Monitoring Adverse events following immunization with HPV-vaccines in Denmark

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Adverse event reporting schedule for vaccines in Denmark

- Reporting by both health care professionals and consumers
- Legal obligation for health care professionals to report all suspected adverse drug reactions for new vaccines for the first 2 years.
- After than legal obligation to report serious or unexpected reactions
- Primarily by e-form, telephone or postal is also available
- Specific reporting scheme for vaccines – focus on batch numbers and other concommitant vaccinations
Steps in surveillance

- Submission of reports to Danish Medicines Agency
- Reports are forwarded to the EMA, WHO, pharmaceutical company databases
- Causality assessment of individual ADR reports
- Assessment of potential signals
Adverse event reports received per year in DK

<table>
<thead>
<tr>
<th>Year</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total reports</td>
<td>288</td>
<td>66</td>
<td>43</td>
<td>96</td>
<td>511</td>
<td>224</td>
<td>822</td>
<td>222</td>
<td>2241</td>
</tr>
<tr>
<td>Serious reports *</td>
<td>25</td>
<td>5</td>
<td>6</td>
<td>18</td>
<td>177</td>
<td>91</td>
<td>475</td>
<td>135</td>
<td>958</td>
</tr>
<tr>
<td>Vaccine doses sold</td>
<td>347.690</td>
<td>151.476</td>
<td>163.374</td>
<td>349.730</td>
<td>488.224</td>
<td>114.457</td>
<td>53.781</td>
<td>42.743</td>
<td>1.711.475</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.
## Start year of adverse event (all reports until 2015)

<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported start date for adverse event</td>
<td>211</td>
<td>334</td>
<td>145</td>
<td>148</td>
<td>360</td>
<td>587</td>
<td>153</td>
<td>81</td>
</tr>
<tr>
<td>Vaccine doses sold</td>
<td>?</td>
<td>347.690</td>
<td>151.476</td>
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<td>349.730</td>
<td>488.224</td>
<td>114.457</td>
<td>53.781</td>
</tr>
</tbody>
</table>
Reported adverse events for HPV-vaccines

Patient/consumer

- Serious: 45%
- Non-serious: 55%

Reporter type

- Patient/consumer: 62%
- Healthcare professional: 38%

Healthcare professional

- Serious: 58%
- Non-serious: 42%
### Most frequently reported reactions

<table>
<thead>
<tr>
<th>Reported reactions according to MedDRA</th>
<th>Number of reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>5629</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>3112</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>2455</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>2226</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>1522</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>1117</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>911</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>713</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>567</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>511</td>
</tr>
</tbody>
</table>

- **Headache**
  - Disturbance in attention
  - Dizziness/Syncope
  - Paraesthesias /sensory disturbances
- **Fatigue**
- **Myalgia**
- **Abdominal pain**
- **Nausea**
- **Dysphoea**
- **Palpitations**
- **POTS**
Causality assessment

**Possible**
1) Consistent temporal relationship between vaccination and symptoms, and there is documentation for the occurrence of the reported type of adverse reaction after vaccination.
2) Adverse events in connection to subscription, dose and vaccine administration
3) Reactions caused by vaccine quality defect
4) Anxiety reaction caused by vaccination

**Insufficient documentation**
1) Consistent temporal relationship between vaccination and symptoms, but there is no or indeterminate documentation for the occurrence of the reported type of adverse reaction after vaccination.
2) Data are conflicting

**Less likely**
Other known disease or other factors are more likely to explain the symptoms.

**Unclassifiable**
The information in the report is inadequate, and it cannot be assessed if the symptoms are related to the vaccine
2015 review:

Review of the 363 serious reports for HPV-vaccines

Large proportion of the reports (34-43%) describe a symptom complex of headache, pain, fatigue, circulatory symptoms and neurological symptoms.

In most cases the patients are left undiagnosed. In some cases the patients fulfill criteria for POTS.

The disease diagnose encompassing most of the symptoms could be a CFS-like condition.

- Need for review of the world-wide data, comparative data on background incidences etc.

EMA referral
Public communications for Healthcare professionals

- Quartely overviews in Danish pharmacovigilance update – monthly bulleting for healthcare professionals – over 4000 subscribers

- Core data for all reported events following immunisation are publicly available on agency website.
Information to public on AEFI monitoring for HPV-vaccines: https://www.youtube.com/watch?v=Qi-J-pMviDo
Thank you