ISSUES RELATED TO HPV VACCINE ACCEPTANCE: LESSONS FROM THE DANISH HPV VACCINE EXPERIENCE

Palle Valentiner-Branth, MD, PhD
Head of VPD group
Department of Infectious Disease Epidemiology & Prevention
Statens Serum Institut, Denmark

BUILDING TRUST, MANAGING RISK: VACCINE CONFIDENCE AND HUMAN PAPILLOMAVIRUS VACCINATION
7-8 June 2017 - LSHTM, London
IMPLEMENTATION OF HPV PROGRAMMES

HPV vaccine implementation in Denmark

2008 and 2009
- Free HPV vaccination for girls aged 13-15 years (catch-up group) and for girls aged 12 years (routine group), respectively.
- Voluntary uptake under medical prescription (self-payment) for women born in 1985-1992, having to pay for it.

August 27th 2012

December 31st 2013

Currently
- Routine HPV vaccination for girls up to the age of 18 years
HPV VACCINE UPTAKE OF FIRST DOSE BY BIRTH COHORT

Source: www.ssi.dk/data
**TIMELINE**

**Summer 2013**: Report of seven cases of POTS to Danish Medicines Agency (DMA), A signal is raised with EMA

**December 2014**: EMA concludes that a causal relationship between Gardasil and POTS could neither be confirmed nor rejected.

**February 2015**: Case series consisting of 53 persons referred to the syncope unit in Copenhagen was published

**March 2015**: Participates in "The vaccinated girls" – a TV documentary. Recommends a suspension of the programme and notes that especially physically active girls are at risk.

**June 2015**: Clinics in the five Danish Regions where girls who suspects HPV side effects can be referred to are established

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Symptoms suspected to be side effects to vaccination against human papilloma virus. The frequency of the symptoms is given as percentages of patients reporting the given symptom out of all patients included in the descriptive analysis.

- Headache
- Orthostatic intolerance
- Fatigue
- Nausea
- Cognitive dysfunction
- Disordered sleep
- Blurred vision
- Feeling bloated
- Abdominal pain
- Light sensitive
- Involuntary muscle activity
- Neuropathic pain
- Dyspnoea
- Skin problems
- Voiding dysfunction
- Limb weakness
- Constipation
- Diarrhoea
- POTS
- Vascular abnormalities
- Recurrent syncope
- Dry mouth
- Hyperventilation
- Irregular periods
- Dry eyes

POTS = postural orthostatic tachycardia syndrome.
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Reporting of adverse events: Stimulated by the programme “The Vaccinated Girls” broadcasted 26 March 2015, by TV2

Features interviews with families and vaccinated girls with medically unexplained symptoms.
An adverse event report is received for 0.4% of the vaccinated (4 per 1000)

In 2016, only 17 non-serious reports related to vaccinations done in 2016 were received.

<table>
<thead>
<tr>
<th>Year</th>
<th>Total reports</th>
<th>Serious reports *</th>
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<tbody>
<tr>
<td>2009</td>
<td>288</td>
<td>25</td>
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<tr>
<td>2010</td>
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<td>2015</td>
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<td>2016</td>
<td>307</td>
<td>182</td>
</tr>
<tr>
<td>Total</td>
<td>2326</td>
<td>1005</td>
</tr>
</tbody>
</table>

* Seriousness defined according to ICH and EMA criteria: Results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

16.06.2017
July 2015: DMA makes a referral to EMA/PRAC regarding POTS and CRPS.

November 2015: EMA concludes that these conditions are not more common in vaccinated compared to unvaccinated. Head of Parliament health committee response to the EMA-report: The doctors in the committee have connections to the industry and can’t be trusted. The programme should be stopped. She believes that the HPV vaccines causes the reported adverse reactions.

December 2015: Public hearing in the Danish Parliament.

June 2016: 1 million Euro for research projects investigating the alleged side effects: More than half of the these funds were awarded to the syncope unit.

Pre-Vaccination Care-Seeking in Females Reporting Severe Adverse Reactions to HPV Vaccine. A Registry Based Case-Control Study

Kåre Mølbak, Niels Dalum Hansen, Palle Valentiner-Branth

Results
The study included 316 cases who received first HPV vaccine between 2006 and 2014. Age range of cases was 11 to 52 years, with a peak at 12 years, corresponding to the recommended age at vaccination, and another peak at 19 to 28 years, corresponding to a catch-up programme targeting young women. Compared with 163,910 controls, cases had increased care-seeking in the two years before receiving the first HPV vaccine. A multivariable model showed higher use of telephone/email consultations (OR 1.9; 95% CI 1.2–3.2), physiotherapy (OR 2.1; 95% CI 1.6–2.8) and psychologist/psychiatrist (OR 1.9; 95% CI 1.3–2.7). Cases were more likely to have a diagnosis in the ICD-10 chapters of diseases of the digestive system (OR 1.6; 95% CI 1.0–2.4), of the musculoskeletal system (OR 1.6; 95% CI 1.1–2.2), symptoms or signs not classified elsewhere (OR 1.8; 95% CI 1.3–2.5) as well as injuries (OR 1.5; 95% CI 1.2–1.9).

Conclusion
Before receiving the first HPV vaccination, females who suspected adverse reactions has symptoms and a health care-seeking pattern that is different from the matched population. Pre-vaccination morbidity should be taken into account in the evaluation of vaccine safety signals.

September 2016
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 Calleux, Henrik Svanström, Nete Munk Nielsen, Sigrid Poulsen, Palle Valentin-Branth, Anders Hviid

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.
THE "DANISH SIGNAL": QUESTIONS AND CONCERNS

- The signal consisted mainly of medically unexplained physical symptoms in vaccinated girls
- No evidence from analytical studies
  - No studies have demonstrated an increased risk among vaccinated girls compared with unvaccinated
- Difficult to analyse in epidemiological studies
  - CFS/ME and POTS are ill-defined conditions
- Reporting has been stimulated by media attention, social media and "infostorms"
  Data from passive adverse events surveillance are biased
  - Females with suspected adverse reactions has symptoms and a health-care seeking pattern that is different from a matched population. Pre-vaccination morbidity should be taken into account in the evaluation of vaccine safety signals
- Next steps planned:
  A large part of the target population, i.e. mothers of the 12 year old girls are hesitant regarding HPV vaccination. They are affected by histories of adverse events and news media. Many gets all information from social media where the authorities are not very active

Information campaign led by Danish Health Authority is now launched
Ny informationsindsats om forebygning af livmoderhalskræft og HPV-vaccination

Sundhedsstyrelsen står sammen med Kræftens Bekæmpelse og Lægeforeningen bag en informationsindsats, der skal levere information til borgere og sundhedsprofessionelle om forebygning af livmoderhalskræft og HPV-vaccination.

Vi bakker op om HPV-vaccination:

Duration two years, facebook, youtube, short movies, homepage, information material to GP’s. HPV vaccination is supported by a broad group of health persons and patient groups
THANK YOU TO

- SWEDEN (TIIA LEPP)
- NORWAY (LILL TROGSTAD)
- FINLAND (HANNA NOHYNEK)
- ICELAND (THOROLFUR GUDNASSON)