PREVENTION AND CONTROL OF HPV AND HPV RELATED CANCERS: THE DANISH EXPERIENCE

New Year's Lectures 2018 of the Austrian Chapter of the American Society for Microbiology (ASM)

Palle Valentiner-Branth, MD, PhD, Head of vaccine preventable diseases group, Department of infectious disease epidemiology and prevention
CERVICAL CANCER IN DENMARK-STATISTICS

- ~370 cases every year
- ~100 deaths every year
- Life time risk cervical cancer 1%
- Incidence 12/100.000/year in 2012, Austria 7, Source International Agency for Research on Cancer (IARC), France
- Uptake cervical screening 75% (number of cases of cervical cancer in the 60’s were 900 per year)

Cervical cancer 1997-2011, Baldur-Felskov et al. CCC 2015
There is a decrease in squamous cervical cancer (SCC) which is driven by women above 45 y but no decrease in those <45 y and there is a rise in adenocarcinoma (AC) driven by those <45 y- cohort effect
The family destroyer

Aldersspecifik incidens af celleforandringer 1997-2011

Baldur-Felskov et al. CCC 2014
THE SUCCESSFULL START OF THE PROGRAM

- 2007: Health technology assessment recommends a girls-only vaccination program
  - Additional recommendation of creating a national immunization registry
- 2008: Catch-up program girls < 15 years
- 2009: Routine vaccinations starts
- 2012-13: 2nd catch-up program (young women 1985-1992, up to 27 years)

- HPV1 vaccine > 90% in birth cohorts 1997 to 2000
  - Completed vaccination ranges from 77 to 80 % in those cohorts
  - Nearly 1 out of 4 of all Danish women has received at least one dose

- Impact can be seen at the population level

A success story for public health!
In the period there was an increase in CIN3 and AIS but in women less than 20 y there was a decrease in 2009-12.
Half-yearly IRs of GWs per 100,000 person-years in Denmark between 2006 and 2013, stratified by sex and age

# Quadrivalent HPV vaccine effectiveness against high-grade cervical lesions by age at vaccination: A population-based study

Eva Herweijer¹, Karin Sundström², Alexander Ploner³, Ingrid Uhnoo⁴, Pär Sparén⁵ and Lisen Amhelg-Dahlström⁶

## Table 3. IRRs comparing fully vaccinated individuals with unvaccinated individuals by age at vaccination initiation in the total population for CIN2+ and CIN3+

<table>
<thead>
<tr>
<th>Age at vaccination initiation</th>
<th>CIN2+</th>
<th></th>
<th></th>
<th></th>
<th>CIN3+</th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Person-years</td>
<td>IR (95% CI)²</td>
<td>IRR (95% CI)²</td>
<td>p values</td>
<td>Person-years</td>
<td>IR (95% CI)²</td>
<td>IRR (95% CI)²</td>
<td>p values</td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>6,647,642</td>
<td>336 (331;340)</td>
<td>Reference</td>
<td></td>
<td>6,688,615</td>
<td>187 (184;190)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>≤16y</td>
<td>441,315</td>
<td>7 (5;11)</td>
<td>0.25 (0.18;0.35)</td>
<td>&lt;0.001</td>
<td>441,355</td>
<td>2 (1;4)</td>
<td>0.16 (0.08;0.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>17–19y</td>
<td>138,960</td>
<td>100 (85;118)</td>
<td>0.54 (0.46;0.64)</td>
<td>&lt;0.001</td>
<td>139,156</td>
<td>37 (28;49)</td>
<td>0.43 (0.33;0.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>20–29y</td>
<td>24,179</td>
<td>513 (430;612)</td>
<td>0.78 (0.65;0.93)</td>
<td>0.006</td>
<td>24,644</td>
<td>268 (210;341)</td>
<td>0.75 (0.59;0.95)</td>
<td>0.019</td>
</tr>
</tbody>
</table>

¹Crude IRs reported per 100,000 person-years.

²IRRs reported were stratified on age at vaccination initiation, and adjusted for attained age, and parental education.
From 2013: Danish Medicines Agency received an increasing number of reports of suspected adverse events (AE)
- 2320 adverse events 2009-2016, of which 1023 were classified as severe
  - Persistent or significant incapacity
- Only 10% of the 488 reports received in 2015 had onset in 2015

Source: Danish Medicines Agency
THE CLINICAL PICTURE

_medically unexplained physical symptoms_
- Symptoms from the nervous systems ("autonomic dysfunctions")
  - Including dizziness, syncope, weakness, headache, disordered sleep
- Fatigue
- Pain
- Musculoskeletal symptoms

_some received the diagnosis POTS – postural orthostatic tachycardia syndrome_
- Mainly from one medical centre (equipped with a tilt table)
From Brinth L et al, Dan Med J 2015

53 patients seen at one centre

Considerable overlap in symptoms between POTS and Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME)
THE FALL: INITIATION PER BIRTH COHORT

Uptake of first HPV-vaccine by year of birth, females, 1993-2005 (September 2017)
Uptake of first HPV vaccine per birth cohort (September 2017, girls only)
THE FALL: WHAT WENT WRONG

- The strong power of stories (versus numbers/evidence)
- The media (television and written media)
- The internet and social media (Facebook)
- The "victims" became recognised by official Denmark
  - Five "HPV centres" were created ("one entrance")
- Public health authorities and scientist were at a loss
  - Discourse driven by safety concern
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  - Five ”HPV centres” were created (”one entrance”)
- Public health authorities and scientist were at a loss
  - Discourse driven by safety concern
- Large shares of the population lost the trust
  - Do you actually recommend the vaccine any more ?
- Consequently:
  - Health professionals lost the trust, or
  - Were not prepared for communication (listen and talking)
- The challenge represents a ”wicked problem”, i.e., a multifaceted complex problem
When men define things as real, they are real in their consequences

The Thomas theorem
Actress Mira Wanting dies of cervical cancer, 34 years of age, in 2012

Girls who are victims from vaccinations and doctors who are at a loss
Reporting of adverse events: Stimulated by the program “The Vaccinated Girls” broadcasted 26 March 2015, by TV2

Features interviews with families and vaccinated girls with medically unexplained symptoms.
Nyheder fra HPV-update

8. april 2016 — Skriv kommentar

Vi har netop udsendt nyhedsbrev til medlemmerne af HPV-update med nyt om forskning, erstatningssager og andet om Dansk Handicap Forbund og specialkredsens arbejde.

Der er desværre mange medlemmer, der ikke har opgivet deres mailadresser i forbindelse med indmelding i specialkredsen, så har du ikke modtaget vores nyhedsbrev, så skriv til mail@hpvupdate.dk

Der er også plads til dig

Selvom tilgangen af medlemmer er stor, så er der fortsat plads til flere. Så vil du støtte vores indsats for udredning og behandling af piger med symptomer efter HPV-vaccinen, og drage fordel af de mange tilbud, vi får som specialkreds under Dansk Handicap Forbund, så kan du tilmelde dig her.
Liselott Blixt affejer HPV-rapport: »Lavet af betalt lobby«

På trods af EMA-kritik stoler DF's udvalgsformand stadig fuldt ud på dansk HPV-center.
Written media coverage (red curve) and HPV 1 vaccination activity (blue curve)

Vertical line marks the tipping point in Pearson´s correlation
Trends in on-line searches

Searches for "HPV vaccine" and "HPV vaccine adverse events"

- Gratis HPV-vaccination til kvinder født i 1985-1992 indføres, august 2012
- Mira Wanting dør af livmoderhalskræft, december 2012
- Artikelserie om HPV, BT, august 2013
- De vaccinerede piger TV2, marts 2015
- Praktiserende læge Stig Gerdes advarer mod HPV-vaccination, Facebook & artikler, august 2015
- Mira Wanting dør af livmoderhalskræft, december 2012
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RESPONSE BY AUTHORITIES AND SCIENTIST

- Research

- Individual reminders sent to parents with children who lacks vaccines

- A campaign STOP HPV was launched May 2017
  - Informed by research
  - Mixed methods approach
    - To get focus back on prevention of cervical cancer
Baseline for immune mediated adverse events and cohort study among vaccinated and unvaccinated

Human papillomavirus immunisation of adolescent girls and anticipated reporting of immune-mediated adverse events

Torbjörn Callréus, Henrik Svanström, Niels Munk Nielsen, Sigrid Poulsen, Palle Valentin-Ranth, Anders Hvid

http://doi.org/10.1016/j.vaccine.2009.02.106

Abstract

Determining incidence rates of potential adverse events before and after an immunisation programme is initiated, provides a useful framework for the evaluation of vaccine safety concerns. Human papillomavirus vaccination (HPV) of adolescent girls has recently been introduced in Denmark. Using a nationwide hospitalisation registry we estimated incidence rates of immune-mediated disorders before HPV vaccination in a cohort of 418,289 Danish girls aged 12–15 years. We further estimated the expected number of cases of immune-mediated disorders occurring in temporal relationship to a hypothetical HPV vaccination schedule purely by chance. Our results and analytical approach provides a framework for the evaluation of adverse event reports following immunisation of adolescent girls.

Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study

Lisen Arnheim-Dahlström, associate professor, Björn Pasternak, postdoctoral fellow, Henrik Svanström, statistician, Pär Sparen, professor, Anders Hvid, senior investigator

Conclusions This large cohort study found no evidence supporting associations between exposure to qHPV vaccine and autoimmune, neurological, and venous thromboembolic adverse events. Although associations for three autoimmune events were initially observed, on further assessment these were weak and not temporally related to vaccine exposure. Furthermore, the findings need to be interpreted considering the multiple outcomes assessed.
April 2016: A case control study showed excess morbidity among women with perceived adverse events following HPV vaccination. Presented at the Nordic Vaccine Meeting, Reykjavik, April 2016.
CARE-SEEKING BEFORE FIRST VACCINE

- Case-control study
- Cases: 361 females with severe adverse reactions reported to DMA
- Controls: 163,910 matched on municipality, age, year of first HPV vaccine
  - Females
  - Vaccinated
  - No reports of adverse reactions
Table 3. Final multivariable model showing health care-seeking in the two years prior to vaccination in 316 Danish females who reported suspected adverse events to HPV vaccination compared with 163,910 matched controls.

<table>
<thead>
<tr>
<th>Type of contact before first HPV vaccination</th>
<th>Multivariable odds ratio for care-seeking</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultation at primary health care provider by phone or e-mail</td>
<td>1.91</td>
<td>1.15–3.16</td>
</tr>
<tr>
<td>Reimbursement of physiotherapy, chiropractor or related treatment</td>
<td>2.13</td>
<td>1.64–2.76</td>
</tr>
<tr>
<td>Reimbursement of psychologist, psychiatrist or related treatment</td>
<td>1.87</td>
<td>1.31–2.66</td>
</tr>
<tr>
<td>Hospital contact, ICD-10 code K00-K93, the digestive system</td>
<td>1.57</td>
<td>1.01–2.45</td>
</tr>
<tr>
<td>Hospital contact, ICD-10 code M00-M99, the musculoskeletal system and connective tissue</td>
<td>1.56</td>
<td>1.09–2.23</td>
</tr>
<tr>
<td>Hospital contact, ICD-10 code R00-R99, symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified</td>
<td>1.77</td>
<td>1.27–2.48</td>
</tr>
<tr>
<td>Hospital contact, ICD-10 code S00-T14, injuries</td>
<td>1.51</td>
<td>1.18–1.93</td>
</tr>
</tbody>
</table>


http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0162520
Psychiatric conditions and general practitioner attendance prior to HPV vaccination and the risk of referral to a specialized hospital setting because of suspected adverse events following HPV vaccination: a register-based, matched case–control study

Aim: No association between human papilloma virus (HPV) vaccination and numerous diseases has been found. Still, a large number of Danish women are reporting suspected adverse events. Other factors may play a role, and the aim of this study is to examine the association
Table 2 Odds ratio for being referred to an HPV-center according to the use of psychiatric medication, hospitalization due to psychiatric disorder and indication for psychological symptoms 5 years prior to the first vaccine registration in women above 18 years

<table>
<thead>
<tr>
<th>Psychiatric exposures</th>
<th>Cases (N=448)</th>
<th>Controls (N=2,240)</th>
<th>Crude OR</th>
<th>Adjusted OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric medication, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any*</td>
<td>128 (28.6)</td>
<td>379 (16.9)</td>
<td>1.96</td>
<td>1.88 (1.48–2.40)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>33 (7.4)</td>
<td>78 (3.5)</td>
<td>2.22</td>
<td>1.91 (1.22–2.97)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>117 (26.1)</td>
<td>331 (14.8)</td>
<td>2.03</td>
<td>1.96 (1.52–2.52)</td>
</tr>
<tr>
<td>ADHD medication</td>
<td>16 (3.6)</td>
<td>37 (1.7)</td>
<td>2.17</td>
<td>2.06 (1.11–3.81)</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>32 (7.1)</td>
<td>82 (3.7)</td>
<td>2.05</td>
<td>1.88 (1.21–2.92)</td>
</tr>
<tr>
<td><strong>Hospitalization due to a psychiatric disorder, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any*</td>
<td>82 (18.3)</td>
<td>207 (9.2)</td>
<td>2.20</td>
<td>2.13 (1.59–2.86)</td>
</tr>
<tr>
<td>Schizophrenia, schizotypal and delusional disorders</td>
<td>6 (1.3)</td>
<td>16 (0.7)</td>
<td>1.87</td>
<td>1.47 (0.56–3.85)</td>
</tr>
<tr>
<td>Affective disorders</td>
<td>21 (4.7)</td>
<td>53 (2.4)</td>
<td>2.01</td>
<td>1.94 (1.15–3.28)</td>
</tr>
<tr>
<td>Neurotic, stress-related and somatoform disorders</td>
<td>39 (8.7)</td>
<td>95 (4.2)</td>
<td>2.21</td>
<td>2.04 (1.37–3.03)</td>
</tr>
<tr>
<td>Eating disorders</td>
<td>9 (2.0)</td>
<td>23 (1.0)</td>
<td>1.97</td>
<td>1.86 (0.84–4.10)</td>
</tr>
<tr>
<td>ADHDs</td>
<td>4 (0.9)</td>
<td>10 (0.4)</td>
<td>2.00</td>
<td>1.80 (0.54–5.94)</td>
</tr>
<tr>
<td><strong>Indication for psychological symptoms, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Talk therapy</td>
<td>126 (28.1)</td>
<td>406 (18.1)</td>
<td>1.78</td>
<td>1.72 (1.35–2.18)</td>
</tr>
<tr>
<td>Psychometric test</td>
<td>123 (27.5)</td>
<td>410 (18.3)</td>
<td>1.72</td>
<td>1.67 (1.30–2.13)</td>
</tr>
</tbody>
</table>

Notes: *Adjusted for household type and family socioeconomic group. *Some participants use >1 psychiatric medication or have hospitalizations for >1 psychiatric disorder. Abbreviations: ADHD, attention deficit hyperactivity disorder; HPV, human papilloma virus; OR, odds ratio.
REASONS FOR BEING OPTIMISTIC…

🔹 Research
  - A high proportion of "vaccine victims" had symptoms before first vaccine (1,2)
  - Norwegian study showing no association between HPV vaccine and CFS/ME (3)

🔹 In the media
  - Media recognize that they have a responsibility for public health
  - The discourse of fake news helps!

🔹 The campaign
  - Investigators and public health people being active on social media
  - While showing empathy, without confronting,

1. Mølbak K et al. PLoS ONE 2016 11(9): e0162520
Scientists from various disciplines need to understand why this gap was created.

- The answer is provided from sociology, anthropology and psychology
- And that the loss of the power of the experts is a permanent postmodernistic condition

That context is everything

Recognize that a medical approach alone won’t work
- But the medical/epidemiological approach is an important element
HOW TO BRIDGE THE GAP?

- Scientists from various disciplines need to understand why this gap was created.
  - The answer is provided from sociology, anthropology and psychology
  - And that the loss of the power of the experts is a permanent postmodernistic condition

- That context is everything

- Recognize that a medical approach alone won’t work
  - But the medical/epidemiological approach is an important element

- We need to be aware and disseminate
  - of the difference between facts and opinions,
  - between good and bad science,
  - understand how “fake news” can amplify.

- We also need to spend time on the social media, to show empathy, and recognize that research may lead to unplanned findings.
ACKNOWLEDGEMENTS

Kåre Mølbak, SSI

Thank you for your attention!
Andel vaccineret med Human papillomavirus-vaccine (HPV) 1, Fødselsår: 1993-2005, Køn: Kvinder