110 years of research
10 years of HPV vaccines & HPV vaccination

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Institut Catala d’Oncologia
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Potential conflict of interest

• Research and educational institutional grants: GSK, SPMSD, Merck, Qiagen
• Personal / speaking / travel grants: GSK, SPMSD, Merck, Qiagen, RMS

This presentation is the sole responsibility of the author
European Union HPV-Related Disease Burden, Men and Women: Annual estimations for Cancers (50,000) and precancerous lesions (6M)

- Penile cancer
- Vulva & Vagina Cancer
- Anal Cancer
- Oropharyngeal Cancer
- AIN2/3 + VaIN2/3 + VIN2/3
- Cervical Cancer
- CIN2+
- Genital Warts
- ASCUS+
- Pop ≥ 20y

Europe: 30 countries from European Medicines Agency (Austria, Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Slovakia, Spain, Sweden, UK) + Switzerland. * Estimations assuming 3.5% of ASCUS+ among women aged 25-65 years.

bi-valent HPV vaccine (Cervarix)

- 16 60µg
- 18 40µg

quadri-valent HPV vaccine (Gardasil)

- 6 20µg
- 11 40µg
- 16 40µg
- 18 20µg

nine-valent HPV vaccine (Gardasil 9)

- 6 30µg
- 11 40µg
- 16 60µg
- 18 40µg
- 31 20µg
- 33 20µg
- 45 20µg
- 52 20µg
- 58 20µg

AAHS 250

ASO4-AL

AAHS 500
HPV type-specific contribution to cervical cancer and potential for prevention of existing vaccines

VIRAL TYPES

<table>
<thead>
<tr>
<th>Type</th>
<th>Gardasil</th>
<th>Cervarix</th>
<th>Gardasil9</th>
</tr>
</thead>
<tbody>
<tr>
<td>16+18</td>
<td>71</td>
<td>95+%</td>
<td>95+%</td>
</tr>
<tr>
<td>+31</td>
<td>75</td>
<td>Parcial</td>
<td>95+%</td>
</tr>
<tr>
<td>+33+45</td>
<td>84</td>
<td>95+%</td>
<td>95+%</td>
</tr>
<tr>
<td>+52+58</td>
<td>89</td>
<td>-</td>
<td>95+%</td>
</tr>
</tbody>
</table>

Type specific Vaccine efficacy

Relative Contribution – RC (%)  95% Confidence Interval

- de Sanjosé S et al. Lancet Oncol, 2010
- Serrano B et al. Infect Ag Cancer, 2012
- Schiller J et al Vaccine 30 S 5 2012
- Lehtinen M et al. Nat Rev Clin Oncol. 10 2013
Effectiveness and Impact of 4vHPV Vaccine in Vaccination Programs demonstrated in numerous publications: Selected Reports

Introduction of 4vHPV vaccine

- Czech Republic
- Australia
- Canada
- United States
- Germany
- New Zealand
- Denmark

Cervical Abnormalities

- Fairley (Sex Transm Infect 6)
- Donovan (Lancet Infect Dis 8)
- Oliphant (NZMJ 10)
- Read (Sex Transm Infect 6)
- Baandrup (J Infect Dis 11)
- Ali (BMC Infect Dis 16)
- Wilson (Sex Transm Infect 20)
- Chung (BMJ 1)
- Harrison (PLoS One 22)

Genital Warts

- Leval (J Infect Dis 11)
- Leval (Clin Infect Dis 11)
- Flagg (Am J Public Health 18)
- Nsouli-Maktabi (MSMF 9)
- Liu (Sex Transm Infect 13)
- Smith (J Infect Dis 24)
- *Baldur-Felskov (Cancer Causes Control 30)
- *Baldur-Felskov (JNCI 4)
- *Crowe (BMJ 61)
- *Hariri (Vaccine 34)
- *Herweijer (Int J Cancer 35)

HPV Prevalence

- *Powell (Vaccine 28)
- *Gertig (BMC Med 32)
- *Tabrizi (J Infect Dis 36)
- Markowitz (Lancet Infect Dis 18)
- *Tabrizi (Lancet Infect Dis 18)
- Deleré (BMC Infect Dis 59)
- *Dunne (J Infect Dis 40)
- *Markowitz (Pediatrics 41)

*Study links effectiveness data to vaccination status.
*Includes reports published in the peer-reviewed scientific literature, and does not encompass reports at scientific conferences.
Beginning on February 1, 2016 the childhood vaccination program switched to the 2vHPV vaccine. 
Meta-analysis of data from 20 studies in 9 countries (United States, Australia, England, Scotland, New Zealand, Sweden, Denmark, Canada, and Germany), including both 4vHPV vaccine and 2vHPV vaccine.
OUTCOME HPV INFECTIONS

STI registries and serum banks in Sweden. Specimens tested for HPV before and after HPV vaccine introduction
HPV16 prevalence according to age in genital swabs with or without urine from women.

Outcome: Genital warts
Declines in under 21 years of age: women from 18.6% to 1.9% heterosexual men from 22.9% to 2.9%
Around 93% reduction of GW – this has been seen also in other countries
OUTCOME: CIN 3 - CARCINOMA IN SITU
Decline in pre-cancer now impacting up to 30 years

Figure 1: Trends in prevalence rates of high grade histologically confirmed cervical abnormalities (CIN2+) diagnosed in Victorian women, Australia, by age group, 2000-2014

Expected results 2017 +

- Reduction of *cervical cancer* (2/3 years)
- Reduction in *RRP* (in 4 / 9 valent vaccine users)
- Reduction on *other HPV related cancers* (vulva, vagina, anal, oropharynx) (at least one decade)
- Reduction of *other cancers* (?)
THE ANTI HPV VACCINE SPECIFICITY

Trump taps vaccine skeptic Robert F. Kennedy Jr. to launch review

President-elect Trump has some doubts about the current vaccine policy, Kennedy says

Thomson Reuters  Posted: Jan 10, 2017 2:57 PM ET  |  Last Updated: Jan 11, 2017 8:44 AM ET
General considerations

• HPV vaccines have arrived at a time in which concerns about safety, surveillance and vaccination programs are of great importance.
  o i.e. crisis with the avian flu vaccines, rotavirus, adjuvants, other.

• Generalized adolescent vaccination is relatively new in the calendar.
  o Group psychogenic responses (Australia, Colombia, Spain).
  o Limited tradition in vaccinating adolescents (i.e. school vs clinics)

• Social image of public institutions and corporations (even WHO) is under scrutiny and significant challenge.
General considerations (2)

• **HPV vaccines** have a special aura:

  o *Long interval* between exposure and disease. Distorted perception of risk over time. Pediatricians *vs.* gynecologists *vs.* oncologists
  o *Sexual behavior* connotations, ethical considerations, religious involvement.
  o *One gender* vaccination recommendations.
  o *New technology* in manufacturing.
  o Very active *anti-vaccine* movements; internet amplified.
Reports of the global committee on safety of vaccination in relation to the HPV vaccine (GACVS 2007/15) / Strategic Advisory Group of Experts in immunization (SAGE)

- **Doses:**
  - 2006: 60M
  - 2007: 109
  - 2008: 175M
  - 2009: 130
  - 2010: 200M

- **Countries:**
  - 2006: 2000
  - 2007: 2000
  - 2008: 2000
  - 2009: 2000
  - 2010: 2000

- **Events:**
  - Post introduction evaluation
  - Syncope
  - Anaphylaxis
  - Massive psychogenic reaction
  - Autoimmunity
  - Venous tromboembolism
  - Premature ovarian failure
  - Chronic regional pain syndrome
  - Vasculitis CNS
  - Guillen Barre
  - Orthostatic postural tachycardia POTS
  - Aluminum
  - Multiple sclerosis
Incidence of new-onset autoimmune disease in girls and women with pre-existing autoimmune disease after quadrivalent human papillomavirus vaccination: a cohort study

O. Grönlund¹, E. Herweijer¹, K. Sundström² & L. Arnheim-Dahlström¹

From the ¹Department of Medical Epidemiology and Biostatistics, Karolinska Institutet; and ²Department of Laboratory Medicine, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden

70,265 women (10-30) with one of 49 pre specified autoimmune diseases (AID) in 2006-12: 16% received at least one dose of HPV vaccine in Sweden

Incidence of second AID in vaccinated: 15.8 x 1000 py
Incidence of second AID in non vaccinated: 22.1 x1000 py
Cumulative incidence (%) of autoimmune diseases in recipients of 1 dose of 4vHPV vaccine compared to an aged matched non-vaccinated group. 1-year follow up IRR: 0.77 (0.65-0.93) p=0.006
## HEALTH PROFILE ASSOCIATED WITH REPORTED SIDE EFFECTS AFTER VACCINATION: DENMARK LINKAGE STUDY

<table>
<thead>
<tr>
<th>2 year before vaccination</th>
<th>Multivariate OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultation GP/Other</td>
<td><strong>1.91</strong></td>
<td>1.15 - 3.16</td>
</tr>
<tr>
<td>Physiotherapy / chiropractor /related treatments</td>
<td><strong>2.13</strong></td>
<td>1.64 - 2.76</td>
</tr>
<tr>
<td>Psychologists / psychiatrists / related treatments</td>
<td><strong>1.87</strong></td>
<td>1.31 - 2.66</td>
</tr>
<tr>
<td>Hospital contact / digestive</td>
<td><strong>1.57</strong></td>
<td>1.01 - 2.45</td>
</tr>
<tr>
<td>Hospital contact / musculoskeletal and connective</td>
<td><strong>1.56</strong></td>
<td>1.09 - 2.23</td>
</tr>
<tr>
<td>Hospital contact / ill defined</td>
<td><strong>1.77</strong></td>
<td>1.27 - 2.48</td>
</tr>
<tr>
<td>Hospital contact / injuries</td>
<td><strong>1.51</strong></td>
<td>1.18 - 1.93</td>
</tr>
</tbody>
</table>
Communication (content and media) are increasingly important and a novel field for the conventional researchers
POTENTIAL NEW INDICATIONS FOR HPV VACCINATION / SCREENING

PROPHYLACTIC (prevent new infections and transmission)
- Adult women
  - To 26, 30, 45+...
- Males
  - To 18, 50+...
- Infants (EPI)
- Two/One doses

AS PART OF THERAPY (interrupt reinfections and prevent transmission)
- HPV + women found in screening
- Post treatments in CIN lesions
- RRP
- GW and survivors of HPV related cancers
- Therapeutic / mixed vaccines

HIGH RISK GROUPS (selective vaccination)
- HIV cohorts / MSM
- Transplants & immunosuppressed
- Autoimmune patients
- STI clinics
- Partners of HPV+
- Migrants / marginal
- Abused children
Searching for the right combinations of vaccination and screening for cervical cancer prevention: The HPV FASTER project

FX Bosch
Institut Catala d’Oncologia
NEW OPTIONS UNDER RESEARCH FOR A NON-INFERIOR LIFETIME PROTECTION

Women 25-65

ONE HPV SCREENING

♣ Two doses
♣ One dose
♣ First dose with first screen

X 5 / 7 / 10y
At each round 3-5% follow up required

1 / 2 visits?

7 to 9 visits

Both arms should offer similar level of high protection

BUT

Much lower global costs
Greater compliance (2 / 3 visits)
Lower burden on the clinical health services

Only opportunity

Individual option
Two doses vs. Three doses

- Price reduction of the program
  - Logistics simplification
- Improve vaccination coverage
Immunogenicity: 9–25 years, seronegative at baseline

(ATP immunogenicity cohort, Month 24)

- All subjects were seropositive one month after vaccination (Month 7) and up to Month 24 for both antigens

ATP = according to protocol, GMT = geometric mean titre, error bars represent 95% confidence intervals
Antibody kinetics

(AtP immunogenicity cohort, Month 24)

- Antibody kinetics were similar between the 2-dose M0,6 (9–14 years) and 3-dose M0,1,6 (15–25 years) groups.

ATP = according to protocol, GMT = geometric mean titre, natural infection = subjects who had cleared infection had GMTs of 29.8 (HPV-16) and 22.7 EL.U/mL (HPV-18) in Study HPV-008; plateau = GMTs at the plateau level in Study HPV-007 (Month 45–50 time point) were 397.8 (HPV-16) and 297.3 EL.U/mL (HPV-18).
### FDA Approvals:

<table>
<thead>
<tr>
<th>Vaccine type</th>
<th>Female</th>
<th>Male</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cervarix</strong>¹</td>
<td>Cervix</td>
<td>No indication</td>
<td>9 – 25 years</td>
</tr>
<tr>
<td><strong>Gardasil</strong>²</td>
<td>Cervix, Vulva, Vagina, Anal, Genital Warts</td>
<td>Anal, Genital Warts</td>
<td>9 – 26 years</td>
</tr>
<tr>
<td><strong>Gardasil 9</strong>³</td>
<td>Cervix, Vulva, Vagina, Anal, Genital Warts</td>
<td>Anal, Genital Warts</td>
<td>9 – 26 years</td>
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### EMA Approvals:

<table>
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<th>Vaccine type</th>
<th>Female</th>
<th>Male</th>
<th>Age</th>
</tr>
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<tbody>
<tr>
<td><strong>Cervarix</strong>⁴</td>
<td>Cervix, Vulva, Vagina, Anal</td>
<td>Anal</td>
<td>&gt; 9 years</td>
</tr>
<tr>
<td><strong>Gardasil</strong>⁵</td>
<td>Cervix, Vulva, Vagina, Anal, Genital Warts</td>
<td>Anal, Genital Warts</td>
<td>&gt; 9 years</td>
</tr>
<tr>
<td><strong>Gardasil 9</strong>⁶</td>
<td>Cervix, Vulva, Vagina, Anal, Genital Warts</td>
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<td>&gt; 9 years</td>
</tr>
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## Posology of HPV Vaccines

<table>
<thead>
<tr>
<th>VACCİNE TYPE</th>
<th>FDA</th>
<th>EMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervarix(^{1,4})</td>
<td><strong>3 Doses</strong>&lt;br&gt;(0, 1, 6 months)</td>
<td>9-14 Years: <strong>2 Doses</strong>&lt;br&gt;The second dose given between 5 and 13 months after the first dose*&lt;br&gt;<strong>+15 Years:</strong> <strong>3 Doses</strong>&lt;br&gt;(0, 1, 6 months)</td>
</tr>
<tr>
<td>Gardasil(^{5})</td>
<td><strong>3 Doses</strong>&lt;br&gt;(0, 2, 6 months)</td>
<td>9-13 Years: <strong>2 Doses</strong>&lt;br&gt;(0, 6 months)*<strong>&lt;br&gt;+14 Years: <strong>3 Doses</strong>&lt;br&gt;(0, 2, 6 months)</strong>**</td>
</tr>
<tr>
<td>Gardasil 9(^{6})</td>
<td><strong>3 Doses</strong>&lt;br&gt;(0, 2, 6 months)</td>
<td>9-14 Years: <strong>2 Doses</strong>**&lt;br&gt;The second dose should be administered between 5 and 13 months after the first dose&lt;br&gt;<strong>+15 Years:</strong> <strong>3 Doses</strong>&lt;br&gt;(0, 2, 6 months)****</td>
</tr>
</tbody>
</table>

* If the second vaccine dose is administered before the 5th month after the first dose, a third dose should always be administered
** If flexibility in the vaccination schedule is necessary, the second dose can be administered between 1 month and 2.5 months after the first dose and the third dose between 5 and 12 months after the first dose
*** If the second vaccine dose is administered earlier than 6 months after the first dose, a third dose should always be administered
**** The second dose should be administered at least one month after the first dose and the third dose should be administered at least 3 months after the second dose. All three doses should be given within a 1-year period
***** If the second vaccine dose is administered earlier than 5 months after the first dose, a third dose should always be administered.
MALE HPV VACCINATION:

Further increase protection of women by interrupting transmission protect vaccinated males against hpv-induced cancers
## QUADRIVALENT HPV VACCINE EFFICACY STUDIES IN MEN

<table>
<thead>
<tr>
<th>Vaccine efficacy against EGL, (mostly GW) in men</th>
<th>Vaccine efficacy against anal intraepithelial lesions in MSM</th>
</tr>
</thead>
<tbody>
<tr>
<td>90.6% (70-98)</td>
<td>77.5% (40-93)</td>
</tr>
<tr>
<td>Giuliano <em>et al</em>. NEJM 2011 Per protocol cohorts</td>
<td>Palefsky <em>et al</em>. NEJM 2011 Per protocol cohorts</td>
</tr>
</tbody>
</table>
COST BENEFIT BALANCE: GENERAL CONSIDERATIONS

Include males

• Recognition of the HPV etiology of significant number of cancers in males
• Impact of GW’s & global burden of disease / health services requirements
• Trends in sexual practices in many countries
• Interrupting the transmission chain to other partners
• Powerful herd effects and program resilience if both genders are included

Australia, US, Canada, Austria

Women only

• Highest burden of severe disease is in women
• Herd immunity may be sufficient if high female vaccination rates are achieved (stable populations)
• High cost of the vaccine
HPV vaccination coverage estimates in Australia for boys aged 15

- ACT: 66.9%
- NSW: 63.8%
- NT: 62.0%
- QLD: 67.4%
- SA: 67.3%
- TAS: 59.0%
- VIC: 71.3%
- WA: 62.9%
- NAT: 66.4%
Potential roles of pediatricians in HPV vaccination

- **Safety net** for female routine vaccination campaigns
  - Identify non / insufficiently vaccinated girls (30%+)
  - Vaccination catch up (*sisters and boys*)
- **Awareness** on the vaccination offer: what protection is granted (HPV) and what protection is not offered (HSV…)
- Introduction of **screening** practices (in collaboration with gynecologists)
- Permanent **safety** vigilance
- General advice to **families** (vaccination of adult women & mothers)
Gracias colegas