### Blood and Lymphatic Infections

- **Plague**
  - *Yersinia pestis* (bacterial pathogen)
  - Lymphadenitis (inflammation of lymph nodes), fever, sepsis, shock
  - Member of Enterobacteriaceae
    - Gram-negative bacillus, facultative
    - Evolved from intestinal species of *Yersinia*
    - Acquisition of additional virulence plasmids
    - Inactivation of chromosomal genes (adaptation to gut has been abandoned)
    - Optimal growth at 28-30°C
    - Bipolar staining in tissue specimens with standard tissue stains (e.g. Wright-Giemsa)
      - “safety pins”

- **Malaria**
  - *Plasmodium* species (apicomplexan protozoan)
  - Fever, anemia, headache, seizures, severe disease in pregnant women and newborns

### Yersinia pestis

- **Disease: Plague**
  - **Bubonic plague**: sudden onset of fever, weakness, headache, and painful regional lymphadenitis (enlarged lymph nodes termed “buboes”). Liver and spleen often enlarged. 2-6 day incubation period. May progress rapidly (2-3 days) to sepsis, shock and death. Mortality is 25-50%.
  - Septicemic plague: fever, sepsis, shock without lymphadenitis

### Yersinia pestis

- **Pathogenesis**
  - Colonization and blockage of flea proventriculus (terminal part of foregut)
    - Biofilm formation dependent on bacterial production of exopolymers
    - Causes starvation of flea resulting in repeated biting, regurgitation of infectious blockage material
    - Plasmid-mediated phospholipase allows survival in flea gut
      - Not present in other Yersinia, mechanism not understood

### Yersinia pestis

- **Primary:** inhalation of *Y. pestis* from respiratory secretions of humans or animals with pneumonic plague
  - Massive lung inflammation
    - Rapidly progressive breathing difficulties, insufficient oxygen, coughing up blood
    - Usually fatal if untreated

### Yersinia pestis

- **Secondary:** hematogenous spread of *Y. pestis* from bubo to lung from bubo (~10% of bubonic plague cases progress to pneumonic form)
  - Massive lung inflammation
    - Rapidly progressive breathing difficulties, insufficient oxygen, coughing up blood
    - Usually fatal if untreated

### Yersinia pestis

- **Pathogenesis**
  - Spread to lymph node from site of flea bite
    - Plasmid mediated surface protease “Pla”
      - Activates plasminogen → plasmin
    - Plasmin is host enzyme that degrades fibrin in blood clots
    - Other proteolytic activities contributing to pathogenesis
      - Destruction of complement components, antimicrobial peptides
      - Not present in other Yersinia

- **Bacteremia and sepsis**
  - Anti-phagocytic properties
    - F1 capsule – fimbrial protein (*Y. pestis* only, plasmid mediated)
    - Type 3 secretion system effector proteins
    - Plasmid mediated, also produced in intestinal *Yersinia* pathogens
    - Inhibits phagocytic function of macrophages and neutrophils
  - Very high level bacteremia – may reach 4 x 10⁷/ml
Mocrom 301 Blood and Lymphatic Infections

Yersinia pestis

Pathogenesis
- Primary pneumonic plague
  - Pla mediates protection against antimicrobial peptides present in airway secretions by proteolytic degradation
  - F1 capsule - antiphagocytic role
  - Edema (fluid accumulation), necrosis (cell death), hemorrhage (bleeding) in lung

Diagnosis
- Tissue stain of blood, bubo aspirate, sputum
- Culture of blood, bubo aspirate, sputum
  - Identification of Y. pestis confirmed by antibody specific for F1 antigen
- Rapid detection methods based on detection of F1 antigen

Antibiotics

Prevention
- Vaccines
  - Live attenuated vaccine used extensively in outbreaks 1935-1955
  - Killed whole cell vaccine used by U.S. military and researchers
    - no longer available
  - New vaccines under development

Epidemiology
- In U.S., plague is endemic in Southwestern states
  - Reservoir animals: burrowing rodents
    - Enzootic cycle - long term maintenance of infection in relatively resistant population, e.g. ground squirrels
  - Epizootic cycle - rapid spread among highly sensitive species, resulting in local extinction of populations, e.g. prairie dogs

Global
- Highest incidence in Africa - rodent reservoirs (mice and rats)
  - Democratic Republic of Congo
  - High endemicity in mouse and rat species
  - Outbreaks of pneumonic plague in remote gold mining camps
  - Madagascar
  - Urban and rural outbreaks

Yersinia pestis

Epidemiology
- Transmission between mammalian hosts by flea vector or by consumption of infected prey
- Transmission to humans
  - Bubonic plague
    - Flea bite
    - Direct contact with infected animal
  - Primary pneumonic plague
    - Respiratory droplet (esp. from cats)
    - Human to human transmission via respiratory droplet important in epidemic disease

Plague Cases, by county, Western U.S. 1970-2004
Malaria

Pathogenesis

- **Fever**: induction of cytokines by lysis of RBCs, release of merozoites
- **Anemia**: lysis and phagocytic removal of infected RBCs, removal of uninfected RBCs, reduced production of RBCs
- **P. falciparum produces most severe disease**
  - Only species that infects all stages of erythrocytes
  - Produces “knobs” on infected erythrocytes which cause blood cells to adhere to walls of blood vessels and to uninfected erythrocytes causing obstruction in capillaries
  - Cerebral malaria most severe form
  - Obstruction of capillaries in brain

- **P. vivax and P. ovale can relapse months to years after initial disease**
  - hepatic schizonts can become dormant (hypnozoites), resistant to treatment
  - P. malariae infects only senescent RBCs, can produce low level chronic infections lasting years
Malaria

- Diagnosis
  - Microscopic examination of blood smears
  - Rapid antigen detection tests

- Therapy
  - Anti-malarial drugs
  - Limited options
  - Resistance, drug toxicity, expense are problems
  - New drugs in development

- Prevention
  - Mosquito control
  - Insecticide-treated mosquito nets
  - No vaccine available yet
  - Anti-sporozoite vaccine in trials
    - Latest results (November, 2012) were disappointing

Half the world's population at risk
250 million cases per year, 1 million deaths
- Developing world
- Children
- Pregnant women