Respiratory System Module
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Haemophilus influenzae

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History /Introduction

- The genus Haemophilus contains many :species, but H. influenzae is the most common pathogen.
- It was first described by Pfeiffer in 1892 during an outbreak of influenzae. ("Pfeiffer's bacillus").
- During this time, the organism was thought to be the causative agent of the flu.
- The organism was then given the name Haemophilus by Winslow, et. al in 1920.
- In 1933 Smith, et al. established that influenzae was caused by a virus and the H. influenzae was a cause of secondary bacterial infections.

Introduction

General characteristics*:*

- Small gram-negative bacilli measuring 0.3-0.5 µm × 1-2 µm
- They are arranged singly, in pairs, or chains.
- Aerobic, Non-motile, Non-spore forming.
- Virulent strains form capsule.

Introduction

General characteristics*:*

- H. influenzae colonizes in the respiratory tract and as many as 50% of children may be carriers.

- Only a small number of people who carry this bacterium develop clinical disease.

- Thus, H. influenzae generally functions as an opportunistic pathogen

Growth Requirments

The genus derives its name from its essential growth requirement of certain factors present in the blood (Haemophilus: Haem: blood; philos: loving).

H. Influenze requires two accessory growth factors present in blood:

1. **X-factor:**

   Is a heat **stable** factor present in blood. It is required for the **synthesis** of iron containing enzymes **cytochrome oxidase, peroxidase** and **catalase.**

2. **V-Factor:**

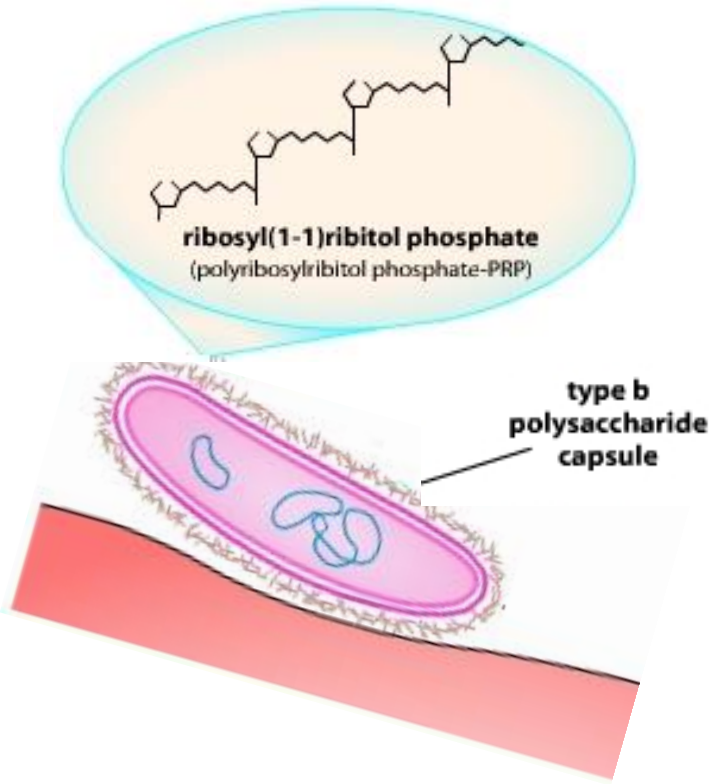
   Is a **thermolabile** NAD and NADP required in oxidation-reduction processes in the growing bacterial cell.

- These factors are present inside the erythrocytes and hence not available to bacteria for their growth. Heating blood till it acquires chocolate colour lyses the erythrocytes thus releasing these factors.

Growth requimnts

Classification

1. **The *Haemophilus influenzae* is divided into**
   A. Typeable (encapsulated): isolates have capsular polysaccharides
   B. Nontypeable (NTHi) (nonencapsulated): isolates lacking capsular polysaccharides.
2. **Haemophilus that have capsule:**
   A. Are divided into six serotypes, designated a to f, based on the capsular polysaccharide antigen.
   B. The capsule is made up of a polymer of ribose, ribitol, and phosphate **called polyribitol phosphate (PRP)**.
   C. These surface polysaccharides are strongly associated with virulence, particularly *H. influenzae* type b (Hib).
3. **The nontypeable, *H. influenzae* can be classified based on outer membrane proteins and other factors.**



Virulence

The capsule material is antiphagocytic, and it is ineffective in inducing the alternative complement pathway, so that the bacterium can invade the blood or CSF without attracting phagocytes or provoking an inflammatory response and complement-mediated bacteriolysis.

↓

Bacteremia and meningitisis directly related to capsule formation.

↓

almost all of these infections are caused by the type b serotype, and its capsular polysaccharide, containing PRP is the proven determinant of virulence.

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For this reason, anticapsular antibody, which promotes both phagocytosis and lysis of bacteria, is the main factor in immune defense

The problem with PRP!!!!!!

- ✓ Polysaccharide PRP is weakly immunogenic
- ✓ Pediatric immunity not mature for processing polysaccharide antigens until ~18 months
- ✓ Conjugated Vaccine:

  PRP conjugated to protein carrier induces protective immunity (carriers may include: diphtheria toxoid, tetanus toxoid or meningococcal OMP)

Virulence

Type b *H. influenzae* is apparently the most virulent of the *Haemophilus* species; 95% of bloodstream and meningeal *Haemophilus* infections in children are due to this bacterium.

In contrast, in adults, nontypable strains of *H. influenzae* are the most common cause of *Haemophilus* infection, presumably because most adults have acquired antibody to PRP.

Epidemiology

- *H. influenzae* can be found in the **normal nasopharyngeal** flora of **20 to 80% of healthy persons.**

- Most of these are **nonencapsulated**, **but capsulated strains**, including Hib may be present.

- In children the age group 6 months -6 years is most prone to infection by the organism (why).

- Peak incidence is from 6 months to 1 year.

- Over 90% of these cases are due to the *H. influenzae* type b.

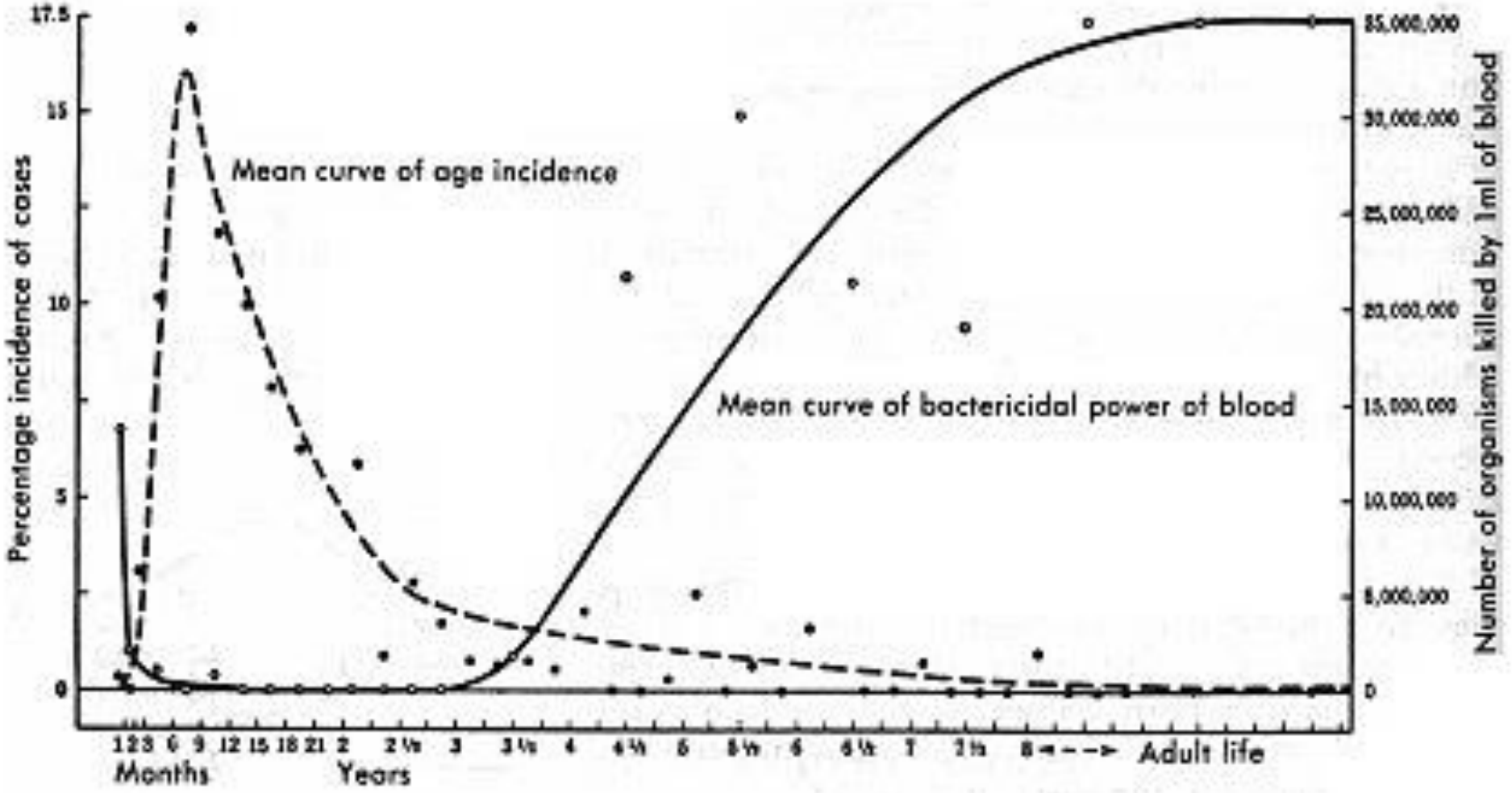
Epidemiology

Haemophilus influenzae type b Epidemiology

Reservoir	- Human - Asymptomatic carriers
Transmission	Respiratory droplets
Temporal pattern	Peaks in Sept-Dec and March-May
Exposure factors	➢ Household crowding ➢Child care attendance ➢Low socioeconomic status ➢Low parental education

Immunity to *H. influenzae*

Immunity to *H. influenzae* without immunization



Relation of the age incidence of bactericidal antibody titers in the blood

Immunity to *H. influenzae*

Without artificial immunization, in children aged 2 months to 3 years, antibody levels are minimal; thereafter antibody levels increase and the disease becomes much less common. From this curve, it is obvious that artificial active immunization should begin at 2 months of age, when nearly all passive immunity has waned, and the child enters a vulnerable non immune period of life

Types of antibodies that mediate protection against *H. influenzae* infection*:*

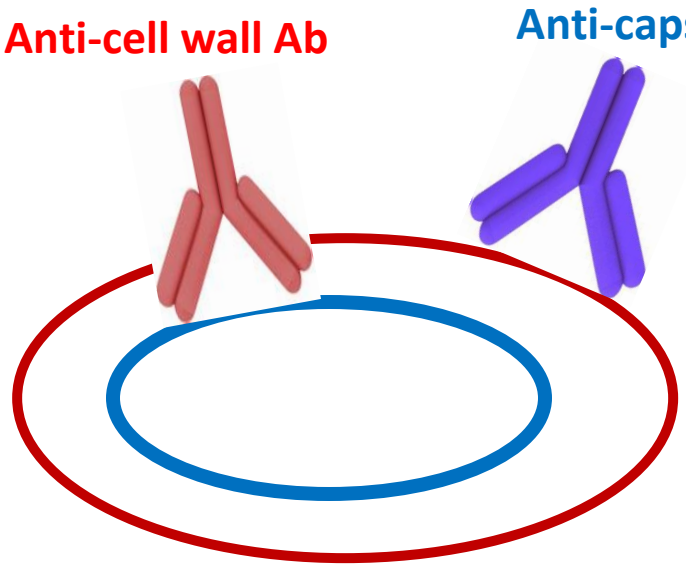
1. Antibody directed against PRP capsule

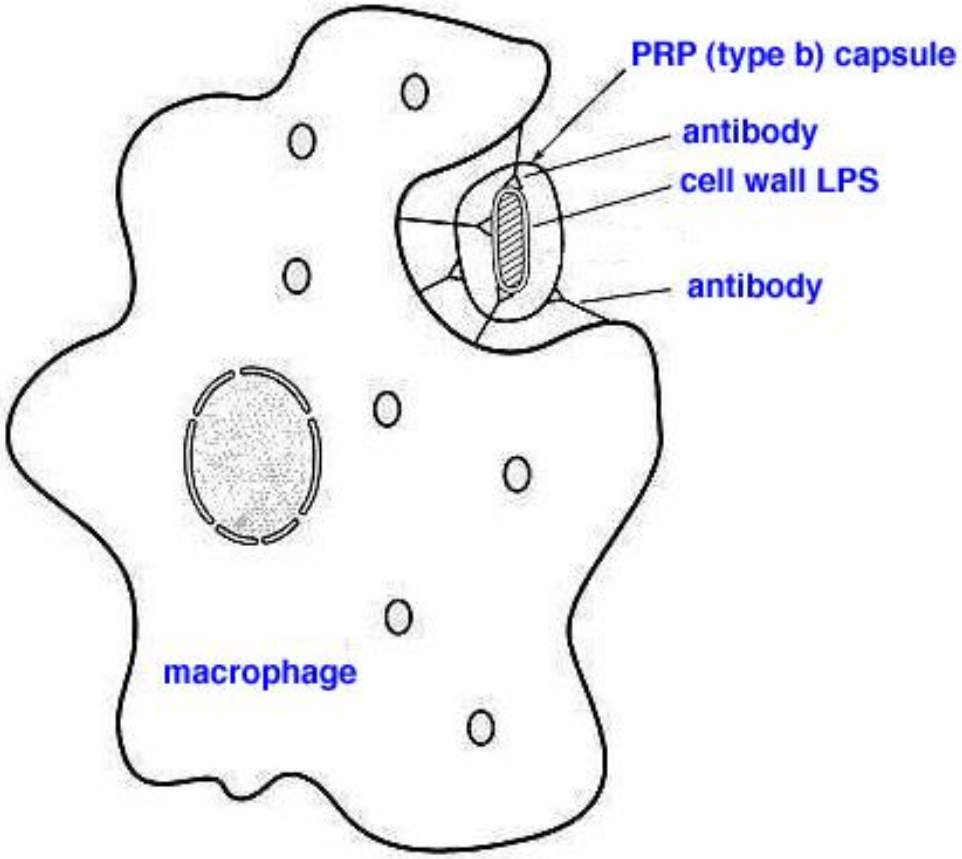
2. Antibody to somatic (cell wall) antigens : bactericidal antibodies that react with individual outer membrane proteins (e.g. P1, P2)

Haemophilus influenzae

Immunity to *H. influenzae*

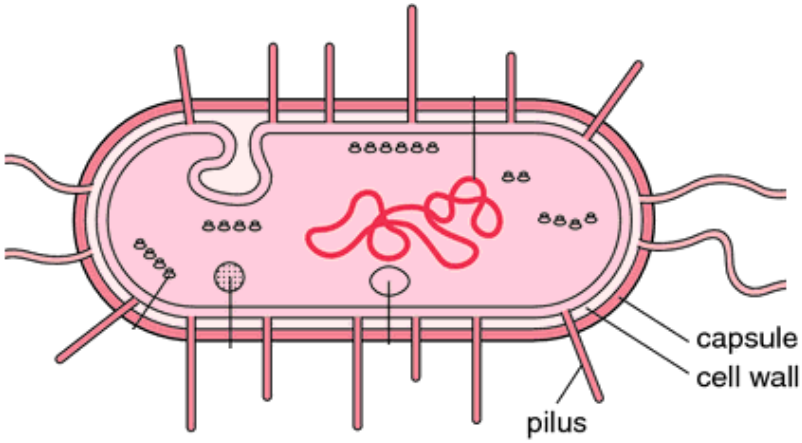
Types of antibodies that mediate protection against *H. influenzae* infection:





Virulence factors associated with invasiveness

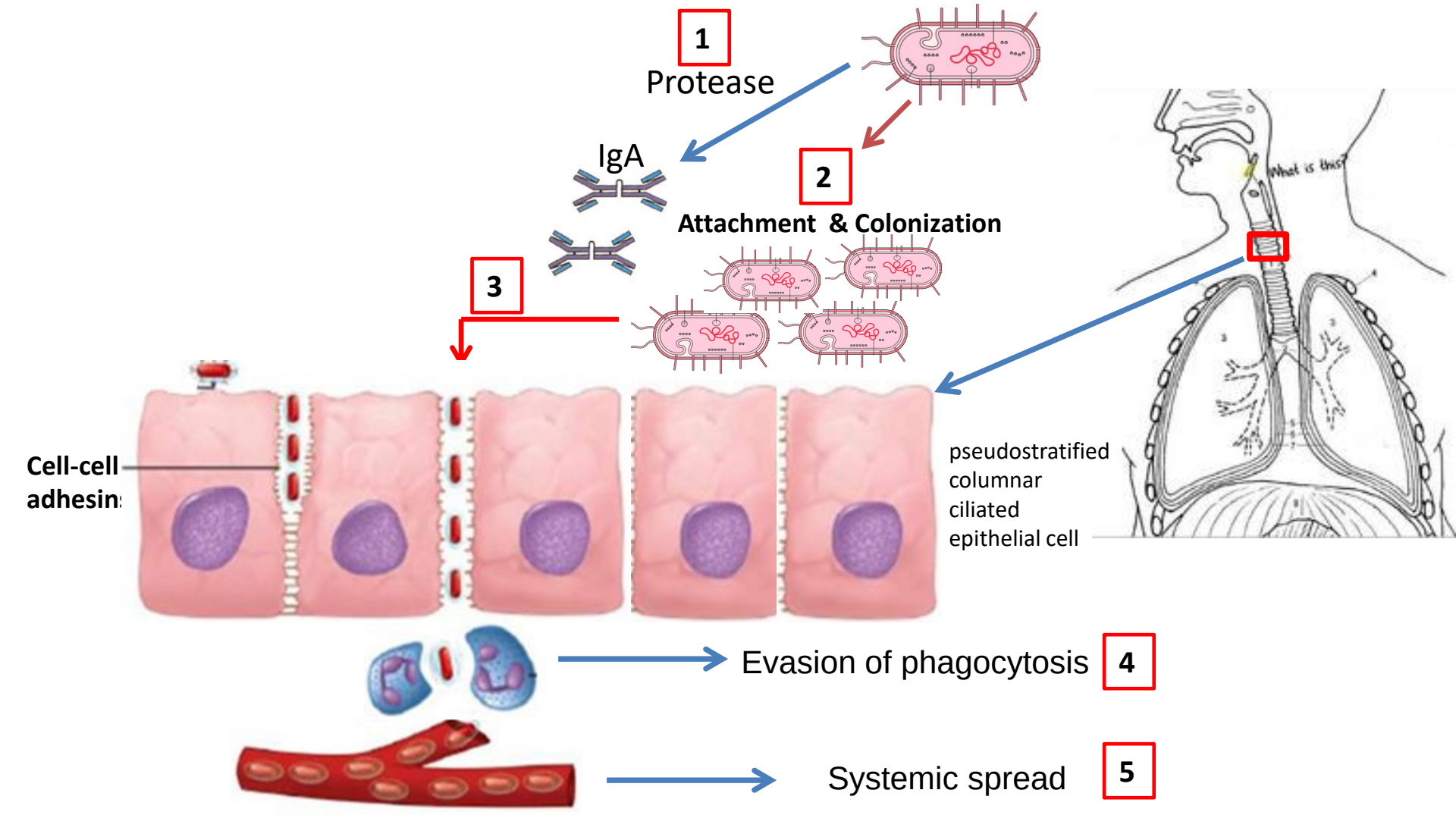
1. **pili**: attachment to respiratory epithelial cells.
2. **Proteases:** destroy IgA and allow the invasion between the cells of the respiratory epithelium.
3. **Antiphagocytic capsule:** confers resistance once past the mucosal barrier
4. **Endotoxin:** in the cell wall is toxic to ciliated respiratory cells.



- Bacteremia then leads to spread to the CNS, bones, and joints.
- Systemic spread is typical only for capsulated *H. influenzae* strains, and over 90% are of type b.

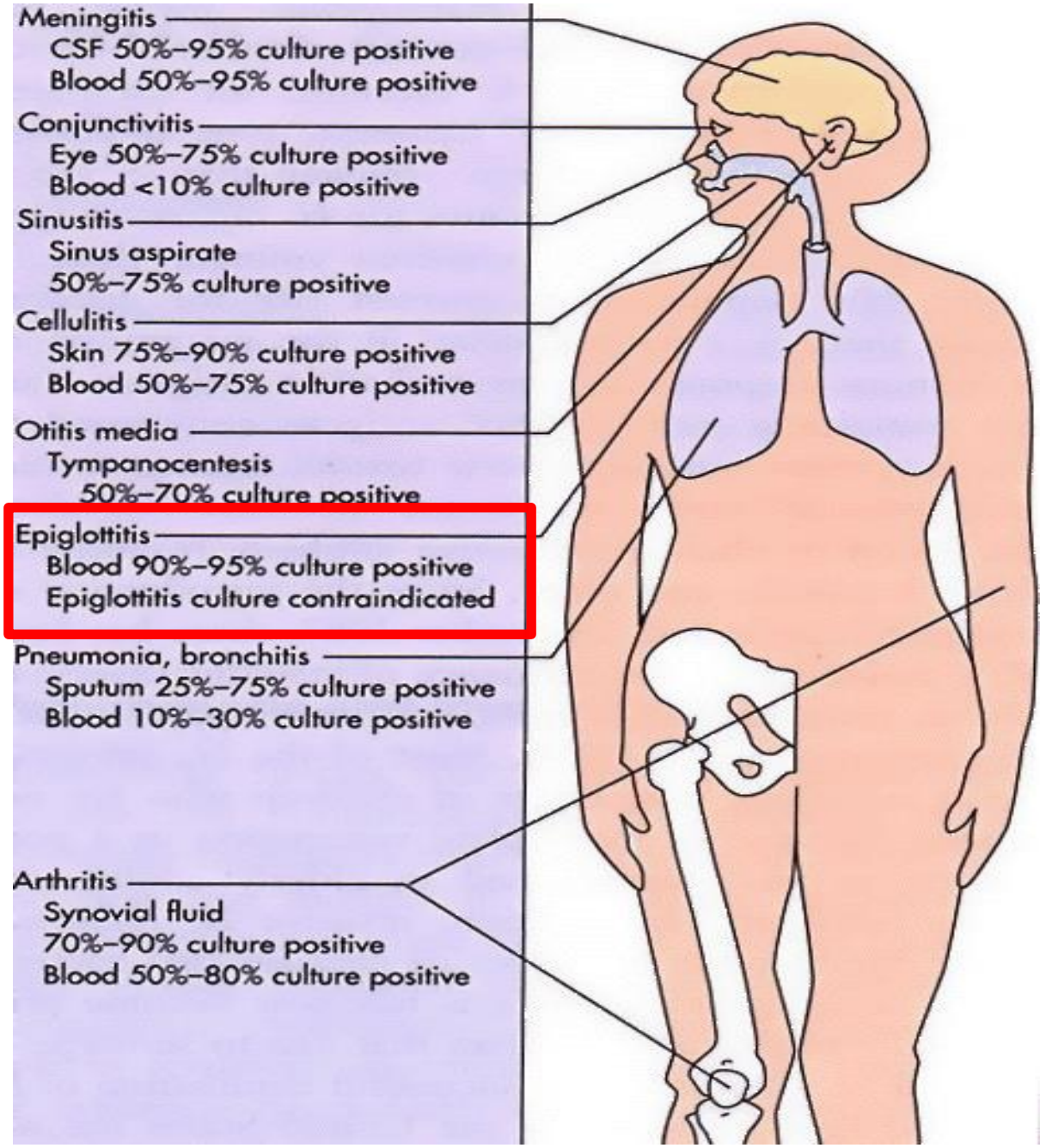
Pathogenesis of Invasive disease

The pathway of Hib reaching reach stream and causing systemic infections



Haemophilus influenzae Infections

Localized disease
Invasive disease



Haemophilus influenzae Infections

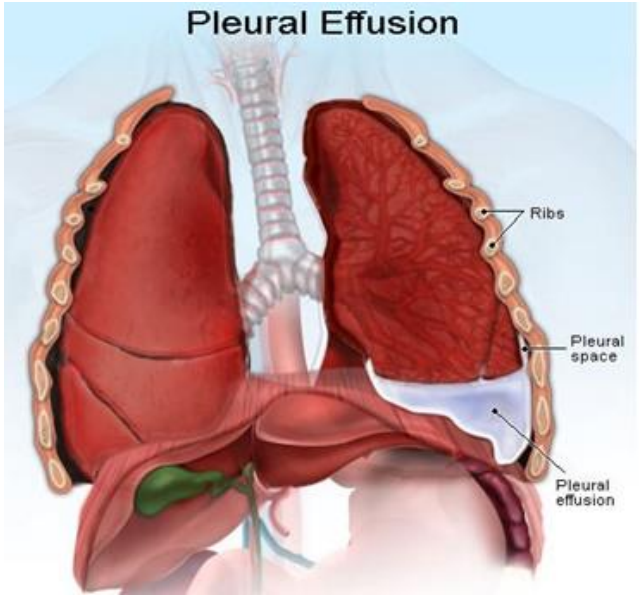
Epiglottitis

- Is a potentially fatal hemophilus infection.
- When the epiglottis is infected, it can swell to the point where it blocks the windpipe.
- The symptoms of epiglottitis include a sudden high **fever**, drooling, the feeling of an object stuck in the throat, and **stridor**.
- Patients with acute painful dysphagia should be considered to have epiglottitis until proven otherwise.
- The epiglottis will look swollen and bright red if the doctor examines the patient's throat with a laryngoscope.

Haemophilus influenzae Infections

Pneumonia

- Occurs when the lungs become infected, causing inflammation (swelling).
  - Non-invasive *H. influenzae* pneumonia: if there's no bacteremia or pleural fluid infection
  - Invasive *H. influenzae* pneumonia: When there is either bacteremia or pleural fluid infection.
- Symptoms of pneumonia usually include:
  - ✓ Fever and chills.
  - ✓ Cough.
  - ✓ Shortness of breath or difficulty breathing.
  - ✓ Sweating.
  - ✓ Chest pain.
  - ✓ Headache.
  - ✓ Muscle pain or aches.
  - ✓ Excessive tiredness.



Haemophilus influenzae Infections

Neonatal infections

- Neonates with *H influenzae* disease present within 24 hours of birth; these infections are caused by NTHi strains, which colonize the maternal genital tract.

- Manifestations may be nonspecific and may include those of bacteremia, sepsis, meningitis, pneumonia, respiratory distress, and conjunctivitis.

- NTHi is a major cause of pneumonia in infants in developing countries.

Transmission

- Transmission occurs through direct contact with respiratory droplets from nasopharyngeal carrier or case patient.

- Neonates can acquire infection by aspiration of amniotic fluid or contact with genital tract secretions containing the bacteria.

Treatment & Prevention

Treatment:

- Ceftriaxone is drug of choice in meningitis and other serious infections
- Otitis media and sinusitis are treated with co-amoxiclav.

Prevention:

- By vaccination
- Given in between 2-15 months.
- Conjugated is more effective than unconjugated one.

Case 1

- **A 33 years** old male presented to the Emergency department with **two days history** of being unwell with
  - **Pyrexia**
  - **Dysphagia**
  - **drooling of saliva.**
- He was **unable** to **phonate**.
- He **was treated immediately** with **intravenous hydrocortisone**, **oxygen**, and **cefotaxime**.
- **Flexible nasal endoscopy** showed **swelling** of the **supraglottic** area, with **oedema** of the **cords**.
- He was **intubated**.
- **Flexible** nasal **endoscopy** on fifth day showed a **normal epiglottis**.
- **H. influenzae** was **isolated** from **blood culture** and treated with **cefotaxime**.

Case 1

- Many **cases of epiglottitis in adults are misdiagnosed** and this may result in the death of a patient who could otherwise survive with correct management.
- **Clues to the diagnosis are:**

1. A sudden onset of sore throat.
2. Dysphagia.
3. Voice change.
4. Respiratory distress or stridor.

Case 2

- A 19-month-old child is brought to the emergency room following a **seizure**.
- His mother says that he had a **cold for 2 or 3 days with a cough**, **congestion**, and **low-grade fever**, but today he became **much worse**.
- He has been **inconsolable**, he would **not eat** and has **slept most** of the morning.
- He **then** had **two seizures**.
- He has **no history of seizures** in the past.
- His **mother** reports that he **has not received** all of his immunizations.
- On examination his temperature is **38.1°C** (100.5°F), his pulse is 110 beats per minute, and he appears very ill.
- He **grimace** when you try to **bend his neck**. His skin is without rash and his HEENT (head, eyes, ear, nose, throat), cardiovascular, lung, and abdominal examinations are normal. His white blood cell count is elevated, and a CT scan of his head is normal

Case 2

Diagnosis: Lumber punture CSF

- Specific diagnosis is based on **culture of the etiologic** organism from the cerebrospinal fluid (CSF).
- **Prior** to culture a rapid **presumptive** diagnosis of bacterial meningitis is based on **increased number** of **polymorphonuclear** leukocytes (PMNs) in the CSF as well as an **elevated protein** and a **decreased glucose**.
- **Gram stain** of the CSF may reveal the presence of bacteria if the number of organisms is high enough.
- In the case of H. influenzae meningitis, the presence of tiny gram-negative coccobacilli is seen in a Gram-stained smear of the CSF.