Brucellosis, also called undulant fever, undulating fever, or Malta fever, is a zoonosis (infectious disease transmitted from animals to humans) caused by bacteria of the genus *Brucella*. It is primarily a disease of domestic animals (goats, pigs, cattle, dogs, etc) and humans and has a worldwide distribution, mostly now in developing countries.

#### Overview
- Organism
- History
- Epidemiology
- Transmission
- Human Disease
- Animal Disease
- Prevention and Control

**Brucella spp.**
- Gram negatif, coccobacilli bacteria
- Facultatif, intraselular organisme
- Persistensi di Lingkungan
  - Temp, pH, kelembaban
  - Material aborsi dan dibekukan
- Multiple species

<table>
<thead>
<tr>
<th>Species</th>
<th>Biovar/Serovar</th>
<th>Natural Host</th>
<th>Human Pathogen</th>
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<tbody>
<tr>
<td><em>B. abortus</em></td>
<td>1-6, 9</td>
<td>cattle</td>
<td>yes</td>
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<tr>
<td><em>B. melitensis</em></td>
<td>1-3</td>
<td>goats, sheep</td>
<td>yes</td>
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<tr>
<td><em>B. suis</em></td>
<td>1, 3</td>
<td>swine</td>
<td>yes</td>
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<td></td>
<td>2</td>
<td>hares</td>
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<td></td>
<td>5</td>
<td>rodents</td>
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<td><em>B. canis</em></td>
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<td>dogs, other canids</td>
<td>yes</td>
</tr>
<tr>
<td><em>B. ovis</em></td>
<td>none</td>
<td>sheep</td>
<td>no</td>
</tr>
<tr>
<td><em>B. neotomae</em></td>
<td>none</td>
<td>Desert wood rat</td>
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<tr>
<td><em>B. mavis</em></td>
<td>marine mammals</td>
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The Many Names of Brucellosis

**Penyakit pada Manusia**
- Malta Fever
- Undulant Fever
- Mediterranean Fever
- Rock Fever of Gibraltar
- Gastric Fever

**Penyakit pada Binatang**
- Bang’s Disease
- Enzootic Abortion
- Epizootic Abortion
- Slinking of Calves
- Ram Epididymitis
- Contagious Abortion

History of Malta Fever

- 450 BC: Described by Hippocrates
- 1905: Introduction into the U.S.
- 1914: *B. suis* Indiana, United States
- 1953: *B. ovis* New Zealand, Australia
- 1966: *B. canis* in dogs, caribou and reindeer

Sir William Burnett (1779-1861)
- Physician General to the Navy
- Differentiated the various fevers affecting soldiers

Sir David Bruce (1855-1931)
- British Army physician and microbiologist who discovered *Micrococcus melitensis*

Jeffery Allen Marston
- Contracted Malta fever
- Described his own case in great detail
Bernhard Bang (1848-1932)
- Danish physician and veterinarian
- Discovered *Bacterium abortus* could infect cattle, horses, sheep, and goats

**History**
- Alice Evans, American bacteriologist
  - Credited with linking the organisms
  - Similar morphology and pathology between:
    - Bang’s *Bacterium abortus*
    - Bruce’s *Micrococcus melitensis*
- Nomenclature today credited to Sir David Bruce
  - *Brucella abortus* and *Brucella melitensis*

**Transmission to Humans**
- Conjunctiva or broken skin contacting infected tissues
  - Blood, urine, vaginal discharges, aborted fetuses, placentas
- Ingestion
  - Raw milk & unpasteurized dairy products
  - Rarely through undercooked meat
- Inhalation of infectious aerosols
  - Pens, stables, slaughter houses
- Inoculation with vaccines
  - *B. abortus* strain 19, RB-51
  - *B. melitensis* Rev-1
  - Conjunctival splashes, injection
- Person-to-person transmission is very rare
- Incubation varies
  - 7-21 days to several months

**Transmission in Animals**
- Ingestion of infected tissues or body fluids
- Contact with infected tissues or body fluids
  - Mucous membranes, injections
- Venereal
  - Swine, sheep, goats, dogs
Who is at Risk?

- Occupational Disease
  - Cattle ranchers/ dairy farmers
  - Veterinarians
  - Abattoir workers
  - Meat inspectors
  - Lab workers
- Hunters
- Travelers

Consumers of unpasteurized dairy products are also at risk

*B. melitensis*

- Latin America, Middle East, Mediterranean, eastern Europe, Asia, and parts of Africa
- Accounts for most human cases
  - In the Mediterranean and Middle East
    - Up to 78 cases/100,000 people/year
    - Arabic Peninsula 20% seroprevalence
- Recent emergence in cattle on Middle Eastern intensive dairy farms

*B. abortus*

- Worldwide
- Some countries have eradicated
- Notifiable disease in many countries
  - Poor surveillance and reporting due to lack of recognition
  - Fever of Unknown Origin (FUO)
**B. suis**

- Biovars 1 and 3
  - Worldwide problems where swine are raised
- Free
  - United Kingdom, Canada
- Eradicated
  - Holland, Denmark
- Low Incidence
  - Middle East, North Africa

- Low Levels
  - United States and Australia
  - Persistent problem in feral swine
- Biovar 1
  - Established in cattle in Brazil and Columbia
- Biovar 2
  - Enzootic in wild hares in Europe

**B. canis**

- Poorly understood
- 1-19% prevalence in United States
- Rarely causes disease in humans

**Brucellosis in U.S.: 1972-2002**

- United States
  - Approximately 100 cases per year
  - Less than 0.5 cases/100,000 people
  - Mostly California, Florida, Texas, Virginia
  - Many cases associated with consumption of foreign cheeses

**Disease in Humans**
Human Disease

- Can affect any organ or organ system
- All patients have a cyclical fever
- Variability in clinical signs
  - Headache, weakness, arthralgia, depression, weight loss, fatigue, liver dysfunction

- 20-60% of cases
  - Osteoarticular complications
    - Arthritis, spondylitis, osteomyelitis
  - Hepatomegaly may occur
  - Gastrointestinal complications
  - 2-20% of cases
    - Genitourinary involvement
      - Orchitis and epididymitis most common

- Neurological
  - Depression, mental fatigue

- Cardiovascular
  - Endocarditis resulting in death

- Chronic brucellosis is hard to define
  - Length, type and response to treatment variable
  - Localized infection
  - Blood donations of infected should not be accepted

Diagnosis in Humans

- Isolation of organism
  - Blood, bone marrow, other tissues
- Serum agglutination test
  - Fourfold or greater rise in titer
  - Samples 2 weeks apart
- Immunofluorescence of organism in clinical specimen
- PCR

Treatment of Choice

- Combination therapy has the best efficacy
  - Doxycycline for six weeks in combination with streptomycin for 2-3 weeks or rifampin for 6 weeks
- CNS cases treat 6-9 months
  - Same for endocarditis cases plus surgical replacement of valves

Prognosis

- May last days, months or years
- Recovery is common
- Disability is often pronounced
- About 5% of treated cases relapse
  - Failure to complete the treatment regimen
  - Sequestered infection requiring surgical drainage
- Case-fatality rate: <2% (untreated)
  - Endocarditis caused by *B. melitensis*
Animals and Brucellosis

Clinical Signs: Cattle & Bison
- Third trimester abortions with *B. abortus*
- Retained placenta
  - Once expelled will have a leathery appearance
- Endometritis
- Birth of dead or weak calves
  - Respiratory distress and lung infections
- Low milk yield

Clinical Signs: Sheep & Goats
- *B. melitensis* causing late term abortions
  - Retained placenta
  - Birth of dead or weak lambs/kids
- Goats - articular and periarticular hygroma localizations
- *B. ovis* causing abortions, fertility problems
  - Orchitis, epididymitis
  - Abnormal breeding soundness exam
  - Organisms present in semen

Clinical Signs: Swine
- *B. suis*
- Prolonged bacteremia
- Abortion, early or late gestation
- Fertility problems
  - Sows temporary
  - Boars, unilateral or bilateral orchitis
- Lameness, posterior paralysis, spondylitis, metritis, abscesses

Clinical Signs: Horses
- *B. abortus* most common
  - Susceptible to *B. suis*
- Fistulous Withers or Poll Evil
  - Inflammation of the supraspinous bursa
  - Exudative process
    - Fills with clear viscous liquid
    - Can eventually rupture

Clinical Signs: Dogs
- Susceptible to
  - *B. melitensis, B. abortus, and B. suis*
- *B. canis* causes abortions
  - Last trimester of pregnancy
  - Prolonged vaginal discharge
  - Bacteremia
  - Failure to conceive, stillbirths, prostatitis, epididymitis
Clinical Signs: Wildlife

- Elk
  - Abortions, no retained placenta
- Moose
  - Weakness, debilitated
- Predators not clinical but are vectors
  - Coyotes, crows, vultures, bears
    - Aid in disease spread by carrying infected tissues away from abortion site

Diagnosis in Animals

- Isolation of organism
  - Blood, semen, other tissues
- Serology
  - Brucellosis card test, ELISA
  - Brucella milk ring test
- Demonstration by fluorescent antibody of organism in clinical specimen
  - Placenta, fetus

Treatment of Animals

- Combination antibiotic therapy has the best efficacy
- Surgical drainage plus antibiotics
- Often expensive
- High rate of failure
- Indemnity program from government

Prognosis

- Disease may last days, months, or years
- Eradication program in the United States often leads to slaughter of certain species
  - Cattle, bison, horses, sheep, goats, swine

Yellowstone National Park

Bison in Yellowstone

- Goal = Brucellosis free by 2010
- Can leave the park to winter feed in Wyoming
- Up to 50% sero-positive
- Congregate at calving
Elk in Yellowstone

- Exposed to *B. abortus* via winter feeding grounds
- Isolate themselves at calving
  - Clean the area
  - Remain separate from herd for a few days
- Less disease transmission between herdmates

Prevention and Control

- Education about risk of transmission
  - Farmer, veterinarian, abattoir worker, butcher, consumer, hunter, public
- Wear proper attire if dealing with infected animals/tissues
  - Gloves, masks, goggles
- Avoid consumption of raw dairy products

Prevention and Control

- Immunize in areas of high prevalence
  - Young goats and sheep with Rev-1
  - Calves with RB51
  - No human vaccine
- Eradicate reservoir
  - Identify, segregate, and/or cull infected animals

Prevention and Control

- *B. suis, ovis, and canis*
  - Veneral transmission
  - Separate females at birthing to reduce transmission on the farm or in kennel

RB51

- Approved for use February 1996 for calves
- Able to differentiate “wild type” exposure from immunization
  - Lacks LPS-O antigen that causes antibody response on serologic or milk tests
- Infectious to humans
  - Serologically negative upon testing exposure
  - CDC registry of human exposures
  - 32 documented exposures as of 1998
**U.S. Eradication Program**

- **U.S. Department of Agriculture**
  - 1934: Cooperative State-Federal Brucellosis Eradication Program
    - Removal of diseased cattle due to drought
  - 1951: APHIS became involved
  - 1957: 124,000 positive herds
- **Approach**
  - Test, slaughter, trace back, investigate, and vaccinate

**Target date for eradication was December 31, 1998**

**Surveillance**

- Brucellosis ring test
- Pooled milk
- Market Cattle Identification
- Blood test, individual

**Indemnity for whole herd depopulation**

- $250 nonregistered cattle/bison
- $750 or 95% of value minus salvage value for registered cattle

**Fiscal Year 2001**

- 4.7 million calves vaccinated
- 9.9 million cattle tested under the Market Cattle Identification program
- 3 brucellosis herds depopulated
  - Indemnity paid = $211,153
  - An additional $47,700 for purchase of animals or diagnostic purposes

**Calves Vaccinated**

**Brucellosis Classes**

- **Free**
- **A**
  - No more than 0.25% infection rate and cattle must be tested before export
- **B**
  - Infection rate of no more than 1.5% and must be tested before interstate movement
- **C**
  - Infection rate >1.5% and herds must be tested twice before and once after export.
**B. abortus Exposure**

- 1997: Kansas State University
  - 14 month old heifer admitted to hospital with calving complications
    - Vaccinated with RB51 at 8 months
    - 10 times the dose for known pregnant cattle
  - 9 humans exposed
  - Treated with doxycycline
    - No clinical signs

**Brucellosis as a Biological Weapon**

- Aerosolized *B. melitensis*
  - City of 100,000 people
  - Inhale 1,000 cells (2% decay per min)
  - Case-fatality rate of 0.5%
  - 50% hospitalized for 7 days
    - Outpatients required 14 visits
    - 5% relapsed
- Results
  - 82,500 cases requiring extended therapy
  - 413 deaths
  - $477.7 million in economic impact
Internet Resources

- USDA APHIS VS Status Report
  - www.aphis.usda.gov/vs/nahps/brucellosis/bruc_erad.html
- USDA APHIS Cattle and Bison
- WHO Fact Sheet Brucellosis
  - www.who.int/inf-fs/en/fact173.html
- Brunet Publication
  - progress.box.co.il/brunet/public_sub2_pl.html