Clinical Manifestations and Treatment of Plague

Dr. Jacky Chan

Associate Consultant

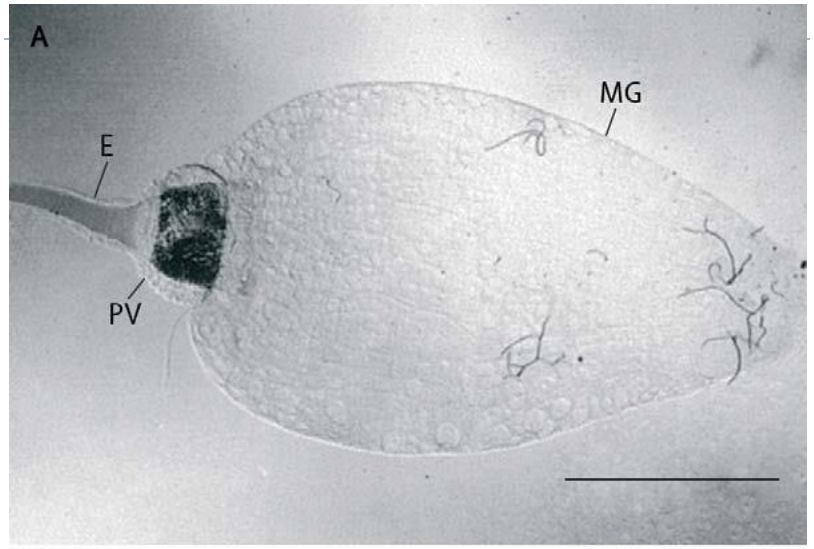
Infectious Disease Centre, PMH

Update of plague outbreak situation in Madagascar

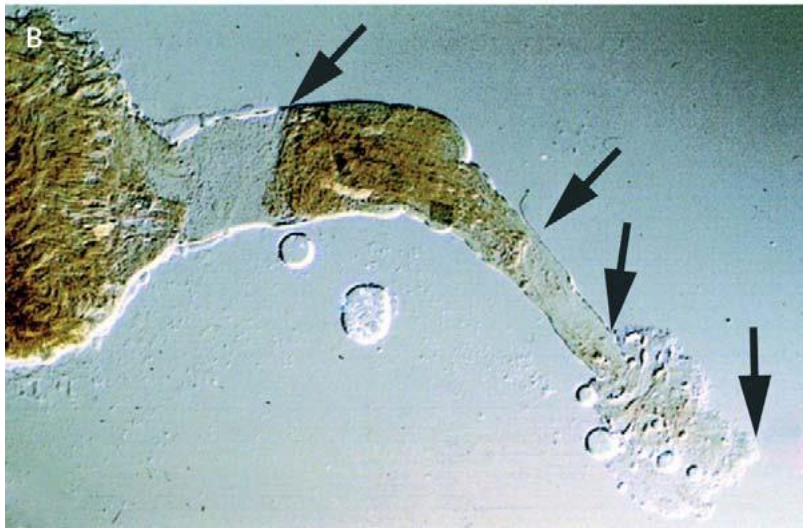
- A large outbreak since 1 Aug 2017
- As of 10 Nov 2017, a total of 2119 confirmed, probable and suspected cases of plague
- 171 deaths (case fatality rate 8%)
  - 76% pneumonic plague
- 82 HCW had illness compatible with plague, none have died

Plague

- Yersinia pestis, a Gram-negative bacillus
- Murine zoonosis, human are incidental hosts
- Transmitted by
  - Bites of rodent fleas
  - Scratches or bites from infected domestic cats
  - Direct handling of infected animal tissues
  - Inhalation of respiratory secretions from infected animals
  - Inhalation of aerosolized droplets from infected humans
  - Consumption of contaminated food
  - Laboratory exposure



- Digestive tract from an uninfected flea, showing the esophagus (E) and midgut (MG)



- Digestive tract from a blocked flea infected with Y pestis

Lancet 2007;369

Clinical manifestations

- Incubation period 2 to 8 days
- Three major clinical syndromes
  - Bubonic plague (80-95%)
  - Septicemic plague (10-20%)
  - Pneumonic plague

Bubonic plague

- Most common form
- Skin lesions (site of flea bite)
  - Usually inapparent
  - Some may have eschars, pustules, even necrotic lesions resembling ecthyma gangrenosum
- Sudden onset of fever, chills, weakness and headache, followed by intense pain and swelling in a lymph node bearing area (Bubo)

Lancet 2007;369

Bubo

- Derives from the Greek word βουβών for 'groin'
- Most frequently in inguinal areas, can also be axillary or cervical areas (particularly in children)
- Acute buboes are painful but lack fluctuation
- Associated with erythema and edema of the overlying skin
- Without treatment, infection disseminates and causes meningitis and pneumonia (secondary pneumonic plague)

Septicemic plague

- 10-20% cases
- Febrile, extremely ill, lack of localizing signs or symptoms
- GI symptoms (nausea, vomiting, diarrhea, abdominal pain) may be observed
- Hypotension, disseminated intravascular coagulation, multi-organ failure may develop at later stages of disease
- Necrosis of small vessels and purpuric skin lesions, gangrene of acral regions -> 'Black Death'

Pneumonic plague

- Can be primary or secondary
- Primary: acquired by inhalation of respiratory secretions or aerosolized droplets from infected animals or humans, or by laboratory exposure
- Secondary
  - More common, hematogenous spread of bacteria from a bubo or other source
  - Delayed treatment of bubonic infections

Primary pneumonic plague

- Short incubation period, ranging from hours to a few days
- Sudden onset of dyspnea, high fever, pleuritic chest pain, cough (may be associated with bloody sputum)
- Can be rapidly fatal

Human to human transmission

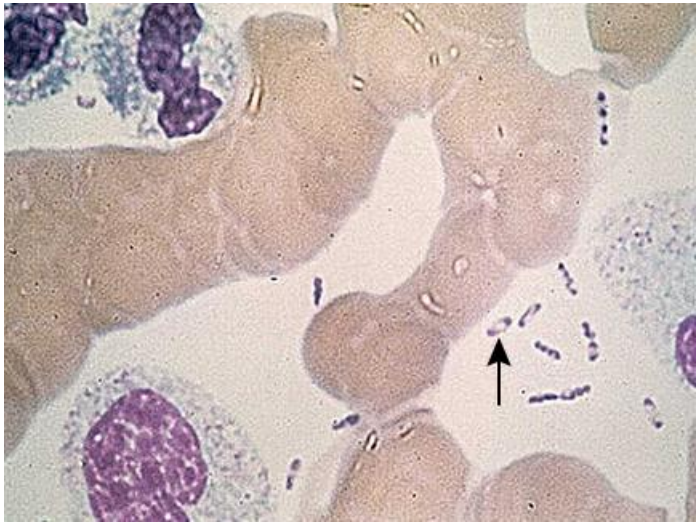
- Human to human transmission of plague via aerosols remains a source of controversy
- In one study in 2000 in Madagascar, 8% of 154 contacts became infected with Y. pestis (Lancet. 2000;355(9198):111)
- A study of cases of plague from an outbreak in Uganda, transmission was observed only in very close contacts (caregivers) and in the patients last days of life. (Emerg Infect Dis. 2006;12(3):460.)

Other manifestations

- Meningitis – any 3 forms of plague
- Pharyngitis, tonsillitis, associated with anterior cervical lymphadenitis, following ingestion of Y. pestis

Diagnosis

- Culture and staining
  - Specimens: bubo aspirate, sputum, blood
  - Blood culture: positive in 27 to 96 % patients
  - Bubo aspirate
    - positive culture in 10- 13%
    - Wayson's stain may demonstrate typical bipolar staining, resembling a 'closed safety pin'

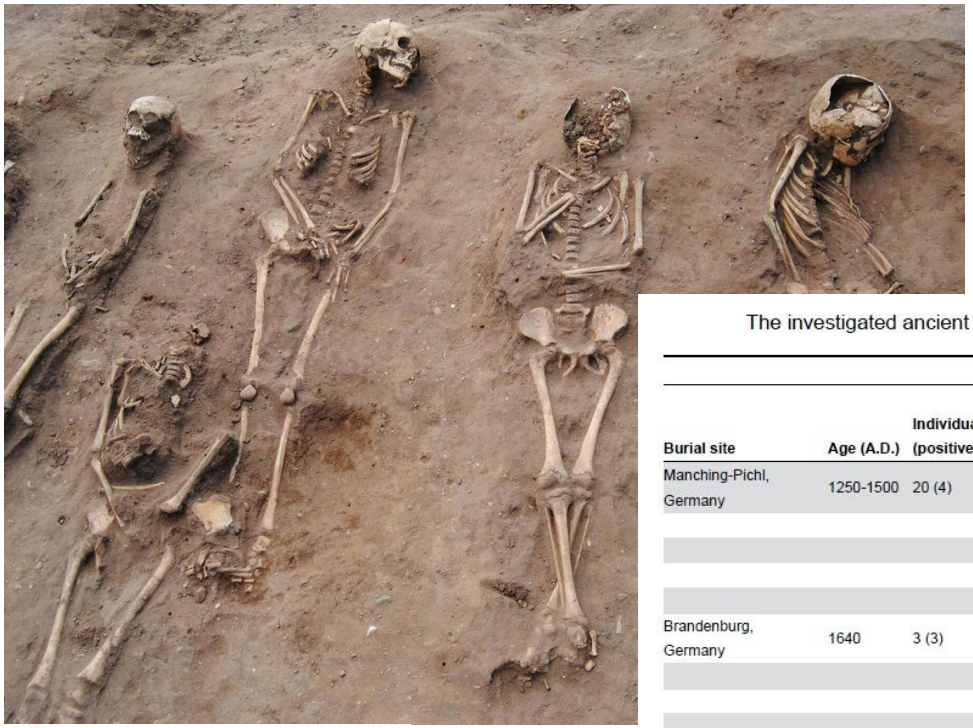


www.cdc.gov

Diagnosis

- Serology
  - Fourfold rise in antibody titers to F1 antigen of Y. pestis (acute and convalescent serum)
- Rapid tests
  - Field testing use
  - Detecting the F1 antigen of Y pestis in sputum or serum
- Y pestis polymerase chain reaction (PCR)

Detection of Y. pestis in Medieval Skeletons



INDEPENDENT

The investigated ancient samples originated from three different burial sites.

Burial site	Age (A.D.)	Individuals tested (positive) in this study	Positive individual	Quantitative screening PCR targeting *pla* (70 bp)	Maximum *pla* gene copies per 1µl	Specific *pla* amplicons & sequence (133 nt)	Specific *caf1* amplicons & sequence (161nt)
Manching-Pichl, Germany	1250-1500	20 (4)					
			MP17-I	4/4	560	3/3	2/3
			MP19-II	4/4	700	3/3	1/2
			MP59-I	4/4	22	3/3	1/3
			MPS01-I	4/4	3	1/3	0/2
Brandenburg, Germany	1640	3 (3)					
			B1	1/4	≤ 1	0/3	n.d.
			B2	2/4	2	0/3	n.d.
			B3	4/4	6	2/3	1/2
Basel, Switzerland	1300-1490	6 (0)		neg			
		13 extraction controls		0/4		0/3	n.d.

Overall results are summarized in Table S1.

PCR assay results are generated from the first DNA extraction round, following the most efficient method [33].

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Treatment

- Timely antimicrobial therapy and chemoprophylaxis
- Antibiotic regime
  - Aminoglycosides
  - Doxycycline/ tetracycline
  - Fluoroquinolones

Streptomycin

- Long history of drug use for plague
- Treatment of thousands of patients in Vietnam between 1960 and 1975
- 30mg/kg/day IMI (up to 2g) in two divided doses
- Duration: 10 days
- Ototoxicity and nephtotoxic

Gentamicin

- As effective as streptomycin in a retrospective study of 50 patients.
- Safer for use in pregnant women and in children
- Dose: 5mg/kg/day
- Duration: 10 days

Clinical outcome measures for 50 cases of human plague in New Mexico, 1985–1999, by antimicrobial treatment group.

Outcome measure	Antimicrobial treatment group				
	Streptomycin (n = 14)	Gentamicin (n = 18)	Gentamicin-tetracycline (n = 10)	Tetracycline (n = 8)	P
Duration of fever, mean days ± SD	3.5 ± 1.9	2.6 ± 1.1	1.9 ± 0.6	2.6 ± 1.2	.23[a]
Duration of hospitalization, mean days ± SD	6.2 ± 3.6	7.2 ± 2.6	6.0 ± 1.9	…[b]	.57[c]
Complication after treatment					…
SIRS	0	0	0	0	
DIC	0	0	0	0	
Meningitis	0	0	0	1[d]	
Death	0	0	0	0	…

CID 2004:38

Doxycycline

- Alternative agents for patients who cannot tolerate aminoglycosides
- Loading: 200mg Q12H for 1 day
- Followed by: 100mg Q12H
- RCT showed favorable responses for either doxycycline or gentamicin

Clinical responses to gentamicin or doxycycline treatment.

Clinical response	Gentamicin recipients (n = 35)	Doxycycline recipients (n = 30)
Death	2	1
Cure or improvement of condition	33	29
Relapse	0	0
Bubo		
Cleared	11	18
Improved	19	11
Suppurated	2	0
Time to defervescence, median days (range)	1 (0–5)	1 (0–4)
Adverse event		
Any event	7[a]	2
Dizziness	1	0
Headache	1	0
Seizure	1	0
Abdominal distention	1	0
Nausea	0	1
Vomiting	1	0
Diarrhea	1	0
Cough	2	1
Upper respiratory infection	1	0
Herpes labialis	0	1
Serum creatinine concentration after 7 days of treatment, mean mg/dL ± SD	1.04 ± 0.44	0.70 ± 0.18

CID 2006:42

Fluroquinolone

- Levofloxacin, ciprofloxacin and moxifloxacin are effective agents against plague in animal studies
- FDA in USA added fluoroquinolone as acceptable antibiotic for plague treatment

Antibiotics which are ineffective

- Septrin (only for bubonic plague)
- Penicillin
- Cephalosporins
- Macrolides

Duration

- Optimal duration of antimicrobial treatment for plague is uncertain
- Most of limited data evaluated 7- 10 day duration
  - Extend doxycycline course to 14 days (bacteriostatic)
  - At least a few days after clinical signs and symptoms resolved

Post exposure prophylaxis

- Unprotected face-to-face contact (within one to two meters) of patients who have not received at least 48 hours of effective treatment
- Doxycyline 100mg BD for 7 days
- Or levofloxacin 500mg daily for 10 days

Summary

- Human acquire plague via bites of rodent fleas, direct handling of infected animal tissues, inhalation of respiratory secretions or aerosolized droplets.
- Bubonic plague is most common presenation, followed by septicemic and pneumonic plague.
- Diagnosis of plague is by isolation of organism in culture
- Streptomycin or gentamicin is the drug of choice, with duration of therapy ranges from 7 to 14 days
- Post-exposure prophylaxis is warranted for individuals with unprotected face-to-face contact. Doxycyline is the drug of choice