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Zoonoses and Meliodosis

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Conflicts of interest

- I have no conflicts of interest related to this presentation
- I am humbled and concerned to have to talk about meliodosis in Thailand!

Pulmonary Zoonoses

- Viruses
  - Hanta virus, MERS, Avian Influenza
- Bacterial
  - Q Fever, Chlamydia spp (inc Psittacosis)., Mycoplasm spp.,
  - Brucella, Leptospira, Tularemia, Yersinia, Streptococcus zooepidemicus
- Protozoa
  - More of a problem in solid organs (Trypanasoma cruzi, Toxoplasma gondii etc)

Question 1

- Spending 24 hours in an enclosed space with which of the following would not put you at risk of a zoonoses causing pneumonia?
- A – a chicken
- B – a pig
- C – a chimpanzee
- D – a camel
- E – a bat
- F – all of the above

Question 1

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- D – a camel
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COMMONLY PERCEIVED BIOTERROSISM THREATS

- CDC category A
  - Easily transmitted or high person to person
  - Likely high mortality
  - High social impact/potential for panic
  - Anthrax, plague, smallpox, tularemia
  - Botulism, Ebola, Marburg, Lassa, other South American haemorrhagic fevers

COMMONLY PERCEIVED BIOTERRORISM THREATS

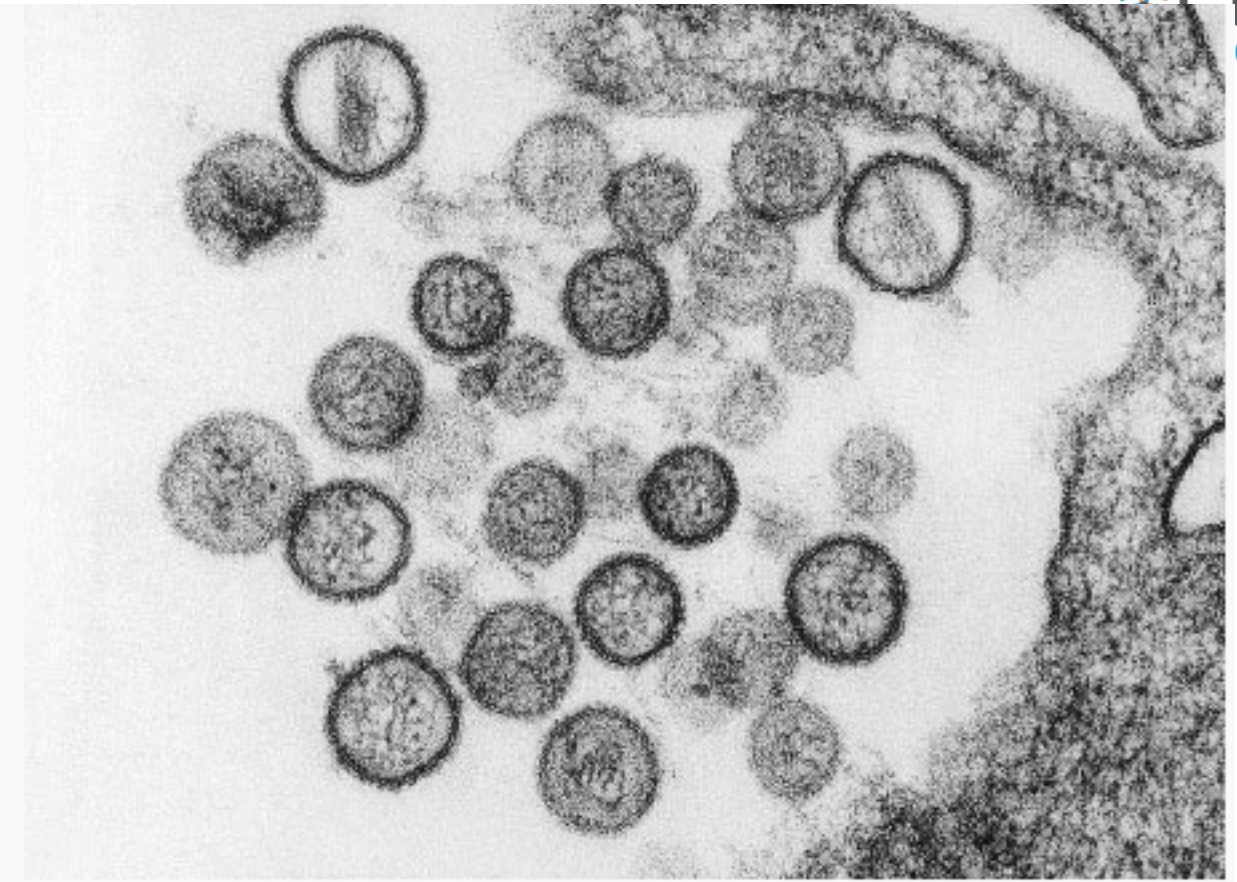
- CDC category B
  - Brucellosis
  - Ricin
  - Glanders (*Burkholderia mallei*)
  - Melioidosis (*Burkholderia pseudomallei*)
  - Psittacosis
  - Staph enterotoxin B
  - Q fever
  - Viral encephalitis

Why zoonoses so scary?

- No herd immunity
- High pathogenicity in “first pass” transfer

Hanta Virus

- Hantaviruses are tri-segmented negative sense single-stranded RNA
- Worldwide
- Two syndromes
  - Haemorrhagic fever with renal syndrome
  - Hantavirus cardiopulmonary sndrome
- Humans contract infection through inhalation of aerosols from the saliva or urine of infected animals (rodents, shrews, moles and bats)
- Different hantaviruses have different manifestations
  - Andes virus typically causes severe cardiopulmonary syndrome
  - Prospect hill virus doesn't cause disease in humans
  - "New World" hantaviruses – Cardiopulmonary, "Old World" hantaviruses – Haemorrhagic fever
- Estimation 20000 cases per year, most in Asia (Jiang et al Virologica Sinica 2017)

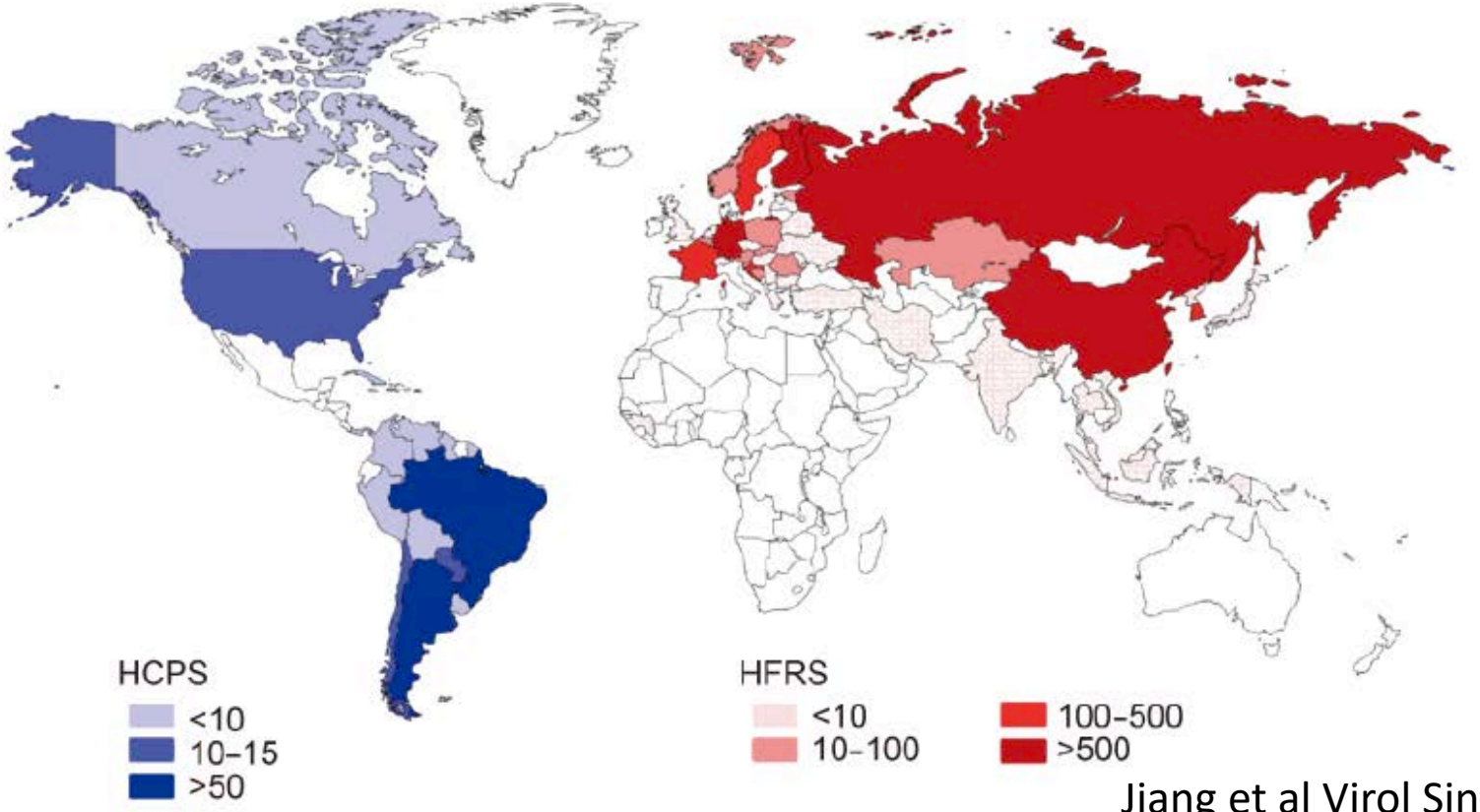


http://cdc.gov

Table 2. Geographic distribution of pathogenic hantaviruses

Virus isolate or strain	Abbreviation	Associated disease	Rodent host	Geographic distribution
Amur virus (Zhang et al., 2013)	AMRV	HFRS	*Apodemus peninsulae*	Russia, China, Korea
Dobrava-Belgrade virus (Papa, 2012)	DOBV	HFRS	*Apodemus flavicollis*	Europe (Balkans)
Hantaan Virus (Jiang et al., 2016)	HTNV	HFRS	*Apodemus agrarius*	China, South Korea, Russia
Puumala virus (Maes et al., 2004)	PUUV	HFRS/NE/ HCPS	*Clethrionomys glareolus Myodes glareolus*	Europe (Finland)
Saaremaa virus (Plyusnina et al., 2009a)	SAAV	HFRS/NE	*Apodemus agrarius*	Europe
Seoul virus (Yao et al., 2012)	SEOV	HFRS	*Rattus norvegicus*	Worldwide
Thailand hantavirus (Pattamadilok et al., 2006; Gamage et al., 2011)	THAIV	HFRS	*Bandicota indica*	Thailand
Tula virus (Nikolic et al., 2014)	TULV	HFRS	*Microtus arvalis*	Europe
Andes virus (Torres-Perez et al., 2016)	ANDV	HCPS	*Oligoryzomys longicaudatus*	Argentina, Chile
Araraquara virus (de Araujo et al., 2015)	ARAV	HCPS	*Necromys lasiurus*	Brazil
Bayou virus (Holsomback et al., 2013)	BAYV	HCPS	*Oryzomys palustris*	North America
Bermejo virus (Padula et al., 2002)	BMJV	HCPS	*Oligoryzomys chacoensis Oligoryzomys flavescens*	Argentina, Bolivia
Black Creek Canal virus (Knust and Rollin, 2013)	BCCV	HCPS	*Sigmodon hispidus*	North America
Castelo Dos Sonhos virus (Firth et al., 2012)	CASV	HCPS	*Oligoryzomys spp.?*	Brazil
Choclo virus (Nelson et al., 2010)	CHOV	HCPS	*Oligoryzomys fulvescens*	Panama
Juquitiba virus (Figueiredo et al., 2014)	JUQV	HCPS	*Oligoryzomys nigripes*	Argentina, Brazil
Laguna Negra virus (Figueiredo et al., 2014)	LANV	HCPS	*Calomys callosus*	Argentina, Paraguay, Bolivia
Lechiguanas virus (Guterres et al., 2015)	LECV	HCPS	*Oligoryzomys flavescens*	Argentina
Maciel virus (Guterres et al., 2015)	MCLV	HCPS	*Bolomys obscurus*	Argentina
Monongahela virus (Rhodes et al., 2000)	MGLV	HCPS	*Peromyscus leucopus*	North America
Muleshoe virus (Rawlings et al., 1996)	MULEV	HCPS	*Sigmodon hispidus*	North America
New York virus (Knust and Rollin, 2013)	NYV	HCPS	*Peromyscus leucopus*	North America
Oran virus (Figueiredo et al., 2014)	ORNV	HCPS	*Oligoryzomys chacoensis*	Argentina
Sin Nombre virus (Brocato et al., 2014)	SNV	HCPS	*Peromyscus maniculatus*	North America

Jiang et al Virol Sinica 2017



Jiang et al Virol Sinica 2017

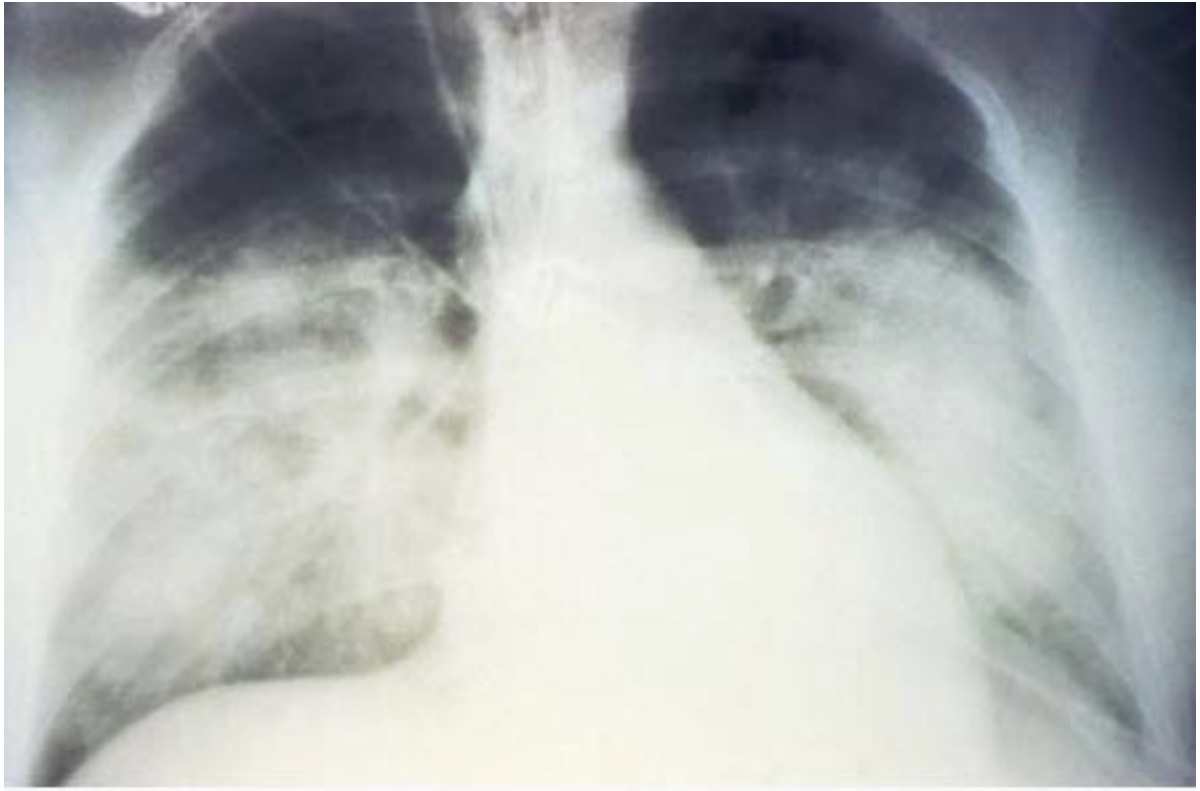
Figure 1. Geographical representation of approximate incidence of hantavirus cardiopulmonary syndrome (HCPS) and hemorrhagic fever with renal syndrome (HFRS) by country per year (data updated to 2016).

Hanta virus

- Primary infect vascular endothelial cells
- Leads to endothelial dysfunction in capillaries and small vessels
- Cardiopulmonary syndrome first described in 1993
- Initial symptoms dry cough, increasing dyspnoea
- Rapidly evolving bilateral interstitial odema
- Common to have renal failure, thrombocytopenia, haemorrhage, vomiting, diarrhoea, shock

Hanta diagnosis

- Clinical syndrome
  - Very easy to misdiagnose as influenza
- History of exposure
- Serology may be negative early on (<1 week) and is not readily available
- PCR assays unreliable



Hanta virus treatment

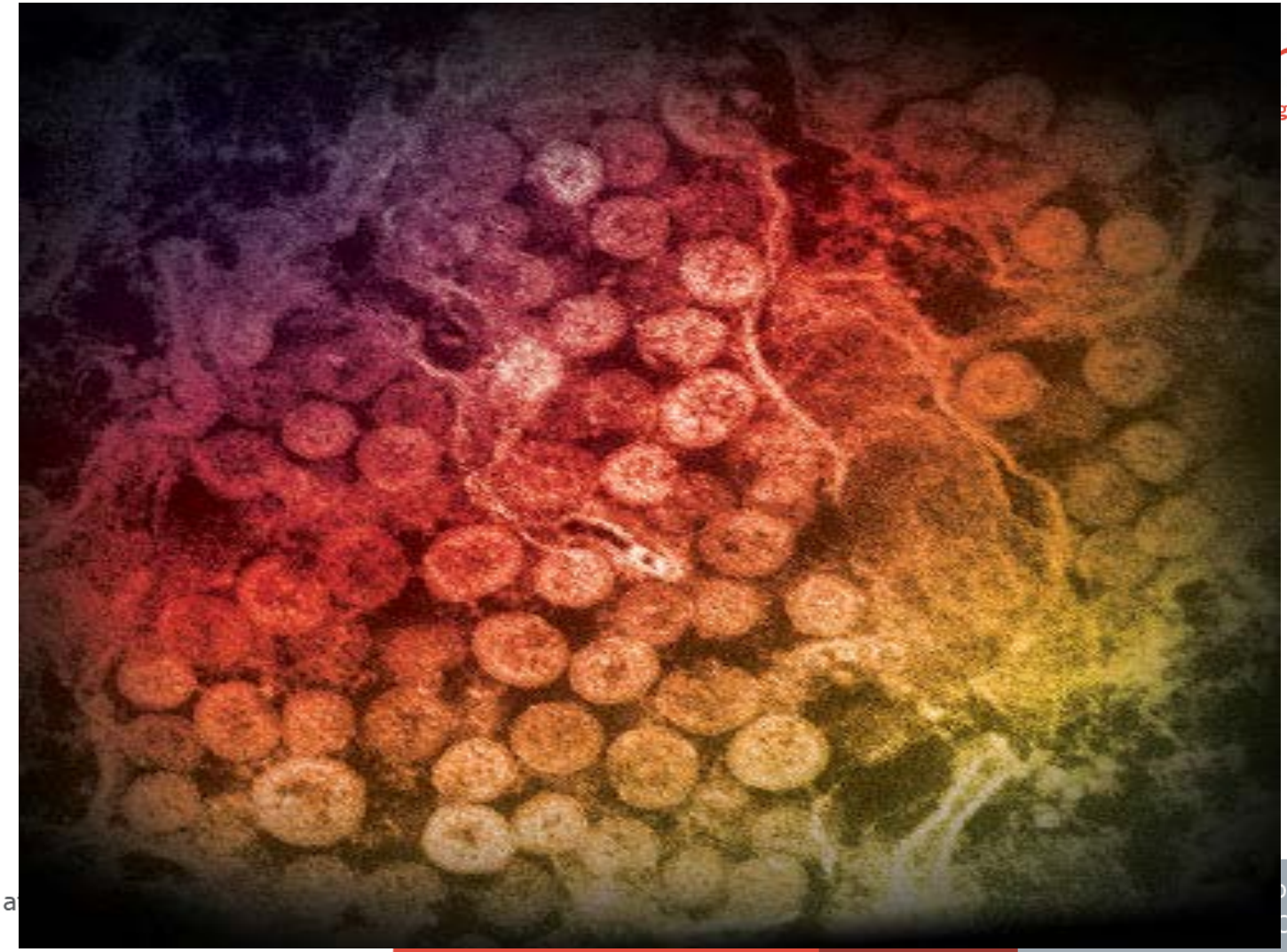
- Supportive care including ECMO
- Human immune plasma?
  - Vial et al Antivir Ther 2015
  - 32 cases, non significant trend to benefit
- Corticosteroids don’t help
  - Vial et al Clin Infect Dis 2013

Hantavirus CPS outcome

- Up to 35% mortality rate in hospitalised cases
  - Vial et al Clin Infect Dis 2013
  - Wernley et al Eur J Cardiothoracic Surg 2011
  - Crowley et al Crit Care Med 1998
- True mortality rate unknown but obviously much lower
- There are no reports of long term adverse outcomes in survivors

Coronaviruses

- Zoonoses that can make the leap to human-human
- SARS
- MERS
- More emerging
  - HKU1 in Thailand from bats
  - Joyjinda et al Microbiol Resour Announc 2019



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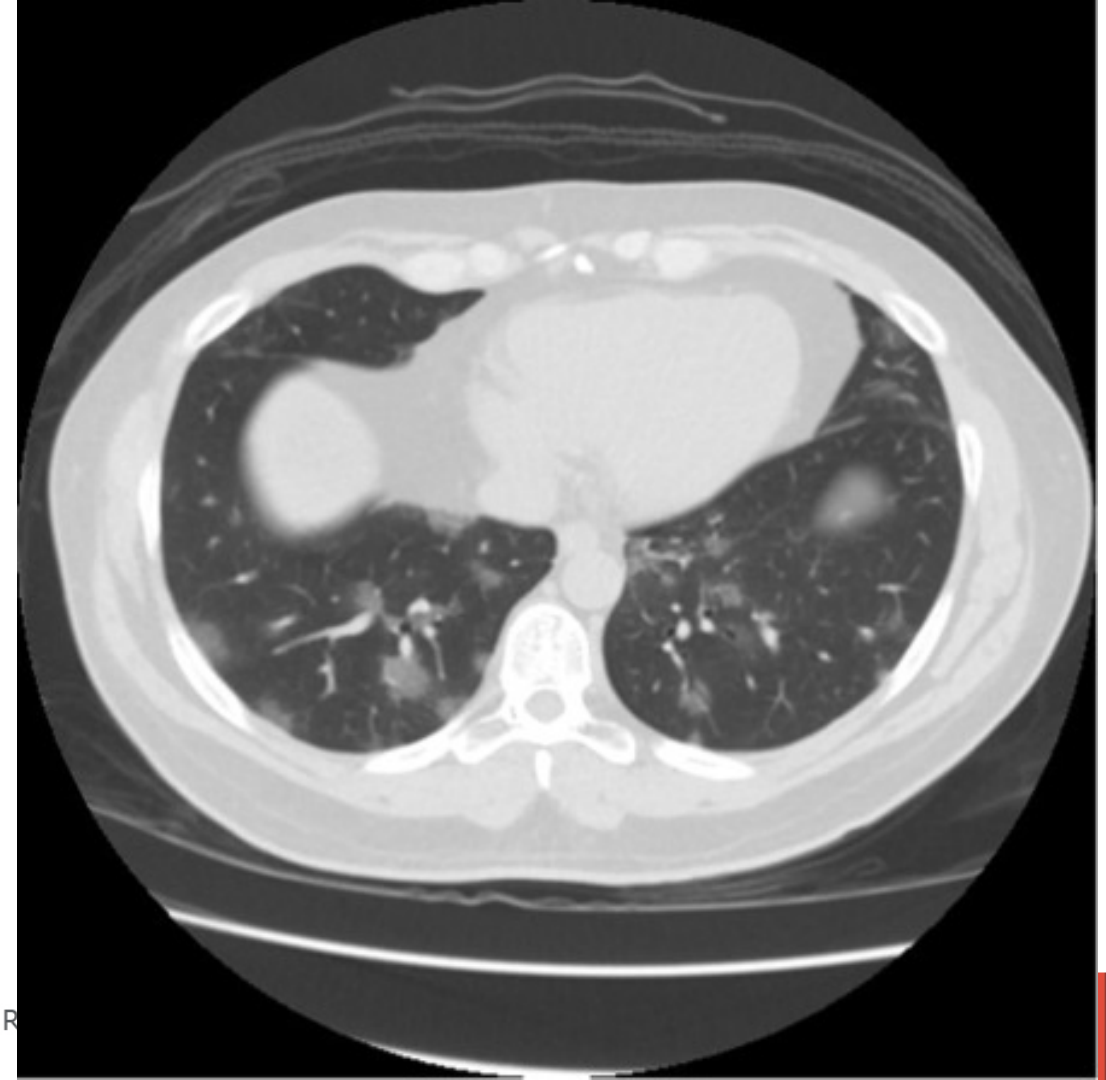

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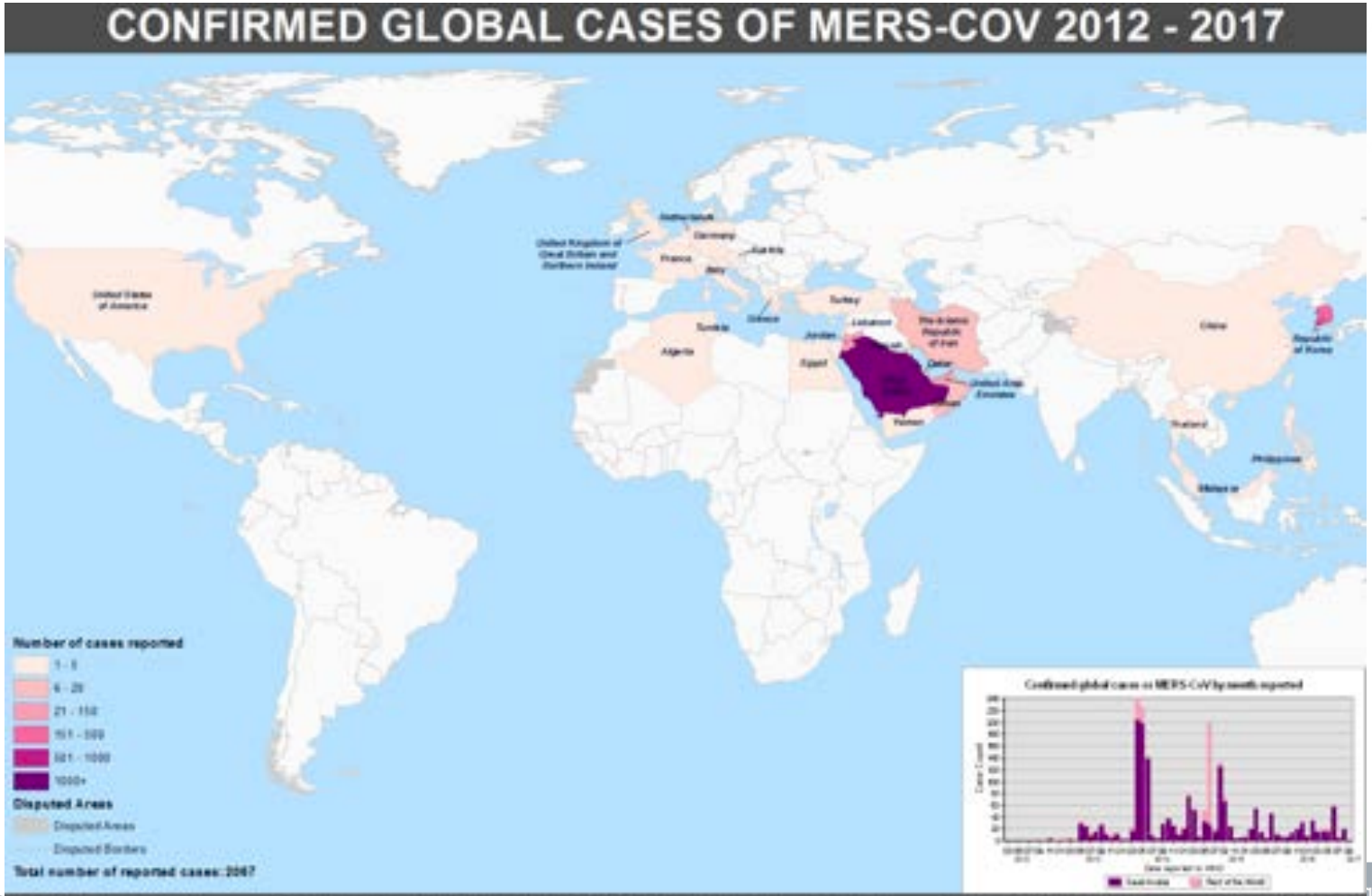
Hamimi et al 2016


CONFIRMED GLOBAL CASES OF MERS-COV 2012 - 2017
Number of cases reported
1 - 5
6 - 20
21 - 150
151 - 500
501 - 1000
1000+
Disputed Areas
Disputed Areas
Disputed Borders
Total number of reported cases: 2067
Data Source: World Health Organization
© WHO 2017. All rights reserved.
World Health Organization

Q-fever

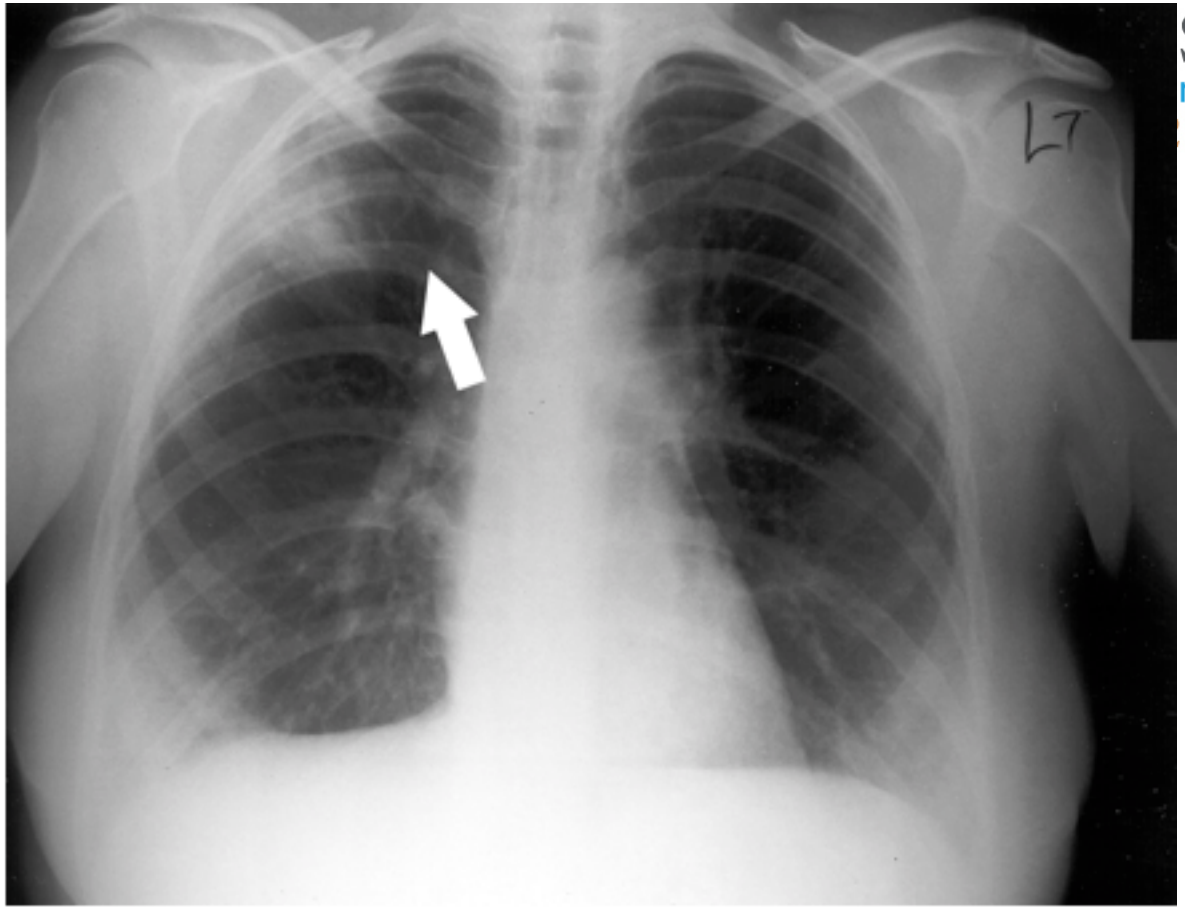
- Coxiella burnetti – obligate intracellular Gram-negative bacteria
- Initially Rickettsia burnetti, now reclassified as a Legionellales
- Worldwide (except New Zealand)
- Cattle, goats, sheep, birds
- Urine, saliva, faeces, milk, especially birth products
- Animals are usually asymptomatic
- Can cause both acute (e.g. pneumonia) and chronic infection (2-5%)
- Is a vaccine (inactivated whole cell) but not widely available outside Australia.
- Cellular response in 60-90% for 5-years , failures have been reported especially with high exposure (Bond et al Vaccine 2017)

Q-fever pneumonia

- Male:Female 5:2
- Usually a mild disease
  - 60% of serological converters are asymptomatic
  - Only 2-4% hospitalised
  - Raoult et al Lancet Infect Dis 2005
- Presents as a flu-like illness 14-40 days post exposure
- High fever is usual (>38.5 °C)
- Pleuritic chest pain not unusual
- Rash 5-20%, punctiform or maculopaular, rarely erythema nodosum
- Hepatosplenomegaly common
- CXR is non specific, typically round opacities +/- pleural effusion, upper lobes>lower
- Can get meningitis/encephalitis, endocarditis, pericarditis, myocarditis

Q-fever pneumonia

- Diagnosis
  - Exposure
  - Serology (IFA) is the reference method
    - IgM and IgG detected
  - PCR assays now also available
  - Persistent high elevation (1:800) of Ab levels at 6months = chronic infection

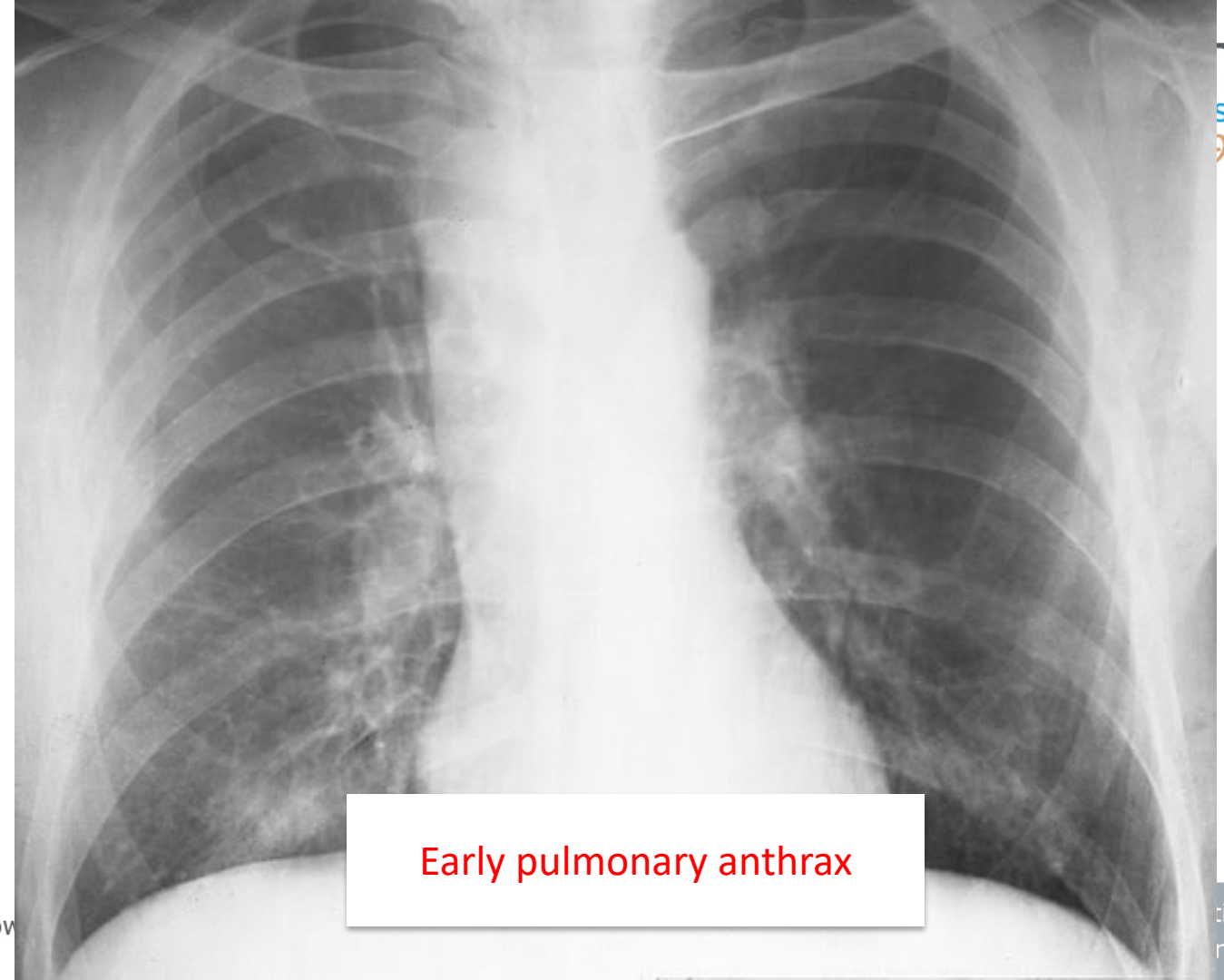


Marrie et al ERJ 2003

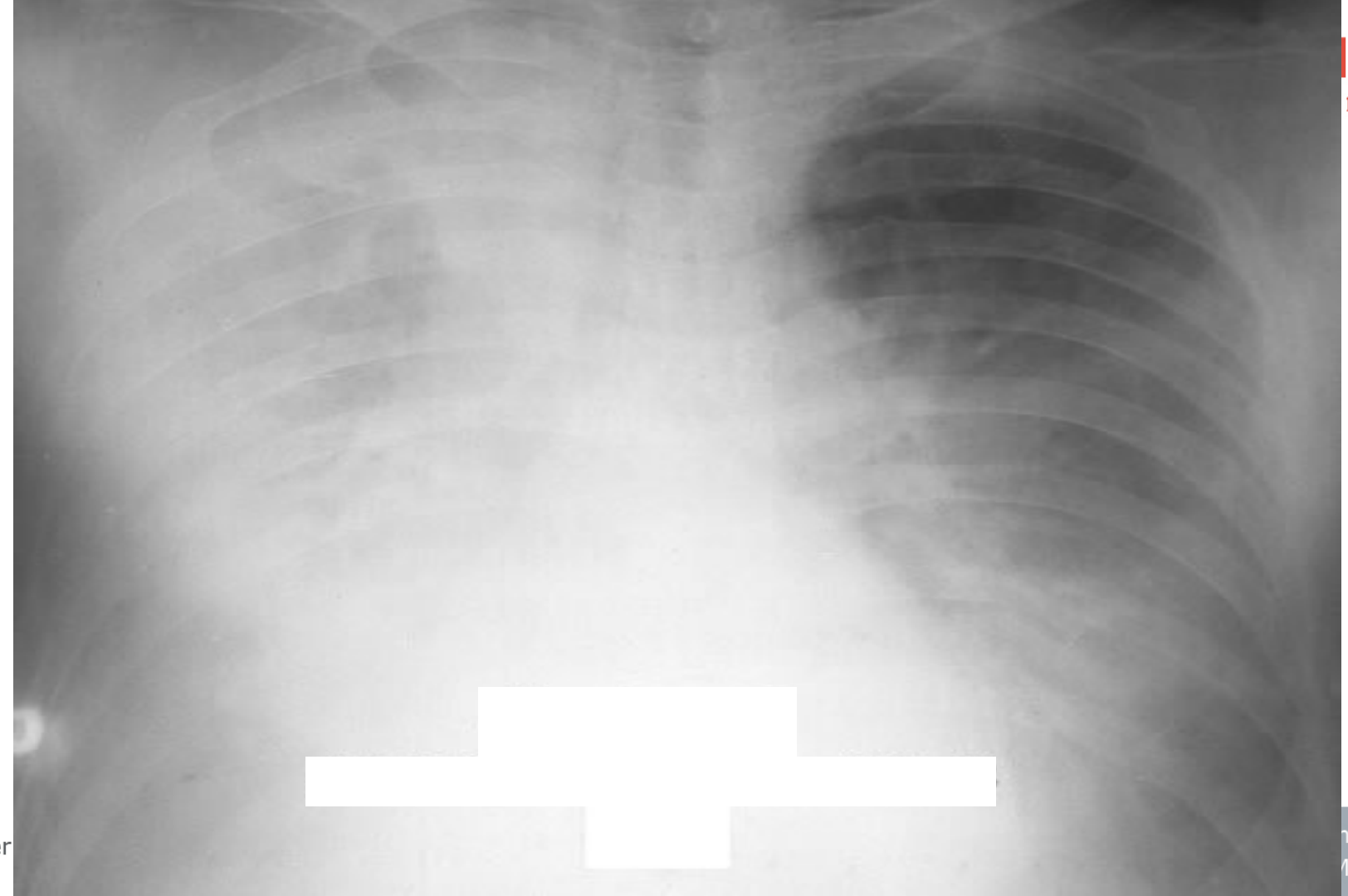
Q-fever pneumonia

- Treatment
  - Doxcycline 100mg BD 15 days drug of first choice
  - Clarithromycin, roxithromycin, azithromycin
  - Fluroquinolones (Ciprofloxacin, moxifloxacin, levofloxacin)
  - Cotrimoxazole and rifampicin if desperate due to allergy or contraindications
  - Need to follow up serology for 3-6 months
  - If have a valvular lesion follow up echocardiography to 12 months is advised

Cutaneous Anthrax



Early pulmonary anthrax



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Tularemia

- Aerosolization
  - Primary pneumonic Tularemia
  - Typhoidal Tularemia
  - Oculoglandular Tularemia
  - Ulceroglandular Tularemia
  - Orophayngeal Tularemia

Tularemia

- Following inhalation
  - Granuloma formation at entry and lymph nodes
  - 3-5 day incubation
  - Fever, chills, headache
  - Non productive cough and chest pain +/- pneumonia (50% have abnormal CXR)
  - Sore throat common and may be severe
  - May see ulcerative respiratory tract lesions
  - Septic shock and ARDS if not treated
- Mortality 35% without therapy, <5% with

Tularemia

- Treatment

- Gentamicin
- Ciprofloxacin, Doxycycline, or chloramphenicol

- Prophylaxis
  - Doxy 100mg bd or cipro 500mg bd

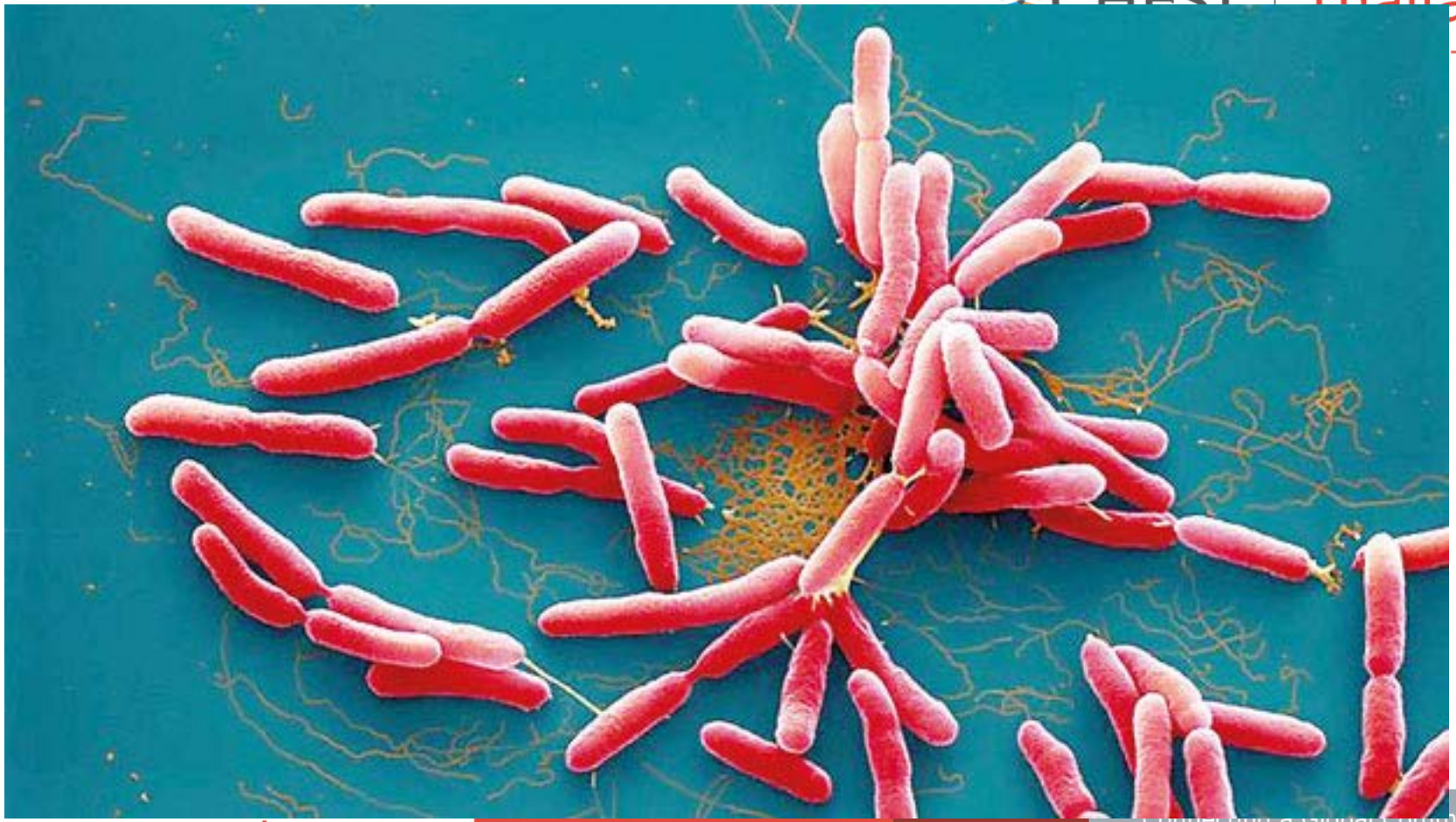
What's the message

- There is no zoonose that is characteristic enough to diagnose every time or even most of the time
- An accurate history is critical
- Need to always be on the alert for emerging infections

Meliodosis

Organism

- *Burkholderia pseudomallei*
  - Aerobic, gram-negative motile bacillus
  - Found in water and moist soil
  - Opportunistic pathogen
  - Produces exotoxins
  - Can survive in phagocytic cells
    - Latent infections common



History

- 1912, Burma
- Alfred Whitmore
- Organism isolated in humans
  - Glanders-like disease
    - Colony growth differed
  - No equine exposure
  - “Whitmore” disease

Alfred Whitmore 1876-1941

History

- 1913, Malaysia
- Stanton and Fletcher
- “Distemper-like” outbreak in animals
  - Isolated *B. pseudomallei*
- Pioneered serological tests for diagnosis

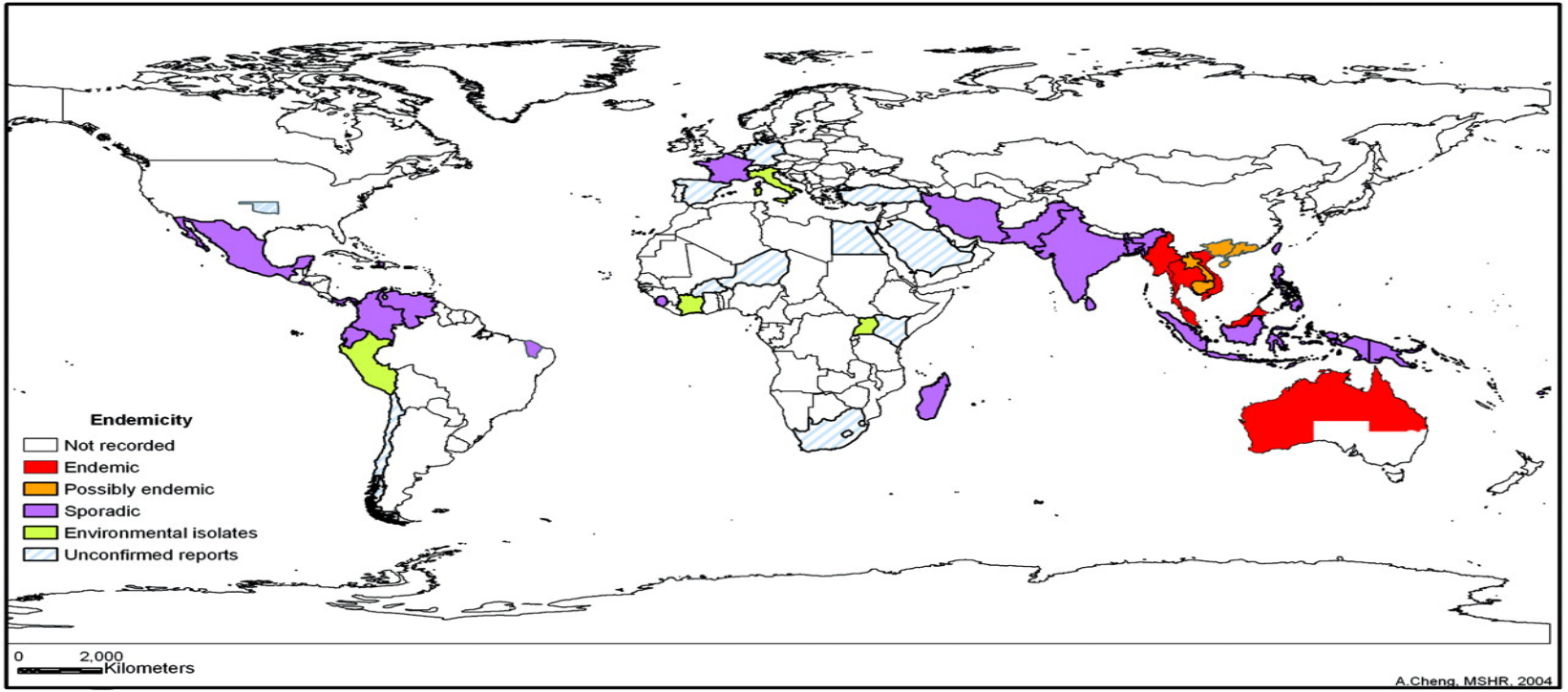
Ambrose Thomas Stanton

William Fletcher

Transmission

- Wound infection
  - Contact with contaminated soil or water
- Ingestion
  - Contaminated water
- Inhalation
  - Dust from contaminated soil
- Rarely
  - Person-to-person
  - Animal-to-person

Worldwide distribution of melioidosis.



Allen C. Cheng, and Bart J. Currie Clin. Microbiol. Rev. 2005;
doi:10.1128/CMR.18.2.383-416.2005

Epidemiology

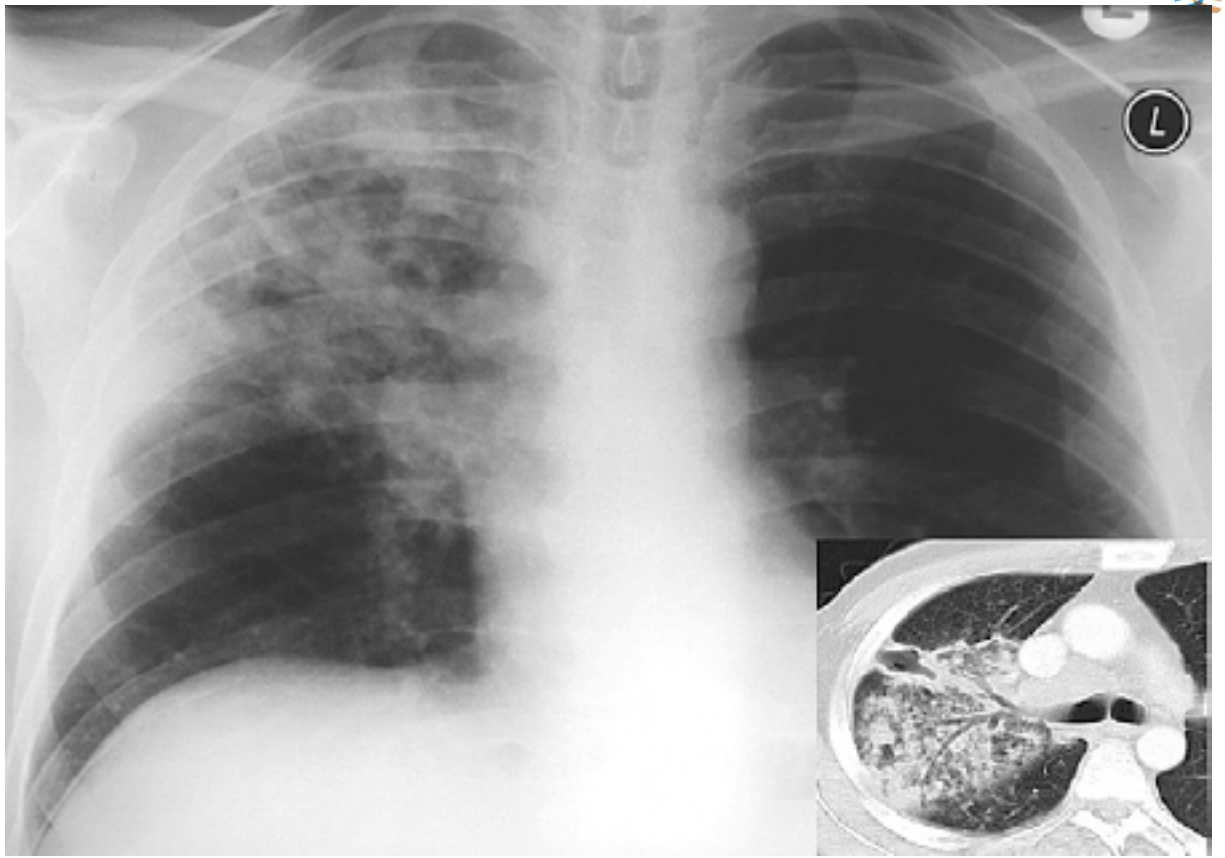
- Clinical disease uncommon
  - In endemic areas
    - Antibodies in 5 to 20% of agricultural workers
    - No history of clinical disease
- Wet season
  - Heavy rainfall
  - High humidity temperature

Human Disease

- Incubation period: <1 day to years
  - Latent infection (~4% of presentations are reactivation)
- Most infections asymptomatic
- Clinical forms
  - Acute pulmonary infection
    - Most common
  - Focal infection
  - Septicemia
  - Neurological (rare)
- Alcoholism has a high association with mortality

Acute Pulmonary Infection

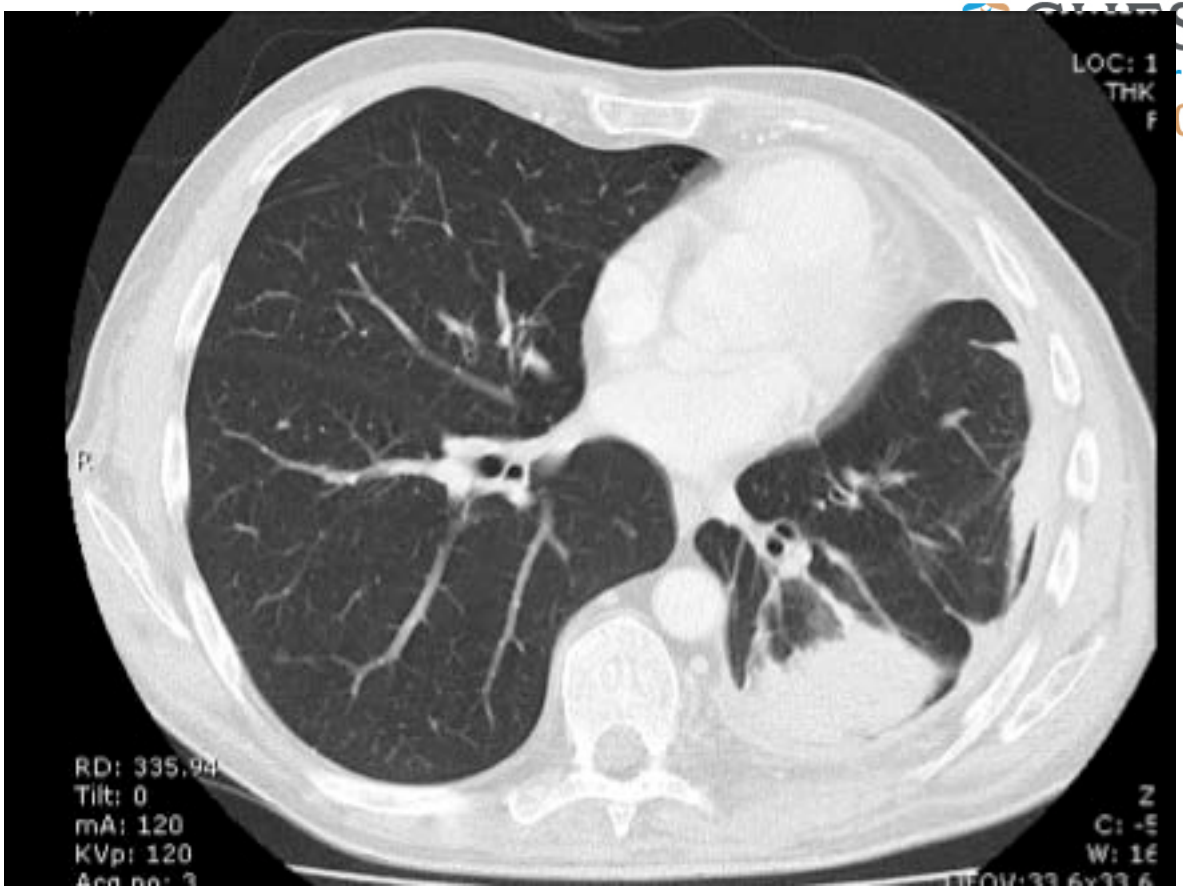
- Most common form
- High fever, headache
- Dull aching chest pain
- Cough, tachypnea, rales
- Chest X-rays
  - Upper lobe consolidation
  - Nodular lesions
  - Pleural effusion



Lie et al Resp Med 2009

Chronic Pulmonary Infection

- Easily misdiagnosed as tuberculosis
- ~10% of all cases of meliodosis reported
- Dull aching chest pain
- Cough, tachypnea, crackles
- Chest X-rays
  - Upper lobe consolidation
  - Nodular lesions
  - Pleural effusion


LOC: 1
THK
F
RD: 335.94
Tilt: 0
mA: 120
KVp: 120
Z
C: -5
W: 16

Melioid antibiotic resistance

- Efflux pumps
  - Aminoglycoside and macrolide resistance
  - Trimethoprim resistance
- Reduced outer membrane permiability
  - Polymyxin resistance
- Enzymatic breakdown
  - Beta-lactamases

Question 2

- For meliodosis, which of the following has been proven in a randomised controlled clinical trial
- A – meropenem is superior to imipenem
- B – meropenem is superior to ceftazidime
- C – ceftazidime is superior to cotrimoxazole
- D – imipenem is superior to cotrimoxazole
- E – imipenem is superior to ceftazidime
- F- none of the above

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Diagnosis and Treatment

- Diagnosis
  - Isolation of organism (Blood cultures positive in up to 55% in some series)
  - Various serological tests

- Treatment
  - Initial Systemic antibiotics 10-14 days, 28 days if extensive/severe disease
    - Carbapenem (meropenem) – Simpson et al CID 1999, Cheng et al Antimicrob Agents Chemother 2004
    - Ceftazidime – RCT vs chlor/doxy/cotrimoxazole 37% vs 74% White et al Lancet 1989
    - Trimethoprim sulfa
  - Surgical drainage of skin wounds
  - Subsequent oral eradication with cotrimoxazole or coamoxyclav from 3 months (Australia) up to 5 months (Thailand)

- No vaccine available – proving difficult

Center for Food Security and Public Health, Iowa State University, 2011

Meliodosis summary

- Know your local epidemiology
- High suspicion in right area
- Need to take a good history in all patients with pneumonia!

Thank you!

- grant.waterer@uwa.edu