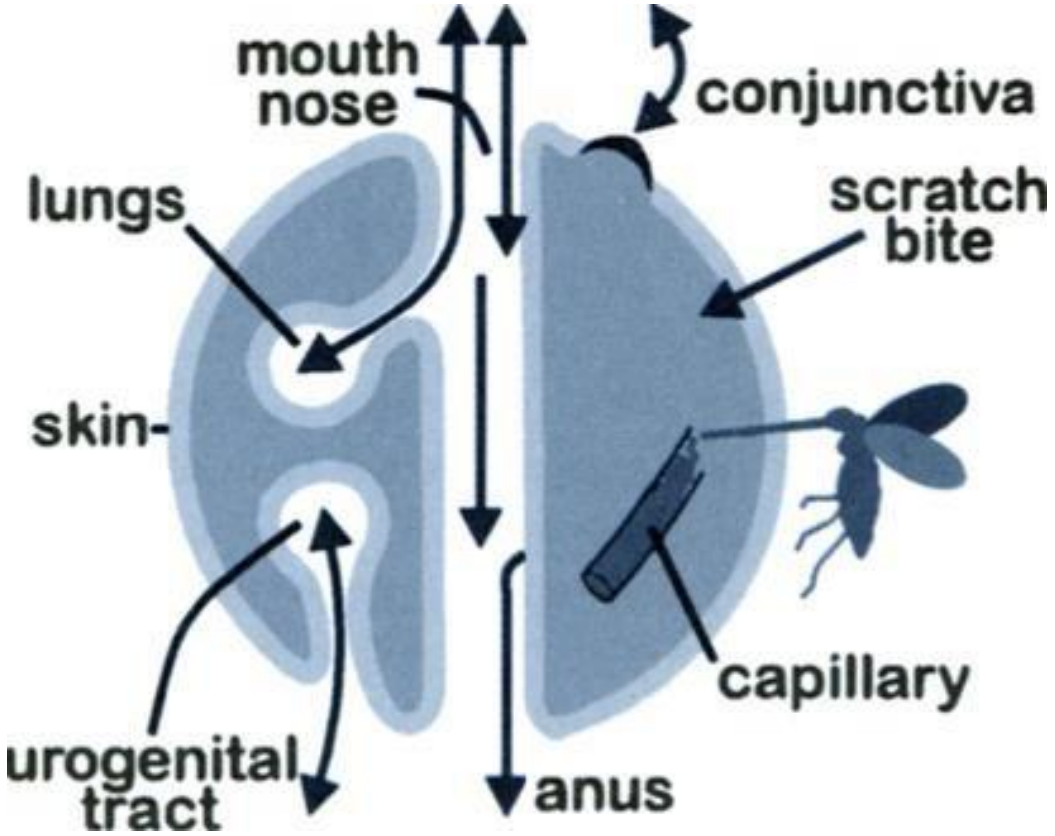


PATHOGENESIS OF VIRAL INFECTIONS AND DISEASES

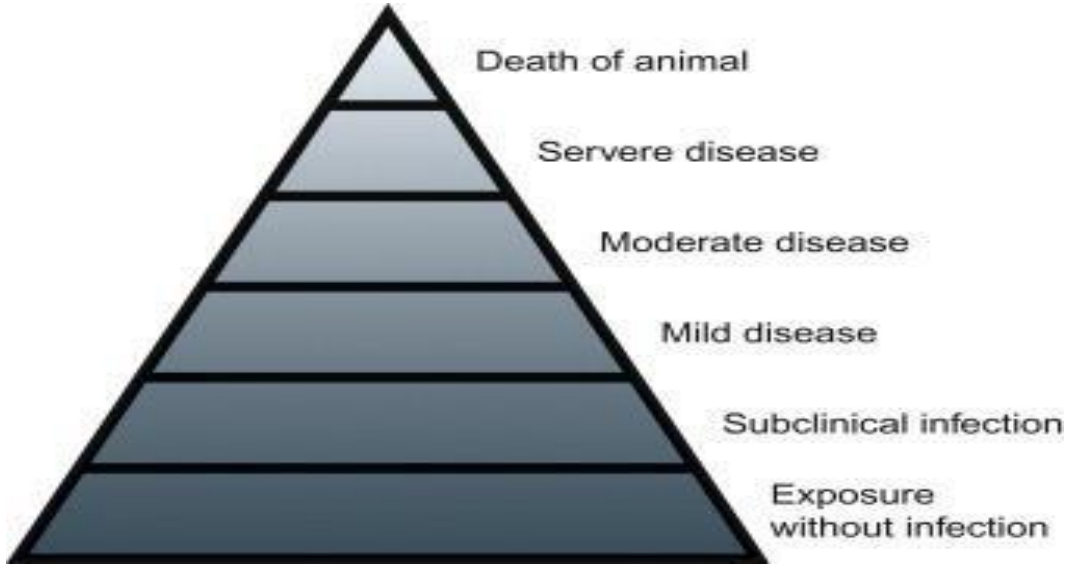
By : Dr. Agharid Ali Hussein ,Department Microbiology, Veterinary College of Veterinary Medicine, Tikrit University

Orcid: https://orcid.org/0000-0001-6551-1045
Google Scholar: http://scholar.google.com/citations?user=AmVA30UAAAAJ&hl=en

Pathogenicity of a virus

- **The terms pathogenicity and virulence refer to the capacity of a virus to cause disease inits host, and are unrelated to the infectivity or transmissibility (contagiousness) of the virus**

- **Viral infection is not synonymous with disease, as many viral infections are subclinical (i.e., asymptomatic, inapparent), whereas others result in disease of varying severity thatis typically accompanied by characteristic clinical signs in the affected host (Figure 1).**



The iceberg concept of viral infection and diseases

Obligatory Steps in Viral Infection

Step in InfectionProcess	Requirement for Virus Survival and Progression of Infection
Entry into host and primary virus replication	Avoid host's natural protective and cleansing mechanisms; at the cellular level, the virus takes over necessary host-cell functions for its own replication processes
Local or general spread in the host (defined by cell and tissue tropism), with secondary virus replication	Avoid immediate host defenses (innate immune and inflammatory responses) and natural barriers to spread Damage to the host may occur at this and later stages
Shedding from host	Exit host body at site and at concentration needed to ensure infection of the next host
Evasion of host inflammatory and immune defenses	Avoid host inflammatory, phagocytic, and immune defenses long enough to complete the virus transmission cycle
Cause damage to host	Not necessary, but this is the reason we are interested in the virus and its pathogenetic processes

❑ Routes of Entry : Entry of viruses via:

- **Respiratory Tract: The respiratory tract is the most common portal of virus entry into the body. The respiratory tract from nasal passages to the distal airways in the lungs protect by the mucociliary blanket produced by goblet cells. Inhaled virions can be trapped in the vicious mucus layer and then carried by ciliary action from the nasal cavity and airways to the pharynx, where they are then swallowed orcoughed out. After invasion, some viruses remain localized or spread from cell to cell to invade other tissues, whereas many Viruses disseminated via lymphatics and/or the bloodstream.**
- **Gastrointestinal Tract : A great number of viruses (enteric viruses) are spread to susceptible hosts by ingestion of virus contaminated food or drink. Viruses that cause purely enteric infection, such as rotaviruses and enteroviruses, are acid and bile resistant. Some enteric viruses (rotaviruses) resist inactivation by proteolytic enzymes in the stomach and intestine that cleavage of an outer capsid protein and enhances theinfectivity. Some viruses reaching cells of the gastrointestinal tract after viremic spread(here viruses enter the bloodstream).**
- **Skin : Viral infection of skin occurs by: Insect or animal bites, cuts, punctures, or scratches display viral infection, which can either remain confined to the skin, such as the papillomaviruses or disseminate(spread) widely. One of the most efficient ways via the bite of arthropods, such as mosquitoes, ticks, Culicoides spp or sandflies. Most viruses that are spread by arthropods replicate in their vector, called "biological" vector. Virus penetrate skin may be result from veterinary or husbandry procedures. transmitted via contaminated needles, twitches, ropes, and harnesses,. In animals without significant areas of keratinized epithelium (eg, fish), the skin and gills serve as an extensive mucosal surface that is the initial site of infection with many viruses.**
- **Entry via Other Routes: Several important pathogens (eg, several herpesviruses and papillomaviruses) are spread through the genital tract, and this is known as venereal transmission.**

❑ Host Specificity and Tissue Tropism

Most viruses do not infect all the cells of a host but are restricted to specific cell types of certain organs. The spectrum of tissues infected by a virus is called tropism. For example, an enterotropic virus replicates in the gut, whereas a neurotropic virus replicates in cells of the nervous system.
Some viruses are pantropic, infecting and replicating in many cell types and tissues.
the results of the initial infection for most viruses, can vary widely depending on

- **the site of entry.**
- **The cell types infected.**
- **The responses of local sentinel immune cells.**
- **The architecture and vasculature of the tissues involved.**
- **The host species being infected.**

All these variable elements during viral infection has led to the concept of viral tropism. Viral tropism refers to the ability of a given virus to productively infect a particular cell (cellular tropism), tissue (tissue tropism) or host species (host tropism).

❑ Virus Spread Within the Body

- ❑ **Local Spread on Epithelial Surfaces: Many viruses replicate in epithelial cells at the site of entry and produce a localized or spreading infection in the epithelium and some are then shed directly into the environment from these sites.The spread of infection along epithelial surfaces usually occurs by the sequential infection of neighboring cells. Many poxviruses produce infection via the skin, but in addition to spreading from cell to cell, there is usually also local subepithelial and lymphatic spread.**
- ❑ **Subepithelial Invasion and Lymphatic Spread : Viruses can enter the network of lymphatics beneath all cutaneous and mucosal epithelia. Virions entering the lymphatics are carried to local draining lymph nodes. Virus particles are exposed to active macrophages and dendritic cells and may be engulfed, inactivated, and/or processed for viral antigen presentation to adjacent lymphocytes, thereby initiating the adaptive immune response.**
- ❑ **Spread via the Bloodstream: Viremia: The blood is the most effective and rapid vehicle for the spread of virus through the body. Once a virus has reached the bloodstream, usually via the lymphatic system, it can localize in any part of the body within minutes. The first entry of virus into the blood is called primary viremia. This early viremia may be clinically silent, known to have taken place only because of the invasion of distant organs. Virus replication in major target organs leads to the sustained production of much higher concentrations of virus, producing a secondary viremia.**
- ❑ **Spread via Nerves : Although infection of the CNS can occur after hematogenous spread, invasion via the peripheral nerves is also an important route of infection for example :Herpesviruses can travelto the CNS in axon cytoplasm and, sequentially infect Schwann cells of the nerve sheath.**

❑ Viral Shedding

Shedding of infectious virions is crucial to the maintenance of infection in populations, shedding of infectious virions us occurs from the same organ system involved in virus entry, shedding can occur from a variety of sites , and some viruses are shed from several sites . The mean routs of Viral Shedding are

1. **RespiratoryTract: Many different viruses that cause localized disease of the respiratory tract are shed in mucusor saliva and are excluded from the respiratory tract during coughing, sneezing, eating, and drinking.**
2. **Oropharynx and Intestinal Tract : Enteric viruses are shed in the feces. In general Enteric viruses are more resistant to inactivation by environmental conditions than respiratory viruses such viruses can persist for some time.**
3. **The Skin: The skin is an important source of virus in diseases in which transmission is by direct contactor via small abrasions: cowpox ad vaccinia viruses, as well as papillomaviruses employ this mode of transmission.**
4. **The Urinary Tract:Urine, like feces, tends to contaminate food supplies and the environment. A number of viruses (e.g., infectious canine hepatitis virus, foot-and-mouth disease viruses) replicate in tubular epithelial cells in the kidney and are shed in urine**
2. **The Genital Tract:Several viruses that cause important diseases of cattle, horses, and sheep are excreted in the semen and are transmitted during coitus.**
4. **Milk :Several viruses replicate in the mammary gland and are excreted in milk, which may serve asa route of transmission, e.g., mouse mammary tumor virus.**
5. **Blood and Tissues :blood and tissues from slaughtered animals must be considered important sources of viral contagion. Blood is the usual source from which arthropods acquire viruses, and blood may also be the source of viruses transferred to the avian egg or mammalian fetus.**
6. **Virus Infection Without Shedding Many sites of virus replication might be considered “dead ends” from the perspective of natural spread. Infection of the brain may not result in shedding in the case of paramyxoviruses, although it is significant from the standpoint of clinical disease.**

❑ Types of Virus -Cell Interactions

Viral infections may be cytocidal (cytolytic, cytopathic) or non-cytocidal, and productive or non-productive (abortive)—that is, not all infections lead to cell death or the production and release of new virions.

A. Cytopathic infections

They are characterized by loss of cell functions that are essential to survival Cell degeneration and necrosis or virus-induced apoptosis known as *Cytocidal or* cell death are final outcomes of cytopathic. While, cytolytic (Cell lysis) is required for release of nonenveloped viral progeny, whereas progeny of enveloped viruses can be released by budding from viable cells.(Production of Infectious Virions).

1. ***Inhibition of Host-Cell RNA Transcription*** this inhibition may be the indirect consequence of viral effects on host-cell protein synthesis that decrease the availability of transcription factors required for RNA polymerase activity. Such in **poxviruses, rhabdoviruses, reoviruses, paramyxoviruses, and picornavi**ruses
2. ***Inhibition of Processing of Host-Cell Messenger RNAs*** occurs during replication of influenza viruses, and herpesviruses, through interference with the splicing(remove) of cellular primary mRNA transcripts that are needed to form mature mRNAs.
3. ***Cytopathic Effects of "Toxic" Viral Proteins*** reflect the accumulation of large amounts of various viral components in the cell late in infection For example, the toxicity of adenovirus penton and fiber proteins appears to be direct and independent of adenovirus replication.
4. ***Interference with Cellular Membrane Function***

Viruses may alter plasma membrane permeability, affect ion exchange and membrane potential, or induce the synthesis of new intracellular membranes or the rearrangement of previously existing ones

B. Persistent, productive(Noncytopathic infections)

Noncytocidal viruses usually do not kill the cells in which they replicate, cause persistent infection, in which infected cells produce and release virions. ´ Mainly occur in RNA Virus noncytopathic infections can be clinically significant when they disruptcell specialized functions. For example, noncytopathicinfections of neurons may cause loss of impulse conduction.(Production of Infectious Virions

C. Persistent, non-productive (Latent infection)

Latent infection ("exists but is not exhibited") may be viewed as a type of persistent infection in which the viral genome is not transcribed and so there is no production of viral proteins or progeny. The viral genomeis maintained indefinitely in the cell, either by the integration of the viral nucleic acid intothe host cell DNA or by carriage of the viral nucleic acid in the form of an episome, and the infected cell survives and may divide repeatedly. (No, **Production of Infectious Virions** but virus may be induced

D. Transformation

It is mean the changes associated with loss of normal homeostatic control, particularly of cell division, which ultimately results in the development of a neoplastic phenotype.

Alteration in cell morphology; cells can be passaged indefinitely; may produce tumors when transplanted to experimental animals there two types of transformation interaction : a) **No, oncogenic DNA viruses** (فيروسات الحمض النووي الغير المسرطنة) such as Polyomavirus, adenoviruses not **produce of Infectious Virions** b) **Oncogenic Retroviruses produce of Infectious Virions)**

E. Ultrastructural Changes in Virus-Infected Cells

Early changes in cell structure often are dominated by proliferation of various cell membranes: for example, herpesviruses cause increased synthesis, even reduplication, of nuclear membranes; flaviviruses cause proliferation of the endoplasmic reticulum; picornaviruses and caliciviruses cause a distinctive proliferation of vesicles in the cytoplasm. Other ultrastructural changes include disruption of cytoskeletal elements, mitochondrial damage, and changes in the density of the cytosol.

D. Virus-Mediated Tissue and Organ Injury

The severity of a viral disease is not necessarily correlated with the degree of cytopathology produced by the causative virus in cells in culture. Many viruses that are cytocidal in cultured cells do not produce clinical signs in vivo (eg, many enteroviruses, whereas some that are noncytocidal in vitro cause lethal disease in animals (eg, rabies virus). depending on the organ affected, cell and tissue damage can occur without producing clinical signs of disease a large number of hepatocytes (liver cells) may be destroyed in Rift Valley fever in sheep without obvious clinical signs.