Brucellosis in the United States: Current Perspectives

Clinician Outreach and
Communication Activity (COCA)
Conference Call
August 25, 2011



Objectives

At the conclusion of this session, the participant will be able to accomplish the following:

- Describe populations at risk for brucellosis in the United States
- List brucellosis diagnostic methods available in the United States and advantages and disadvantage of each
- Discuss main causes of Brucella laboratory exposures and risk assessment
- Discuss treatment regimens for brucellosis and patient follow up

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TODAY'S PRESENTER



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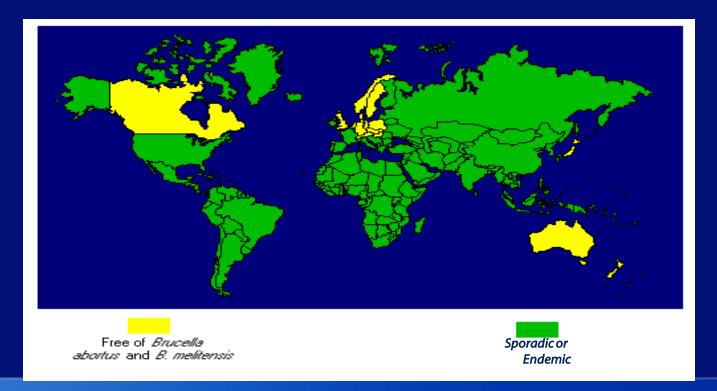


Outline

- Introduction
- History and Epidemiology
- Sources of Infection in the United States
- Surveillance
- Clinical Presentation
- Diagnosis
- Treatment
- Risk Groups
- Summary

Introduction

- Brucellosis worldwide zoonotic infection
- Economically important disease of domesticated animals
- Worldwide incidence of human brucellosis unknown
 - Varies from <0.01 to >200 per 100,000 population



Identification of Species

■ 1887: Bruce isolates *B. melitensis* from ill patient

■ 1895: Bang identifies *B. abortus* in cattle – Denmark

■ 1920: K.F. Meyer/E.B. Shaw- named changed to *Brucella* gen. nov.

□ 1929: I.F. Huddleston B. suis

■ 1956: M.B. Buddle *B. ovis*

□ 1957: H.B. Stoenner B. neotomae

1968: L.M. Jones
B. canis



Sir David Bruce

http://www.the-icsp.org/subcoms/Brucella.htm

Identification of Species

2001: A. Cloeckart
B. ceti, B. pinnipedialis

2008: Scholz et al.
B. microti

2010: Scholz et al.
B. inopinata

- Species have primary animal host preference
 - Secondary hosts may have lesser role in maintenance and/or transmission
- Four Brucella species- well known human pathogens

http://www.the-icsp.org/subcoms/Brucella.htm

History - Steps toward Eradication in the U.S.

Brucellosis Eradication Program

- Implemented in 1934 in cattle
- Expanded in 1954 and 1970s
- 2008- no affected herds for first time (only lasted 3 months)
- Continued surveillance by USDA and states



- Pasteurized Milk Ordinance (PMO) 1924
- Model regulation helping states and municipalities have an effective program to prevent milk borne disease



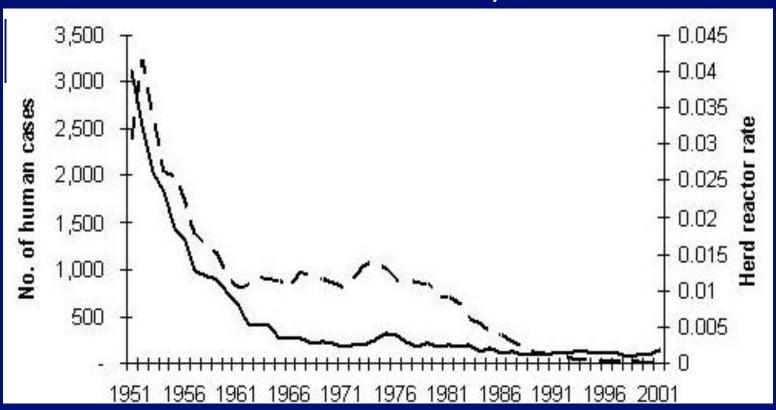


^{*} Ragan, VE. Brucellosis in the United States. Past, present, and future. JAMA. 1980. 244: 2318-22



Epidemiology - Incidence and Prevalence

Annual Numbers of Reported Human Brucellosis Cases and Cattle Herd Reactor Rates in the US, 1951-2001



Glynn MK, Lynn TV. Brucellosis J Am Vet Med Assoc 2008;233(6):902

Sources of Infection in the US - B. abortus

Reproductive disease

- Cattle primary host
- Other primary hosts bison, buffalo, elk, camels
- Secondary hosts goats, horses, dogs, wolves

Persistence in wildlife - bison and elk

- Present in Yellowstone Park and vicinity
- Obstacle to eradication in US

Risk of importation

- Continued surveillance
- Vigilance along southern border



http://www.aphis.usda.gov/animal health/animal diseases/brucellosis/downloads/yearly rpt.pdf

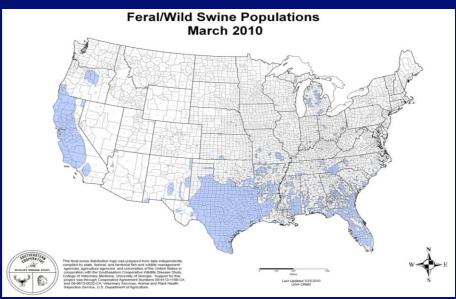
Sources of Infection in the US - B. suis

Primary host: swine

 Secondary hosts-horses, caribou and reindeer (Alaska)

USDA Eradication Program

- Commercial swine
- Expansion of the USDA cattle program to swine herds in 1972
- Currently, only Texas not declared free of swine brucellosis



Brucellosis present in feral swine populations (4-5 million)

- Reported in 33 states
- Largest populations in California, Texas, Florida and Hawaii
- Range in U.S. increasing

* http:\\www.usda.aphis.gov

Sources of Infection in the US - B. melitensis

Primary hosts- sheep and goats

Secondary hosts-cattle, camels, wild ruminants

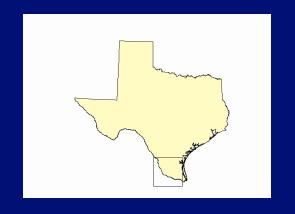
B. melitensis -found in sheep and goats in the U.S. until

the early 1970s

1999- last diagnosis in US

Texas border county

Considered FAD foreign animal disease





Sources of Infection in the US - B. canis

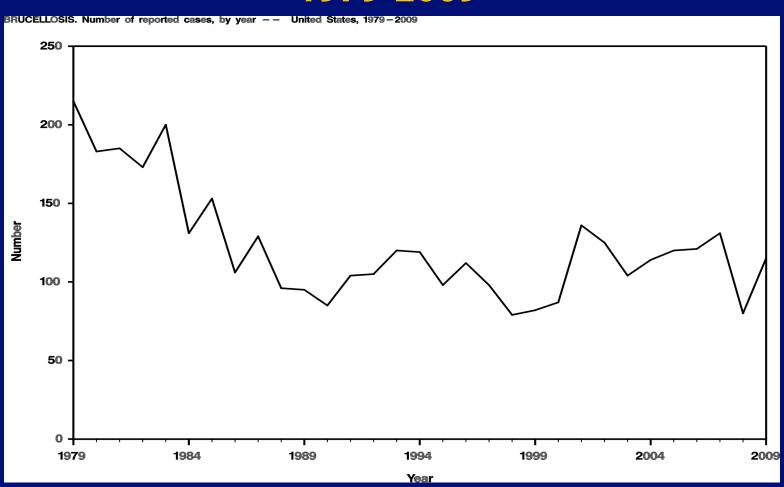
- Dogs considered principal reservoir
- Cause of abortion and reproductive failures in dogs
 - Female dogs may shed B. canis through vaginal discharge
 - Male dogs may shed B. canis in urine
- Euthanasia versus treatment
 - Even with repeated testing- may be difficult to conclude that dog testing negative for B. canis is not infected
- Outbreaks kennels and shelters
- Reportable disease- varies by state



Surveillance

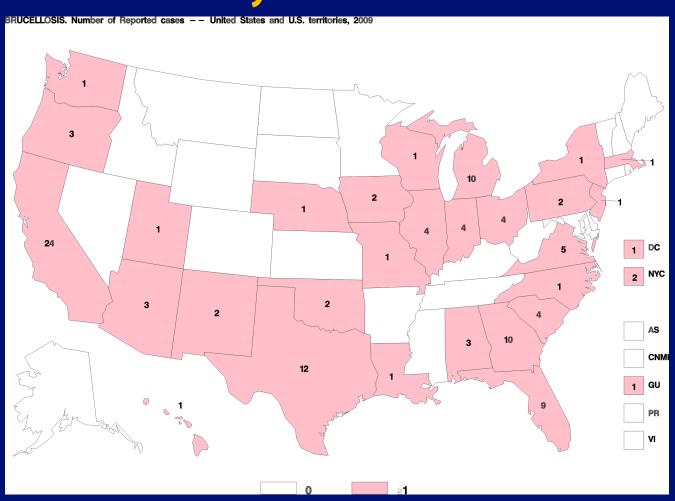
- Brucellosis nationally notifiable disease
- Select agents B. abortus, suis and melitensis, not B. canis
- Cases reported through NNDSS National NotifiableDiseases Surveillance System
 - Minimal number of variables age, sex, state of residence
 - Species not reported
 - Method of confirmation not reported

Human Cases of Brucellosis in the US 1979-2009



http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5853a1.htm?s cid=mm5853a1 w

Human Cases of Brucellosis in the US by State- 2009



Surveillance - Revised CSTE case definition - 2009

Clinical description

Surveillance - Revised CSTE case definition - 2009

Laboratory criteria for diagnosis

Confirmed

- Culture and identification of Brucella spp. from clinical specimens, or
- Evidence of a 4-fold or greater rise in *Brucella* antibody titer between acute- and convalescent –phase serum specimens obtained ≥ 2 weeks apart

Probable

 Brucella total antibody titer ≥ 160 by standard tube agglutination test (SAT) or Brucella microagglutinaiton test (BMAT) in 1 or more serum specimens obtained after onset of symptoms,

Detection of Brucella DNA in a clinical specimen by PCR assay

or

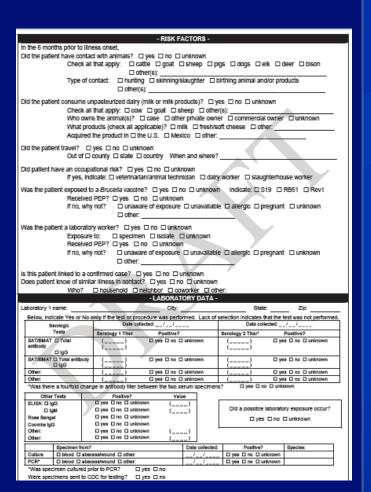
Surveillance - Revised CSTE case definition - 2009

Case classification

- <u>Confirmed</u>: a clinically compatible illness with definitive laboratory evidence of clinical infection
- Probable: a clinically compatible illness with at least one of the following;
 - Epidemiologically linked to a confirmed human or animal brucellosis case
 - Presumptive laboratory evidence, but without definitive laboratory evidence, of *Brucella* infection

Surveillance

- New Case Report Form developed
- Capture additional information:
 - Brucella species etiology
 - Risk factors
 - Mode of transmission
 - Demographics-ethnicity
 - History of travel



Routes of Transmission

- Foodborne
 - Ingestion of unpasteurized dairy products
- Direct or indirect exposure of organism to broken skin or mucous membranes
 - Aborted fetuses, placental fluid and tissues
 - Contaminated fomites
 - Inoculation with animal vaccine
 - Slaughtering and butchering process
- Aerosol transmission
 - Inhalation or conjunctival inoculation
- Person-to-person transmission very rare







Transmission Potential

- Products of parturition and abortion infectious
 - Can contain up to 10¹⁰ bacteria/ml
- Brucellae viable in placental tissues for 20 weeks
- □ Infectious dose (aerosol): 10²-10³ organisms





Pathogen Characteristics

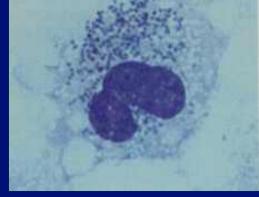
- Small, aerobic, nonmotile, nonsporulating, Gramnegative coccobacilli
- Slow-growing in culture
- Intracellular pathogen
- Lipopolysaccharide is main antigen
 - Smooth = more pathogenic
 - Rough = less pathogenic



B. abortus

Pathogenesis of Disease

- Systemic infection can involve most organs
- Initially localize in regional lymph nodes
- Bacteremic phase (2-8 weeks)
- May localize in:
 - Spleen
 - Liver
 - Bone marrow
 - Joints
 - Reproductive organs



B. melitensis inside macrophage

Severity in humans: B. melitensis > B. suis > B. >abortus > B.
canis

Clinical Presentation

- Incubation period variable: 2-4 weeks
 - (range: 5 days to 5 months)
- Clinical presentations:
 - Fever undulant, periodic
 - Often presents as fever of unknown origin (FUO)
 - Nonspecific- muscle aches, chills, fatigue, headache, night sweats
 - Arthritis, meningitis, osteomyelitis, endocarditis
 - Relapse and chronic disease can occur
 - Often difficult to recognize, diagnose, and treat



Chronic Manifestations I

- Undulant fever (continuous or intermittent)
- Localized infections in 30% of patients
- Hepatomegaly or splenomegaly (20-30%)
- Osteoarticular complications (20-60%)
 - Sacroilitis most common, spondylitis
- Genito-urinary complications (2-20%)
 - Orchitis and epididymitis- most common

Chronic Manifestations II

- Endocarditis (2-3%)
 - Primary cause of mortality
- Neurobrucellosis- rare
- Neuropsychiatric symptoms
 - Depression
 - Difficulty concentrating
 - Sleep disturbance

Diagnosis I

Culture – diagnostic gold standard

- Best yield from blood, bone marrow
 - Occasionally from tissues, cerebrospinal fluid, joint aspirate, urine if focal infection present
 - May require prolonged incubation
- Sample obtained before antimicrobial treatment
- Species identification reference laboratory
- PCR- performed after isolation
- Select agent must be reported (not B. canis)

Diagnosis II

- Serology- most common method of diagnosis
 - Acute-phase serum specimens- as soon as possible after fever onset
 - Convalescent-phase specimens- 14-21 days after symptom onset
- Serum agglutination test (SAT)- standard

- Serum agglutination test (SAT)
 - Measures agglutinating antibodies
 - Detects IgM, IgG1&2, IgA
- Rose bengal plate test (RBT)
 - Useful for screening, highly sensitive
 - Detects IgG1



- Complement fixation test (CFT)
 - Useful for confirmation, highly specific
 - Detects IgM & IgG1
- Anti-globulin Coombs test
 - Detects IgG2
 - Confirmatory, useful when SAT is positive and CFT inconclusive

- Enzyme-linked immunoassay (ELISA)
 - Commercially available
 - Cross-reactivity with Yersinia enterocolitica Y0:9
 - Positive results confirmed by second method
 - Not useful for screening

- Brucella microscopic agglutination test (BMAT)
 - Performed at CDC
 - Uses less antigens, shorter incubation time
 - More sensitive
 - Useful for testing large number of specimens (up to 70-100 specimens in a single run)
 - Use 2-mercaptoethanol and rivanol tests to separate IgM and IgG agglutinating antibodies

Diagnostics - Issues

Serology – primary method of diagnosis

- Commercially available tests not validated
- IgM tests result in increased number of false negatives
- Need acute and convalescent samples
- BMAT and other agglutination tests may not diagnose chronic infections
- Lack of awareness that available serological tests cannot diagnose
 B. canis infections
- Qualitative versus quantitative tests

Culture and isolation

- High rate of laboratory exposures
- Identification of species performed at Laboratory Response Network (LRN) laboratories
- PCR performed on isolates, not clinical specimens

Treatment

Uncomplicated brucellosis

- Doxycycline 100mg bid + rifampin 600- 900 mg/day (for 6 weeks)
- Doxycycline 100mg bid (6 weeks) + streptomycin
 1g/day (for first 2-3 weeks)

Pediatric patients (uncomplicated)

- Doxycycline + rifampin (children >8 yrs)
- Trimethoprim-sulfamethoxazole + rifampin (6 weeks)

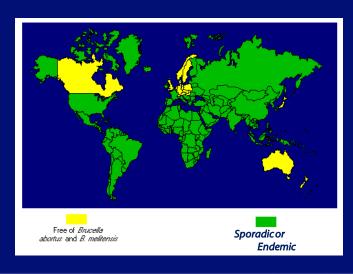
Relapses

- Late initiation of therapy
- Premature discontinuation of therapy

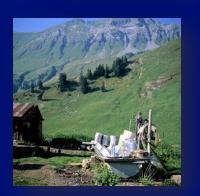
Ariza et al. Perspectives for the treatment of brucellosis in the 21st century: the loannina recommendations. PLoS Med. 2007.; 4:1872-8. Al-Tawfiq. Therapeutic options for human brucellosis. Expert Rev Anti Infect Ther. 2008: 6:109-20.

Risk Groups Dairy Consumers

- Ingestion of unpasteurized dairy products (soft, fresh cheeses, e.g. queso fresco)
- Brucella melitensis
- Persons at risk
 - Immigrants from endemic countries
 - Travelers to endemic countries













Interventions/Collaborations

- Collaboration with Border Infectious Disease Surveillance Program (CDC), US border states and Mexico
- Development of educational materials for US Hispanic population
- Assessment of seroprevalence of brucellosis among Iraqis immigrating to the US
- Collaboration with USDA to assess risk of B. melitensis in US- sheep and goat farms, ethnic markets



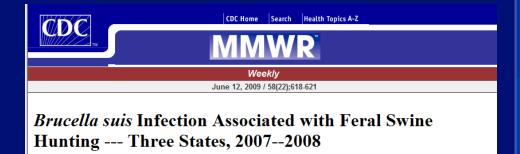


Risk Groups Hunters

- Contact with meat and other tissues from infected animals
- Brucella suis
- Persons at risk:
 - Consumers of infected wild game
 - Hunters
- Feral swine important source of human brucellosis infection through field dressing and butchering

Interventions/Collaborations

Investigation of cases of brucellosis in feral swine hunters



Development of educational brochure with USDA for hunters



http://www.cdc.gov/nczved/divisions/dfbmd/diseases/brucellosis/brucellosis and hoghunters.pdf

Risk Groups Dog Breeders / Kennel Workers

- Exposure to B. canis –
 materials associated
 with birthing process
- □ First human cases 1968
- Considered mild disease,
 <u>but</u>reported human cases of:
 osteomyelitis
 endocarditis

Symptom	% with symptom (n=32)		
Fever	66%	(21)	
Fatigue	34%	(11)	
Headache	31%	(10)	
Chills	28%	(9)	
Weight loss	28%	(9)	
Malaise	22%	(7)	
Sweats	22%	(7)	
Vomiting	16%	(5)	
Cough	13%	(4)	
Diarrhea	6%	(2)	

Compiled data of symptoms from 32 human cases reported in the literature

Interventions/Collaborations

- National Association of State Public Health Veterinarians (NASPHV) - assembled working group during CSTE 2010 mtg. to study B. canis
- Goals:
 - Increase awareness of diagnostic issues
 - Develop and standardize guidelines for public health investigations
 - Explore options for development of diagnostic tests
- CDC assisting in survey led by IA and WI PH veterinarians to collect information on B.canis among state health departments and laboratories

Risk Groups Populations Working with Marine Mammals

- Marine Brucella species- few reports of human cases of neurobrucellosis
- Populations at risk:
 - American Indian/Alaska Native- hunt marine mammals
 - Marine mammal rescue workers
 - Wildlife researchers
 - Veterinary staff

Interventions/Collaborations

- Collaboration with Alaska state health dept. and CDC Arctic Investigations Program
 - Assessment of laboratory submissions
 - Serological survey among AI/AN population
- Collaboration with National Institute of Occupational Safety and Health (NIOSH) and CDC Rickettsial Zoonoses Branch
 - Serological survey of persons working with marine mammals at a rescue and rehabilitation facility

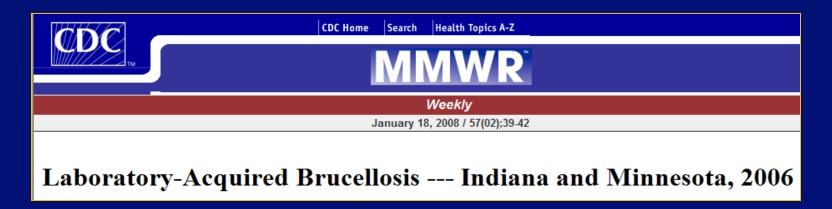
Risk Groups Laboratory Workers

- Brucellosis one of 10 most frequently reported labacquired infections (LAIs) in the US*
- Transmission can occur via:
 - Inhalation
 - Direct or indirect exposure of organism to broken skin or mucous membranes
- Infections due to:
 - Direct handling of organism or close vicinity to handling
 - Routine clinical laboratory procedures completed outside of a Biological safety Cabinet**
 - Accidents- e.g. malfunction of centrifuge

^{*}Harding AL, Byers KB. Laboratory-associated infections: summary and analysis of 3921 cases. In: Fleming DO, Hunt DL, eds. Biological Safety: Principles and Practices. 4th ed. Washington DC: ASM Press; 2006:53-77.

^{**}Pike RM. Laboratory-associated infections: incidence, fatalities, causes, and prevention. Annu Rev Microbiol 1979;33:41-66.

CDC Guidelines: Laboratory Exposure



- Multi-state multi-laboratory exposure 2006
- Demonstrated need for published guidelines
 - Tracking of isolate through laboratories
 - Risk assessment for potentially exposed laboratory workers
 - Recommendations for post-exposure prophylaxis

Assistance to States with Laboratory Exposures

Follow up requires information on:

- number of exposed laboratory workers
- demographics
- pregnancy status
- risk assessment
- PEP compliance
- serological results
- development of disease

Information reviewed at CDC from three sources:

- Requests for assistance from state health departments
- National Select Agent Registry reports (forms 3 & 4)
- Sera and isolate submissions to CDC laboratory for ID or confirmation

Workers assessed as high or low risk based on exposure

- Serological monitoring
- Post-exposure prophylaxis
- Information analyzed to evaluate program efficacy

Laboratory Exposure Incidents January 2008 – June 2011

Year	Exposure Incidents	Laboratories Involved	States
2008	12	15	10
2009	49	56	23
2010	58	72	27
2011 Jan-June	17	17	10
Total	136	160	44

Exposure Incidents

- Of cases reported to CDC:
 - **2**008: 12 of 80 (15%) had associated exposures
 - **2**009: 49 of 115 (43%) had associated exposures
 - **2**010: 58 of 115 (50%) had associated exposures
 - 2011: 17 of 32 (53%) had associated exposures
- □ B. melitensis and B. suis most common species identified
- CDC processed 2,728 serum samples—2008 June 2011
 - 1,090 Brucella-exposed laboratory workers in 21 states

5 Laboratory-acquired Infections Jan. 2008 – June 2011

<u>Case</u>	<u>Risk</u>	<u>Date of</u> <u>Exposure</u>	Date Onset	Began PEP	<u>Incubation</u>
Α	Unk	Unk	8/15/08	NA	Unk
В	High	7/14/09	11/27/09	7/27/09	19 wks
С	High	12/2009	~5/25/10	NA	~22 wks
D	Unk	12/2009	~3/14/10	NA	~12 wks
Е	High	6/2/10	~10/1/10	NA	~17 wks

Interventions/Recommendations

- No changes to the current recommendations
 - Consider obtaining additional serum samples from 8-24 weeks
 - Recommendations may require revision
- Prevent exposures
 - Increase physician awareness of brucellosis
 - Laboratory training
 - Proper handling of the organism
 - Use of personal protective equipment (PPE)
 - Use of Biological Safety Cabinets (BSL-3)
- Prevent infection after an exposure
 - Early identification of the exposure
 - Risk assessment of exposure for each worker
 - Use of antimicrobial PEP as indicated

Summary

Source of infection

- □ Historically an occupational disease caused by *B. abortus*
 - Veterinarians, livestock/abattoir workers, dairy farmers
- Currently most frequent sources of infection B. melitensis and B. suis
 - B. melitensis from unpasteurized dairy products
 - B. suis associated with feral swine hunting

Surveillance

- Case definition and laboratory criteria updated
- Utilization of new Case Report Form capture of additional data to:
 - Characterize risk factors
 - Identify trends
 - Identify Brucella species

Summary - cont'd

- Laboratory exposure intervention
 - Increase in reporting of laboratory exposures
 - 50% increase of reported cases from 2008 to 2009
 - >300% increase of reported laboratory exposures
 - Increased number or increased recognition?
 - Lab-acquired infections demonstrate the need for:
 - Prompt identification and assessment of an exposure incident;
 prompt prophylaxis of workers
 - Adherence to CDC recommendations for PEP and monitoring
 - Banking of isolates from case patients for comparison if an exposed person develops brucellosis
 - Role of clinicians, veterinarians
 - Role of laboratorians

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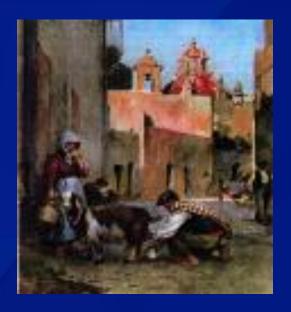
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Thank you

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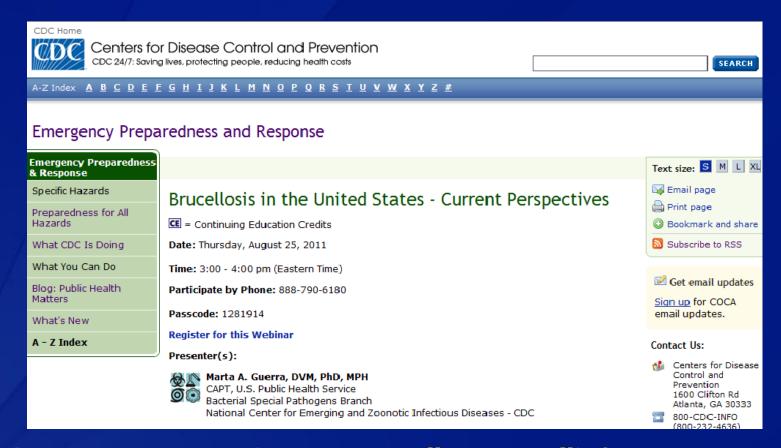


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http://emergency.cdc.gov/coca/calls/2011/callinfo_082511.asp

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