Brucellosis
An emerging disease with public health implications?

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Brucellosis

- Infectious & contagious disease due to *Brucella* sp.
- Of major public health and worldwide importance
  *annual human incidence: 500,000*
- Causes significant economic losses to livestock production due to:
  - reproductive disorders (abortion, orchitis)
  - reduced productivity (milk, infertility)
Brucella: species & biovars

<table>
<thead>
<tr>
<th>Species</th>
<th>Biovars</th>
<th>Preferred natural host</th>
<th>Main geographical area</th>
<th>Pathogenicity for man</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. melitensis</td>
<td>1, 2, 3</td>
<td>Sheep, Goats</td>
<td>Mediterranean countries</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wild ungulates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. abortus</td>
<td>1, 2, 3, 4, 5, 6, (7), 9</td>
<td>Bovines</td>
<td>Europe, Americas, Africa, Asia</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wild ungulates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. suis</td>
<td>1</td>
<td>Suids</td>
<td>Americas, Asia, Oceania</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Suids, Hares</td>
<td>Central &amp; Western Europe</td>
<td>Very low</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Suids</td>
<td>USA, China</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Reindeer</td>
<td>USA, Canada, Russia</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Wild rodents</td>
<td>Russia</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. neotoma</td>
<td></td>
<td>Desert wood rat</td>
<td>USA</td>
<td>Unknown</td>
</tr>
<tr>
<td>B. ovis</td>
<td></td>
<td>Sheep (males)</td>
<td>Mediterranean countries</td>
<td>No</td>
</tr>
<tr>
<td>B. canis</td>
<td></td>
<td>Dogs</td>
<td>USA, South America, Central/Eastern Europe</td>
<td>Low</td>
</tr>
<tr>
<td>B. ceti</td>
<td></td>
<td>Cetaceans</td>
<td>USA</td>
<td>High / Unknown</td>
</tr>
<tr>
<td>B. pinnipedialis</td>
<td></td>
<td>Pinnipeds</td>
<td>USA, Oceania</td>
<td>High / Unknown</td>
</tr>
</tbody>
</table>

Brucellosis: the global cycle

Wild Ruminants, Rodents, Carnivores, Swine

B. abortus

B. melitensis

B. suis

B. canis

B. ceti

B. pinnipedialis

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Brucellosis

• **A zoonosis of worldwide importance**
  - **Sources:** animals infected by
    - *Brucella melitensis* (small ruminants)
    - *Brucella abortus* (large ruminants)
    - *Brucella suis* (pigs)
  - **Transmission route:**
    - occupational direct contact or exposure
    - unpasteurised dairy food consumption

• **A significant public health challenge**
  - Of major economic & financial importance
  - **Human brucellosis is:**
    - The commonest zoonosis worldwide: 500,000 cases/year (WHO)
    - Minimal mortality but,
    - Substantial residual disability if not treated promptly & effectively
    - Important cause of travel-associated morbidity
    - Endemic in the major part of the World

Human brucellosis: worldwide incidence

- Incidence <2 / million
- *B. melitensis* does not exist
- Incidence >2 / million
- Incidence > 50 / million
- Data not available
Human brucellosis: worldwide incidence

From Pappas et al., The Lancet Inf. dis., 2006, 6:91-99

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Significant economic losses

- Decreased productivity:
  - Abortions, orchitis
  - Weak offspring, infertility
  - Decreased milk production

- Lost trade opportunities: WTO/OIE/EU Trade rules

A significant public health challenge

- Sheep and goats are the main reservoir of B. melitensis
- However increasing evidence of emergence in cattle and camels
Bovine brucellosis global status

Never reported | Eradicated | Infected | Reported in past | Data not available

Sheep and goat brucellosis global status

Never reported | Eradicated | Infected | Reported in past | Data not available
**B. suis infection global status**

<table>
<thead>
<tr>
<th>B. suis never reported</th>
<th>B. suis infection reported in the past</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. suis infected countries</td>
<td>Data not available</td>
</tr>
</tbody>
</table>

**Porcine brucellosis – Domestic / wild suids**
Brucellosis in the EU - History

Animal Brucellosis historically endemic all over Europe

- B. abortus (B. suis?)
- B. abortus & B. melitensis (B. suis?)
- Never reported

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Brucellosis in the EU – The tools

- Regulation on trade:
  - EC 64/432 (cattle and pigs)
  - EC 91/68 (sheep and goats)
  - Other regulations on animal products, AI, animal identification, etc.

- European agencies
  - EDQM: European Directorate for the quality of medicines
  - ECDC: European Centre for Disease Prevention & Control (2005)
  - EFSA: European Food Safety Authority (2002)

- Co-financed eradication programmes:
  - Task Force for Monitoring Diseases Eradication (2000)
  - Eradication programmes expert groups (2012)

- The EURL (2006)
Brucellosis in the EU – *Control & Eradication strategies*

- In low prevalence areas: Test-and-slaughter  
  *e.g.* in Scandinavia, where the disease was eradicated in the fifties (but later in the UK - 1984)
- In mean prevalence areas:
  Test-and-slaughter  
  + Vaccination of replacement females (at least in early stages)  
  - S19 and Rev.1 in large and small ruminants mainly (*e.g.* France)  
  - RB51 more recently in Spain, Portugal and Greece
- In some high prevalence areas: mass vaccination  
  *e.g.* Greece mainland, several counties in Spain and Portugal

\[\text{Since 2000, the Task Force has progressively contributed to the harmonisation of strategies, in particular in enhancing the use of vaccination as an efficient tool for controlling the disease}\]


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Brucellosis in the EU – *Human cases*

- **Evolution of human cases reported in the EU**

% exotic cases

*Human cases of brucellosis in the EU (1999-2012)*
Brucellosis in the EU - **Large & small ruminants (2012)**

- Sporadic or endemic occurrence in the 50s
- Cases never reported:
  - Finland, Sweden, Norway and UK
- Sporadic cases reported, mainly in outdoor ranged pig farms:
  - Austria, Czech Rep., Croatia, Denmark, France, Germany, Montenegro, Portugal, Romania, Serbia, Spain, Switzerland
- Low to high prevalence in many EU countries in wild-boars (+hares)
- *B. suis* biovar 2 the most frequent
- Few cases in humans, cattle and sheep
- However biovars 1 and 3 reported in Croatia.
- No systematic surveillance
- Depopulation in place in outbreaks in many countries

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Brucellosis in the EU - **Swine**

- Sporadic or endemic occurrence in the 50s
- Cases never reported:
  - Finland, Sweden, Norway and UK
- Sporadic cases reported, mainly in outdoor ranged pig farms:
  - Austria, Czech Rep., Croatia, Denmark, France, Germany, Montenegro, Portugal, Romania, Serbia, Spain, Switzerland
- Low to high prevalence in many EU countries in wild-boars (+hares)
- *B. suis* biovar 2 the most frequent
- Few cases in humans, cattle and sheep
- However biovars 1 and 3 reported in Croatia.
- No systematic surveillance
- Depopulation in place in outbreaks in many countries
Brucellosis in the EU – *Dogs (B. canis)*

- Sporadic cases recently reported in:
  - Austria, Finland, France, Italy, Hungary, Poland, Sweden, Turkey
  - &
  - Canada, USA, Central and South-America, South-Africa, Eastern-Asia, Oceania (French Polynesia)

- Real prevalence / Real risk of introduction?

- No trade control for *B. canis* infection
Animal brucellosis in the EU – Possible risks

- **Underestimation of the prevalence**
  - Northern Ireland (cattle): surveillance lightened
  - Greece (sheep & goats): vaccination stopped

- **Unknown source**
  - Belgium 2010 (1 outbreak) & 2012-13 (6+1)

- **Introduction**
  - From infected neighbouring countries: UK 2004 (→ Ireland or NI)
  - From OBF neighbouring countries: France 2012 (→ Belgium)

- **Wildlife reservoir** (*B. abortus/B. melitensis*)
  - Up to recently: no wild reservoir identified in the EU
  - Few sporadic cases of *B. abortus & melitensis* is wild ruminants: considered as dead-end hosts
  - However: primary reservoir identified in Alpine Ibex in France in 2012 (transmission to dairy cattle with human cases)

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**Northern Ireland: BR annual herd and animal incidence: 1995 to 2012**

- % Herd
- % Animal

Year: 1995 to 2012

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Unexpected outbreak of Brucellosis due to *Brucella melitensis* in the Alpine Ibex in the French Alps


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**Brucellosis in French ruminants & humans**

- No cases of brucellosis in cattle, sheep and goats since 2003
- France officially free of Bovine brucellosis since 2005
- Consequently, incidence decreased in humans:
  - only 32 human cases, mostly imported, in 2012
  - (29 in 2013)
The 2012 outbreak in the French Alps

- January 2012: one human case in Grand-Bornand* village (Bargy massif, Haute-Savoie, France) followed by a second case later (2013 - focalised form)
  *An area famous for its well-known raw-milk *Reblochon* cheese

- April 2012: confirmation of one case in an aborted cow in the same village due to Brucella melitensis biovar 3

- May 2012: serological control of livestock (> 12,000 animals tested)
  -> all results negative

- Last ovine/bovine breakdown in the massif in 1999

What about wildlife???

An extensive survey in wildlife in 2012-2013...2014....

- **In hunted species:**
  blood, lung, spleen, testes and uterus sampled by hunters for serological and bacteriological analyses

- **In Alpine Ibex (protected species)**
  - Detection of clinical signs (arthritis and orchitis) in the field
  - Random captures by dart-gun anaesthesia in the Bargy and neighbouring massifs
Test protocol

• Serology
  ➢ Rose Bengal (RBT)
  ➢ Complement fixation (CFT)
  ➢ iELISA (IDEXX, France)
  ➢ cELISA (Ingenasa, Spain)
  ➢ If blood unavailable, lung extracts tested

➔ in 2014, whole-blood rapid test:
  Anigen Rapid GS Brucella Ab Test (Bionote, South Korea)

• Bacteriology
  ➢ Culture
  ➢ Real-time-PCR

Results

Hunted species
Two hunting seasons (2012-2013 and 2013-2014)

<table>
<thead>
<tr>
<th></th>
<th>Aravis</th>
<th>Total</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bargy / Borne</td>
<td>115</td>
<td>39</td>
<td>154</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 positive</td>
</tr>
<tr>
<td>61</td>
<td>4</td>
<td>65</td>
<td>All negative</td>
</tr>
<tr>
<td>55</td>
<td>1</td>
<td>56</td>
<td>All negative</td>
</tr>
</tbody>
</table>

2 chamois females (6 and 7 years old) killed in Sept. 2012 and Oct. 2013 in the same municipality

Arthritis due to Brucella on the 1st chamois found infected
Serological results in Alpine Ibex 2012-2013

<table>
<thead>
<tr>
<th>Massif</th>
<th>Killed clinical suspects</th>
<th>No. tested</th>
<th>No. positive</th>
<th>Seroprevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bargy</td>
<td>8</td>
<td>77</td>
<td>29</td>
<td>38% [28 -48]</td>
</tr>
<tr>
<td>Aravis</td>
<td>0</td>
<td>60</td>
<td>0</td>
<td>0% [0 -5]</td>
</tr>
<tr>
<td>Sous-Dine</td>
<td>0</td>
<td>30</td>
<td>0</td>
<td>0% [0 -8]</td>
</tr>
</tbody>
</table>

Distribution by sex and age (%)

- 2 – 5 years: 15%
- > 5 years: 56%

Bacteriological results in Alpine Ibex 2012-2013

- Isolation of the same strain of Brucella melitensis bv. 3 in humans, domestic ruminants (1999 and 2012), chamois and ibex (same MLVA genotype)
- Necropsy of 37 positive ibex (seropositive or with clinical signs): isolation of B. melitensis in 16 animals
  - Lymph nodes
  - Urine
  - Orchitis
  - Spleen
  - Uterus
  - Udder
  - Vagina
  - Prepuce
  - Arthritis
Population studies

to monitor movements, spatial behaviour and habitat selection

- Aerial counts (helicopter)
- Pedestrian counts twice a month

- 20 ibex equipped with GPS collars
- 53 ibex equipped with VHF collars (Capture-Mark-Recapture – CMR)

- Visual surveillance of 10 farms to evaluate contacts between domestic and wild animals

Population studies: results

- Population size - CMR estimation: **500 ibex**
- Reproduction index very low: 0.23
- Inverted population pyramid: 68% > 6 years

**Ageing population**

- GPS and VHF collars: movements on short distances only between the Bargy and neighbouring massifs (Aravis and Sous-Dine)
- Contacts between wild and domestic ruminants: **do exist but occur rarely**
Conclusions

• A Brucellosis reservoir has been identified in Alpine Ibex, with a very high prevalence, particularly in the over 5 year-old ibex.
• This reservoir has probably been present for a long time (≤1999?)
• Transmission to other species seems to be difficult and/or very rare (only two chamois and one cow)
  ➔ Mainly venereal transmission within Ibex?....
• Ibex population dynamics seem disrupted
• Direct and indirect contacts between ibex and domestic ruminants are rare but do exist and are unpredictable.

The challenge:
How to manage a spread of Brucellosis, a major contagious and zoonotic disease, with a wild reservoir in a protected species living in the main production area of the famous raw-milk cheese “Reblochon”??

Management....

• Stamping out of the ibex population: technically difficult and socially unacceptable
• Capture-test-and-kill: technically impossible
• Vaccination?? Impossible at short term (innocuousness, efficacy, route, side-effects, how long...?)

October 2013, the French authorities decided to cull all over 5-year old ibex

➔ 233 ibex killed
• 78 ibex (40 young, 38 old) captured and tested in the remaining population (ca. 300 animals)
  ➔ Global seroprevalence = 45% (38% in 2013)
  ➔ Prevalence in young ibex = 50% (15% in 2013)

The general situation has not improved. Moreover, it has worsened in young ibex..!!

....what would happen in the future....?????
Brucellosis in the EU: a re-emerging disease?

• Present situation:
  – Huge improvement in the last decade
    • Improvement of control strategies (identification/movements/regular checks)
    • Re-introduction of the vaccine tool for controlling the disease
  – Eradication reached in France and Cyprus
  – Eradication almost reached in Northern Ireland
  – Excellent results in Spain
  – Slower eradication in Portugal and Italy
  – No good information from Greece

• Possible dangers:
  – Introduction: always possible even from free countries
  – Wild reservoir: may be identified after years of absence in the domestic population
  –*B. canis*? *Marine Brucella*?

  ▶ Adequate strategies proved to be efficient
  ▶ Maintaining a good surveillance is essential in free areas (*Human strains*)

Brucellosis: a re-emerging disease?

• No in developed countries
• Yes in the third world
  – Pure or crossed breeds with increased sensitivity
  – Increase in herd size and animal density
  – Increase in world animal/animal products trade and human movements

  ▶ Increased risks from an enlarged reservoir of the disease and multiple routes of introduction in free areas
  ▶ A rapid and accurate diagnosis is therefore essential for:
    ▶ Identifying the disease introduction as rapidly as possible
    ▶ Identifying the source of the disease and its spread
    ▶ Implementing the appropriate diagnostic tools and epidemiological studies

  ▶ This does not mean necessarily to maintain a high level of specific research
  ▶ But to maintain a high and up-to-date level of skills/knowledge

  ▶ Active commitment in the EU Brucellosis network
Merci de votre attention  
Thank you for your attention  
Jag tackar för er uppmärksamhet.