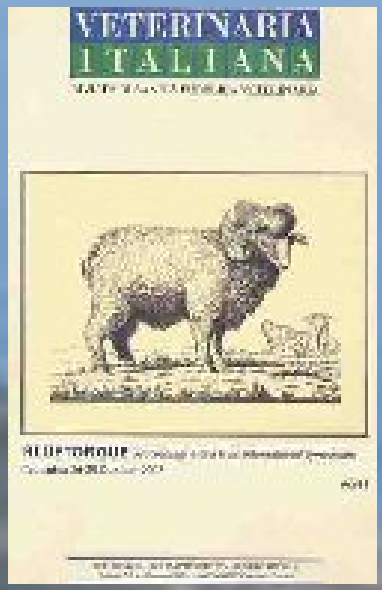
OIE INTERNATIONAL STANDARDS ON BLUETONGUE VACCINATION

Vincenzo Caporale

Conference on
"Vaccination strategy against bluetongue"
Bruxelles, 16 January 2008

Bluetongue in the 3rd Millennium

- In the year 2000 a large research effort was undertaken, consequent to the spread of BTV in the European Mediterranean Countries
- There was significant progress in bluetongue molecular virology, diagnosis, epidemiology, vectors and remarcable ***innovation in vaccine use and vaccination strategies***
- Therefore, the 3rd OIE BT Conference was organized



Third International OIE Bluetongue Conference

Taormina, 26-29 October 2003

http://www.izs.it/

Main Conclusions of 3rd OIE Conference in relation to BT control strategies

- Reduction of the infective period from 100 to 30 days
- Recognition of the value of vaccination of all domestic ruminant species
- Movement of susceptible antibody-positive ruminants from infected zones through the coherent & integrated use of:
  - Surveillance
  - Vaccination

The updating of the OIE standards

Review of standards

- Following the Taormina's meeting conclusions
  - The relevant ***Terrestrial Animal Health Standard Code (TAHSC)*** & ***Manual Of Diagnostic Tests and Vaccines for Terrestrial Animals*** Chapters have been updated
  - ***Surveillance guidelines*** for BT was introduced (*Appendix 3.8.10*) to the last *TAHSC* edition (2007)
- In ***2007*** following the appearance of BTV infection in Northern Europe an OIE consultation was launched and the expert confirmed that the Northern European epidemic DID NOT PRESENT ANY SCIENTIFIC ELEMENT - not taken into account in the Taormina conference - and, therefore, NO CHANGE WAS REQUIRED neither in the *OIE Code* nor in the *OIE Manual*

Case definition

1. BTV has been isolated and identified as such from an animal or a product derived from that animal

OR

2. Viral antigen or viral RNA specific to one or more of the serotypes of BTV has been identified in samples from one or more animals showing clinical signs consistent with BT, or epidemiologically linked to a confirmed or suspected case, or giving cause for suspicion of previous association or contact with BTV

OR

3. Antibodies to structural or nonstructural proteins of BTV that are not a consequence of vaccination have been identified in one or more animals that either show clinical signs consistent with BT, or epidemiologically linked to a confirmed or suspected case, or give cause for suspicion of previous association or contact with BTV


BTV FREE COUNTRY OR ZONE

BTV free country or zone

- The country or zone lies wholly north of **53°N** or south of 34°S, and is not adjacent to a country or zone not having a free status;

OR

- A surveillance program in accordance with Appendix 3.8.10. has demonstrated no evidence of BTV in the country or zone during the **past 2 years**;

OR

- A surveillance program has demonstrated no evidence of *Culicoides* likely to be competent BTV vectors in the country or zone.

Northern limit

- In 2006 (when the last version of TAHSC was prepared) the global BTV distribution laid between latitudes of approximately 53°N and 34°S.
- In TAHSC it was stated that “BT is known to be expanding in the northern hemisphere”
- Actually BT outbreaks northern than 53°N have been notified in Denmark


Surveillance

Purpose of surveillance

- The purpose of surveillance is the detection of virus circulation in a country or zone and *NOT* to determine individual animals or herds status
- Surveillance deals with both the occurrence of clinical signs caused by BTV, *AND* evidence of infection with BTV in the absence of clinical signs.

Surveillance

- In the absence of clinical disease in a country or zone within 53°N and 34°S, its BTV status should be determined by an ongoing surveillance program (in accordance with Appendix 3.8.10.)

- All countries or zones adjacent to a country or zone not having free status should be subjected to similar surveillance.


Import from infected
countries or zones

Import from infected Countries
Live ruminants

1. Were protected from attack from *Culicoides* likely to be competent BTV vectors since birth or for at least 60 days prior to shipment;

OR

2. Were protected from attack from *Culicoides* likely to be competent BTV vectors for at least 28 days prior to shipment, and were subjected during that period to a serological test according to the Terrestrial Manual to detect antibody to the BTV group, with negative results, carried out at least 28 days after introduction into the quarantine station;

OR

Import from infected Countries
Live ruminants

3. were protected from attack from *Culicoides* likely to be competent BTV vectors for at least 14 days prior to shipment, and were subjected during that period to an agent identification test according to the Terrestrial Manual, with negative results, carried out at least 14 days after introduction into the quarantine station;

OR

Import from infected Countries
Live ruminants

4. were vaccinated in accordance with the Terrestrial Manual at least 60 days before shipment, *against all serotypes whose presence in the source population* has been demonstrated through a ***surveillance program*** in accordance with Appendix 3.8.10., and were identified in the accompanying certification as having been vaccinated;

OR

Import from infected Countries
Live ruminants

5. Are not vaccinated, a surveillance programme in accordance with Appendix 3.8.10. has been in place in the source population for a period of 60 days immediately prior to shipment, and no evidence of BTV transmission has been detected;

AND

were protected from attack from *Culicoides* likely to be competent BTV vectors during transportation to the place of shipment

In brief

Protection from *Culicoides* attack

For 60 days

OR

For 28 days

Negative serological test

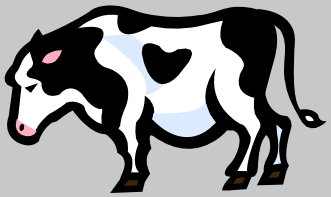
OR

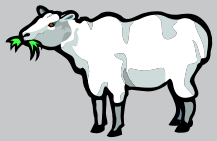
For 14 days

Negative agent identification test

OR

In brief





Vaccinated **60 days** before

OR

Surveillance has not detected evidence of BTV transmission in the **60 days** before

AND

Animals are protected from *Culicoides* attack during transportation

OR

Vaccinated **60 days** before or had antibodies against serotypes in zones of transit

Import from infected Countries
Semen of ruminants

Donor animals:

1. were protected from attack from *Culicoides* likely to be competent BTV vectors for at least 60 days before commencement of, and during, collection of the semen;

OR

2. were subjected to a serological test according to the Terrestrial Manual to detect antibody to the BTV group, with negative results, at least every 60 days throughout the collection period and between 21 and 60 days after the final collection for this consignment;

OR

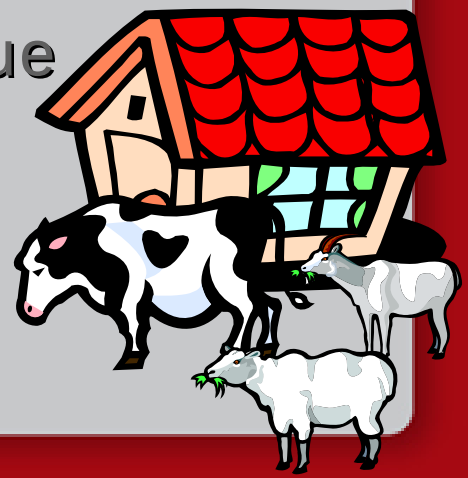
3. were subjected to an agent identification test according to the Terrestrial Manual on blood samples collected at commencement and conclusion of, and at least every 7 days (virus isolation test) or at least every 28 days (PCR test) during, semen collection for this consignment, with negative results

Guidelines for surveillance of BT

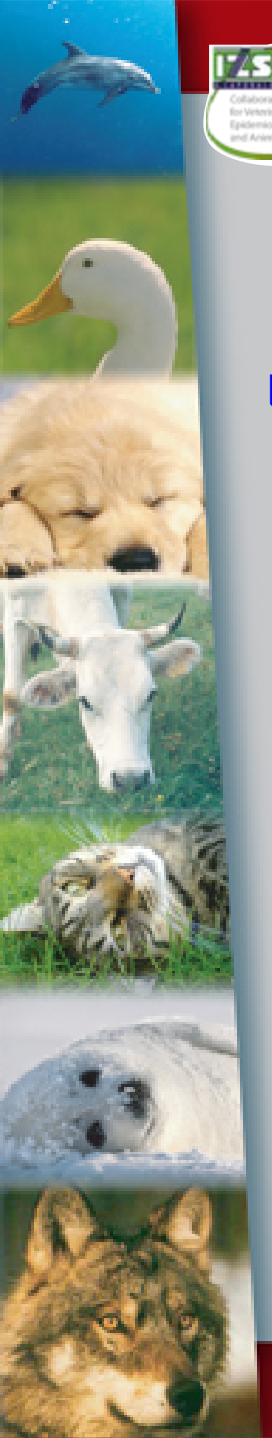
Article 3.8.10.3. - General conditions and methods

In general, the conditions to prevent exposure of susceptible animals to BTV infected vectors will be difficult to apply. However, under specific situations like artificial insemination centres or quarantine stations exposure to vectors may be preventable.

The COMPARTMENTALIZATION issue




BTV seasonally free zone



BTV seasonally free zone

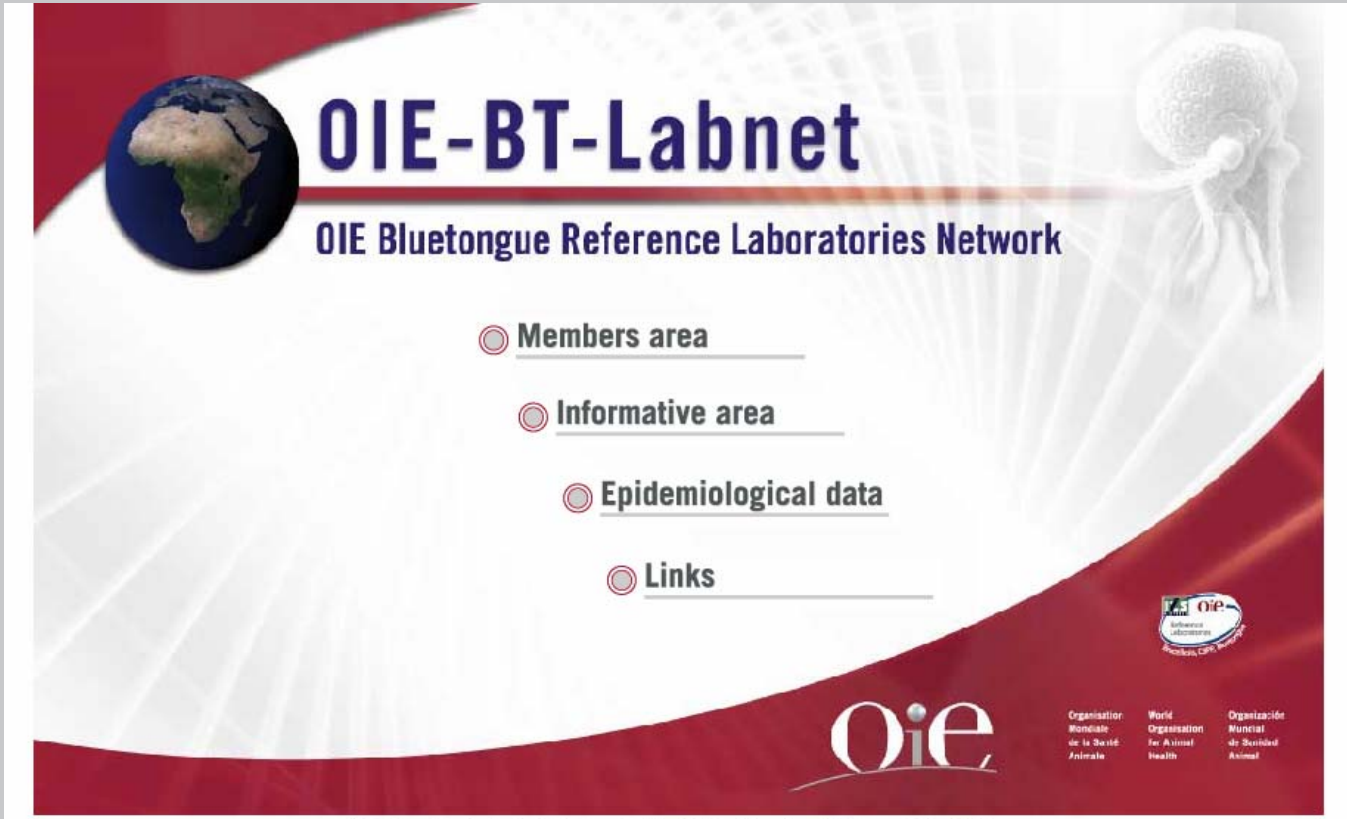
- A BTV seasonally free zone is a part of an infected country/zone for which for part of a year, surveillance demonstrates no evidence either of BTV transmission or of adult *Culicoides* likely to be competent BTV vectors
  - The seasonally free period begins the day following the last evidence of BTV transmission (as demonstrated by surveillance), and of the cessation of activity of adult *Culicoides* likely to be competent BTV vectors
  - The seasonally free period ends:
    - at least 28 days before the earliest date that historical data show bluetongue virus activity has recommenced;

      OR
    - immediately if current climatic data or data from a surveillance programme indicate an earlier resurgence of activity of adult *Culicoides* likely to be competent BTV vectors.

BTV seasonally free zone

- A BTV seasonally free zone in which surveillance has found no evidence that *Culicoides* likely to be competent BTV vectors are present will not lose its free status through the importation of vaccinated, seropositive or infective animals, or semen or embryos/ova from infected countries or zones.

OIE Bluetongue Reference Laboratories Network



THE OIE VACCINE STANDARD

OIE REQUIREMENTS FOR VACCINES AND DIAGNOSTIC BIOLOGICALS

SEED MANAGEMENT

❑ Characteristics of seed

- Primary seed virus
  - MUST be free of contaminating bacteria, viruses, prions, fungi and mycoplasmas, particularly pestivirus contamination
  - MUST be shown to have the desired serotype specificity;
  - SHOULD be sequenced and the data made available to relevant databases

- Secondary seed lots
  - Should not be >3 passages beyond the primary seed lot

- For live, attenuated vaccines only:
  - The master or primary virus seed:
    - ✓ MUST prepared from a *single plaque* of serially passaged, attenuated BTV
    - ✓ SHOULD be tested for transmissibility and reversion to virulence
  - Samples of vaccine prepared from secondary seed virus at the maximum permitted passage level should be tested in sheep for avirulence, safety and immunogenicity

OIE REQUIREMENTS FOR VACCINES AND DIAGNOSTIC BIOLOGICALS

Validation of seed as a vaccine

- Avirulence
- Safety
- Efficacy
- Transmissibility
- Reversion to virulence

VALIDATION OF SEED AS A VACCINE

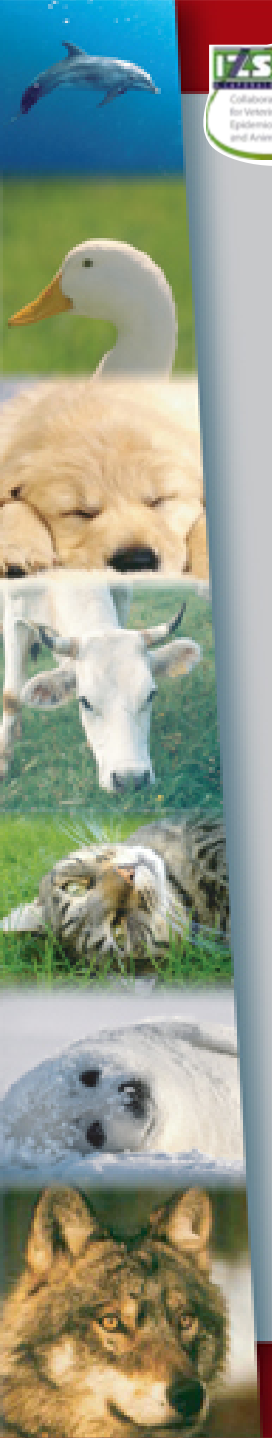
Avirulence

- Avirulence
  - Inoculation in susceptible sheep w/ primary seed stock and observation for 28 days and record:
    - Temperature
    - Local or systemic reaction
    - Viraemia and antibody measurements
  - The test shall be valid if all of the vaccinated sheep
    - show evidence of virus replication
    - do not display signs of disease other than mild transient illness

VALIDATION OF SEED AS A VACCINE

Safety

- Safety
  - All vaccines must be safety tested;
  - Live attenuated vaccines can be teratogenic and should not be administered to pregnant sheep during the first half of pregnancy



VALIDATION OF SEED AS A VACCINE

Efficacy

- Efficacy
  - Should be tested by challenge w/ virulent homologous serotype using wild type virus preferably passaged only in ruminant animals and with no ECE or cell culture passages
  - Animals are monitored twice a day for
    - clinical signs of BT
    - rectal temperatures
  - The test shall be valid if
    - all unvaccinated show sign of disease or temperature rise of at least >1.7°C above the pre-challenge mean while vaccinated sheep do not

VALIDATION OF SEED AS A VACCINE

Transmissibility

- Transmissibility
  - As no suitable **experimental model** exist to monitor virus transmission from vaccinated sheep → insect → sheep it is difficult to design a method to define transmissibility of vaccine strains;
  - In general virus titers in blood **<10^3TCID50/ml** have traditionally been considered a “safe” threshold. In any case virus titers induced by live attenuated vaccine should be kept to an absolute minimum

VALIDATION OF SEED AS A VACCINE

Reversion to virulence

- Reversion to virulence
  - Blood from vaccinated animals during the viraemic stages is serially passaged 3 times in sheep without reversion to virulence, the chances of reversion in the field will be infinitely small

METHOD OF MANUFACTURE

Live vaccines

- No relationship between passage number and extent of attenuation for individual virus isolates or serotypes;
- Field isolates are adapted to cell culture and passaged *in vitro* >40 times
- Ideally, a number of plaque-purified viruses are picked at this stage and each is examined to determine the level of viraemia they generate and their ability to elicit a protective immune response in vaccinated sheep
- The most suitable virus is one that replicates to low titer but generates a protective immune response, and this may represent the source of vaccine primary seed stock virus.

METHOD OF MANUFACTURE

Inactivated vaccines

- BTV for killed vaccines is produced, under aseptic and controlled conditions, in large-scale suspension cell systems that must be proven to be free from contaminating microrganisms;
- Cells are disrupted and the virus culture clarified and filtered
- Viral suspension is inactivated, (i.e.: by addition of binary ethyleneimine (BEI) or other inactivants) according to the legislation relevant for the intended market and be validated to ensure complete inactivation and be supported by the appropriate documentation. The inactivation process should not significantly alter the immunogenic properties of the viral antigens
- The suspension is purified, (i.e.: by chromatography) and concentrated (i.e.: by ultrafiltration) and stored;
- The inactivated, chromatography-purified and concentrated BTV antigens are made into vaccine by dilution in a buffer solution and addition of adjuvants

IN-PROCESS CONTROL

- All ingredients of animal origin, including serum and cells must be checked for the presence of viable bacteria, viruses, fungi or mycoplasmas;
- Virus concentration of attenuated vaccines is assessed by infectivity and ELISAs;
- For inactivated vaccines
  - Timed samples are taken at regular intervals are used to monitor the rate and linearity of the inactivation process
  - Virus titres in the samples are determined by inoculation of BHK-21 or other appropriate cell cultures
  - At the end of the inactivation process, the vaccine must be checked to ensure that there is no live virus.

BATCH CONTROL

- Sterility
- Safety
- Potency
- Duration of immunity
- Stability
- Precautions (hazards)

BATCH CONTROL

Sterility

- Every batch of vaccine should be tested for the presence contaminant viruses of viable bacterial, fungal or mycoplasmal contamination according to Pharmacopeia;

Safety

- Every batch of *live attenuated vaccine* is tested in
  - newborn and adult mice
  - guinea-pigs
  - sheep
- Each batch of *inactivated vaccines* is tested in
  - sheep
- If **adverse reactions or significant signs** such as increase in the body temperature of the target animal that above the level expected for the vaccine under test are noted, the test is repeated;
- If the results are unsatisfactory after a **second attempt**, the batch is disqualified

BATCH CONTROL

Potency

- Every batch of vaccine should be tested by inoculation of susceptible sheep;
- Prevaccination, and 21- and 28-day post-vaccination sera are tested by **VN assay** to determine neutralising antibody levels;
- To be passed, the **antibody titre** must be equal to or higher than a set standard based on international vaccine standards ***[do not exist at present]***.

Duration of immunity

- Antibody in sheep vaccinated with live attenuated vaccines persist for ***well over a year***;
- Initial studies with inactivated vaccines show that a second dose of vaccine boosts the antibody titre and data to demonstrate the expected **duration of immunity is under development.**

BATCH CONTROL

Stability

- Procedures have been developed for attenuated vaccines and they are deemed to have shelf lives >2 years;
- Each batch of vaccine is subjected to an accelerated shelf-life test by storing it at 37°C for 7 days. It is then titrated and evaluated according to a set standard, as determined in the initial testing of the vaccine;
- Requirements and procedures for routine commercial use of inactivated vaccines have not been developed.

Precations (hazards)

- Attenuated vaccines should not be used in ewes during the first half of pregnancy. Lambs possessing colostral immunity cannot be effectively vaccinated before 6 months of age (?)


THANK YOU!