EDQM Workshop
Bluetongue Vaccines
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Strasbourg, France

Session 1
Current Situation
Vaccination against bluetongue in Southern Europe: a challenging experience

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Italy

BTV incursions in the Mediterranean Basin from 1998 to 2006
European reaction

• After the incursion of BTV into Southern Europe:

  - Spanish, French, Italian and Portuguese authorities have all carried out compulsory vaccination campaigns to reduce direct losses due to disease and indirect losses due to trade embargoes caused by the presence of BTV.

European reaction

• After the incursion of BTV into Southern Europe:

  - At that time, the MLVs produced by Onderstepoort Biological Products were used as they were the only commercially available BTV vaccines. Based on the serotype(s) present in a given country/area, various MLV monovalent serotype formulations have been used.
Live-modified vaccine

- Attenuation by egg passages and plaque purification
- Used for decades in South Africa but only in sheep
- MLV used in USA (BTV-10; 11; 13 and 17)
- MLV (produced by OBP) have been used in Israel, Bulgaria, France (Corsica), Spain, Portugal and Italy,
**Advantages**

- It is a good product if used properly (right season and gestation period):
  - Cheap
  - One injection
  - Strong and long lasting immunity

**Live-modified vaccine**
Efficacy of vaccination campaign

- The efficacy of MLV vaccination has widely been demonstrated in the field.
- Following the 2000-2001 and 2003 BT vaccination campaigns in the Balearic Islands, no outbreaks have been detected since December 2003 in the area.

Efficacy of vaccination campaigns

**Vaccination coverage**

<table>
<thead>
<tr>
<th>Year</th>
<th>0%</th>
<th>&lt;40%</th>
<th>40% - 59.9%</th>
<th>60% - 79.9%</th>
<th>≥80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
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<td>2002</td>
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<td>2003</td>
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</tr>
</tbody>
</table>

**Clinical outbreaks**

- **Sardinia:** 24 cases
- **Tuscany:** no cases
- **BTV4 New serotype**

- Outbreaks: 6,869
  - Diseased animals: 262,759
- Outbreaks: 6,807
  - Diseased animals: 250,662
- Outbreaks: 432
  - Diseased animals: 3,698
- Outbreaks: 3,709
  - Diseased animals: 93,954
**Vaccination coverage**

- 2004
- 2005
- 2006
- 2007

**Clinical outbreaks**

- 2004: Outbreaks: 127, Diseased animals: 2,481
- 2005: Outbreaks: 0, Diseased animals: 0
- 2006: Outbreaks: 238, Diseased animals: 4,861
- 2007: Outbreaks: 15, Diseased animals: 609

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**Results of the 2002 BTV vaccination campaign**

- BTV 2
- BTV 2 and 9
- Not available
- 0 %
- < 40 %
- 40 % - 59.9 %
- 60 % - 79.9 %
- ≥ 80 %
Virus circulation (outbreaks and seroconversions) in the regions where more than 80% of the livestock animals were vaccinated

2001 2002

Virus circulation (outbreaks and seroconversions) in the regions where less than 80% of the livestock animals were vaccinated
Adverse events observed in the use of MLV

- **Mild symptoms** (5-7 dd post vaccination)
- Possible vaccine virus circulation because of high viraemic titers

Sheep inoculated with BTV-4 vaccine virus

- Acute respiratory dysfunction
- Swelling and discoloring of the lips and tongue and copious salivation
- Cyanosis of the whole oral cavity including the tongue (acute oxygen deficiency)
Most drawbacks are limited if the vaccine isolates are well attenuated (BTV-2 and 4) however they could be considerable if the strains are not well attenuated (BTV-16).

Adverse events observed in the use of MLV

![Graph showing viraemic titers (TCID50/ml) over days following vaccination for BTV-9 and BTV-2.]
Circulation of BTV-16 vaccine strain in Italy

2006

2007

2008

2009
BTV-16 in Croatia

... or if the vaccines are administered in animals with existing infections .......
According to the results of a field trial, flocks positive to Maedi-Visna have a 2.5 fold increased risk of suffering from side effects compared to flocks with no Maedi Visna infection.

Adverse events observed in the use of MLV

- Possibility that the vaccine virus crosses the placental barrier causing abortion, stillbirth or neonatal mortality
- Preliminary studies were carried out prior and during the BT mass vaccination
  - No adverse effects on reproduction were observed in CATTLE (BTV2 and BTV2-BTV9)
During 2002-2003 BTV Italian outbreaks:

- 1264 ovine, bovine, goat and buffalo foetuses were tested for the presence of BTV by VI.
- Foetal spleens and/or brains of:
  - 663 ovines,
  - 429 bovines,
  - 155 goats
  - 17 buffaloes

BTV strains were isolated from 31 foetuses (2.4% IC 95% 1.7-3.4%):

- 24 (3.6%; IC 95% 2.4-5.3%) from ovine foetal tissues;
- 6 (1.4%; IC 95% 0.6-3.0%) from bovine foetal tissues;
- 1 (0.6%; IC 95% 0.2-3.5%) from the spleen of a goat foetus.
Malformation induced by MLVs
Field data (first vaccination campaign): adverse effects were notified in 312 of 87,245 holdings (0.16% of cattle herds and 0.5% of small ruminant flocks). The presence of vaccine virus was confirmed by the laboratory.

- As a purely indicative quantitative assessment of the adverse event observed, one can examine data collected between 1991 and 2001 in the US by the Vaccine Adverse Event Reporting System (VAERS). During the study, 1.9 billion doses of 27 different types of human vaccine were administered and the prevalence of adverse events was 11.4 per 100,000 (equivalent to 0.01%).

Adverse events observed in the use of MLV

- Effect on semen:
  - A decrease in semen quality was also observed after the second vaccination (BTV-2) in 23 rams; however, at day 69, the semen quality of the vaccinated animals was not significantly different from those of the 23 controls.
Adverse events observed in the use of MLV

Effect on milk production:
• transient decrease of 30% a week after vaccination with bivalent BTV2 and BTV9 vaccine to sheep. However it was not accompanied by significant changes in milk quality (cell count, pH, fat, protein and lactose)
• A study involving more than 18,000 dairy cows in 220 herds vaccinated with BTV-2 MLV did not demonstrate any negative effects either on the quality or quantity of milk produced.
Effect of BTV-2 and BTV-9 MLV on milk production in cattle

Adverse events in the use of MLV

Possible reversion to virulence of the vaccine viruses and reassortment between vaccine and field strains of the virus

- The reassortment of BTV strains has been monitored in Italy over the last eight years.
- No reassortment between vaccine and field strains has been observed, while it has been witnessed between vaccine virus strains present in the same vaccine
  - Between BTV2 and BTV4
  - Between BTV2 and BTV16 (in Israel)
Despite the reassortment hypothesis, the number of existing serotypes is constant and remains **24 (now 26)**.

- Claims of the factual dangers of the use of MLV vaccine against BT due to either reversion to virulence of the vaccine viruses and reassortment between vaccine and field strains of the virus remain **hypothetical** for the time being and are not supported by factual scientific data.
Conclusions

• Both experimental and field experiences proved that MLVs are immunogenic and capable of protecting and preventing viraemia in vaccinated animals after challenge or infection.

• Following several years of vaccination campaigns, several Member States concluded that MLV vaccines, when used correctly, were relatively safe and successful.

Conclusions

• In the absence of effective inactivated vaccines and in an emergency, MLVs a valid option for vaccination, provided that the quality, safety and efficacy of the MLV strains match the International standards.

• These vaccines can be an alternative also in a non-emergency situation when local conditions (e.g. in case a large amount of animal must be immunized in a very short period of time) indicate their use.
... last year BTV outbreak in Sardinia ....

Thank you
VACCINATION AGAINST BLUETONGUE IN NORTHERN EUROPE: ANOTHER CHALLENGING EXPERIENCE

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JRU Virology ANSES/INRA/ENVA
Maisons-Alfort, France

EDQM, 2013, Strasbourg

Vectors: Culicoides (imicola,...)
> 1,500 species

Orbivirus

26 serotypes BTV
9 serotypes AHSV
7 serotypes EHDV
Epidemiological situation in Europe

2006 to 2013

Control

Modified live vaccines
Inactivated vaccines

1998: Free of BTV
Situation in the Mediterranean basin (1998-2006)

Summer 2006

Emergence in 2006
New serotype
New area
New clinical pattern
2006

Unbelievable year!!

The Netherlands, 2006

beginning mid-August, 2006
2 sick/90 sheep
Clinical bluetongue in cattle

End 2006
695 outbreaks in Belgium
914 in Germany
7 in France
The depression !!!

31 848 cases of BTV
- 26 925 cases of BTV8.
- 4 829 cases of BTV1.
- 99 cases BTV 1 and 8 in the same farms

December 31, 2008
2006: 7 cases
2007: 14,000
2008: 38,000
2009: 83
2010: 1
2011: 0
2012: 0
2013: free status

New introductions 2008-2009
Clinical disease has not been reported associated with these cases.

Modified live vaccines

• Bottle A includes BTV serotypes 1, 4, 6, 12, 14

• Bottle B includes serotypes 3, 8, 9, 10, 11

• Bottle C includes the serotypes 2, 5, 7, 13, 19

OBP, South Africa

BTV occurrence

from 1/1/2012 to 31/8/2012

• All cases are seroconverted animals tested in the framework of the national surveillance system
• No clinical signs were observed
THE PREVENTION: VACCINATION

Epidemiological situation in Europe

2006 to 2013

Control

Modified live vaccines
Inactivated vaccines

Serological relationships between BTV serotypes

- Strong
- weak
- very weak
Vaccination Serotype 2

49 outbreaks

2000

BTV 2 wt
Vaccine BTV 2

2001

Vaccination Serotype 2

335 outbreaks

BTV 2 Vaccine w/BTV 2 ?

2002

Vaccination Serotype 2

0 outbreaks

BTV 4
Vaccine BTV 4
BTV 2 wt
Vaccine BTV 2

BTV 2 ?

2003

Vaccine BTV 4
Vaccine BTV 2
BTV 2 ?

17 outbreaks

BTV-16 in Corsica (2004)

• no BTV 16 vaccination performed in Corsica
• first cases in sheep in September 2004
• Virus isolated and typed (16)

November : vaccination with live BTV-16 vaccine

• 19 herds vaccinated in December 2004 (serotype 16)
+ vaccination 2 and 4

• 11/19 herds with BT-like clinical signs
Characteristics of the Bluetongue virus vaccine strains (OBP)

<table>
<thead>
<tr>
<th>MODIFIED LIVE VACCINE</th>
<th>STRAIN</th>
<th>DATE AND PLACE OF ISOLATION</th>
<th>HISTORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTV-2</td>
<td>VRYHEID/5036</td>
<td>1958, REPUBLIC OF SOUTH AFRICA</td>
<td>Virus passed 50 times in embryonated chicken eggs and plaque selected three times and passed twice in BHK23 cells</td>
</tr>
<tr>
<td>BTV-4</td>
<td>THEILER/79043</td>
<td>1900, REPUBLIC OF SOUTH AFRICA</td>
<td>Virus passed 60 times in embryonated chicken eggs, followed by 3 small plaque selections and 9 passages in BHK23 cells.</td>
</tr>
<tr>
<td>BTV-9</td>
<td></td>
<td>1900, REPUBLIC OF SOUTH AFRICA</td>
<td>Virus passed 70 times in embryonated chicken eggs, followed by 3 small plaque selections and 6 further passages in BHK23 cells.</td>
</tr>
<tr>
<td>BTV-16</td>
<td>PAKISTAN/7766</td>
<td>PAKISTAN</td>
<td>Virus passed 37 times in eggs, followed by 3 large plaque selections, 2 passages in BHK23 cells and 1 in VERO cells.</td>
</tr>
</tbody>
</table>
## Current global position of bluetongue live attenuated vaccines

<table>
<thead>
<tr>
<th>Country/Origin</th>
<th>Serotype</th>
<th>Details of the strain</th>
<th>Passage history</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSA, 1958</td>
<td>BTV-1</td>
<td>Biggarsberg/8012</td>
<td></td>
</tr>
<tr>
<td>RSA, 1958</td>
<td>BTV-2</td>
<td>Vryheid/5036</td>
<td></td>
</tr>
<tr>
<td>RSA, 1934</td>
<td>BTV-3</td>
<td>Cyprus/2311</td>
<td></td>
</tr>
<tr>
<td>RSA, 1900</td>
<td>BTV-4</td>
<td>Theiler/70043</td>
<td></td>
</tr>
<tr>
<td>RSA, 1953</td>
<td>BTV-5</td>
<td>Mosap/4408</td>
<td></td>
</tr>
<tr>
<td>RSA, 1958</td>
<td>BTV-6</td>
<td>Strasbourg/5011</td>
<td></td>
</tr>
<tr>
<td>RSA, 1955</td>
<td>BTV-7</td>
<td>Utrecht/1504</td>
<td></td>
</tr>
<tr>
<td>RSA, 1937</td>
<td>BTV-8</td>
<td>Camp/5438</td>
<td></td>
</tr>
<tr>
<td>RSA, 1942</td>
<td>BTV-9</td>
<td>Universit Farm/2766</td>
<td></td>
</tr>
<tr>
<td>Portugal, 1956</td>
<td>BTV-10</td>
<td>Portugal/2627</td>
<td></td>
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<tr>
<td>RSA, 1941</td>
<td>BTV-11</td>
<td>Nevisper/7735</td>
<td></td>
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<tr>
<td>RSA, 1959</td>
<td>BTV-12</td>
<td>Estanus/75005</td>
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<tr>
<td>RSA, 1959</td>
<td>BTV-13</td>
<td>Westlands/7238</td>
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<tr>
<td>RSA, 1959</td>
<td>BTV-14</td>
<td>Kaledumu/8379</td>
<td></td>
</tr>
<tr>
<td>RSA, 1959</td>
<td>BTV-15</td>
<td>Pakistan/7766</td>
<td></td>
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<tr>
<td>RSA, 1976</td>
<td>BTV-19</td>
<td>Modified live virus of serotype 10</td>
<td></td>
</tr>
<tr>
<td>Colorado serum Co., Denver, Colorado, USA</td>
<td>BTV-10</td>
<td>Modified live virus of serotype 10</td>
<td></td>
</tr>
<tr>
<td>Central Veterinary Control &amp; Research Institute, Ankara, Turkey</td>
<td>BTV-4</td>
<td>Freeze-dried modified, sheep</td>
<td></td>
</tr>
<tr>
<td>Biopharma, Morocco</td>
<td>BTV-4</td>
<td>Live attenuated, sheep</td>
<td></td>
</tr>
<tr>
<td>California, USA</td>
<td>BTV-10</td>
<td>Bluevac-10</td>
<td></td>
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<tr>
<td></td>
<td>BTV-11</td>
<td>Bluevac-11</td>
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<td>BTV-17</td>
<td>Bluevac-17</td>
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<tr>
<td></td>
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<td>(EFSA, AHAW 2007)</td>
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</table>

### Onderstepoort Biological Products

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<tr>
<th>Country/Origin</th>
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<tr>
<td>RSA, 1958</td>
<td>BTV-1</td>
<td>Biggarsberg/8012</td>
<td>50E 3P 4BHK</td>
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<td>RSA, 1958</td>
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<tr>
<td>RSA, 1934</td>
<td>BTV-3</td>
<td>Cyprus/2311</td>
<td>45E 2BHK 3P 8BHK</td>
</tr>
<tr>
<td>RSA, 1900</td>
<td>BTV-4</td>
<td>Theiler/70043</td>
<td>60E 3P 9BHK</td>
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<tr>
<td>RSA, 1953</td>
<td>BTV-5</td>
<td>Mosap/4408</td>
<td>50E 2BHK 3P 6BHK</td>
</tr>
<tr>
<td>RSA, 1958</td>
<td>BTV-6</td>
<td>Strasbourg/5011</td>
<td>65E 3P 7BHK</td>
</tr>
<tr>
<td>RSA, 1955</td>
<td>BTV-7</td>
<td>Utrecht/1504</td>
<td>60E 3P 7BHK</td>
</tr>
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<td>RSA, 1937</td>
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<td>Camp/5438</td>
<td>50E 3BHK 10P 7BHK</td>
</tr>
<tr>
<td>RSA, 1942</td>
<td>BTV-9</td>
<td>Universit Farm/2766</td>
<td>70E 2BHK 9P 3BHK 7P 4BHK</td>
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<td>Portugal, 1956</td>
<td>BTV-10</td>
<td>Portugal/2627</td>
<td>E81</td>
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<tr>
<td>RSA, 1941</td>
<td>BTV-11</td>
<td>Nevisper/7735</td>
<td>35E 3P 4BHK</td>
</tr>
<tr>
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<td>BTV-12</td>
<td>Estanus/75005</td>
<td>55E 3P 4BHK</td>
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<tr>
<td>RSA, 1959</td>
<td>BTV-13</td>
<td>Westlands/7238</td>
<td>45E 2BHK 3P 4BHK</td>
</tr>
<tr>
<td>RSA, 1959</td>
<td>BTV-14</td>
<td>Kaledumu/8379</td>
<td>60E 3P 4BHK</td>
</tr>
<tr>
<td>RSA, 1959</td>
<td>BTV-15</td>
<td>Pakistan/7766</td>
<td>37E 3F 2BHK 1Vero</td>
</tr>
<tr>
<td>RSA, 1976</td>
<td>BTV-19</td>
<td>Modified live virus of serotype 10</td>
<td>29E 3P 3BHK</td>
</tr>
</tbody>
</table>

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## Modified live vaccines

### Infection and teratogenicity of MLVs for the developing fetus:
MLVs have the capacity to cross the ruminant placenta leading to embryonic or fetal death and cerebral malformations (hydroencephaly in calves) after infection of older fetuses that survive congenital infection.

### BT related reproductive disorders:
Include early embryonic deaths, abortions, malformed fetal calves or lambs, transient infertility in bulls and rams.

### Possibility that vaccine viruses will infect vectors and establish in the environment as quasispecies with possible reversion to virulence or creation of new strains of BTV (reassortment)
Number of vaccinated animals with the modified live vaccines (adverse effects)

- Balearic Islands (2000-2001) : 320 000 sheep and goats (BTV-2)
- Corsica (2001-2004) : > 130 000 sheep and goats (BTV2) ; 130 000 sheep and goats (BTV4)
- Italy (from 2002) : 4 000 000 sheep and goats (BTV2 and BTV2-4) ; 400 000 cattle (BTV2-4) ; 1 700 000 (BTV2-9) ; 1 000 000 sheep, goats and cattle (since 2005)(BTV2-4-9)
- Corsica (2004) : BTV16 : adverse effects
- Sardinia : BTV2, 4 and 16 : adverse effects (sheep and goats)
- South of Italy : BTV2-4-9-16 : 600 000 animals : no adverse effects

Inactivated vaccines
Current global position of bluetongue inactivated vaccines (EFSA, AHAW 2007)

<table>
<thead>
<tr>
<th>Country</th>
<th>Serotype</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merial SAS, Lyon, France</td>
<td>BTV-2, BTV-4, BTV-8, BTV-9, BTV-1</td>
<td>Liquid, mono/multivalent. Commercialized under ATU in France, Italy, Spain and Portugal</td>
</tr>
<tr>
<td>Intervet (MSD)</td>
<td>BTV-8, BTV-1</td>
<td>(i) Bivalent, BEI-Formaldehyde inactivated &amp; adjuvanted Montanide ISA50. Passed in house and field trials.</td>
</tr>
<tr>
<td>Fort Dodge (Pfizer)</td>
<td>BTV-8, BTV-1</td>
<td>(ii) BEI-Formaldehyde inactivated &amp; adjuvanted with a combination of mineral oil, Span 80 and Tween 80 (Aqueous: 40 parts, Oil: 60 parts) Passed in house and field trials</td>
</tr>
<tr>
<td>India (TANUVAS)</td>
<td>BTV-1, BTV-23</td>
<td>Hydroxylamine inactivated &amp; adjuvanted with saponin, aluminium hydroxide individually &amp; in combination</td>
</tr>
<tr>
<td>IAH &amp; VB, Bangalore</td>
<td>BTV1, BTV2</td>
<td>BEI inactivated &amp; saponified BTV1</td>
</tr>
<tr>
<td>Italy</td>
<td>BTV2, 4</td>
<td>Bivalent inactivated BT vaccine</td>
</tr>
</tbody>
</table>

Bluetongue vaccination campaigns in European countries (EFSA, AHAW 2007)

<table>
<thead>
<tr>
<th>Year of vaccination</th>
<th>BTV2</th>
<th>BTV4</th>
<th>BTV8</th>
<th>BTV2&amp;4</th>
<th>BTV2&amp;4</th>
<th>BTV2&amp;9</th>
<th>BTV16</th>
<th>BTV2,4,9</th>
<th>BTV2,4,9,16</th>
<th>BTV2,4,9</th>
<th>BTV2,4,9,16</th>
<th>BTV2,4,9,16</th>
<th>BTV2,4,9,16</th>
</tr>
</thead>
</table>

2008 : vaccination > 120 000 000 inactivated vaccine BTV-8
2008 – 2009:

BTV8 Vaccination on a **COMPULSORY** basis:
- in Belgium for cattle (young animals in priority) and sheep
- in Germany

**VOLUNTARY** basis:
- in Germany in 2010
- in the Netherlands

2006-2007: Lack of BTV-8 **inactivated** vaccines

**Vaccination Roll-out plan – UK in 2008**

Voluntary vaccination policy

High and early coverage in areas infected with BTV

Around 80-90%

C Oura, IAH
The Netherlands

<table>
<thead>
<tr>
<th></th>
<th>2008</th>
<th>2009</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheep</td>
<td>73%</td>
<td>42%</td>
</tr>
<tr>
<td>Cattle</td>
<td>71%</td>
<td>58%</td>
</tr>
<tr>
<td>Goats</td>
<td>43%</td>
<td>19%</td>
</tr>
</tbody>
</table>

voluntary basis in both years 2008 and 2009
In 2008, farmers could receive reimbursement directly. 2009, they had to pay all by their selves. Decrease of the willingness to vaccinate!!!

Situation in France (beginning of 2008)

18,339 cases

Initial zone of vaccination

DGAl
### Vaccination in France

**2009 -2010**

Vaccination in France

- Vaccination against BTV1 and 8 : compulsory
- Cattle > 2.5 months of age
- Sheep > 3 months age
- Beginning 2 of November 2009 for 12 months
- Budget : 98 millions € (State)

<table>
<thead>
<tr>
<th>Name of the vaccine</th>
<th>Name of the lab</th>
<th>species</th>
<th>Site of vaccination</th>
<th>ml/dose</th>
<th>boost</th>
<th>Minimal Age at vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTV1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zulvac 1 cattle</td>
<td>FORT DODGE (PFIZER)</td>
<td>Cattle</td>
<td>IM</td>
<td>2</td>
<td>12</td>
<td>2.5 months</td>
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<tr>
<td>Zulvac 1 ovine</td>
<td>FORT DODGE (PFIZER)</td>
<td>Ovine</td>
<td>SC</td>
<td>2</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Bluvec 1</td>
<td>CZ</td>
<td>Cattle</td>
<td>SC</td>
<td>4</td>
<td>12</td>
<td>2</td>
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<tr>
<td>Bluvec 1</td>
<td>CZ</td>
<td>Ovine</td>
<td>SC</td>
<td>2</td>
<td>12</td>
<td>2.5</td>
</tr>
<tr>
<td>Syvazul 1</td>
<td>SYVA</td>
<td>Ovine</td>
<td>SC</td>
<td>2</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>BTV8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bovils</td>
<td>INTERVET (MSD)</td>
<td>Cattle</td>
<td>SC</td>
<td>1</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Bovils</td>
<td>INTERVET (MSD)</td>
<td>Ovine</td>
<td>SC</td>
<td>1</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>BTV Pur Alsap 8</td>
<td>Merial</td>
<td>Cattle</td>
<td>SC</td>
<td>1</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>BTV Pur Alsap 8</td>
<td>Merial</td>
<td>Ovine</td>
<td>SC</td>
<td>1</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Zulvac 8 Bovis</td>
<td>FORT DODGE (PFIZER)</td>
<td>Cattle</td>
<td>IM</td>
<td>2</td>
<td>6</td>
<td>2.5</td>
</tr>
</tbody>
</table>
Vaccination against BT in Spain

Luis Jose Romero Gonzalez, MAPA

November 2007 to December 2008

- compulsory vaccination
- vaccination of cattle, sheep > 3 months-old in restriction zones
- vaccination costs: State, Commission

**COBERTURA VACUNAL MEDIA**

- **OVINO-ST1**: 96.6%
- **OVINO-ST8**: 76.3%
- **BOVINO-ST1**: 90%
- **BOVINO-ST8**: 73.6%
Prevention: summary

From 2000 to 2006

Kris de Clercq

Modified live vaccine: OBP, South Africa
From 2006 to 2010

in 2010:
Piemonte Region: vaccination with BTV8 inactivated vaccine

in 2010-2012:
Sardinia: vaccination with BTV1, BTV2 and 4 inactivated vaccines

Giovanni Savini
Conclusion

- Control by (compulsory) vaccination (live/inactivated vaccines)

- Bivalent 2-4 and 1-8 inactivated vaccines

- Eradication of BTV in the North of Europe

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Martin Beer, FLI, Germany
Bernd Hoffmann, FLI, Germany
Giovanni Savini, IZST Teramo, Italy
Peter Mertens, Pirbright Institute, UK
Piet van Rijn, CVI, The Netherlands
...

...
VACCINATION AGAINST BT VIRUS: SPANISH EXPERIENCE

Luis J. Romero González: ljromero@magrama.es

Subdirectorate General for animal health, animal hygiene and traceability

Strasbourg, 19th February 2013
BALEARIC ISLANDS 2000: BTV-2

Adopted measures:

• Control of susceptible species movements
• Vaccination of ovine population: attenuated vaccine BTV-2 (>322,000 animals, October 2000-May 2001)
• Virus circulation not detected during 2001-2002

BALEARIC ISLANDS 2003: BTV-4

Adopted measures:

• Control of susceptible species movements
• Vaccination of ovine population: attenuated vaccine BTV-4 (>339,000 animals, October 2003-March 2004)
• BTV-2 free since 2002 and BTV-4 free since 2005.
SPAINISH MAINLAND 2004-2006: BTV-4

Adopted measures:

• Control of susceptible species movements


• Problems with the cattle movement: inactivated vaccine?

• No outbreaks of BTV-4 (November 2006-October 2010)

BT SITUATION IN SPAIN 2007: BTV-4 and 1

2007 first BTV-1 incursion: high level of ovine mortality

Vaccination a must!!!!
BT SITUATION IN SPAIN 2008: BTV-4, 1 and 8

First BTV-8 incursion in 2008

BT SITUATION 2010-2013: BTV-4, 1 and 8

Reintroduction of BTV-4 October 2010

BTV-8 free since January 2013
**OBJECTIVE**: vaccination of all the ruminant population (sheep and cattle) within the restricted zone so that:
- the viral circulation diminishes
- neither clinical signs nor deaths in ovine
- allowing movements to free zone
- achieving the eradication of the disease

**VACCINES USED**
- 2001-2005 and first semester of 2006; attenuated live vaccine (Onderstepoort – South Africa)
- Five laboratories attend the request of development of BTV-4 inactivated vaccines: Merial, CZ, Calier, SYVA and FortDodge
- Efficacy trials were performed in different Spanish BSL-3 animal facilities, and the laboratorial tests in LCV of Algete (Spanish NRL for BT)
- Since May 2006: BTV-4 inactivated vaccine
INACTIVATED vs LIVE ATTENUATED

- It can be used not only in sheep, BUT ALSO in bovine
- It can be used along all the year
- Useful tool to facilitate animal movements (no viraemia)
- More expensive and two doses per animal (at least for cattle)
- Safer

BLUETONGUE VACCINATION PROGRAMME

- Compulsory vaccination programme (until July 2011)
- All the ovine and bovine population older than 3 months in the restricted zones
- The cost of the vaccine was supported by the Ministry of Agriculture (co-financed by Commission), and the cost of the vaccination by the Autonomous regions
- The vaccine could be applied by official veterinary services or by authorised veterinaries, depending on the Autonomous region, but always under official control
- Vaccinated animals must be marked by ear tag, microchip or in the bovine identification passport
# Vaccination Data

<table>
<thead>
<tr>
<th>YEAR</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Bovine in Restricted Zone</strong></td>
<td>1,424,161</td>
<td>7,723,787</td>
<td>2,351,115</td>
<td>6,327,685</td>
<td>5,951,452</td>
<td>5,835,901</td>
<td>6,532,594</td>
</tr>
<tr>
<td>Bovine Vaccinated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BTV-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>51,060</td>
<td>4,660,000</td>
<td>5,600,947</td>
<td>5,302,145</td>
<td>1,457,952</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BTV-4</td>
<td>43,497</td>
<td>140,123</td>
<td>1,178,499</td>
<td>1,615,000</td>
<td>293,708</td>
<td>141,986</td>
<td></td>
</tr>
<tr>
<td>BTV-8</td>
<td></td>
<td>4,200,000</td>
<td>5,643,323</td>
<td>5,303,344</td>
<td>340,627</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Ovine in Restricted Zone</strong></td>
<td>6,977,990</td>
<td>6,086,632</td>
<td>11,185,980</td>
<td>16,698,938</td>
<td>16,649,010</td>
<td>16,804,479</td>
<td>17,047,105</td>
</tr>
<tr>
<td>Ovine Vaccinated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BTV-1</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>1,170,197</td>
<td>16,000,000</td>
<td>14,992,099</td>
<td>14,544,559</td>
<td>6,925,672</td>
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<td></td>
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<tr>
<td>BTV-4</td>
<td>6,287,965</td>
<td>3,409,742</td>
<td>8,014,031</td>
<td>6,460,000</td>
<td>483,697</td>
<td>214,091</td>
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<tr>
<td>BTV-8</td>
<td>14,000,000</td>
<td>14,908,306</td>
<td>14,528,249</td>
<td>749,230</td>
<td></td>
<td></td>
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</table>

# Vaccination Coverage

<table>
<thead>
<tr>
<th>YEAR</th>
<th>Ovine BTV-1</th>
<th>Ovine BTV-8</th>
<th>Bovine BTV-1</th>
<th>Bovine BTV-8</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>96.60</td>
<td>76.30</td>
<td>90.00</td>
<td>73.60</td>
</tr>
<tr>
<td>2009</td>
<td>95.00</td>
<td>93.00</td>
<td>91.00</td>
<td>90.00</td>
</tr>
</tbody>
</table>
INMUNISATION CONTROL

- Antibody detection by ELISA
- Vaccinated bovine-ovine animals 3-12 moths old
- 15 days after vaccination
- 95/5: 115 bovine samples and 45 ovine samples per AR

<table>
<thead>
<tr>
<th></th>
<th>Ovine Samples</th>
<th>Ovine Positive</th>
<th>Ovine % (IC95%)</th>
<th>Bovine Samples</th>
<th>Bovine Positive</th>
<th>Bovine % (IC95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>2.115</td>
<td>2.072</td>
<td>97,97% (97,38:98,36)</td>
<td>2.121</td>
<td>1.954</td>
<td>92,13% (91,09:93,02)</td>
</tr>
<tr>
<td>2009</td>
<td>515</td>
<td>462</td>
<td>89,71% (87,09:92,33)</td>
<td>1.238</td>
<td>970</td>
<td>78,35% (75,76:80,94)</td>
</tr>
</tbody>
</table>

BLUETONGUE EVOLUTION
CURRENT SITUATION: BT RESTRICTION ZONES

FUTURE: BTV-1 VACCINATION ZONES?
CONCLUSIONS

- Vaccination prevents clinical signs and mortality
- It controls viral circulation and leads to decrease of outbreaks number
- It facilitates animal movements
- It led to eradication of BTV-2 in 2002, BTV-4 in 2005 (Balearic Islands), BTV-4 in 2009 (Spanish Mainland) and BTV-8 in 2013
- Benefit is not only for own country but also for the rest of the region

THANK YOU FOR YOUR ATTENTION!
Outline

- Evolution bluetongue in the EU 2001 – 2012
- EU reaction: policy and measures
- Impacts and Costs
- Lessons learnt
- Conclusions
**Bluetongue in the EU**

**2002 - 2006:**
Bluetongue mainly present in Mediterranean area (serotypes 1, 2, 4, 9, 16)

**Autumn 2006:**
Start of BTV-8 epidemic
Netherlands, Luxembourg, Belgium and Germany

---

**Bluetongue in the EU**

**2007:** BTV-8 spreads southwards towards France

BTV-1 in Spain, Portugal and France

Start of mass vaccination campaign against BTV-1 and BTV-8
Bluetongue in the EU

2009-2012
Due to successful vaccination campaigns:
- BTV8 disappeared
- BTV1 only sporadically in Spain and Portugal

Local circulation of BTV 1, 2, 4, 9 and 16 in Italy, Greece and Cyprus

Evolution Bluetongue in the EU

http://ec.europa.eu/food/animal/diseases/controlmeasures/bt_outbreaks_en.htm
Evolution Bluetongue in the EU
Number of outbreaks notified by year

**EU Response: four pillars**

**EU legislation**
- Commission Regulation (1266/2007)

**EU funds**
- Council Decision 2009/470/EC

**OIE Terrestrial Animal Health Code**
- Chapter 8.3

**European Food Safety Authority (EFSA)**
http://www.efsa.europa.eu/
EU response: Measures in the EU

- Movement restrictions
- Sustainable control
  - Vaccination
  - Surveillance

EU response: Changes in legislation

- Commission Regulation (EC) No 1266/2007 as amended 12 times
  - Vaccinated animals can always move

  - No restriction for vaccination with inactivated vaccines
  - Still some restrictions for live attenuated vaccines
EU response: Vaccination

- Inactivated vaccines approved under exceptional circumstances
- Mass emergency vaccination campaign in 2007-2008 against BTV1 and BTV8
- Vaccination essential part of eradication programmes
- EU initial allocation of funds for bluetongue vaccination and surveillance:

EU response: EU funds

![Graph showing EU funds allocation over years]
Lessons learnt

- *EU rules not easy to understand*
- *Impact of bluetongue*
- *Economics: Costs (vaccination) vs Benefits (disease control)*
Impact of Bluetongue depends on:

- (un-) favourable conditions for virus persistence
  - weather
  - density of susceptible animals
- importance of trade:
  - mainly sending animals
  - or receiving animals
- susceptible population:
  - mainly ovine
  - bovine animals
- virus serotype

Impact – calves born 2005-2012

Source: FAVV, Belgium
Impact – milk production 2007-2012

Source: FAVV, Belgium

Impact: Trade movements within the EU

5 million European cattle cross the borders every year (7% of the EU livestock)

Movement of cattle in Europe in 2011 (x 1000 heads)

Source: GEB-Animal Breeding Institute as per Eurostat
Impact: Domestic movements

France
Has 1/3 of the European suckler cows

50% of male calves are exported as weanling (around 1Mln)

17% of the cows are relocated within France to deliver young cattle (200 000)

EXAMPLE: Movement of weanlings within France for the production of young cattle

Costs of disease control measures

➢ Swiss study:

"the surveillance and intervention programme [vaccination] implemented in 2008–2009 was economically beneficial, while its continuation in the same form in 2010–2012 [when free status was regained] would produce net costs"
Costs of disease control measures: EU contribution

Costs of vaccination: Unitary costs per vaccine dose claimed by MSs for EU co-funding
Costs of vaccination: Unitary costs per vaccine dose claimed by MSs for EU co-funding

Lessons learnt on vaccination (I)

- Vaccination is effective as a tool for control and eradication
  - Example BTV8 and BTV1 in many MSs
    - But not everywhere...
- Preventive vaccination in high risk areas can be worthwhile
  - Legal obstacles to perform vaccination were removed
    - But currently not so widely implemented...
- Mass vaccination is very expensive
  - Successful exercise
    - But doubts about proportionality...
Lessons learnt on vaccination (II)

- It takes time to develop and produce inactivated vaccines (~ 18 months?)
  - Live vaccines are available...
- Pharmaceutical industry expected a big-long lasting vaccines market
  - However this was not the case...
- Responsibility on vaccination moved from policy makers to animal keepers
  - As they know best...

Conclusions

- Bluetongue is an actual disease...
- Bluetongue is a problem with many dimensions:
  - Production
  - Veterinary
  - Scientific
  - Environmental
  - Climatic
  - Economic
  - Trade
  - Political...
- Bluetongue is there and will continue to be there...
- Vaccine is the only control tool
Thanks
MULTI-STRAIN DOSSIER CONCEPT
Impact on drafting potential PhEur
Monographs on Bluetongue vaccines

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Mail : jean-claude.rouby@anses.fr

Agence Nationale de Sécurité Sanitaire de l’Alimentation, de l’Environnement et du Travail
Agence Nationale du Médicament Vétérinaire
8 rue Claude Bourgelat, Parc d’activités de la Grande Marche - Javené
BP 90203 – 35302 FOUGERES CEDEX, France

BACKGROUND (1)

Directive 2001/82/EC (as amended by Directive 2009/9/EC), Title IV, section 1B – Multi-strain dossier :

• For certain immunological veterinary medicinal products (foot-and-mouth disease, avian influenza and bluetongue) the concept of the use of a multi-strain dossier is introduced.
BACKGROUND (2)

• A multi-strain dossier means a single dossier containing the relevant data for a unique and thorough scientific assessment of the different options of strains/combinations of strains permitting the authorisation of vaccines against antigenically variable viruses.

⇒ multi-strain ≠ multivalent !

BACKGROUND (3)

• Scientific guidelines for the submission and evaluation of multi-strain dossiers shall be adopted by the Agency.

⇒ Guideline EMA/CVMP/IWP/105506/2007 (in effect since 1 July 2010)
BACKGROUND (4)

multi-strain concept

NOT compulsory!

↓

standard dossier

or

multi-strain dossier

CURRENT SITUATION (1)

FORMULATION A

- MSV 1
- MSV 2
- MSV 3
- Formulation A
- Finished Product A
- Safety A
- Potency A
- Efficacy A

FORMULATION B

- MSV 4
- MSV 5
- Formulation B
- Finished Product B
- Safety B
- Potency B
- Efficacy B
CURRENT SITUATION (2)

BT = 24 serotypes ⇒

3 MSV CHOSEN → 2,024 POSSIBILITIES

5 MSV CHOSEN → 42,504 POSSIBILITIES

multi-strain concept = pragmatic approach

MULTI-STRAIN DOSSIER PRE-REQUISITES (1)

• Diseases:
  Avian Influenza, Foot-and-Mouth Disease, Bluetongue

• Inactivated vaccines only

• Not to be built in emergency situation!
  ⇒ multi-strain dossier ≠ emergency dossier
MULTI-STRAIN DOSSIER
PRE-REQUISITES (2)

• Maximum number of strains/subtypes/Ag/Al → fixed by the Applicant
• Same method of preparation of each Active Ingredient
• Standardized blending
  - volume, excipients, adjuvants, target content for each Active Ingredient
• Control of Finished product: specific of each Active Ingredient (cross-reactions to be limited)
MULTI-STRAIN DOSSIER
PRINCIPLES (2) - POTENCY AND EFFICACY

Finished Product A

POTENCY A = POTENCY 1 and POTENCY 2 and POTENCY 3
INDICATION A = INDICATION 1 + INDICATION 2 + INDICATION 3

MULTI-STRAIN DOSSIER
PRINCIPLES (3) - SAFETY

Max. Ag amount

FINISHED PRODUCT A

SAFETY A
MULTI-STRAIN DOSSIER
PRINCIPLES (4) - SAFETY

Max. Ag amount → FINISHED PRODUCT A = FINISHED PRODUCT B

SAFETY A

MULTI-STRAIN DOSSIER
PRINCIPLES (5) - STABILITY

1st Option

MSV 1 MSV 2

FINISHED PRODUCT 1 FINISHED PRODUCT 2

STABILITY 1 STABILITY 2

THE SHORTEST SHELF-LIFE
MULTI-STRAIN DOSSIER PRINCIPLES (6) - STABILITY

2nd Option

Pre-requisites!

FINISHED PRODUCT A

FINISHED PRODUCT B

STABILITY on 3 batches of FINISHED PRODUCT A

STABILITY on 3 batches, related to active ingredient 3

Shelf-life of FINISHED PRODUCT A

That’s all folks!