The WHO/FAO/OIE joint consultation on emerging zoonotic diseases held in Geneva, 3-5 May 2004, defined an emerging zoonosis as "a zoonosis that is newly recognized or newly evolved, or that has occurred previously but shows an increase in incidence or expansion in geographical, host or vector range".
Some of the "lingering" zoonoses are re-emerging in some regions, although they seem to attract less public awareness. Brucellosis, dog rabies and parasitic diseases such as cysticercosis/taeniasis and echinococcosis/hydatidosis for example.
History of Malta Fever

- 450 BC: Described by Hippocrates
- 1530: Malta was given to the Knights of the Order of St. John, and contagious fevers were noted from that time well into the 19th century
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

• Discovered *Micrococcus melitensis*
History of Malta Fever

- 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
Human brucellosis is the commonest zoonotic disease worldwide with more than 500,000 new cases annually.

- Associated with substantial residual disability
- Important cause of travel-associated morbidity

*Lancet Infect Dis 2006; 6: 91–99*
Global incidence of human brucellosis
Incidence (annual cases per million of population)
Passively acquired national data in many brucellosis-endemic countries are likely to underestimate the true disease burden.

Global Burden of Human Brucellosis: A Systematic Review of Disease Frequency

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* Systematic review of scientific literature published between 1990-2010, commissioned by WHO.
* Using strict exclusion criteria, 28 scientific articles published between January 1990-June 2010 which included high quality data were identified.
* Brucellosis incidence varied widely between, and within, countries.
* Demographic, occupational and socioeconomic factors likely play a role.
Incidence (annual cases per million of population)

Lancet Infect Dis 2006; 6: 91–99
Brucella spp.

- Brucella are small, Gram-negative coccobacilli that lack capsules, endospores or native plasmids.
- Aerobic, facultative intracellular pathogens
Animal hosts

- B. melitensis           Goats, sheep
- B. abortus        Cattle
- B. suis            Swine
- B. canis            Dogs
- B. neotomae   Desert wood rats
- B. ovis            Sheep
- B. pinipedialis  Marine mammals
- B. ceti            Marine mammals
Human Brucellosis Outbreak Acquired through Camel Milk Ingestion in Southern Israel

Shalom Ben Shmuel MD\textsuperscript{1,2}, Larissa Dukhan MD\textsuperscript{3}, Ilana Belmaker MD\textsuperscript{3}, Svetlana Bardenstein DVM PhD\textsuperscript{4}, David Sibirsky MD\textsuperscript{2}, Chiya Barrett MS\textsuperscript{2} and David Greenberg MD\textsuperscript{1,2}

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The most important route of animal to human transmission of Brucella

Brucella bacteria is usually transmitted to humans by contact with infected farm animals.
Transmission

- Consumption of infected unpasteurized milk, milk products, or meat.
- Direct contact with infected animals, aborted fetus, the placenta and the discharge from vagina.
- Accidental self inoculation of vaccines.
- **High risk** for slaughter house workers, animal handlers and veterinarians.
Transmission

- Inhalation of aerosols containing the bacteria
- Aerosol contamination of the conjunctiva

High risk groups
- Laboratory workers
Pathogenesis of brucellosis

1. Entry into the host
2. Stimulation of T-lymphocytes → IFN-γ
3. Induction by IFN-γ → T-lymphocytes against brucella
4. Induction by IFN-γ → NK cells and macrophages kill brucella
5. Inhibition of TNF-α → Reduced killing by NK cells and macrophages
6. Release of incompletely killed brucella to infect other cells
7. Production of antibodies by B-lymphocytes
Clinical presentation

- Incubation period: 1-4 weeks, may be months
- Broad clinical spectrum
- Acute brucellosis
  - Insidious onset of fever, night sweats
  - Arthralgias, myalgias, low back pain
  - Weakness, fatigue, malaise
  - Headache, dizziness, depression, anorexia
  - Dyspepsia, abdominal pain, cough
  - Hepatomegaly, splenomegaly, and/or lymphadenopathy
✧ Osteoarticular involvement is the most common presentation.
✧ Sacroiliac joints and large joints of lower limbs
✧ Spondylitis is a serious complication, more common in older patients
✧ There have been reports of rates of osteoarticular involvement as high as 59% (Skopje) and 69% (Turkey)

Croat Med J. 2004;45(6):727
Demographic characteristics and clinical and microbiological findings for patients with brucellosis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients/no. of samples studied</td>
<td>39/130</td>
</tr>
<tr>
<td>Demographic characteristic</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>30 (77)</td>
</tr>
<tr>
<td>Female</td>
<td>9 (23)</td>
</tr>
<tr>
<td>Age, mean years (range)</td>
<td>41 (16–78)</td>
</tr>
<tr>
<td>Clinical characteristic</td>
<td></td>
</tr>
<tr>
<td>Duration of symptoms, mean days (range)</td>
<td>32 (7–270)</td>
</tr>
<tr>
<td>Fever</td>
<td>36 (92.3)</td>
</tr>
<tr>
<td>Constitutive symptoms</td>
<td>22 (50)</td>
</tr>
<tr>
<td>Osteoarticular complications</td>
<td>16 (41)</td>
</tr>
<tr>
<td>Hepato/splenomegaly</td>
<td>7 (18)</td>
</tr>
<tr>
<td>Orchiepididymitis</td>
<td>3 (10)</td>
</tr>
<tr>
<td>CNS disorders</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Diagnostic test result</td>
<td></td>
</tr>
<tr>
<td>Titer ≥1:160, by Wright test</td>
<td>36 (92)</td>
</tr>
<tr>
<td>RBP test (from 2+ to 4+)</td>
<td>37 (95)</td>
</tr>
<tr>
<td>ELISA test</td>
<td>39 (100)</td>
</tr>
<tr>
<td>Proportion (%) of patients with positive blood culture results</td>
<td>13/24 (54)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. RBP, rose Bengal plate.
Clinical presentation

Chronic brucellosis

- Clinical manifestations for more than one year after the diagnosis of brucellosis is established
- Characterized by localized infection
- In some cases patients may have a cyclical course with intermittent back pain, arthralgias, sweats and signs of psychoneurosis
Diagnosis

- Clinical manifestations
- Exposure history
- Occupation
- History of past infection

Laboratory findings
Diagnosis

- Culture
- Serologic tests
- Molecular tests
- Imaging
Diagnosis
Culture

- Blood, bone marrow, other tissues
- Positive in 15 to 70 percent of cases
- Positive between 7th and 21st day
- Semiautomatic methods (e.g., BACTEC) shorter
- Bone marrow culture: gold standard
- Reserved for patients with abnormal hematologic findings, fever of unknown origin and negative brucellosis serology

Diagnosis
Serology

- Serum agglutination (standard tube agglutination)
- ELISA (enzyme-linked immunosorbent assay)
- Rose Bengal agglutination
- Coombs test
- Immunocapture agglutination (Brucellacapt)
- 2-mercaptoethanol agglutination
Serum agglutination test (Wright)
- Four-fold or greater rise in titer
- Samples 2 weeks apart

ELISA: IgM, IgG and IgA
- High sensitivity and specificity

Rose Bengal plate agglutination test is often used as a rapid screening test, with very high sensitivity (>99 percent), and fairly high specificity
The interpretation of serological tests can be difficult, particularly in the setting of chronic infection, reinfection, relapse, and in endemic areas where a high proportion of the population has antibodies against brucellosis.

Cross-reactivity with other bacteria is a problem with standard tube agglutination.
Diagnosis
Molecular

- PCR
- Positive as early as 10 days after inoculation
- Not standardized
Diagnosis

Imaging

- Plain radiographs
- MRI
- Radionuclide bone scintigraphy
- CT scanning
- Joint sonography

*Fig. 1—46-year-old man with brucellosis. Posterior planar image from radionuclide bone scintigraphy shows increased uptake in region of right sacroiliac joint.*
--MRI of 55-year-old woman with brucellosis and spondylodiskitis in contiguous thoracic and lumbar vertebrae

--MRI of a 6 year old boy with brucellosis of the tibia

Noncontrast CT of the liver of patient at the time of admission to the hospital, showing large calcium density without surrounding hypodensity. Serological test results at this time were as follows: rose bengal, negative; agglutination, negative; and Coombs' test, 1/80. Diagnoses of liver abscess and brucellosis were delayed.

Three goals:

1. Use antibiotics with activity in the acidic intracellular environment (doxycycline, rifampin)
2. Use of combination regimens
3. Prolonged duration of treatment
**Antibiotics Used in the Treatment of Brucellosis in Humans.**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Minimum Inhibitory Concentration (µg/ml)</th>
<th>Dose</th>
<th>Combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxycycline</td>
<td>0.06–1</td>
<td>100 mg twice daily for 6 wk</td>
<td>Doxycycline combined with streptomycin, with rifampin, with gentamicin, or with ciprofloxacin; doxycycline and streptomycin combined with rifampin or trimethoprim–sulfamethoxazole; doxycycline combined with rifampin and trimethoprim–sulfamethoxazole</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>0.25–16</td>
<td>15 mg/kg of body weight intramuscularly for 2-3 wk</td>
<td>Streptomycin and doxycycline; streptomycin and doxycycline combined with rifampin or trimethoprim–sulfamethoxazole</td>
</tr>
<tr>
<td>Rifampin</td>
<td>0.1–2</td>
<td>600–1200 mg/day for 6 wk</td>
<td>Rifampin and doxycycline; rifampin and doxycycline combined with streptomycin or trimethoprim–sulfamethoxazole; rifampin and ofloxacin; rifampin and ciprofloxacin</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>0.25–2</td>
<td>5 mg/kg/day in 3 divided intravenous doses for 3–7 days</td>
<td>Gentamicin and doxycycline</td>
</tr>
<tr>
<td>Trimethoprim–sulfamethoxazole</td>
<td>0.38–8</td>
<td>960 mg twice daily for 6 wk</td>
<td>Trimethoprim–sulfamethoxazole combined with doxycycline, with rifampin, or with streptomycin; trimethoprim–sulfamethoxazole and doxycycline combined with streptomycin or with rifampin</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>0.1–2</td>
<td>400 mg twice daily for 6 wk</td>
<td>Ofloxacin and rifampin</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.25–1</td>
<td>500 mg twice daily for 6 wk</td>
<td>Ciprofloxacin with doxycycline or rifampin</td>
</tr>
</tbody>
</table>

Treatment
Major regimens

A. **Doxycycline** (100mg x 2 for 6 weeks) plus **streptomycin** (1g IM for the first 14 to 21 days)
B. **Doxycycline** plus **rifampin** (600 to 900mg orally for 6 weeks)

* Regimen A is slightly more efficacious in preventing relapse
  
  Med Clin (Barc) 1994;102:731-738

* Parenteral administration of streptomycin is a problem

* The use of rifampin in areas in which brucellosis is endemic, where tuberculosis is also usually endemic, raises concern about the development of community resistance to rifampin.

**Neurobrucellosis, endocarditis, localized suppurative lesions:** 3 drugs for longer periods of time

**Spondylitis:** Two or three drugs, for 12 weeks

**Neurobrucellosis:** Doxycycline plus rifampin plus either ceftriaxone or cotrimoxazole. Prolonged duration (months)

**Endocarditis:** Few data. Combination of surgery and antimicrobial agents.
Prevention
Recommendations for safe laboratory practices to avoid exposure to *Brucella* spp.

When brucellosis is suspected, clinicians or forwarding laboratories should note on the laboratory submission: "Suspect or rule out brucellosis."

Review laboratory containment methods and microbiologic procedures to ensure compliance with recommendations in the *Biosafety in Microbiological and Biomedical Laboratories, Fifth Edition*.

Use primary barriers (ie, safety centrifuge cups, personal protective equipment, and Class II or higher biological safety cabinets [BSCs]) for procedures with a high likelihood of producing droplet splashes or aerosols.

Use secondary barriers: restrict access to the laboratory when work is being performed and maintain the integrity of the laboratory air-handling system by keeping external doors and windows closed.

Avoid causing splashes or aerosols when performing procedures on unidentified isolates.

Prohibit sniffing of open culture plates to assist in the identification of isolates.

Manipulate isolates of small gram-negative or gram-variable rods initially inside a BSC.

Data from: MMWR Surveill Summ 2008; 57:39.
Prevention

- Vaccination of cattle, sheep and goats
- Quarantine of herds and slaughter of infected animals
- Pasteurization of milk very important
- Active surveillance
BRUCELLOSIS IN SHEEP AND GOATS IN CYPRUS

Last isolation 2009, animal without identification suspected to originate from the occupied by Turkey areas of the Republic of Cyprus

SCOFCAH 7-8- September 2011
BOVINE BRUCELLOSIS - last single outbreak in 2008, last isolation 2005

Herd prevalence
Herd incidence

SCOFAH 7-8 - September 2011
Re-emergence of brucellosis in cattle in France and risk for human health

A case of human brucellosis was diagnosed in France in January 2012. The investigation demonstrated that the case had been contaminated by raw milk cheese from a neighbouring dairy farm. As France has been officially free of bovine brucellosis since 2005, veterinary investigations are being conducted to determine the origin of the infection and avoid its spread among other herds. Hypotheses about the source of this infection are discussed.
Outbreak investigation of brucellosis in Thassos, Greece, 2008

I Karagiannis¹, K Mellou¹, K Gkolfinopoulou (kassy1golf@yahoo.com)¹, G Dougas², G Theocharopoulos³, D Vourvidis², D Ellinas³, M Sotolidou³, T Papadimitriou¹, R Vorou¹

1. Hellenic Center for Disease Control and Prevention, Athens, Greece
2. Ministry of Rural Development and Food, Athens, Greece
3. Primary Health Care Center of Prinou, Thassos, Greece

This outbreak has clearly demonstrated that control and eradication of brucellosis is not only a question of designing a strategy, but rather of ensuring its continuous, strict implementation through well organised policies and programmes. Political will, commitment for inter-sectoral collaboration between all involved parties and close monitoring and evaluation of the measures implemented are unquestionable prerequisites for disease control and eradication [16].
Seroprevalence of brucellosis in animals and human populations in the western mountains region in Libya, December 2006–January 2008

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1. Department of Microbiology and Parasitology, Faculty of Veterinary Medicine, Al Fateh University, Tripoli, Libya
2. Department of Microbiology, Biotechnology Research Centre, Tripoli, Libya

Conclusion
We conclude that in the north-western region of Libya, Brucellosis seroprevalence is high in animals and human populations. Our data highlights the need for further research, including the isolation and characterisation of the causative agents, reliable epidemiological studies and the need to implement a transparency policy and effective control measures in Libya.
Thank you!