Tan Tock Seng Hospital | IIDE Institute of Infectious Diseases and Epidemiology

Hong Kong Health Authority
Bioterrorism Workshop – 16 February 2017

Black Swans, White Powder:
Challenges in Diagnosis & Management as Clinicians

Poh Lian Lim, MD, MPH

Senior Consultant, IIDE, Tan Tock Seng Hospital, Singapore
Senior Consultant, CDD, Ministry of Health, Singapore
Associate Professor, Lee Kong Chian School of Medicine
Associate Professor, NUS School of Public Health & Medicine

Workshop Objectives

1. Equip healthcare workers with knowledge & skills on major ID emergencies & bioterrorism preparedness

2. Share experience / expertise on latest trends & practice from global perspective

3. Identify enhancement & training needs for ID emergency preparedness in Hong Kong with international communities

Overview

This talk will approach bioterrorism preparedness by considering the problem from these perspectives:

1. Black swans
2. White powder
3. Challenges in diagnosis
4. Challenges in management
5. Challenges as clinicians

- 1400-bed acute care general hospital, 8000 staff
- Institute of Infectious Diseases & Epidemiology (IIDE)
- National Centre for Infectious Diseases (NCID)
- Travellers' Health & Vaccination Clinic (THVC)

Case Scenario 1: CAP

(slide adapted from Dr Ray Lin)

- 48 yr old man admitted from ED yesterday with fever x 1d, headache, chest pain and breathlessness
- Working diagnosis: community-acquired pneumonia (CAP)
- Blood cultures taken, IV Augmentin started
- 6 hrs in → hypotensive, O2 sats drop to 86%, had to be transferred to ICU.

Case Scenario 1

(slide adapted from Dr Ray Lin)

- You are called a day later because blood cultures are flagging positive, with gram-positive rods (GPR) in 2/4 bottles

What are you thinking now?

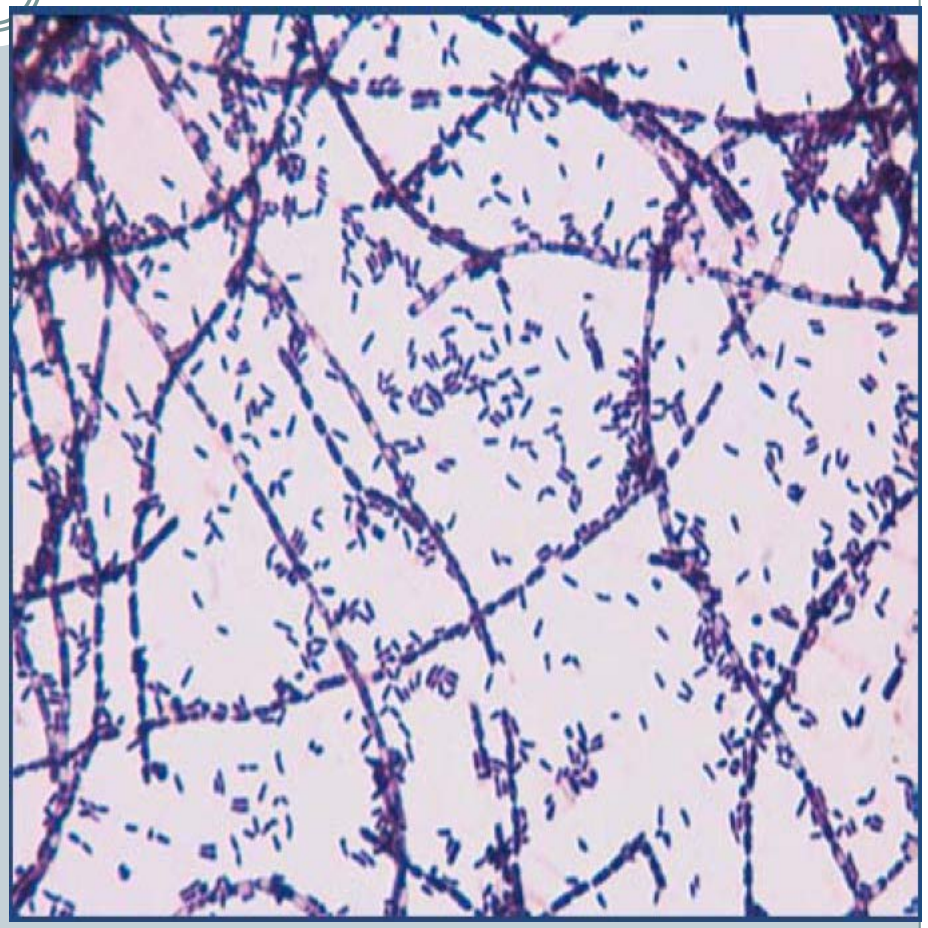
A) Bacillus anthracis

B) Listeria monocytogenes

C) Nocardia asteroides

D) Streptococcus pyogenes

E) It's a contaminant – ignore it



Gram Positive, non-motile bacillus.

Case Scenario 1: What should you do?

- If anthrax is considered, does it change management?
  - Should you change antibiotics? Any adjunctive therapies?
  - Do you need to order any infection control precautions?
  - Do you need to notify the public health authorities?

- The nurses in the ward who took care of him are calling you a day later to ask if they are at risk of anthrax
  - How do you determine who is exposed? Any tests?
  - Any effective counter-measures to prevent clinical disease?
  - Do staff caring for this patient need PEP? How about lab staff?
  - Would these answers change for a scenario with white powder?

Case Scenario 2: Maid in Singapore

- 26/F from Philippines, working as a maid in Singapore for 5 months
- Admitted on 23 April with 2d fever, vomiting, diarrhea
- Employer's mother-in-law arrived from Vietnam with ham on 18/4. Family ate it on 19/4, illness onset 20/4
- Employer, daughter, mother-in-law & maid all sick

T38.9 toxic-appearing
BP 120/70 P95
non-acute abdomen
no rash
no neuro deficits

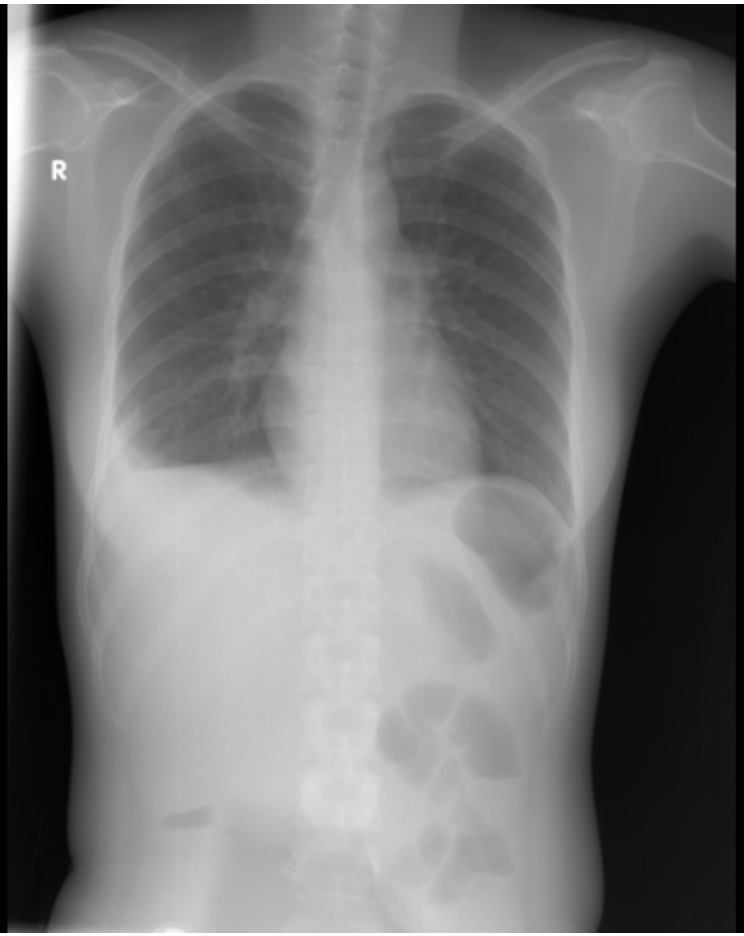
Labs:
WBC 4.0, Hct 43, plts 128k
Na 131, K 3.8, Cr 90, urea 3.3
CRP 211

Blood cultures at 24 hours:
Gram-positive rods

Toxic Filipino patient with pork exposure & GPR bacteremia

Gastrointestinal anthrax? Streptococcus suis? Ebola Reston???

Chest Xray 23/4/09



The Ham-pire Strikes Back

Listeria septicemia!

Black Swans, White Powder

Black swans are events that contradict all your previous experience

- Extremely improbable, unpredictable
- Extreme impact
- Retrospective plausibility

White powder – mail anthrax attacks came after 9-11

- Can be false alarms, can be a hoax
- But until we know it's NOT dangerous, we have to take the possible risk seriously

Singapore Airlines flight (Beijing-Singapore) grounded due to white powder found onboard (ST June 9, 2014)

SINGAPORE

Singapore Airlines flight grounded due to white powder found on board

Lee Jian Xuan
THE STRAITS TIMES
Monday, Jun 9, 2014

Photos: Twitter/Bernie Baker, Bloomberg

SQ806, bound for Beijing from Singapore, was scheduled to depart at 4.50 pm from Changi Airport, but tweets from passengers said that the plane was

The problem of needles in haystacks

- Outbreak severe acute respiratory infections (SARI)
  - MERS, SARS, H5N1, H7N9, HxNy…
- Viral hemorrhagic fevers (VHF)
  - Ebola, Marburg, Lassa fever, Rift Valley, CCHF, bunyavirus
- Intentional release
  - Anthrax, smallpox, ricin
- Naturally occuring severe infections
  - Bacterial: Plague, tularemia, melioidosis
  - Viral: Adenovirus, parainfluenza, RSV

At the inflection point – one degree north

Thailand: 175 Exposed to MERS Case

http://www.bangkokpost.com/learning/learning-from-news/596844/first-mers-case-confirmed-in-thailand

An Approach to BT Preparedness

- What is the external threat landscape? (Who/When)
  - State/non-state/lone wolves; covert vs overt; new biotech (CRISPR/cas9 gene editing)
- What is possible? What is feasible or likely? (What)
  - Bacteria, viruses, toxins
  - Combined attack - all hazards (chem/bio/rad/nuclear/cyber)
- What are routes of transmission & spread? (How/Where)
  - Respiratory, food/water, mail, bomb, what else?
  - Public places, transit hubs, restaurants, what else?
- What is the intended impact & gain? (Why)
  - Mass impact vs mass casualties

Bioterrorism: Challenges in Diagnosis

- UNEXPECTED
  - If covert/unannounced, the first case(s) may be missed
  - Wrong diagnosis can cause confusion, loss of credibility
  - Need a high index of suspicion in clinicians & microbiologists
  - Red flags: Severity, unusual epidemiology

- UNAVAILABLE
  - Testing to confirm diagnosis may be unavailable
  - Clinicians may be unfamiliar with which clinical samples to send, what transport tubes to use etc
  - Delays due to long turnaround time, confirmatory testing

The Mission: 4 Eyes For Bioterrorism!

- **IDENTIFY**
  - Clinicians & microbiologists
- **ISOLATE**
  - Clinicians, infection control, hospital admin
- **INFORM**
  - Clinicians/labs to public health authorities, government, media
- **INVESTIGATE**
  - Police, internal security, governments, international agencies

Everything Hangs on the Correct Diagnosis

- All subsequent actions & countermeasures flow from the diagnosis. So we have to get the diagnosis & pathogen right.
  - Incubation period
  - Ro reproductive number
  - Case fatality rate
  - PPE & isolation required
  - Staff protection countermeasures & post-exposure prophylaxis
  - Treatment for patients
  - Risk communications for exposed individuals
  - Credibility with the media & the public
  - Reputational damage

Diagnostic Yield & De-isolation

- A common mistake: To focus only on test sensitivity & specificity

- Diagnostic yield depends on 4 factors:
- Intrinsic test characteristics (sensitivity & specificity)
- Pre-test probability (positive & negative predictive values)
- Adequacy of clinical sample
  - Nasopharyngeal swabs may not be adequate for lower respiratory tract infections
- Time course in clinical disease
  - Negative results in early illness may not exclude infection, (depending on pathogen) but de-isolation may expose others

Expecting the Unexpected: The Role of Clinicians

- 27M student, no travel history
  c/o fever x 8 days,
  headache & arthralgia,
  minimal dry cough x 2 days
- Seen in the ED on day 3 of illness and sent home
- Exam: T37.6, RA sat 98%
  Otherwise unremarkable
- Labs: Mild leukopenia,
  mild thromobocytopenia,
  mildly elevated AST, ALT
- This graduate student worked with West Nile virus in the lab
- Blood cultures: negative
  Dengue PCR: negative
  Dengue serology: negative
  Malaria films: negative

  WNV PCR: negative
  CMV IgM: negative
  EBV IgM: negative

CXR (illness day 8): unremarkable

CXR (illness day 16): Left LZ infiltrate

Chest CT (illness day 18): Left LZ opacity

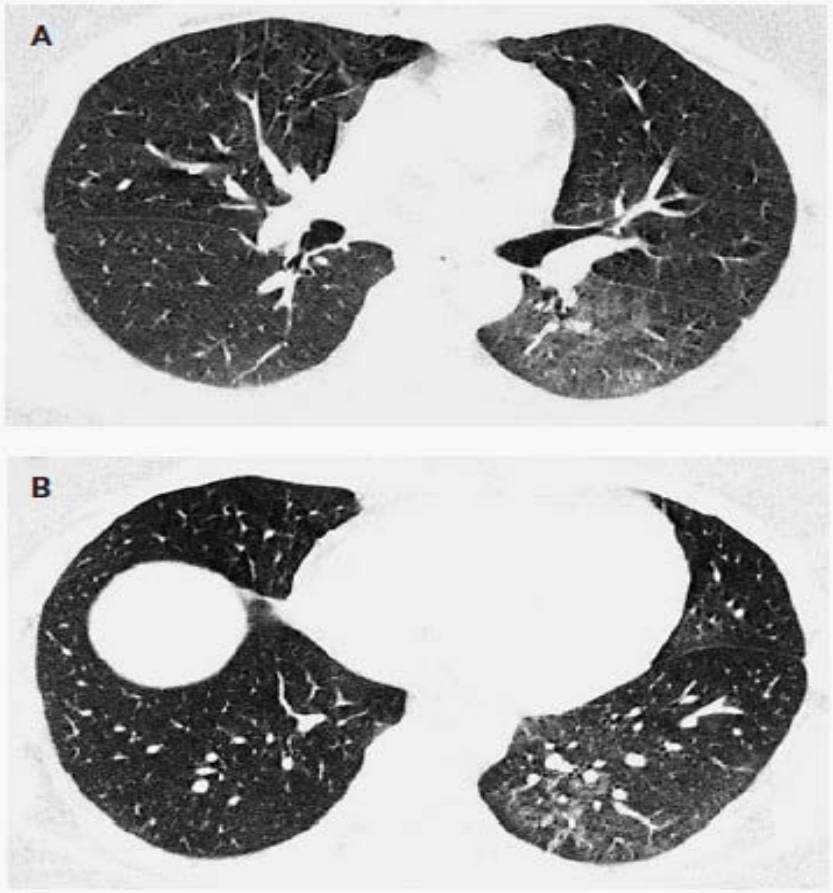


Figure 1. High-Resolution Computed Tomographic Scan of the Chest Showing Ground-Glass Opacity at the Apical Segment (Panel A) and Superior Aspect of the Posterior Segment (Panel B) of the Left Lower Lobe.

Early Detection: casting the net wide

But this was Sept 2003

SARS-CoV PCR

- Illness day 8 (HD1): negative
  Illness day 9 (HD2): negative
  Illness day 13 (HD6): positive
  Serum EIA day 13 (HD6): 6400

- Patient was de-isolated on HD 4 after first 2 PCR tests returned negative.

- All exposed HCW had to be quarantined, including the ID physician who treated him

Lab-Acquired SARS
Lim PL NEJM 2004;350:1740

- The patient had not worked with SARS-CoV. WNV is a BSL-2 pathogen (attenuated)
- But the cryovial of WNV he used tested positive for WNV and SARS-CoV
- Both viruses are cultivated on Vero E6 cells
- GIS sequencing showed that the patient's strain was most similar to SIN2774, the predominant lab strain in SG

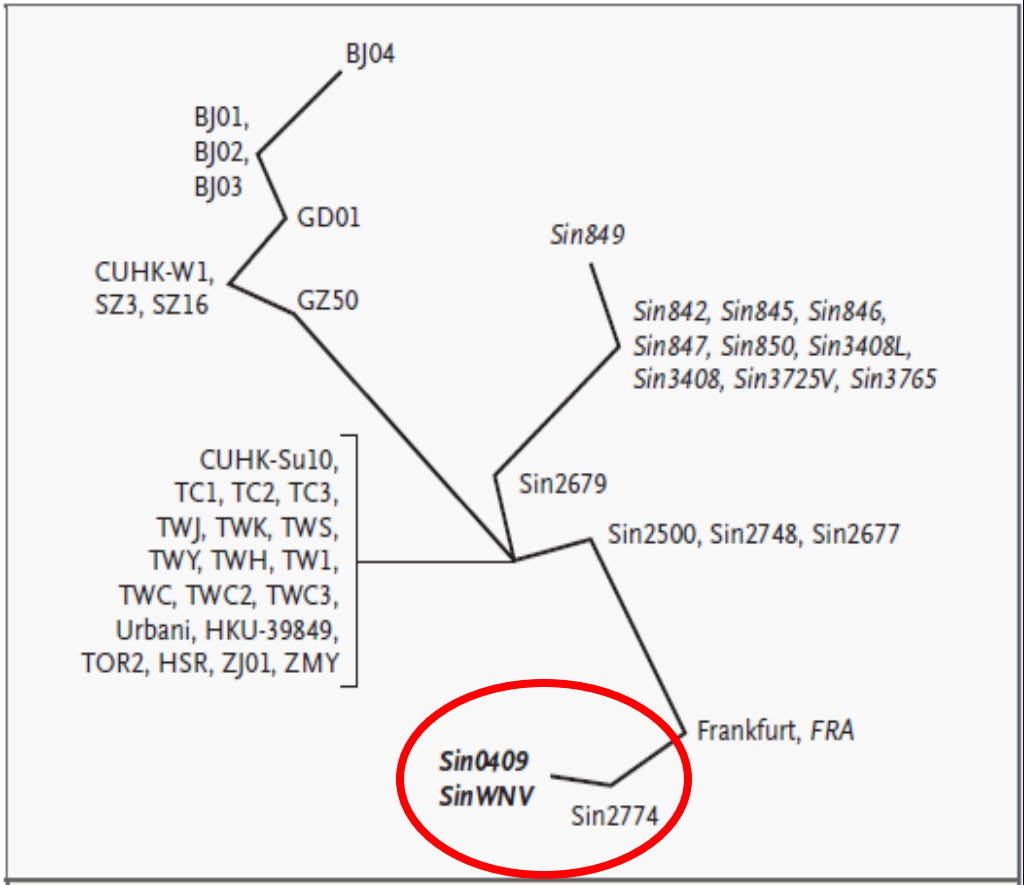


Figure 2. Molecular Relationships among 47 SARS-CoV Genomes.

A phylogenetic tree was constructed by means of a maximum-likelihood method[9] with the use of sequence information from 13 informative positions (nucleotides 9404, 9854, 17564, 18965, 19084, 19838, 21721, 22222, 22549, 23174, 23735, 23792, and 28268 in the Urbani strain; GenBank accession number AY278741) and 1 deletion (position 27760 to 27807). Sin0409 (the strain isolated from the patient) and SinWNV (the strain isolated from the sample of West Nile virus) appear on the same branch, indicating complete equivalence at all 14 sites. All SARS-CoV sequences were obtained from GenBank except for those indicated in italics, which were from the Genome Institute of Singapore.

Those who don't know history are destined to repeat it.

Edmund Burke
British statesman (1729-1797)

Commemoration of the SARS outbreak in 2013
Tan Tock Seng Hospital, Singapore

Bioterrorism: 3 Challenges in Management

- Dealing with the unfamiliar
- Dealing with high mortality
- Dealing with surge volumes

Challenges in Management: The Unfamiliar

- How do we train clinical teams to work in high risk, high stress situations, taking care of severely ill patients with diseases they may never have seen?
- How do we get it right the first time, and every time?
- And how do we provide care safely - to staff and to patients, families & visitors in the hospital?

Educating & Training: BT essential information

(slide courtesy of Dr Ray Lin)

Table 2. Selected Features of the Conditions Discussed.

Condition	Contagious	Clinical Form or Forms	Vaccine Available	Treatment
Anthrax	No	Three primary forms: cutaneous, inhalational, and gastrointestinal	Yes	Combination antimicrobials, effusion drainage, monoclonal antibody
Smallpox	Yes	Centrifugal rash with same-stage lesions	Yes	Supportive treatment
Plague	Yes	Pneumonic or bubonic	No	Antimicrobials
Botulism	No	Inhalational or gastrointestinal	No	Antitoxin
Tularemia	No	Inhalational or ulceroglandular	No	Antimicrobials

Amesh et al. Clinical management of potential bioterrorism-related conditions NEJM 2015; 372:954-62

Some Solutions to Managing the Unfamiliar

- Education & training a range of healthcare professionals
- Intensive training of core teams
  - Technically sound, flexible & resilient (respond to changes), imaginative (ability to think on their feet & think outside box), good interpersonal & communication skills, willing to accept risk/hardship
- Drills & exercises (PMIU)
- Simulations (ORPD)
- High level support & resources, sustainability (turnover)
- Deploy overseas for field experience
- Clinical care paths (eg.Ebola, Zika, dengue, lepto)
- Prepared kits & FAQs

Portable Medical Isolation Unit (PMIU) Exercise Changi Airport, Singapore – August 2014

Challenges in Management: High Mortality

- Anticipate high levels of anxiety & pressure from patients/families/media, other medical professionals

- Early diagnosis → prompt treatment → reduced case fatality
- Accurate risk communications for exposed individuals to seek care early → save lives & reduce spread

- Best supportive care
- Investigational therapeutics (regulatory & ethics approvals)
- New advances: mRNA vaccines, immunotherapy (mAb's), molecular forensics

Challenges in Management: Dealing with Surge

- Bottlenecks may develop in many areas:
  - ED, wards, lab, mortuary, ICU, ventilators, antibiotics, vaccines
- Surge response requires:
  - Capacity (pre-planning)
  - Stockpiles (pre-positioning, funds)
  - Operational capability
  - Expedited lines of communication, clear reporting structures
  - Ability to look up & down the chain (vertical/horizontal integration)
  - Prioritization of resources that is ethically & socially acceptable

Bioterrorism: 3 Challenges as Clinicians

- Infection control issues
- Staff protection
- Staff support & surveillance

Challenges as Clinicians: Infection Control

- PPE (Personal Protective Equipment)
  - Staff training, stockpiles, distribution
- Infrastructure
  - Enough isolation rooms, NEP, lifts, call & changing rooms
- Protocols
  - Precautionary principle, discipline
- Problems
  - Difficult situations – Children, mental illness, special needs
  - Fall back positions – safe cohorting protocols

Challenges as Clinicians: Staff Protection

In addition to PPE & training, for several BT pathogens, counter-measures are being developed to protect exposed individuals (war-fighters, first responders, healthcare workers)

- Pre-exposure countermeasures: Vaccines
- Post-exposure countermeasures: Monoclonal antibodies (mAb), medications, vaccines

Challenges as Clinicians: Staff Support

- Front-line work
  - Fear (staff, patients/families, public)
  - Fatigue (mistakes, heat, hydration)
  - Failure (patient fatalities, media criticism)

- Staff surveillance & support
  - Illness surveillance, protocols for admission, travel restrictions
  - Psychological support, morale
  - Clear HR policies, coverage for illness/death
  - Day-to-day realities: Meals, housing, call rooms

Summary – Key Take-Home Messages

- Bioterrorism & other black swan events are risks we face. Preparedness requires investing thought and resources
- Challenges in diagnosis:
  - Accurate diagnosis & confirmation is critically important
- Challenges in management:
  - Train for dealing with the unfamiliar, high mortality, surge
- Challenges as clinicians:
  - Infection control – PPE, infrastructure, protocols, problems
  - Staff protection, support & surveillance

Email: poh_lian_lim@ttsh.com.sg

Singapore 2017

http://www.singaporeair.com/images/local/dk/t04%20singapore/singapore-skyline-630x420.jpg