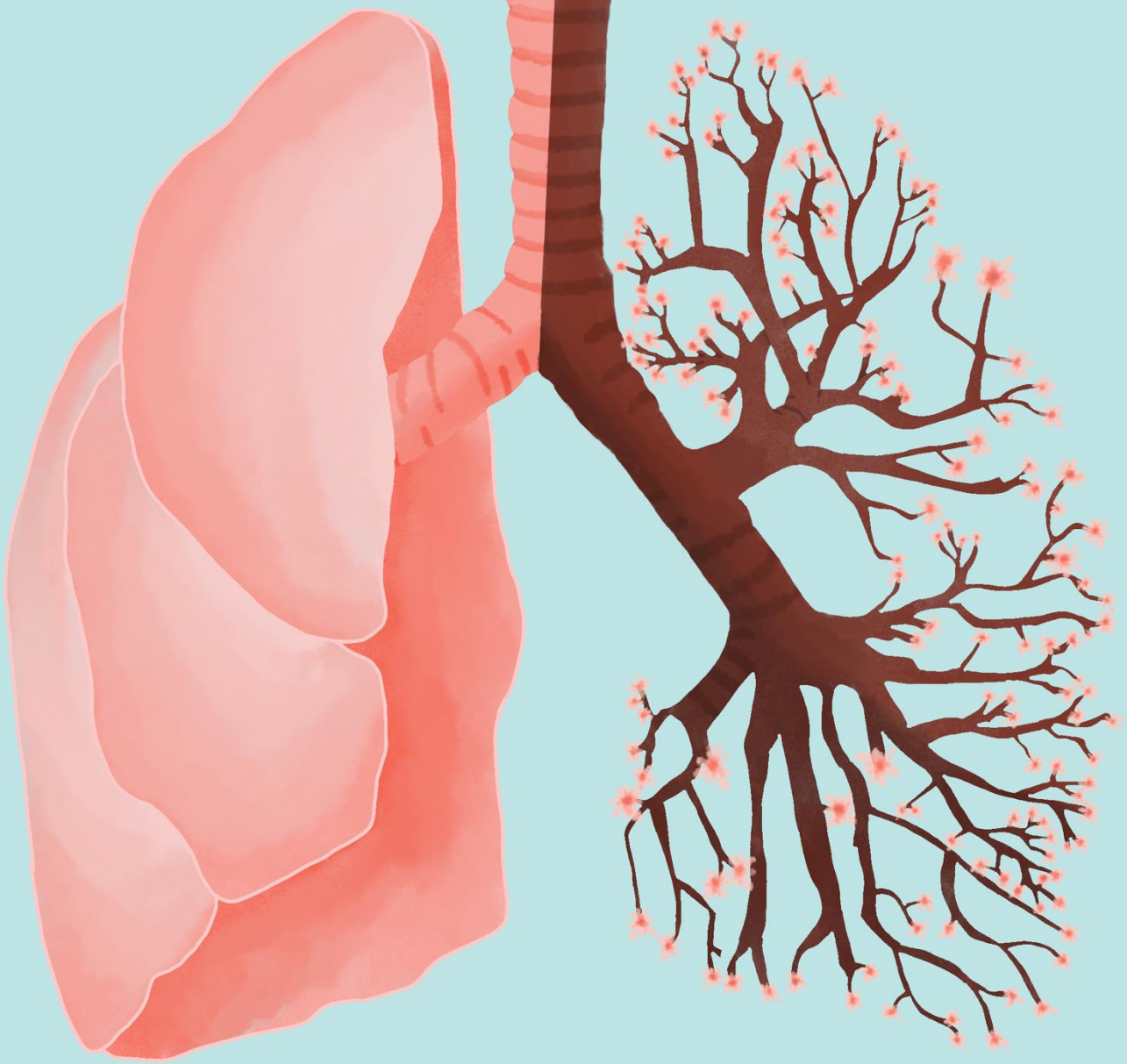
RESPIRATORY SYSTEM

MICROBIOLOGY



Title: Sheet 3 – S. Pneuomnia, H. Influenza

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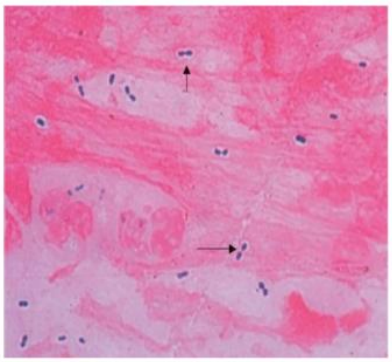
❃ Streptococcus Pneumoniae



- Pneumococci are gram-positive lancet-shaped cocci arranged in pairs (diplococci) or short chains.
- The term lancet-shaped means that the diplococci are oval with somewhat pointed ends rather than being round.
- On blood agar, they produce **α-hemolysis**. This is a shared feature with **viridans streptococci.**

☑ **How do we differentiate between S. Pneumoniae and S. Viridans?**

☞ In contrast to S. Viridans:

- S. Pneumoniae are sensitive to optochin (optochin inhibits their growth).
- S. Pneumoniae are lysed by bile or deoxycholate (dissolve in bile).

↳ We test the organism's bile solubility by adding human bile acid.

- Since they are gram (+), they have **peptidoglycans.**
- All virulent strains have surface capsules, composed of high-molecular-weight polysaccharide polymers.
- S. Pneumoniae also have **Pneumolysin** which is a pore-forming toxin that causes **α-hemolysis.** The secretion of this toxin is stimulated by the release of **Autolysin**.
- Both S. Pneumoniae and H. Influenza are part of the **normal flora** of the **upper** respiratory tract. The lower respiratory tract is completely sterile.
- They have a special virulence factor which is the **capsular polysaccharide**. This capsule has more than 90 serotypes.

❍ Pathogenesis:

- Since S. Pneumonia is part of the normal flora of the **upper** respiratory tract, then most probably the infection caused is of endogenous origin caused by the bacteria moving to the **lower** respiratory tract by aspiration.
- S. Pneumonia causes a disease derived from its name (pneumonia).

❍ Virulence Factors:

1. **Capsular Polysaccharide:** it's the most important virulence factor for S. Pneumonia and H. Influenza. Vaccines are easily made for them targeting this capsule (anticapsular antibody)
2. **Lipoteichoic acid**: complement activator, it induces inflammatory cytokine production contributing to the inflammatory response and to the septic shock syndrome that occurs in some immunocompromised patients (a bit similar to protein A in LPS in Gram negatives)
3. **Pneumolysin**: the hemolysin that causes α-hemolysis, may also contribute to pathogenesis
4. **IgA Protease**: pneumococci produce IgA protease that enhances the organism's ability to colonize the mucosa of the upper respiratory tract

Factors that Predispose People to Pneumococcal Infections:

- It is worth asking, if S. Pneumonia is already part of the normal flora of the upper respiratory tract then how does it causes pneumonia?
- People become susceptible to pneumococcal infections by factors that lower resistance and predispose persons to pneumococcal infection.
- These factors either reduce mucus clearing or decrease immune reaction. These include:

1. Anything that can **depress the cough reflex**: alcohol, drug intoxication or other cerebral impairment (geriatrics, cerebrovascular accident {CVA}, mental impairment)

☞ All contribute to an increase **aspiration** of secretions and thus pneumonia.

2. **Abnormality of the respiratory tract** (e.g., viral infections), pooling of mucus, bronchial obstructions, and respiratory tract injury caused by irritants which disturb the integrity and movement of the mucociliary blanket

☞ All **prevent clearing of the mucus** and predispose to **community acquired pneumonia** caused by pneumococcus.

3. **Abnormal circulatory dynamics** (e.g., pulmonary congestion and heart failure)

☞ Blood will congest in the lung → **increase pulmonary secretions** → pneumococcus.

4. **Splenectomy** (spleen clears encapsulated organisms) and certain chronic diseases such as **sickle cell anemia** and **nephrosis**

☞ Patients with sickle cell anemia auto-infarct their spleen → become functionally asplenic, and are predisposed to pneumococcal sepsis.

5. **Trauma to the head**

☞ Causes leakage of spinal fluid through the nose → predisposes to pneumococcal meningitis.

Transmission:

- Humans are the **natural hosts** for pneumococci; there is no animal reservoir.
- Because a proportion (5%–50%) of the healthy population harbors virulent organisms in the oropharynx, pneumococcal infections are **not considered to be communicable** (**endogenous origin**; *it happens from your own flora*).
- Resistance to infection is **high** in healthy young people, and disease results most often when predisposing factors are present.

Diseases Caused by S. Pneumonia:

- Streptococcus Pneumonia causes many diseases that vary according to the geographical region. These diseases include:

a. Pneumonia
b. Bacteremia.
c. Meningitis.
d. URTIs such as otitis media, mastoiditis, and sinusitis.
e. Conjunctivitis, especially in children.

- Pneumococci are **the most common cause** of community-acquired pneumonia, meningitis, otitis media, and sinusitis.
- Pneumococci are the **leading cause of sepsis** in patients **without a functional spleen.**

A. Pneumonia:

- Str. pneumoniae is the **most frequent cause** of *bacterial* pneumonia with an estimated annual incidence of 1–3 per 1000 of the population, with a **5% case fatality rate**
- Note that the most common cause of pneumonia is **viral**. However, the most common **bacterial** cause is S. Pneumonia.

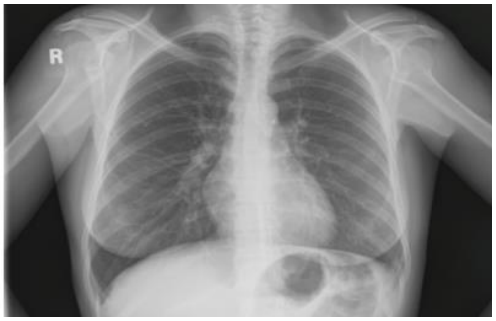
Viral Pneumonia	Bacterial Pneumonia
Infiltration of both lungs.	Usually involves only one lobe or a segment of a lobe.

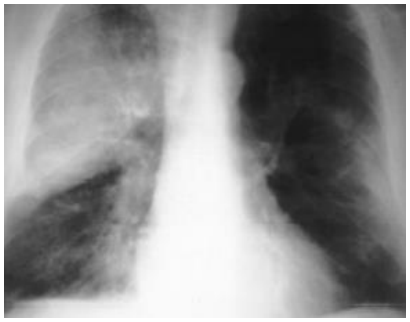
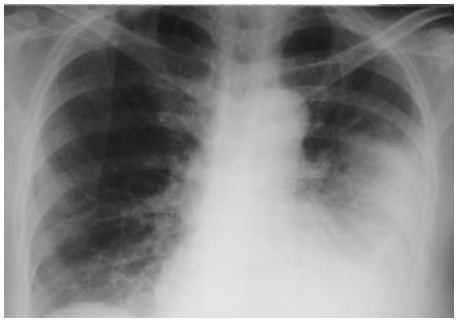
✸ Pathogenesis:

- Pneumococcal pneumonia usually **follows aspiration**; it happens when a person aspires S. Pneumonia from their URT to the bronchial mucosa with subsequent migration through the bronchial mucosa to involve the surrounding lymphatics.
- The inflammatory reaction is focused primarily within the alveolus of **a single lobule or lobe**, although **multi-lobar disease can also occur.**
- S. Pneumonia as mentioned earlier, **autolyzes** itself. This causes the release of its toxin, pneumolysin, which recruits RBCs and WBCs in the lung. This collection is called **consolidation.**
- Most common lobes affected by S. Pneumonia are the **middle right and lower left lobes.**

✸ Complications

- **Opacification** is one of the manifestations of pneumonia. It occurs as a result of gas reduction in the lung due to its replacement by blood / fluids. Opacification is seen as a white shadow on X- Rays.
- Pneumonia causes high fever and chills. Patients also experience chest pain that's usually increased when inhaling.
- Patients have a **productive cough** (cough with sputum). The sputum is cold and rusty due to RBCs.
- Contiguous spread commonly results in inflammatory involvement of the pleura; this may progress to empyema.
- Pericarditis is an uncommon but well recognized complication.



✸ **Clinical Findings (Pneumonia):**

- Sudden chill, fever, cough, and pleuritic pain (chest pain that increases with chest movement-breathing)
- Sputum is a red or brown "rusty" color
- Bacteremia occurs in 15% to 25% of cases
- Spontaneous recovery may begin in 5 to 10 days and is accompanied by development of **anticapsular antibodies**
- Patients start feeling better after taking penicillin

B. Otitis media & Sinusitis

- Middle ear infections (otitis media) affect approximately half of all children between the ages of 6 months and 3 years; approximately one-third of cases are caused by S. pneumoniae. Acute otitis media is also called **hot ear disease.**
- As there are almost 90 serotypes of the capsular polysaccharide, the person that gets infected by S. Pneumonia can get re-infected with another strain (a new capsule), which the body has no pre-existing immunity to (there is a constant exchange of pneumococcal strains).
- The prevalence is highest among children attending kindergarten or primary school.

C. Meningitis

- Str. pneumoniae is among the three leading causes of bacterial meningitis. Causes of meningitis vary according to geographical regions.
- It is assumed that invasion arises from the pharynx to the meninges via the blood-stream, as bacteremia usually coexists.
- Meningitis may occasionally complicate pneumococcal infection at other sites, such as the lung and middle ear.
- The incidence of pneumococcal meningitis is bimodal and affects children less than 3 years of age and adults of 45 years and above.
- The fatality rates are 20% and 30%, respectively, considerably higher than those associated with other types of bacterial meningitis.
- S. Pneumonia can also cause **sepsis** in patients without a functional spleen.

❹ Laboratory Diagnosis:

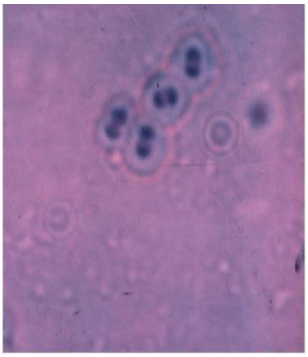
☞ **In sputum**: lancet-shaped gram-positive diplococci in Gram-stained smears.

☞ If we only want to detect the presence of S. Pneumonia, we use the omnivalent serum:

- The **omnivalent serum** contains antibodies targeting more than 90 capsular serotypes
- We add the serum in addition to methylene blue; the bacteria will appear blue, surrounded by a hallow area or capsular swelling (**Quellung reaction**)

↳ **Quellung reaction**: antibody against the capsule which shows swelling of the capsule if contained the antigen for the provided antibody

- Cross-linking reactions between the bacteria can be seen



Quellung reaction

☞ **On blood agar:** pneumococci form small **α-hemolytic** colonies

☞ The colonies are **bile-soluble** (i.e., are lysed by bile), and growth is **inhibited by optochin**

- Blood cultures are positive in 15% to 25% of pneumococcal infections

✸ Note: we classify pneumococcus as invasive if it causes meningitis or sepsis, but if it only causes a URTI, we classify it as non-invasive.

Treatment:

✓ Most pneumococci are **susceptible to penicillins** and **erythromycin**, although significant resistance to penicillins has emerged.

✓ In **severe** pneumococcal infections, **penicillin G is the drug of choice**, whereas in **mild** pneumococcal infections, **oral penicillin V** can be used.

✓ A **fluoroquinolone** with good anti-pneumococcal activity, such as **levofloxacin**, can also be used

✓ In **penicillin-allergic patients**, **erythromycin** or one of its long-acting derivatives (e.g., azithromycin) can be used

✓ An increasing percentage of isolates, ranging from 15% to 35% depending on location, show **high-level resistance**, which is attributed to multiple **changes in penicillin binding proteins**

✓ They **do not produce β-lactamase**. **Vancomycin** is **the drug of choice for the penicillin- resistant pneumococci**, especially for **severely** ill patients.

✓ **Ceftriaxone** or **levofloxacin** can be used for **less severely ill patients**.

Prevention:

- Despite the efficacy of antimicrobial drug treatment, **the mortality rate** of pneumococcal infections is **high** in immunocompromised (especially **splenectomized**) patients and children under the age of 5 years. Such cases should be immunized with the **13-valent pneumococcal conjugate vaccine** (Prevnar 13).

a) **Immuno-compromised**: are given the **13-valent conjugate** pneumococcal vaccine (Prevnar 13)

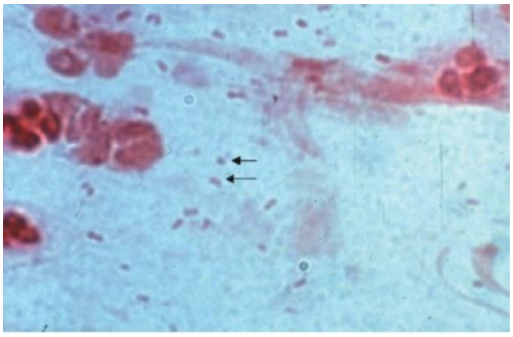
↳ The **immunogen** in this vaccine is the **pneumococcal polysaccharide of the 13 most prevalent serotypes** conjugated (coupled) to a carrier protein (**diphtheria toxoid**).

↳ Must be given **booster doses** every **5 years.**

b) **Healthy individuals age 50 years or older**: are given the **unconjugated 23-valent** pneumococcal vaccine (Pneumovax 23)
(booster doses at 65)

- **These vaccines are safe and effective and provide long-lasting (at least 5 years) protection**

❋ Hemophilus Influenza



- H. influenzae are **gram negative rods (coccobacillary)**, encapsulated with a polysaccharide capsule
- One of the three important encapsulated pyogenes (pneumococcus and the meningococcus)
- Using serologic methods against the antigen of the polysaccharide capsule, six serotypes are detected, with serotype B (group B) being the most significant one
- **Serotype B** is responsible for more **serious illnesses** (meningitis, epiglottitis, sepsis)
- The type B capsule is composed of polyribitol phosphate, promotes anti- phagocytosis and invasiveness
- **Unencapsulated** strains are **less invasive** but can cause disease usually **limited to the upper respiratory tract** (sinusitis and otitis media)
- Growth of the organism on laboratory media requires the addition of two components:

↳ **Heme (factor X)** and **NAD (factor V):** for **adequate energy production**

- H. influenzae used to be the leading cause of meningitis in young children, now it's the **third most common**.
- We have 1 representative from each gram reaction and shape that is a respiratory organism (four in total):
  1. **Pneumococcus G+ve coccus**: capsulated respiratory organism causes mengitis and URTI
  2. **Meningiococcus G-ve coccus:** capsulated which can colonize the respiratory epithelium
  3. **The gram-negative ROD, Haemophilus**: also a respiratory capsulated organism that is the **third most common cause of meningitis**.
  4. **Corynbacterium diphteriae G+ve ROD**: not capsulated, doesn't cause meningits

➔ Note that the three **capsulated** ones are **causative of meningitis** and **have vaccines** made against the capsule

❍ Pathogenesis & Epidemiology:

- **Reservoir**: H. influenzae infects only humans with no animal reservoir
- **Transmission**: similar to other respiratory pathogens, it is **transmitted** by the inhalation of **airborne droplets** into the respiratory tract. This can result in asymptomatic colonization or infection (otitis media, sinusitis, pneumonia)
- **Virulence Factors**: also like all respiratory pathogens, to be able to survive in this environment, the organism produces an **IgA protease** that degrades secretory IgA which would otherwise **inhibit its attachment to the mucosa**.
- After becoming established in the upper respiratory tract, the organism can enter the bloodstream (bacteremia) and spread to the meninges

- As mentioned earlier, capsulated strains can cause meningitis (they have to have antiphagocytic capability to survive the trip through the blood to reach the meninges, this is true for Pneumococcus and Meningiococcus)
- Meningitis caused by capsular type b has been greatly **reduced by vaccines** that contain the type b polysaccharide as the immunogen
- Similar to pneumococcus and meningococcus, the pathogenesis of **H. infleunza is pyogenic with no exotoxin production** (*capsule and endotoxin based*)

Clinical Findings:

Meningitis:

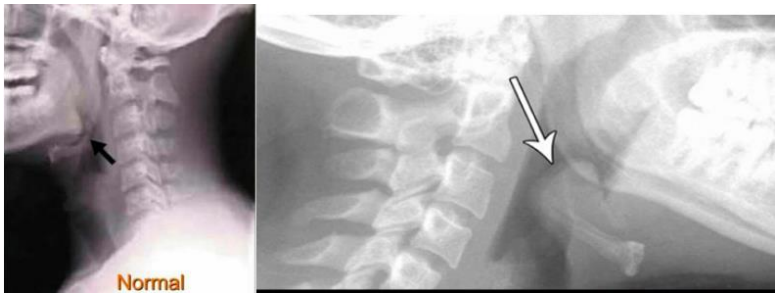
- Meningitis caused by H. influenzae produces a clinical picture that is almost identical to pneumococcal or meningococcal meningitis
- The rapid onset of fever, headache, stiff neck, (neurological symptoms; drowsiness), is typical

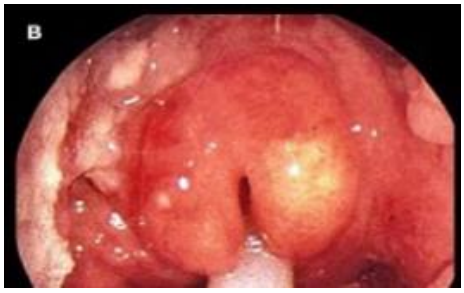
Respiratory Tract Infections:

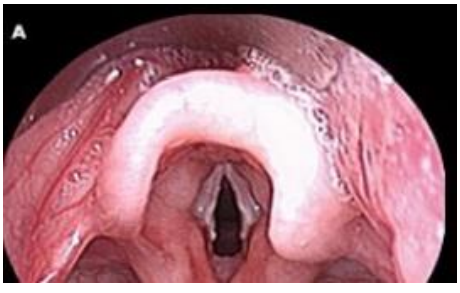
- Sinusitis and otitis media cause pain in the affected area, opacification of the infected sinus, and redness with bulging of the tympanic membrane
- H. influenzae is second only to the pneumococcus as a cause of these two infections
- Other serious infections : septic arthritis, cellulitis, and sepsis (more in asplenic patients, due to the fact that this is a capsulated organism)
- Pneumonia in elderly adults, especially those with chronic respiratory disease, can be caused by untypeable (not capsulated) strains of H. influenzae

Epiglottitis:

- Rare, but can obstruct the airway and CAN BE FATAL
- Upon inspection, a swollen “cherry-red” epiglottis is seen
- This life-threatening disease of young children is caused almost exclusively by H. influenzae
- Symptoms include, drooling, stridor (high pitched breathing noise) and comfort on sitting up.







Laboratory Diagnosis:

- Need to isolate the organism to make the diagnosis
- Inactivated blood must be used (chocolate agar, to remove inhibitors of growth in the blood) enriched with two growth factors required for bacterial respiration (chocolate agar +factor x and factor V)

➔ An organism that grows on **Chocolate + Factors X and V** is assumed to be H. influenzae; other species of Haemophilus, such as Haemophilus parainfluenzae, do not require both factors

- Quellung reaction and biochemical tests can be used
- Additional means of identifying encapsulated strains include fluorescent antibody staining of the organism and counter immune-electrophoresis or latex agglutination tests, which detect the capsular polysaccharide

Treatment:

- For meningitis and serious systemic infections (remember these are more invasive and aggressive) caused by H. influenzae **the treatment of choice is ceftriaxone (3rd gen)**
- From 20% to 30% of H. influenzae type b isolates produce a β-lactamase that degrades penicillinase-sensitive β-lactams such as ampicillin but not ceftriaxone
- It is important to **institute antibiotic treatment promptly**, because the incidence of neurologic sequelae (subdural empyema) is high
- **Untreated** H. influenzae meningitis has a **fatality rate of approximately 90%**
- H. influenzae **upper respiratory tract infections** (such strains as mentioned are less aggressive and less invasive), that cause otitis media and sinusitis, are **treated with either amoxicillin-clavulanate or trimethoprim- sulfamethoxazole**

Prevention:

✓ Vaccine contains the capsular polysaccharide of H. influenzae type b **conjugated** to diphtheria toxoid or other carrier protein

✓ Depending on the carrier protein, it is given some time between the ages of 2 and 15 months.

✓ This vaccine is **much more effective** in young children **than the unconjugated** vaccine and has reduced the incidence of meningitis caused by this organism by approximately 90% in immunized children

✓ **Meningitis** in close contacts of the patient **can be prevented by rifampin**

↳ Rifampin is used because it is secreted in the saliva to a greater extent than ampicillin

↳ Rifampin decreases respiratory carriage of the organism, thereby reducing transmission

A special thanks to Basma AbuMahfouz for her contribution in this sheet