The Gram-negative coccobacilli

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The Gram-Negative Coccobacilli

This group includes:

- Haemophilus
- Neisseria
- Bordetella
- Moraxella
- Francisella
- Brucella
- Pasteurella

Similar in bacterial shape and Gram stain

They are very different with respect to:

- Diseases they cause & populations they infect
- Virulence factors & pathogenesis
- Their ability to infect animals as well as humans
- Invasive versus non-invasive pathogenesis

Genus: Haemophilus

- **H. influenzae (serotypes a – f), Hib**
- **H. parainfluenzae**
- **H. haemolyticus**
- **H. ducreyi** - causes ulcus molle (soft chancre, chancroid) – a tropical venereal disease/painful readily bleeding ulcer occurring mainly in the genital area (endemic in Africa, Asia)
- **H. aegypticus** – causes a purulent conjunctivitis & Brazilian purpuric fever (endemic in Northern Africa/Egypt)

Haemophilus influenzae

Virulence factors:

- PRP (polyribitol phosphate) capsule – antiphagocytic
- LPS = endotoxin (fever, inflammation), impairs ciliary function
- IgA1 protease – role in colonization
- Pili & nonpilus adhesin – colonization of the oropharynx
- Survival in respiratory epithelial cells

Haemophilus influenzae

Reservoir: humans (carriers, infected individuals) – **mostly endogenous/exogenous**

Transmission: close contact, via respiratory droplets (air-borne route)

Enters upper respiratory tract: attaches to cells (fimbriae, IgA1 protease)

Endotoxin stops respiratory tract cilia from beating & clearing the bacterial cells, & induces inflammation

Local spread (ears, sinuses, lungs, soft tissues)

Systemic spread (blood & brain)

Haemophilus

H. influenzae

Endogenous and exogenous infections

Encapsulated strains
a, b, c, d, e, f

Type b (Hib): invasive infections in young children:
bacteremia, meningitis, epiglottitis, cellulitis
Other: sinusitis, otitis media, bronchitis

Endogenous infections

Unencapsulated strains

Noninvasive RTI
(otitis media, sinusitis, bronchitis, tracheobronchitis), pneumonia, arthritis

Other species: otitis media, conjunctivitis, sinusitis, endocarditis, dental abscesses, meningitis

Haemophilus

Systemic infections (meningitis, sepsis)

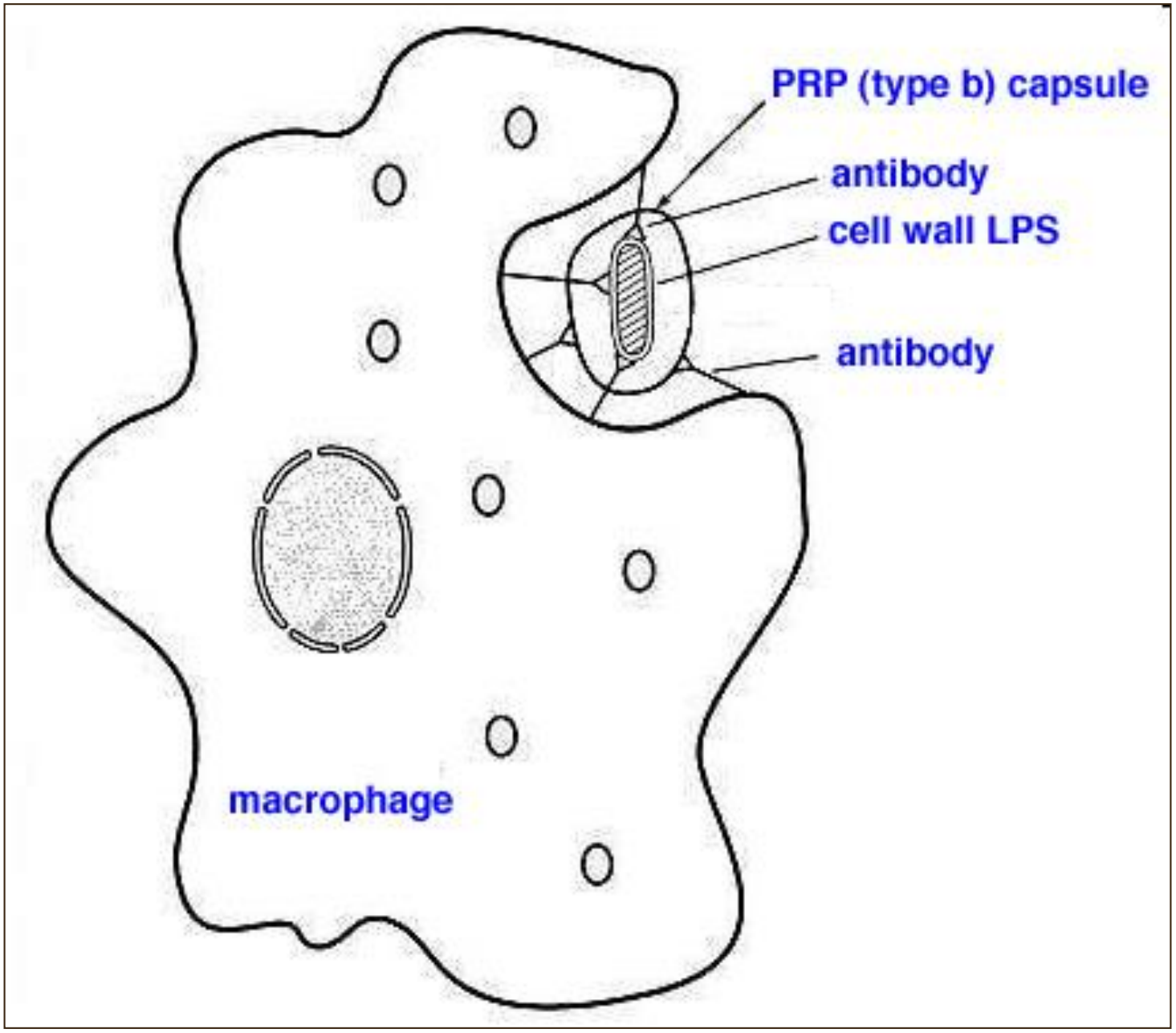
Most prevalent in kids age 6 months to 4 year

The key is protective antibody against capsule

Birth to 6 months maternal antibodies protect children - after 6 months these maternal antibodies disappear

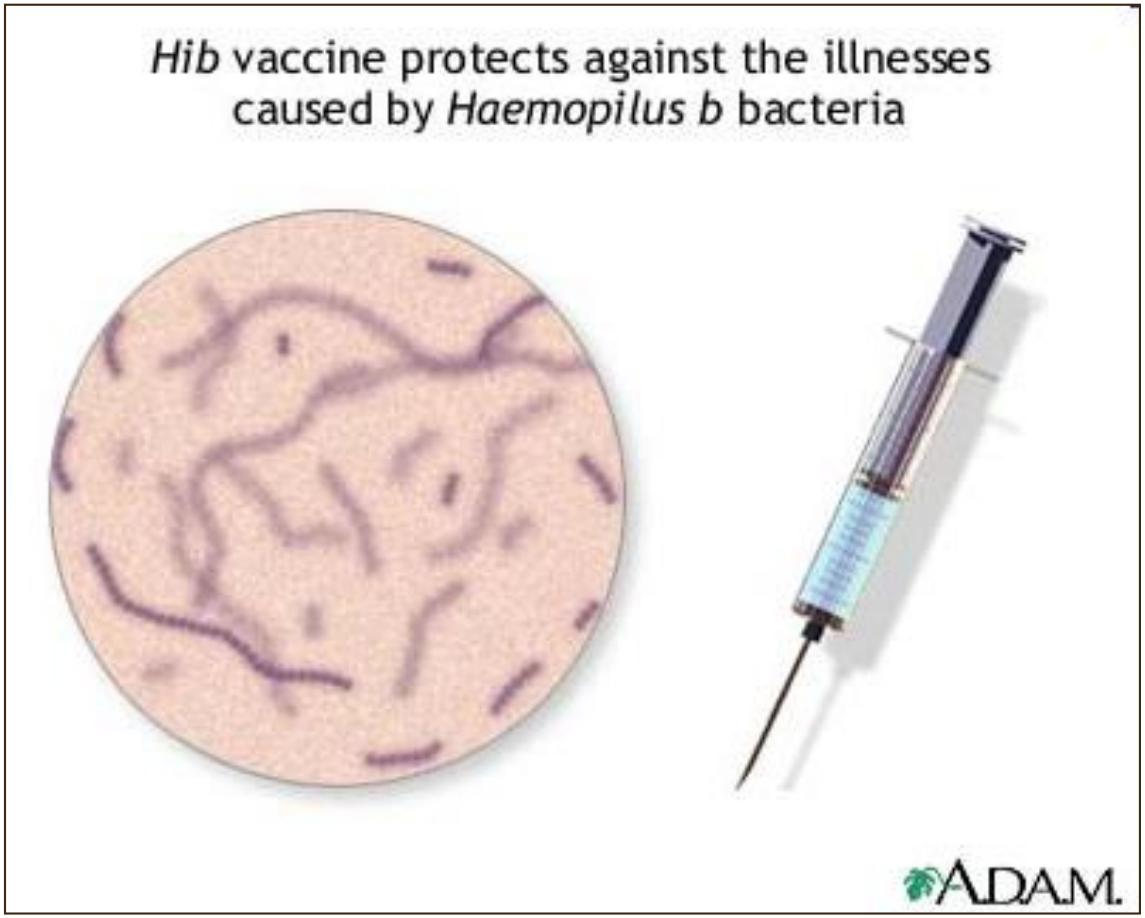
Infants & children (6 months to 4 years) can not make antibody to sugars so no protection from infection

4 years on, make own antibody to sugars and start to make their own protection


PRP (type b) capsule
antibody
cell wall LPS
antibody
macrophage

Hib immunization/vaccine

Vaccine composed of capsule (PRP) polysaccharide conjugated with protein



Genus: Neisseria

GN cocci in pairs

Many saprophytic strains:
normal flora of the oropharynx and genitourinary mucosal surfaces

Strict human pathogens:

- N. meningitidis
- N. gonorrhoeae

Transmission:

Infectious respiratory aerosols

Sexual intercourse

Neisseria meningitidis

Virulence factors

- Polysaccharide capsule – serotypes:

A, B, C, Y, X, W135

- Pili
- IgA1 protease
- LOS = LPS
- Able to survive intracellular killing
- OMVs (outer membrane vesicles)

Lack of specific antibodies and complement deficiencies – predisposing factors

Genus: Neisseria

Meningitis (neurologic sequelae low: hearing deficits, learning difficulties)

Bacteremia/sepsis (meningococcemia)

Purpura fulminans (skin necrosis with DIC)

Waterhouse-Friderichsen syndrome : Acute hemorrhagic adrenalitis

Pneumonia (preceded by pharyngitis)

Other: arthritis, urethritis

Chemoprophylaxis for contact: rifampin, ciprofloxacin, ceftriaxone

Specific prevention
Vaccine against meningococci: polysaccharide capsules - A, B, C, Y, W135

Neisseria gonorrhoeae

Virulence factors

- **Pili** – prevent phagocytosis by PMNs
- **Porin proteins (PorB)** : resistance to complement-mediated bactericidal serum activity, facilitates invasion into epithelial cells etc.
- **IgA1 protease**
- **LOS = LPS**
- **Able to survive intracellular killing**
- OMVs (outer membrane vesicles)

Neisseria gonorrhoeae

Gonorrhoea – sexually transmitted

Men – urethritis

Complications rare: epididymitis, prostatitis, periurethral abscesses

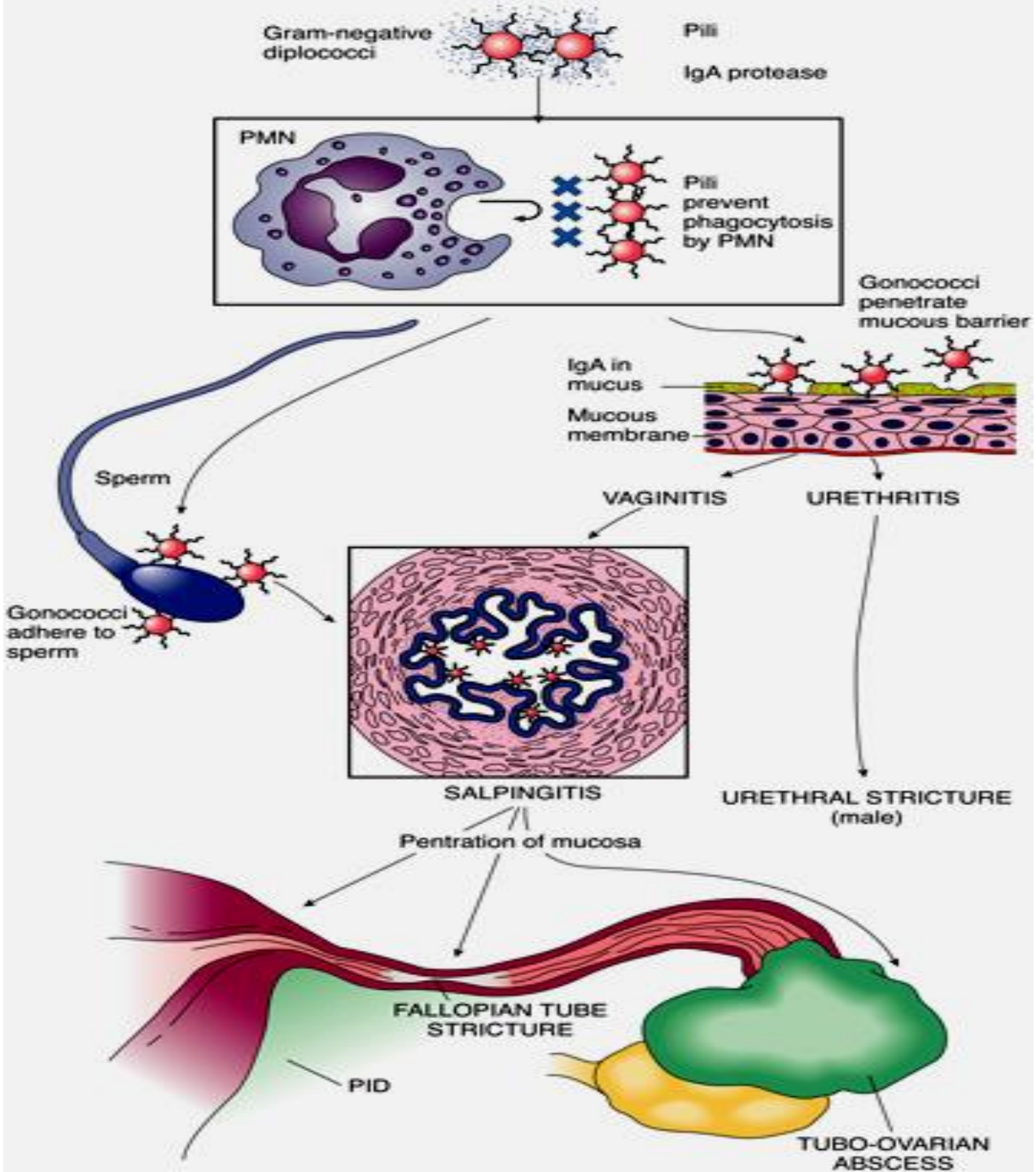
Women – cervicitis

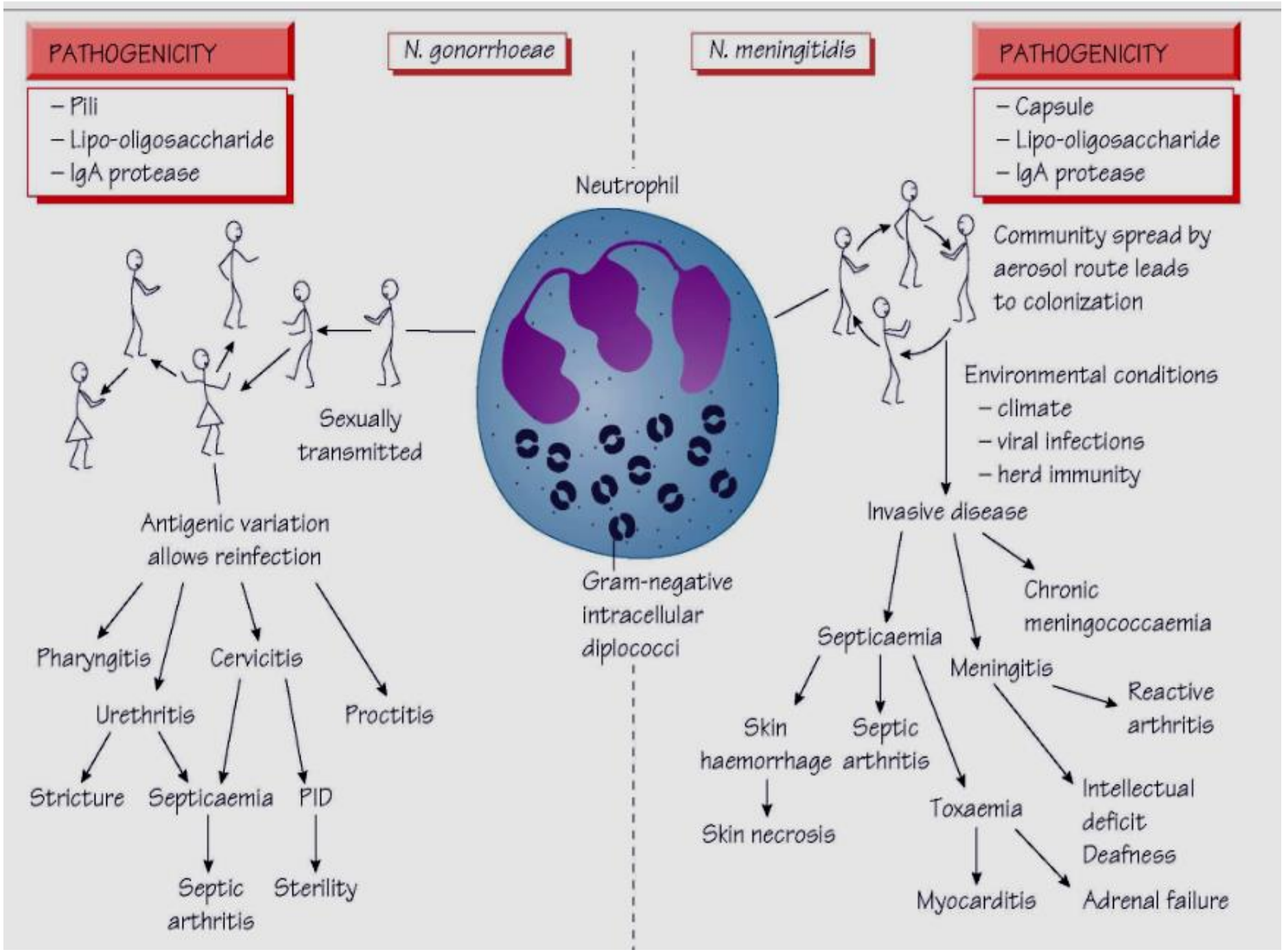
In 10-20% **ascending infection**: salpingitis, tuboovarian abscesses, PID

In 2-3% **disseminated infection** with septicemia, pustular rash on extremities and purulent arthritis

Fitz-Hugh-Curtis syndrome (perihepatitis)

Ophthalamia neonatorum (purulent conjunctivitis)


Gram-negative diplococci
Pili
IgA protease
PMN
Pili prevent phagocytosis by PMN
Gonococci penetrate mucous barrier
IgA in mucus
Mucous membrane
Sperm
VAGINITIS
URETHRITIS
Gonococci adhere to sperm
SALPINGITIS
URETHRAL STRICTURE (male)
Pentration of mucosa
FALLOPIAN TUBE STRICTURE
PID
TUBO-OVARIAN ABSCESS


PATHOGENICITY
– Pili
– Lipo-oligosaccharide
– IgA protease
N. gonorrhoeae
N. meningitidis
PATHOGENICITY
– Capsule
– Lipo-oligosaccharide
– IgA protease
Neutrophil
Sexually transmitted
Antigenic variation allows reinfection
Gram-negative intracellular diplococci
Community spread by aerosol route leads to colonization
Environmental conditions
– climate
– viral infections
– herd immunity
Invasive disease
Pharyngitis
Cervicitis
Urethritis
Proctitis
Stricture
Septicaemia
PID
Septic arthritis
Sterility
Septicaemia
Chronic meningococcaemia
Meningitis
Reactive arthritis
Skin haemorrhage
Septic arthritis
Skin necrosis
Toxaemia
Intellectual deficit
Deafness
Myocarditis
Adrenal failure

Genus: Moraxella

Gram-negative cocci in pairs

Pathogenic species:

M. catarrhalis

Commonly colonizes URT of children

Endogenous infections:

Otitis media, sinusitis, bronchitis, pneumonia

Risk group: patients with underlying chronic lung disease

Immunosupressed: meningitis, bacteremia

Normal pharyngeal and conjunctiva flora

Genus: Bordetella

Reservoir: humans

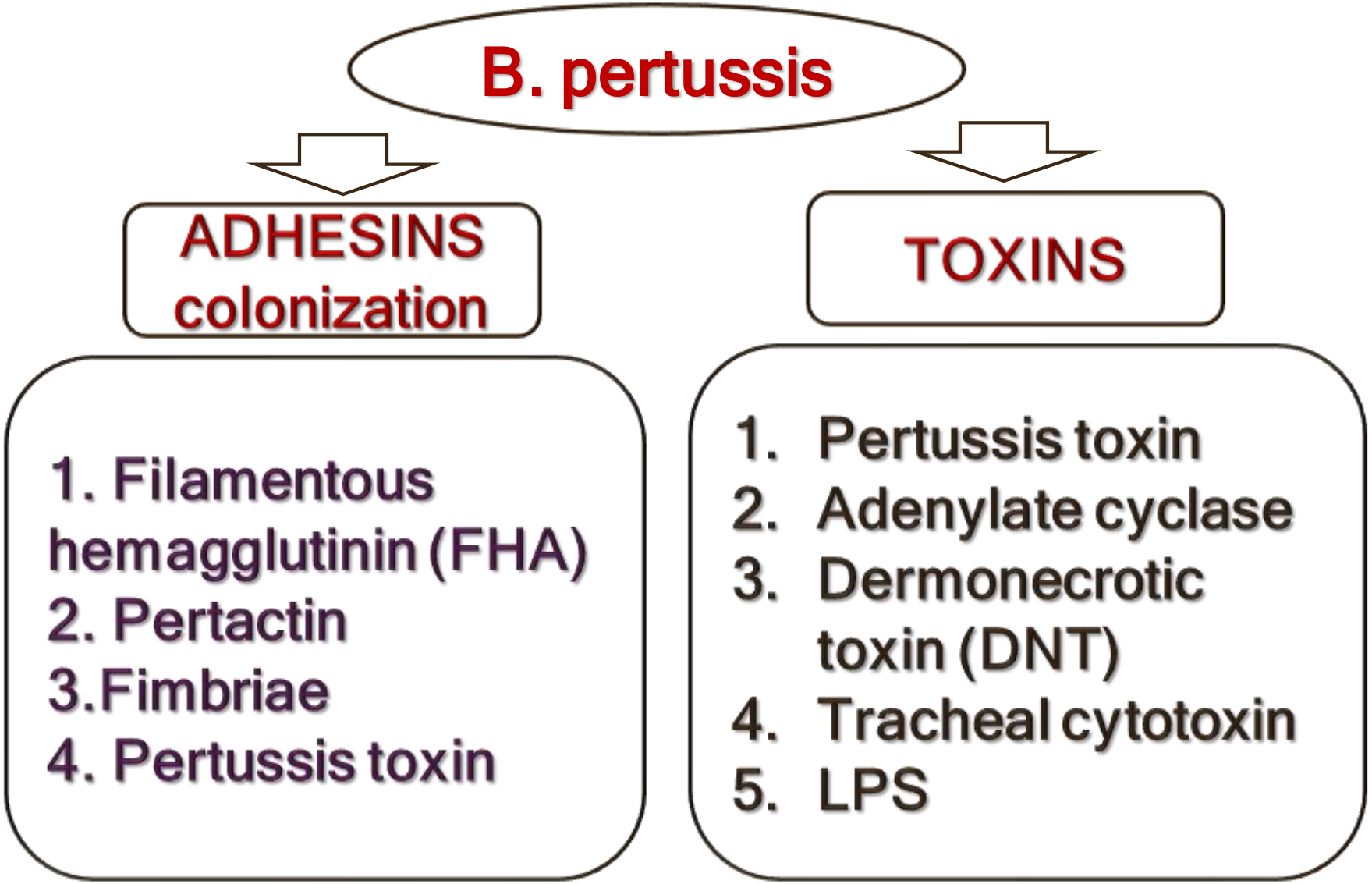
Transmission: air-borne droplets

Whooping cough – occur primarily in non-immune children

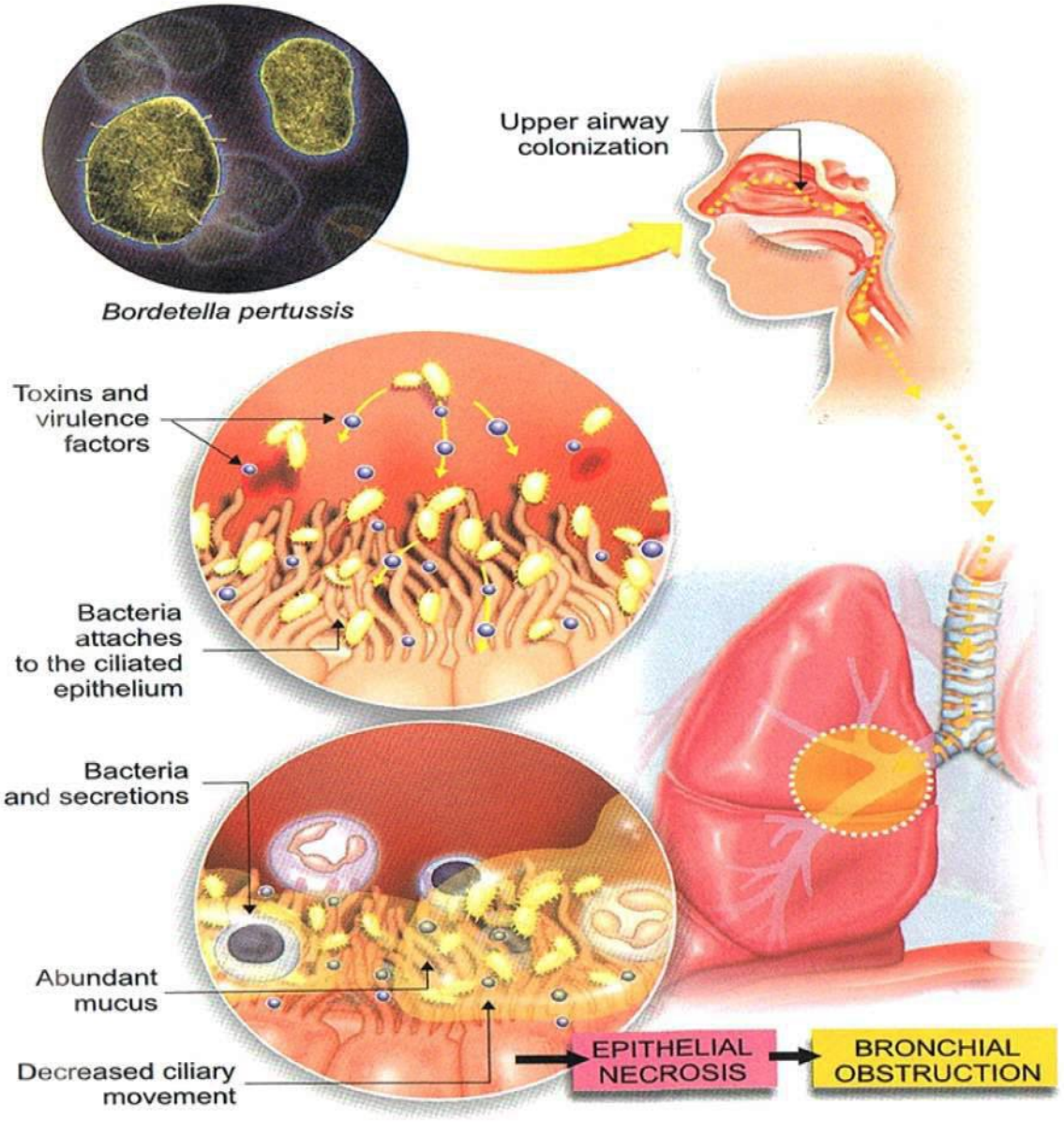
Adults with waning immunity: milder disease misdiagnosed as cold or flu

B. pertussis
B. parapertussis

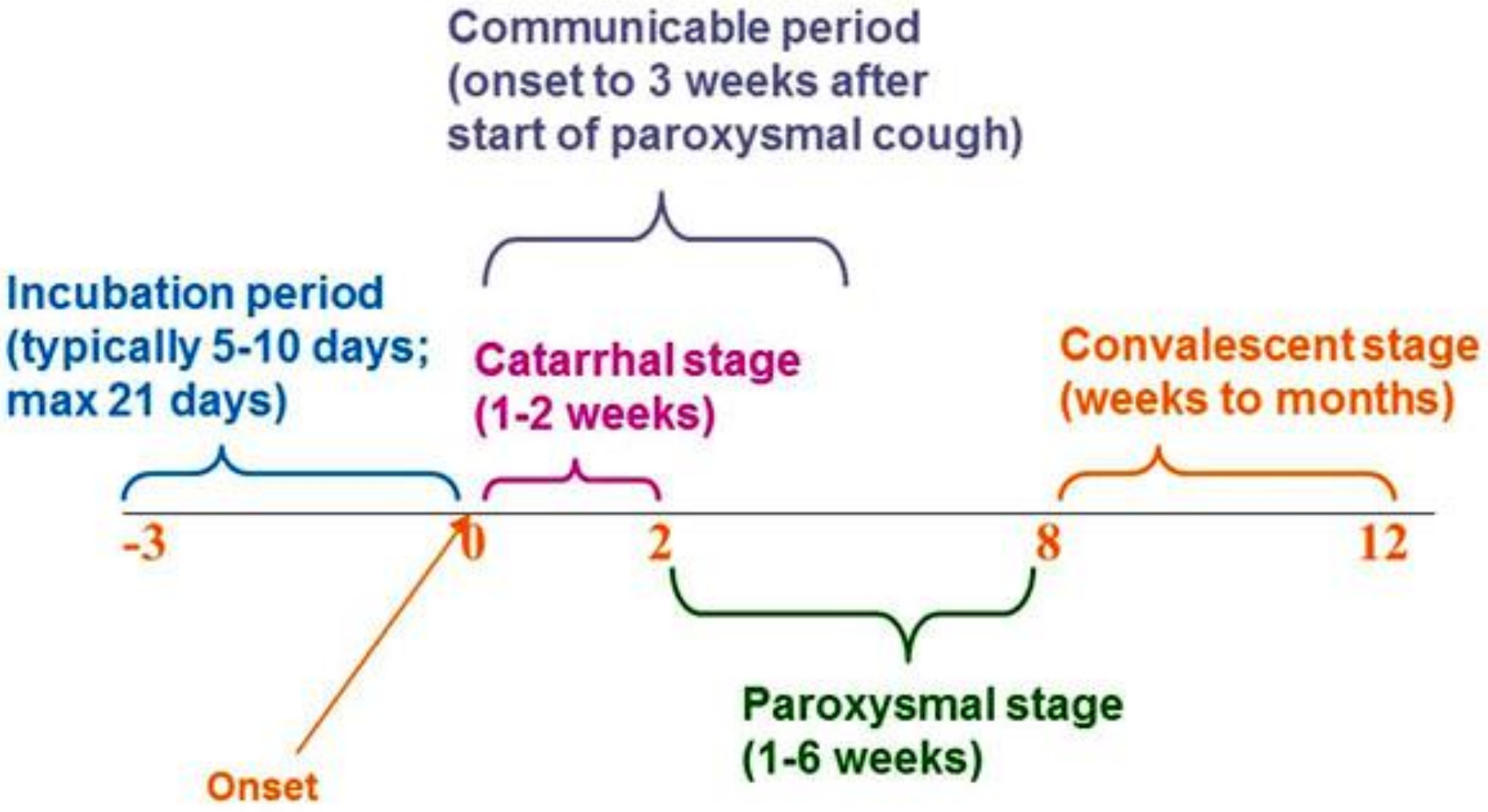
B. bronchoseptica
B. holmesii


B. pertussis
ADHESINS
colonization
TOXINS
1. Filamentous hemagglutinin (FHA)
2. Pertactin
3.Fimbriae
4. Pertussis toxin
1. Pertussis toxin
2. Adenylate cyclase
3. Dermonecrotic toxin (DNT)
4. Tracheal cytotoxin
5. LPS

Whooping cough



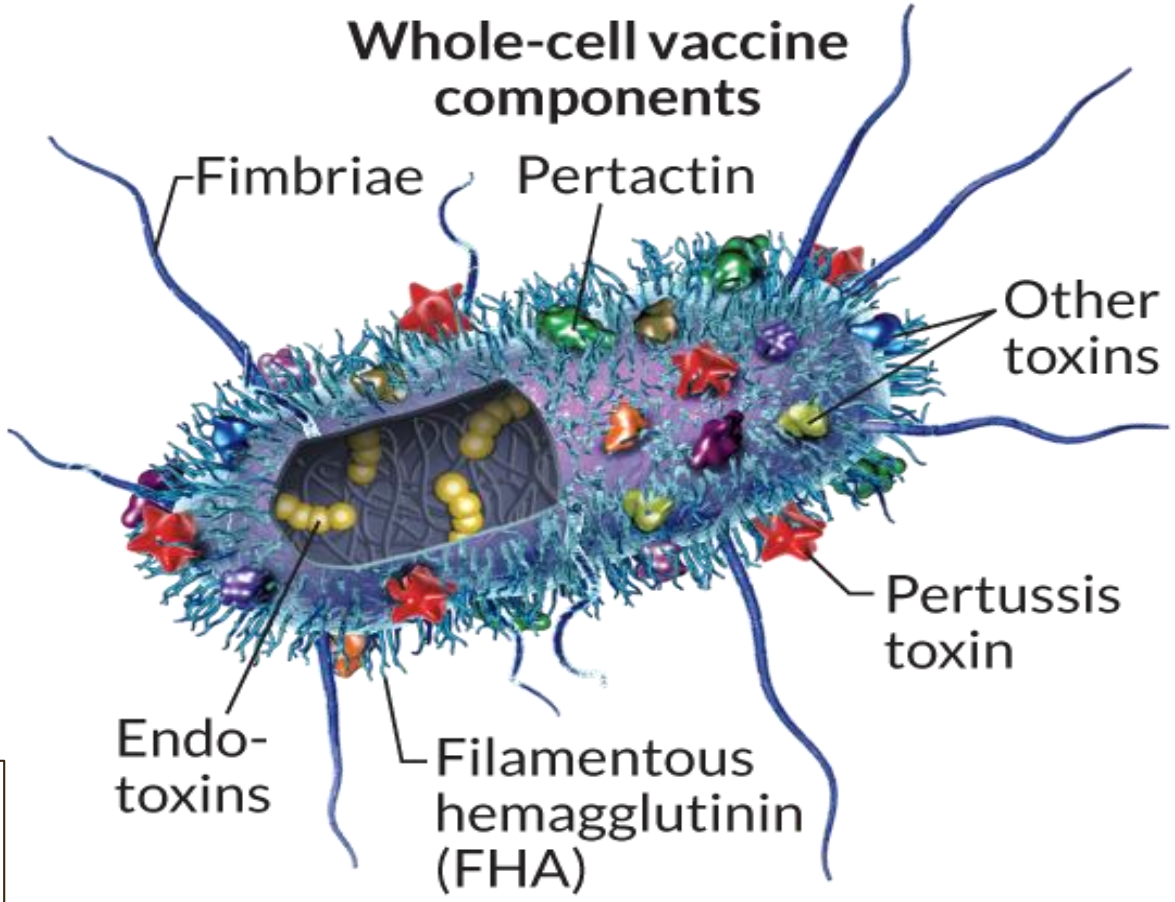
Clinical Course (in weeks)



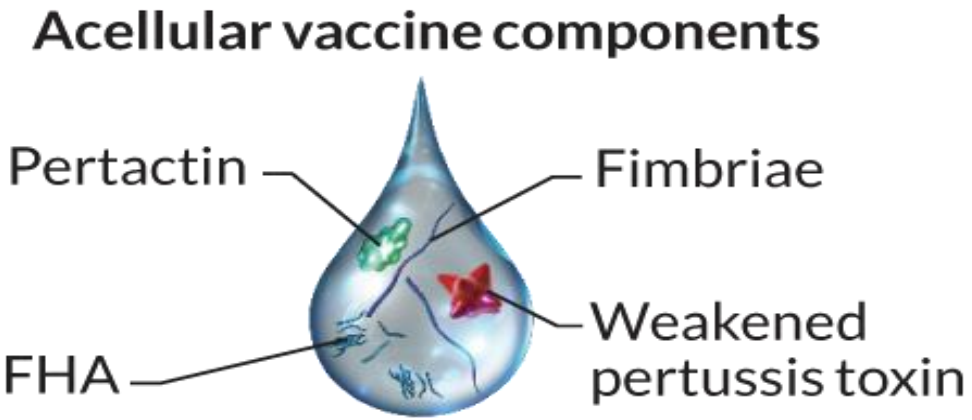
	Incubation	Catarrhal	Paroxysmal	Convalescent
Duration	7–10 days	1–2 weeks	2–4 weeks	3–4 weeks (or longer)
Symptoms	None	Rhinorrhea, malaise, fever, sneezing, anorexia	Repetitive cough with whoops, vomiting, leukocytosis	Diminished paroxysmal cough, development of secondary complications (pneumonia, seizures, encephalopathy)
Bacterial culture				

or death

DPT:
Diphtheria
Pertussis
Tetanus



Prophylaxis:
azithromycin



Zoonosis = a disease of animals that may be transmitted to humans under natural conditions

Examples: brucellosis, pasteurellosis, tularemia

Brucella & brucellosis

Medically important species named for the livestock they commonly come from

Brucella abortus (cattle)
Brucella melitensis (goats/sheep)
Brucella canis (dogs)
Brucella suis (pigs)

Facultative intracellular pathogen

Brucella & brucellosis

- Human brucellosis usually presents as an acute febrile illness
- Most cases are caused by B. melitensis
- All age groups are affected
- Complications may affect any organ system
- The disease may persist as relapse, chronic localized infection or delayed convalescence

Virulence factors:

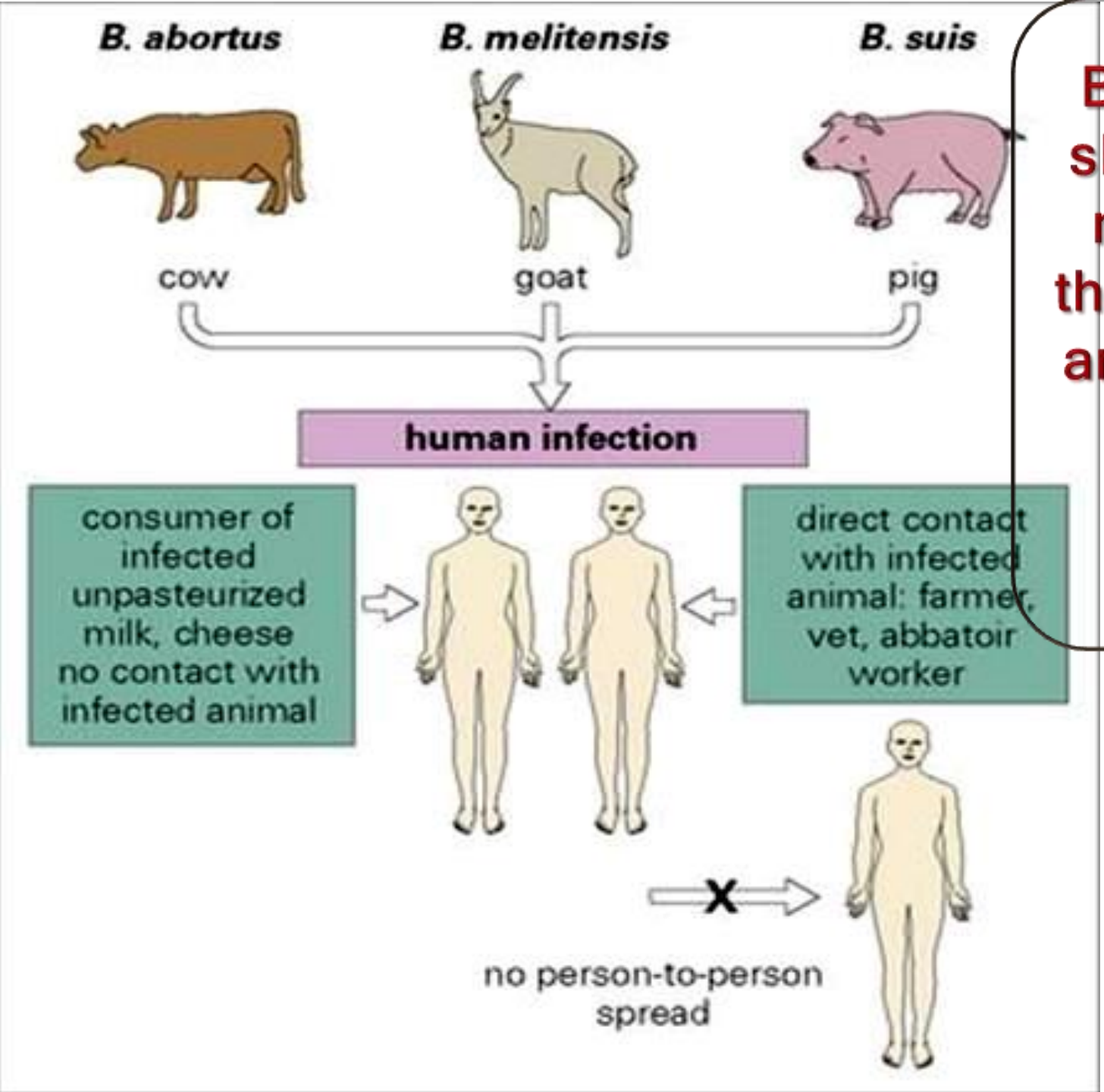
LPS

Intracellular multiplication in reticuloendothelial system and macrophages

Toxic enzymes (catalase, superoxide dismutase)

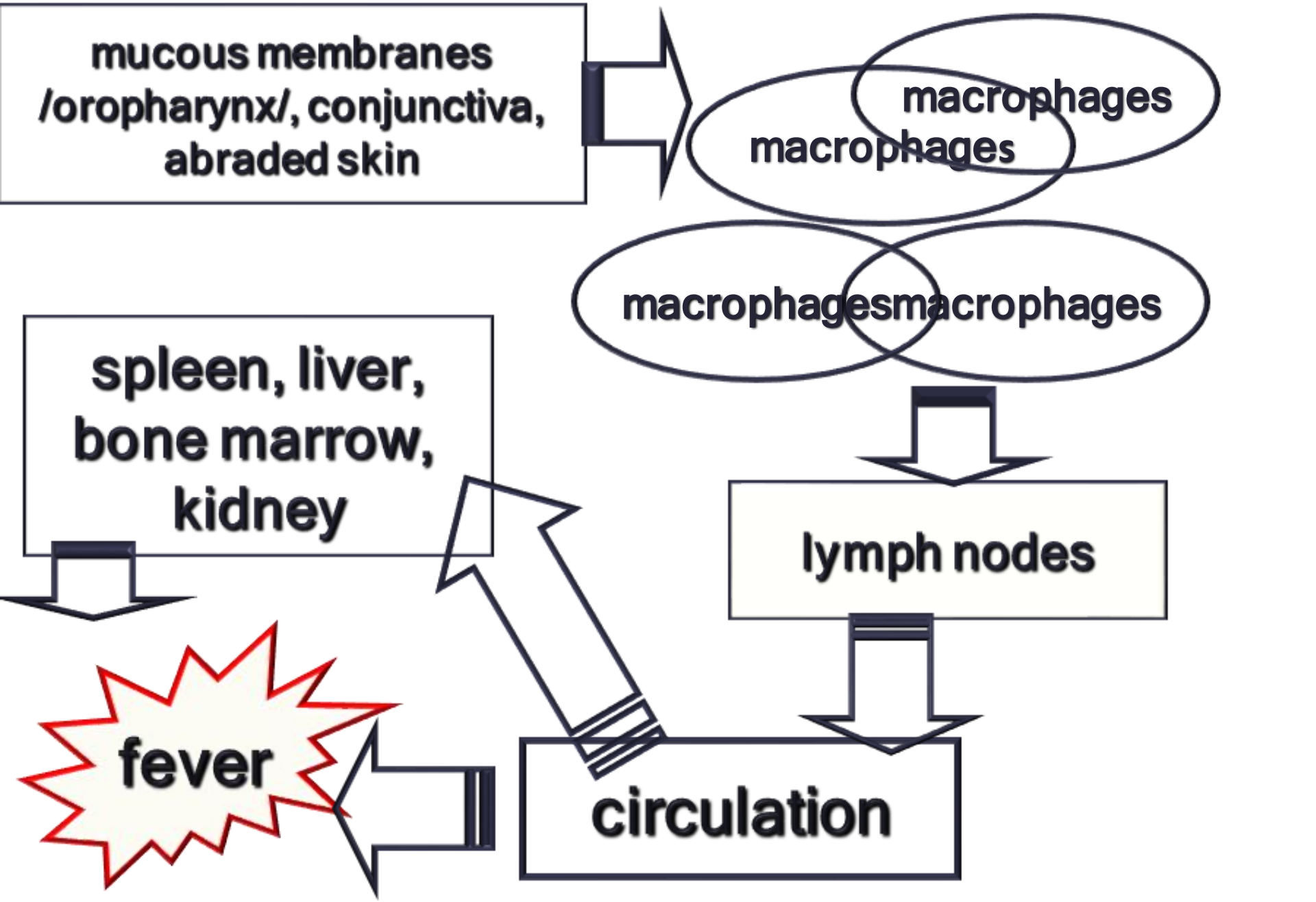
Brucella & brucellosis

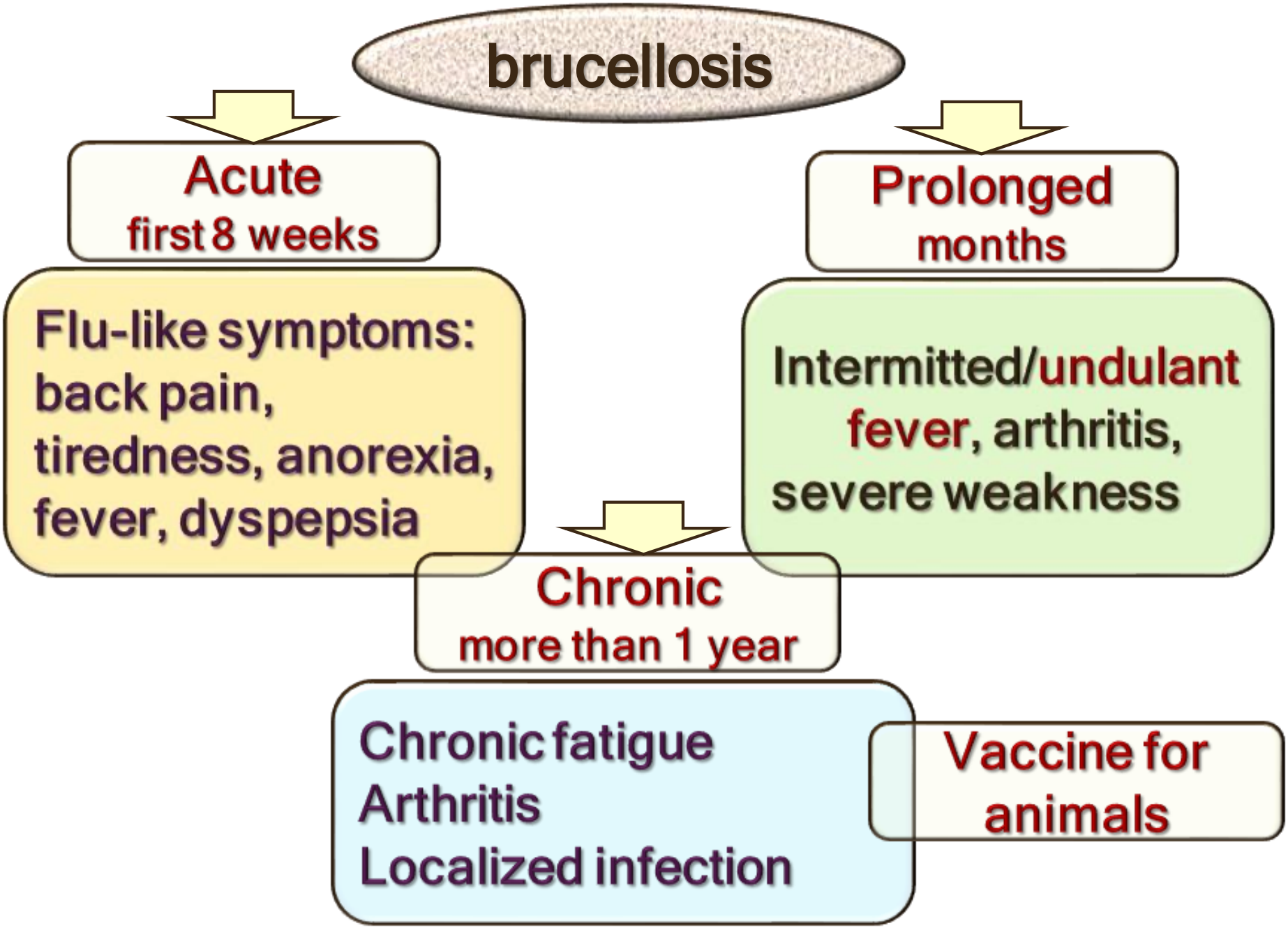
- Cattle, sheep, goats and pigs are the main reservoirs of Brucella
- Transmission to humans occurs through occupational or environmental contact with infected animals or derived food products
- Food of animal's origin is a major source of infection
- Brucellosis can be a travel-associated disease
- Blood or organ/tissue transfer are possible sources of infection
- Person-to-person transmission is extremely rare (inhalation)

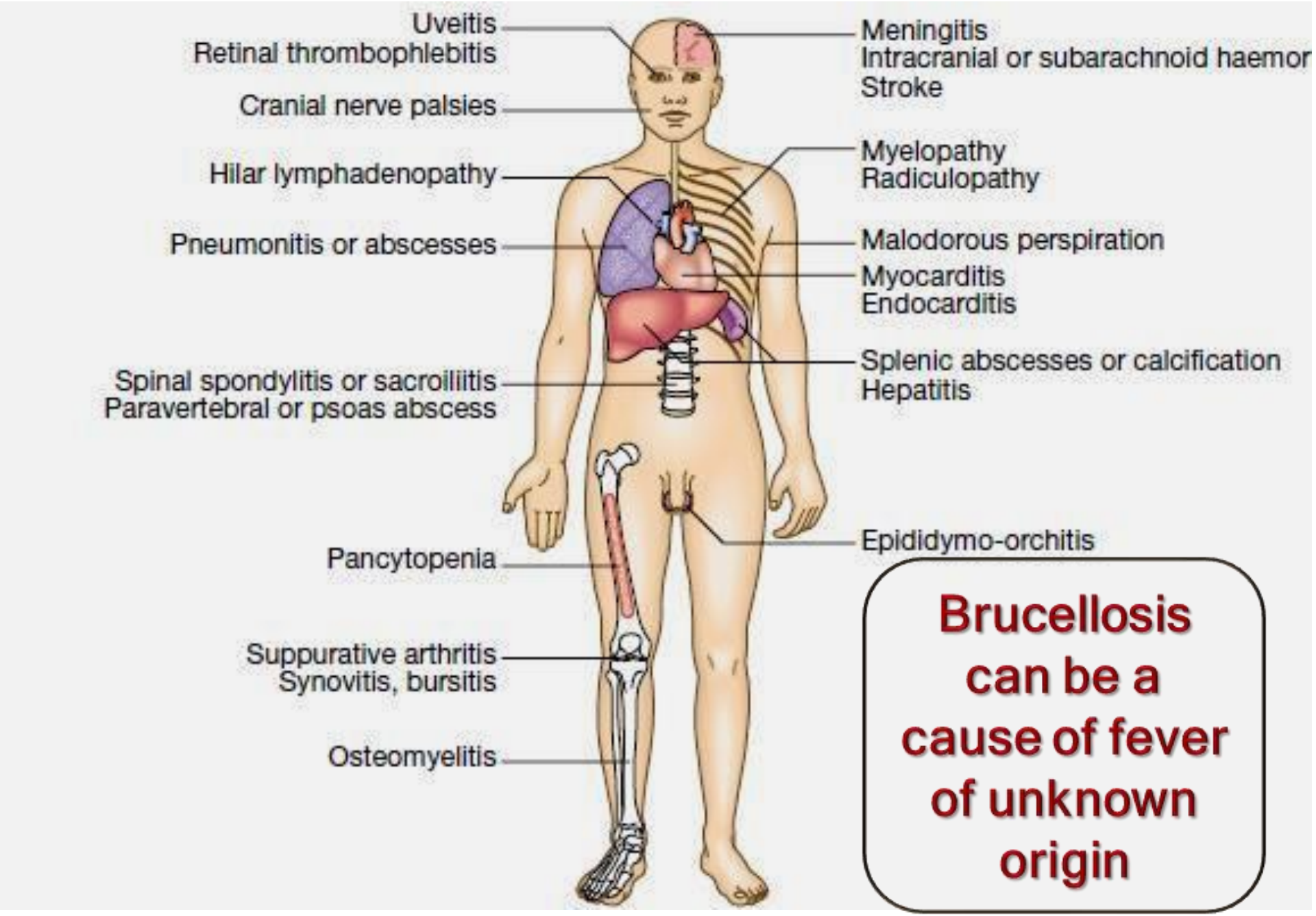


Brucella are shed in large numbers in the urine, milk and placental fliud of infected animals

Intracellular multiplication induces chronic inflammatory response and tissue lesions – minute granulomas composed of epitheliod cells, PMNs, lymphocytes etc.


mucous membranes /oropharynx/, conjunctiva, abraded skin
macrophages
macrophages
macrophages
macrophages
spleen, liver, bone marrow, kidney
lymph nodes
fever
circulation


brucellosis
Acute
first 8 weeks
Prolonged
months
Flu-like symptoms:
back pain,
tiredness, anorexia,
fever, dyspepsia
Intermitted/undulant
fever, arthritis,
severe weakness
Chronic
more than 1 year
Chronic fatigue
Arthritis
Localized infection
Vaccine for
animals


Uveitis
Retinal thrombophlebitis
Cranial nerve palsies
Hilar lymphadenopathy
Pneumonitis or abscesses
Spinal spondylitis or sacroiliitis
Paravertebral or psoas abscess
Pancytopenia
Suppurative arthritis
Synovitis, bursitis
Osteomyelitis
Meningitis
Intracranial or subarachnoid haemor
Stroke
Myelopathy
Radiculopathy
Malodorous perspiration
Myocarditis
Endocarditis
Splenic abscesses or calcification
Hepatitis
Epididymo-orchitis
Brucellosis can be a cause of fever of unknown origin

Francisella tularensis

Facultative intracellular pathogen

One of the most infectious pathogenic bacterium known

Infectious dose (inoculation, inhalation):

10 - 50 CFU

It is consider as biological weapon because of its extreme infectivity, easy dissemination & capacity to cause illness and death

Francisella tularensis

Worldwide prevalence

Found in >100 species of animals (HARES, RABBITS)

Routes of Transmission

- **Infected tissue**
- **Inhalation**
- **Ingestion**
- **Insect bites**

Incubation period, clinical syndromes & severity of the disease depends on
- Subspecies (types A & B)
- route of transmission
- dose

Virulence factors:
Capsule
LPS
Intracellular multiplication

Francisella tularensis

Tularemia

There are 5 clinical forms of tularemia based on the route of exposure to the pathogen

Ulceroglandular

- **most common manifestation**
- **ulcer with regional lymphadenopathy**
- **75 – 85% of all cases**

Francisella tularensis

Oculoglandular

- **Conjunctivitis**, ulceration of conjunctiva, ocular discharge/ contaminated fingers or contaminated material splashed into eye
- **Regional lymphadenopathy**

Oropharyngeal and gastrointestinal

- hand-to-mouth, consumption of undercooked meat (especially rabbit) or water
- painful **pharyngitis** (with or without ulcer), diarrhea, vomiting, abdominal pain, bleeding, nausea
- pseudomembranes may develop over tonsils = can be mistaken with diphtheria

Francisella tularensis

Typhoidal – **systemic infection**/ can develop from oropharyngeal form

- **acute septicemia**
- without lymphadenopathy or ulcer

Pulmonary (pneumonic)

- inhalation of infectious aerosol
- spread through bloodstream
- complication from other forms – typhoidal (50%) or ulceroglandular (10-15%)
- **Most severe forms of tularemia**
- Case fatality/untreated: 30 – 60%

Pasteurella multocida & canis

Similar general characteristics to Brucella and Francisella, but **multiply extracellulary**

Veterinary problem (re-emerging bovine pathogen)

- both domestic and wild animals
- animal's natural flora (cats & dogs)

Virulence factors:

- LPS
- Mitogenic (dermonecrotic) toxin (PMT)-can promote cancer
- capsule

Pasteurella multocida

Human disease

Localized abscesses (edema & fibrosis) on extremities or face from animal bites, scratches or licking developing within 24 hours - key for differential diagnosis

Osteomyelitis and septic arthritis may complicate localized infection

Exacerbation of chronic respiratory disease in patients with pulmonary disorders (aerosol)

Immunosuppressed individuals – disseminated disease (septicemia) - can also occur in infants that are licked by infected dogs or cats in the face

Zoonotic Gram-negative coccobacilli

Facultative intracellular pathogens persist in macrophages

Yersinia pestis - plague

Yersinia enterocolitis - enterocolitis

Yersinia pseudotuberculosis - appendicitis-like syndrome

Francisella tularensis - ulceroglandular, typhoidal or oculoglandular disease

Brucella melitensis
Brucella suis
Brucella abortus
} undulant fever

Extracellular pathogen humoral response important

Pasteurella multocida