Update on the BTV situation in France

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BTV IN EUROPE
1999-2012
EMERGENCE
The Southern Outbreaks (2001-2004)

- **Before 2001**, Bluetongue (BTV) was a tropical disease (35°S / 40°N), with irregular incursions into European, no overwintering
- **2001-2004**
  - Multiple introductions in Southern Europe (serotypes 2, 4, 9, 16)
  - Northward drift of vectors linked to increase in temperatures
  - Some countries import live attenuated vaccine from Sth Africa (safety issues)

- An **EU consortium** (Public/Private) was formed to develop a control strategy
- Merial was identified as the only industrial partner, thanks to its experience with African Horse Sickness vaccine
- First inactivated BTV vaccine launched in 2004
The Northern Outbreaks (2006-2012)

- 2006: introduction of BTV-8 in Belgium, most northern incursion ever reported
- 2006-2007: rapid spread to Germany, France, UK
- Serotype 8 outbreak was exceptional in many ways:
  - **Severity of clinical signs in sheep**
  - **Pathogenic in cattle**
  - **Adapted to northern European vectors**
  - **Vertical transmission**
- Merial launched first BTV-8 vaccine in 2008

2006: more than 1756 farms infected within 13 weeks

2007: more than 14,000 cases in France and England
Focus on France in 2007
France 2008: BTV8 AND BTV1!

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

Calf mortality: +23%  +33% <1 month of age
+23% 1-38 month

Abortions notifications: +175%
Increase in birth of weak calves, abnormal calves
Decrease of fecondity: about -10%
2009 - 2010 Vaccination in France

- Vaccination against BTV1 and 8: compulsory
  - Cattle > 2.5 months of age
  - Sheep > 3 months age

- Budget: 98 millions € (State)
Outbreak evolution in France

# of cases

- 2011: 0
- 2010: 1
- 2009: 83
- 2008: 38,000
- 2007: 14,000
- 2006: 7

Dec 14., 2012: free status

2010
BTV circulation in Europe in 2013

Bluetongue
Restricted zones* as of 11 December 2013

This map includes information on the bluetongue virus serotypes circulating in each restricted zone, which permits, for the purposes of Articles 7 and 8 of Regulation 1255/2007, the identification of the restricted zones demarcated in different Member States where the same bluetongue virus serotypes are circulating.

Zone (serotypes)
- A (2,4,9,16)
- B (2,16)
- D (16)
- G (1,2,4,16)
- I (1,4)
- J (1)
- T (1,2,4,8,16)
- V (2,4,8,9,16)
- W (1,8,16)
- X (4,16)
- Y (2,0,16)
- Z (1,16)
- A1 (1,2,4,9,16)

* as defined in Article 2 of Commission Regulation No 1255/2007 geographic areas where surveillance and control protection zones have been demarcated by the Member States in accordance with Article 8 of Council Directive 2000/56/EC.

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BTV IN EUROPE
2014-2015
RE-EMERGENCE
2014 – BTV4 in Eastern Europe

This map includes information on the bluetongue virus serotypes circulating in each restricted zone, which permits, for the purposes of Articles 7 and 8 of Regulation No 1266/2007, the identification of the restricted zones demarcated in different Member States where the same bluetongue virus serotypes are circulating.

Restricted zones as of 25 November 2014

Zone (serotypes)
- B (2,16)
- G (1,2,4,16)
- H (1,4)
- J (1)
- T (1,2,4,8,16)
- X (4,16)
- Z (1,16)
- A1 (1,2,4,9,16)
- A2 (1,2,16)
- A3 (4)
- A4 (1,4,8,16)
- A5 (1,2,9,16)

* as defined in Article 2 (c) of Commission Regulation No 1266/2007; geographic areas where surveillance and/or protection zones have been demarcated by the Member States in accordance with Article 5 of Council Directive 2009/78/EC.

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Sept 2015, Allier "département"
Sept 2015 – Index case

- 5-yr old ram with clinical signs (since August 21, 2015)
- 209 sheep + 145 cattle on farm
- Samples (blood/EDTA) sent 27 Aug to regional lab (Eurofins)

Courtesy of S. Zientara, ANSES
18 Sept 2015

Légende
Zones réglementées
- Périmètre interdit
- Zone de protection
- Zone de surveillance

Courtesy of S. Zientara, ANSES
Surveillance Strategy

- Vets and farmers: raised alert on clinical suspicions

- Programmed surveillance in France to assess extension of infected zone

- Objective: detection of herd-prevalence of 5% and intra-herd prevalence of 10%

  - 60 cattle herds randomly selected/region (22 regions in France)
  - 30 cattle/herd (herds > 30 animals)
  - 37,800 PCR to perform asap in 1260 herds

Courtesy of S. Zientara, ANSES
Surveillance Strategy

Légende
Nombre de cheptels tirés par commune
- 1 cheptel
- 2 à 3 cheptels
- 4 à 6 cheptels

Courtesy of S. Zientara, ANSES
Surveillance results

- Results of surveillance program October 1\textsuperscript{st}, 2015:
  - in red: infected herds
  - in blue: negative herds
- 150 animals (73 cattle, 72 sheep, 5 goats) from 64 herds of 31 départements with suspect clinical signs. All PCR are negative except for 1 cattle in Cher

Courtesy of S.Zientara, ANSES
Zoning, Oct. 1st 2015

Courtesy of S. Zientara, ANSES
Zoning, Oct 8th, 2015

Légende
Foyers de FCO au 08/10/2015
- Périmètre d’infection
- Zone de protection
- Zone de surveillance

Courtesy of S. Zientara, ANSES
Zoning, Oct 15th, 2015

Fusion of zones

Légende
- Zone réglementée au 08/10/15
- Proposition de zonage

Courtesy of S.Zientara, ANSES
Vaccination program

- Vaccine available, but in limited quantities.

- Vaccination implemented in priority for:
  1. Ruminants from farms in infected zones
  2. Ruminants in artificial insemination centers, testing centers and individual control centers
  3. Ruminants prior to exportation

Courtesy of S. Zientara, ANSES
THE CHALLENGES OF A MANUFACTURER
The initial outbreaks: a new development model

- To respond to the emergency situation in EU, Merial had to put in place an accelerated development model
- Framework defined with authorities: minimal data package needed to have confidence in the product, balanced with risk / benefit analysis
- Characteristics:
  - **Highest priority level within R&D: P1**
  - **Timelines reduced to absolute minimum, most tasks done concurrently**
  - **Financial risk taking: industrial batch produced before clinical POC**
  - **Dedicated resources**
  - **Use of existing technical platform (BHK-21 cells, inactivation, purification)**
  - **Adjusted regulatory procedure: Temporary Authorization of Use**
  - **Investment in BSL3 labs and animal facilities**
- The same model was applied to develop serotypes 2, 4 and 9

\[\begin{align*}
\text{~ 7 years} & \quad \text{1.5 years}
\end{align*}\]
Development continued with other serotypes

- At least one introduction per year from 2000 to 2008

**Serotype introduction**

- BTV1, 1998/99
- BTV2, 1998/99
- BTV9, 1998/99
- BTV1, 2000
- BTV16, 2000
- BTV4, 2001
- BTV16, 2001
- BTV8, 2003
- BTV1, 2004
- BTV25, 2004
- BTV6, 2005
- BTV25, 2005
- BTV1, 2006
- BTV1, 2007
- BTV1, 2008
- BTV1, 2009
- BTV1, 2010

**Technical issue**

- At least one introduction per year from 2000 to 2008
Return on investment

- Bluetongue 8 vaccine sales peaked in 2008 at, paying off all the R&D investment

- Retrospectively, it was a very good investment for the company
Return on investment

- But it could have looked like this...
  (Schmallenberg example)
Challenges of re-emergence

- Industrial capacity occupation
  Demand going from 70M doses per year to 0

- Inventory management
  - Serotype / volumes?

- Potential solution:
  - Development of the **antigen bank** model for BTV
  - First bank supplied to France in 2015
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Thank you for your attention