Vaccination and Narcolepsy
Causal or Not?

Hanna Nohynek
Advanced Course in Vaccinology
Annecy 30 May 2016
MD PhD clinical trials vaccinologist with special competence in international health
FTM RCGFTM

\[ VE = 1 - RR \]

Since 8 / 2010 Chief physician THL
Sweden opens inquiry into suspect flu vaccine

AFP / STOCKHOLM — Sweden's Medical Products Agency opened an inquiry Wednesday into vaccinations for swine flu made by British pharmaceutical company GlaxoSmithKline, suspected of provoking narcolepsy.

"The MPA has received six reports from health care professionals regarding narcolepsy as suspected adverse drug reaction following Pandemrix flu vaccination," it said in a statement.

"The agency will, in consultation with external experts, assess the possible relationship between the vaccination and the reported reactions."
The only pandemic vaccine available for Finland in 2009 = Pandemrix\textsuperscript{R} =A(H1N1) virusantigen and AS03 adjuvant

EMA licensed; Safety profile acceptable in Phase II

A similar AS03 adjuvanted vaccine Arepanrix\textsuperscript{R} used in Canada
Narcolepsy-cataplexy
ICSD-2 2005, ICD10 G47.4
rare chronic disease, 1/100 000

A. Excessive day time sleepiness >3 mo, daily

B. Cataplexy (= abrupt temporary loss of muscle tension in association with emotional / tense situations)

C. Diagnosis confirmed with polysomnography and multiple sleep latency test MSLT / alternatively Li-hypocretin (orexin) concentration ≤110 pg/mL

D. No other better explanation
Peak age at onset is ~15 years of age. But diagnosis is often delayed.
## Clinical forms of narcolepsy

<table>
<thead>
<tr>
<th></th>
<th>Prevalence among narcoleptic patients</th>
<th>HLA DQB1*0602 positive</th>
<th>Li-Hypocretin / Orexin Low ≤110 pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narcolepsy - cataplexy</td>
<td>&gt;50 %</td>
<td>&gt; 90 %</td>
<td>&gt; 90 %</td>
</tr>
<tr>
<td>Narcolepsy without cataplexy</td>
<td>10-50 %</td>
<td>41 %</td>
<td>10-21 %</td>
</tr>
<tr>
<td>Symptomatic narcolepsy(^1)</td>
<td>116 patients (review)</td>
<td>17 %</td>
<td>most</td>
</tr>
<tr>
<td>Population</td>
<td>-</td>
<td>11-35 %</td>
<td>0</td>
</tr>
</tbody>
</table>

ICSD-2 2005; \(^1\)Nishino and Kanbayashi 2005; Knudsen et al. 2010; Ritchie et al. 2010

According to Hublin 2010

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2016-05-30  Vacc&Narcolepsy / HNohynek
DQB1*0602

Image from Solberg et al. (2008) – see www.pypop.org/popdata for more info.
Etiology of narcolepsy?
The multifactorial model
So what happened?
Sweden opens inquiry into suspect flu vaccine

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"The MPA has received six reports from health care professionals regarding narcolepsy as suspected adverse drug reaction following Pandemrix flu vaccination," it said in a statement. "The agency will, in consultation with external experts, assess the possible relationship between the vaccination and the reported reactions."
Those vaccinated in specific age groups as indicated

Laboratory confirmed A(H1N1) cases
Exposure
The number of Pandemrix\textsuperscript{R} vaccinated in Finland

Number of vaccinated

Vaccine coverage, %

Years of age

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Is there a signal? Based on hospital discharge register data

Years of observation

Narcolepsy cases by age and calendar time

<table>
<thead>
<tr>
<th>Age groups</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-19 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Expected = 1 / 100 000
Observed = 8 / 100 000
ROKOTEKNOLOGIJA
VAIETTU

PUSKAN PIIIKKI

NANOTEKNOLOGIJA
NARKOLEPSIA?!
Are others seeing a signal? Should we alert others?

How many individuals in the susceptible age group were exposed?

<table>
<thead>
<tr>
<th>Country</th>
<th>Pandemrix&lt;sup&gt;R&lt;/sup&gt; Doses given to 4-19 yr old</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden</td>
<td>~1 000 000</td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>668 000</td>
<td></td>
</tr>
<tr>
<td>Ireland</td>
<td>339 312</td>
<td></td>
</tr>
<tr>
<td>Norway</td>
<td>470 000</td>
<td>5-18 year olds</td>
</tr>
<tr>
<td>France</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>~700 000</td>
<td></td>
</tr>
<tr>
<td>Great Britain</td>
<td>~295 000</td>
<td>5-16 year olds</td>
</tr>
<tr>
<td>Canada, entire country</td>
<td>~1 200 000</td>
<td>Pandemrix-like, Arepanrix&lt;sup&gt;R&lt;/sup&gt;</td>
</tr>
<tr>
<td>Canada, Quebec</td>
<td>793 448</td>
<td>5-18 year olds</td>
</tr>
</tbody>
</table>

Kilpi et al. ESPID2011
Studies initiated to verify signal

- In Sweden
- In Finland
- The European Medical Agency EMA
  - ECDC contracted the VAESCO consortium study in 8 European countries,
  - GSK contracted a study in Canada with Arepanrix®
VAESCO background rates

Figure 3: Pooled incidence rates and secular trends over last 10 years in Europe
In Finland, Retrospective cohort study
Materials and methods (1)

- Cohort = born ≥1991 & officially living in Finland
- Primary follow up period 1.1.2009 - 16.8.2010
- Variables entered into analysis
  - Pandemrix\textsuperscript{R} vaccination
  - Onset of narcolepsy
- Pandemrix vaccination records systematically collected from primary health care
- 1000 vaccination records validated
Retrospective cohort study
Materials and methods (2)

- Listings of all newly diagnosed narcoleptic cases (ICD10 code G47.4) registered during years 2009-10 in the central hospital registers
- Two sleep medicine experts independently of each other reviewed all the patient records of these cases
- Brighton Collaboration narcolepsy-cataplexy diagnostic criteria were used (Poli F et al. Vaccine 2013)
- Disagreement solved by a panel of 3 other sleep medicine experts = final decision
Narcolepsy
Brighton Collaboration case definition

• Level 1
  – Excessive daytime sleepiness and/or suspected cataplexy AND
  – CSF hypocretin-1 deficiency

• Level 2
  – Excessive daytime sleepiness AND
  – Definite cataplexy AND
  – Level 1 or 2 MSLT abnormalities

• Level 3
  – Excessive daytime sleepiness AND
  – Level 1 MSLT abnormalities
  – Absence of other mimicking disorders

Levels 1-3 included as cases
? Time of onset of the disease?

- Onset of symptoms EDS
- First contact to healthcare
- Referral to specialist care, MSLT
- Diagnosis G47.4
Retrospective cohort study final results

Onset time differences related to date of vaccination

Diagnosis

Referral to a specialist

Referral

First contact to health care

First contact

Parent/patient recall

EDS

(Confirmed cases with recalled onset after vaccination)
Relative risk of narcolepsy among Pandemrix vaccinated vs. not vaccinated in Finland
Register linkage, retrospective cohort study

<table>
<thead>
<tr>
<th>Follow-up period</th>
<th>Narcolepsy cases</th>
<th>Follow-up years</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not vacc</td>
<td>Vacc</td>
<td>Not vacc</td>
</tr>
<tr>
<td>First contact: 2009-01-01 to 2010-12-31</td>
<td>7</td>
<td>57</td>
<td>1069247</td>
</tr>
<tr>
<td>First contact: 2009-01-01 to 2010-08-15</td>
<td>7</td>
<td>46</td>
<td>986195</td>
</tr>
</tbody>
</table>

Vaccine attributable risk for developing narcolepsy
= 6 / 100 000 among those vaccinated 4-19 years of age
= 1 / 16 000

THL Final Report 31.8.2011
Nohynek et al. PLOS One 2012
MPA Sweden press release on association

Adolescent vaccinations and narcolepsy onset in calendar time

- **Week**: 1-48
- **Frequency of vaccinated**: 0-20,000
- **Narcolepsy cases**: 0-7

**Legend**:
- Green: Vaccinated with Pandemrix
- Pink: Narcolepsy onset based on excessive daytime sleeping, 1st contact to health care, referral to specialist, date of diagnosis

- **EDS**: Vaccination spikes coincide with narcolepsy cases.
- **1st contact**: Similar pattern.
- **Referral**: Narcolepsy cases follow vaccination.
- **G47.4**: Narcolepsy onset.

2016-05-30
Vacc&Narcolepsy / HNohynek
Dear Dr. Nohynek,

… After a detailed and long discussion, the feeling among the rest of the editorial board was that it is best to let go the two narcolepsy papers due to lack of known mechanism to explain it and recall bias. I am so, so very sorry….

The official Lancet email will be arriving shortly.

BMJ – also NoGo
AS03 Adjuvanted AH1N1 Vaccine Associated with an Abrupt Increase in the Incidence of Childhood Narcolepsy in Finland

Hanna Nohynek¹*, Jukka Jokinen¹, Markku Partinen², Outi Vaarala¹, Turkka Kirjavainen³, Jonas Sundman¹, Sari-Leena Himanen⁴, Christer Hublin⁵, Ilkka Julkunen⁶, Päivi Olsén⁷, Outi Saarenpää-Heikkilä⁸, Terhi Kilpi¹

Increased Incidence and Clinical Picture of Childhood Narcolepsy following the 2009 H1N1 Pandemic Vaccination Campaign in Finland

Markku Partinen¹,²,¹⁵*, Outi Saarenpää-Heikkilä³, Ismo Ilveskoski⁴, Christer Hublin⁵, Miika Linna⁶, Päivi Olsén⁷, Pekka Nokelainen⁸, Reija Alén⁹, Tiina Wallden¹⁰, Merimaaria Espo¹⁰, Harri Rusanen¹¹, Jan Olme¹², Heli Sätilä¹³, Harri Arikka¹⁴, Pekka Kaipainen¹⁵, Ilkka Julkunen¹⁶, Turkka Kirjavainen¹⁷

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European Medicines Agency recommends restricting use of Pandemrix

In persons under 20 years of age Pandemrix to be used only in the absence of seasonal trivalent influenza vaccines, following link to very rare cases of narcolepsy in young people. Overall benefit-risk remains positive.
Could the association be verified in other than the signaling countries Sweden and Finland?
Could other countries verify the signal?

**Exposure**

Those 4-19 years of age vaccinated with Pandemrix\textsuperscript{R}/Arepanrix\textsuperscript{R} and narcolepsy cases spontaneously notified to AEFI registers by 24 January 2011

<table>
<thead>
<tr>
<th>Country</th>
<th>Notified cases</th>
<th>Vaccinated 4-19 year olds</th>
<th>Cases / 100 000 vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Island</td>
<td>3</td>
<td>31 958</td>
<td>9,4</td>
</tr>
<tr>
<td>Finland</td>
<td>54</td>
<td>668 000</td>
<td>8,1</td>
</tr>
<tr>
<td>Sweden</td>
<td>58</td>
<td>1 193 000</td>
<td>4,9</td>
</tr>
<tr>
<td>Norway</td>
<td>8</td>
<td>510 000*</td>
<td>1,6</td>
</tr>
<tr>
<td>The Great Britain</td>
<td>2</td>
<td>295 000**</td>
<td>0,7</td>
</tr>
<tr>
<td>Germany</td>
<td>5</td>
<td>928 000***</td>
<td>0,5</td>
</tr>
<tr>
<td>Canada</td>
<td>2</td>
<td>~ 2 000 000</td>
<td>0,1</td>
</tr>
</tbody>
</table>

*5-19-year olds / **5-16 –year olds / *** 0-17-year olds

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In all countries where Pandemrix\textsuperscript{R} was used in large numbers in susceptible age group, significant association was observed.

<table>
<thead>
<tr>
<th>Country</th>
<th>Age group yrs</th>
<th>Study design</th>
<th>Definition of onset</th>
<th>Follow up period</th>
<th>Risk (RR/ OR)</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland</td>
<td>4-19</td>
<td>Cohort</td>
<td>1. contact with HC</td>
<td>1.1.2009-15.8.2010</td>
<td>12.7</td>
<td>6.1 - 30.8</td>
</tr>
<tr>
<td>Sweden</td>
<td>≤19</td>
<td>Cohort</td>
<td>Date of dg G47.4</td>
<td>1.10.2009-31.12.2010</td>
<td>4.06</td>
<td>2.87 - 5.58</td>
</tr>
<tr>
<td></td>
<td>21-30</td>
<td>Cohort</td>
<td></td>
<td>1.10.2009 – 31.12.2011</td>
<td>2.18</td>
<td>1.00-4.75</td>
</tr>
<tr>
<td></td>
<td>31-&lt;40</td>
<td>Cohort</td>
<td></td>
<td></td>
<td>1.58</td>
<td>0.68-3.44</td>
</tr>
<tr>
<td>Ireland</td>
<td>5-19</td>
<td>Cohort</td>
<td>1. contact with HC</td>
<td>1.4.2009-31.12.2010</td>
<td>13.0</td>
<td>4.6 - 34.7</td>
</tr>
<tr>
<td>France</td>
<td>&lt;19</td>
<td>Case-Control</td>
<td>Date of referral MSLT</td>
<td>1.4.2009-30.4.2011</td>
<td>5.1</td>
<td>2.11 - 12.3</td>
</tr>
<tr>
<td></td>
<td>≥19</td>
<td>Case-Control</td>
<td></td>
<td></td>
<td>3.9</td>
<td>1.4 - 11.0</td>
</tr>
<tr>
<td>Norway</td>
<td>4-19</td>
<td>Cohort</td>
<td>Date of EDS by patient</td>
<td>1.10.2009 - 30.6.2010</td>
<td>14.5</td>
<td>N.A.</td>
</tr>
<tr>
<td>UK</td>
<td>4-19</td>
<td>CaseCohort SCCS</td>
<td>Date of EDS recorded by GP/centre</td>
<td>6 months post vaccination</td>
<td>16.2</td>
<td>3.1 – 84.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.9</td>
<td>2.1 – 47.9</td>
</tr>
</tbody>
</table>
Significant also in ADULTS although risk less than in children
Association between Pandemrix and narcolepsy

<table>
<thead>
<tr>
<th>Country</th>
<th>Age group yrs</th>
<th>Study design</th>
<th>Definition of onset</th>
<th>Follow up period</th>
<th>Risk (RR/OR)</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>≥19</td>
<td>C-C</td>
<td>Date of referral MSLT</td>
<td>1.4.2009-30.4.2011</td>
<td>3.9</td>
<td>1.4 - 11.0</td>
</tr>
<tr>
<td>Ireland</td>
<td>20-</td>
<td>RC</td>
<td>1. contact with HC</td>
<td>1.4.2009-31.12.2010</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sweden</td>
<td>21-30</td>
<td>RC</td>
<td>Date of dg G47.4</td>
<td>1.10.2009-31.12.2011</td>
<td>2.18</td>
<td>1.00-4.75</td>
</tr>
<tr>
<td></td>
<td>31-&lt;40</td>
<td></td>
<td></td>
<td></td>
<td>1.58</td>
<td>0.68-3.44</td>
</tr>
<tr>
<td>Finland</td>
<td>20-</td>
<td>RC</td>
<td>1. contact with HC</td>
<td>1.1.2009-31.12.2011</td>
<td>2.8 – 5.5</td>
<td>1.6 – 14.1</td>
</tr>
<tr>
<td>UK</td>
<td>17-</td>
<td>SCCS CaseC</td>
<td>Date of EDS recorded by GP/centre</td>
<td>6 months post vaccination</td>
<td>4.24</td>
<td>1.45-12.38</td>
</tr>
</tbody>
</table>
"The authors acknowledge that currently available data suggest an increased risk of narcolepsy following vaccination with Pandemrix; however, from an epidemiologist’s perspective, significant methodological limitations of the studies have not been fully addressed and raise questions about the reported risk estimates."

Verstraeten et al. Pandemrix and narcolepsy. A critical appraisal of the observational studies. Human Vaccines & Immunotherapeutics 2015
In Canada slightly increased risk i.e. 1 / million Arepanrix\textsuperscript{R} doses given

24 cases
3 different study designs
- Cohort
- Case-control
- Self-controlled case series

Obs. In Finland 1 / 16 000 doses !
CDC statement on narcolepsy following Pandemrix influenza vaccination in Europe

An increased risk of narcolepsy was found following vaccination with Pandemrix, a monovalent 2009 H1N1 influenza vaccine that was used in several European countries during the H1N1 influenza pandemic. Narcolepsy is a chronic neurological disorder caused by the brain's inability to regulate sleep-wake cycles normally. This risk was initially found in Finland, and then some other European countries also detected an association. Most recently, scientists at the United Kingdom’s (UK) Health Protection Agency (HPA) have found evidence of an association between Pandemrix and narcolepsy in children in England. The findings are consistent with studies from Finland and other countries.

Pandemrix is manufactured by GlaxoSmithKline in Europe and was specifically produced for pandemic 2009 H1N1 influenza. It was not used before 2009, and has not been used since the influenza pandemic season (2009-2010). It contains an oil-in-water emulsion called AS03. Adjuvants are substances added to a vaccine to increase the body’s immune response to that vaccine.

Pandemrix was not licensed for use in the United States. In fact, no adjuvanted influenza vaccines are licensed in the United States, and no adjuvanted influenza vaccines were used in the United States during the influenza pandemic or in any other influenza season.

In response to the events in Europe, CDC reviewed data from the U.S. Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink (VSD) and to date have found no indication of any association between U.S. licensed H1N1 or seasonal influenza vaccine and
Conclusions from the first set of epidemiological studies

• Pandemrix vaccination is associated with an abrupt increase in narcolepsy-cataplexy among children and teens, and also, to lesser degree, in adults

• The relative risk varies between 3 to 14 / 100 000 in the susceptible age group in children and teens

• The vaccine associated absolute risk is small (<7 /100 000) but consistently seen in different populations where Pandemrix was used in large numbers in susceptible age group

• Of the Bradford Hill criteria for causality, fulfilled are at least 4: strength, consistency, specificity and temporality

• Most likely such a rare event would not have been picked up in prelicensure trials

• In most countries, the postlicensure passive safety surveillance did not pick up the signal either
Critical comments on the epidemiological studies

Pandemrix™ and narcolepsy: the observational studies

Thomas Verstraeten, Catherine Cohet, Gaël Dos Santos, Germano LC Ferreira, Kaatje Bollaerts, Vincent Bauchau & Vivek Shinde
Detection bias. Awareness of a potential association between narcolepsy and vaccination amongst physicians and the general public could result in earlier diagnosis for vaccinated cases compared to unvaccinated cases, making vaccinated cases more likely to be included in observational studies with limited observation time. SELECTION BIAS

Differential exposure misclassification. The onset of symptoms is misattributed, resulting in misclassification of onset dates to the period following vaccination. As narcolepsy symptoms often develop gradually and onset of symptoms is not always clearly identifiable, studies into narcolepsy are particularly prone to recall bias. We hypothesize that recalling onset of EDS with knowledge of a putative association between vaccination and narcolepsy could lead a patient to recall that symptoms started after vaccination. RECALL BIAS
Impact of detection bias on incidence of narcolepsy over time
Children in Finland with narcolepsy
Impact of enhanced diagnostic workup or true phenomenon?

Hospital discharge register G47.4 diagnoses during years 2006-14
## Followup of newly diagnosed cases in Finland years 2009-2012

<table>
<thead>
<tr>
<th>Follow-up period to 1st contact to HC</th>
<th>Born in 1991–2005</th>
<th>Born in 1936–1990</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk ratio</td>
<td>95% confidence interval</td>
<td>Risk ratio</td>
</tr>
<tr>
<td>First year after vaccination</td>
<td><strong>13.4</strong></td>
<td>6.7–31.8</td>
</tr>
<tr>
<td>Second year after vaccination</td>
<td><strong>4.7</strong></td>
<td>2.2–11.7</td>
</tr>
<tr>
<td>Two years or more after vaccination</td>
<td><strong>1.7</strong></td>
<td>0.7–4.6</td>
</tr>
</tbody>
</table>
If the association is causal, what could be the biological mechanism?

See Paul-Henri Lambert lecture
Suggested biological mechanism: immune mediated. Pandemrix as an accelerator of narcolepsy: rapid disease development after vaccination.

HLADQB1*0602

Immune response Against neurons

Hypocretin / Orexin producing neurons in hypothalamus

Day time sleepiness

Pandemrix by-stander effect and/or a booster of autoimmunity

0 5 8 10 years

Diagnosis

2016-05-30

Vacc&Narcolepsy / HNohynek
Gaps in knowledge – significance to vaccine development and NVPs

• What is the biologically plausible mechanism; how can we study it?

• How long will those Pandemrix vaccinated with HLA DQB1*0602 be at risk?

• What does this incident mean to the future development of adjuvanted influenza / pandemic / other influenza vaccines?

• What does this mean to the future seasonal influenza vaccination of those Pandemrix\(^R\) exposed?

• How to contain the negative safety messages and impact to influenza vaccination / vaccinations in general?

• How to help those chronically affected?
Borg to consult on possible narcolepsy research

European Health Commissioner Tonio Borg is set to discuss with Máire Geoghegan-Quinn the possibility of funding of research narcolepsy.

Borg will consult with the European Commissioner for Research, Innovation and Science after an EU-wide group representing at least 1,000 victims met with the European Health Commissioner in Brussels. The group are advocating research for treatments, as well as to raise awareness and promote best practice in managing the condition. Gathering data on those affected is also thought to be a priority. Borg said he would discuss with Geoghegan-Quinn how money could be used from the Health programme and how data could also be collected.
Meeting report

Where are we in our understanding of the association between narcolepsy and one of the 2009 adjuvanted influenza A (H1N1) vaccines?∗

K. Johansen a, D. Brasseur b, N. MacDonald c, H. Nohynek d, J. Vandeputte e, D. Wood f, P. Neels e, g, h, on behalf of the Scientific Committee

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c Dalhousie University, IWK Health Center, Halifax, Nova Scotia, Canada
d Vaccine Programme Development Team, Vaccine Programme Unit, National Institute for Health and Welfare, Helsinki, Finland
e International Alliance on Biological Standards, Switzerland
f Technologies Standards and Norms, Essential Medicines and Health Products Department, World Health Organization, Geneva, Switzerland
g Vaccine-Advice BVBA, University of Namur, Zoersel, Belgium
h
Acknowledgements

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• The THL Narcolepsy Research Team - Jukka Jokinen, Terhi Kilpi, Outi Vaarala, Ilkka Julkunen, Pirjo-Riitta Saranpää, Susanna Jääskeläinen, Jonas Sundman
In summary

• New adjuvants are needed for vaccine development
• Safety of adjuvants can be tested in preclinical studies, clinical trials and in postlicensure
• However, rare events can only be observed in wide scale use, and even then they may go unnoticed
• Regulators, vaccine developers and public health scientist need to work together
• With the rare AEFI narcolepsy-catalepsy associated with Pandemrix, it is unlikely that the AS03 adjuvant played any major role
Backup slides
All those fallen ill with narcolepsy have the known risk factor HLA DQB1*0602: Biological explanation to the onset of narcolepsy triggered by the vaccine

<table>
<thead>
<tr>
<th>Näyte-nro</th>
<th>Haplotype 1</th>
<th>Haplotype 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>N001</td>
<td>(DR15)-DQB1*0602</td>
<td>(DR11/12/13)-DQA1<em>05-DQB1</em>0301</td>
</tr>
<tr>
<td>N002</td>
<td>(DR15)-DQB1*0602</td>
<td>(DR4)-DQA1<em>03-DQB1</em>0301</td>
</tr>
<tr>
<td>N003</td>
<td>(DR15)-DQB1*0602</td>
<td>(DR8)-DQB1*04</td>
</tr>
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What is the role of A(H1N1) infection?

Narcolepsy Onset Is Seasonal and Increased following the 2009 H1N1 Pandemic in China

Fang Han, MD, Ling Lin, MD, PhD, Simon C. Warby, PhD, Juliette Faraco, PhD

A. Occurrences of Narcolepsy Onset

B. Narcolepsy Onset (average count/month)

C. Narcolepsy Onset (annual count)

Flu Occurrences (count x 100,000)

Graphical display showing the seasonal increase in narcolepsy onset following the 2009 H1N1 pandemic in China.
Analysis of NS1 protein-specific antibody responses in human sera by using recombinant influenza A virus NS1 proteins.


http://www.plosone.org/article/info:doi/10.1371/journal.pone.0068402
Hypothesis I by Prof. Outi Vaarala, THL

In the process of manufacturing Pandemrix\textsuperscript{R} vaccine AH1N1 antigen, a structure is formed which resembles the autoantigen of narcolepsy. The immune response associated with narcolepsy was caused by the virus antigen suspension of Pandemrix\textsuperscript{R} and the adjuvant strengthened this response.
Comparison of Pandemrix and Arepanrix, two pH1N1 AS03-adjuvanted vaccines differentially associated with narcolepsy development

Louis Jacob a, Ryan Leib b, Hanna M. Ollila a, Mélodie Bonvalet a, Christopher M. Adams b, Emmanuel Mignot a,*

a Center for Sleep Sciences and Medicine, Stanford School of Medicine, Palo Alto, CA, USA
b Stanford University Mass Spectrometry, Palo Alto, CA, USA

Table 2
Protein composition in Pandemrix versus Arepanrix.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Pandemrix</th>
<th>Arepanrix</th>
<th>Estimated OR P/A</th>
<th>95% confidence interval</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Nucleoprotein (NP)</td>
<td>PR8</td>
<td>24% (3660)</td>
<td>16% (3671)</td>
<td>1.6</td>
<td>[1.5–1.7]</td>
</tr>
<tr>
<td>Hemagglutinin (HA)</td>
<td>pH1N1</td>
<td>21% (3149)</td>
<td>23% (5328)</td>
<td>0.84</td>
<td>[0.80–0.89]</td>
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<tr>
<td>Matrix protein 1 (MA1)</td>
<td>PR8</td>
<td>9.2% (1444)</td>
<td>12% (2701)</td>
<td>0.75</td>
<td>[0.70–0.80]</td>
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<tr>
<td>Neuraminidase (NA)</td>
<td>pH1N1</td>
<td>6.9% (1050)</td>
<td>5.5% (1249)</td>
<td>1.2</td>
<td>[1.1–1.3]</td>
</tr>
<tr>
<td>Polymerase 1 (PB1)</td>
<td>pH1N1</td>
<td>1.1% (161)</td>
<td>1.2% (262)</td>
<td>0.93</td>
<td>[0.76–1.1]</td>
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<tr>
<td>Other viral proteins</td>
<td>PR8</td>
<td>3.9% (603)</td>
<td>3.4% (767)</td>
<td>1.2</td>
<td>[1.1–1.3]</td>
</tr>
<tr>
<td>PDCD6IP</td>
<td>Gallus gallus</td>
<td>1.0% (160)</td>
<td>0.32% (72)</td>
<td>3.3</td>
<td>[2.5–4.4]</td>
</tr>
<tr>
<td>Tubulin beta (and related)</td>
<td>Gallus gallus</td>
<td>1.3% (200)</td>
<td>0.76% (172)</td>
<td>1.8</td>
<td>[1.5–2.2]</td>
</tr>
<tr>
<td>HSP70 (and related)</td>
<td>Gallus gallus</td>
<td>0.59% (91)</td>
<td>0.31% (70)</td>
<td>1.9</td>
<td>[1.4–2.6]</td>
</tr>
<tr>
<td>TA3C (and related)</td>
<td>Gallus gallus</td>
<td>0.38% (58)</td>
<td>0.37% (84)</td>
<td>1.1</td>
<td>[0.76–1.5]</td>
</tr>
<tr>
<td>Tetrspanin 8</td>
<td>Gallus gallus</td>
<td>0.37% (56)</td>
<td>0.18% (41)</td>
<td>2.0</td>
<td>[1.4–3.0]</td>
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<tr>
<td>Ovostatin</td>
<td>Gallus gallus</td>
<td>0.27% (42)</td>
<td>0.33% (74)</td>
<td>0.84</td>
<td>[0.57–1.2]</td>
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<tr>
<td>HFABP</td>
<td>Gallus gallus</td>
<td>0.20% (30)</td>
<td>0.022% (5)</td>
<td>9.5</td>
<td>[3.7–25]</td>
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<tr>
<td>Other non viral proteins</td>
<td>Gallus gallus/others</td>
<td>0.36% (61)</td>
<td>0.36% (72)</td>
<td>0.80</td>
<td>[0.77–0.84]</td>
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<tr>
<td>Total</td>
<td></td>
<td>15,323</td>
<td>22,708</td>
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Data reported include relative protein amounts in percent and MS peptide counts under parenthesis. MS peptide counts were obtained by adding peptide counts obtained in the 6 MS runs. Odd Ratios between Pandemrix and Arepanrix (OR P/A) indicating protein relative abundance versus all other proteins were obtained using a Cochran–Mantel–Haenszel test on the six mass spectrometry data. Proteins overrepresented in Pandemrix and Arepanrix are in green and orange respectively. PDCD6IP: programmed cell death 6-interacting protein, HSP70: heat shock protein 70, TA3C: tropomyosin alpha-3 chain, HFABP: heart fatty acid binding protein. For tubulin beta, HSP70 and TA3C, peptide numbers were merged with peptide numbers of proteins belonging to the same family (ex: HSP70 and 90 merged together as they shared homology).
Retracted in August 2014
A/H1N1 antibodies and TRIB2 autoantibodies in narcolepsy patients diagnosed in conjunction with the Pandemrix vaccination campaign in Sweden 2009–2010

Alexander Lind a,1, Anita Ramelius a, Tomas Olsson b, Lisen Arnheim-Dahlström c, Favelle Lamb c, Mohsen Khademi b, Aditya Ambati d, Markus Maeurer e, Anna-Lena Nilsson f, Izaura Lima Bomfim b, Katharina Fink b, Åke Lernmark a

a Department of Clinical Sciences, Lund University/CRC, Skåne University Hospital SUX, Malmö, Sweden
b Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
c Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
d Department of Medicine, Karolinska Institutet, Stockholm, Sweden
e TIM, LabMed, Karolinska Institutet and CAST, Karolinska Hospital, Stockholm, Sweden
f Paediatric Clinic, Östersund Hospital, Östersund, Sweden
Narcolepsy as an autoimmune disease: the role of H1N1 infection and vaccination

Markku Partinen, Birgitte Rahbek Kornum, Giuseppe Plazzi, Poul Jennis, Ilkka Julkunen, Outi Vaara

Narcolepsy is a sleep disorder characterised by loss of hypothalamic hypocretin (orexin) neurons. The prevalence of narcolepsy is about 30 per 100,000 people, and typical age at onset is 12–16 years. Narcolepsy is strongly associated with the HLA-DQB1*06:02 genotype, and has been thought of as an immune-mediated disease. Other risk genes, such as T-cell-receptor α chain and purinergic receptor subtype 2Y11, are also implicated. Interest in narcolepsy has increased since the epidemiological observations that H1N1 infection and vaccination are potential triggering factors.
Review

Narcolepsy, 2009 A(H1N1) pandemic influenza, and pandemic influenza vaccinations: What is known and unknown about the neurological disorder, the role for autoimmunity, and vaccine adjuvants

S. Sohail Ahmed, Peter H. Schur, Noni E. MacDonald, Lawrence Steinman

Global Clinical Sciences, Vaccines Research, Novartis Vaccines Srl, via Fiorentina 1, Siena 53100, Italy
Harvard Medical School, Division of Rheumatology, Brigham and Women’s Hospital, 45 Francis Street, Boston, MA 02115, USA
Dalhousie University, Division Pediatric Infectious Diseases, IWK Health Center, 5850/5980 University Avenue, PO Box 9700, Halifax, Nova Scotia B3K 6B8, Canada
Beckman Center for Molecular Medicine, 8002, 279 Campus Drive, Stanford University, Stanford, CA 94305, USA

Editorial

Childhood narcolepsy and H1N1 vaccination: stirring up a sleeping menace?
Ruotsin lääkeviranomaisten koordinoima symposio ja katsaus siihen mitä tiedetään Uppsala 6-7.11.2014

Grupp Genetik och patogenes

Grupp Virusimmunologi och vaccinsäkerhet

Grupp Epidemiologiska data för beräkning av incidenser och risk

Grupp Kunskaps- och informationsspridning
Narrating narcolepsy--centering a side effect.

Lundgren B.

Author information

Abstract
The mass-vaccination with Pandemrix was the most important preventive measure in Sweden during the A(H1N1) influenza pandemic of 2009-2010, and covered 60% of the population. From 2010, an increased incidence of the neurological disease narcolepsy was reported, and an association with Pandemrix was confirmed for more than 200 children and young adults. The parental experience of this side effect provided a starting point for a collectively shaped critical narrative to be acted out in public, but also personalized narratives of continual learning about the disease and its consequences. This didactic functionality resulted in active meaning-making practices about how to handle the aftermath--using dark humor, cognitive tricks, and making themselves and their children's bodies both objects and subjects of knowledge. Using material from interviews with parents, this mixing of knowledge work and political work, and the potential for reflective consciousness, is discussed.

KEYWORDS: A(H1N1); mass-vaccination; narcolepsy; parents' narratives; side effects

PMID: 25457625 [PubMed - in process]
Epidemological evidence 1
only significant increase in narcolepsy

- Epidemiological studies suggest that there is a narcolepsy specific trigger in Pandemrix
  - No similar increase in other immune-mediated diseases (Persson et al. J Intern Med 2013)
  - If it was by-stander activation, the increase in events should not be restricted to narcolepsy specific immunity
Epidemiological evidence 2: only Pandemrix

- Pandemrix associated narcolepsy risk is about 4 to 13 fold, whereas the risk associated with another AS03 adjuvanted vaccine, Arepanrix, is manyfold lower (if any risk).

- No risk observed in association with seasonal H1N1 vaccinations or MF59 adjuvanted H1N1 vaccines

- AS03 alone does not trigger narcolepsy

- (not even together with H1N1 antigen of Arepanrix)

- H1N1 protein(s) in other vaccines do not trigger narcolepsy in the same magnitude
Seasonal trivalent influenza vaccine (TIV) coverage in Finland

Seasonal influenza vaccine coverage (%)

- Age 6 to 35 months
- Age 65 years and older

Pandemic influenza season

THL (unpublished data).

Vacc&Narcolepsy / HNohynek
Miten pikkulasten kansallinen rokotusohjelma on toteutunut?
VAESCO CASE CONTROL STUDY (HYPOTHESIS TESTING)

- **Design:** Case control study
- **Study Period:** April 2009-July 2010 (after July: sensitivity analysis)
- **Setting:** 8 countries: FI, SW, NO, DK, NL, UK, FR, IT
- **Cases:** Validated by Brighton case classification
- **Index date:** Date of first referral to sleep center (primary) date of diagnosis and date of first symptoms (sensitivity)
- **Controls:** Matched on country/age/sex/index date
- **Exposure:** H1N1 vaccine, other vaccines, infections
- **Data collection:** harmonized methods and pooling

Ongoing, preliminary results soon available
History of narcolepsy
<table>
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<tr>
<th>Mechanism</th>
<th>Description</th>
<th>References</th>
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<td><strong>Partinen ym Lancet Neurol 2014</strong></td>
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</table>
The association of the HLA DR and DQ–gene region alleles with autoimmune diseases

- Diabetes mellitus, type 1
  - HLA DQB1*0302 ja HLA DQB*02 ↑
- MS-disease
  - HLA DRB1*1501 ↑
- Coeliacia
  - HLA-DQA1*05 and HLA-DQB1*02 ↑
- Narcolepsy-cataplexy
  - HLA DQB1*0602 ↑
Confirmed narcolepsy cases in 5 to 19 year-olds with estimated onset date after vaccination

(c) THL 01.03.2011

Jokinen 2011
Exposures and followup times in the study cohort

Pandemrix vaccinations started 1.11.2009

3 285 550 persons

Unvaccinated

Vaccinated

3 151 477 Person years

6 705 173 Person years

1.1.2009

2009

2010

2011

31.12.2011
Sensitivity analysis of RR: onset dates vs. follow-up times among those with DG G47.4 given by 31.12.2010
GSK - Currently available evidence does not yet allow to distinguish between potential mechanisms.
Onset of immune mediated disease
Analogy to Type 1 Diabetes Mellitus

- Insulin
- producing beta-cells
- in pancreas

0 Genes
5 Autoantibodies
8 Glucose tolerance
10 years Diagnosis

Vacc&Narcolepsy / HNohynek