# CENTRAL NERVOUS SYSTEM INFECTIONS

•**The brain and spinal cord are protected** from mechanical pressures or deformations by enclosure in rigid containers (skull and vertebral column), which also act as barriers to the spread of infection.

•**The blood vessels and nerves** that traverse the walls of the skull and vertebral column are the **main routes of invasion.**

•**Blood-borne invasion** is the commonest (e.g. poliovirus, meningococcus), while invasion via peripheral nerves is less common (e.g. herpes simpler, varicela-zoster, rabies viruses).

•**Local invasion from infected ears or sinuses**, or from local injury or congenital defects, such as spina bifida, also occurs.

# Blood-borne invasion

- **Blood-borne invasion** takes place across
  - the blood-brain barrier to give **encephalitis,**
  - or the blood-cerebrospinal fluid (CSF) barrier to given **meningitis**. Microbes can traverse these barriers by:
    - growing across, infecting the cells that comprise the barrier;
    - being passively transported across in intracellular vacuoles; or
    - carried across by infected white blood cells.

  - **Poliovirus and Mumps virus** for instance, invades the CNS across the blood-brain barrier. After oral ingestion of virus, a complex of events provides the mechanism for CNS invasion. Poliovirus also invades the meninges after localizing in vascular endothelial cells, and can cross the blood-CSF barrier.

  - as do circulating ***Haemophilus influenzae*, meningococci or pneumococci.**

  Once infection has reached the meninges and CSF, the brain substance can in turn be invaded if passage across the pia takes place. In poliomyelitis, for instance, a meningitic phase often precedes encephalitis and paralysis.

## •CNS invasion

• is a rare event because **most microorganisms fail to pass from blood to CNS across the natural barriers**.

•A large variety of **viruses** can grow and cause disease **if introduced directly into the brain**, but circulating viruses generally fail to invade, and CNS involvement by **polio, mumps, rubella or measles viruses is seen only in a very small proportion** of infected individuals. The factors which determine such GNS invasion are unknown.

•**Invasion of the CNS via peripheral nerves** takes place in several viral infections:

• **Herpes simplex and varicella-zoster viruses** present in skin or mucosal lesions travel up axons using the normal retrograde transport mechanisms that can move virus particles (as well as foreign molecules such as tetanus toxin), to reach dorsal root ganglia.

•**Rabies virus** introduced into muscle or subcutaneous tissues by the bite of a rabid animal, infects muscle fibres and muscle spindles after binding of the virus to the nicotinic acetyl- choline receptor. It then enters peripheral nerves and travels up to the CNS, to reach glial cells and neurones, where it multiplies.

# THE RESPONSE TO INVASION

- **The response to invading viruses** is reflected by an **increase in lymphocytes (mostly T cells) and monocytes in the CSF**. A slight increase in protein also occurs, the **CSF remaining clear**. This is termed 'aseptic' meningitis.
- **The response to pyogenic bacteria shows a more spectacular and more rapid increase in polymorphonuclear leucocytes and proteins**, so that the CSF becomes visibly turbid. This is termed '**septic' meningitis**.
- Certain **slower growing or less pyogenic microorganisms** induce less dramatic changes, such as in **tuberculous or listerial meningitis**.
- In the CNS itself viruses can infect neural cells, sometimes showing a marked preference.
  - **Polio and rabies viruses**, for instance, invade neurones whereas
  - **Invading bacteria and protozoa** generally induce more dramatic inflammatory events which limit local spread, so that infection is soon localized to form abscesses.
- The pathological consequences of CNS infection depend on the microorganism.
- Viruses induce perivascular infiltration of lymphocytes and monocytes, sometimes, as in the case of polio, with direct damage to infected cells.

•Associated immune responses not only to **viral** but often to host CNS components play a part. **Infiltrating B cells produce antibody** to the invading microorganism and T cells react with microbial antigens to release cytokines that attract and activate other T cells and macrophages. The pathological condition evolves over the course of several days, and occasionally, when partly controlled by host defences, (e.g. subacute sclerosing panencephalitis) over the course of years.

•**Bacteria** cause more rapidly evolving pathological changes, with local responses to bacterial antigens and **toxins playing an important part.**

• When dorsal root ganglion neurones are invaded, as an essential step in **establishing latency** (**herpes simpler and varicella-zoster viruses**). This gives a mechanism for reactivation and further episodes of shedding from mucosal or skin lesions;

• **In the case of rabies** , where CNS invasion in the animal host is necessary for two reasons. First, it enables the virus to spread from the CNS, down peripheral nerves to the salivary glands, from which transmission takes place. Second, **invasion of the limbic system of the brain causes a change in behaviour of the infected animal**, so that it becomes **less retiring, more aggressive and more likely to bite, thus transmitting the infection**.

# BACTERIAL MENINGITIS

•Acute bacterial meningitis is a life-threatening infection, needing urgent specific treatment. It is more severe, but fortunately less common, than viral meningitis. The important causative agents are shown in the table.

- *Neisseria meningitidis*,
- *Haemophilus influenzae*,
- *Streptococcus pneumoniae*

•invade the meninges in healthy individuals and account for more than **three-quarters of all bacterial meningitis.**

•These three pathogens have several virulence factors in common, including possession of a polysaccharide capsule.

# Non viral meningitis-causes, treatment and prevention

| Pathogen | Treatment | Prevention |
|---|---|---|
| ***N.meningitidis*** | Penicillin(chloramphenicol) | Rifampicin –for close contacts<br>Polysacharide vaccine |
| ***H.influenzae*** | Ampicillin, or chloramphenicol, or cefotaxime | Rifampicin –for close contacts<br>vaccine |
| ***S.pneumoniae*** | penicillin or chloramphenicol | Prompt treatment of otitis&respiratory infections |
| *E.coli*, **coliforms, group B streptococci,** *L.monocytogenes, S.epidermidis* | Gentamicin&penicillin or chloramphenicol | No vaccine avaible |
| ***M.tuberculosis*** | Isoniasid &riphampicin &pyrazinamide | BCG vaccination |
| ***C.neoformans*** | Amphotericin B | No vaccine avaible |

# Meningoccal meningitis

- *Neisseria meningitidis* is a Gram-negative diplococcus which closely resembles *N. gonorrhoeae* in structure, but with an additional polysaccharide capsule that is antigenic and by which the serotype of *N. meningitidis* can be recognized.
- The bacteria are **carried asymptomatically in up to 20%** of the population, **attached by their pili to the epithelial cells in the nasopharynx**.
- **Invasion of the blood and meninges** is a rare and poorly understood event. The known virulence factors are summarized the table.

## Bacterial menigitis –virulence factors for major pathogens

| **Virulence factors** | ***N.meningitidis*** | ***H.influenzae*** | ***S.pneumoniae*** |
|---|---|---|---|
| capsula | + | + | + |
| IgA protease | + | + | + |
| Pili | + | + | - |
| Endotoxine | + | + | - |
| OMP | ? | + | - |

•People **possessing specific, complement-dependent bacterial antibodies to capsular antigens** are protected against invasion.

• **Those with C5-C8 complement deficiencies** show increased susceptibility to bacteraemia (as they do to *N. gonorrhoeae* bacteraemia).

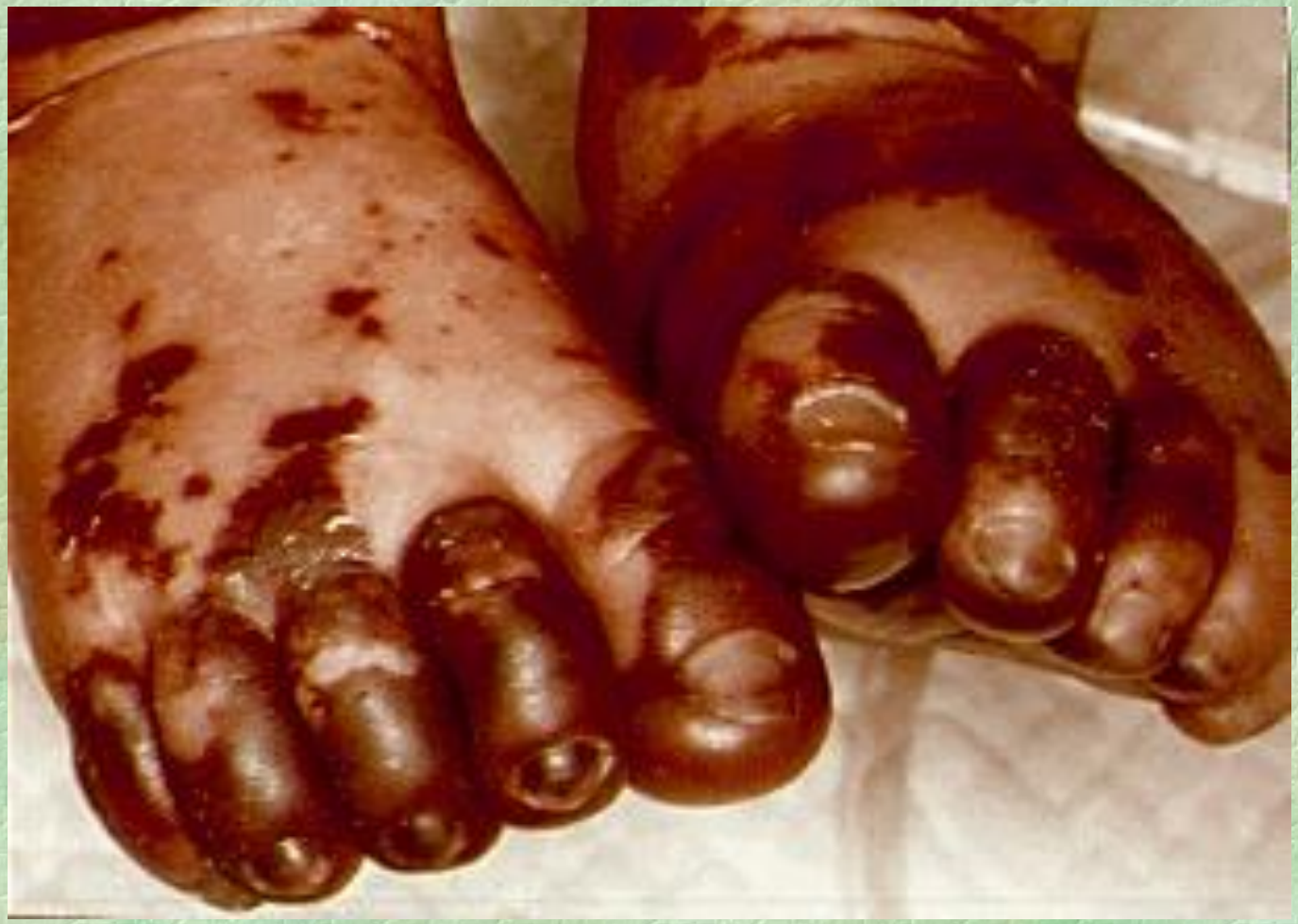
•Those **most often infected are young children, who have lost the antibodies acquired from their mother**, and **adolescents** who have not previously encountered the infecting serotype and therefore have no type-specific immunity.

• **Person-to-person spread** takes place by droplet infection, and is facilitated by other (viral) respiratory infections which cause increased respiratory secretions, and by over-crowding.

•During outbreaks of meningococcal meningitis the carrier rate may reach 70%.

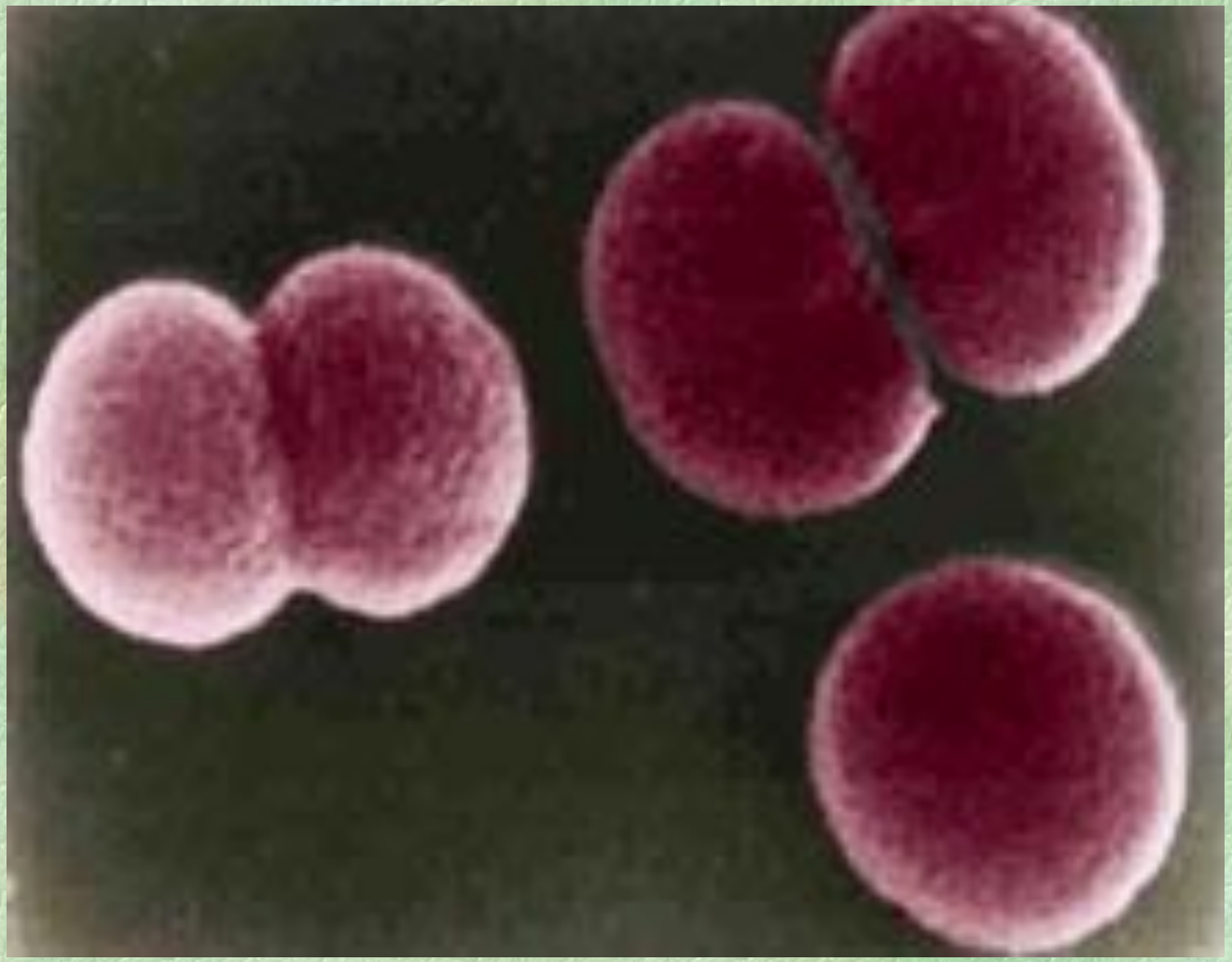
# Clinical features

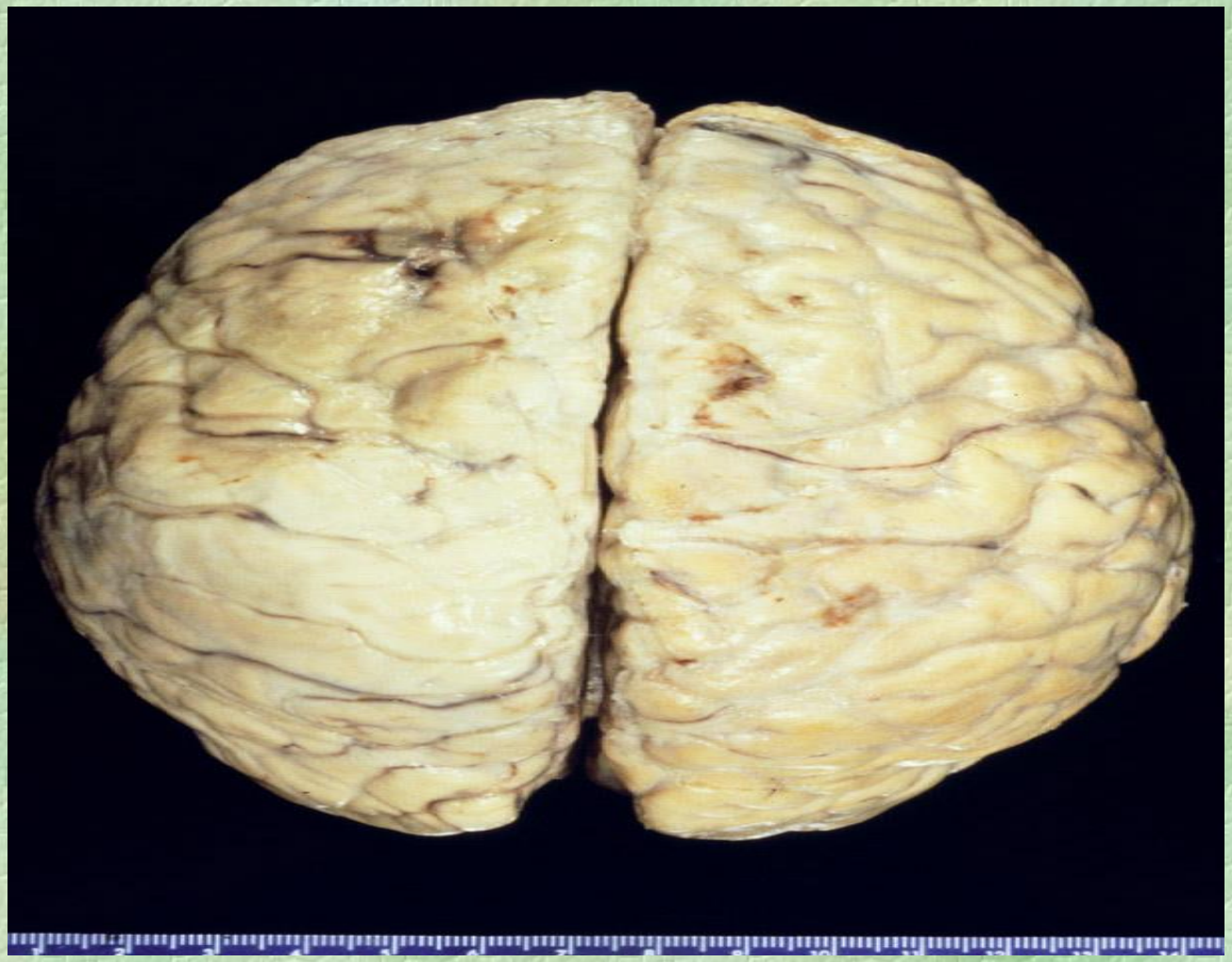
- After an incubation period of 1-3 days, the **onset is sudden with sore throat, headache, development of meningitis signs (fever, irritability, neck stiffness**). There is often a **haemorrhagic skin rash, with petechiae**, reflecting the associated septicaemia.
- In about one- third of patients this is **fulminating, with complications due to disseminated intravascular coagulation (DIC), endotoxaemia and shock, and renal failure**.
- In the most severe cases there is an acute addisonian crisis, with bleeding into the brain and adrenal glands (**Waterhouse-Friederichsen syndrome**).
- **Mortality** from meningococcal meningitis reaches 100% if untreated but remains around 10% even if treated. However, serious sequelac are uncommon in survivors compared with the outcome of *H. Influenzae* and *S.pneumoniae* meningitis.

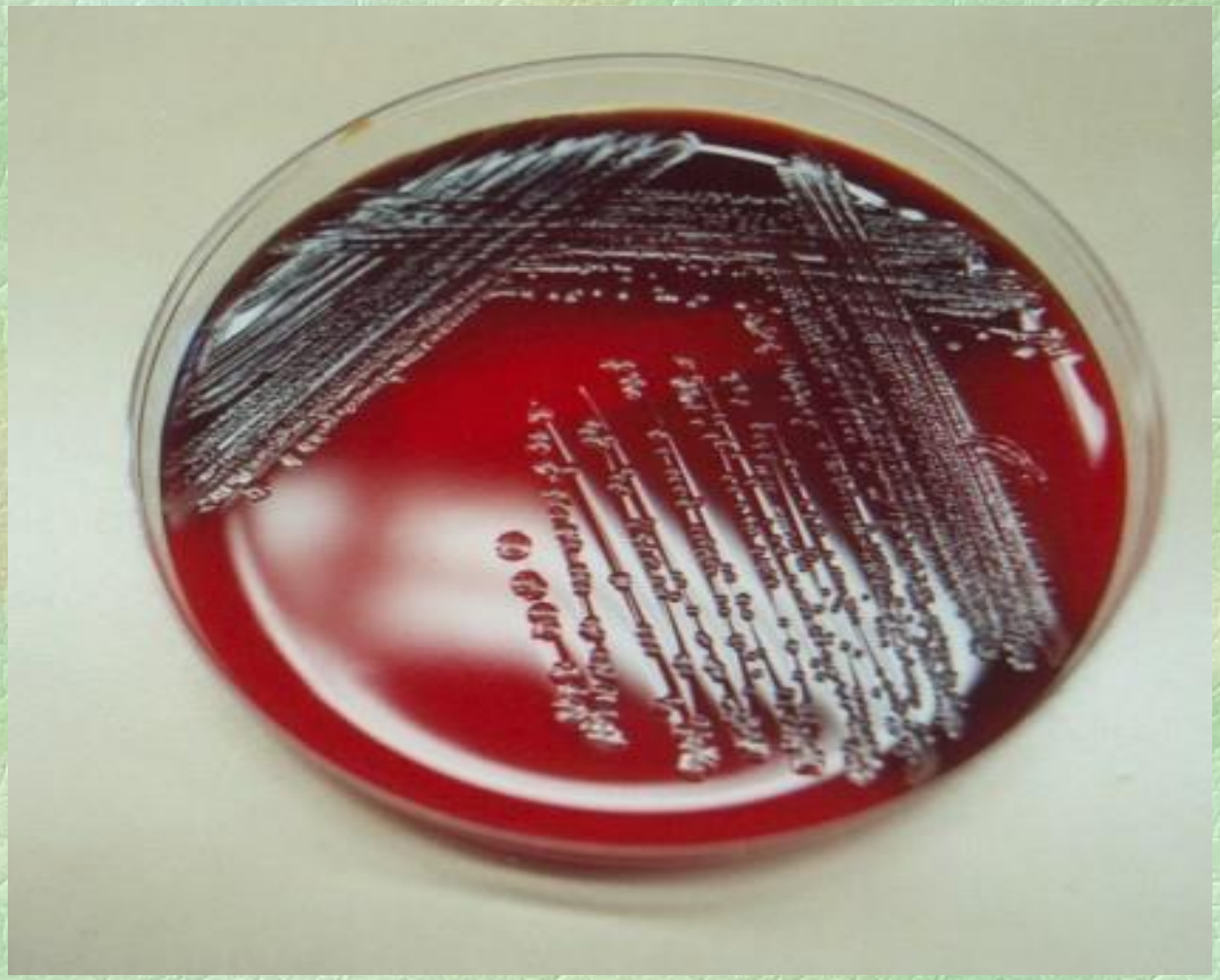


## Diagnosis, Treatment, Prevention

- The diagnosis of acute meningitis is usually **suspected on clinical examination**
- **Laboratory identification** of the bacterial cause is essential, however, so that appropriate antibiotic therapy can be given and prophylaxis of contacts initiated. Preliminary results should be available within an hour of receipt of the CSF sample in the laboratory. Results of culture of CSF and blood should follow after 24 hours. Serology is not helpful in the diagnosis of bacterial meningitis because the infection is too acute for an antibody response to be detectable.
- **Bacterial meningitis** is a medical emergency and antibiotic therapy (usually penicillin or ampicillin) should be investigated if the diagnosis is suspected. Early treatment saves lives, although it may make recovery of viable organisms from specimens more difficult.
- **Close** contacts in the family ('kissing contacts') should be given rifampicin chemoprophylaxis for 2-3 days. Penicillin is not used for prophylaxis because it does not eliminate nasopharyngeal carriage of meningococci. Patients should be given a course of rifampicin to clear carriage after the acute phase of the infection is passed. Sulphonamides can no longer be relied upon for prophylaxis because resistance in meningoeocci is common.





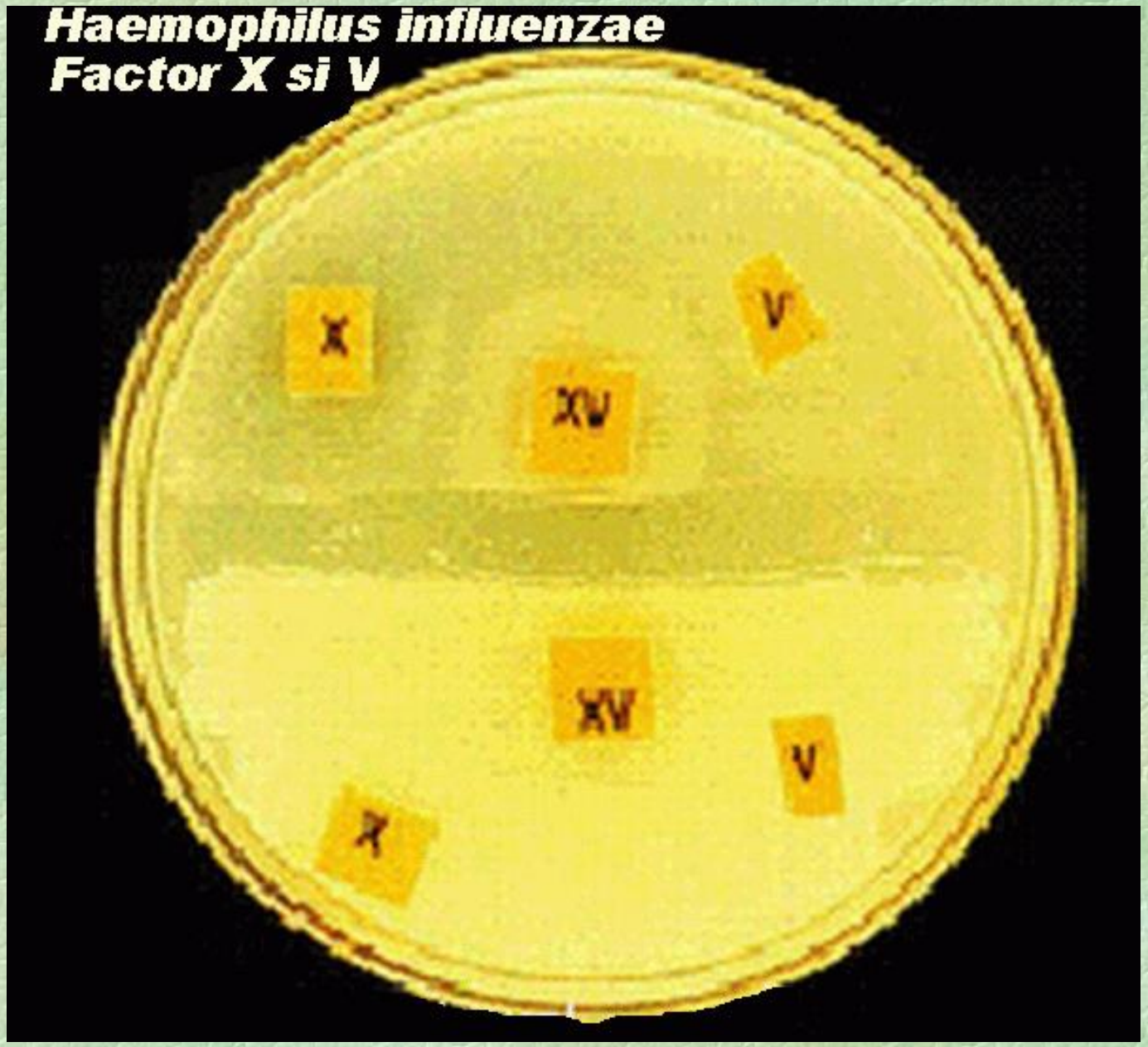


# Haemophilus meningitis

- *Haemophilus influenzae* is a Gram-negative coccobacillus. 'Haemophilus' means 'blood-loving', and the name 'influenzae' was given because it was originally thought to be the cause of influenza, but **is now known to be a common secondary invader in the lower respiratory tract**.
- **There are six types (a-f) of *H. influenzae***, distinguishable serologically by their capsular polysaccharides. Unencapsulated strains are common and are present in the throat of most healthy people. It is the ***capsulated type b***, a common inhabitant of the respiratory tract of infants and young children (where it may cause infection), that very occasionally invades the blood and reaches the meninges.
- **Maternal antibody** protects the infant up to 3-4 months of age but as it wanes there is a 'window of susceptibility' until the child produces its own antibody. **Anticapsular antibodies** are good opsonins, which allow the bacteria to be phagocytosed and killed, but children do not generally produce them until 2-3 years of age, possibly because these antibodies are T independent.

# Clinical features, Diagnosis Treatment and prevention

- The **incubation period is 5-6 days** and the onset often more insidious than meningoeoccal or pneumococcal meningitis . The condition is **less frequently fatal** but there **is a higher incidence of serious sequelac** (hearing loss, delayed language development, mental retardation and seizures) than with meningococcal infection.
- **General diagnostic features** are the same as for meningococcal meningitis, as explained above. It is important to note than the organisms may be difficult to see in Gram-stained smears of CSF, particularly if they are present in small numbers.
- **General features of treatment** are referred to above, under meningococcal meningitis;
- There is a vaccine containing the capsular polysaccharide of *H. influenzae* type b, but unfortunately this is ineffective in those less than 2 years old, who are most vulnerable. More effective vaccines are, however, becoming available. Close contacts of patients are sometimes given rifampicin prophylaxis.


Haemophilus influenzae
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# Pneumococcal meningitis

- *Streptococcus pneumoniae* was first isolated more than 100 years ago and has since received intensive study both as a pathogen and as the subject of early work on bacterial transformation. Despite this, relatively little is known about its virulence attributes apart from its polysaccharide capsule and the pneumococcus remains a major cause of morbidity and mortality.
- *Strep. pneumoniae* is also of major importance as a cause of bacterial meningitis. It is a capsulate Gram- positive coccus carried in the throats of many healthy individuals. Invasion of the blood and meninges is a rare event, but is more common in the very young (less than 2 years of age), in the elderly, in those with sickle cell disease, in debilitated or splenectomized patients and following head trauma.
- **Susceptibility to infection is associated with low levels of antibodies to capsular polysaccharide antigens**: antibody opsonizes the organism and promotes phagocytosis, thereby protecting the host from invasion. However, this protection is type-specific and there are more than 85 different capsular types of *Strep. pneumoniae*.


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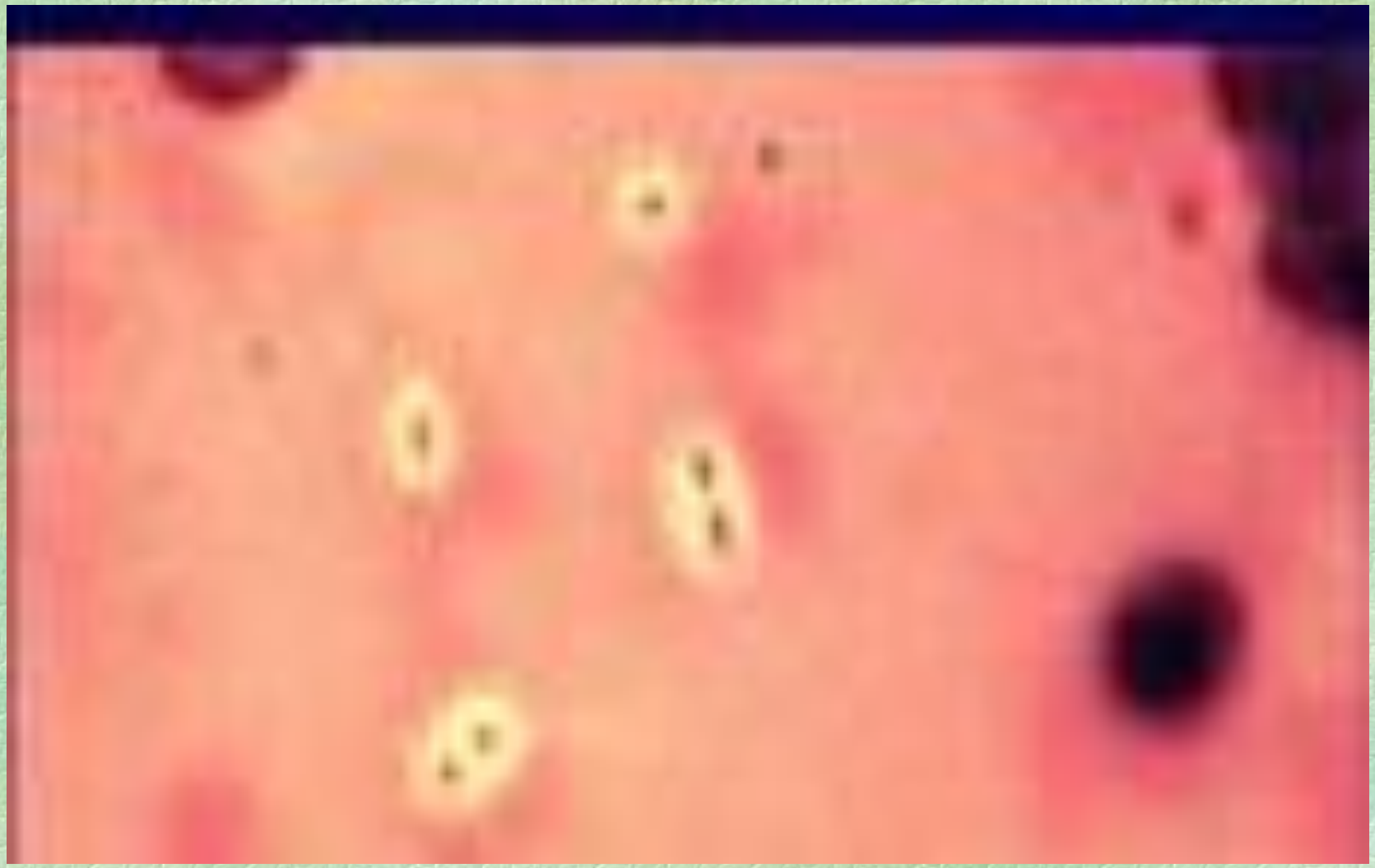


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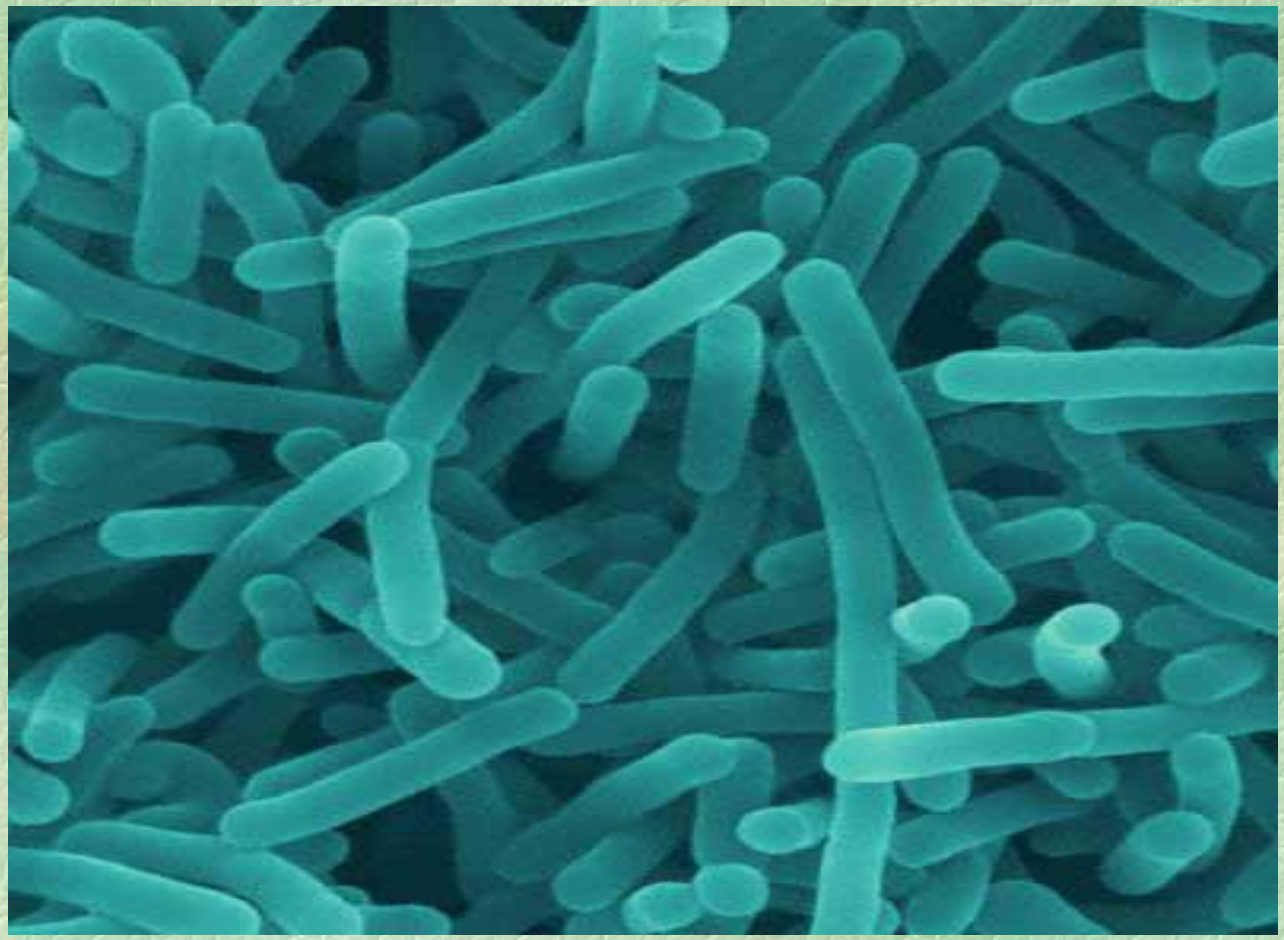
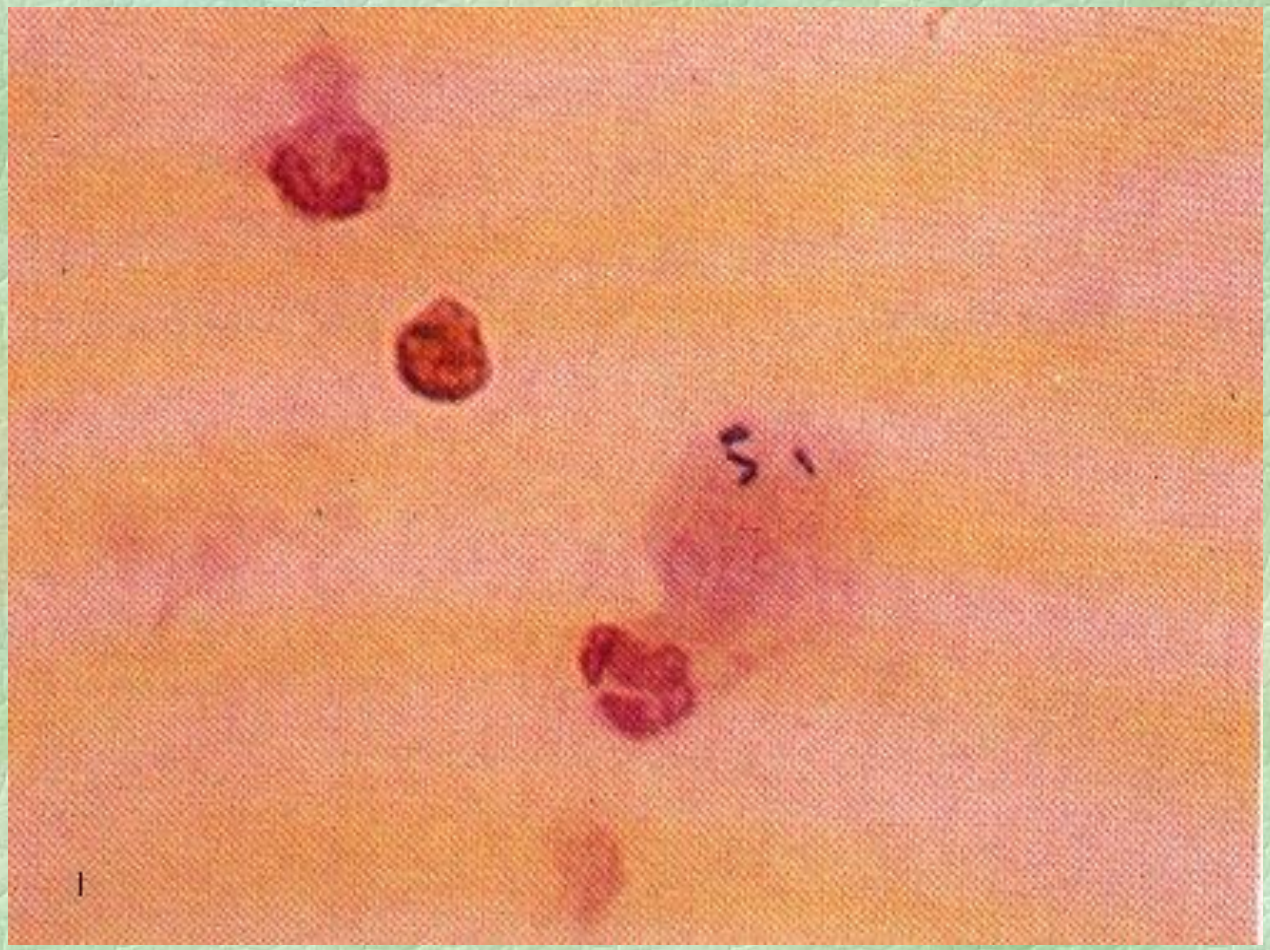
# Bacterial meningitis-clinical features

| **Pathogen** | **Host (patient)** | **Clinical features** |
|---|---|---|
| ***N.meningitidis*** | Children&adolescents | Acute onset (6-24h)skin rash |
| *H.infuenzae* | Children<5years | Onset often less acute (1-2 days) |
| *S.pneumoniae* | All ages, especially children<2 years and elderly | Acute onset may follow pneumonia&/or septicemia in elderly |

# *Listeria monocytogenes* meningitis

- This **gram-positive coccobacillus** is an important cause of meningitis in immunocomprornised adults, especially in **renal transplant and cancer patients.**
- It also causes intra- uterine infections and infections of the **newborn.**
- *L. monocytogenes* is less susceptible than *S. pneumoniae* to penicillin and the recommended treatment is a combination of penicillin or ampicillin with gentamicin.

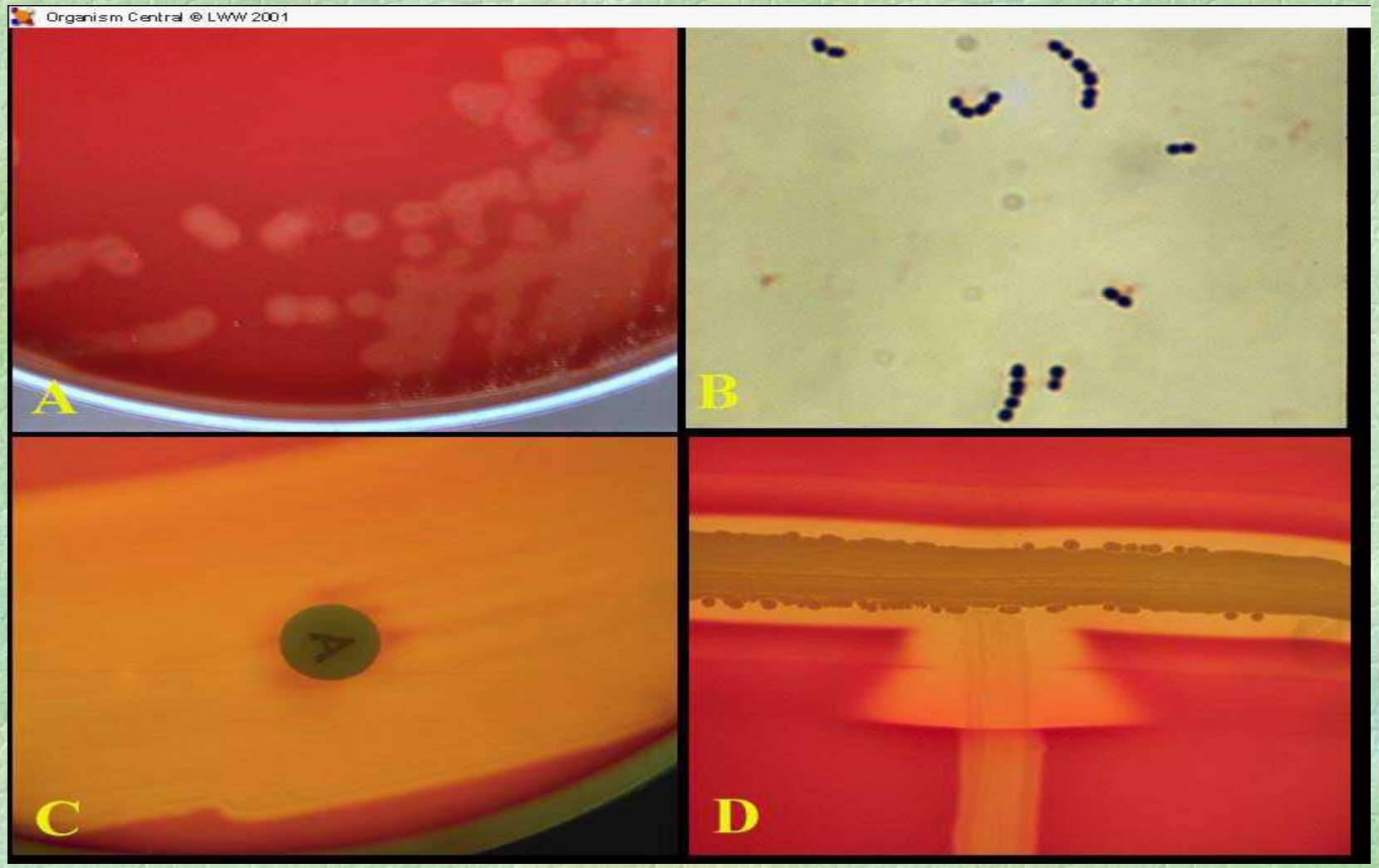




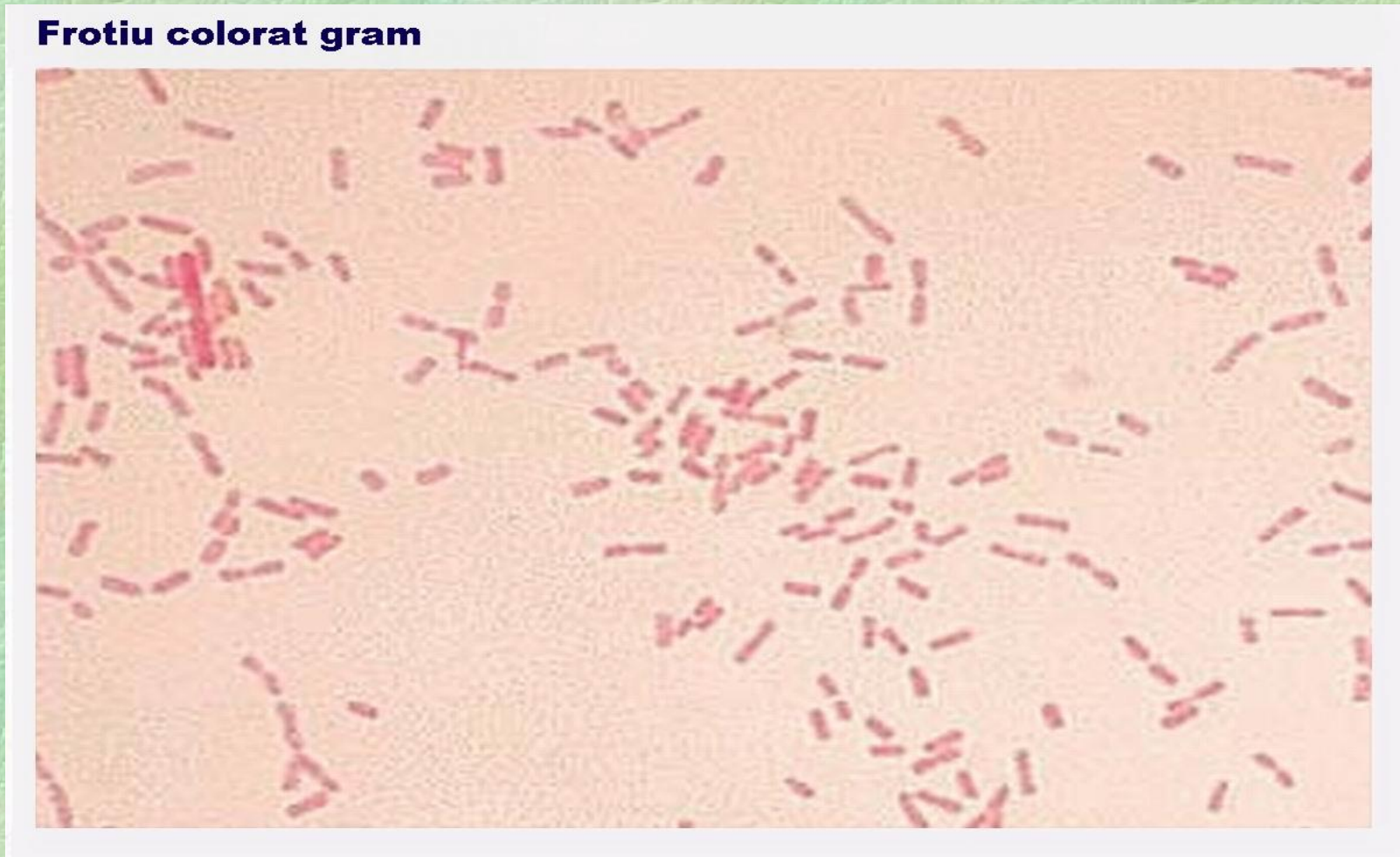
# Neonatal meningitis

- This can be caused by a wide range of bacteria but the most frequent are ***E. coli*** and group **B haemolytic streptococci**.
- Infection is fatal in about one-third of cases and in others often leads **to permanent sequelae such as cerebral or cranial nerve paralsy, epilepsy, mental retardation or hydrocephalus.** This is partly because the clinical diagnosis of meningitis in the neonate is difficult, perhaps with no more specific signs than fever, poor feeding, vomiting, respiratory distress or diarrhoea.
- Because the possible range of organisms is wide, 'blind' antibiotic therapy, in the absence of susceptibility tests, may not be optimal and many antibiotics penetrate inadequately into the CSF. Host defences are poor, especially in low birth weight (less than 1000g) babies.

# Streptococcus agalactiae



# E.coli-Gram stain

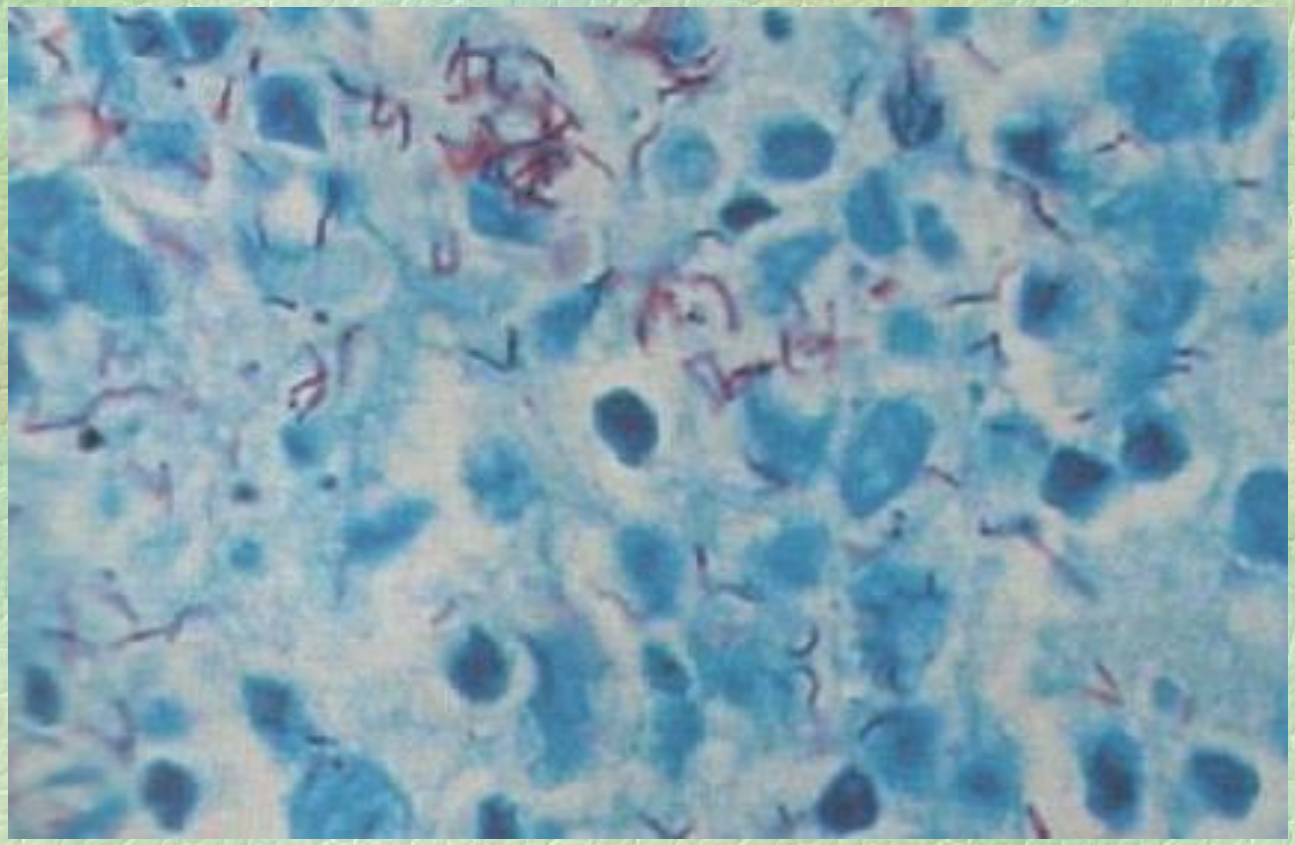


# E.coli- culture

# Tuberculous meningitis

- Patients with tuberculous meningitis always have a focus of infection elsewhere, but one in four have no clinical or historical evidence of such an infection. In more than half the cases, **meningitis is associated with acute miliary tuberculosis**.
- There is a **gradual onset of generalized illness** beginning with malaise, apathy and anorexia and proceeding within a few weeks to **photophobia, neck stiffness and impairment of consciousness**. Occasionally the onset is much more rapid and may be mistaken for a sub-arachnoid haemorrhage. The variability of presentation means that the clinician needs to maintain an awareness of possible tuberculous meningitis to make the diagnosis. A delay in making the diagnosis and in starting appropriate antimicrobial therapy results in serious complications and sequelac.
- In **spinal tuberculosis**, uncommon now except in developing countries, bacteria in the vertebrae destroy the intervertebral discs to form epidural abscesses, which compress the spinal cord and lead to paraplegia.

# M.tuberculosis-Ziehl Nielsen stain




10 Doses
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Active Immunizing Agent
For Intracutaneous Injection Only.
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# FUNGAL MENINGITIS

- ***Cryptococcus neoformans and Coccidioides immitis* can invade the blood from a primary site of infection in the lungs and thence to the brain to cause meningitis. *Cryptococcus neoformans* meningitis is seen in those with depressed cell- mediated immunity and is a problem in AIDS patients. The onset is usually slow, over days or weeks.**
- **The capsulate yeasts** can be seen in India ink stained preparations of CSF and can be cultured. Antigen detection is also a useful diagnostic tool and evidence of a decline in antigen and an increase in antibody levels in the CSF can be used as a measure of successful therapy. Treatment with the antifungal drugs amphotericin B and flucytosine in combination is recommended.
- **Exposure to *Coccidioides immitis*** infection is very common in particular geographical locations, notably south-west USA, Mexico and South America. GNS infection may be part of the generalized disease or may represent the only extrapulrnonary site. It occurs in fewer than 1% of infected individuals but is fatal unless treated. The organisms are rarely visible in the CSF and cultures are positive in less than half of cases, but the diagnosis can be made by demonstrating complement-fixing antibodies in the scrum. **Treatment with amphotericin B or miconazole is recommended.**

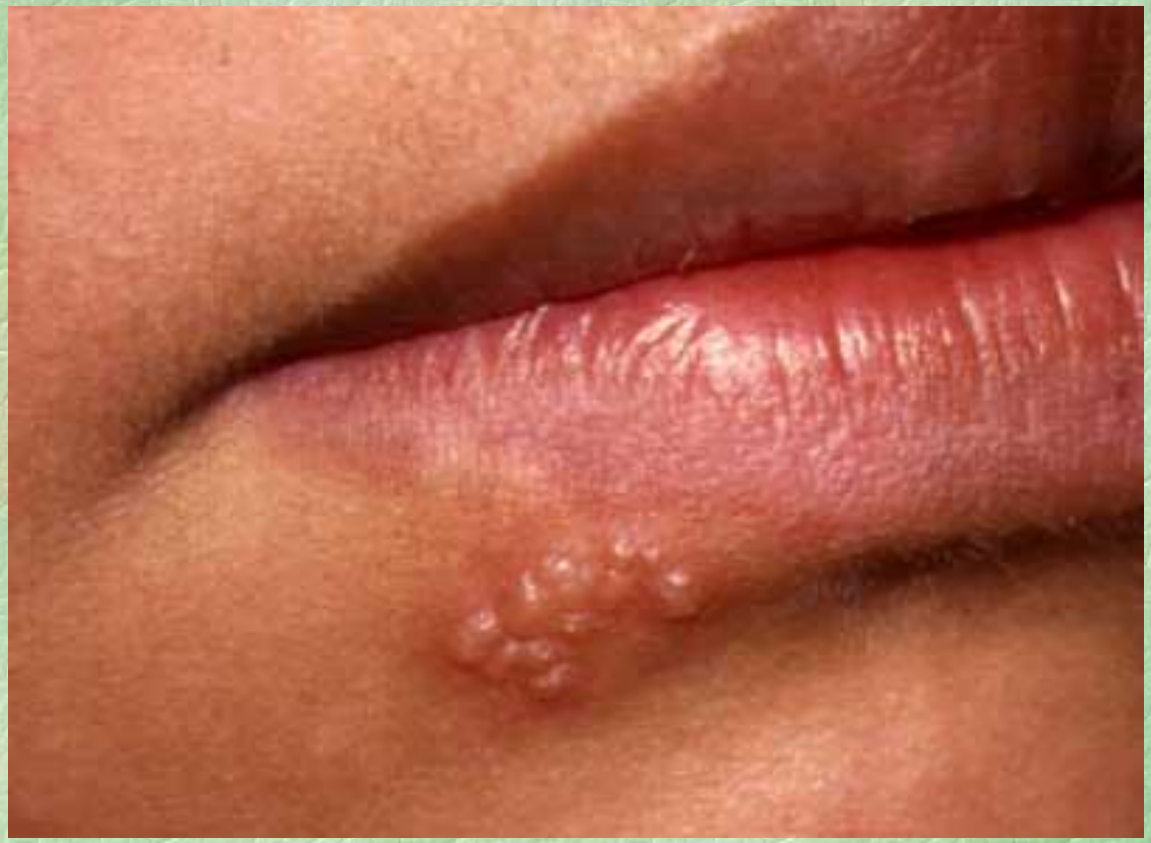
# VIRAL MENINGITIS

- **This is the commonest type of meningitis**.
- It is a **milder disease** than bacterial **meningitis, with** headache, fever and general illness but less neck stiffness. The CSF is clear, bacteria-free, and the cells are mainly lymphocytes, although polymorphs may be present in the early stages.
- The causes of viral meningitis are listed in the table, but viruses are isolated from the CSF in less than 50% of cases.
- Because there are many types of enteroviruses (32 echoviruses, 29 coxsackic viruses, 3 polioviruses) and because infection is commonly asymptomatic, **a virus isolated from throat or stool of a child with mild meningitis may be of no aetiological significance**.
- In contrast to bacterial meningitis, and in spite of the fact that there are no antiviral drugs (except for herpes simplex), complete recovery generally takes place.

# Viral meningitis

| Virus | Virus group | Comments |
|---|---|---|
| Herpes simplex | Alpha herpes | Uncommon |
| Mumps | Paramyxovirus | A quite common complication |
| Lymphocytyc choriomeningitis | Arenavirus | Uncommon |
| Polio, Coxsackie, Echo Picornaviruses | enteroirus | Commonly seen Especially echovirus |
| Japanese encephalitis | togavirus | India, Asia, Japan |

# Herpes simplex



# Varicella