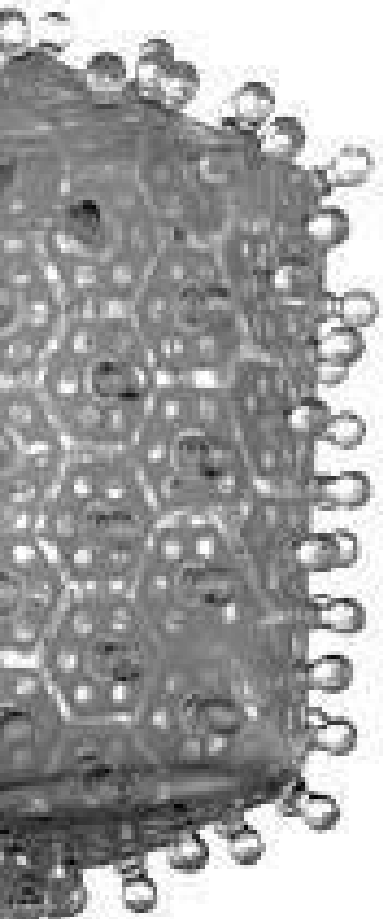


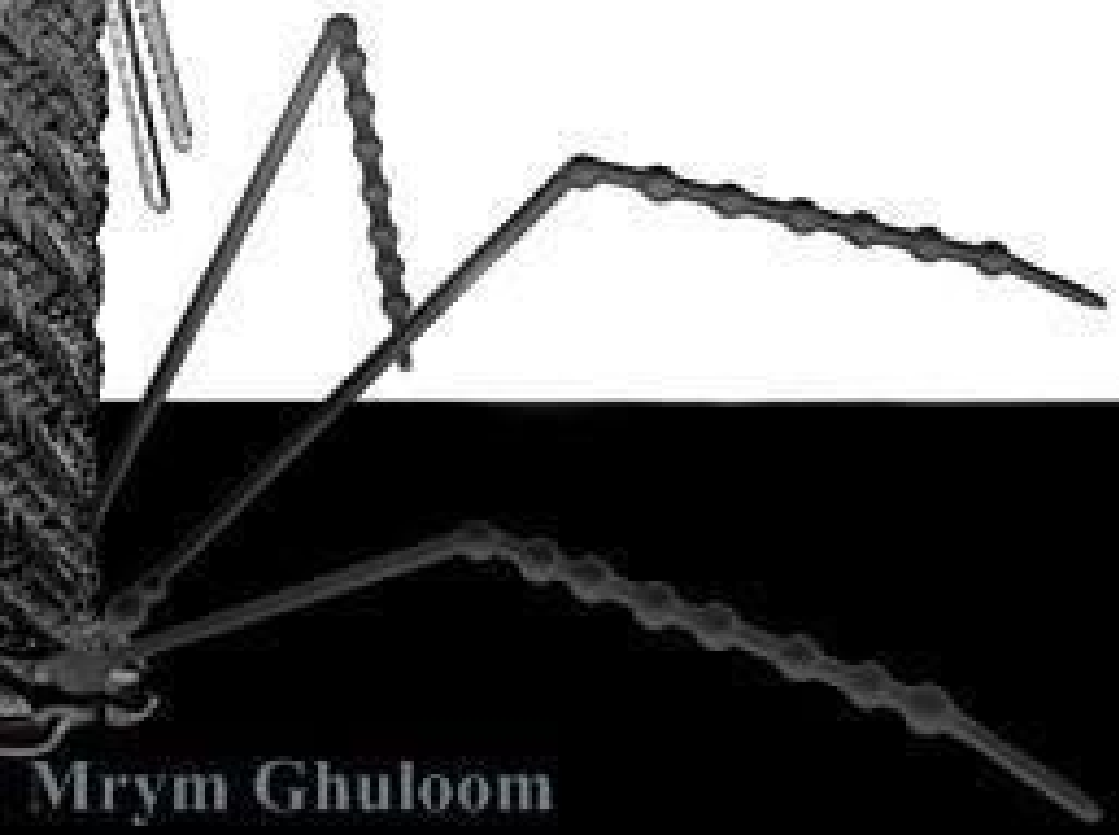
Microbiology

Lecture No: 15 (5-viro)

Dr Name: Dr. Hamed alZoubi

Done by: Alia Khamis

Sheet ■ Slide □



Mrym Ghuloom

Pathogenesis of Viral Infections

I. Introduction

Pathogenesis: The mechanism of causing the disease.

Look at the picture below, notice how each manifestation (disease) is caused by a *different virus*. Therefore, the mechanism that causes each manifestation is different (*different pathogenesis of each manifestation*).

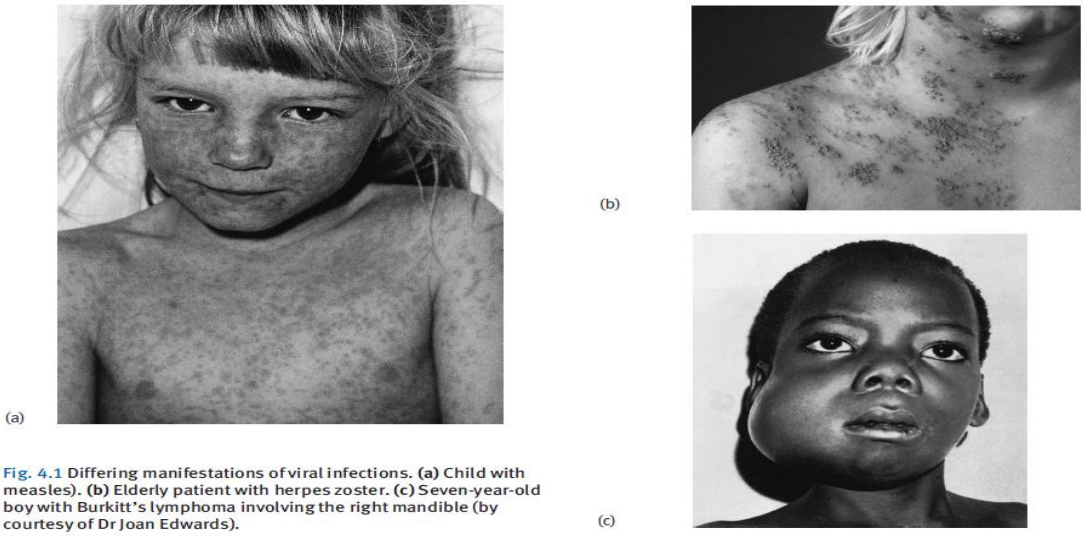


Fig. 4.1 Differing manifestations of viral infections. **(a)** Child with measles). **(b)** Elderly patient with herpes zoster. **(c)** Seven-year-old boy with Burkitt's lymphoma involving the right mandible (by courtesy of Dr Joan Edwards).

on the left side this is a viral disease caused by measles; we don't see it too much these days; it started to extinct in the countries the provides the vaccines against it; however, from time to time we in Jordan have cluster of cases because we have some people who have migrated from harsh areas where they don't find something to eat and are not vaccinated.

Pathogenicity & Virulence

These two terms are often used incorrectly and interchangeably.

Both compare the severity of the disease, but they are not the same.

So what's the difference between them?

Pathogenicity: compares disease severity *between 2 different micro-organisms* (like viruses).

E.g.: Rabies is more pathogenic than Measles/Influenza is more pathogenic than Rhinovirus.

Virulence: compares severity between *2 strains of the same micro-organism.*

Reminder: a "strain" is a sub-type of the same micro-organism.

Here is an illustrative example:

Imagine you have a family of viruses, Herpes Simplex Virus (HSV) for instance.

This family has 2 members (strains): Type A and Type B. Both of them cause the same manifestation: skin lesions or vesicles.

In Type A, only 10 virus particles are needed to kill a small animal (rabbit/mouse).

In Type B, 10,000 virus particles are needed to kill a small animal.

Conclusion: Type A is 1,000x more virulent than Type B.

<u>This due to the nucleotide differences in the DNA or RNA (mutations/substitutions).</u>

E.g.:

A) **Polio Virus Type 3** has a *virulent strain (causes muscle atrophy)* as well as an *avirulent strain* which stimulates the immune system, but doesn't cause the disease *(used in vaccines).*

These 2 strains differ in 10 bases out of a total of 7430 bases. One of these ten bases different bases is responsible for changing a codon which forms a new amino acid leading to an avirulent (attenuated) strain so we can use such strain in the seek of vaccination.

B) **Avian Influenza B** infects birds, but doesn't infect humans due to a barrier that cannot be crossed. Nevertheless, amutation can occur in 1 base near the

receptor binding site in the hemagglutinin of the virus (this mutation near the binding site changes the conformation for the protein responsible for binding of the receptor to the cell); this mutation enables it to cross the barrier, infect a human, and is then considered more virulent (may lead to pandemics).

* Heamgglutinin is a glycoprotein found on the surface of the influenza viruses.

Steps in Pathogenesis

1) **Invasion:** invasion of the host and attachment to the receptors**.**
2) **Replication:** replication locally at the site of infection/port of entry (primary site).
3) **Escape from the immune system**
4) **Spreading (usually from the primary site) to a target organ** (e.g.: Hepatitis B spreads to the liver).
5) **Exit from the host and start the infectious cycle again to ensure survival**

Incubation Period

The time from the moment of exposure to an infectious agent until signs and symptoms of the disease appear.

Short: a matter of hours or days, less than a week (RESP, ARBOVIRUSES, Common Cold).

* In respiratory tract infections the incubation period is usually short.

Medium: 1-3 weeks (MMR: **"**Mumps, Measles, and Rubella**"**; Polio, SARS)

Long: weeks-months (HEPATITIS~6 months, RABIES).

* Rabies may take from weeks to months depending on the inoculation site (site where it was introduced/site of the rabid dog bite). If the bite was on the leg, the incubation period would be longer than if the bite was in the face because rabies affects the brain (nervous system).

Very long: years (SSPE,PRIONS, PML)

* SSPE (Subacute sclerosing panencephalitis) is a long term manifestation of Measles and the incubation period make take as long as 20 years.

*Prions are responsible for Creutzfeldt-Jakob disease and Mad Cow Disease.

*****PML (Progressive Multifocal Leukoencephalopathy) is a manifestation of Polio.

** Infectivity period: the period in which the person can infect other humans; it starts after the entry of the virus and continues until the appearance of symptoms and could continue after the end of them so it could be longer than the incubation period and it differs between viruses.

Reproduction number (Ro)

The average number of secondary cases generated by one primary case. This measures how infectious the virus is.

i.e.: How many people can get infected from an "infected person" in a susceptible community (Epidemiological calculations).

- R_0 **smallpox = 2** *(one person can infect 2 other people)*
- R_0 **Influenza = 6-8** *(one person can infect 6-8 other people)*
- R_0 **measles = 10** *(one person can infect 10 other people)*
- $R_0 < 1$ *(the case "passed away"/"died" before it could be transmitted to another person)*

<u>The incubation period should also be taken in consideration.</u>

II. Interaction Between Viruses and Host Cells

It determines the infection site, type, and outcome.

1) **Cellular factors**

- Presence of receptor: it is necessary for an interaction between the virus and the cell to occur. (Attachment/Adsorbtion); we have different receptors naturally present on the cells to get some nutrients and some molecules so the virus might use these receptors.
- Proper environment: some respiratory viruses (e.g.: Rhinovirus) replicate at a temperature of 33°C in the nose (upper respiratory tract infection) and some at alveoli 37 °C (lower respiratory tract infection).

2) **Cytopathogenic Effects (CPEs)**

The effect on the cell itself (kill/lyse, fuse, uncontrolled growth, inclusion bodies). Some viruses won't kill cells, instead they utilize them until the last moment. Other viruses can transform in cells and make them malignant/tumorogenic.

A) Cell Lysis

- In the early stage of the viral life cycle, viral early proteins will stop the cellular expression (synthesis) of the cellular macromolecules (macroproteins) to utilize mechanism of the cell to its own self and enable viral proteins synthesis.
- Accumulation of viral capsid proteins (e.g.: Adenovirus) will lead to stopping of viral and cellular proteins and the cell will be full – burst and die and the virus will be released (those viruses are called bursters).

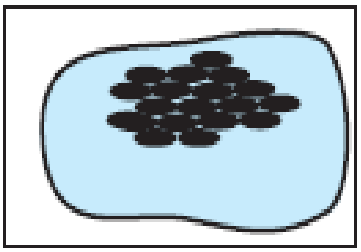
B) Cell Fusion

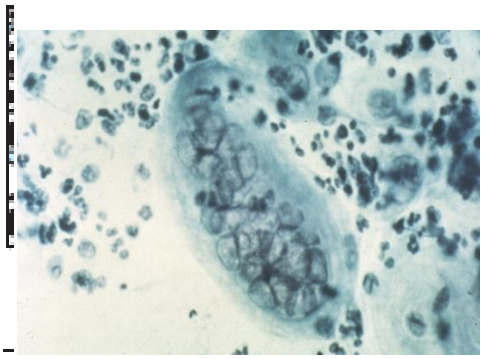
Some viruses carry "fusion proteins" like the enveloped viruses which fuse with the cell membrane and are involved in endocytosis.

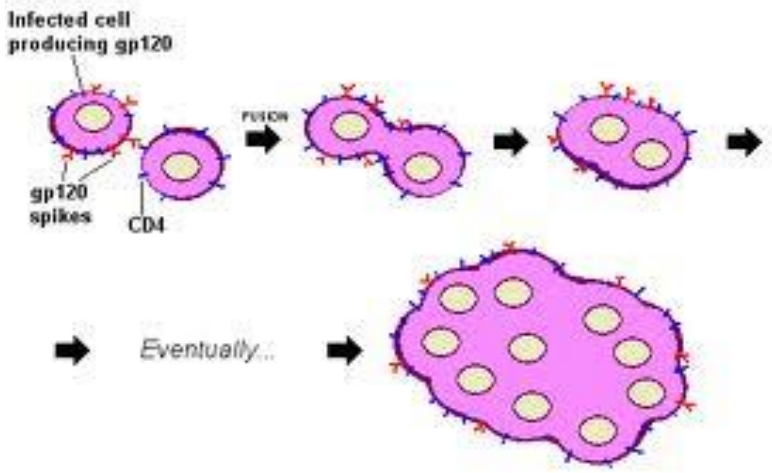
Viral fusion proteins will facilitate entry into the cell. The virus leaves its membrane on the cell membrane. The viral envelope that has been left behind has fusion proteins which act as magnets and "pull" the cells together resulting in cellular fusion and the formation of **multinucleated giant cells** (**syncytia**).

E.g.: Paramyxoviruses (measles, respiratory syncytial virus, parainfluenza), herpesviruses (responsible for cold sores الحمو or genital warts) and some retroviruses (like: HIV).

Such viruses are described as creepers because they can spread from cell to cell without bursting the cell.







C) Inclusion bodies

Aggregates of the viruses (papovaviruses: papilloma and polyoma viruses)

or altered staining of the viral synthesis sites in the cell (basophilic, eosinophilic).

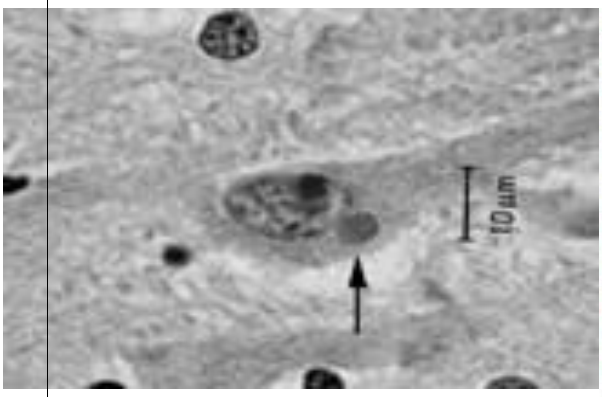
Site: intranuclear, intracytoplasmic or both.

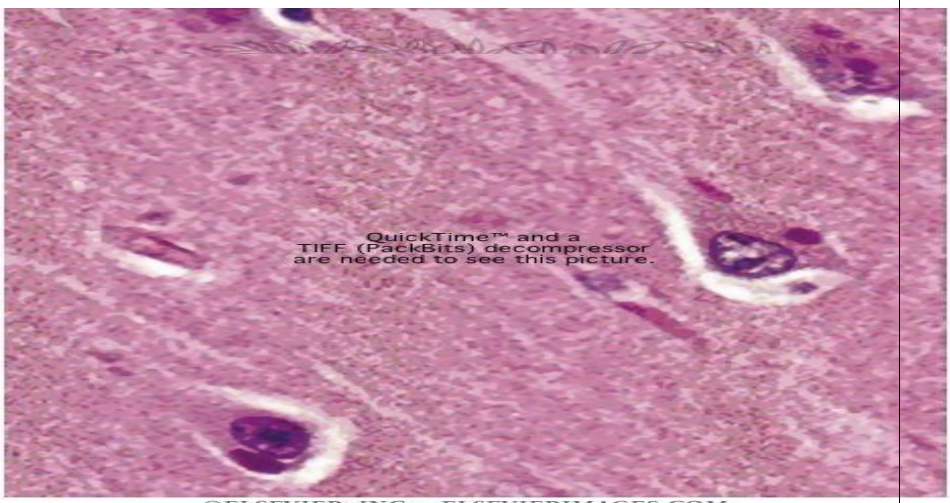
Detection: by staining or molecular methods.

Inclusion bodies might help in diagnosis.

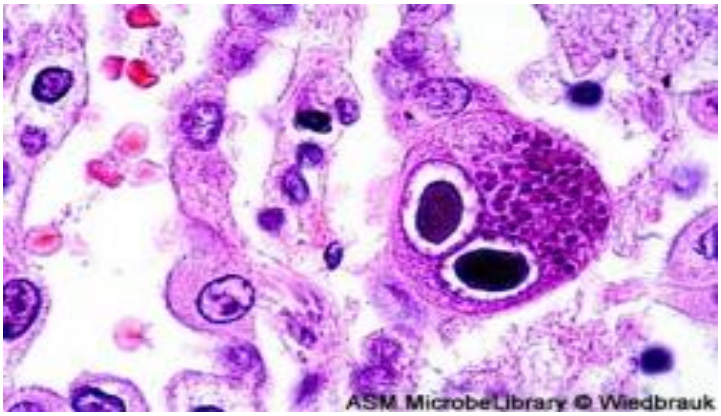
Examples (diagnosis):

Intracytoplasmic Eosinophilic: **Negri bodies→Rabies**





Intranuclear Basophilic: **Owl Eyes→ Cytomegalovirus**



D) New Cell Surface Antigens

- Enveloped viruses will leave antigens on cellular surface.
- This stimulates attack by cytotoxic T-cells.
- Detection by IF staining.

E) Malignant Changes

Oncoviruses

we will talk about malignancy and viruses in a separate lecture; it is a big area of interest nowadays.

III. Spread & Shedding:

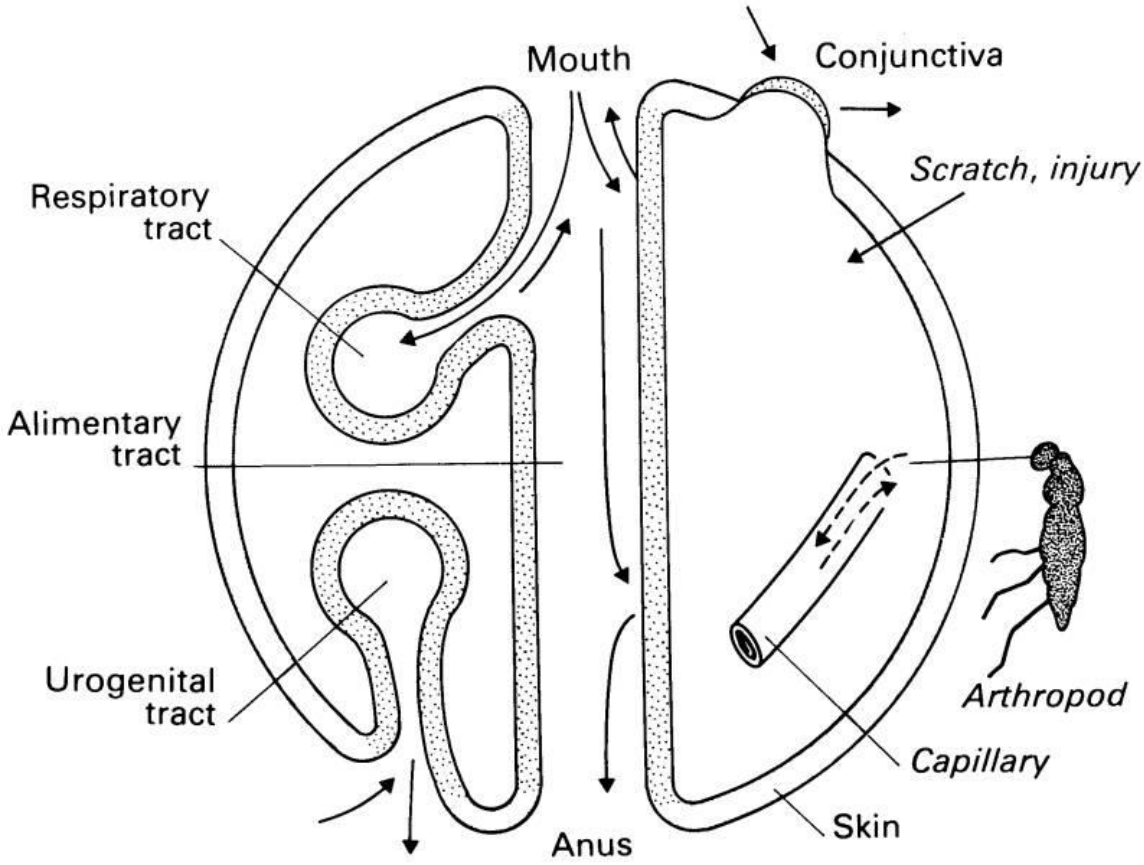
The virus needs to continue his lifecycle and survive to be able to infect other host so it needs to shed from the body to spread the infection to other host.

SPREAD

Any part of the body can be a portal of entry for the virus.

*Some viruses are carried by Arthropods like mosquitoes (arboviruses), which can inject them into the blood stream.

Arbovirus is a term used to refer to a group of viruses that are transmitted by arthropod vectors. The word arbovirus is an acronym (ARthropod-BOrne virus).



Skin

-There must be at least some kind of minor *trauma* in order for the virus to enter through the skin because the stratified squamous cells of the skin are usually protected.

-The effect is usually localized like in the formation of warts (skin lesions) e.g.: poxvirus, herpesvirus, papillomaviruses

-Generalized effect that *might affect body systems* (migrate from the skin to another part of the body). e.g.: Hepatitis B via skin abrasions, it might enter the body from a needle prick containing a very small blood drop that may reach microns then it migrates from the skin through the blood to the liver.

Mucous Membranes

Respiratory mucosa might be affected, but the *effect is on another site* e.g.: the skin

Enterovirus: via GIT but *affect CNS and muscles*

Respiratory route

Small (usually invisible) droplets disseminate and penetrate the respiratory tract better than large ones. Also small droplets "hang" in the air for a longer time.

Crowdedness and humidity also help.

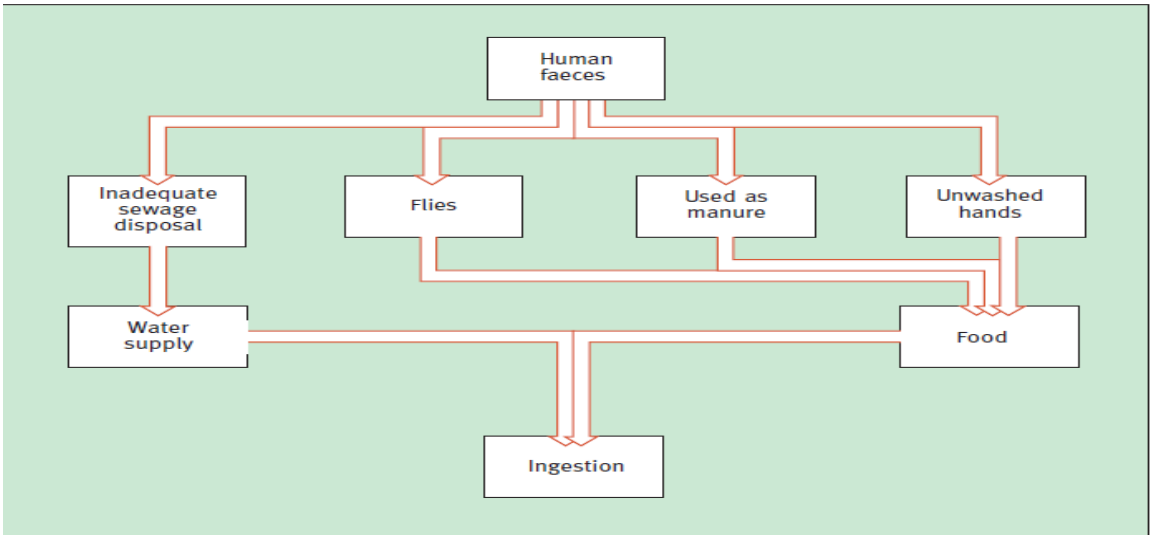
The best practice is to use a handkerchief when you sneeze or cough and to wash your hands when you touch something.

Gastrointestinal tract

- Fecal oral (contamination doesn't have to be "direct")
- Usually resistant to acidity (e.g.: stomach acid); if the virus is not resistant then it will not be able to initiate the infection.

Fecal material may be transported by flies, contaminated food and water due to improper disposal of sewage, unwashed hands,…etc. (So it is not necessary to be direct; it can be indirect).

It is not something strict to the developing countries; it can be found in the developed countries and the developing countries). The level of hygiene is important.



Sexually transmitted diseases:

- AIDS, Hepatitis.
- Multiple partners, homosexuality and even some infections may be transmitted among heterosexual people; they can facilitate the transmission of sexually transmitted diseases like AIDS and Hepatitis.

Organ transplants: One of the rare and disastrous routes of infection; it is disastrous because when you transplant an organ usually it is precious.

- CMV (This virus might infect the kidney) and EBV (Epstein–Barr virus) asymptomatic in donor.
- Disastrous in immunocompromised recipient (due to the administration of immunosuppressants to avoid rejection of the organ). So the asympotmatic infection in the donor might become symptomatic in the recipient and might lead to rejection of the new organ.

This can be avoided by screening and administration of antivirals.

Surgical:

Creutzfeldt-Jakob Disease and Rabies : contaminated instruments and corneal transplants.

Instead of discarding the instruments after 44:44 surgery, he sterilized or disinfect it not knowing that this person was having Creutzfeldt-Jakob disease, this disinfection or sterilization will not kill the resistant prions so when these instruments are used on another patient, he will be infected.

Mother to fetus: well known route of transmission

Specialized form of transmission (Congenital)

can be vertical or horizontal

SHEDDING

From the primary site or from the target organ

Asymptomatics or carriers may shed and infect others and if the infected person is immunocompromised he will shed the virus for longer period than the immunocompetent.

e.g.:

Herpes Simplex Virus (HSV)→ Saliva

Cytomegalovirus (CMV) → Urine and Milk

** Correction Note: Read only

A person who has an immunodeficiency of any kind is said to be **immunocompromised**.

Immunosuppression involves an act that reduces the activation or efficacy of the immune system.

Immunocompetence is the ability of the body to produce a normal immune response following exposure to an antigen. **Immunocompetence** is the opposite of **immunodeficiency** or **immuno-incompetent** or **immuno-compromised.**