



PATHOGENESIS OF VIRUSES

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Topics discussed in the lecture

1- Principles of viral diseases

- Important terms: viral disease, clinical symptoms, syndrome, subclinical infection, viral pathogenesis, disease pathogenesis, pathogenic virus, virulent virus
- Most of viral infections are subclinical, The outcome in any case is done by both viral and host factors

2- Degree of a disease virulence

4 classes: viruses don't enter the cell/ enter the cell but don't mature and slow replication/ cytopathic effects and cell lysis/ severe cell lysis causing death

3- Types of infections

Acute/ chronic/ latent

Acute infections are two types:

- 1) Local: Replicate at side of entry
- 2) Systemic: Side of entry □ Lymph node □ Blood (viremia) □ endothelial system □ blood (Secondary viremia) □ target cells

4- Steps in viral pathogenesis

Entry and primary replication/ spread/ cell injury and symptoms/ resolve/ virus shedding

5- Routes of entry

Respiratory tract/ GI tract/ Skin (by a trauma, injection or a bite)

6- Symptoms of infected organs

- Respiratory tract infections: common cold, pharyngitis, laryngitis, tracheobronchitis, bronchiolitis, pneumonia
- Skin infections: macule, patch, papule, plaque, vesicle, bulla, fissure, erosion, ulcer
- CNS infections: encephalitis, meningitis, encephalomyelitis.
- Congenital infections: perinatal, natal, postnatal (transmitted to the fetus through the blood, vagina, ova)

7- Different types of virus-host interactions (Just take a general idea)

8- Diagnosis of viral diseases

Done by: signs and symptoms, microscope examination, cell culturing, virus detection by electron microscope, PCR, serological tests

9- Immunity response against viruses

- Done by: Interferons, cytotoxic t cells, Neutralizing antibodies, Iga antibodies
- Viruses have some mechanisms to evade immune response
- Young and old people have weak immunity

10- Treating of viral infections

- Anti- viral drugs: two types are nucleoside analogue and non-nucleoside analogue/ acyclovir is the most famous type
- Interferon alpha is used nowadays as drug
- Vaccines are available, there are 4 types of vaccines: live-attenuated, killed, subunits and mRNA

1- Principles of Viral Diseases

- viral disease: The disease that is caused by virus infection.
- clinical disease caused by a viral infection: It is the collection of symptoms that result from the viral infection.
- syndrome: It is a collection of different signs and symptoms that are associated with virus disease.
- subclinical infection: It is the presence of a virus in the body actively replicating without producing any signs or symptoms.

1- Principles of Viral Diseases

- viral pathogenesis: It is the collection of processes from which the disease process takes place.
- disease pathogenesis: It is the collection of the direct viral effects besides the direct human factors that play a role in the development in the disease, for example the inflammatory and immune process are involved beside the direct viral process.
- pathogenic virus: The virus that is able to cause disease in the human.
- virulent virus: A virus that is associated with more severe disease causing more extensive damage in the infected host.

1- Principles of viral diseases

- Most of viral infections are subclinical
- The same disease may be produced by a variety of viruses
- The same virus may produce a variety of diseases
- The disease produced bears no relationship to viral morphology
- The outcome in any case is determined by both viral and host factors and is influenced by the genetics of each

2- Degree of virulence of a disease

◦ We can classify the pathogenesis of the virus regarding its degree of virulence into 4 types:

1) When the cell is exposed to the virus without its attachment or entry, **there won't be any infection**

2) When the virus replicate without visible change or incomplete viral maturation, **subclinical infection will occur (asymptomatic infection)**

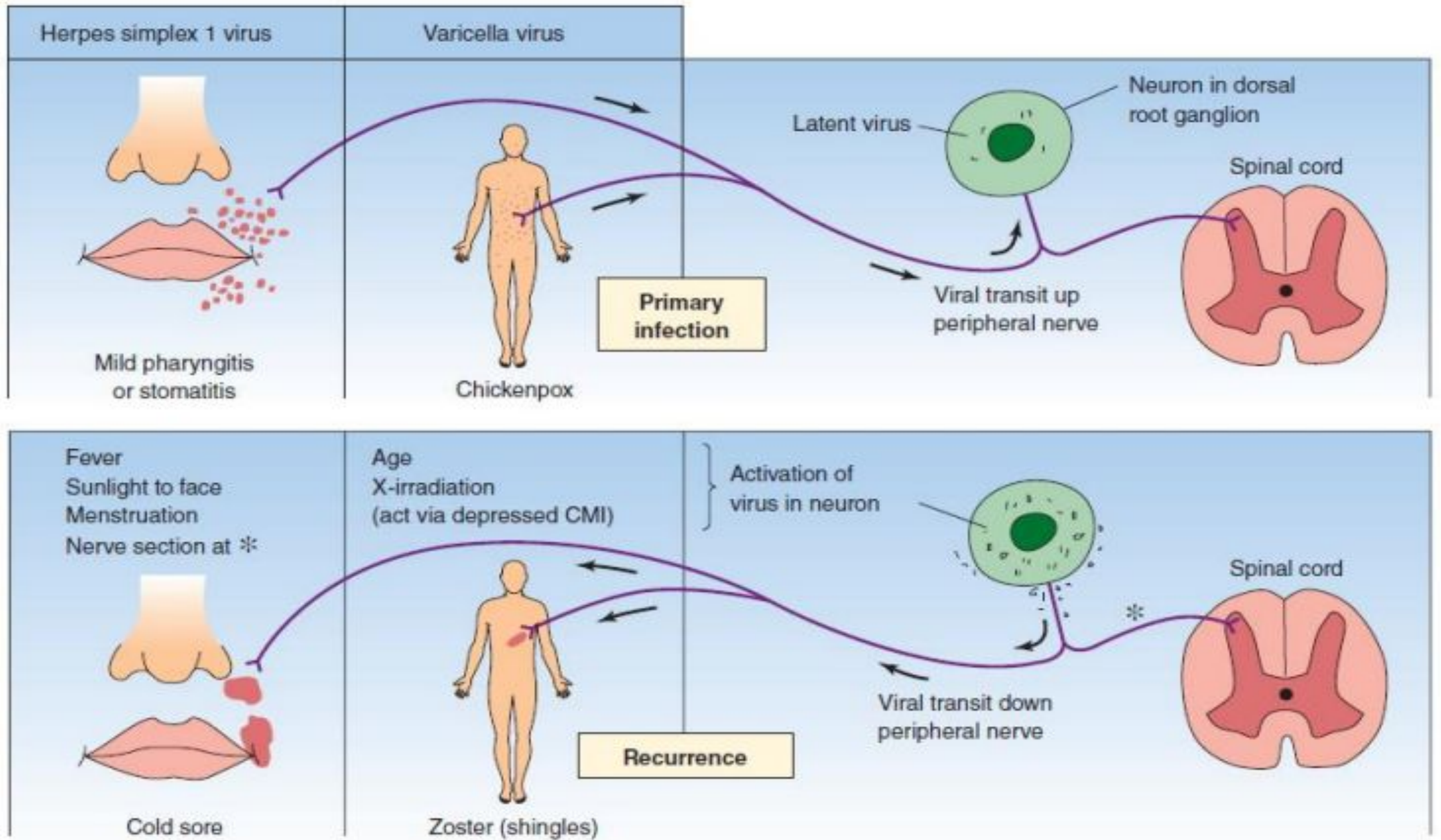
3) When the cell is affected (e.g. inclusion body formation, cell transformation or cell dysfunction) or killed (lysis or apoptosis), **there will be a disease with different rates (e.g. Mild, moderate and severe)**

4) When many cells are affected and killed, and an essential function is defected in the body, **the host dies**

□ Note: the majority of viral diseases are subclinical, fatal viruses are rare

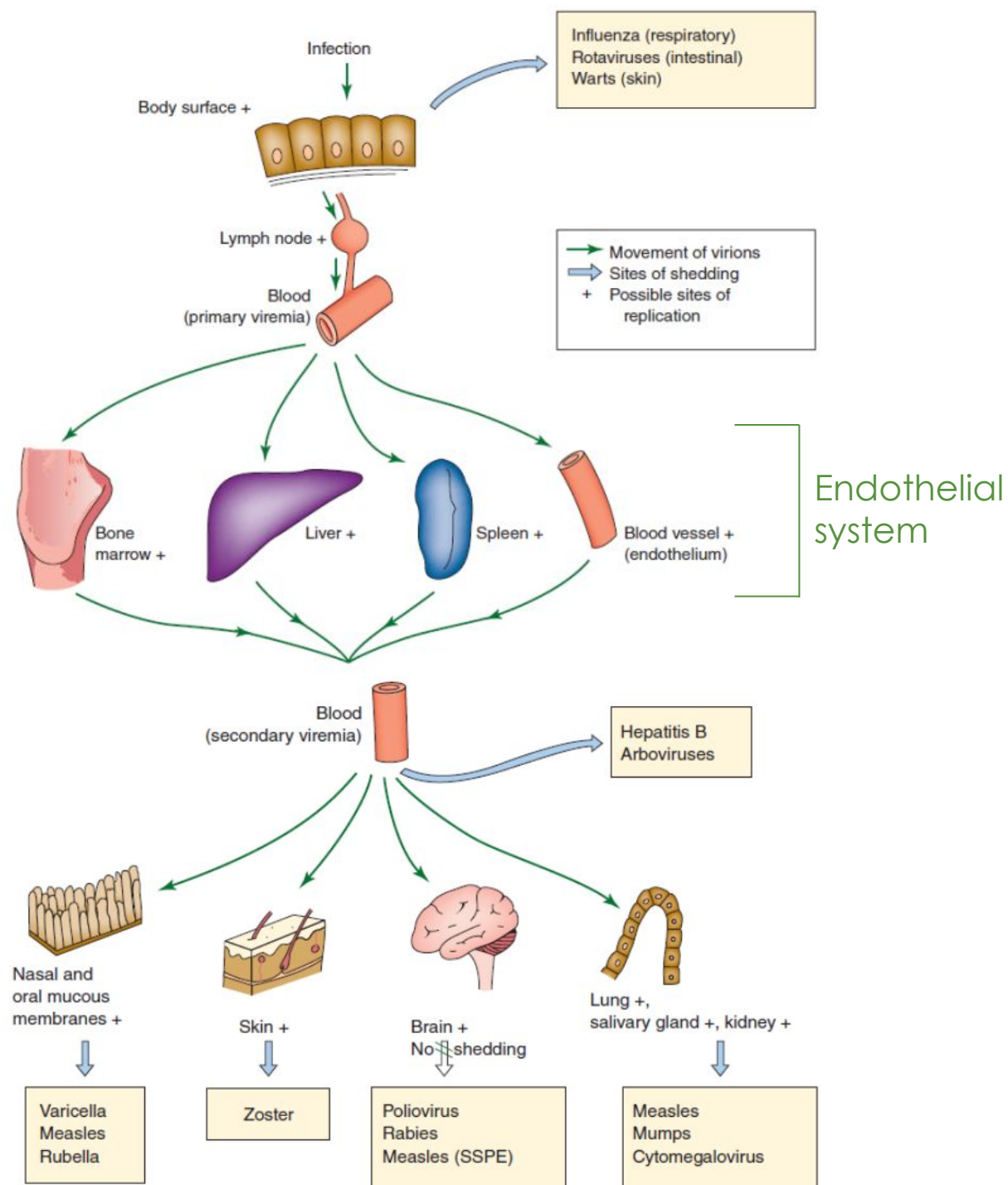
3- Types of infections

- Acute infection: Causes more severe symptoms than chronic infections, but usually resolve completely after a short period of time (unless it causes death)
- Chronic infection: Causes milder symptoms than Acute infections, but usually continue a long period of time (sometimes lifelong)
- Latent infection: occurs sometimes after acute infection where the virus hide inside the host without replication, it remains silent until the immune system is disrupted then it attacks the host again.



- Acute infections are two types: Local and systemic

	Local Infections	Systemic Infections
Specific disease example	Respiratory (rhinovirus)	Measles
Site of pathology	Portal of entry	Distant site
Incubation period	Relatively short	Relatively long
Viremia	Absent	Present
Duration of immunity	Variable—may be short	Usually lifelong
Role of secretory antibody (IgA) in resistance	Usually important	Usually not important



□ Steps of systemic inflammation

- 1) Viruses replicate in the side of entry
- 2) Transported into a lymph node
- 3) They're NOT eliminated in the lymph node so they travel to the blood causing primary viremia
- 4) They travel then to endothelial system and replicate there
- 5) They travel then to the blood again causing secondary viremia
- 6) They travel at last to their cellular target causing infection

Viruses Spread Via the Bloodstream

Cell Type Associated	Examples	
	DNA Viruses	RNA Viruses
Lymphocytes	Epstein-Barr virus, cytomegalovirus, hepatitis B virus, JC virus, BK virus	Mumps, measles, rubella, human immunodeficiency virus
Monocytes-macrophages	Cytomegalovirus	Poliovirus, human immunodeficiency virus, measles virus
Neutrophils		Influenza virus
Red blood cells	Parvovirus B19	Colorado tick fever virus
None (free in plasma)		Togavirus, picornavirus

4- Steps in Viral Pathogenesis

1. Entry and Primal Replication.
2. Viral Spread (their movement toward target cells) and Cell Tropism (the cells that are able to support viral replication and they have the cellular receptors for attachment of that virus).
3. Cell Injury and the Production of Clinical Illness.
4. Recovery form Infection.
5. Virus Shedding.

5- Routes of entry



Common Routes of Viral Infection in Humans – Respiratory Tract



Virus Group	Produce Local Symptoms at Portal of Entry	Produce Generalized Infection Plus Specific Organ Disease
Parvovirus		B19
Adenovirus	Most types	
Herpesvirus	Epstein-Barr virus, herpes simplex virus	Varicella virus
Poxvirus		Smallpox virus
Picornavirus	Rhinoviruses	Some enteroviruses
Togavirus		Rubella virus
Coronavirus	Most types	
Orthomyxovirus	Influenza virus	
Paramyxovirus	Parainfluenza viruses, respiratory syncytial virus	Mumps virus, measles virus



Common Routes of Viral Infection in Humans – Mouth, Intestinal Tract

Virus Group	Produce Local Symptoms at Portal of Entry	Produce Generalized Infection Plus Specific Organ Disease
Adenovirus	Some types	
Calicivirus	Noroviruses	
Herpesvirus	Epstein-Barr virus, herpes simplex virus	Cytomegalovirus
Picornavirus		Some enteroviruses, including poliovirus, and hepatitis A virus
Reovirus	Rotaviruses	

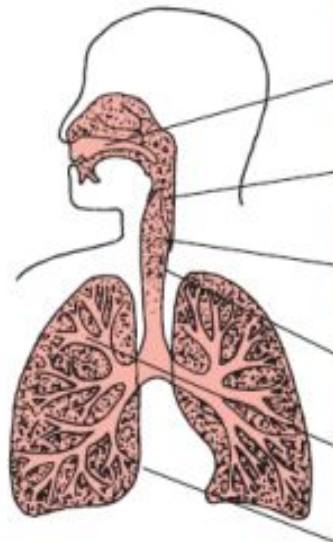


Common Routes of Viral Infection in Humans – Skin

	Virus Group	Produce Local Symptoms at Portal of Entry	Produce Generalized Infection Plus Specific Organ Disease
Mild trauma	Papillomavirus	Most types	
	Herpesvirus	Herpes simplex virus	
	Poxvirus	Molluscum contagiosum virus, orf virus	
Injection	Hepadnavirus		Hepatitis B
	Herpesvirus		Epstein-Barr virus, cytomegalovirus
	Retrovirus		Human immunodeficiency virus
Bites	Togavirus		Many species, including eastern equine encephalitis virus
	Flavivirus		Many species, including yellow fever virus
	Rhabdovirus		Rabies virus

6- Symptoms of infected organs

Viral Infections of the Respiratory Tract



Syndromes	Main Symptoms	Most Common Viral Causes ³		
		Infants	Children	Adults
Common cold	Nasal obstruction, nasal discharge	Rhino Adeno	Rhino Adeno	Rhino Corona
Pharyngitis	Sore throat	Adeno Herpes simplex	Adeno Coxsackie	Adeno Coxsackie
Laryngitis or croup	Hoarseness, "barking" cough	Parainfluenza Influenza	Parainfluenza Influenza	Parainfluenza Influenza
Tracheobronchitis	Cough	Parainfluenza Respiratory syncytial	Parainfluenza Influenza	Influenza Adeno
Bronchiolitis	Cough, dyspnea	Respiratory syncytial Parainfluenza	Rare	Rare
Pneumonia	Cough, chest pain	Respiratory syncytial Influenza	Influenza Parainfluenza	Influenza Adeno

³Most commonly reported respiratory viruses vary, depending on the study design, subject population, detection methods and other factors (eg, time of year).



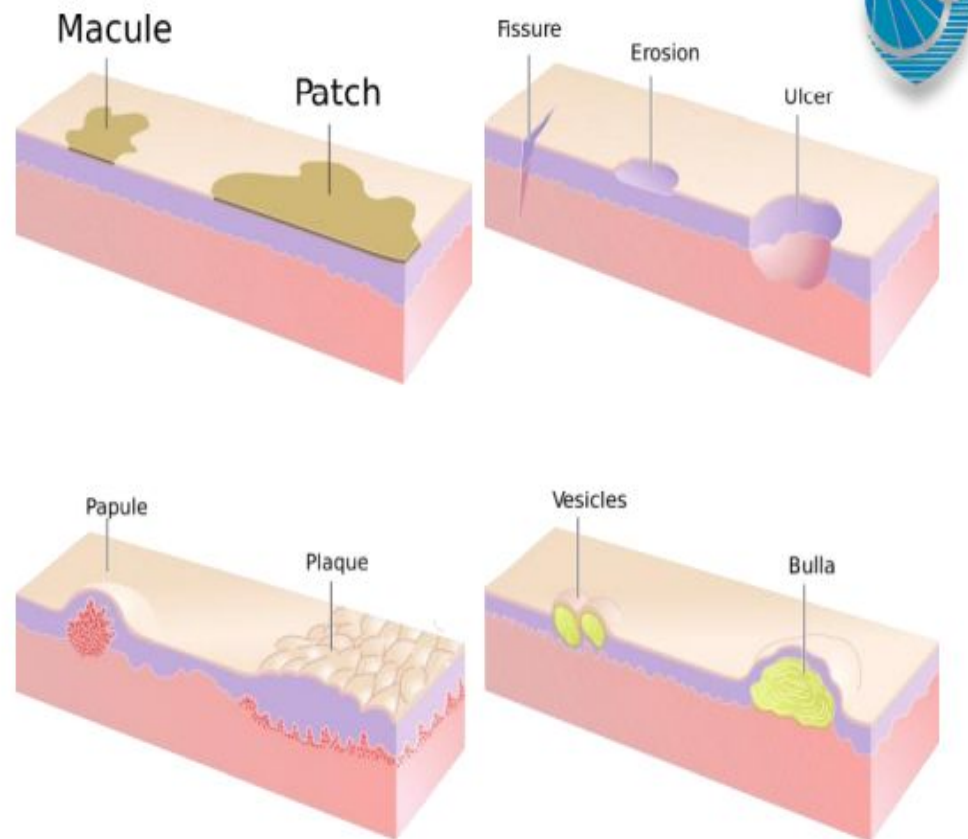
Overview of Viral Skin Infections

Pox, Papilloma, HSV, MCV

Arbo

Rabies, herpes B

HBV, HIV



6- Symptoms of infected organs

HSV: Herpes simplex virus

MCV: molluscum contagiosum virus

HBV: Hepatitis B

Viruses

CMV

EV

HSV-1

HSV-2

HHV-6

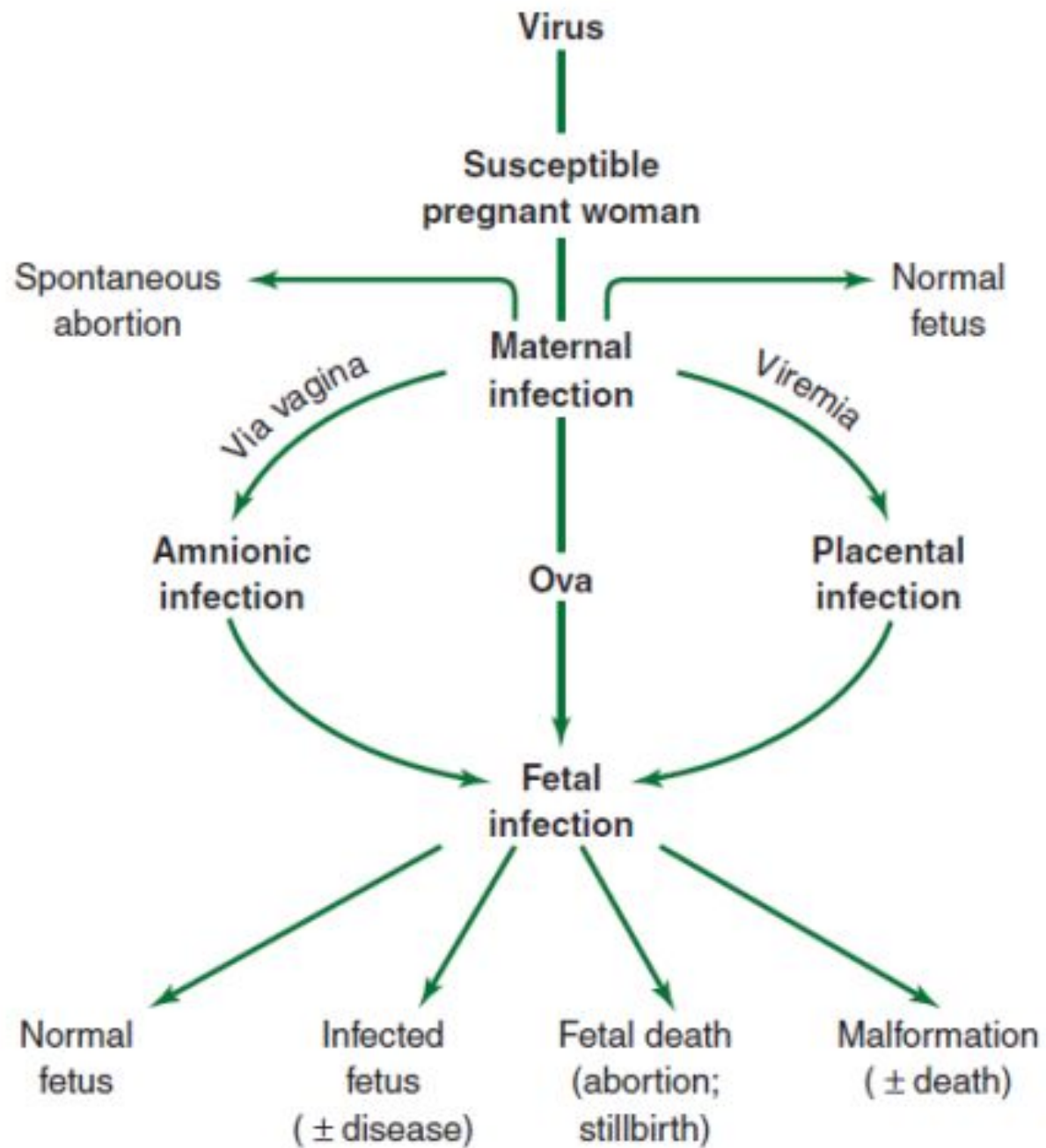
HPeV

VZV

Overview of Viral CNS Infections

Causes:

1. Encephalitis
2. Meningitis
3. Encephelomeningitis

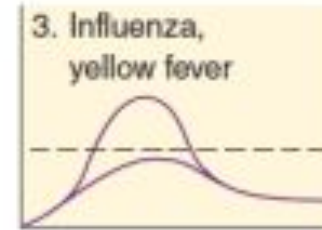
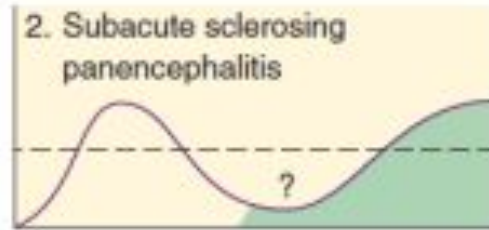
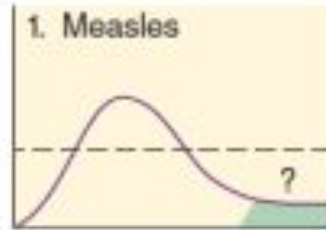


◦ This is a very important table about the acquisition of significant perinatal viral infections, whether it occurs prenatally, in delivery or following it, the most common among all congenital infections **cytomegalovirus**. As you can see, in prenatal or natal happen most frequently in a majority of viruses except for Rubella and Parvovirus, prenatal infection occurs almost in all of these viruses in different periods in the first/second/third trimesters resulting in different outcomes from abortion to the presence of developmental abnormalities in the fetus.

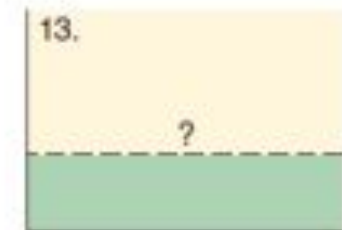
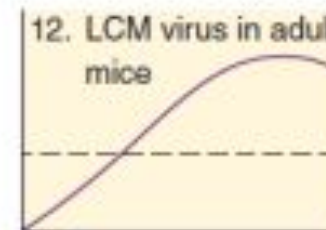
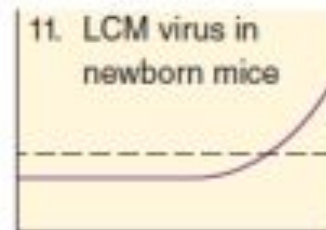
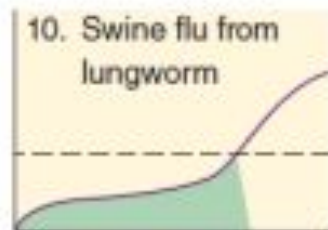
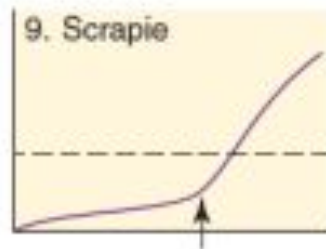
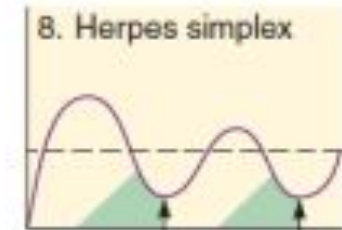
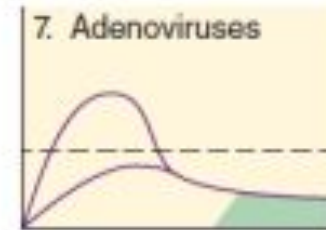
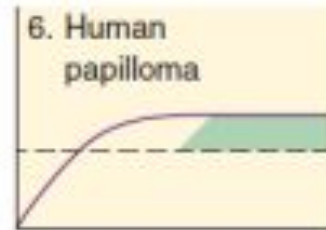
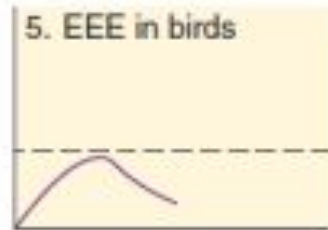
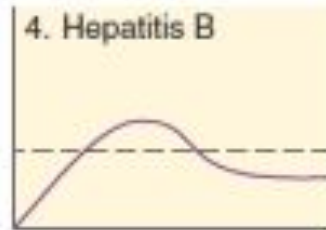
Virus	Frequency of Time of Infection			Neonatal Incidence (per 1000 Live Births)
	Prenatal (In Utero)	Natal (during Delivery)	Postnatal (after Delivery)	
Rubella	+	-	Rare	0.1-0.7
Cytomegalovirus	+	++	+	5-25
Herpes simplex	+	++	+	0.03-0.5
Varicella-zoster	+	Rare	Rare	Rare
Hepatitis B	+	++	+	0-7
Enterovirus	+	++	+	Uncommon
Human immunodeficiency virus	+	++	+	Variable
Parvovirus B19	+	-	Rare	Rare



7- Different types of virus-host interactions



--- = Threshold of apparent infection (clinical disease)
↑ = Activation of virus production in the original host
— = Course of disease
■ = Presence of occult virus



7- Different types of virus-host interactions

- 1) in measles, following an incubation period there is high frequency of symptomatic disease that is present for relatively short period of time followed by resolution. In some cases, there will be some latency to the virus and it can be reactivated in the form of 2) SSP in a few patients.
- 3) in Influenza and yellow fever, a short symptomatic disease.
- 4) in Hepatitis B there is an acute infection followed by either resolution of symptoms or persistence of the virus as a chronic disease.
- 5) in Eastern equine encephalitis the replication will stop in the bird and it will form a reservoir for this virus infection.
- 6) in the Human Papilloma virus, it might remain as an occult infection without apparent active replication of the virus but it can result in malignancy for certain types.

7- Different types of virus-host interactions

- 7) Adenovirus can produce a symptomatic disease and remain occult or latent later on.
- 8) for Herpes simplex frequently activation, following latent infection can happen.
- 9) scrapie is not caused by a virus, it is caused by a prion and following a long incubation without symptoms the disease will be apparent.

7- Different types of virus-host interactions

- The doctor: I will not discuss the remaining 3 because they are in animal, but in the last one here is a subject for investigation especially in cancer where there might be a relationship and this was very hot topic for research in 1960s and 70s there was this hypothesis that the majority of cancers are related to infections in humans but this turned out to be not accurate, although an identification of certain viruses that can be classified as oncoviruses took place at that period, for example the human teeth and lymphotropic viruses, so some types of cancer might be associated with certain infections that are difficult to be detected because they are either not replicating at a detectable level, or they might represent an occult infection that is hard to be detected or discovered.

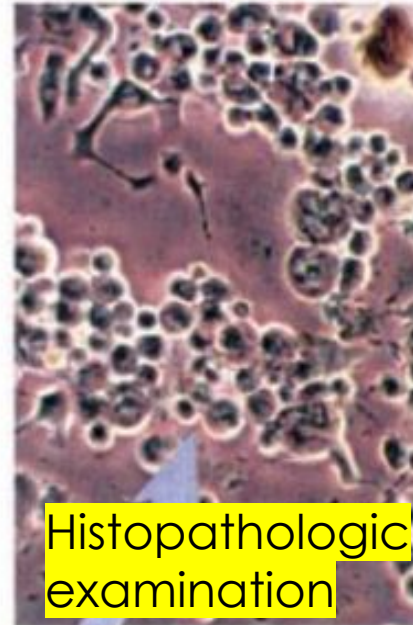
8- Diagnosis of viral diseases

- 1) signs and symptoms
- 2) microscope examination: such as histopathologic examination and immunofluorescence microscopy
- 3) cell culturing
- 4) virus detection by electron microscope: Not used anymore except for some enteroviruses
- 5) PCR: two types are real-time and conventional
- 6) serological tests:



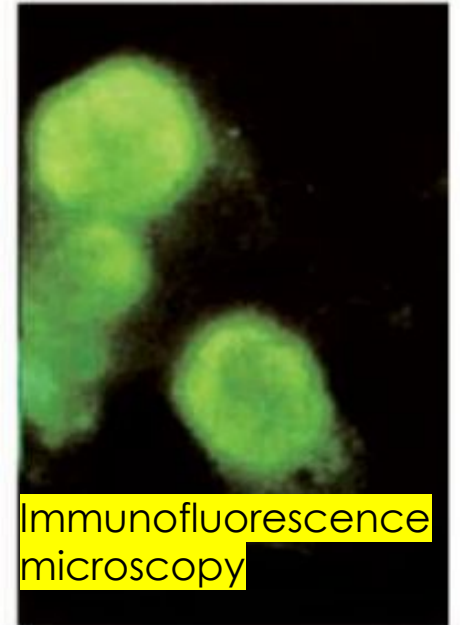
Signs and symptoms: Patient is observed for manifestations of typical virus infections. This is herpes simplex, type 1. (cold sores)

(1) Cells infected with herpes simplex virus



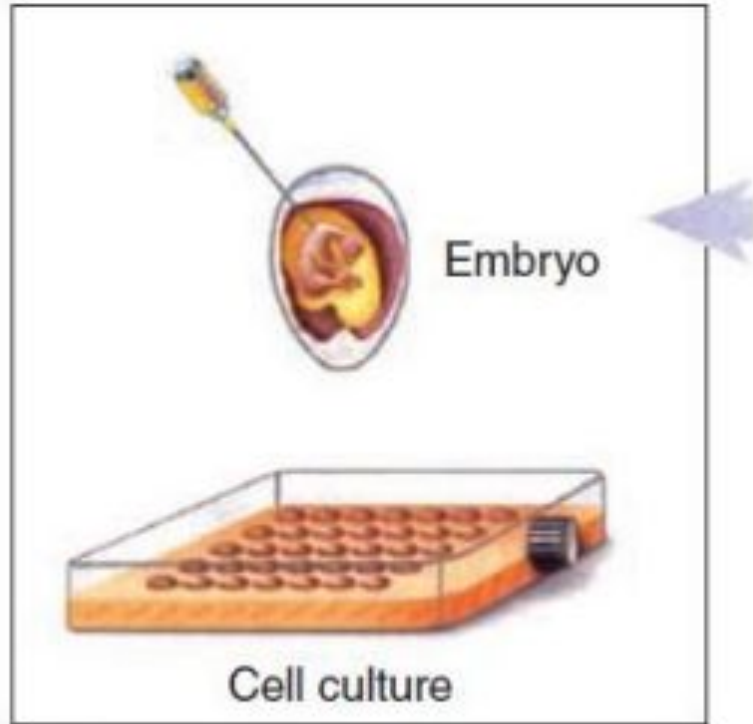
Histopathologic examination

(2) Cells infected with influenza virus

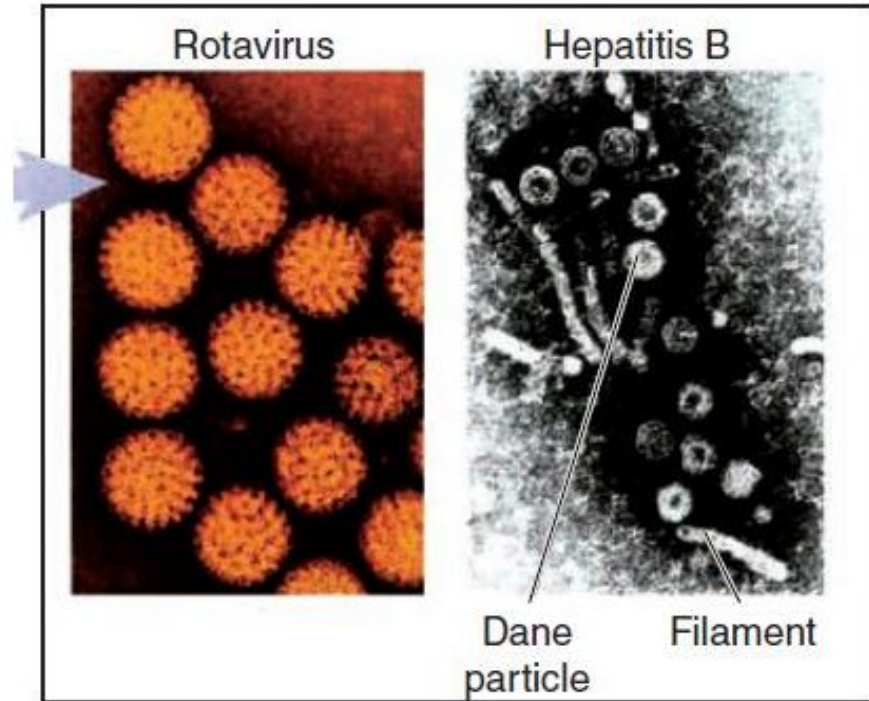


Immunofluorescence microscopy

Cells taken from patient are examined for evidence of viral infection, such as cytopathic effects (1) or virus antigen detected by fluorescent staining (2).

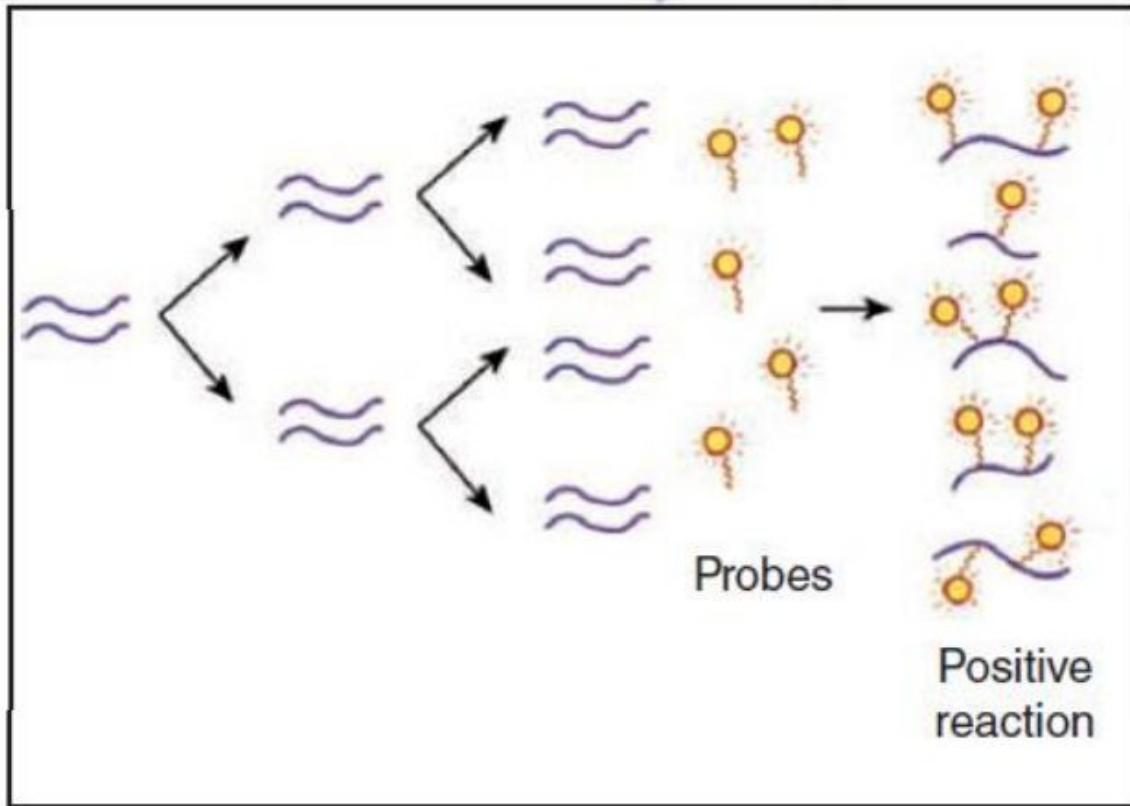


Culture techniques: Viruses require a living host to multiply.



Electron microscope is used to view virus directly. Viruses are sufficiently unique in structure that they can be differentiated to family or genus.

Some enteroviruses



Genetic analysis (PCR): Detection of viral nucleic acid using specific probes.

Types of PCR:

- 1) real-time PCR: Used mainly
- 2) nucleic acid hybridization
- 3) Conventional PCR: needs more time, still used for detection of HIV and Hepatitis B resistance to anti-viral drugs

The image shows a Western blot for HIV. The table below lists various HIV antigens and antibodies, with a positive result indicated by a band in the 'Western Blot' column.

Specimen Number	Lab Name	Western Blot
1	1180555555	Positive
2	1180555555	Positive
3	1180555555	Positive
4	1180555555	Positive
5	1180555555	Positive
6	1180555555	Positive
7	1180555555	Positive
8	1180555555	Positive
9	1180555555	Positive
10	1180555555	Positive
11	1180555555	Positive
12	1180555555	Positive
13	1180555555	Positive
14	1180555555	Positive
15	1180555555	Positive
16	1180555555	Positive
17	1180555555	Positive
18	1180555555	Positive
19	1180555555	Positive
20	1180555555	Positive

Western blot for HIV

Serological testing for antibodies

Types of serological testing for antibodies:

- 1) enzyme immunoassay
- 2) chemiluminescent assays
- 3) western blot: used for confirmation of HIV infection

9- Immunity response against viruses

IFNs

Cytotoxic T lymphocytes

Neutralizing antibody

Secretory IgA antibody

9- Immunity response against viruses

- Interferons: its role is very important in initiating innate immune defense against any type of virus infection, so it produces a non-specific immune response, resulting in antiviral resistance state of the nearby cells to infection by the invading virus.
- the Secretory Iga antibody: main component of mucus, secreted from mucosal membrane

9- Immunity response against viruses

- Cytotoxic lymphocytes & Neutralizing antibody play a major role, and this is an important issue here to measure the magnitude and the scope of protection to a certain virus usually it is done by measuring the neutralizing antibody but this might not be sufficient to investigate whether the adaptive immune response that has occurred in the body is sufficient to protect from infection or upon exposure or upon initial exposure following vaccine introduction so cytotoxic lymphocytes play a major role and form a memory T cells that can result in an immune reaction that is earlier compared to the primary exposure and more intense in magnitude, which is difficult to be measured but it should be considered because it is one of the most important host immune responses to virus infection

9- Immunity response against viruses



**Infecting cells
of the immune
system**



**Infecting cells
with low level
of MHC
molecules**



**Encoding
immunomodula
tory proteins
that inhibit MHC
function**



**Encoding
immunomodula
tory proteins
that inhibit
cytokine activity**



**Developing
immune escape
mutations**

9- Immunity response against viruses

- Effect of Host Age:

In neonates, the infection might be severe because the immune system has not developed to a mature level yet, so the infection might be severe or might result in chronic infection. Also, in very old age, death of memory cells might result in more severe disease as well.

10- Treating of viral infections

- It is a bit difficult to treat viral infections compared to bacterial, parasitic or fungal infection, because the virus depends on the host cell for its replication, so specific targeting for viral proteins or enzymes might be difficult, because antiviral therapies sometimes affect the hosts and their mechanisms and it can result in severe side effect.
- For the other drugs, we have the nucleoside analogues and non-nucleoside analogues, we will come into these in depth when we speak about the specific virus families, but you have take a general idea about these different drugs.

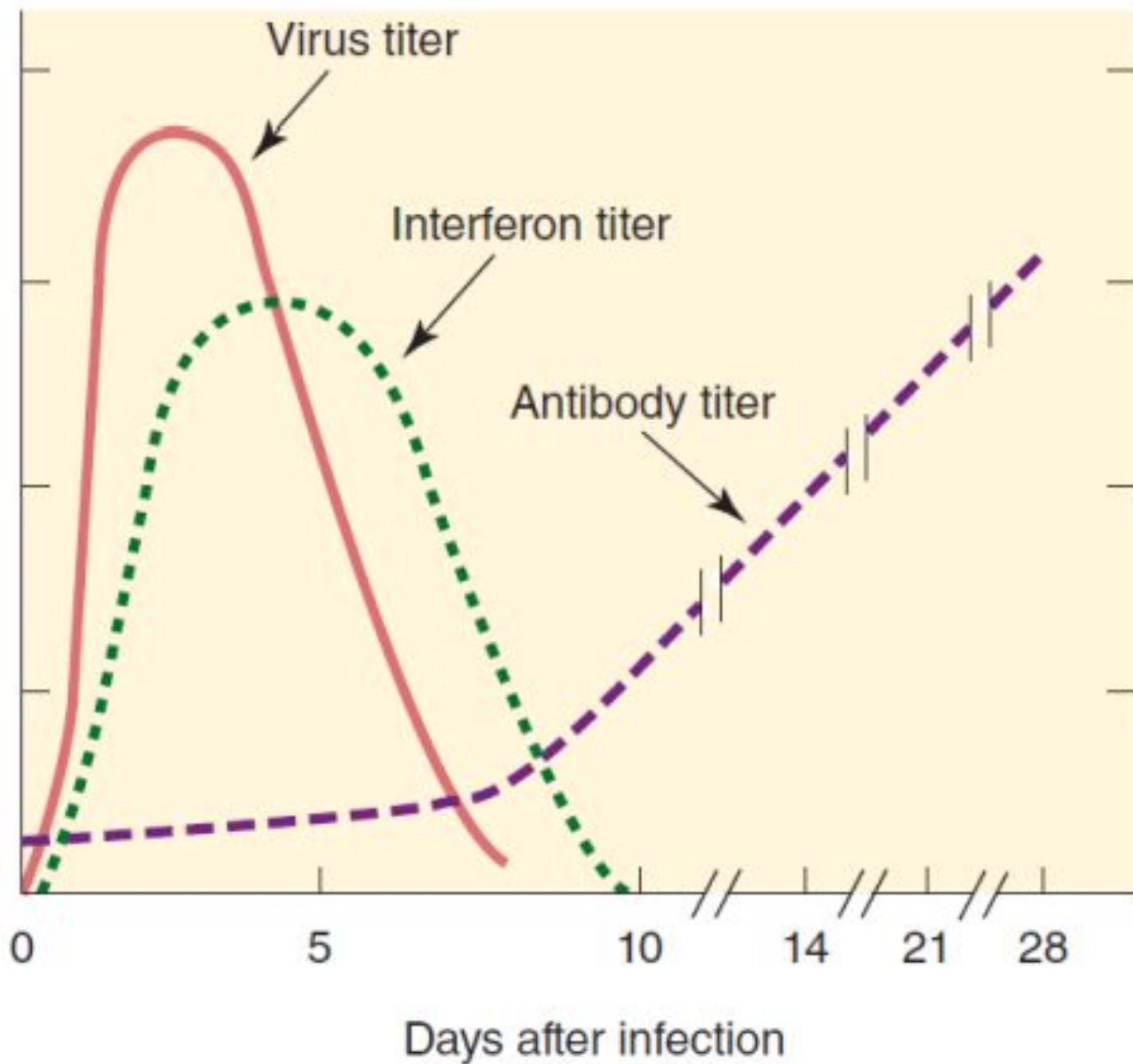
Drug	Nucleoside Analog	Mechanism of Action	Viral Spectrum
Acyclovir	Yes	Viral polymerase inhibitor	Herpes simplex, varicella-zoster
Amantadine	No	Blocks viral uncoating	Influenza A
Boceprevir	No	HCV protease inhibitor	HCV genotype 1
Cidofovir	No	Viral polymerase inhibitor	Cytomegalovirus, herpes simplex, polyomavirus
Didanosine (ddI)	Yes	Reverse transcriptase inhibitor	HIV-1, HIV-2
Entecavir	Yes	Reverse transcriptase inhibitor	HBV
Foscarnet	No	Viral polymerase inhibitor	Herpesviruses, HIV-1, HBV
Fuzeon	No	HIV fusion inhibitor (blocks viral entry)	HIV-1
Ganciclovir	Yes	Viral polymerase inhibitor	Cytomegalovirus
Indinavir	No	HIV protease inhibitor	HIV-1, HIV-2
Lamivudine (3TC)	Yes	Reverse transcriptase inhibitor	HIV-1, HIV-2, HBV
Lopinavir	No	HIV protease inhibitor	HIV-1
Maraviroc	No	Entry inhibitor (blocks binding to CCR5)	HIV-1
Nevirapine	No	Reverse transcriptase inhibitor	HIV-1
Oseltamivir	No	Viral neuraminidase inhibitor	Influenza A and B
Raltegravir	No	Integrase inhibitor	HIV-1
Ribavirin	Yes	Perhaps blocks capping of viral mRNA	Respiratory syncytial virus, influenza A and B, Lassa fever, hepatitis C, others
Ritonavir	No	HIV protease inhibitor	HIV-1, HIV-2
Saquinavir	No	HIV protease inhibitor	HIV-1, HIV-2
Stavudine (d4T)	Yes	Reverse transcriptase inhibitor	HIV-1, HIV-2
Trifluridine	Yes	Viral polymerase inhibitor	Herpes simplex, cytomegalovirus, vaccinia
Valacyclovir	Yes	Viral polymerase inhibitor	Herpesviruses
Vidarabine	Yes	Viral polymerase inhibitor	Herpesviruses, vaccinia, HBV
Zalcitabine (ddC)	Yes	Reverse transcriptase inhibitor	HIV-1, HIV-2, HBV
Zidovudine (AZT)	Yes	Reverse transcriptase inhibitor	HIV-1, HIV-2, HTLV-1



□ Interferon

- One of the major drugs that have been used for treatment of virus infections especially chronic virus infections and is being tried for every novel virus is Interferon, interferon alpha is being used because of its general antiviral properties.
- We are talking about the interferon alpha, its major use was the treatment of chronic hepatitis infections, chronic hepatitis B, chronic hepatitis C, but for hepatitis C nowadays the presence of direct acting antivirals spurred some of the side effects and sometimes non-electiveness of interference for certain genotypes.

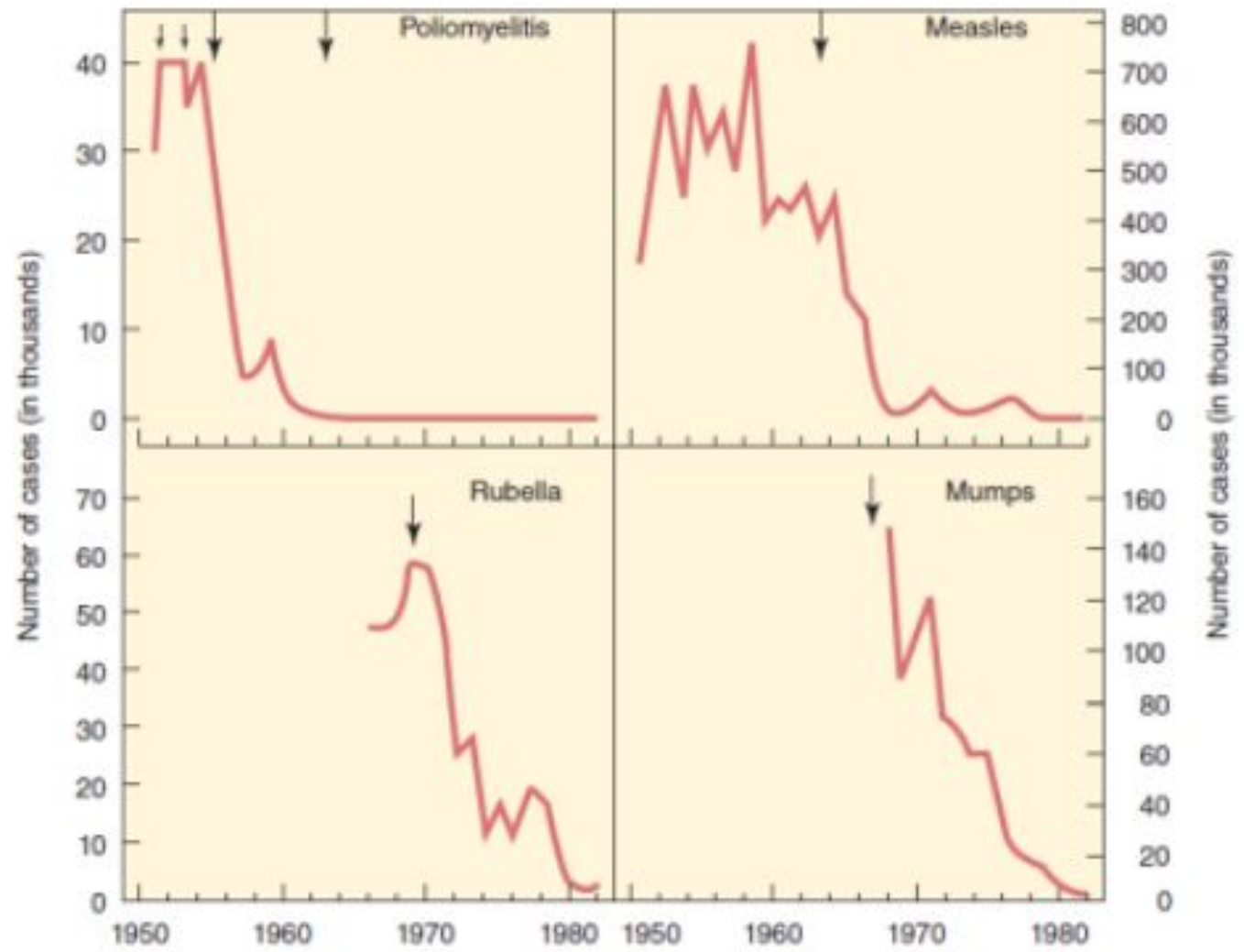
- Interferons act by producing an antiviral state by inhibition of the production of viral proteins by blocking the initiation factor EIF2, they can also degrade the viral messenger RNAs that are present in the infected cells if it gets infected, so the initial infection (the cell that is already infected before the production of interferon) is not affected by the effects of interferons, but the neighbouring cells will develop an antiviral state.



Property	Type		
	Alpha	Beta	Gamma
Current nomenclature	IFN- α	IFN- β	IFN- γ
Former designation	Leukocyte	Fibroblast	Immune interferon
Type designation	Type I	Type I	Type II
Number of genes that code for family	≥ 20	1	1
Principal cell source	Most cell types	Most cell types	Lymphocytes
Inducing agent	Viruses; dsRNA	Viruses; dsRNA	Mitogens
Stability at pH 2.0	Stable	Stable	Labile
Glycosylated	No	Yes	Yes
Introns in genes	No	No	Yes
Homology with IFN- α	80-95%	30%	<10%
Chromosomal location of genes	9	9	12
Size of secreted protein (number of amino acids)	165	166	143
IFN receptor	IFNAR	IFNAR	IFNGR
Chromosomal location of IFN receptor genes	21	21	6

□ viral vaccines

- We have different types of viral vaccines, we have to-kill vaccines, life-attenuated vaccines, subunit vaccines and recently we have the mRNA viruses -like different formulas of covid19- vaccines.
- It is important to know the types for each viral infections and in which cell substrate (you will take them later), for example, sometimes people who are allergic to eggs can take certain types of vaccines, so it is important to know which is the cell substrate that is being used to produce these viral vaccines.



Use	Vaccine	Type	Cell Substrate
Common	Hepatitis A	Killed	Human diploid fibroblasts (MRC-5)
	Hepatitis B	Subunit (HBsAg)	Yeast (recombinant DNA)
	Influenza A and B	Killed	Embryonated chicken eggs
	Influenza A and B	Live (intranasal)	Embryonated chicken eggs
	Measles	Live	Chicken embryo fibroblasts
	Mumps	Live	Embryonated chicken eggs and chicken embryo fibroblasts
	Papilloma	Subunit (L1)	Yeast (recombinant DNA)
	Poliovirus (IPV)	Killed	Monkey kidney cells (Vero)
	Poliovirus (OPV)	Live	Monkey kidney cells
	Rabies	Killed	Human diploid fibroblasts (MRC-5) or rhesus fetal lung diploid cells or chicken fibroblasts
	Rotavirus ^a	Live	Monkey kidney cells (Vero)
	Rubella	Live	Human diploid fibroblasts (WI-38)
	Varicella	Live	Human diploid fibroblasts (MRC-5)
Zoster	Live	Human diploid fibroblasts (MRC-5)	
Special situations	Adenovirus ^b	Live	Human diploid fibroblasts (WI-38)
	Japanese encephalitis ^c	Killed	Mouse brain
	Smallpox	Live	Calf lymph
	Yellow fever ^c	Live	Embryonated chicken eggs