بسم الله الرحمن الرحيم

MICROBIOLOGY

MID – Lecture 3
Viral replication and pathogenesis (Pt.1)

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

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Click on me if you want to make sure that you studied the last lecture perfectly!

بسم الله بدأنا وعلى الله توكلنا :)

Steps in Viral Pathogenesis

As mentioned before, even though there are general characteristics of viruses, their clinical consequences and effect on the host are different.

1. Viral entry & primary replication

Initial entry point of the virus and its site of replication. Each entry point has its unique subsequent effects that differ from other entry points.

2. Viral spread & cell tropism

The 1st step of viral replication is attachment. This attachment could be :

1) Specific, receptor-mediated, and affects certain cells only.
2) Wide-spread and affects a larger number of cells.

This variety manifests into different pathogenic effects and clinical consequences.
Tropism determines the pattern of systemic illness produced during a viral infection.

3. Cellular injury & clinical illnesses

The viral replication cycle usually takes place inside the cell, and this can affect the cell in various ways. Some viruses have mild effects, using up about ~10% of the cell's metabolic activity, which allows the cell to continue functioning. Other viruses completely shut down the cell's function and drain its resources, causing a more significant impact. A different group of viruses may cause complete cell lysis and damage to the cell, leading to a variety of consequences such as tissue damage and immune system activation. In other words: **the amount and magnitude of cellular injury affects viral pathogenesis and clinical illnesses.**

Continued... :)

Steps in Viral Pathogenesis

4. Recover from infection

After the viral infection of a cell, the virus goes to another. During this transition, if the body could attack the virus, it marks the recovery process. This process entails repairing infected cells to their original (pre-infection) states. If this recovery does occur, then the clinical consequences of the virus will be inhibited and reversed. If not, then onto the 5th step.

5. Viral clearance or persistence

Some viruses possess the ability to persist cellular invasion, replication, and damage for a longer period. This could, over time, transform into chronic diseases in some cases.

6. Viral shedding

Following the viral infection, the virus will shed from the host cell through various mechanisms. Shedding is essential for the virus to spread and infect other cells (sometimes other individuals or environments). It also impacts the host cell during the final stages of pathogenesis.

Viral Entry

Viral infections can enter the human body through many portals:

- Skin - through cuts or abrasions, animal bites e.g. Rabies virus

The skin is a tough mechanical barrier that prevents the entry of microorganisms. However, viruses can exploit wounds in the skin (such as cuts, bites, or grazes). In the case of a bite from a rabies-infected animal, rabies can enter the human body through this route. Consequently, pathogenesis and cellular damage resulting from this virus begin at the site of entry: the bite. Early pathological effects include a localized infection at the site of the bite.

- Respiratory tract e.g. Influenza, Parainfluenza virus

This is a common pathway of viral entry. It can occur through respiratory droplets or direct contact with polluted air. The virus, therefore, enters the respiratory tract and inhabits it initially. Early pathological effects are connected to the respiratory system.

- Gastrointestinal tract e.g. Rotavirus, Poliovirus

Symptoms include diarrhea, abdominal pain, vomiting, etc.

This viral entry occurs through food consumption. Accordingly, initial pathogenesis starts off in the gastrointestinal tract, and the effect are associated with the site of entry (digestive system).

Continued... :)

Viral Entry

- Conjunctiva and other mucous membranes

Virus enters through the conjunctiva (in the eye). Pathogenesis takes place at the site of entry. Viral infections causes eye infection, redness, tearing (crying, not ripping), irritation.

- Genitourinary tract e.g. HIV

Virus enters the genitourinary tract through sexual contact. Early symptoms affect the genitourinary tract.

HIV: human immunodeficiency disease
HBV: hepatitis B virus
HCV: hepatitis C virus

- Directly into bloodstream by
  - Needles: HBV, HIV — Through contaminated or shared needles that have the virus. This leads to bloodstream infections.
  - Blood transfusion: HIV, HCV, HBV — Contaminated blood that wasn't tested aids in the transmission of the virus from the donor to the recipient.
  - Insect vectors: Arboviruses — Some viruses transmit through insects. When the insect "bites" through the human skin, it injects it with the virus and therefore the bloodstream. Pathogenetic effects show up around the insect bite initially and then rapidly spread through the bloodstream.

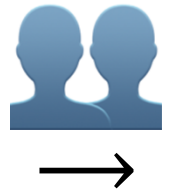
Can you see the pattern now? As you can deduce from the previous two slides, viral symptoms manifest differently depending on the site of entry. Viral effects are specific to each entry point because damaging different tissues requires different mechanisms. Each symptom reflects the viral damage specific to the tissue or tract that the virus entered through.

Feeling stressed?

وَتَوَكَّلْ عَلَى ٱلْحَيِّ ٱلَّذِى لَا يَمُوتُ وَسَبِّحْ بِحَمْدِهِۦ ۚ وَكَفَىٰ بِهِۦ بِذُنُوبِ عِبَادِهِۦ خَبِيرًا

Routes of Transmission

- Horizontal transmission: Transmission of a virus from one person to another
  - Direct contract (secretions, blood etc.)
  - Respiratory (aerosol) or respiratory droplets
  - Contaminated inanimate objects
  - Insect vector (mosquitoes, ticks, etc.)
  - Zoonoses Some viruses have intermediate host that get transmitted to the animal then to the human



- Vertical transmission:
  - Mother to fetus [Transplacental (Congenital), Perinatally]

The mother shares her nutrition and blood circulation with her baby. If she becomes infected with a virus, there's a high likelihood that the virus is going to be transmitted to the baby due to the virus's small-particle nature. This leads to perinatal or congenital viral infections.

The 2nd factor that affects viral pathogenesis

Course of Viral Infection

- **Primary Replication** Most viruses follow this mechanism
  - Viruses usually replicate at the site of initial entry into the host.
  - The infection remains localized at the site of entry

Causes cellular damage at point of entry.
For example, if a virus enters the respiratory system, it can cause cellular damage in the RS, leading to RS-related symptoms, such as coughing, or sneezing.

- **Systemic Spread**

Will discuss in the next slide :)

- **Secondary Replication**
  - Secondary replication takes place at susceptible organs/tissues following systemic spread.

For example, a virus with brain specificity will travel through the bloodstream & replicate there. This can be referred to as "secondary replication", which will lead to a new set of symptoms in the secondary organ of replication (in this case: the brain). A virus can undergo all three courses. Recall the previous rabies bite example. **Primary replication:** early symptoms localized around the bitemark, which is the site of entry (pain, infection, inflammation). the virus travels through the bloodstream, causing transient viremia, with a preference to neurons. **Systemic spread:** the virus spreads through the nervous system to reach the brain. **Secondary replication:** the virus causes neurodegeneration, a high fever, and other neurological symptoms in specific ganglia or neuronal cells, such as hydrophobia.

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Course of Viral Infection

- **Systemic Spread**
  - Many viruses produce disease at sites distant from point of entry

Some viruses produce diseases around the site of entry, others produce diseases away from it. Suitably, these different courses of viral pathogenesis produce different effects.

  - After primary replication, they spread via blood, neurons or lymphatics to other organs.

★ Primary site could be the RS, GI, skin, etc. The virus then transmits to the blood (through certain methods), therefore, systematically spreading.

★ Some viruses take advantage of neurons to move from one place to another in the nervous system.

★ The lymphatic system drains most of the body's tissues. The virus can also utilize this to systemically spread.

  - Presence of virus in blood is called VIREMIA
  - Viral spread is determined by its organ & cell specificity – CELL TROPISM

If a virus enters the bloodstream, it can access most of the body's cells. However, not all viruses can infect every cell type in the body. Some viruses have cell tropism or organ specificity (they prefer to infect a certain cell/tissue). Therefore, the virus travels to that specific organ/cell through the bloodstream. For example, a virus with specificity for a receptor in the brain receptor will specifically target the brain and replicate there. Similarly, another virus could travel to the liver and infect hepatocytes, leading to liver failure. Viruses with broad specificity can enter the bloodstream and affect various tissues and organs, increasing the risk for severe disease. In conclusion, the virus's specificity is what determines its destination within the body once it enters the blood.

The virus has now infected the cell and can be replicated. This produces direct effects on the cell. The magnitude of these effects leads to:

Effects of Viral Infection on Cells

- Cells can respond to viral infections in following ways:
  - No apparent change Clinically: there are no symptoms, and no effect on the host.
  - Cell death or lysis e.g. poliovirus

The effect of the virus depend on the replicative ability of the infected tissue. If the cells cannot be replicated or have limited replication, such as neurons, the virus's effect is severe and even catastrophic. Whereas, if the affected cells are reproduced easily, the virus's effect is limited.

  - Cellular proliferation e.g. Molluscum

Some viruses can affect cellular proliferation by speeding it up or slowing it down. This manifests into various effects on the host.

  - Malignant transformation e.g. Oncogenic viruses

Unfortunately, some viruses can perform genetic manipulation and produce oncogenetic effects. The cell is then transformed into a cancer cell.

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Effects of Viral Infection on Cells

– Cytopathic effects as in tissue cultures

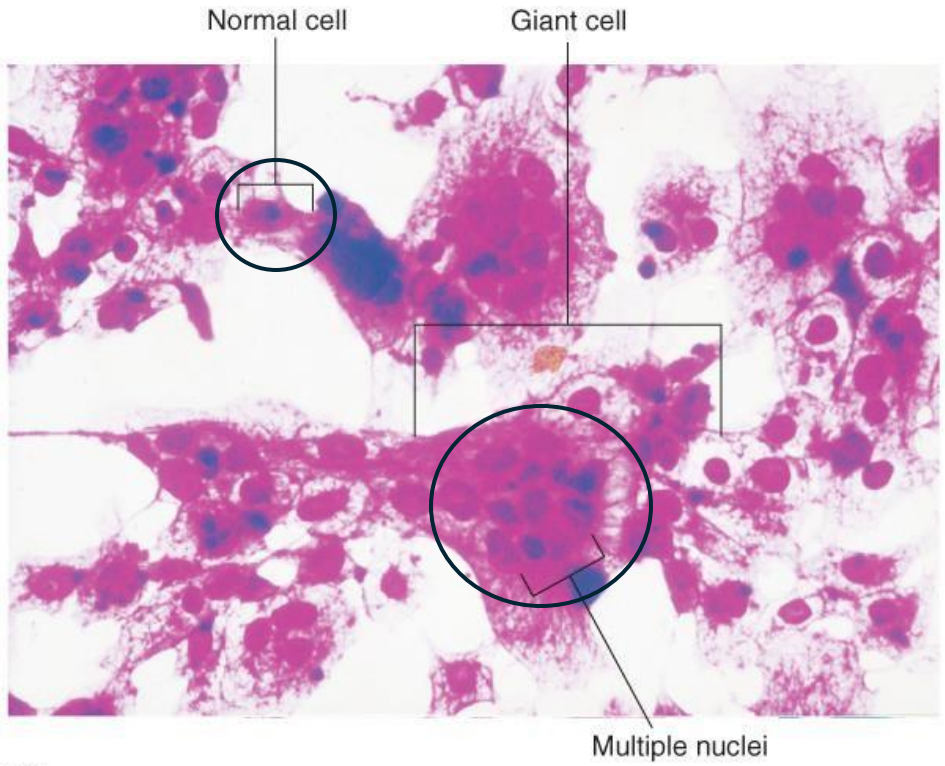
- Cytopathic effects- virus-induced damage to the cell that alters its microscopic appearance

Cytopathic effects aid in the identification process and the viral culture needed to investigate the virus's effect on the host cell. If a virus's effect on the host is trivial, it won't produce morphological effects, and the virus cannot be detected. Such morphological effects include:

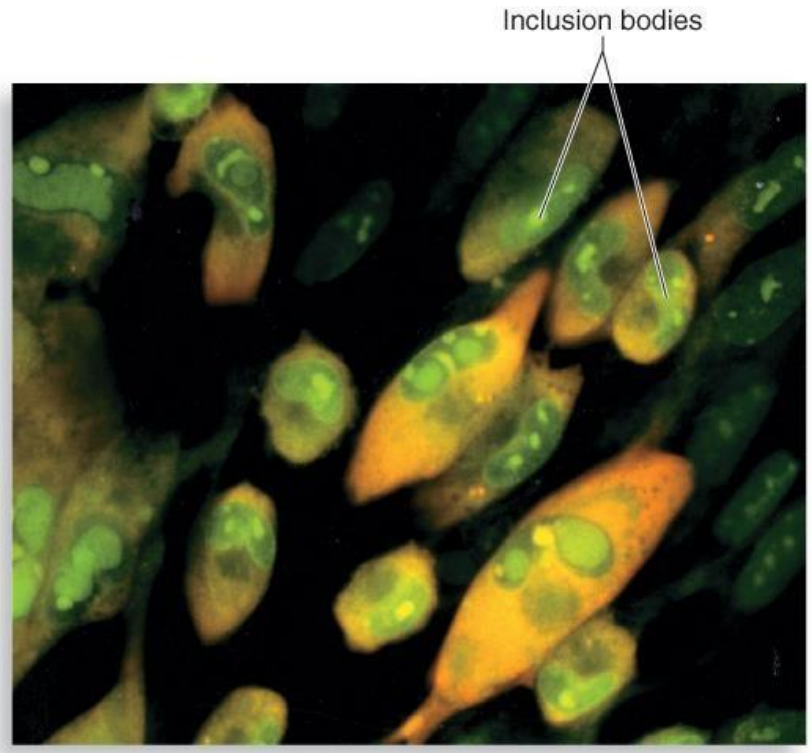
1. Change in size and shape, e.g., giant cells.
2. Change in nuclei, e.g., multiple nuclei

- Inclusion bodies- compacted masses of viruses or damaged cell organelles

Some viruses compact masses of cell organelles and proteins and construct inclusion bodies. These can be seen under a light microscope. it's one of the only times we're able to see viruses clearly under the LM.



(a)

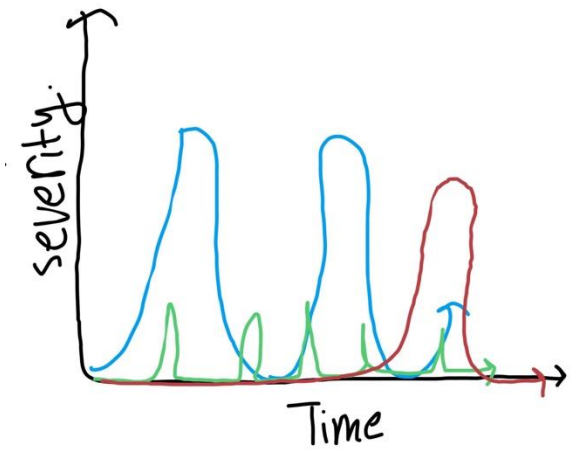


(b)

Outcome of Viral Infection

- Clinical outcome– subclinical (Inapparent) or clinical (apparent) infections. Clinical infections can be:

1. Acute Infection Rapid and severe
   - Complete recovery Returns to its natural state
   - Recovery with residual effects
   - Proceed to chronic infection (latency)
2. Chronic Infection
   - Silent subclinical infection for life The virus is detected with no symptoms(subclinical infection)
   - A long silent period before disease
   - Reactivation to cause acute disease
   - Chronic disease with relapses and excerbations
   - Cancers



Virus Shedding

- Last stage in pathogenesis
- Necessary step to maintain a viral infection in a population of hosts(the virus must enter a new host and go through all the steps again.)
- Usually occurs from the site of entry

  If a virus entered the RS through air droplets causing the disease and pathogenesis, it would shed with air droplets and enter a new host
  And if it enters through the GIT with food it would shed with feces and infect the food of another host

- Occurs at different stages of disease depending on the agent Depends on the entry and systematic spread.

Virus Shedding

- Represents the time at which an infected individual is infectious to contacts

The host becomes infectious during viral shedding
If the virus infects the RS and starts replication with a two-week delay, after these two weeks it'll start to shed, meaning that that person is infectious.
If you're exposed to a diseased person within the first two weeks of infection(it's unlikely you'll get sick). However, if you're exposed to them weeks after you're more likely to get infected

- In certain cases, shedding does not occur e.g.

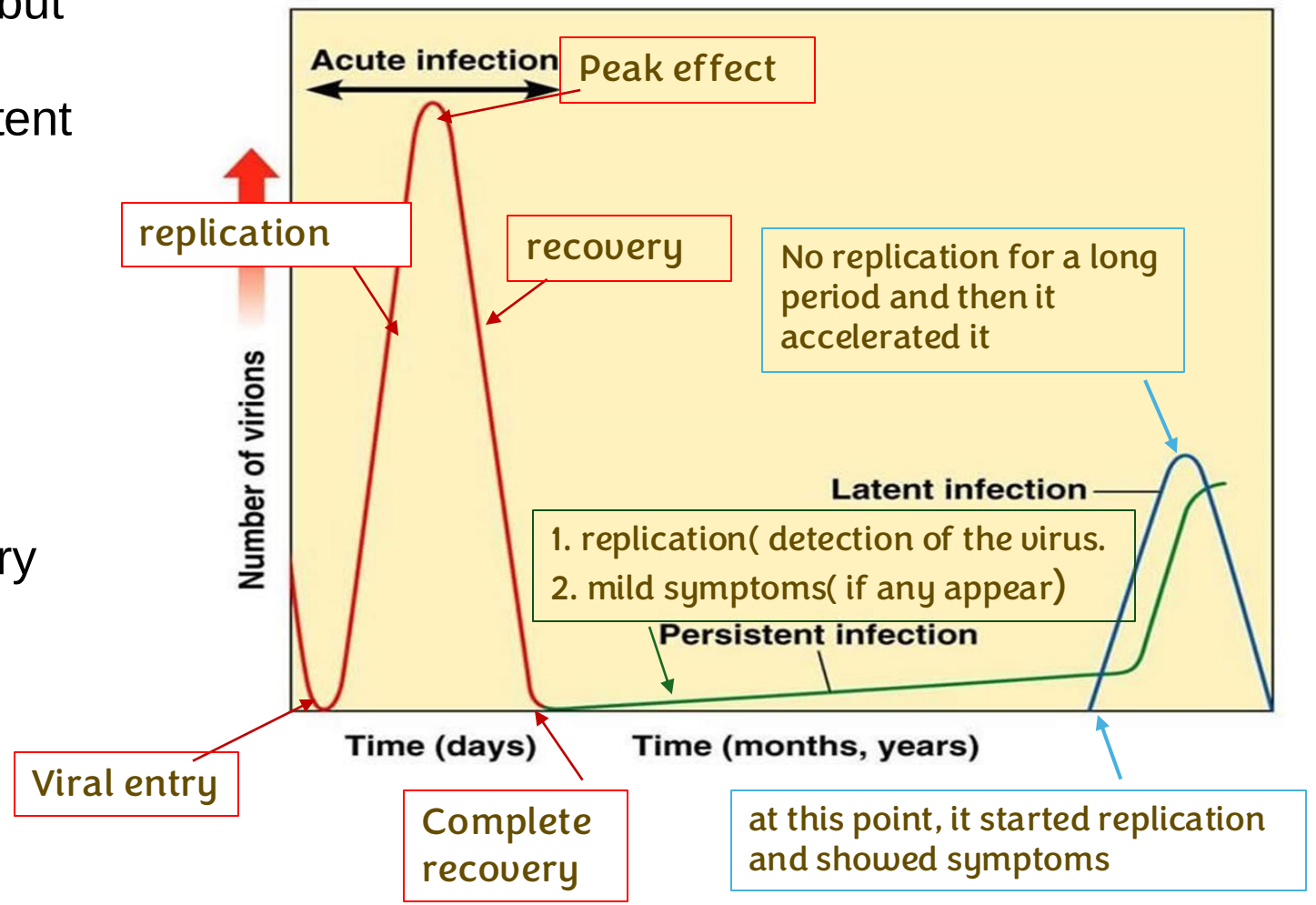
Rabies because the portal entry is through the infected animal's bite-> it doesn't shed(in humans)
Human-> human ×
Animal-> human ✓

*The doctor didn't mention but I wanted to add it :)*Rabies shed in the animal's saliva but replicate in the nervous system
So it could be transmitted through biting or saliva getting an open wounds

Viral Persistence

Majority of viral infections are cleared but certain viruses may cause persistent infections. There are 2 types of persistent infections:

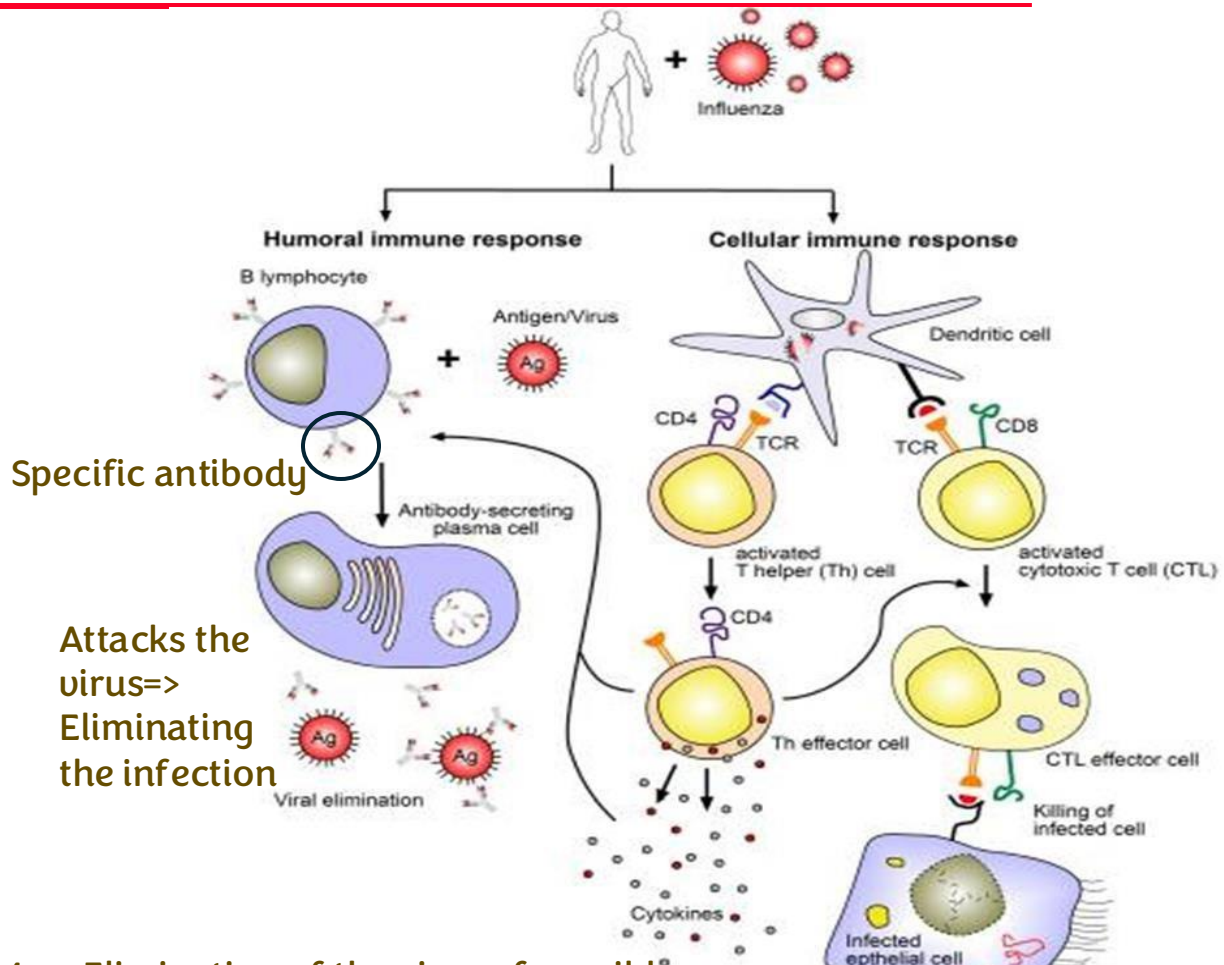
1. Chronic infections– virus is continuously detected but at low levels
2. Latent infections- virus remains completely latent following primary infection. Intermittent flare ups of disease



Host Responses to Viral Infections

- Innate immunity– Interferons
- Humoral response– protects the host against reinfection by same virus
  - IgG & IgM : Blood & tissue
  - IgA : mucosal surfaces of respiratory & gastrointestinal tract
  - Neutralising Abs prevents initiation of infection
- Cellular response– recovery from viral infection, destroy viral infected cells
- Mostly gives lifelong protection

Detailed explanations about each response will be in separate slides :)



1. Elimination of the virus of possible.
2. Recovery of the cells and returning to normal.
3. Antibodies and T-cells create memory T and B cells in case of future re-exposure.

Host Responses to Viral Infections

- Innate immunity– Interferons **None specific immunity**

Interferons are cytokines(proteins):

- INF α
- INF β

They're classified as type 1; potent anti-viral effect(killing and inhibiting viral replication), it affects RNA viruses.

- INF γ

Secretion by Body cells and Immune cells(macrophages)
Their response is rapid(within hours) and non specific.

Mechanism:
The virus's entry affects the host cell by pathogenesis and replication which leads to the secretion of INF targeting the viral growth and replication(RNA generation/ capsid and glycoprotein synthesis/ assembly)=> stopping the infection.

Is there a case were INF can't stop the infection? Yes!
Some viruses build resistance by synthesizing **viral-blocking protein.**

Host Responses to Viral Infections

- **Adaptive-Cellular response(T–cells)- recovery from a viral infection, destroy viral infected cells**
- **Mostly gives lifelong protection**

Viral entry promotes T-cell activation and this is a more complex mechanism because it involves viral presentation.
T-cells work with a limited peptide(not the entire microbe) so we need specific cells that will prepare the virus (aka cut up this virus, choose the most important part/ peptide/ protein of it), and present the antigen on itself so that the T-cells can recognize it, these cells are called dendritic cells present almost everywhere in the body.
T-helper cells(CD4+) and cytotoxin(CD8+) recognize the protein and bind to it.
The defense mechanism happens through:

- **T-cells:**

1. Viral killing with the assistance of macrophages
2.B-cells will produce specific antibodies(we will talk about them more in the next slide).
3. cytotoxic cells that kill virally infected cells.

- **Cytotoxic cells:**

Immediately recognizes the virus and kills it and any other infected cells.(so it can act either directly or indirectly through T-cell activation).

Host Responses to Viral Infections

- **Adaptive-Humoral response(B-cells)– protects the host against reinfection by same virus**

This mechanism is concerned with the B-cells especially to clear and kill viruses.

- **Attachment(IgA)= neutralization:**

The viral replication starts by attaching at the site of entry and cells present there.
The body needs to neutralize the effect of the foreign body(virus) by either the usage of IgA from a previous infection or if the body has a good response in a couple of days it could produce a neutralizing antibody that blocks the attachment site preventing the infection before it could proceed into its later stages and cause great damage.

- **Antibody mediated killing:**

B-cells can't recognize viruses especially if they're within a host cell but they're gonna leave eventually that's when they're recognized by B-Cells in most cases by either its glycoproteins, envelope, or a specific repeated epitope. The B-cell then interacts with the viral antigen, releasing an antibody and killing it.

- T-Helper B-Cells activation:

Because of the weak detection property of B-cells, it uses the assistance of T-helper cells. After the presentation of the viral antigen on dendritic cells T-helper cells recognize it and deliver it to B-cells so they can produce antibodies against it thus activating the B-cells.

Can a virus resist this mechanism? Yes! HIV is a virus that targets the immune system but how? By targeting T-cells(CD4), they can replicate inside it and destroy it when they're done thus 1- lowering the immune system's ability to attack the virus. 2- gradual weakening of the immune system as a whole leading to immune deficiency (hence the name)

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slide 19 They refers to both alpha and beta INF		
V1 → V2			

Additional Resources:

Extra References :

1. https://youtu.be/jkNxmTrrZSk?si=H-t8ayTP8tij30qn
2. https://youtu.be/yjAZXlMpw3k?si=unTqU0ks_ffqgWxe
3. https://youtu.be/Vm9T6QoDnck?si=4-7sqScDK4NcwxYq
4. https://youtu.be/5GELx45kWPw?si=GL1oMrB8yPS30lkR
5. https://youtu.be/_N1xX49AqwQ?si=ByIYE8HqI3tKK-yy (kinda shows the mechanism of T-cell but it's also so cool to see)
6. https://youtu.be/fSEFXl2XQpc?si=T7Kzi-bCs4rcc3Wd

رسالة من الفريق العلمي:

إنَّ اللَّهَ عزَّ وجلَّ يقولُ يومَ القِيامَةِ: يا ابْنَ آدَمَ، مَرِضْتُ فَلَمْ تَعُدْنِي، قالَ: يا رَبِّ، كيفَ أعُودُكَ وأَنْتَ رَبُّ العالَمِينَ؟! قالَ: أَما عَلِمْتَ أنَّ عَبْدِي فُلانًا مَرِضَ فَلَمْ تَعُدْهُ؟ أَما عَلِمْتَ أنَّكَ لو عُدْتَهُ لَوَجَدْتَنِي عِنْدَهُ؟ يا ابْنَ آدَمَ، اسْتَطْعَمْتُكَ فَلَمْ تُطْعِمْنِي، قالَ: يا رَبِّ، وكيفَ أُطْعِمُكَ وأَنْتَ رَبُّ العالَمِينَ؟! قالَ: أَما عَلِمْتَ أنَّه اسْتَطْعَمَكَ عَبْدِي فُلانٌ، فَلَمْ تُطْعِمْهُ؟ أَما عَلِمْتَ أنَّكَ لوْ أطْعَمْتَهُ لَوَجَدْتَ ذلكَ عِندِي، يا ابْنَ آدَمَ، اسْتَسْقَيْتُكَ، فَلَمْ تَسْقِنِي، قالَ: يا رَبِّ، كيفَ أسْقِيكَ وأَنْتَ رَبُّ العالَمِينَ؟! قالَ: اسْتَسْقاكَ عَبْدِي فُلانٌ فَلَمْ تَسْقِهِ، أَما إنَّكَ لو سَقَيْتَهُ وجَدْتَ ذلكَ عِندِي.

لسا بدري season على الأبواب

There's still plenty of time for you to study and catch up, don't feel discouraged and try to utilize this time as much as you can :) استهدي بالله