DOCTOR 2020 | JU

VIROLOGY

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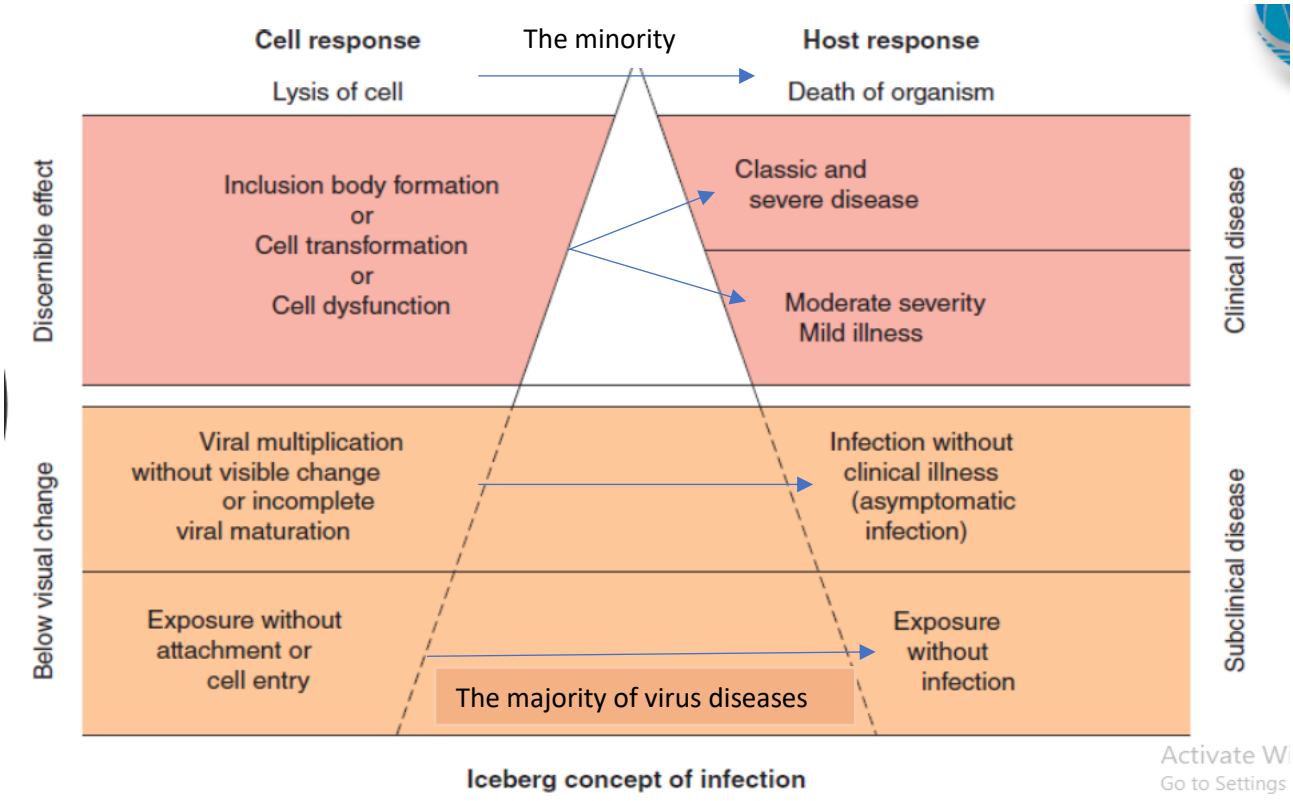
Pathogens and Control of Viral Diseases

#Principles of viral disease:

- What is the viral disease? The disease that is caused by virus infection.
- What is the clinical disease caused by a viral infection? It is the collection of symptoms that result from the viral infection.
- What is a syndrome? It is a collection of different signs and symptoms that are associated with virus disease, we are speaking in the context of viral infection.
- What is the subclinical infection? It is the presence of a virus in the body actively replicating without producing any signs or symptoms.
- What is the viral pathogenesis? It is the collection of processes from which the disease process takes place.
- What is the 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.
- What is a pathogenic virus? The virus that is able to cause disease in the human.
- What is a virulent virus? A virus that is associated with more severe disease causing more extensive damage in the infected host.

Types of Host and Cellular Responses to Virus Infection



**This picture is important

Does the virus really want to kill the host? Think!!

It is not of interest of virus to kill its host because the host supports its replication and this is a general rule in virus infections.

We will continue with principles of viral diseases:

- ♣ Many viral infections are subclinical, for a group of viruses it is the rule, the majority of virus infection are subclinical, for example Herpes viruses.
- ♣ The same disease may be produced by a variety of viruses, for example respiratory illnesses/ respiratory viral infections can result from common cold from a variety of viruses like cryovirus, coronaviruses and adenoviruses, all can similar clinical disease
- ♣ The same virus may produce a variety of diseases, for example the picornavirus the eco one or the coxsackie one they can cause skin disease
- ♣ The disease produced beers no relationship to viral morphology, so the geometry of the virus, nuclear capsid, its morphology does not have a role in the type of disease reduced by the virus
- ♣ The outcome in any case is determined both viral and host factors to a varying degree, for example in hepatitis viruses the role of direct viral pathogenicity and viral factors appear to be minimal compared to host factors, while it is more apparent and clearer in HIV infection the role of the viral factors where some viruses are more variant compared to the others and it can result in rapid progression toward AIDS, and the outcome is influenced by genetics of each.

Important Features of Two General Categories of Acute Viral Diseases (Local vs 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

Here the cellular arm of the adaptive immune system plays an important role as well beside the rule of antibodies.

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.

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

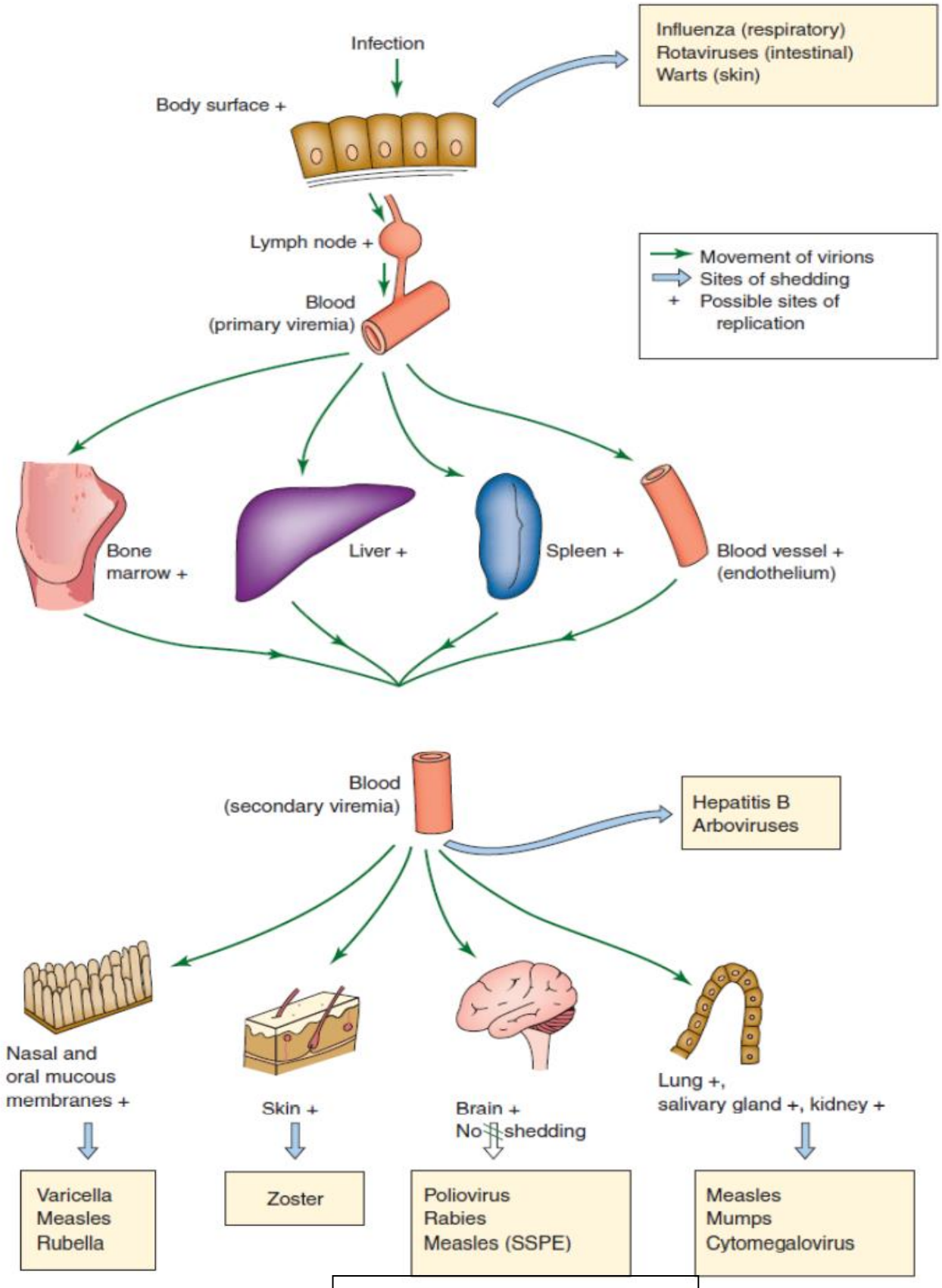
Virus Group	Produce Local Symptoms at Portal of Entry	Produce Generalized Infection Plus Specific Organ Disease
Adenovirus	Some types	
Calicivirus	Noroviruses	
Herpesvirus	Epstein-Barr virus, herpes simplex virus	Cytomegalovirus
Picornavirus		Some enteroviruses, including poliovirus, and hepatitis A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

The doctor almost read everything in these tables, so I believe they are required.

Mechanism of Spread of Virus Through the Body in Huma Viral Infections



The mechanism of spread depends if the virus infection is localized or systemic, here we are talking about systemic disease where the virus entry into the local site and then if there is systemic spread the virus will move into the nearby lymph nodes followed by entry into the blood forming the primary viremia, and then moving into the cells of the reticular endothelial system in the liver and spleen and other sites locally replicating and then it will re-enter the blood forming a secondary viremia moving into its target cells and organs.

For example, varicella measles rubella the target cells will be the mucocutaneus surfaces, for zoster it will be the skin, for poliovirus rabies and in case of SSPE it will be the CNS, it could be salivary glands in mumps, it can be the lungs in measles it can cause pneumonia, and cytomegalovirus can cause pneumonia in the kidney and can establish latency in the renal cells.

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

viruses can spread an association with certain cells, or it can be free and circulate freely in the plasma.

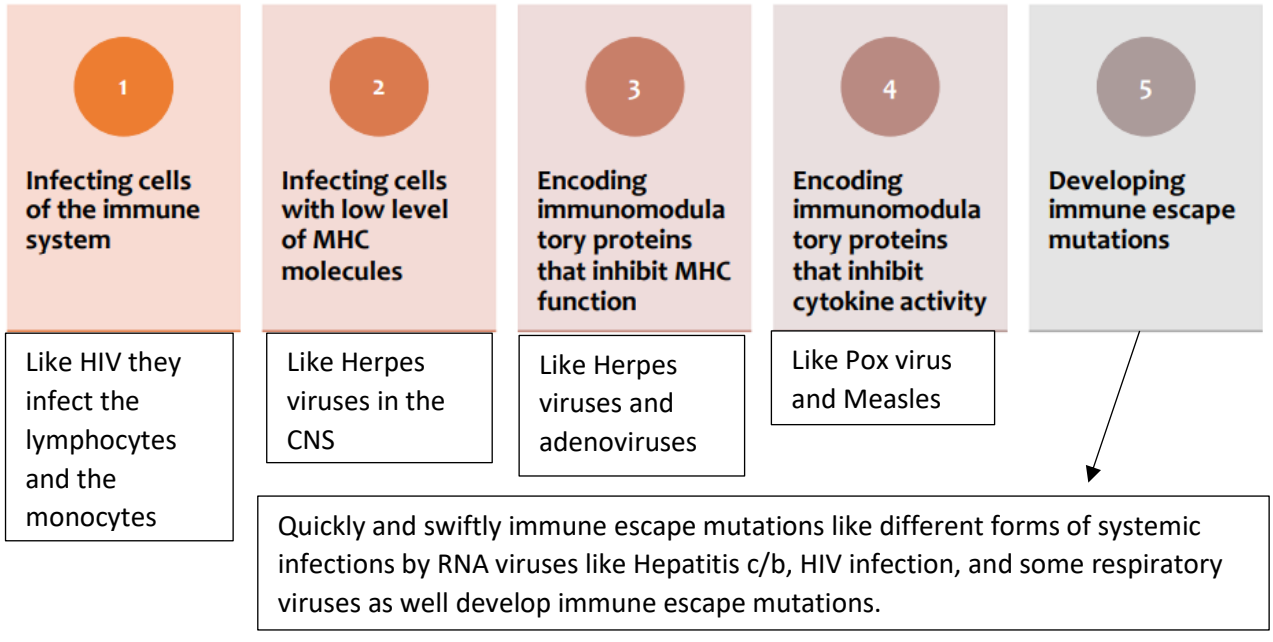
Note: infection by Influenza is mostly localized to the upper &lower respiratory tract

Host Immune Response

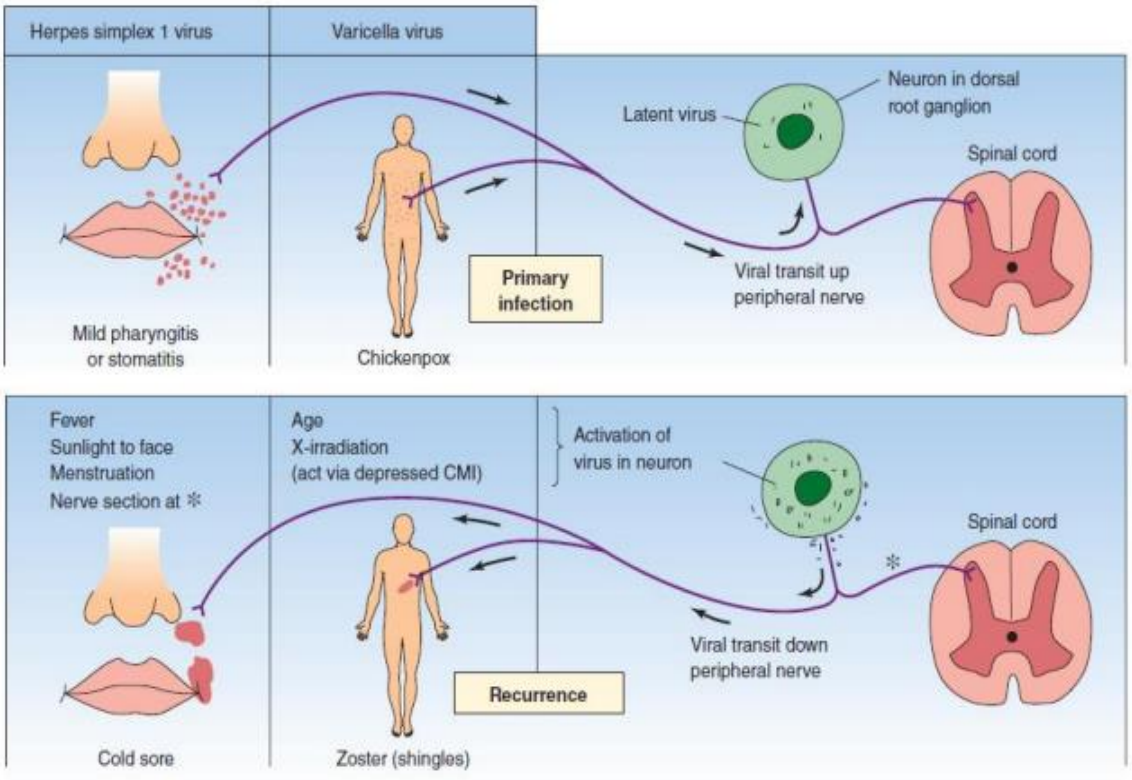
It is important in both getting rid of virus infection and in the production of the clinical disease.

- 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.
- 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 form 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 considered because it is one of the most important host immune responses to virus infection
- the Secretory Iga antibody which is important to the defense against re-exposure in localized infections.

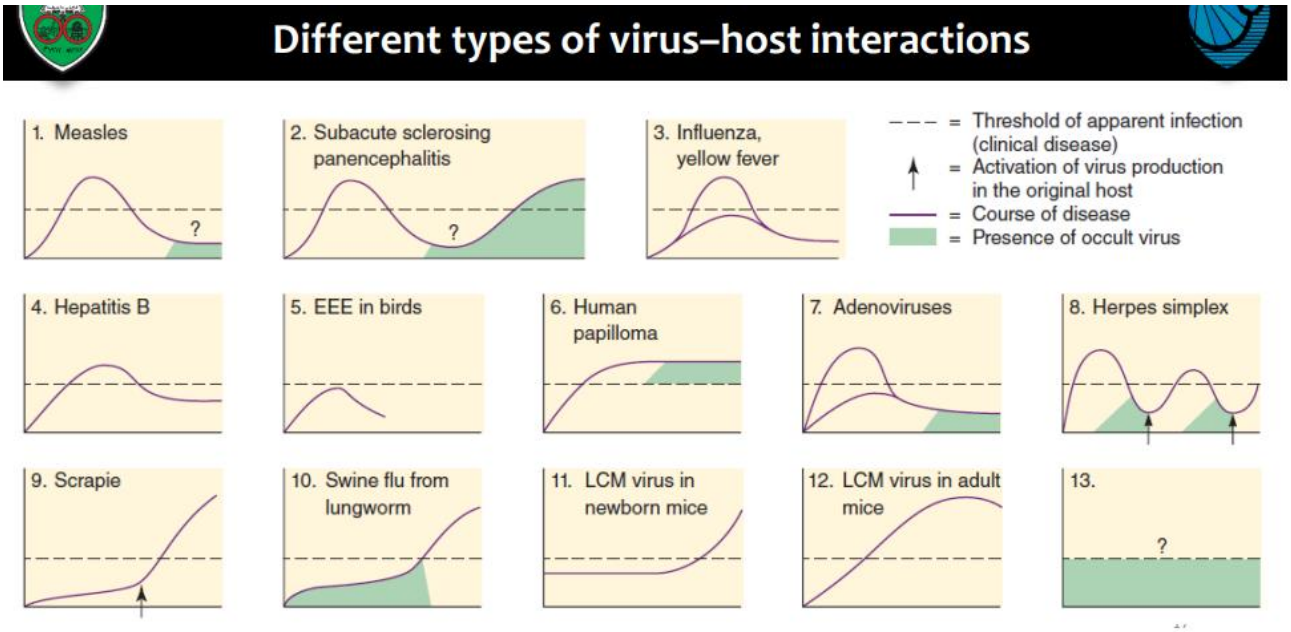
How Viruses Evade Host Immune Response



Viral persistence: chronic and latent virus infection



We have the example of Herpes simplex 1 virus and Varicella virus were following the acute manifestations of the disease the body can not get rid of the virus and the virus remains latent in certain sites in the dorsal root ganglia and it can be subjected to reactivation periodically. That's all what the doctor said here



---= the threshold of apparent infection where there is a clinical disease above it.

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 of persistence of the virus as a chronic disease.

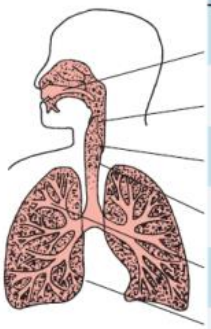
5) in Eastern equine encephalitis the replication will stop in the bird and it will form a reservoir for this virus infection.

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) 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. 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.



Viral Infections of the Respiratory Tract

Syndromes	Main Symptoms	Most Common Viral Causes[a]		
		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

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

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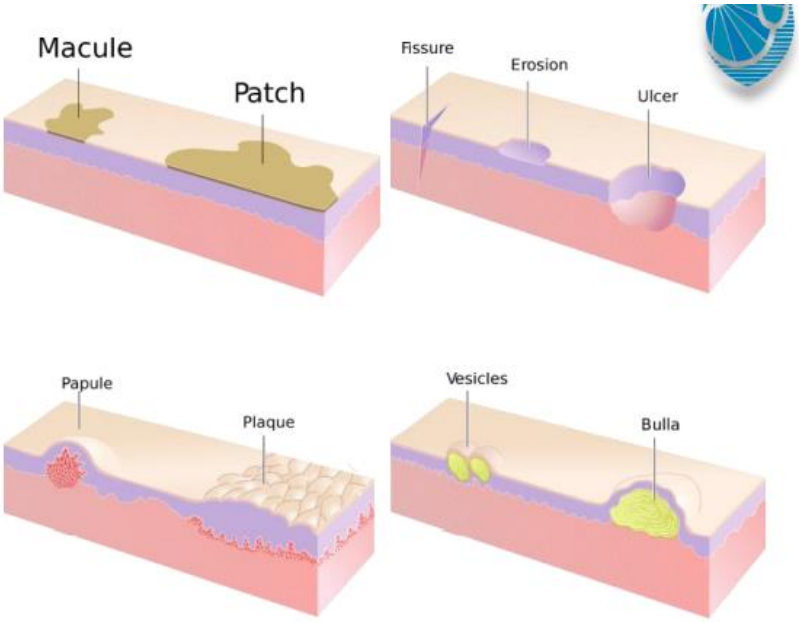
the doctor only read the names of the syndromes.

Overview of a Viral Skin Infections



For the skin infections we have a variety of viruses that may be initiated by entry throw the skin as a portal of entry, or to cause disease in the skin like papilloma, molluscum contagious virus (MCV), Herpes simplex (HSV), Arbo, Rabies, Herpes B (that is associated with contact with the primates and different types of skin), HBV &HIV. Different types of skin lesions are associated with these viral infections, like macules that are flat small lesions, or papule of vesicles with Herpes for example, etc.

Overview of Viral CNS Infections

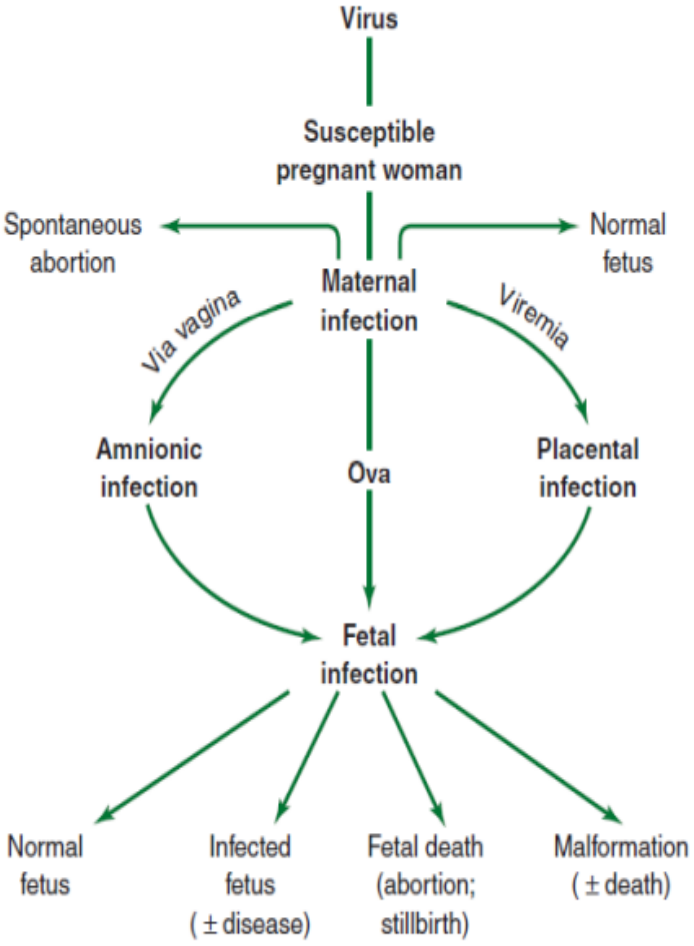
They are mostly related to the interior viruses like Herpes simplex, we are talking here about both meningitis and encephalitis, human heavies virus 6 might cause meningoencephalitis as well, varicella zoster and CMV.

Viruses
- CMV
- EV
- HSV-1
- HSV-2
- HHV-6
- HPeV
- VZV

Overview of congenital Viral Infections

There are different routes through which the fetus can be exposed or the neonate to infection from a susceptible mother when she is exposed to the virus, the outcome might be spontaneous abortion, or the production of normal fetus.

The maternal infection can happen resulting in the spread of the virus to the fetus through vaginal exposure, or through the viremia and placental infection, and the outcome for the fetus might be:



This is a very important table about the **acquisition of significant perinatal viral infections**, whether it occurs prenatally, in delivery of following it, the most common among all congenital infections cytomegalovirus.

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 immuno-deficiency virus	+	++	+	Variable
Parvovirus B19	+	–	Rare	Rare

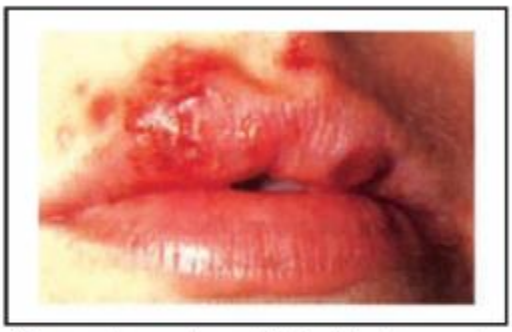
As you can see, in prenatal or natal happen most frequently in a majority of viruses except for Rubella and Parvovirus, prenatal infection occurs almost in all of these viruses in different periods in the first/second/third trimesters resulting in different outcomes from abortion to the presence of developmental abnormalities in the fetus.

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.

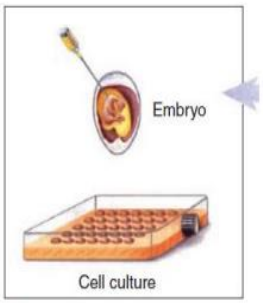
Diagnosis of Viral Infections

the approach to diagnose viral infections start with the clinical diagnosis by taking a detailed history and doing physical examination so signs and symptoms can clues to what type of viral infection we are dealing with, so the presence of cold sores on the lips can be sufficient to diagnose simplex virus infection, sometimes we can depend on using material from the tissue and examining it either by immunofluorescence microscopy, histopathologic examination, we might depend on

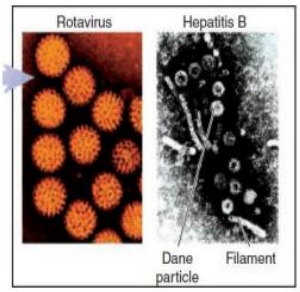


Signs and symptoms: Patient is observed for manifestations of typical virus infections. This is herpes simplex, type 1.

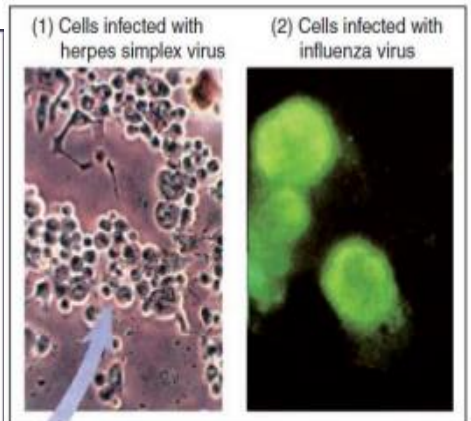
cell or viral culture using impregnated eggs, and electron microscopy is usually done but not routinely nowadays for the detection of GI viruses.



Culture techniques: Viruses require a living host to multiply.

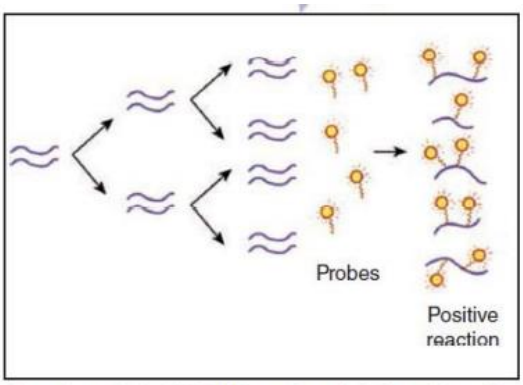


Electron microscope is used to view virus directly. Viruses are sufficiently unique in structure that they can be differentiated to family or genus.

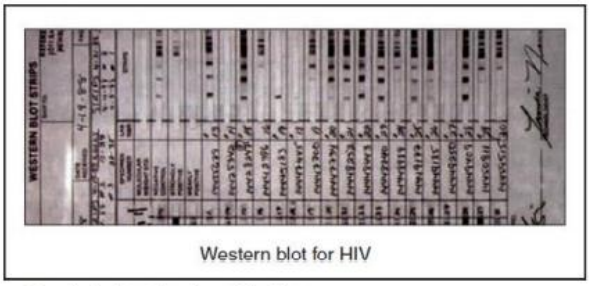


Cells taken from patient are examined for evidence of viral infection, such as cytopathic effects *(1)* or virus antigen detected by fluorescent staining *(2)*.

One of the most common methods to diagnose viral infections that are used nowadays is the molecular detection using mainly real-time PCR, but other methods like nucleic acid hybridization or conventional PCR, might be used as well sequencing for the detection of antiviral drug resistance in HIV or Hepatitis, and some serologic testing for antibodies including enzyme immunoassay chemiluminescent assays and western platform confirmation of HIV infection might be used as well.



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


Western blot for HIV

Serological testing for antibodies

Antiviral Chemotherapy

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.

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.

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

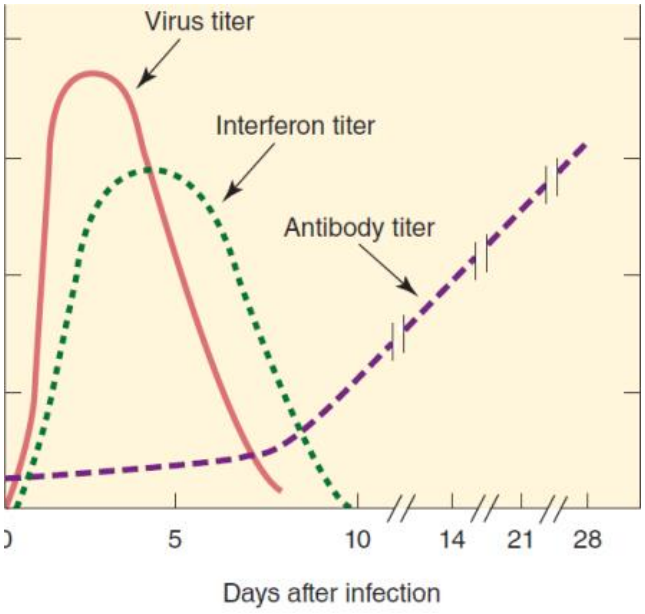
Interferons

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.

The doctor said nothing in this table.

Property	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

Kinetics of interferon and antibody synthesis after respiratory viral infection

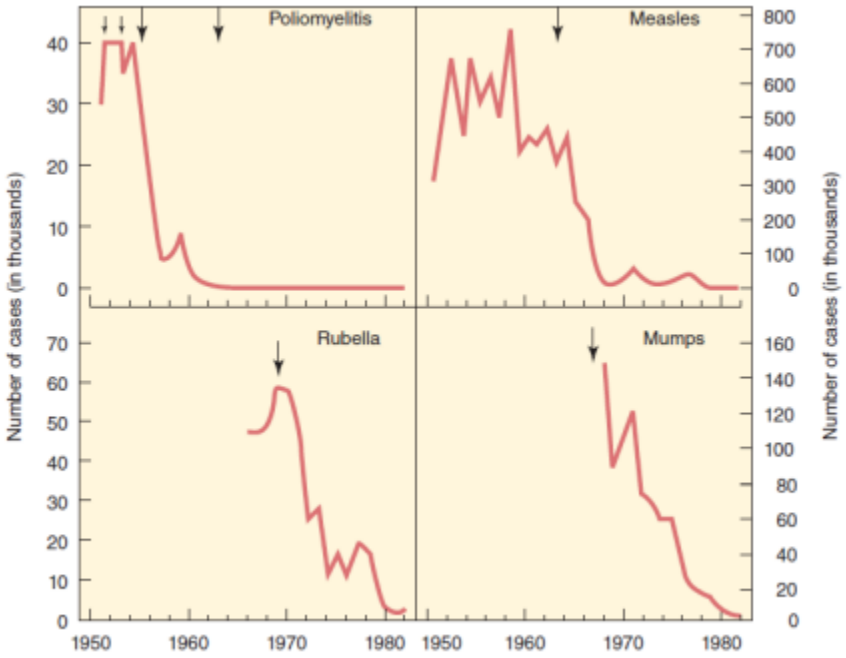


As you can see, the interferons are part of the innate immune system, and they are considered cytokines, so they are produced in a very brief period, immediately following the infection.

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 <u>if it gets infected</u>, 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.

So, interferons kick in early before the rise in antibody titer that is considered part of the adaptive immune system.

Finally, regarding **Viral Vaccines,** its effect has been huge as you can see, every arrow represents introduction of different vaccines or formulas of vaccine, you can see the enormous effect in reducing the number of cases.



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

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, 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.