifications</th>
<th>%</th>
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<tbody>
<tr>
<td>Doses Previously Given</td>
<td>2193</td>
<td>60.4%</td>
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<tr>
<td>New Doses Given</td>
<td>1438</td>
<td>39.6%</td>
</tr>
<tr>
<td>Total</td>
<td>3631</td>
<td>100%</td>
</tr>
</tbody>
</table>

Trends in histologically confirmed high-grade cervical abnormalities, 2004-2014, Australia

Source: Cervical Screening in Australia 2013-2014, AIHW 2016
Population HPV vaccine effectiveness for cervical histological outcome, by age in 2007, for completed vaccine course

Adj VE CIN3+
47.5%
(22.7%-64.4%)

6. Be prepared for AEFI

• 7 May 2007: 26/720 girls in a school – chest pain, palpitations, lethargy, neurological symptoms
  – 5 to hospital, 2 admitted, all resolved within 24 hours
6. Be prepared for AEFI

• Cases referred to Victoria’s Surveillance of Adverse Events Following Vaccination in the Community (SAEFVIC) Unit
• No organic cause identified
• 3 of 4 referred to children's hospital were revaccinated without problem
Thank you

www.hpvregister.org.au
jbrother@vcs.org.au

• NHVPR is owned and funded by the Australian Government Department of Health and operated by VCS
• VCCR is funded by the Victorian Government and operated by VCS
Implementing HPV Vaccination: Key Lessons

Integrated School Health Programme: Service Delivery Platform for Human Papilloma Virus (HPV) Vaccination in South Africa

Dr NR Dlamini. MBChB  MMed(Paeds)
Chief Director: Child, Adolescent and School Health

HPV
Cape Town
Feb 2017
Outline of Presentation

1. Establishment of School Health Services
2. Political will
3. Ring fenced budget
4. Detailed micro planning
5. Social mobilisation
6. Integration
7. Strong M and E System
8. Challenges
Background: HPV introduction

• Before HPV vaccination could be introduced a service delivery platform had to be established.
• The platform was the Integrated School Health Programme.
• As is normal, in any policy formulation process, there were stakeholder consultations and engagement before the new School Health Policy could be launched. School Governing Bodies, School Principals’ Association, Labour Unions were consulted.
• Launched in 2012.
School health teams lead the way

NHI pilots are showing results by getting doctors out to far-flung communities and focusing on prevention, write Kerry Cullinan, Sibongile Nkosi, and Ayanda Mkhwanazi.

One common medical aid for all South Africans, as envisaged by the government’s proposed National Health Insurance (NHI) scheme, is many years away. But most of the 16 NHI pilot districts – with the exception of OR Tambo in the Eastern Cape – are making reasonable progress to improve public health, according to a Health-e News investigation.

The most immediate success is that of school health teams, which have seen over 200,000 pupils for eye, ear, dental and nutritional problems.

The pilot districts, covering 20 percent of the population, were set up almost five years ago after Health Minister Aaron Motsoaledi announced the NHI as government policy while the White Paper to map out how
• Commitment to introduce HPV vaccine in 2014 was made in the 2013 Health Budget speech.
• The platform for delivery of HPV vaccine would be through the School Health Programme.
• Ring fenced budget secured.
• Aim was to vaccinate girls in grade 4 who were over 9 years old.
• The target group was quantified to approximately 520 000 girls in almost 18 000 schools (Data-base from Dept of Basic Education)
Delivery of HPV Vaccination-detailed micro planning

• HPV vaccine Medicine Control Council (MCC) registration and licensure: minimum eligibility age of 9 years
• Two doses of the bi-valent vaccine
• Offered to Grade 4 girls, aged 9 years and above in public schools and special schools
• Campaign style: twice a year; every year
• HPV vaccination teams visit schools twice a year, every year, to administer the vaccine
<table>
<thead>
<tr>
<th>January</th>
<th>February</th>
<th>March</th>
<th>April</th>
<th>May</th>
<th>June</th>
<th>July</th>
<th>August</th>
<th>September</th>
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**1\(^{st}\) Round Annual HPV Vaccination Campaign (Dose 1)**

21 February – 28 March 2016

**2\(^{nd}\) Round Annual HPV Vaccination Campaign (Dose 2)**

2 August – 6 September 2016
Social Mobilisation & Communication

- Social mobilisation and communication toolkit
  - Fact sheets
  - FAQ
  - Posters
  - Leaflets (girls & parents)
  - Script information session
  - Media statements
  - Press release
  - Radio/TV adverts
  - B’Wise information pamphlets
The government is introducing HPV* vaccination for girls in Grade 4

Date of 1st DOSE
March 2014

Date of 2nd DOSE
October 2014

Remember to ask your parents/caregiver/guardian to sign and return the consent form to be vaccinated.

Protecting young girls, future women of South Africa

*Human Papilloma Virus
Deworming

- Administered during the HPV vaccination sessions

**Target Group**

All learners, boy & girls in:

- Quintiles 1-3 schools
- Grades R-7
List of materials delivered:

• Worms FAQ
• Worms Fact Sheet
• Worm information for teachers
• “Learn about worms” leaflet
• Deworming invitation letter from Ministers
Data Management, M & E

- Implementation of an electronic data capturing system in all provinces

- Each vaccination team given an Android Tablet PC for recording purposes. 2 250 tablets procured

- Implement an HPV campaign management system that monitors:
  1. School and learner coverage
  2. Tracking system to identify missed schools
  3. Vaccine stock management
  4. Adverse events management
Challenges

• Shortage of staff: issue contracts (especially retired nurses)
• Shortage of transport: hire cars
• Not everyone is computer savvy
Performance

• Since introduction in 2014:
• Total of 1 208 000 girls immunised.
Thank you
www.doh.gov.za
Public Health Workshop

Future of cervical cancer screening in the post-vaccination era

Eduardo L Franco, DrPH, FRSC, FCAHS, OC
Professor and Chairman, Department of Oncology
Director, Division of Cancer Epidemiology
McGill University, Montreal, Canada
Editor-in-Chief, Preventive Medicine
Disclosure (lifetime)

- Occasional paid consultant to Merck and GSK on HPV vaccines, to Qiagen, Roche, and Becton & Dickinson on HPV diagnostics.

- Three unconditional grants to my institution from Merck in partial support of investigator-initiated research related to HPV in my unit (to supplement CIHR and NIH funding).

- Fees received from Elsevier to maintain editorial team for a top tier medical journal (Preventive Medicine).

- Entire research program funded by CIHR, NIH, NCIC, CRS, CCSRI, FRQS; salary awards: CIHR Distinguished Scientist, FRSQ Chercheur National, James McGill Chair, Minda de Gunzburg Endowed Chair.

Creed: It is a duty and a privilege for experienced scientists to advise industry in bringing new technologies to advance medicine and public health. Pharmaceutical or biotechnology companies cannot obtain the same wealth of knowledge and insights from a lay advisory board and that would be detrimental to the public.
Points to cover:

✓ Knowledge about the cause of cervical cancer led to two prevention fronts: screening and vaccination

✓ The scientific evidence for molecular HPV testing as a better technology than Pap cytology

✓ The unexpected rapid progress on HPV vaccination will interfere on screening practices

✓ Screening paradigm changes: now and in the future
Correlation between phylogenetic relatedness and carcinogenicity of HPVs: Type inclusion in vaccines and screening tests

Adapted from: Schiffman et al., JNCI 103:368,2011
Women who have sex with HPV-infected men

- (within weeks to months, some will acquire) HR-HPV infection
- (within months, some will develop) Persistent HR-HPV infection
- (within months to years, some will develop) HG cervical lesions
- (within months to years, some will develop) Cervical cancer

Pap Cytology
- Detected with low sensitivity

HR-HPV Testing
- Detected with high sensitivity

Detected with moderate sensitivity

Perceived as cause of low specificity

Franco & Cuzick, Vaccine 2008
Evidence for HPV Primary Screening is Overwhelming

HPV primary screening is clinically superior, more cost-effective and less burdensome for women than the Pap test:

• HPV testing more effective at detecting high-grade precancerous lesions and eliminates the ambiguity of equivocal smears (i.e., ASC-US).

• A negative HPV test provides greater and longer reassurance to women that they are at very low risk of cervical cancer.

• HPV testing has efficiency and quality benefits. Fewer lifetime screens with HPV screening contributes to cost-effectiveness.

• HPV testing offers greater protection against cervical adenocarcinoma.

• Self-sampling with HPV test could help reduce disparities and increase screening rates.

• Cytology will be less effective in a vaccinated population. (Franco et al., Vaccine 2006; Palmer et al., British Journal of Cancer 2016)
Competing scenarios for the introduction of HPV testing in cervical cancer screening (not ASCUS triage)

- Co-testing Pap cytology + HPV (widely used in the US):
  - ages 30-65, every 5 years if both negative
  - 1-year repeat if HPV+/Pap-
  - referral to colposcopy if LSIL+ or HPV+/ASC

- HPV primary screening followed by Pap triage of HPV+ (approved in Canada, Netherlands, Italy, Turkey):
  - ages 30-65, every 5-7 years if HPV-
  - 1-year repeat if HPV+/Pap-
  - referral to colposcopy if HPV+/ASC+

- HPV primary screening via genotyping and conditional Pap cytology (approved in US):
  - ages 25-65, every 3 years if HPV-
  - 1-year repeat if 12HR+/Pap-
  - referral if 16/18+ or 12HR+/Pap+
Co-testing adds little to primary HPV testing:
Risk of CIN3+ according to baseline test results in European studies

Dillner, J. et al. BMJ 2008;337:a1754
Primary screening

• Human papillomavirus (HPV) DNA testing is recommended in all resource settings.

• Visual inspection with acetic acid may be used in basic settings.

• The recommended age ranges and frequencies in each setting are as follows:
  
  ➢ Maximal: 25-65 years, every 5 years
  
  ➢ Enhanced: 30-65 years, if two consecutive negative tests at 5-years intervals, then every 10 years
  
  ➢ Limited: 30-49 years, every 10 years
  
  ➢ Basic: 30-49 years, one to three times per lifetime
Secondary Prevention of Cervical Cancer: ASCO Resource-Stratified Clinical Practice Guideline (Jeronimo et al., J Glob Oncol Published online before print October 12, 2016)

**Triage**

- In basic settings, visual assessment for treatment may be used after positive HPV DNA testing.
  - If visual inspection with acetic acid was used as primary screening with abnormal results, women should receive treatment.
- For other settings, HPV genotyping and/or cytology may be used.
Secondary Prevention of Cervical Cancer: ASCO Resource-Stratified Clinical Practice Guideline (Jeronimo et al., J Glob Oncol Published online before print October 12, 2016)

**Screening in vaccinated population**

- Under the assumption that women were vaccinated before becoming sexually active, in the enhanced and maximal settings, women may receive routine screening with HPV testing at ages 30, 45, and 60 years.

- However, age and frequency cannot be fully addressed until there are more data.

- Speculatively, a single screening of women approximately 35 or 40 years of age may be valuable if it leads to the detection of early-stage cervical cancer caused by hrHPV types not covered by the nonavalent HPV vaccine.
Detection rate will be evaluated at their second screening episode. If DR is below 1/1000 the interval will be increased by one year. If DR is not below 1/1000 the interval will be fixed at the length of the previous cohort.
Arguments against HPV testing as the primary technology (heard in policy committees everywhere)

- No change needed; cervical cancer rates are low enough with Pap cytology screening
- Too many choices for HPV testing (vendors, molecular target); must wait for the evidence of which one is best
- Changes will be costly; HPV testing more expensive than Pap cytology
- Proponents of HPV testing are in conflict of interest
- Unmentionable concerns: loss of income by professions that rely on continued use of Pap cytology
- We must first organize the cervical cancer screening program before we change the technology
- Let us do it in two steps: first we adopt HPV testing for ASC-US triage, then if all works well we can adopt HPV as the primary technology
- HPV-based screening will lead to an excess in colposcopy referrals, thus increasing costs of the screening program
Cervical cancer prevention activities are inherently components of a single process.
The Castle model of risk threshold management

<table>
<thead>
<tr>
<th>Risk of ≥CIN2* (%)</th>
<th>Suggested management*</th>
</tr>
</thead>
<tbody>
<tr>
<td>~0</td>
<td>Regular screening</td>
</tr>
<tr>
<td>2</td>
<td>Rescreen after 1 year</td>
</tr>
<tr>
<td>10</td>
<td>Immediate referral to colposcopy</td>
</tr>
<tr>
<td>40</td>
<td></td>
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</tbody>
</table>

* Note: screening history will also influence management

There is urgency to change the screening paradigm now but how will screening perform in the future?

• With high vaccination coverage in all age cohorts, cross-protection, and herd immunity, HPV transmission will be kept at a minimum.

• Molecular tests (HPV) may eventually lose its clinical utility in identifying disease that has become so rare relative to (false) positive findings.

• Cervical cancer screening is not devoid of immediate and long term risks for women’s reproductive health.

• Today, such risks are far outweighed by the benefits of screening.

• The question is: will that balance change in the future?
When will we know that screening should stop?

- Risk tolerance will vary among populations; there will be a need for benchmarks of acceptable disease risk.
- Some countries may decide to eliminate screening programs based on consensus that an acceptably low level of cervical cancer risk has already been attained.
- Comparison of the projected post-vaccination incidence of cervical cancer with that of cancers for which there are established screening policies.
- Compare the case-fatality/prognosis of different cancers.
- Examples of benchmarks: Vaginal and vulvar cancers (both amenable to be detected early via cytology)
Age-specific incidence rates of selected cancers in women in the United States (SEER program 2007-11)
Survival rates for selected cancers in women in the United States (SEER program 1988-2010)
Conclusions and Conjectures

- Vaccination will have an impact on screening test performance and practices.
- Can screening begin later in life, be done less frequently, and be stopped earlier among vaccinated women than among those who were not vaccinated?
- Answer is dependent on society’s tolerance to risk and public health acceptance of low-grade scientific evidence.
- The time will come in ~30 years when we will have to decide if cervical cancer screening should be stopped altogether or be done only once in a lifetime.
- We will not have the luxury of RCT-level evidence for such decisions.
HPV related disease
my remaining research questions in 7 minutes!

Marc Steben
STI Unit
Chair of the National STI committee
www.inspq.qc.ca
## Disclosure Statement

<table>
<thead>
<tr>
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<th>Company/Organization</th>
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<tr>
<td>I am a member of an Advisory Board or equivalent with a commercial organization.</td>
<td>Merck, Genocea, Inovio</td>
</tr>
<tr>
<td>I am a member of a Speaker Bureau.</td>
<td>Merck</td>
</tr>
<tr>
<td>I have received payment from a commercial organization (including gifts or other consideration or ‘in kind’ compensation).</td>
<td>Beckton-Dickinson, Cepheid, Hologic/Gen-Probe, Genocea, Innovio, Merck/Merck Sharp Dohme/Sanofi-Pasteur, Paladin, Roche molecular systems, Valeant.</td>
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<tr>
<td>I hold a patent for a product referred to in the CME/CPD program or that is marketing by a commercial organization</td>
<td>No</td>
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<tr>
<td>I hold investments in a pharmaceutical organization, medical devices company or communications firms.</td>
<td>I own a communication company (Communications Action-Santé Inc.)</td>
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<tr>
<td>I am currently participating in or have participated in a clinical trial within the past two years.</td>
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Vaccine delivery in high income countries
How can we increase HPV vaccine uptake with all we know about it’s safety?
HPV Vaccine Safety

Major agencies endorsing HPV vaccine safety:\textsuperscript{1,2}

World Health Organization (WHO)
Public Health Agency of Canada (PHAC)
Centers for Disease Control and Prevention (CDC)
Food and Drug Administration (FDA)
European Medicines Agency (EMA)
Medicines & Healthcare Products Regulatory Agency of the UK (MHRA)
Therapeutic Goods Administration of Australia (TGA)
International Federation of Gynecology and Obstetrics (FIGO)
International Papillomavirus Society (IPVS)

Merck Data on File, May 3, 2016;
1. Papillomavirus Research 2016 (2):9-10;
20 November 2015
EMA/749763/2015

HPV vaccines: EMA confirms evidence does not support that they cause CRPS or POTS

Reports after HPV vaccination consistent with what would be expected in this age group

EMA has now completed its review of the evidence surrounding reports of two syndromes, complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) in young women given human papillomavirus (HPV) vaccines. These vaccines are given to protect them from cervical cancer and other HPV-related cancers and pre-cancerous conditions. In line with its initial recommendations, EMA confirms that the evidence does not support a causal link between the vaccines (Cervarix, Gardasil/Silgard and Gardasil 9) and development of CRPS or POTS. Therefore there is no reason to change the way the vaccines are used or amend the current product information.
Hospital discharge records of children aged 7 to 17 main diagnosis of GBS were analyzed. Age- and sex-specific incidence rates according to HPVV program eligibility were period October 1999 to March 2014.

**Results**
One hundred SGB cases were retrieved and included in the analysis. The total hospitalisation rate for GBS in 7-17 year-olds was 0.73/100 000 person-years. Increasing age and H1N1 pandemic period were significantly associated with higher risk of hospitalisation for GBS. The adjusted relative risk of GBS in the HPVV targeted population (grade 4 and 9 girls) was estimated at 0.86 (95%CI: 0.29-2.26).

**Conclusion:** In Québec, no increase in hospitalisation rates for GBS was observed in HPVV targeted compared to non-targeted cohorts. This study eliminates the possibility of an excess of 1/100,000 GBS case in HPV immunized girls

A total of 70,265 girls and women had at least one of the 49 predefined autoimmune diseases; 16% of these individuals received at least one dose of qHPV vaccine. In unvaccinated girls and women, 5,428 new-onset autoimmune diseases were observed during 245,807 person-years at a rate of 22.1 (95% CI 21.5–22.7) new events per 1000 person-years. In vaccinated girls and women, there were 124 new events during 7,848 person-years at a rate of 15.8 (95% CI 13.2–18.8) per 1000 person-years. There was no increase in the incidence of new-onset autoimmune disease associated with qHPV vaccination during the risk period; on the contrary, we found a slightly reduced risk (incidence rate ratio 0.77, 95% CI 0.65–0.93).
How can we increase HPV vaccine uptake by refuting apprehended negative outcomes?
Effect HPV vaccination on clinical indicators of sexual behaviour among adolescent girls: the Ontario grade 8 HPV vaccine cohort.

«Strong evidence that HPV vaccination does not have any significant effect on clinical indicators of sexual behaviour among adolescent girls»
Not having cervical cancer screening in vaccinated females an issue?

Concerns have been raised that HPV-vaccination might affect women’s cervical cancer screening behaviour. A cohort of 629,703 women born 1977-87 was invited to screening with a follow-up from 10-2006 to 12-2012. Attendance after 3 years of FU, first round of screening:

- 86% in vaccinated cohort
- 75% in unvaccinated cohort

How can we improve the quality of vaccine delivery in healthcare
Best practice guidance //

How to respond to vocal vaccine deniers in public
The method exists
How to pass the skills in our healthcare system?
How can we neutralize the effects of pseudoscience communications

What will it take to stop the pseudoscience to influence parents’/patients’ mind?
This is not only for HPV vaccine!
HPV is seen as the test before more STI vaccines such as HIV, HSV, CT and GC become available
Cancer is not enough to have some people immunized!

How to stop medical exemption growth
Are caregivers really delivering HPV vaccines as recommended?

- Proofs that males and females are not receiving the same infos…
- I see a lot of differences between surveys and action on the ground!
- In an web poll for the Society of Ob-Gyn of Canada
  - Patients seems not informed but willing when informed and
  - Physicians underestimate the patient’s intent to be vaccinated (posters presented in CapeTown)
Are we delivering to those that need it the most?

- Are worried well shadowing the situation for most at risk population
  - Vulnerable women: aboriginals, street-involved, IDU, refugees and immigrants, immunocompromised and HIV+
  - Vulnerable men: MSM HIV- as well as HIV+ and other immunocompromised men...
Are we reaching the optimal return reach on our investment?

- Marc Brisson’s mathematical modeling projected maximum return and benefits would be seen if we adapted our cervical cancer screening

*Conclusion:* Vaccinating adolescent girls against HPV is likely to be cost-effective. The main benefit of vaccination will be in reducing CC mortality. However, unless screening is modified, the treatment costs saved through vaccination will be insignificant compared to the cost of HPV immunization.
We will cause more harm than benefit if we do not change our screening paradigm!
New screening paradigm

Vaccinated women should start screening at age 30, instead of 25, with HPV test. Furthermore, there is a strong rationale for applying longer intervals for re-screening HPV negative women than the currently recommended 5 years, but research is needed to determine the optimal screening time points.

For non-vaccinated women and for women vaccinated in their fifteenth year or later, the current protocol should be kept

http://dx.doi.org/10.1016/j.ypmed.2016.11.020
Vaccine delivery in low and middle income countries
The future of politics

How are politicians going to make preventive care decisions where long-term effects do not match politicians electoral interests?

Where will vaccines make the list of funded preventive measures?
Will we flatly accept that we are loosing the communication war?

“I’m sorry, Jeannie, your answer was correct, but Kevin shouted his incorrect answer over yours, so he gets the points.”
When will see the benefits of HPV vaccine in LMIC?
4vHPV Vaccine: Systematic Review of 10 Years of Real-world Experience

Cervical cancer claims younger lives than most cancers

Cx Ca is second to only breast cancer as the leading cause of cancer in women worldwide.¹

- Global prevalence: ~2.3 million
- Global incidence: ~500,000

GLOBOCAN about cx ca deaths in LMIC

- 2002 = >80% of cx ca deaths
- 2008 = 88%
- And by 2030 = >98%

Nearly every minute of every day a woman is diagnosed with cx ca

Where is cervical cancer risk the worst?

1.1 CURRENT CERVICAL CANCER MORTALITY RATE
ESTIMATED AGE-STANDARDIZED MORTALITY RATE PER 100,000, CERVIX UTERI

The misdistribution of preventive resources!
The future of HPV prevention for LMIC

• We need
  • To create the business plan
  • And to get the funding
• Why can’t we be part of the Global fund with HIV, malaria and TB?
• The technologies are here to prevent HPV and the major complications
• Will get the support from funding agencies?
Conclusion

- My main research questions are about communication and allocation of resources
- How to be more effective
When will we see coverage rates similar to other recommended vaccines in our public health programs?
Estimated vaccination coverage for complete schedule
February 13th, 2015

**JOINT POSITION STATEMENT: Safety of Gardasil HPV vaccine**

The Society of Obstetricians and Gynaecologists of Canada (SOGC), the Society of Canadian Colposcopists (SCC), the Society of Gynecologic Oncology of Canada (GOC), and the College of Family Physicians of Canada (CFPC) are releasing this joint position statement to reaffirm that the Gardasil HPV vaccine, based on the very extensive evidence available to us, is safe and that vaccination remains one of the recommended actions for prevention of cervical cancer and other HPV associated diseases.

As professional medical associations, our work is founded on using evidence-based science to guide recommendations for ensuring that patients receive the highest standards of quality care. The Gardasil HPV vaccine has been thoroughly tested and extensive pre- and post-licensure data on the safety of HPV vaccines are available. The Government of Canada’s decision to approve use of HPV vaccination in Canada was based on many clinical trials and studies, all of which concluded that it is safe. Internationally, the safety of HPV vaccination has been reviewed, tested, and approved by the Global Advisory Committee on Vaccine Safety (GACVS) of the World Health Organization (WHO).

The Gardasil HPV vaccine has been used in more than 130 countries, with more than 175 million doses distributed globally. The vaccine has been in clinical use for 8 years and has been found to be both safe and effective in reducing pre-cancers and the high risk HPV lesions that lead to cancers of the cervix, the second most common cancer in girls aged 15-45 years, along with several other HPV-related cancers affecting both men and women.
A review of the safety of Gardasil by Health Canada was triggered by media reports of autoimmune and cardiovascular diseases. The safety review by Health Canada concluded that there is no evidence of an increased risk of autoimmune or cardiovascular diseases. Recent international reports are in line with Health Canada's findings.

Since its authorization in 2006, nearly 2 million Canadians, and more than 63 million people worldwide, have been vaccinated with Gardasil. Approximately 1800 people in Canada, which represents approximately 1 out of 1,000 Canadians, reported side effects following vaccination with Gardasil. These include light-headedness, dizziness, nausea, headache, fever, and pain, swelling or redness at the injection site. The side effects are known and described in the Canadian labelling information. The benefits of using the vaccine outweigh the risks and potential side effects. [http://www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/gardasil-eng.php](http://www.hc-sc.gc.ca/dhp-mps/medeff/reviews-examens/gardasil-eng.php)
Taux d'incidence de SGB et intervalle de confiance selon l'âge et l'exposition des cohortes à la vaccination


Auteurs : Geneviève Deceuninck, Centre de recherche du CHU de Québec-Université Laval; Chantal Sauvageau, Vladimir Gilca, Nicole Boulianne et Gaston De Serres, Centre de recherche du CHU de Québec-Université Laval et Institut national de santé publique du Québec.
Reassuring Patients/Parents About Safety of HPV Vaccines

• The vaccines do not contain any living virus
• More than 175 million doses of the quadrivalent vaccine have been distributed globally
  • 8 million in Canada
• Approximately 7 million doses of the bivalent vaccine have been distributed worldwide
  • 6,473 in Canada
• There is ongoing surveillance by healthcare authorities, companies and registries
• No serious adverse events found to be associated with the vaccine and with no greater risk of adverse events than with placebo
What Is Needed to Prove That HPV Vaccines Induce Autoimmunity?

1. Investigators must show that one or more of the L1 proteins that comprise HPV4 mimic self antigens and that self antigen–specific T or B cells are present in the circulation.

2. Second, self antigens must be present in quantities necessary to evoke autoimmune responses.
   - The HPV4 vaccine contains 20μg, 40 μg, 40 μg, and 20 μg of the L1 proteins from HPV serotypes 6, 11, 16, and 18, respectively. That is not likely to be enough protein to induce autoimmunity.
   - Another way to look at this would be to note the differences between Lyme disease and Lyme vaccine. Lyme disease causes autoimmune arthritis, but Lyme vaccine doesn't, even though the Lyme vaccine contains a protein that mimics a selfantigen. Lyme bacteria replicate in joints, generating large amounts of self proteins. The Lyme vaccine (LYMErix™), on the other hand, contained only 30 μg of the outer surface A protein, which—although it mimicked the LFA1 self antigen—wasn't enough to induce autoimmunity.[5,6]

3. Co stimulatory signals, cytokines, and other activation signals produced by antigen presenting cells like dendritic cells are necessary to drive autoimmune responses.
   - Although live viruses and bacteria can drive these responses at levels necessary to induce autoimmunity, inactivated viruses or purified proteins don't drive these response nearly as strongly—at least not without a powerful adjuvant, like squalene or oil in water emulsions.

4. Peripheral tolerance mechanisms, which the body uses to prevent autoimmune responses from the moment of birth, must fail.

Again, no evidence for breaking tolerance has been shown for HPV vaccines.
Promiscuity is an issue for vaccinated females?

Population-based cohorts

- 2 years before HPV vaccine program (2005-6 and 2006-7)
- 2 years after HPV vaccine program (2007-8 and 2008-9)

**Data on indicators of sexual behaviour**

- Pregnancies
- Non HPV-STI

Effect of HPV vaccination on clinical indicators of sexual behaviour among adolescent girls: the Ontario grade 8 HPV vaccine cohort study. Smith LM et all. CMAJ2015 Feb 3;187(2): E74-E81
Effect HPV vaccination on clinical indicators of sexual behaviour among adolescent girls: the Ontario grade 8 HPV vaccine cohort.

Table 2:
Cumulative risk of outcomes, according to eligibility for Ontario’s quadrivalent human papillomavirus vaccination program and birth year

<table>
<thead>
<tr>
<th>Clinical indicator of sexual behaviour</th>
<th>Program eligibility; birth year; no. (%) of participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ineligible</td>
</tr>
<tr>
<td></td>
<td>1992 (n = 66 653)</td>
</tr>
<tr>
<td>Composite outcome</td>
<td>4 203 (6.3)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>2 854 (4.3)</td>
</tr>
<tr>
<td>STIs</td>
<td>1 609 (2.4)</td>
</tr>
</tbody>
</table>
Promiscuity is an issue for vaccinated boys?

This issue has never brought up by parents!
Not having cervical cancer screening in vaccinated females an issue?

Table 2. Crude and adjusted hazard ratios from the main effects model of screening attendance in HPV-vaccinated women compared to unvaccinated women during the entire study period, and by round 1 and 2 during follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Attendance over entire study period</th>
<th>Attendance to screening round 1</th>
<th>Attendance to screening round 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude HR (95% CI) a</td>
<td>P value</td>
<td>HRadj ≥1 dose (95% CI)b</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>Ref.</td>
<td></td>
<td>Ref.</td>
</tr>
<tr>
<td>HPV-vaccinated</td>
<td>1.28 (1.24–1.32)</td>
<td>&lt;0.0001</td>
<td>1.05 (1.02–1.08)</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>Ref.</td>
<td></td>
<td>Ref.</td>
</tr>
<tr>
<td>HPV-vaccinated</td>
<td>1.31 (1.27–1.35)</td>
<td>&lt;0.0001</td>
<td>1.09 (1.05–1.13)</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>Ref.</td>
<td></td>
<td>Ref.</td>
</tr>
<tr>
<td>HPV-vaccinated</td>
<td>1.26 (1.21–1.32)</td>
<td>&lt;0.0001</td>
<td>1.15 (1.10–1.20)</td>
</tr>
</tbody>
</table>

a Unadjusted hazard ratios (HRs) with corresponding confidence intervals (CIs).
b HRs with corresponding CIs adjusted for income and education. Women were HPV-vaccinated with at least 1 dose.
Will we flatly accept that we are losing the communication war?

Wrong articles attract more attention than true articles!

Why can’t we use the same language and tactics as anti-vaxxer

Spreading wrong information about vaccination is morally and ethically wrong

It equates to denial of care!

Tuskegee, Oslo, Krever inquest… are we just in the same denial mood and leave it to the population’s appreciation
Faut-il vacciner les filles contre le VPH?

Ses convictions :

Faut-il vacciner nos filles contre le VPH? C'est une question que se posent tous les parents, d'autant que la campagne de vaccination touche des petites filles de moins de 13 ans. J'ai personnellement beaucoup travaillé sur le sujet. J'ai d'ailleurs co-préfacé un livre tout récent, La piqure de trop, de Jean-Pierre Spinosa et Catherine Riva, respectivement gynécologue obstétricien et journaliste. L'ouvrage est paru en Suisse, et n'est pas disponible encore dans les librairies du Québec, mais on peut le commander sur les sites de librairies en ligne d'Europe.