Monitoring and assessing vaccine safety – a European perspective

Johan Giesecke, Chief Scientist
ESCMI D, Prague, 2 April 2011
Outline

- Background
- Exposure data in immunization registries
- Routine reporting of Adverse Events following Immunization
- Safety signal assessment

Experiences from Finland

- Building European capacity
- Future challenges/opportunities
Vaccines mainly offer benefits but also some risks......

Benefits

- Protection against disease
  - individual-level
  - population-level (herd immunity)
- Increased quality of life
- Cost effective

Risks

- Adverse reactions
- False alarms
- True – and false – alarms may lead to insecurity and reduced vaccination coverage
Vaccine scares are inevitable – some turn out to be just scares … but

Cervarix®

Gardasil®

Cervical cancer drug Gardasil linked to deaths

By Lucy Page

12:07 PM GMT 29 Oct 2006

Fears have been raised over the safety of a cervical cancer vaccine which health officials plan to give to thousands of girls after it was revealed that the drug has been linked to several deaths.

Three young women are reported to have died after the drug Gardasil was administered, while the jab is also suspected of triggering "adverse reactions" in 1,700 patients. The figures were uncovered by campaigners who made a freedom of information request in the US, where the vaccine was approved for use a year ago.

The vaccine works by making girls immune to strains of a STI.
Examples where vaccine products still may cause true adverse reactions

Smallpox vaccines – generalized vaccinia, excema vaccinatum, myopericardit

BCG - disseminated BCG, osteomyelitis, BCG abscesses and lymphadenitis

Oral poliovirus vaccines - vaccine-associated polio paralysis (VAPP)

MMR vaccines - transient trombocytopenia 1:30,000
Narcolepsy signal after Pandemrix currently investigated

August, 2010 - narcolepsy reported in vaccinated children in Sweden and Finland - ECDC contacts VAESCO

September, 2010 - EMA reviews data and concludes "available evidence insufficient …further studies necessary" - VAESCO submits protocol

February, 2011 – Finland reports 9-fold increase of narcolepsy in vaccinated Finnish adolescents

March, 2011 - Sweden reports 4-fold increase of narcolepsy... new EMA review? ...
Rise in sleep illness cases linked to swine-flu jab

Eight people now suffering from narcolepsy after getting vaccine
It is with gladness of heart that I note that Dr Andrew Wakefield, the gastric surgeon and one of the principal authors of perhaps the stupidest and most unnecessary health scare of recent Western history has been struck off the General Medical Council for being “dishonest”, “misleading” and “irresponsible” in his research into the MMR vaccine and its purported links to autism

- TOM CHIVERS
Measles coverage, Sweden

Percentage MMR-vaccinated at the age of 2
Questions

How can we build European monitoring systems to avoid vaccine scares and at the same time monitor for true adverse events?

Real-time linkage of continuously updated immunization registries and health-outcome databases is the golden standard – how can we get there?
Exposure data in immunization registries
## EU Immunization Registries

<table>
<thead>
<tr>
<th>Country</th>
<th>Population covered</th>
<th>Size of population covered (10^6)</th>
<th>Type of Immunization Information System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden</td>
<td>Regional</td>
<td>5.3</td>
<td>Immunization registry</td>
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<tr>
<td>Norway</td>
<td>National</td>
<td>4.8</td>
<td>Immunization registry</td>
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<tr>
<td>Denmark</td>
<td>National</td>
<td>5.5</td>
<td>Immunization registry</td>
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<tr>
<td>United Kingdom</td>
<td>Sample of GPs</td>
<td>5</td>
<td>Medical record system</td>
</tr>
<tr>
<td>Belgium*</td>
<td>Almost national</td>
<td>10</td>
<td>Insurance-based database</td>
</tr>
<tr>
<td>Netherlands</td>
<td>National</td>
<td>16</td>
<td>Immunization registry</td>
</tr>
<tr>
<td>Germany*</td>
<td>Regional</td>
<td>13</td>
<td>Insurance claims databases</td>
</tr>
<tr>
<td>Italy</td>
<td>Regional</td>
<td>?</td>
<td>Immunization registry</td>
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<tr>
<td>Spain</td>
<td>Regional</td>
<td>?</td>
<td>Immunization registry</td>
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</table>
Routine reporting of adverse events following immunization
Routine/ passive surveillance of adverse events following immunization (AEFI s)

- Reports by health professionals responsible for vaccination
- Reports by consumers/child guardian increasing
  → Known limitations to these systems are delay in reporting and underreporting (and no denominator)
- All severe and unusual AEFI s are forwarded to the European Medicines Agency Eudravigilance database in London
- Stimulated routine/passive reporting (forms sent to vaccinators for return, eg yellow card in the UK, US VAERS system)
Safety signal detection and assessment of adverse events following immunization
Vaccine Safety Signal detection and assessment in Europe

- Routine reporting of adverse events following immunization
- Validation of safety concerns – case ascertainment
- Causal association studies
- Benefit/risk evaluations
- Risk communication

Post-licensure monitoring for AEFI's shared responsibility between manufacturers, Public Health Institutes/ECDC and National Regulatory Agencies/EMA
Role of laboratories

- Support case ascertainment
- Rule out other concomitant disease
- Immunology (pathogen-specific antibody response, autoimmune antibodies)
- Virology (virus culture, PCR, vaccine/wild-type genotype)
- Bacteriology (bacteria culture, PCR, vaccine/wild-type genotype)
- Genetic markers (HLA-type, genome-wide association studies)
Before licensure in practice......

- Only limited safety data available

- low number of subject included in trials (n=10,000 - 60,000)

- only healthy subjects included in trials (eg special healthy groups such as pregnant women and premature children almost never included)
Validation - different methodology to be chosen dependent on signal

- Case ascertainment -
  - Case definitions (Brighton collaboration)
  - Laboratories may play an important role

- Observed versus expected analysis using background incidence data during a longer time period

- Case control studies

- Self case control studies

- Cohort studies

*Unpublished ECDC - VAESCO II study 2010*
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Global Safety of Vaccines
Strengthening Systems for Monitoring, Analysing and Management
Example of Pandemrix vs. Narcolepsy

Hanna Nohynek  THL, Vaccines and Immune Protection
Slide withheld at request of author
Should we vaccinate? 
Risks and benefits to consider

Antivaccinists
Risks of vaccinating

MDs and HCWs
Risks of disease
Risks of not vaccinating
**Enhanced passive reporting of AEFI**

### Table: Enhanced Passive Reporting of AEFI

<table>
<thead>
<tr>
<th>Tietutain</th>
<th>Rokotetun sukunimi</th>
<th>Rokotetun etunimi</th>
<th>Henkilötunnus</th>
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<tr>
<td>Sukupuoli</td>
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<th>Tietutain</th>
<th>Rokotusaika</th>
<th>Rokotuspaikan määrä osoite (jos eri kuin ilmoittajan)</th>
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<tr>
<th>Tietutain</th>
<th>Rokote</th>
<th>Kauppanimi</th>
<th>Erännumero</th>
<th>Rokotustapa</th>
<th>Pistokohta</th>
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<thead>
<tr>
<th>Tietutain</th>
<th>1 Kuume korkommillaan ___ ° C, (jos ainoo raportoitava oire, oltava yli 40 °C)</th>
<th>9 Bellin pareesi (kasvohemohalvaus)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 Rokotusraajan voimakas puuitois, turvotus, kuumotus tai kipu (ylä seuraavan nivelen ulottuva)</td>
<td>10 Neuriitti (hermotulehdus)</td>
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<td>Rokote</td>
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<td></td>
<td>3 Laaja-alainen nokkoshottuma keholla, paikka</td>
<td></td>
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Adverse events reported to the Finnish AEFI register in 1997- August 2010
... and just when we thought we were back to normal .... In August 2010
Slide withheld at request of author
Is this a true signal?

Expected vs Observed numbers?
Newly diagnosed narcolepsy cases (G47.4) among children and adolescents in 2006-2010

Hospital registry discharge data

TERVEYDEN JA HYVINVOINNIN LAITOS

28.1.2011
Newly diagnosed narcolepsy cases (G47.4) among adults in 2006-2010

Hospital registry discharge data

TERVEYDEN JA HYVINVOINNIN LAITOS

28.1.2011
Yes there is a signal among children and adolescents 4 to 19 years of age. Number of observed narcoleptic cases exceeds that expected.

- In years 2006-2009 observed
  - 5-16 cases
  - Approximately 1 case / 100,000 persons

- In year 2010 among those vaccinated with Pandemrix®
  - 54 cases
  - 8.1 cases / 100,000 vaccinated persons
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Slide withheld at request of author
Those 4 to 19 years of age vaccinated with Pandemrix\textsuperscript{R}/Arepanrix\textsuperscript{R} and 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>Iceland</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

Kilpi et al. ESPID 2011
Could Pandemrix have caused narcolepsy?
Factors to consider in assessment of causality
Relevant to non-serious and serious AEFIs
Which epidemiological method to choose to study the strength of association?
Retrospective cohort study done
Materials and methods (1)

• Study population: all those born at or after 1.1.1991 and officially living in Finland
• Primary follow up period 1.1.2009 - 16.8.2010
• Two variables in analysis
  – Pandemrix<sup>R</sup> vaccination
  – Onset of narcolepsy
• Vaccination records were systematically collected from the primary care records with the help of several software companies (there is no national vaccination registry in Finland)
The number of Pandemrix\textsuperscript{R} vaccinated in Finland

Number of vaccinated  Vaccine coverage, %

![Diagram showing the number of Pandemrix vaccinated in Finland and the vaccine coverage percentage.](image)
Retrospective cohort study done
Materials and methods (2)

- Listings of all newly diagnosed narcoleptic cases (ICD code 47.4) registered during years 2009-10 in the central hospital registers
- Case definition: international Brighton Collaboration narcolepsy-cataplexy diagnostic criteria
- Case validation by two sleep medicine experts independently of each other
- Discrepant cases subjected to a panel of three sleep medicine experts
Narcolepsy
Brighton Collaboration case definition
... work in progress...

- **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
When did the disease start? What date to use for onset of narcolepsy?

- Estimate from medical records
  - Based on opinion of reviewing neurologists after reading all the documentation available of a patient
- First documented contact because of EDS to healthcare
- Referral to neurologist
- Diagnosis
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Cohort study analysis of risk

Risk ratio = \[
\frac{\text{Narcolepsy cases / person years among vaccinated}}{\text{Narcolepsy cases / person years among nonvaccinated}}\]
Results of main analysis
Followup period 1.1.2009-16.8.2010*

<table>
<thead>
<tr>
<th>Persons with onset of narcolepsy during followup period</th>
<th>Never received Pandemrix R</th>
<th>Received Pandemrix R during followup period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons</td>
<td>269 405</td>
<td>646 449</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Persons with onset of narcolepsy during followup period</th>
<th>Unvaccinated</th>
<th>Vaccinated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons</td>
<td>8</td>
<td>36</td>
</tr>
<tr>
<td>Person years</td>
<td>1 000 667</td>
<td>487 595</td>
</tr>
</tbody>
</table>

Risk among vaccinated / Risk among nonvaccinated
= 9.2 (95% CI 4.5-21.4)

*date of media attention to narcolepsy in Sweden
# Results of analysis with extended follow-up period 1.1.2009-31.12.2010

<table>
<thead>
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<tr>
<td>Persons with onset of narcolepsy during followup period</td>
<td>8</td>
<td>52</td>
</tr>
<tr>
<td>Person years</td>
<td>1 101 694</td>
<td>730 014</td>
</tr>
</tbody>
</table>

Risk among vaccinated / risk among nonvaccinated = **9.8** (95% CI 4.9-22.3)
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But demonstrating strength of association is not proof of causality
Factors to consider in assessment of causality
Relevant to non-serious and serious AEFIIs

WHO Aide Memoire: AEFI Investigation, 2004
Etiology of narcolepsy

Multifactorial model

Figure 1—Model for the etiology of narcolepsy, modified from a similar model proposed for type 1 diabetes.122
Slide withheld at request of author
Age distribution of vaccinated and unvaccinated cases

**Vaccinated**

- Ages 10 and 12 are the most common among vaccinated cases.

**Unvaccinated**

- Ages 10 and 16 are the most common among unvaccinated cases.
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Prior to releasing own conclusions

• Extensive discussions with
• VAESCO
• Independent International Advisory Board
• Global Advisory Committee on Vaccine Safety
• WHO Geneva and Europe
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Slide withheld at request of author
Slide withheld at request of author
The conclusions of the Finnish Task Force on Narcolepsy

• It is probable that during fall-winter 2009-10, Pandemrix\textsuperscript{R} vaccination contributed to the observed 9-fold increase in narcolepsy among those 4 to 19 years of age and vaccinated.

• It is most likely that the Pandemrix\textsuperscript{R} vaccine has increased narcolepsy in a joint effect in those genetically disposed with some other, still unknown genetic and/or environmental factor.

• The strength of the association between narcolepsy and Pandemrix\textsuperscript{R} vaccination is of such magnitude that it is unlikely that a confounding factor alone could be behind the observation.
Further studies are needed

- The Finnish retrospective registry based cohort study will be completed
- The European VAESCO led study with 9 member states will explore the role of Pandemrix® and other risk factors in the onset of narcolepsy, Finland participates in this
- The role of vaccine batches?
  None; based on the review of the age wise distribution of the different batches of Pandemrix® in Finland and in Sweden
- The role of immune responses
- The role of the different contributing factors
  Genetic, Environmental
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How can we trust the quality of AEFI data (on narcolepsy and other conditions) and analyses from the different parts of the world?
58 countries have a functional NRA to regulate vaccines

- Blue: NRA functional
- Light grey: NRA not functional or no data available
- Green: Countries where AEFI system have documented progress or and is functional
Building European capacity
ECDC funds a consortium of researchers in Denmark, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, UK:

*Vaccine Adverse Event Surveillance & Communication*

- Major component - data linkage of different health registries
- Rationale: For rare events populations of one country is too small
**Proof of concept – using data linkage in Denmark and England (MMR and ITP)**

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Period after MMR (days)</th>
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<tbody>
<tr>
<td></td>
<td>0-13</td>
<td>14-27</td>
<td>28-42</td>
<td>0-42</td>
</tr>
<tr>
<td>Pooled data with common age effect</td>
<td>1.38 (0.76-2.50)</td>
<td>3.09 (2.02-4.73)</td>
<td>1.97 (1.18-3.28)</td>
<td>2.13 (1.55-2.94)</td>
</tr>
<tr>
<td>Pooled data with country specific age effects</td>
<td>1.30 (0.71-2.38)</td>
<td>2.87 (1.85-4.46)</td>
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On-going studies

Assessment of GBS and pandemic vaccines
- CCS – submitted
- SCCS – in manuscript

Assessment of narcolepsy and pandemic vaccines
- Case definition finalized together with European network of narcolepsy experts
- Case control study on-going
Future challenges and opportunities
Possible model of vaccine AE and Risk Assessment

Signal Detection:
Eudravigilance
EMA
Manufacturers

Risk management:
MS, European Commission

Signal Follow-up:
E-VSD
VAESCO, ECDC
Manufacturers
Challenges and opportunities -

- Expanding and standardizing immunization registry capacity
- Creating sustainable infrastructure for analytical data linkage in EU/EEA Member States
- Sustainable funding
- Prospective monitoring for upcoming vaccines (MenB)
- **Real-time vaccine safety data linkage** – future golden standard
For real-time vaccine safety data linkage the following is needed

- Immunization registries without data lag for more than 1-2 wks
- Health-outcome data bases without data lag for more than 1-2 wks
- On a weekly basis run immunization registry against health out-come registry – already in practice in the health centres participating in the US VSD (14 million population)
- Software/statistician/epidemiologist/safety assessor with capacity to immediately help with case ascertainment
Transparency - good example during H1N1 pandemic

- 24 countries reported weekly or biweekly on AEFI's for pandemic vaccines on their medical product agency websites

- EMA published (first time) summary of AEFI's reported to the Eudravigilance database on pandemic vaccines and antivirals
Continuing the good experience from the pandemic?

Should National Regulatory Agencies and/or National Public Health Institutes continue publishing

- AEFI reports
- Assessed AEFI reports

For the general public

- Newsletter with examples of AEFI cases (IMPACT, Canada)
Acknowledgements

Kari Johansen, ECDC Project leader
Piotr Kramarz, Deputy Chief Scientist
Pier Luigi Lopalco, Head of Vaccine Preventable Diseases Programme