Clinical Lectures

Introduction to Infectious Diseases

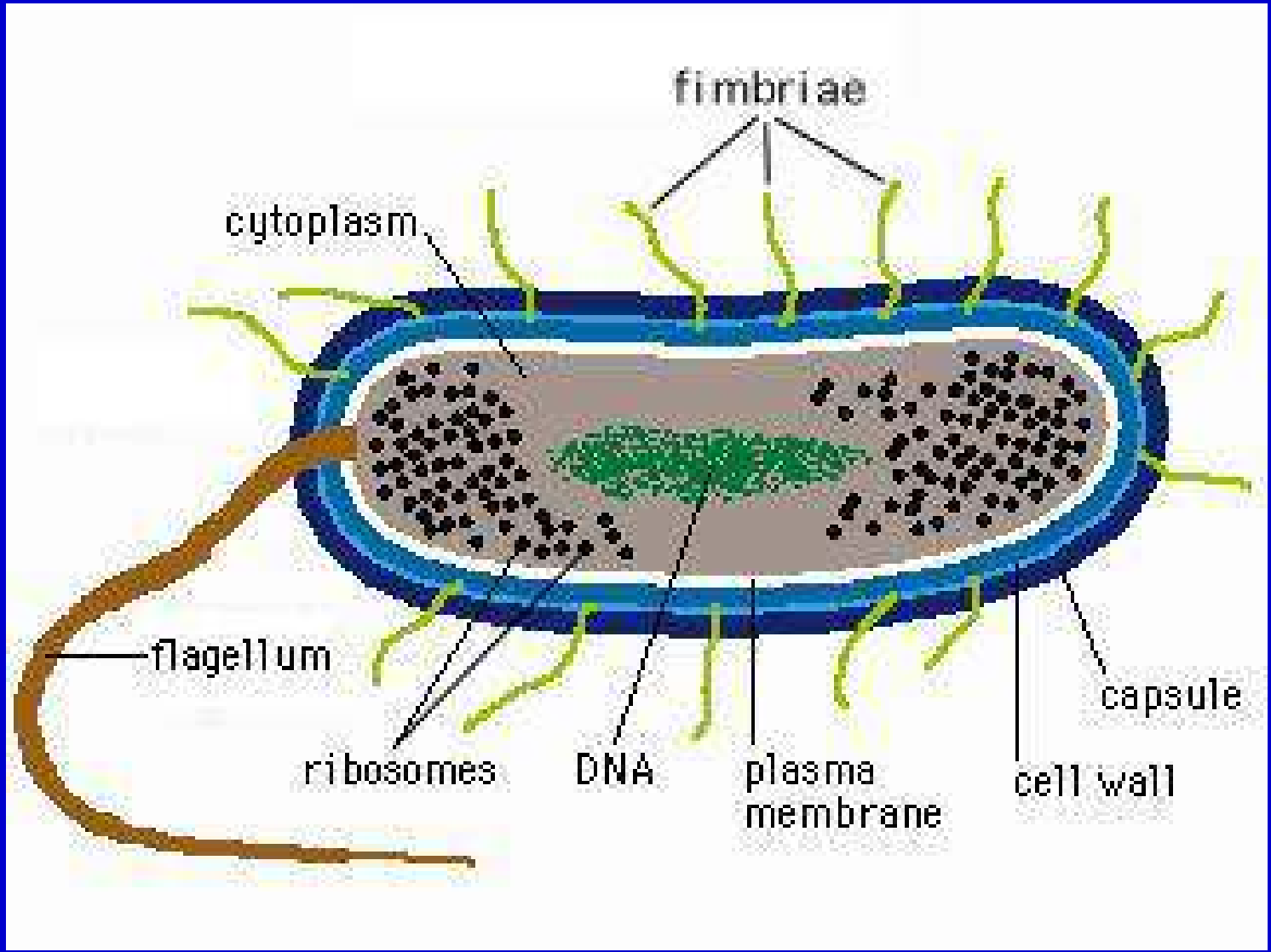
Infective agents

- **Gram Positive Bacteria**
- **Gram Negative Bacteria**
- **Viruses**
- **Protozoa**
- **Fungi and Yeasts**
- **Worms**
- **Prion disease**

Bacteria

- Unicellular organisms
- Single circular DNA molecule
- No nuclear membrane (prokariotic)
- No mitochondria
- Rigid cell wall
- Reproduce by binary fusion
- Can also form spores
- Varied oxygen and nutritional requirements

bacterium



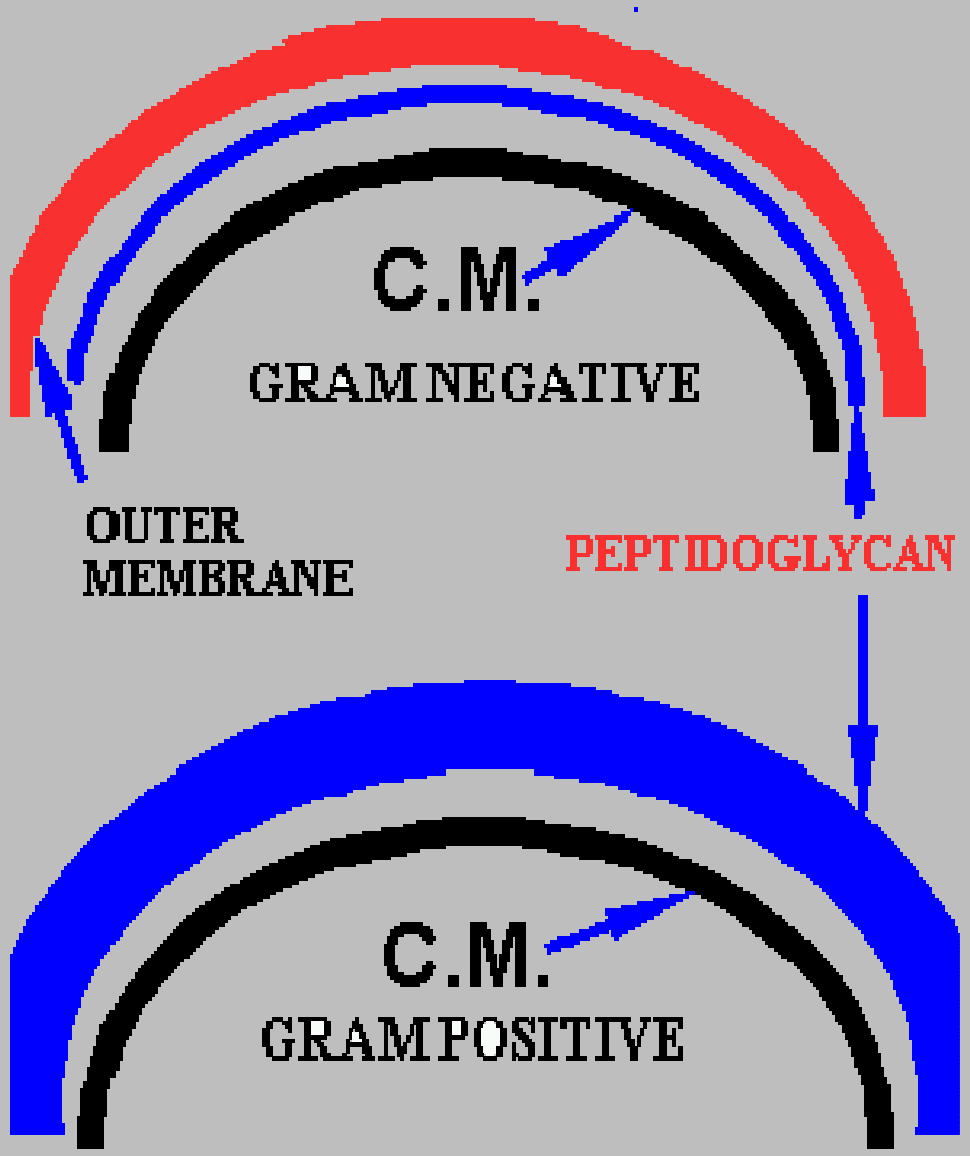
CLASSIFICATION OF BACTERIA

Lab characteristics

- Shape
- Staining
- Growth characteristics
- Biochemical reactions
- Antigenicity activity

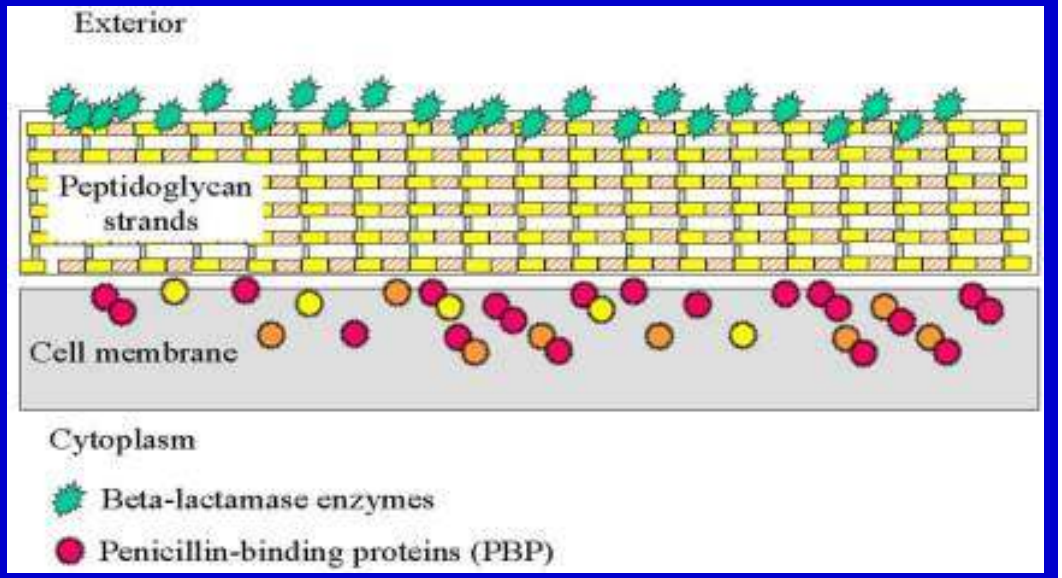
Shape

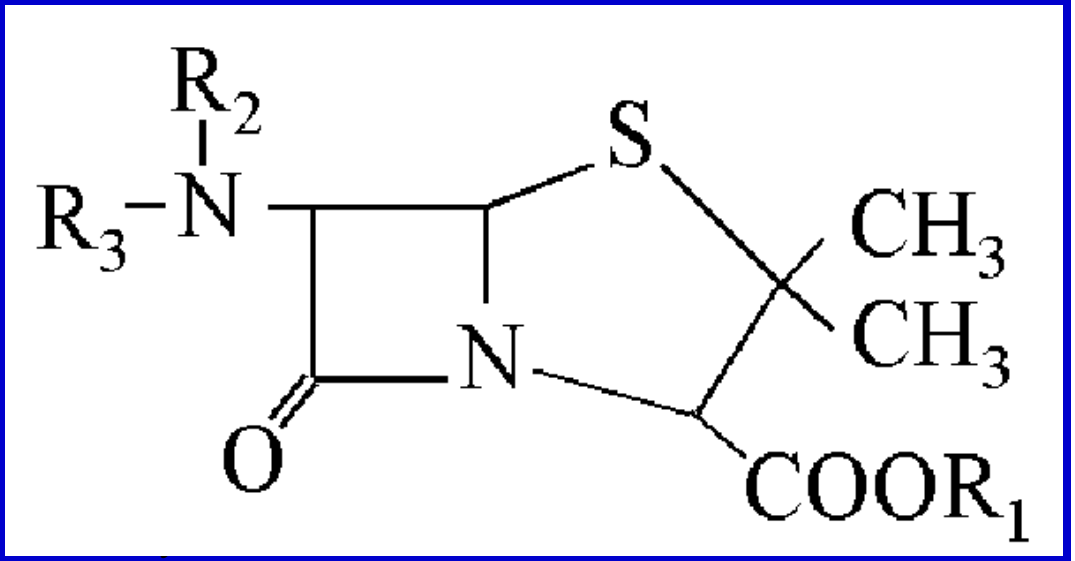
- Spherical
- Cylindrical
- helical



Gram positive

- Stain black-blue
- Staphylococci
- Streptococci
- Aerobic & anaerobic





Gram positive

AEROBIC

- Staphylococcus
  - Boils, carbuncles, abcesses
- Streptococcus
  - Scarlet fever, bacterial endocarditis, pneumonia

(Anaerobic Various)

Gram positive

AEROBIC

- **Bacilli**
  - Corynebacterium diphtheriae: Diphtheria, nerve and heart exotoxins
  - Listeria: meningo-encephalitis
  - Lactobacillus: in dairy, commensal in gut and vagina
  - Mycobacterium: leprosy, TB

Gram positive

ANEROBIC

- Clostridium: reproduction by spores, powerful exotoxins, food poisoning, gas gangrene, tetanus

- Actinomycosis

PROTOZOAL INFECTIONS

- **Amoebic dysentery**
- **Babesiosis**
- **Cryptosporidial diarrhoea**
- **Giardiasis**
- **Leishmaniasis**
- **Malaria**
- **Toxoplasmosis**
- **Trichomoniasis**
- **Trypanosomiasis**

Fungal infections

- **Actinomycosis**
- **Fungal infections of the nervous system**
- **Aspergillosis**
- **Candidiasis**
- **Cryptococcosis**
- **Dermatophyte infections**
- **Histoplasmosis**
- **Mycetoma**
- **Fungal nail disease**
- **Pityriasis versicolor**
- **Pneumocystis carinii pneumonia**

Fungal infections of the nervous system

- **Fungal infection** of the nervous system usually occurs in patients with impaired immunity.
- Classically the most common pathogens were candida and aspergillus; with the advent of AIDS, cryptococcal infection has become more frequent.
- Clinically there are two main presentations:
- meningitis, often subacute
- multifocal encephalitis
- One should look for fungal infection elsewhere, such as skin or lung.
- Diagnosis usually comes from analysis of cerebrospinal fluid or biopsy tissue

Aspergillosis

- **Aspergillosis** is a fungal condition, caused by aspergillus fumigatus.
- Illness occurs in cases of allergic reaction, immune suppression, or in previously damaged lung.
- Principally three clinical syndromes are seen:
- An aspergilloma
- Allergic bronchopulmonary aspergillosis
- Invasive aspergillosis
- Aspergillus species are also associated with causing:

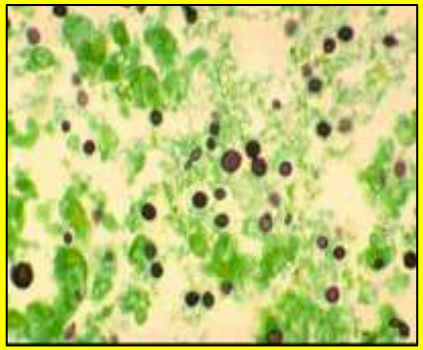
- Asthma
- Otomycosis
- Extrinsic allergic alveolitis
- Cerebral infarctions or brain abscesses, endocarditis, and problems in the ears and sinuses.
- Most disease is due to aspergillus fumigatus but there are many other members of the genus - e.G. A. Clavatus, A. Flavus, A. Niger - which may result in these conditions.

Candidiasis

- **Candidiasis** is usually caused by infection with the yeast Candida albicans.
- Candida albicans is a normal commensal in the gastrointestinal tract, mouth and vagina but not on the skin.
- Infection with yeasts is the most common identifiable cause of vaginitis and vaginal discharge. They are also a common cause of balanitis and balanoposthitis. Occasionally, and especially in women, candidiasis may cause onycholysis.

Cryptococcus

- Infection with **cryptococcus** neoformans is most common in the immunosuppressed:
- The elderly
- AIDS
- Patients receiving chemotherapy
- Hodgkin's disease
- It may result in meningitis, pulmonary, or gastrointestinal involvement.



DERMATOPHYTE INFECTIONS

- Tinea is a very common skin infection. It causes athlete's foot, nail infections, tinea corporis and scalp ringworm. Dermatophyte infections invade keratin only and do not penetrate living tissue. The resultant inflammation is due to delayed hypersensitivity or due to metabolic products produced by the fungus.
- There are three types of genera of dermatophyte infection:
- microsporum - skin and nail infections
- trichophyton - hair, skin, nail infections
- epidermophyton - skin and nail infections

HISTIOPLASMOSIS

- This disease is caused by Histoplasma capsulatum. This is a non-capsulated, dimorphic fungus. The spores of this fungus can survive in the soil for a number of years. The survival of the spores is enhanced is soil that is enriched by bat or bird droppings.
- Histoplasmosis has a world-wide distribution. However it is commonly seen in the USA especially in Ohio and the Mississippi river valley.
- The infection is acquired by inhalation of the spores.

MYCETOMA

- This is a lesion that occurs as a result of chronic fungal infection of the deep soft tissues and bones. Mycetomas may affect the head, limbs or trunk.
- The causative organisms are eumycetes or actinomycetes.
- Clinical features:
- It may present as a painless swelling at the site of impregnation. Other features such as sinuses, abscesses, scarring and deformity are produced.

Fungal nail infection

- may occur as a primary event or following other disease or damage to the nail. Fungal organisms affecting the nail may be divided into the following:
- dermatophytes (Tinea, 85-90% of fungal nail infections)
- yeasts (Candida often involved in chronic paronychia)
- moulds
- Treating these infections may be difficult but appropriate treatment is important as spontaneous resolution does not occur. There may also be co-existent bacterial infection which will influence management.

Pityriasis versicolor

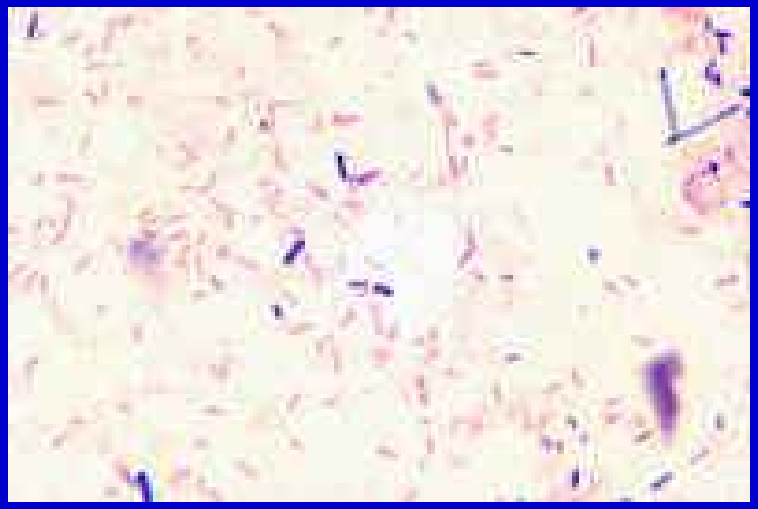
- **Pityriasis versicolor** is a skin infection which often presents as patches of relatively depigmented skin. The cause is overgrowth of the yeast Malassezzia furfur.
- If the skin is not tanned, the skin appears fawn with a slight brawny scaling and wrinkling. It is slightly itchy.
- It is usually a disease of young adults, predominantly affecting the upper trunk.
- Often, it is difficult to tell if treatment is successful until the patient acquires a tan in the following year.

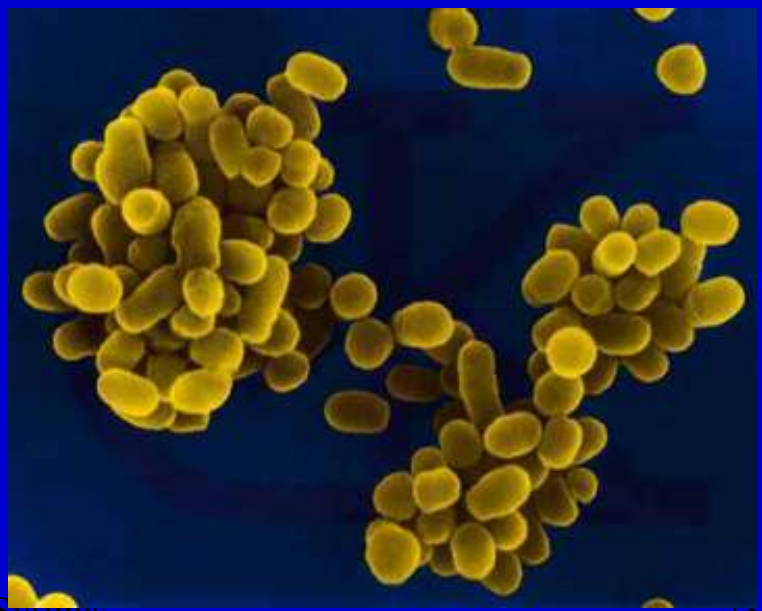
Pneumocystis carinii

- **Pneumocystis carinii** is an organism that appears as minute oval bodies or cysts 5-10 mu metres in length. It is now believed to be a fungus, although it may yet be classified as a protozoan. It is a common commensal in the human lung, but in infants of a few months of age, or adults who are immunosuppressed, it can cause a debilitating pneumonia.
- In Europe and North America, Pneumocystis carinii is the most common cause of pneumonia in patients who are antibody positive for HIV. It occurs when the CD4 positive count falls below 200 and up to 80% of all AIDS patients will suffer from P. carinii pneumonia at some stage. In Africa however P. carinii pneumonia is relatively unusual with tuberculosis being more common.
- Pneumocystis carinii pneumonia is an illness that satisfies the diagnostic criteria for AIDS.

GRAM NEGATIVE

- Stain pink with Gram's method
- Inc large number of bowel commensals (the coliforms)
- Many release endotoxins
- Cocci & bacilli
- Aerobes and anaerobes





Gram negative

Aerobes

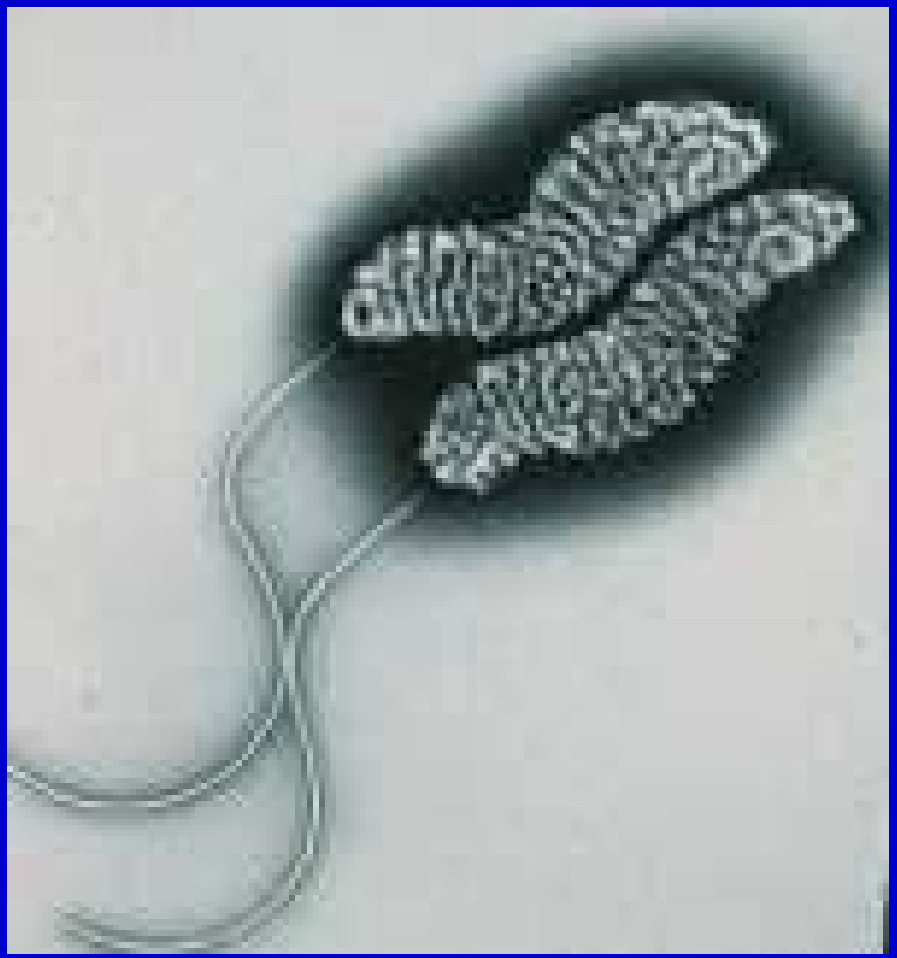
- Cocci
  - Neisseria (gonorrhoea, meningitis)
- Bacilli
  - Pseudomonas
  - Enterobacteria (Escherichia, Proteus, Klebsiella, Salmonella, Shingella
  - haemophylus
  - Brucella
  - Vibrio

Gram negative

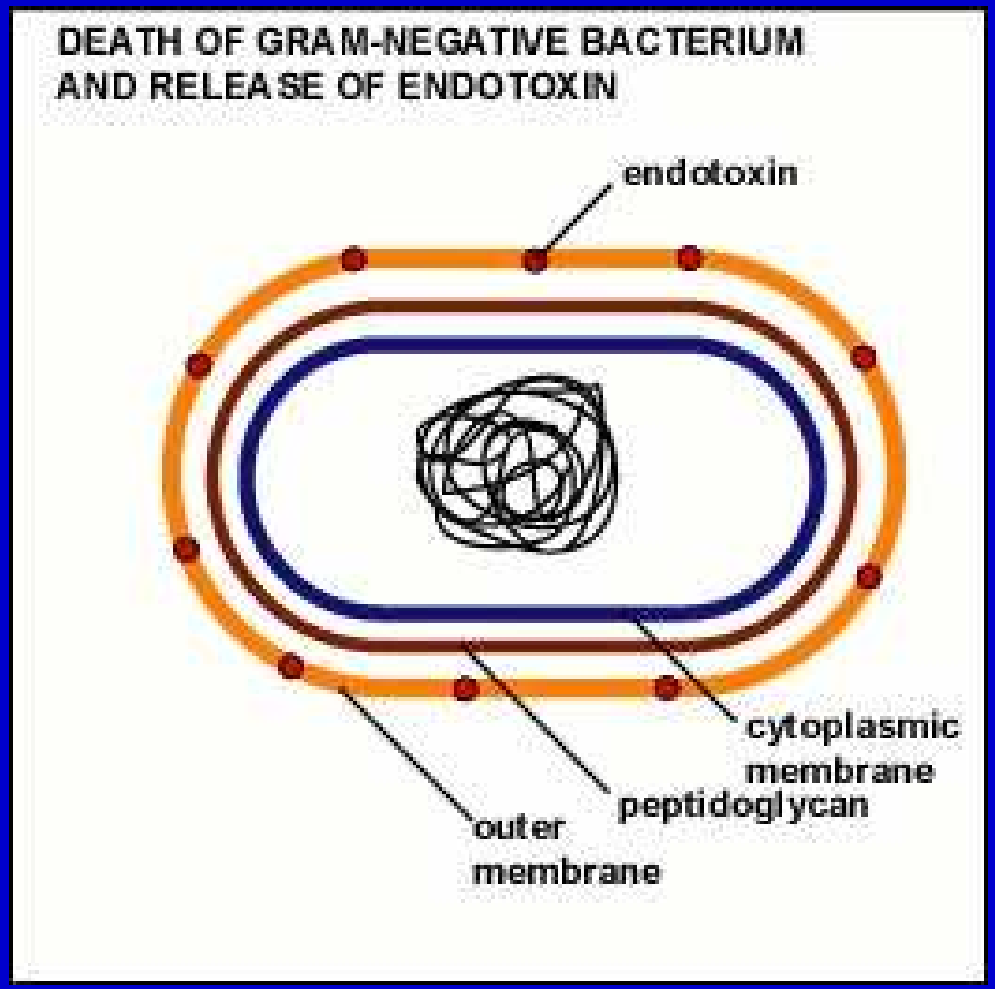
Anaerobes

- Campylobacter
- Bacteroides

Campylobacter
Pylori & Jejuni
(Enteric infections and ulceration of the gut)



Death of Gram-negative bacterium and release of endotoxin



Viruses

- Much smaller than bacteria
- Contain only one type of nucleic acid DNA or RNA
- No mitochondria
- No ribosomes
- No rigid cell wall
- “an infectious piece of nucleic acid surrounded by protective protein coat”
- Can only reproduce inside living cells
- Not susceptible to antibiotics
- “obligatory intracellular parasites”

Classification of viruses

- Pox – DNA – Smallpox
- Herpes – DNA – Herpes, E-Barr, Cytomegalovirus
- Papova – DNA – Warts
- Myxo – RNA - Influenza A+B
- Paramyxo – RNA – Para-inluenza, measles, mumps
- Picorna – RNA – Polio
- Rhabdo – RNA – Rabies

Chickenpox

- Mostly in children
- Droplet spread
- Serious in pregnant woman
- Inculpation 2 weeks
- Fever ➔ malaise ➔ sore throat ➔ macules ➔ papules ➔ vescicles ➔ crusting
- Complications: secondary bacterial infections, pneumonitis, encephalitis

German measles

- Incubation 18-21 days
- Droplet spread
- Fever, malaise, runny nose, sore throat
- Flat pink spotty rash on face and neck spreading inferiorly
- Lymphadenopathy esp. around neck
- Complications for the pregnant: defects of eyes, ears, heart

Mumps

Viral infectious disease causing systemic disturbances with inflammation of the salivary glands esp. the parotids

Cytomegalovirus

- A herpes virus
- May cause: Viremia, pneumonia, retinitis (cotton wool spots)
- Causes glandular fever: serious for immunosuppressed
- Spleen enlargement

Epstein-Barr Virus

- Herpes type virus
- Causes: infectious mononucleosis (glandular fever)
- Affects adults
- Spread by close contact
- Long incubation
- Tiredness
- Lymphadenopathy
- Spleen enlargement
- Complications

Herpes zoster

- Varicella-type virus of chickenpox
- Virus dormant in dorsal root ganglion
- Activated when immune system is run down
- Initially skin sensitivity then vesicular rush which crusts after 1 week
- Complications: corneal damage, post-herpetic neuralgia

HIV & AIDS

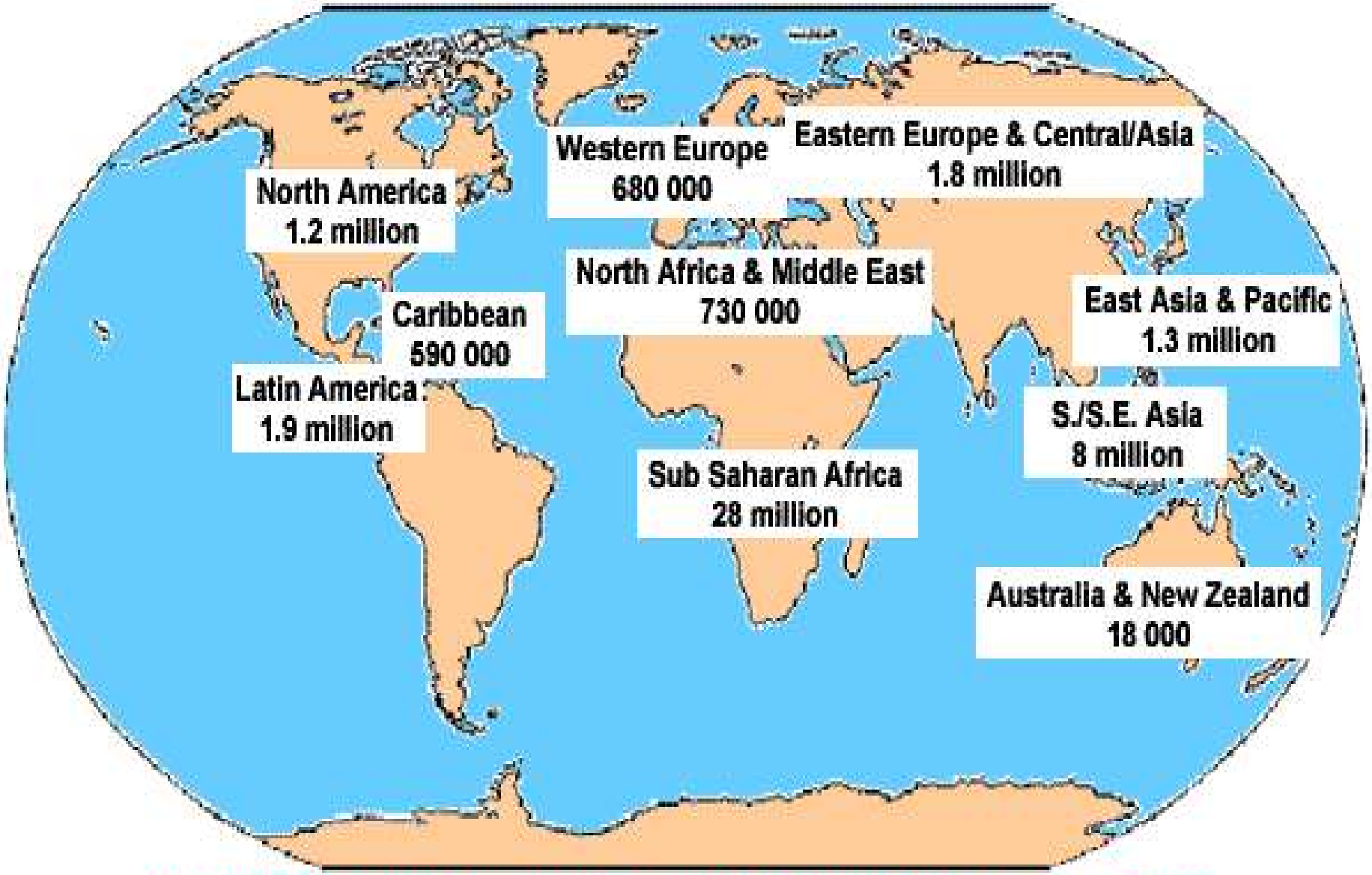
- **Different subtypes of HIV**
- **Epidemiology**
- **Genetics of HIV**
- **Structure of HIV**
- **Natural history of HIV infection**
- **Laboratory tests for HIV infection**
- **Treatment of HIV/AIDS**
- **AIDS**

What is HIV?

- The human immunodeficiency virus (HIV) is the cause of the acquired immune deficiency syndrome (AIDS).
- HIV replicates rapidly in CD4 positive cells throughout all stages of the infection. Initially replacement of CD4 cells matches the rate of destruction, but in AIDS the gap between destruction and replacement widens and immunological failure occurs. Many of the characteristic consequences of AIDS are due to immunological failure.
- HIV is a member of the lentivirus family of retroviruses. Along with other members of this family, such as the simian immunodeficiency virus, HIV causes a slowly progressive but fatal disease.

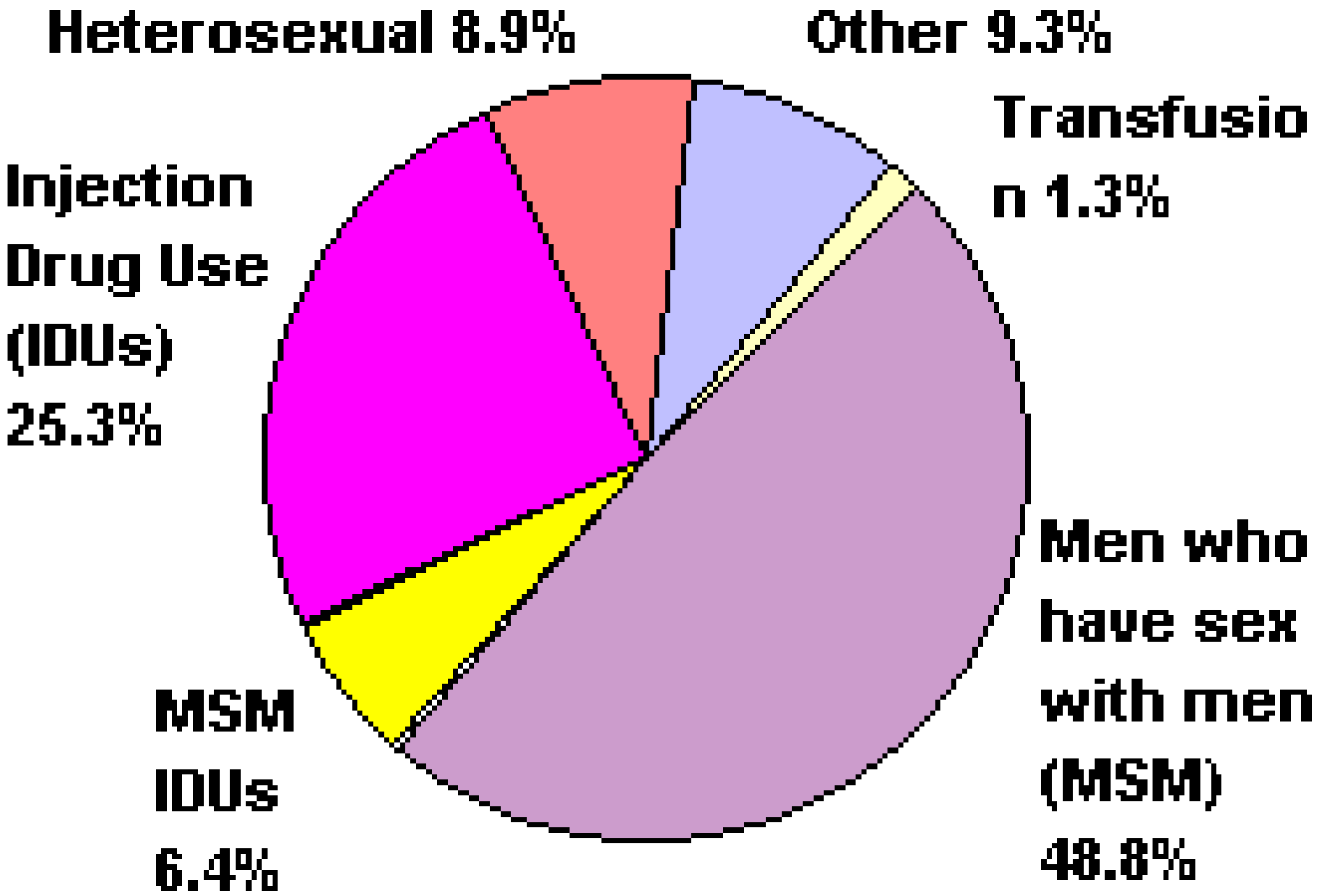
Different subtypes of HIV

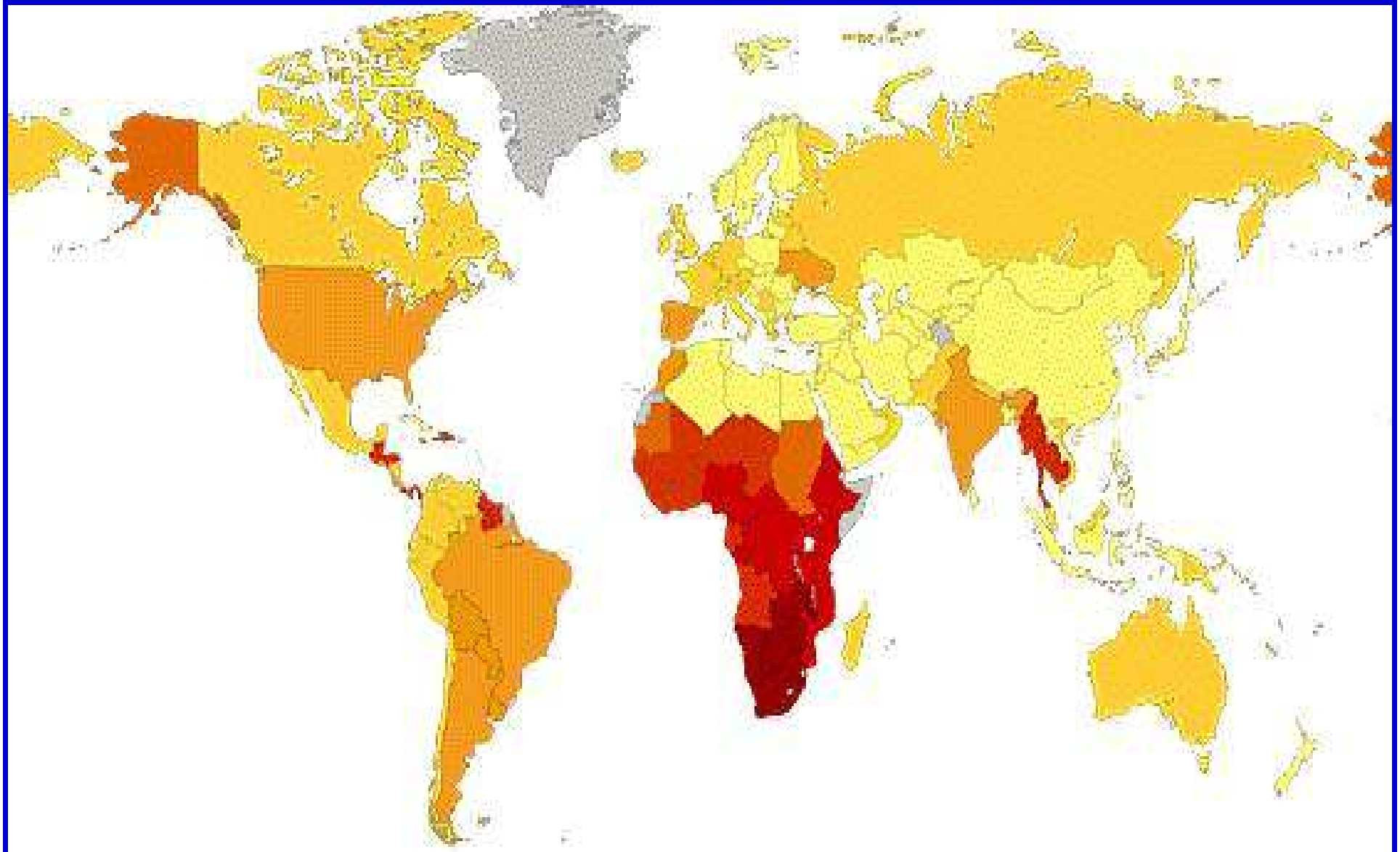
- The causative agent of AIDS was originally identified as HTLV-3 in 1983. This is now termed HIV-1 and is the predominant serotype worldwide.
- In 1985 a second serotype, known as HIV-2, was identified. It is more closely related to the Simian Immunodeficiency Virus (SIV) of macaques. HIV-2 has been found in East Africa, Asia, Southern Europe, Latin America and North America, but it is most extensive in Western African countries.
- Compared with HIV-1, HIV-2 is characterised by lower rates of sexual and perinatal transmission, decreased CD4 cell killing, slower progression to AIDS and death, and relative geographical confinement.



Total population living with HIV/AIDS (end 2003): 46 million

AIDS Cases by Transmission Category, United States, 1980-Present





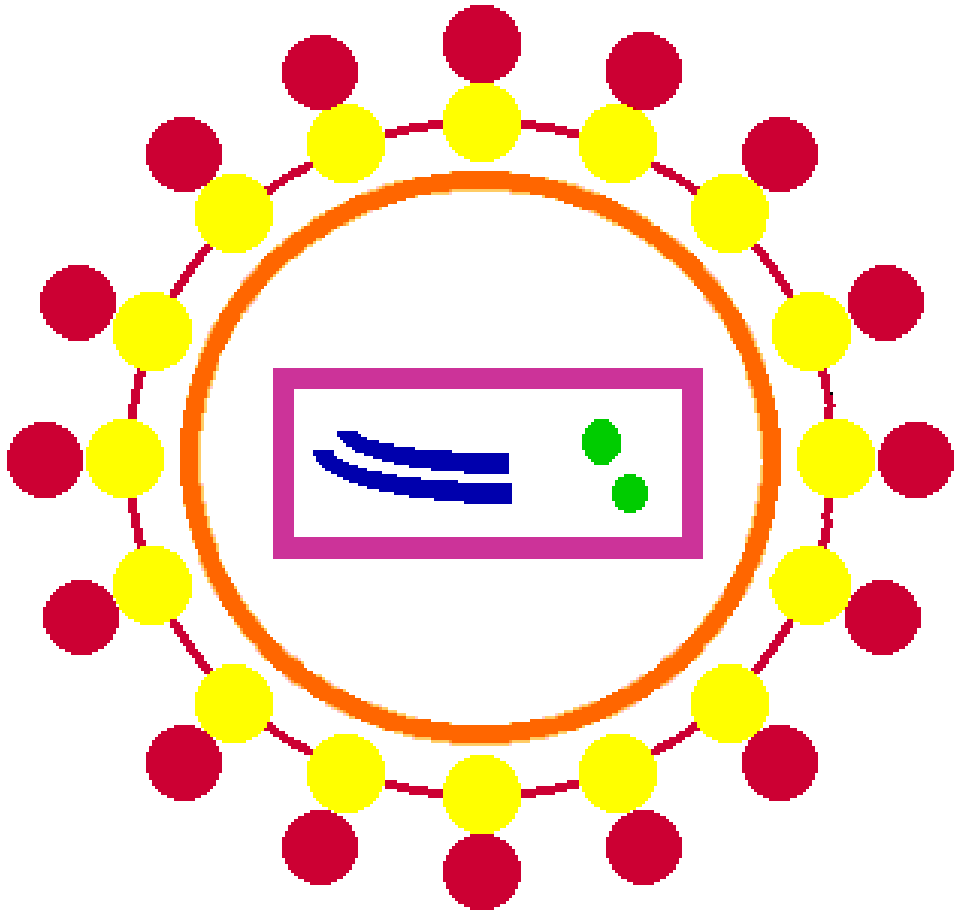
Genetics of HIV

- There are three genes in HIV which are characteristic of all retroviruses:
- gag:
  - encodes a precursor protein (Pr55)
  - cleavage yields:
    - p17 matrix protein
    - p24 capsid protein
    - p9 nucleocapsid protein
    - p6
- pol encodes reverse transcriptase, endonuclease and protease activities
- env:
  - encodes a precursor protein p160
  - cleavage yields:
    - p41 a transmembrane protein which anchors p120
    - p120 binds non-covalently to p41 and acts as the CD4 receptor
- In addition to these typical genes there are other regulatory genes.

Structure of HIV

- HIV has an envelope composed of membrane derived from the host cell and two virus-encoded proteins gp41 & gp120:
- Gp41:
  - Is the transmembrane envelope glycoprotein
  - Binds gp120 and p17
- Gp120:
  - Binds non-covalently to gp41
  - Is the receptor for CD4, being involved in entry of HIV into susceptible cells
- P17 matrix protein lines the inner surface of the viral membrane and anchors the overlying p41.
- P24 capsid protein forms part of the rna-containing core of hiv. P9 coats the diploid RNA genome. The capsid contains enzymatic proteins including reverse transcriptase and integrase.

Structure of HIV



gp120

gp41

membrane

p17 matrix

p24 capsid

enzymes

diploid RNA genome coated with p9

Progression of HIV infection

- The natural history of HIV infection may be characterised by:
- Stage 1:
- Infection and seroconversion
- Stage 2:
  - Asymptomatic stage
- Stage 3:
  - Increased susceptibility to pathogenic organisms:
  - CD4 count 200-350x10^6 per litre
- Stage 4:
  - Appearance of opportunistic infections and tumours
  - CD4 count <200x10^6 per litre
- Stage 5:
  - Multiple opportunistic infections with relapses
  - CD4 count <50x10^6 per litre

Laboratory tests for HIV

These include:

- HIV culture - in stimulated lymphocytes
- HIV antigen - p24 antigen test
- HIV nucleic acid - using the polymerase chain reaction
- HIV antibody - ELISA or Western blot

HIV antibody tests are used for diagnosis and screening

‘Treatment’ of HIV

- **Antiretroviral chemotherapy in HIV infection**
- **Prophylactic chemotherapy against PCP**
- **Prevention of TB in hiv-infected persons**
- **Immunization of hiv-infected individuals**

CDC 1993 definition of AIDS

- As from january 1993, the definition of AIDS will expand the 1987 definition to include all HIV positive individuals with CD4 T lymphocyte counts of less than 200 per microlitre, irrespective of clinical manifestation. Three new indicator diseases have also been added:
  - Pulmonary tuberculosis
  - Invasive cervical carcinoma
  - Recurrent bacterial pneumonia

Streptococci bacteria

- β-haemolytic streptococci (group A,B,C & G)
  - Sore throat, skin infections
  - Cause post infectove complications: glomerulonephritis, rheumatic fever, erythema nodosum
  - Throat infection ➔ systemic ➔ scarlet fever
- α -haemolytic streptococci
  - Bacterial endocarditis, dental caries
- Faecal streptococci: pneumonia, meningitis

Cholera

- Severe epidemic diarrhoeal disease caused by the toxin of Vibrio cholerae
- Faecal oral spread
- Incubation 5 days
- Vomiting
- Watery mucus diarrhoea
- Shock and renal failure

Dysentery

Collective name for a group of conditions characterised by bloody diarrhoea

Amoebic

- Entamoeba histolytica
- Occurs in tropics
- Faecal-oral spread
- Fever, colic, bloody diarrhoea, prolonged
- Comp: Amoebic hepatitis, liver abscess
- Metronidazole

Bacillary

- Shigella group
- Worldwide problem
- Also airborne spread
- Prolonged faecal infection
- Usually resolves within one week
- Comp: Arthritis, haemolysis, renal failure

Typhoid

Intestinal infection caused by the organism Salmonella typhi

- Large group of organisms
- Contaminated meat & poultry
- Water ➔ sewage ➔ food
- Asymptomatic carriers possible
- Incubation 2 weeks
- Infected food ➔ multiplication in gut ➔ mesenteric lymph nodes ➔ bloodstream ➔ re-infection via liver

Complications: Coma, GI bleed, cholecystitis, myocarditis, pyelonephritis, pneumonia, DVT, death

Pyrexia of unknown origin (PUO)

Causes can be considered in terms of:

- infective causes
- malignant causes
- connective tissue disease
- drugs - virtually any drug
- endocrine causes
- inherited causes
- others

Consider notifiable diseases!!!

Diagnosing the tropical traveller

- Malaria
  - Fever, malaise, anorexia, vomiting, sweating
- Typhoid
  - Fever, tachycardia, abdo pains, cough, rose spots
- Amoebic liver abscess
- Jaundice
  - Hepatitis, malaria, yellow fever

- Hepatosplenomegaly
  - Malaria, schistosomiasis, typhoid, brucellosis, kala-azar
- Diarrhoea & Vomiting
  - Salmonella, shigella, campylobacter, cholera, giardia, E histolitica
- Erythema nodosum
  - TB, leprosy, fungi, sarcoid, streptococcal

Worms

Endemic helminthic diseases in the UK:

- **Threadworm**
- **Whipworm**
- **Toxocara canis**
- **Dwarf tapeworm**
- **Echinococcosis**
- **Roundworms**
- **Tapeworms**
- **Flukes**

Roundworms

- Roundworms are relatively uncommon in the UK; however, they represent a major problem in many areas in the world.
- Classification:
- gut-dwelling nematodes of humans:
  - confined to the gut:
    - enterobiasis - threadworms
    - trichuriasis - whipworm
  - with tissue migration:
  - hookworms - Ancylcostoma duodenale; Necator americanus
    - ascariasis
    - strongyloides
- gut-dwelling nematodes of animals with tissue spread in humans - toxocariosis
- tissue nematodes - worms of human origin dwelling in human tissues - filiarial worms

Roundworms

Enterobiasis (Threadworm)

- Infestation with Enterobius vermicularis is the most common helminthic infection seen in the UK. The adult worms reside in the caecum with the female migrating to the anus when ready to lay eggs; this usually occurs at night when they cause pruritus ani. The eggs are transmitted by the faeco-oral route.

Flukes

- Flukes can be subdivided on the basis of the part of the body they colonise:
- Liver:
  - Fasciola
  - Clonorchiasis
- Blood vessels:
  - Schistosoma

Schistosomiasis

- Infection with a fluke worm
- Affects 200 million people in 75 countries
- Acute and chronic symptoms
- May lead to complications if untreated

Meningitis

- Mon-infectious meningitis
- Aseptic meningitis (viral)
- Bacterial meningitis

Non-infectious meningitis

- Meningeal inflammation may result from a variety of infectious aetiologies, but also importantly from non- infectious aetiologies ones such as:

- Carcinomatous leptomeningitis
- Chemical meningitis

Aseptic meningitis

- Aseptic meningitis is a term used to refer to conditions where there are features of meningeal inflammation, but no bacterial growth from cerebrospinal fluid.
- The term covers a variety of aetiologies, some of which are certainly infectious, and it is for this reason that the description is less frequently used these days.

Viral meningitis

- Viral meningitis may be caused by a variety of different agents:
- enteroviruses - frequently late summer or autumn
- mumps - most common perennial cause

Rarer causes include:

- herpes simplex virus
- adenoviruses
- varicella zoster virus
- measles
- HIV
- coxsackie
- Epstein Barr

Infective meningitis

Infective organisms in meningitis classified by patient age

The likely meningitic causative-organism varies with age. Listed in order of likelihood in the UK:

- Neonates - ie less than one month:
  - E.Coli (K1)
  - Group B beta-haemolytic
  - Streptococci
  - Listeria monocytogenes
  - Staphylococcus aureus
  - Pneumococcus
- Children from one month to 15 years:
  - Haemophilus influenzae B
  - Meningococcus
  - Pneumococcus
- Adults over 15 years:
  - Pneumococcus
  - Meningococcus
- Elderly adults:
  - Staphylococcus aureus
  - Gram negative organisms

Clinical features of meningitis

- The clinical features of meningitis include:
- rapid development - faster than two days - of fever and reduced alertness with lethargy
- meningism
- nausea and vomiting
- delirium purpuric rash, especially in meningococcal meningitis
- seizures
- tachycardia
- uncommonly, meningitis may cause unequal pupils
- There may rarely be focal neurological signs such as gait disturbances.

Clinical Lectures

End of lecture