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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), Mycoplasma 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
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COMMONLY PERCEIVED BIOTERRORISM 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 pathogenicicity 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 syndrome
- 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)
<table>
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<tr>
<th>Virus Isolate or strain</th>
<th>Abbreviation</th>
<th>Associated Disease</th>
<th>Rodent Host</th>
<th>Geographic Distribution</th>
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<td>Amur virus (Zhang et al., 2013)</td>
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<td>HFRS</td>
<td>Apodemus penicillae</td>
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<td>Dobrava-Belgrade virus (Papa, 2012)</td>
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<td>HFRS</td>
<td>Apodemus flavicollis</td>
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<td>Hantaan Virus (Jiang et al., 2016)</td>
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<td>Saaremaa virus (Pulssuina et al., 2009a)</td>
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<td>Thailand hantavirus (Pattamadik et al., 2006; Garnage et al., 2011)</td>
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<td>Tula virus (Nikolic et al., 2014)</td>
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<td>Microtus arvalis</td>
<td>Europe</td>
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<td>Andes virus (Torres-Perez et al., 2016)</td>
<td>ANDV</td>
<td>HCP0</td>
<td>Oligozygomyzis longicaudatus</td>
<td>Argentina, Chile</td>
</tr>
<tr>
<td>Araucana virus (de Araujo et al., 2015)</td>
<td>ARAV</td>
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<td>Necromys lasiurus</td>
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<td>Bayou virus (Holzembourg et al., 2013)</td>
<td>BAYV</td>
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<td>Bermejo virus (Padula et al., 2002)</td>
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<td>Black Creek Canal virus (Knust and Rolin, 2013)</td>
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<td>Castro Dos Bonhos virus (Firth et al., 2012)</td>
<td>CADV</td>
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<td>Choco virus (Nelson et al., 2010)</td>
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<td>Jojutla virus (Figueiredo et al., 2014)</td>
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<td>Laguna Negra virus (Figueiredo et al., 2014)</td>
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<td>Calomys callosus</td>
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<td>Leliquanuas virus (Gutierrez et al., 2015)</td>
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<td>HCP0</td>
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<td>Argentina</td>
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<td>Maciel virus (Gutierrez et al., 2015)</td>
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<td>Bolomys obscurus</td>
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<td>Monongahela virus (Rhodes et al., 2000)</td>
<td>MGLV</td>
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<td>Peromyscus leucopus</td>
<td>North America</td>
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<tr>
<td>Muleshoie virus (Rawlings et al., 1996)</td>
<td>MULEV</td>
<td>HCP0</td>
<td>Sigmodon hispidus</td>
<td>North America</td>
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<tr>
<td>New York virus (Knust and Rolin, 2013)</td>
<td>NYV</td>
<td>HCP0</td>
<td>Peromyscus leucopus</td>
<td>North America</td>
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<td>Orn virus (Figueiredo et al., 2014)</td>
<td>ORNV</td>
<td>HCP0</td>
<td>Oligozygomyzis chacoensis</td>
<td>Argentina</td>
</tr>
<tr>
<td>Sin Nombre virus (Brocato et al., 2014)</td>
<td>SNV</td>
<td>HCP0</td>
<td>Peromyscus maniculatus</td>
<td>North America</td>
</tr>
</tbody>
</table>
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 oedema
• 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
• 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
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 maculopapular, 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 6 months = chronic infection
Q-fever pneumonia

- **Treatment**
  - Doxycycline 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
Tularemia

• Aerosolization
  – Primary pneumonic Tularemia
  – Typhoidal Tularemia
  – Oculoglandular Tularemia
  – Ulceroglandular Tularemia
  – Oropharyngeal 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

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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
History

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

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
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
Melioid antibiotic resistance

• Efflux pumps
  – Aminoglycoside and macrolide resistance
  – Trimethoprim resistance
• Reduced outer membrane permeability
  – 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
    • 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!

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