Vaccinovigilance
The specifics of immunological medicinal products
Klaus Cussler
The PEI is the Federal Institute for Vaccines and Biomedicines. National regulatory authority and research institute in this field of human and veterinary medicine. The PEI reports to the German Federal Ministry of Health.
Vaccines - a story of great success

Global eradication of diseases
- Smallpox
- Rinderpest

National eradication (DE)
- Aujeszyk’s disease
- BTV-8
- Rabies

On the way:
- Bovine Herpesvirus 1
- Bovine Viral Diarrhoea
Vaccinovigilance

• „Vaccinovigilance“
• Data and Facts for Germany
• „Highlights“ & Case Reports
  – Local reactions
    • Feline Injection Site Sarcoma
    • Accidental injection in humans
  – Systemic reactions
    • Endotoxins
    • Abortions in cattle after BTV-8 vaccination
  – Immune mediated diseases
    • Hypersensitivity Type I reactions
    • Bovine Neonatal Pancytopenia
  – Lack of efficacy
    • RHD-2
Vaccines are very different from other pharmaceuticals:
• Vaccines are generally given to healthy, often very young individuals.
• Low threshold for tolerance of adverse events.
• Vaccines protect the individual, but also the community; herd protection
• Most adverse events are easily recognised.

It is vital to maintain and promote the positive image of immunization by producing reliable information on adverse effects of vaccines and distributing it transparently and effectively.
Some countries have special authorities responsible for veterinary immunological medicines:

- **USA**: Center for Veterinary Biologics (CVB), Ames, IOWA
- **CH**: Institut für Virologie und Immunologie (IVI), Mittelhäusern
- **DE**: Paul-Ehrlich-Institut (PEI), Langen

Vaccine Adverse Event Reporting System (VAERS) in the US for human vaccines

WHO has also a special focus on Vaccinovigilance

AEFI: Adverse Events Following Immunisation

Pharmacovigilance in Europe also covers veterinary vaccines. All PhV rules apply.
Reporting

**General form**

- Feline fibrosarcoma
- Bovine Neonatal Pancytopenia

**Electronic reporting**

**Pharmaceuticals**

**Vaccines**
Veterinary Medicines in Germany

Adverse event reports for animals

<table>
<thead>
<tr>
<th>Year</th>
<th>Pharmaceuticals</th>
<th>Immunologicals</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>BVL</td>
<td>PEI</td>
</tr>
<tr>
<td>2011</td>
<td>689</td>
<td>411</td>
</tr>
<tr>
<td>2012</td>
<td>666</td>
<td>521</td>
</tr>
<tr>
<td>2013</td>
<td>828</td>
<td>583</td>
</tr>
<tr>
<td>2014</td>
<td>1373</td>
<td>703</td>
</tr>
<tr>
<td>Average (2011-14)</td>
<td>62 %</td>
<td>38 %</td>
</tr>
</tbody>
</table>
Breakdown of sources of spontaneous reports

2016

- Marketing authorisation holder: 84%
- Veterinarians: 13%
- Other: 3%

Legends:
- Blue: Marketing authorisation holder
- Red: Veterinarians
- Green: Other
Spontaneous reports - Immunologicals
2009 to 2016
## Spontaneous reports per animal species

01.01. bis 31.12.2016

<table>
<thead>
<tr>
<th>Spezies</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
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<tbody>
<tr>
<td>Bovine</td>
<td>94</td>
<td>109</td>
<td>148</td>
</tr>
<tr>
<td>Ovine</td>
<td>5</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Porcine</td>
<td>159</td>
<td>152</td>
<td>211</td>
</tr>
<tr>
<td>Equine</td>
<td>45</td>
<td>42</td>
<td>54</td>
</tr>
<tr>
<td>Canine</td>
<td>218</td>
<td>301</td>
<td>340</td>
</tr>
<tr>
<td>Feline</td>
<td>47</td>
<td>78</td>
<td>84</td>
</tr>
<tr>
<td>Rabbits</td>
<td>111</td>
<td>72</td>
<td>203</td>
</tr>
<tr>
<td>Chicken</td>
<td>16</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Pigeon</td>
<td>5</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>
Spontaneous reports per animal species
01.01. bis 31.12.2016
Feed-Back on Pharmacovigilance Reporting

- We publish in the German Veterinary Journal
- PDF available on the PEI and BVL website
- only in national language

Pharmacovigilance Corner
(3 times a year, together with BVL)

Annual Reports
Vaccinovigilance

• „Highlights“ & Case Reports
  – Local reactions
    • Feline Injection Site Sarcoma
    • Accidental injection in humans

Suffolk ewe with a patch of black wool on the neck following vaccination against footrot

AGNES WINTER: Vaccination programmes for sheep flocks
In Practice (2009) 31, 326-332
Feline Injection Site Sarkome (FISS)

- Iatrogenic tumor, recognized for > 20 years, extremely locally invasive.
- First vaccines against rabies and feline leukemia were blamed → vaccine-associated sarcoma
- PhV data → Injection site sarcoma
- Pathogenesis is still unknown, but inflammation induced by vaccines or other injections is likely to play a critical role.
Accidental injection with veterinary vaccines may be dangerous.

Cave: Oil adjuvanted products

→ Information of the public
Human exposure to veterinary medicines

Equilis StrepE
(live streptococcus vaccine against strangles in horses)

The capping of the needle lead to a high rate of self-injections → modification of the adapter
Vaccinovigilance

• „Highlights“ & Case Reports
  – Systemic reactions
    • Endotoxins
    • Abortions in cattle after BTV-8 vaccination
Clinical effects of endotoxin in vaccines

- Recumbency
  - High endotoxin content of vaccines prepared from gramnegative germs
  - Often batch related
  → Endotoxin content is limited today

- Vomiting

- Convulsions
When BTV-8 mass vaccination started in Europe many complaints about side-effects (abortions, death, milk-drop) were received. A critical evaluation of the reports by the PhV teams across Europe could not verify these complaints. On the contrary, today the BTV-8 vaccines are acknowledged as very safe and efficient products.
Vaccinovigilance

• „Highlights“ & Case Reports
  – Immune mediated diseases
    • Hypersensitivity Type I reactions
    • Autoimmune disease
      (Bovine Neonatal Pancytopenia)

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**Table 2. Gell And Coombs Classification Schema Of Hypersensitivity Reactions.**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Effector Mechanism</th>
<th>Typical Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I (Immediate)</td>
<td>IgE</td>
<td>Anaphylaxis, angioedema, urticaria</td>
</tr>
<tr>
<td>Type II (Cytotoxic)</td>
<td>IgM, IgG, complement, phagocytosis</td>
<td>Cytopenia, nephritis</td>
</tr>
<tr>
<td>Type III (Immune Complex)</td>
<td>IgM, IgG, complement, precipitins</td>
<td>Serum sickness, vasculitis</td>
</tr>
<tr>
<td>Type IV (Delayed)</td>
<td>T Lymphocytes</td>
<td>Contact dermatitis</td>
</tr>
</tbody>
</table>
Angioedema of the face of a Doberman Pinscher puppy
The eye lids are swollen and the muzzle is severely distorted by edema.

More research is needed on the causes and prevention of hypersensitivity reactions in animals.
Bovine Neonatal Pancytopenia (BNP)

- A new disease appeared 2007 in Germany: bleeding calf syndrome
- Calves around two weeks of age developed a bleeding disease, mainly fatal
- Thrombocytopenia, Leukopenia and Pancytopenia
- Related to farms with a history of BVD vaccination, indeed emerging epidemiological data strongly pointed towards a specific inactivated vaccine
Bovine Neonatal Pancytopenia (BNP)

Mechanism of Neonatal Pancytopenia Linked to Vaccination.

• Allo-antibodies are raised in the dams against self proteins present on remnants from the cell line used for vaccine production.
• Allo-antibodies are transferred with colostrum to the calf.
Bovine Neonatal Pancytopenia (BNP)

PhV measures:

- Recall of batches in Germany
- Suspension of the marketing authorisation

However, due to the long term effect of antibody production, we still noted BNP cases until this year.
Suspected Lack of Expected Efficacy

• „Highlights“ & Case Reports
  – Suspected lack of expected efficacy (SLEE)
    • RHD-2
Suspected Lack of Expected Efficacy

- In 2010 PhV reports about outbreaks in vaccinated farms in France raised concerns about the efficacy of RHD vaccines.
- Soon it became evident that a new variant of RHD (RHDV2) was emerging.
- This information was spread via PhV channels three years in advance before outbreaks reached Germany.
Thank you for your attention!

“He was in perfect health until you gave him that rabies shot three years ago.”

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WE NEED YOUR SUPPORT TO PROMOTE PHARMACOVIGILANCE
Causality Assessment

“ABON” Code

A – the medicine probably caused the event observed
B – the medicine possibly caused the event observed
O – there is insufficient evidence to judge if the medicine caused the event observed
N – the medicine probably did not cause the event observed.
ABON and BTV-8 Vaccination

Reports for all species
- A: 33%
- B: 32%
- O: 15%
- N: 15%

Reports for cattle (without Bluetongue)
- A: 24%
- B: 23%
- O: 38%
- N: 15%

Reports for cattle only Bluetongue
- A: 7%
- B: 15%
- O: 77%