The Paramyxoviridae

The Paramyxoviridae include some of the great and ubiquitous disease-causing viruses of humans and animals, including one of the most infectious viruses known (measles virus), some of the most prevalent viruses known (parainfluenza viruses, mumps virus, Rinder pest, Canine distember and respiratory syncytial virus), a virus that has been targeted by the World Health Organization(WHO) for eradication (measles virus).

Also important viruses that have a major economic impact on poultry and animal rearing (**Newcastle disease virus and rinderpest virus**).

Classification

The family Paramyxoviridae is classified into two subfamilies the Paramyxovirinae and the Pneumovirinae.

The **Paramyxovirinae** contains five genera:

1- **Respirovirus** which cause (Human parainfluenza virus1and 3).

2- **Rubulavirus** which included, Mumps virus, Para influenza virus 2,4a, 4b.

3- **Avulavirus** (Members of this genus include the Newcastle disease virus).

4-**Morbillivirus**:- which included, rinderpest virus, Canin distember virus and measles virus.

5- **Henipavirus** which included Hendra virus (HeV) and Nipah virus (NiV).

The Pneumovirinae contains two genera:

1- **Pneumovirus**:- which included Human respiratory syncytial virus (HRSV), bovine syncytial respiratory virus (BRSV).

2- **Metapneumovirus**:- which include Avian metapneumovirus cause Turkey rhinotracheitis virus.

Morphology and Structure

Nonsegamented single- stranded RNA of **negative sense**, replicated **entirely in the cytoplasm**, their genomes are 15 to 19 kB in length. Paramyxoviridae are generally spherical, 150 to 350 nm in diameter, but can be pleomorphic in shape, and filamentous forms can be observed.

Structural units of capsid protein called nucleocapsid surrounded the RNA genome to give a helical symmetry with a zipper like appearance by negative staining.

The envelope is composed of a lipid bilayer which contains matrix protein.

A lipid envelope containing two surface glycoproteins which comprise separate spikes (fusion glycoprotein (F) and a second glycoprotein variously called hemagglutinin-neuraminidase (HN) surrounds the virions

Host Range

Man:- Can be infected with Mumps, Parainfluenza(PI) 2, 4a, 4b, Measles, Respiratory syncytia virus, Newcastle disease virus of poultry (conjunctivitis).

Cow:- Can be infected with Rspiratory syncytial virus, PI-3, Rinderpest virus.
Sheep, goats, Pigs:- PI-3, Rinderpest virus
Dog:- PI-5, Canine distember virus (CDV).
Horse:- PI-3(rarely).
Mouse:- Pneumonia virus of mice.
Mouse and Hamster:- PI-5 which is also called Simiun virus-5
Bird:- Newcastle disease virus in chickens, Turkeys, Pheasant, Duck, Psittacine and Pigeons.

Genus/ Avulavirus:-

Species Newcastle disease virus (NDV)

NDV:- Is a contagious disease caused by virulent avian paramyxovirus in the genus *Avulavirus*. There are ten serotypes of avian paramyxoviruses designated APMV-I to APMV-10 and ND virus (NDV) has been designated APMV-1.

The disease affected a wide range of avian species including Chickens, Turkey, Pigeons. Ducks and Geese are less susceptible.

Pathogenesis:

Virus spreads by ingestion or inhalation. The virus replicates in epithelial cells of R. T and intestinal tract, then spread by blood to spleen and bone marrow and then from later to lung, intestine and CNS, the spared depended on the strain virulence.

NDV Isolates can be divided into:

a-Lentogenic: which are a virulent that remain localized causing subclinical infection (Hitchners form).

b-Mesogenic: Causing mild disease with mortality about 25% confined to young birds (Beudette's form).

c-Viscerotropic Velogenic: This isolates causing severe fatal disease characterized by hemorrhagic intestinal lesions(Doyle's form) and high mortality rate may reach 100%.(fowl pest).

d- **Neurotropic Velogenic** : This isolates causing acute disease characterized by nervous and respiratory signs with high mortality (Beach's form).

CLINICAL SIGNS AND LESIONS

Incubation period(I.P) 5 days

The clinical signs depend on virulence of viral strain. Tissue tropism, age and immune system status of the host.

1-prostration and depression in the birds.

2- Ruffled feathers.

3- Greenish white diarrhoea.

4-The head turned to one side, a condition known as **torticollis**.

5-Paralysis of the legs, wings or other neurological signs.

6-Other typical characteristics of the disease include: rapid spread; death within 2-3 days.

7- On necropsy, typical lesions are mucus in the trachea, and usually haemorrhages in the intestine, particularly in the proventriculus.

Diagnosis:-

1- CLINICAL SIGNS AND LESIONS

For a definitive diagnosis of ND, both virus isolation and laboratory characterization are necessary.

2- SEROLOGICAL DIAGNOSIS

The presence of specific antibodies against the ND virus indicates that the bird has been infected by the virus. In practice, a high antibody titre is indicative of a recent infection. Two methods are used to measure antibody titres: the **haemagglutination inhibition (HI)** test, and **the enzyme-linked immunosorbent assay (ELISA)**. For both, it is necessary to collect blood samples from the chickens.

VIRUS ISOLATION

The definitive diagnosis of ND is done through isolation and identification of the virus. Tracheal and cloacal swabs are good sources of virus for isolation from living birds without having to kill them. Virus can also be isolated from homogenised organs from dead birds, chosen to reflect the clinical signs. Nine-day-old embryonated fowls' eggs are injected with 0.1 mL of the suspension into the allantoic cavity and returned to incubation. The eggs are candled twice daily. As dead eggs occur, they are chilled, together with d all eggs after 5-7 days incubation, are chilled at 4°C at which point the allantoic fluid is then harvested and tested for its ability to haemagglutinate chicken red blood cells. Diagnosis is based on the inhibition of haemagglutination by specific anti-NDV serum. This proves infection of the bird by the virus, but does not indicate whether the virus is **a pathogenic** or **avirulent strain**.

Control, No treatment:

Restriction of eggs and chicken importation.

In new outbreaks, cleaning, and disinfection are essential and movement must be restricted.

Vaccination with lentogenic strains at 7 days old and repeated in 21 days old.

Vaccination is done by aerosol or drinking water.

-One age group per farm ('all in-all out') breeding is recommended; disinfection between groups during outbreaks.

Vaccination:-

One of the most important considerations for any vaccination programmed is the type of vaccine to be used, **the immune and disease status of the birds** to be vaccinated, **the level of maternal immunity in young chickens** and **the level of protection required in relation to any possibility of infection** with field virus under local conditions.

Bird must be vaccinated with lentogenic strain (e.g. Hitchner-B1, Lasota) at 7 days old chicks and repeated of 21 days old.

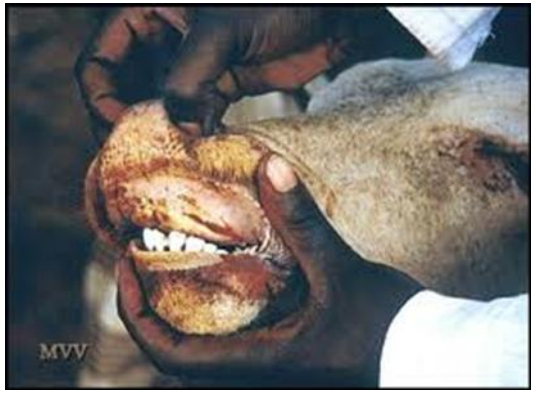
Live virus vaccines administered to birds by incorporation in the drinking water, or **as a coarse spray**, or by intranasal or conjunctival instillation; some mesogenic strains are given by wing-web intradermal inoculation.

Inactivated vaccines tend to be more expensive than live vaccines application entails handling and injecting individual birds prepared from allantoic fluid that has had its infectivity inactivated by formaldehyde incorporated into an emulsion with mineral oil, and is administered intramuscularly or subcutaneously.

Rinderpest:- Rinderpest (**RV**) (**cattle plague)**was an acute to subacute **contagious viral disease of ruminants and pigs that could cause morbidity and mortality rates in excess of 90%.**

Host: Cattle, domesticated buffalo and some species of wildlife can be infected naturally. Rabbits, mice, hamsters and chicks embryos can be infected experimentally.

The classical form of rinderpest is one of the most lethal diseases of cattle, and can have a catastrophic effect. Despite its extreme lethality, the virus is particularly fragile and is quickly inactivated by heat.



Pathogenesis and Clinical Signs:

1- Highly infectious virus is excreted on aersol in nasal and ocular exudates and in saliva and faeces.

2- Primary replication occurs in epithelium of lymphoid cells of the orophorynx followed by viremia.

3- Incubation period 3-10 days. The secondary localization of the virus in the alimentary tract and respiratory tract.

4- Diarrhoea and dysentery, salivation and exudative dermatitis.

Stage of pathogenesis

1-Prodromal period lasts approximately 3 days: affected animals develop a pyrexia of between 40 and 41.5°C together with partial anorexia, depression, reduction of rumination, constipation, lowered milk production, increase of respiratory and cardiac rate, congestion of visible mucosae, serous to mucopurulent ocular and nasal discharges, and drying of the muzzle.

2- **Erosive phase** with development of necrotic mouth lesions at height of fever: flecks of necrotic epithelium appear on the lower lip and gum and in rapid succession may appear on the upper gum and dental pad, on the underside of the tongue, necrotic material works loose giving rise to shallow, nonhaemorrhagic mucosal erosions

• Gastrointestinal signs appear when the fever drops or about 1–2 days after the onset of mouth lesions.

Control

Slaughter of infected and in contact animals, along with incineration, disinfection and movement restriction may be made in controlled systems of husbandary.

In enzootic areas mass vaccination is practised. All susceptible ruminants must be vaccinated .

Originally virus passaged in rabbits, goats or eggs was given as live or inactivated vaccine. Currently the vaccine used is freeze dried virus which has been attenuated by repeated passage in calf kidney cells. It is highly protective under adequately organised systems of husbandry and animal movement.

Orthomyxoviridae

Orthomyxoviridae

The family of Orthomyxoviridae is defined by viruses that have **a negative-sense, single-stranded, and segmented RNA genome.**

The family includes six genera: Influenza virus A, Influenza virus B, Influenza virus C, Isavirus, Thogotovirus and Quaranjavirus

The orthomyxoviridae comprise the influenza viruses which are usually spread within a species by droplet or direct contact lead to upper respiratory infections.

Classification

The Orthomyxoviridae are a family of RNA viruses that includes five genera:

1- Influenza virus A (infects birds, humans, and other mammals like, horses, swine, mink seals, and whales).

2-Influenzavirus B (infects humans only).

3- Influenzavirus C (infects humans and pigs).

4-Isaviruses: infect fish causes severe anemia of infected fish.

5-Thogotoviruses infect vertebrates and invertebrates, such as mosquitoes and sea lice.

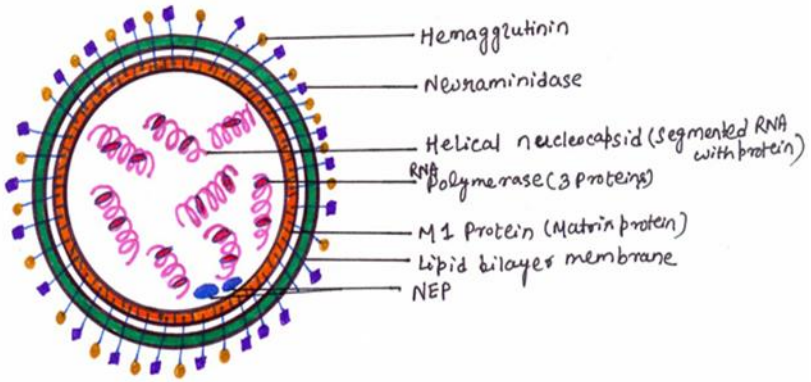
6-Quaranjavirus: is a new genus of enveloped RNA viruses, one of six genera in the virus family Orthomyxoviridae that infect arthropods and birds.

Structure

The influenza A virus particle or virion is 80-120 nm in diameter and usually roughly spherical, although filamentous forms can occur. Virions consist of an envelope with large peplomers surrounding eight (genera *Influenzavirus A and Influenzavirus B),* seven (genus *Influenzavirus C), or six (genus Thogotovirus)* helically symmetrical nucleocapsid segments of different sizes. Transcription and RNA replication occur **in the nucleus**, budding takes place on the plasma membrane.

Because of the segmented nature of the genome surface antigens, when a host cell is infected with two different influenza viruses, the progeny virus can be a mixture of both "parent" viruses.

Reassortment provides for increased biological variation that increases the ability of the virus to adapt to new hosts.



The appearance of variant viruses not only depends on genetic drift, i.e., point mutations (nucleotide substitutions, insertions, deletions), but also on genetic shift, i.e., genomic segment reassortment. Drift and shift of two genes.

Genetic Drift: Minor mutation in hemaglutinin or neuraminidase; does not require a new vaccine.

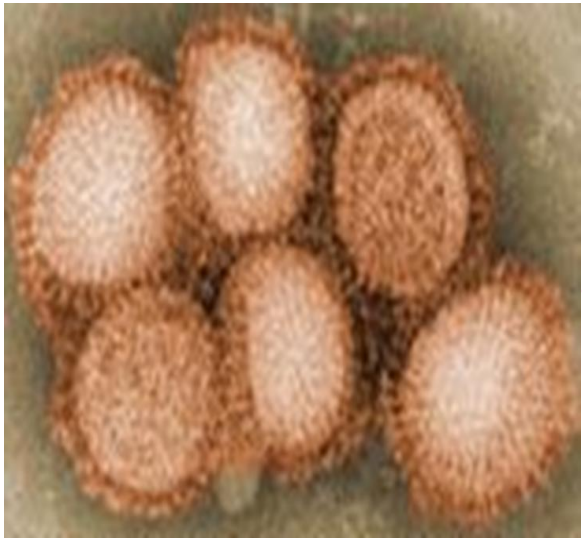
Genetic Shift :Major mutation in hemagluttinin or neuraminidase; need a new vaccine.

Unusually for a virus, the influenza A genome is not a single piece of nucleic acid; instead, it contains **eight pieces** of segamented negative-sense RNA (13.5 kilobases total) which encode 11 proteins (HA, NA, NP, MI, M2, NS1,NEP, PA, PB1, PB1-F2, PB2), the best characteristic of these viral proteins are **hemagglutinin and neuraminidase**, two large glycoproteins found on the outside of the viral particles.

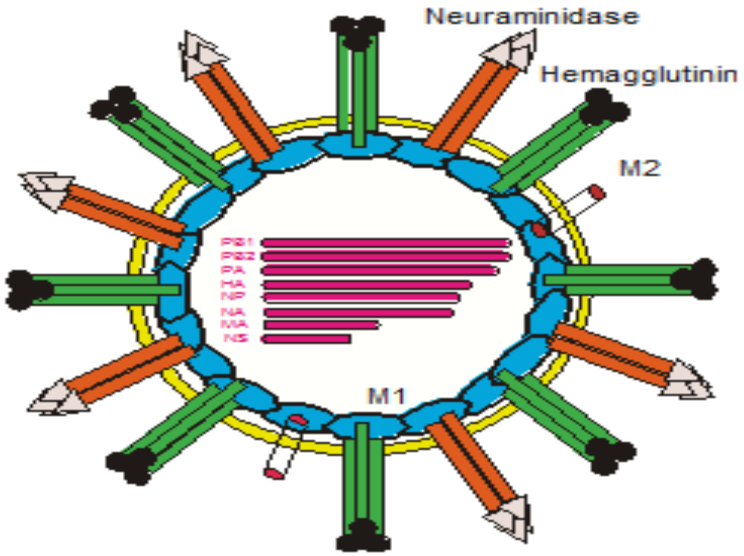
Hemagglutinin is a lectin that mediates binding of the virus to target cells and entry of the viral genome into the target cell. By contrast,

Neuraminidase is an enzyme involved in the release of progeny virus from infected cells, by cleaving sugars that bind the mature viral particles.

The hemagglutinin (H) and neuraminidase (N) proteins are targets for antiviral drugs. These proteins are also recognized by antibodies, i.e. they are antigens. The responses of antibodies to these proteins are used to classify the different serotypes of influenza A viruses, hence the *H* and *N* in *H5N1*.



16 Hemagglutinin subtypes
9 Neuraminidase Subtypes



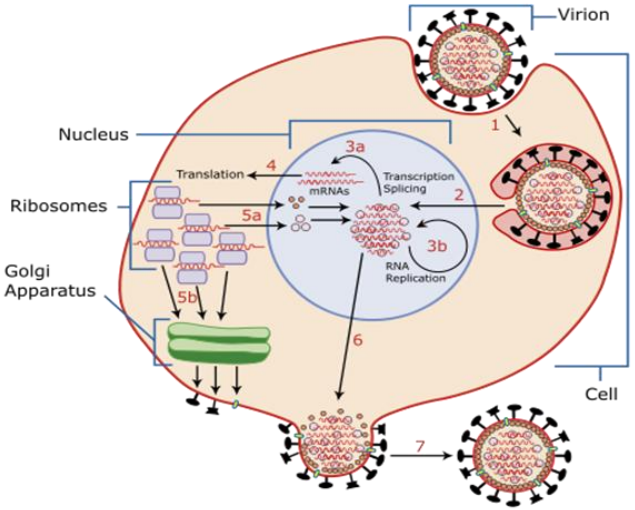
At present eighteen hemagglutinin subtypes (H 1-18) and eleven neuraminidase subtype (N 1-11) of influenza A viruses have been recognized, all this types were extremely variable in virulence.
H5 and H7 are the most dangerous, highly virulent AI viruses cause the disease fowl plague.
The nucleocapsid is helical. The virus have 2 Pathotypes: HPAI, LPAI

Replication cycle

Orthomyxoviridae viruses are one of the only RNA viruses that replicate in **the nucleus**. This is because the machinery of orthomyxo viruses cannot make their own mRNAs.

Typically, influenza is transmitted from infected mammals through the air by coughs or sneezes, creating aerosols containing the virus, and from infected birds through their droppings. Influenza can also be transmitted by saliva, nasal secretions, feces and blood.

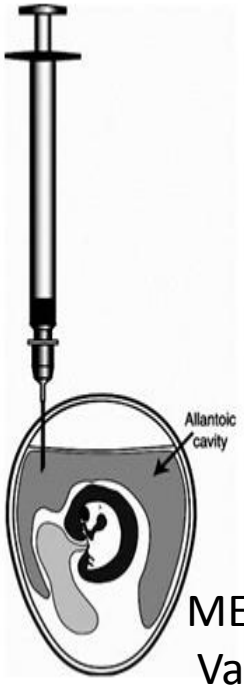
During the production of progeny virus, the host cell's own protein synthesis is effectively shut down. Finally, having produced many thousands of new virus particles, the cell lyses and dies as a result of the infection.



Cultivation and Cytopathic effect

1-Influenza viruses are routinely grown to high titer in the allantoic cavity of 10-days fertile eggs.

2-Some influenza isolates grow in cell cultures and yield cytopathic effect characterized by cells rounding and later detachment from the flask. Eggs are therefore still used for isolation of virus and preparation of vaccines.



METHODS OF CULTIVATION

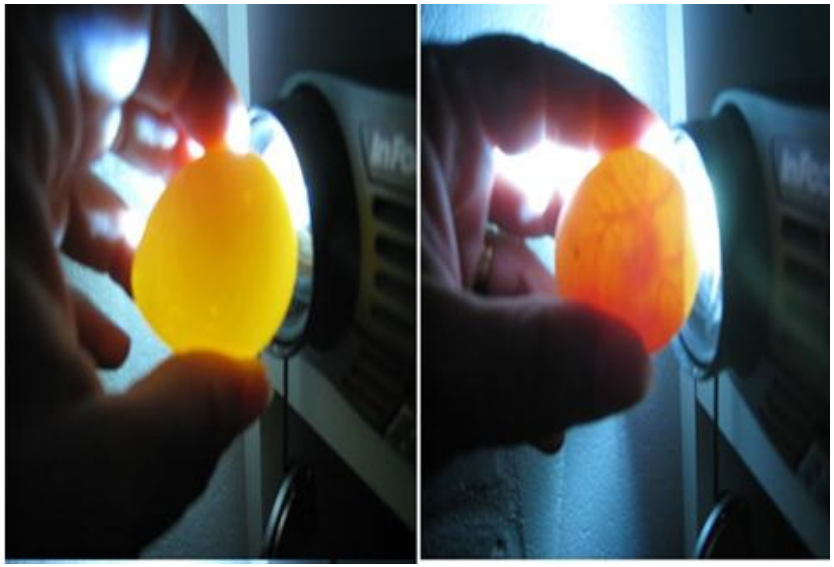
Various routes of inoculation

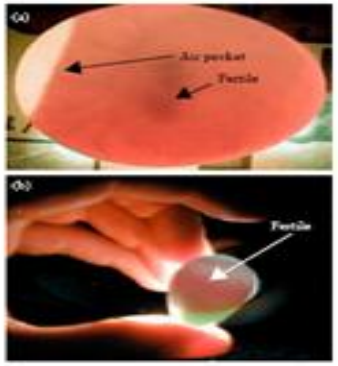
a)Yolk sac

b) Allantoic sac

c) Chorioallantoic membrane (CAM)

d) Amniotic cavity




(a)
Air pocket
Fertile
(b)
Fertile

Influenza Nomenclature

A/Chicken/Pennsylvania/1370/83 (H5N2)

1) Antigenic type

2) Isolate host of origin

3) Geographic location

4) Isolate reference

5) Year of isolation

6) Hemagglutinin subtype

7) Neuraminidase subtype

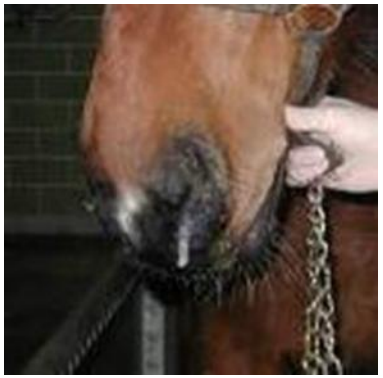
Established by WHO in1980, the nomenclature of Influenza A consists of: type of host, in case the virus has not been isolated from humans; geographical region of origin; number of lineage; year of isolation and; protein antigen type, described by letter and number, H1 to H18 known to date, and N1 to N11. The current pandemic influenza, for example:

A/California/04/2009(H1N1) Influenza type A, isolated firstly in California, lineage number 04, year of 2009 and type H1N1.

Equine Influenza

Is highly contagious and spreads rapidly among naive horses. Horses 1–5 yr old are the most susceptible to infection. The disease caused by strains of influenza A that are enzootic in horse species. Equine influenza occurs globally, and is caused by **two main strains** of virus: equine-1 **(H7N7)** and equine-2 **(H3N8).**

The differentiation of equine influenza from other equine respiratory diseases was established in 1956 when influenza virus ***A/equine/Prague/1/56 (H7N7)*** (*equine influenza* virus 1) was isolated in an epidemic in central Europe and subsequently in the United States; a second virus, **A/equine/Miami/I/63 (H3N8)** (equine influenza virus 2), was first isolated in 1963. Since then, the disease has been reported in horses and also in donkeys and mules in all parts of the world except Australia, New Zealand, and Iceland.



Pathogenesis

Influenza virus replicates within **respiratory epithelial cells,** resulting in **destruction of tracheal and bronchial epithelium and cilia**. Cough develops early in the course of infection and may persist for several weeks. Nasal discharge, although scant and serous initially, may become mucopurulent due to secondary bacterial infection.

Mildly affected horses recover uneventfully in 2–3 weeks; severely affected horses may convalesce as long as 6 months. Recovery may be hastened by complete restriction of strenuous physical activity. Respiratory tract epithelium takes ~21 days to regenerate; during this time, horses are susceptible to development of secondary bacterial complications such as pneumonia, pleuropneumonia, and chronic bronchitis.

Clinical Findings and Lesions

1-The incubation period of influenza is ~1–3 days.

2-High fever (up to 106°F [41.1°C]),

3- Serous nasal discharge, submandibular lymphadenopathy, and coughing that is dry, harsh, and nonproductive

4-Depression, anorexia, and weakness are frequently seen.

5- Clinical signs usually last <3 days in uncomplicated cases.

Avian Influenza (AIV)

Is a disease caused by an influenza virus that primarily affects Domestic and Wild Birds characterized by the full range of responses from almost no signs of the disease to very high mortality. The incubation period is also highly variable, and ranges from a few days to a week. The disturbing form of influenza in chickens known as "fowl plague" was recognized as a distinct disease entity as early as 1878.

The isolation of an **avian influenza virus** in 1901 preceded the discovery of **mammalian and human influenza viruses**, but it was not until 1955 that it was recognized that avian and mammalian influenza viruses are **closely related**.

From the **1970s** onward, avian influenza came into ecological focus when surveillance indicated the ubiquitous presence of viruses in waterfowl and the risk these birds pose to commercial chicken industries. **The first human case** of illness from **highly pathogenic avian influenza** was identified in **1997**, and more than 560 cases have been identified since then, with deaths worldwide exceeding 300 cases.

Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2015

Country	2003-2009*		2010		2011		2012		2013		2014		2015		Total	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Azerbaijan	8	5	0	0	0	0	0	0	0	0	0	0	0	0	8	5
Bangladesh	1	0	0	0	2	0	3	0	1	1	0	0	0	0	7	1
Cambodia	9	7	1	1	8	8	3	3	26	14	9	4	0	0	56	37
Canada	0	0	0	0	0	0	0	0	1	1	0	0	0	0	1	1
China	38	25	2	1	1	1	2	1	2	2	2	0	4	1	51	31
Djibouti	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Egypt	90	27	29	13	39	15	11	5	4	3	37	14	119	30	329	107
Indonesia	162	134	9	7	12	10	9	9	3	3	2	2	2	2	199	167
Iraq	3	2	0	0	0	0	0	0	0	0	0	0	0	0	3	2
Lao People's Democratic Republic	2	2	0	0	0	0	0	0	0	0	0	0	0	0	2	2
Myanmar	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Nigeria	1	1	0	0	0	0	0	0	0	0	0	0	0	0	1	1
Pakistan	3	1	0	0	0	0	0	0	0	0	0	0	0	0	3	1
Thailand	25	17	0	0	0	0	0	0	0	0	0	0	0	0	25	17
Turkey	12	4	0	0	0	0	0	0	0	0	0	0	0	0	12	4
Viet Nam	112	57	7	2	0	0	4	2	2	1	2	2	0	0	127	64
Total	**468**	**282**	**48**	**24**	**62**	**34**	**32**	**20**	**39**	**25**	**52**	**22**	**125**	**33**	**826**	**440**

* 2003-2009 total figures. Breakdowns by year available on next table

Total number of cases includes number of deaths
WHO reports only laboratory cases
All dates refer to onset of illness

World Health Organization

Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2009

Country	2003		2004		2005		2006		2007		2008		2009	
	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths	cases	deaths
Azerbaijan	0	0	0	0	0	0	8	5	0	0	0	0	0	0
Bangladesh	0	0	0	0	0	0	0	0	0	0	1	0	0	0
Cambodia	0	0	0	0	4	4	2	2	1	1	1	0	1	0
China	1	1	0	0	8	5	13	8	5	3	4	4	7	4
Djibouti	0	0	0	0	0	0	1	0	0	0	0	0	0	0
Egypt	0	0	0	0	0	0	18	10	25	9	8	4	39	4
Indonesia	0	0	0	0	20	13	55	45	42	37	24	20	21	19
Iraq	0	0	0	0	0	0	3	2	0	0	0	0	0	0
Lao People's Democratic Republic	0	0	0	0	0	0	0	0	2	2	0	0	0	0
Myanmar	0	0	0	0	0	0	0	0	1	0	0	0	0	0
Nigeria	0	0	0	0	0	0	0	0	1	1	0	0	0	0
Pakistan	0	0	0	0	0	0	0	0	3	1	0	0	0	0
Thailand	0	0	17	12	5	2	3	3	0	0	0	0	0	0
Turkey	0	0	0	0	0	0	12	4	0	0	0	0	0	0
Viet Nam	3	3	29	20	61	19	0	0	8	5	6	5	5	5
Total	**4**	**4**	**46**	**32**	**98**	**43**	**115**	**79**	**88**	**59**	**44**	**33**	**73**	**32**

Distrbution

These viruses occur naturally among wild migratory aquatic birds worldwide and can infect domestic poultry and other bird and animal species. Wild aquatic birds are the natural reservoir and can be infected with avian influenza A viruses in their intestines and respiratory tract, but usually do not get sick.

Diagnosis

A definitive diagnosis of avian influenza is established by:

1) Direct detection of AI viral proteins or genes in specimens such as tissues, swabs, cell cultures, or embryonating eggs.

2) Isolation and identification of AI virus. By inoculated chicken embryos, 10—11 days old, via the allantoic cavity with approximately 0.2 mL of sample.

3) Serologic tests are used to demonstrate the presence of AI specific antibodies, which may be detected as early as seven days after infection. ELISA assays have been developed to detect antibodies to avian influenza virus. Once influenza is detected by ELISA, HI tests can be used to determine the HA subtype.

Clinical Signs:

Mildly Pathogenic Avian Influenza Viruses:

1-Most infections by MP AI viruses in wild birds produce no clinical signs.

2-In domestic poultry (chickens and turkeys), clinical signs reflect abnormalities in the respiratory, digestive, urinary, and reproductive organs.

3-Mild to severe respiratory signs such as coughing, sneezing,
rales, rattles, and excessive lacrimation.

4-In layers and breeders, hens may exhibit increased broodiness and decreased egg production.

5- In addition, domestic poultry will exhibit generalized clinical signs including huddling, ruffled feathers, depression, decreased activity, decreased feed and water consumption, and occasionally diarrhea.

Highly Pathogenic Avian Influenza Viruses:

In wild birds and domestic ducks, HP AI viruses either replicate poorly or replicate to a limited degree and produce few clinical signs.

In domestic chickens and turkeys, the virus replication and damage to multiple visceral organs and cardiovascular and nervous systems lead to:

1-Depression is common

2-Decreased feed and water consumption

3-Precipitous drops in egg production

4-Mild to severe rales, sneezing, and coughing, sinusitis and edema of head and wattles.

5-Diarrhea

6-Whitens the shell of broiler breeder eggs.

7- Mortality reached 90%.

Gross Lesions

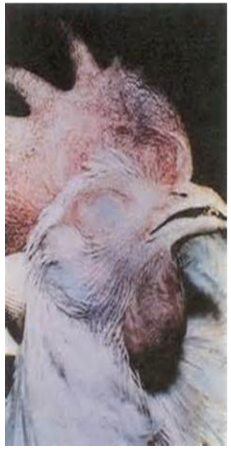
Highly Pathogenic Avian Influenza Viruses:

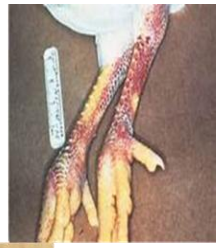
1-Swelling of the head, face, upper neck, and feet are common as the result of subcutaneous edema and may be accompanied by petechial to ecchymotic hemorrhages.

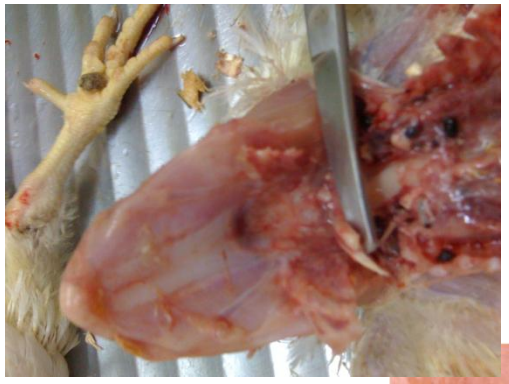
2-Necrotic foci, hemorrhage, and cyanosis of the nonfeathered skin is common, especially wattles and combs.

3- Hemorrhages in proventriculus and heart.

4- Necrotic foci are common in pancreas, spleen, and heart, and occasionally in liver and kidney.







Prevention:

1- Biosecurity is the first line of defense

2-Separation of susceptible birds from infected birds because transmission can occur when susceptible and infected birds are in close contact.

3- Another consideration is that there should be no contact with recovered flocks because the length of time birds within a population shed virus is not clearly defined.

4- The wild birds should be considered a major source of infection for domestic birds, particularly those on open range, so it is important to reduce the contact between these two groups.

5-Bury the dead birds.

Control

1-Control bird-to-bird transmission by cleaning and disinfection equipment.

2-All methods for controlling the spread of influenza are based on preventing contamination and controlling the movement of people and equipment.

3-With an HP AI virus governmental eradication procedures (quarantine, slaughter, disposal, and clean-up) are employed.

4-Vaccination by using inactivated influenza virus vaccines, which have been used to preventing clinical signs and mortality.

Treatment

Presently, no practical, specific treatment exists for avian influenza virus.

Amantadine has been shown experimentally to be effective in reducing the mortality.

Picornaviridae

The name is derived from *pico*, meaning small, and RNA, referring to the ribonucleic acid genome, so "pico-rna means *small* RNA virus 20-30 nm

They replicate in the cytoplasm .

This virus family contains many important human and animal pathogens, including poliovirus, hepatitis A virus, foot-and-mouth disease virus (FMDV), Avian Encephalomyelitis and rhinovirus.

Poliomyelitis as a viral disease was first recognized by Landsteiner and Popper, 1909 (though the virus was not isolated until the 1930's).

Members of the Picornaviridae are **nonenveloped** viruses with a single-stranded RNA (ssRNA) genome of **positive polarity(positive sense) with an icosahedral capsid.**

The genome RNA is **unusual** because it has a protein on the 5' end that is used as a primer for transcription by RNA polymerase.

Classification

Picornaviruses are separated into a number of genera and include many important pathogens of humans and animals.

The family *Picornaviridae is divided into* ***nine*** *genera:*

*1-**Aphthovirus***

2-Enterovirus

*3-**Cardiovirus***

*4- **Rhinovirus***

5-Hepatovirus

6-Parechovirus

7- **Kobuvirus**

8-Erbovirus

9-Teschovirus

Physical &Chemical Properties of picornavirus

They are more resist to most chemicals, the virus can survive well in the external environment, being relatively resistant to heat, desiccation and low temperature.

Caustic soda is the most commonly used disinfectant for FMD virses.

They are more resistant to most other disinfectants.

Genus	Number of Serotypes	Type Species	
Aphthovirus	7	Foot- and Mouth disease virus O, A, C, Asia1, SAT1, SAT2, SAT3	PH Labile
Cardiovirus	2	Encephalomycarditis virus	PH /Stable
Enterovirus	100	Poliovirus 1, 2, 3, Bovine enteroviruses 1 and 2, Human coxsackieviruses A1a, A22, A24, B1, B5, Human enteroviruses 68a, 71, Porcine enteroviruses 8a,10,	PH /Stable
Hepatovirus	2	Human hepatitis A virus, Simian hepatitis A virus	PH Labile
Rhinovirus	100	Human Rhinovirus A1,Human Rhinovirus 2-100	PH Labile

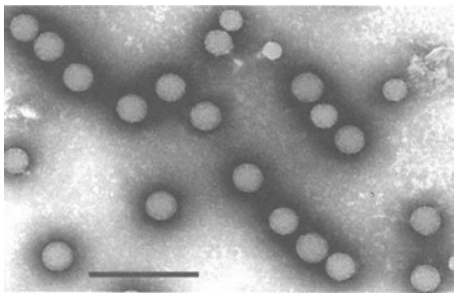
Virion Properties

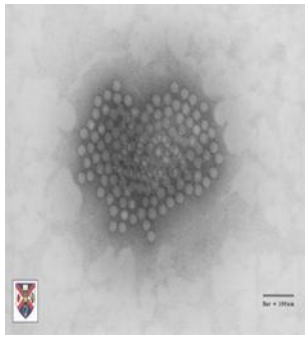
Picornavirus virions are nonenveloped, **(20-30 nm)** in diameter, and have icosahedral symmetry. Virions appear smooth and round in outline in electron micrographs.

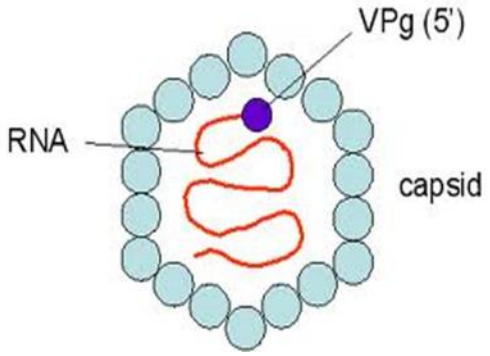
Picornaviruses are classed under Baltimore's viral classification system as group **IV** viruses as they contain a single stranded, positive sense RNA genome. Their genome ranges between 7.1 and 8.9 kb (kilobases) in length.

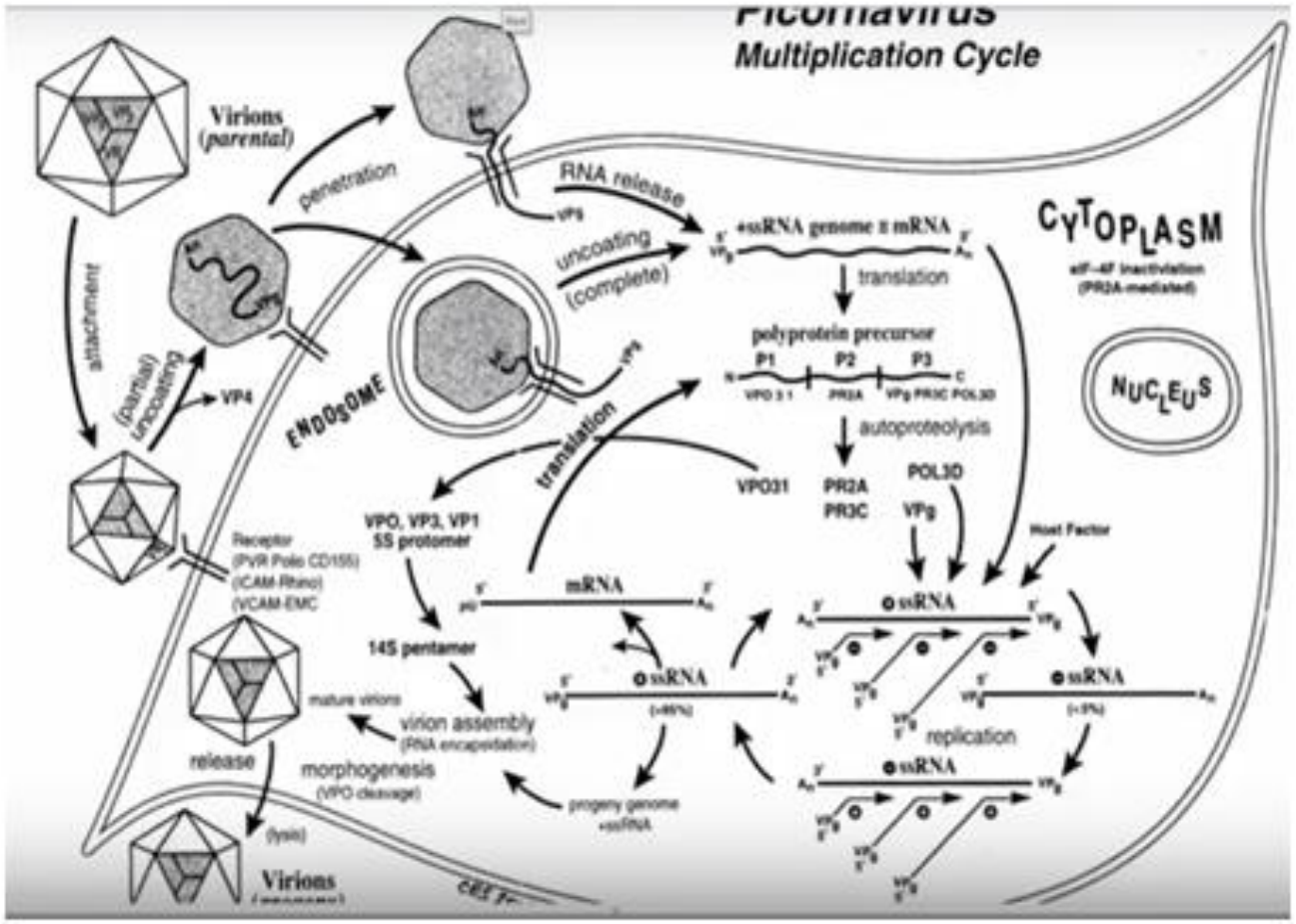
The genomic RNA is polyadenylated at its 3' end and has a protein, VPg, linked covalently to its 5' end.

Like most positive sense RNA genomes, the genetic material alone is infectious.








Picornavirus
Multiplication Cycle
Virions
(parental)
penetration
attachment
(partial)
uncoating
VP4
ENDOSOME
RNA release
uncoating
(complete)
+ssRNA genome ≡ mRNA
translation
polyprotein precursor
P1
P2
P3
VPO 3 1
PR2A
VPg PR3C POL3D
autoproteolysis
CYTOPLASM
eIF–4F inactivation
(PR2A-mediated)
NUCLEUS
VPO31
PR2A
PR3C
POL3D
VPg
translation
VPO, VP3, VP1
5S protomer
Receptor
(PVR Polio CD155)
(ICAM-Rhino)
(VCAM-EMC
mRNA
14S pentamer
Host Factor
-ssRNA
(-)ssRNA
(~95%)
(~5%)
mature virions
virion assembly
(RNA encapsidation)
replication
release
morphogenesis
(VPO cleavage)
progeny genome
+ssRNA
(lysis)
Virions

Viral Replication

Polioviruses, which in nature only infect humans and nonhuman primates, have been the principal models for studying the replication of RNA viruses.

The viral particle binds to cell surface receptors. Cell surface receptors are **characterized** for each serotype of picornaviruses.

For example, poliovirus receptor is glycoprotein CD155(also known as the poliovirus receptor (PVR). which is special **receptor for human and some other primate species**. For this reason, poliovirus couldn't be made in many laboratories until transgenic mice having a CD155 receptor on their cell surface were developed in the 1990s. These animals can be infected and used for studies of replication and pathogenesis.

CD155 facilitates an irreversible conformational change of the viral particle necessary for viral entry.

The replication cycle of Picornaviridae family characterized by:
1-Its happened in the cytoplasm
2- Short life cycle 6-8 hrs
3-High yield 1 viral particle produced 10^5 virus

Poliovirus infection is initiated when the virus protein (VP1) binds to the host-cell-surface poliovirus receptor (Pvr or CD155).
A unique and fascinating characteristic of viruses that have a positive sense ss RNA molecule as their genome is that this molecule can function **as an mRNA molecule as soon as it gets into the cytoplasm** of the host cell.
When the viral particle binds to cell surface receptors, it causes a conformational change in the viral capsid proteins, and myristic acid are released. These acids form a pore in the cell membrane through which RNA is injected. The viral particle now may be directly penetrated the cell wall or in some cases it is taking via a receptor mediated endocytosis and allowing the VPG to enter the cytoplasm for transcription by RNA polymerase.

Once inside the cell,

The (+) RNA can easily translated to make protein and a polyprotein began to translated in the first began of replication and star to prepare in side the cytoplasm. The (+) strand RNA genome is replicated **through a double-stranded RNA** intermediate that is formed using viral RDRP (RNA-Dependent RNA polymerase), by making the (+) strand RNA as a template to make (-)strand RNA. Now from the double strand RNA, they make the (-) strand RNA as a template to synthesis another (+) strand RNA and so it can generated many copy of positive strand RNA.

Genus/ Aphthovirus

Foot-and-Mouth Disease(FMD)

Introduction

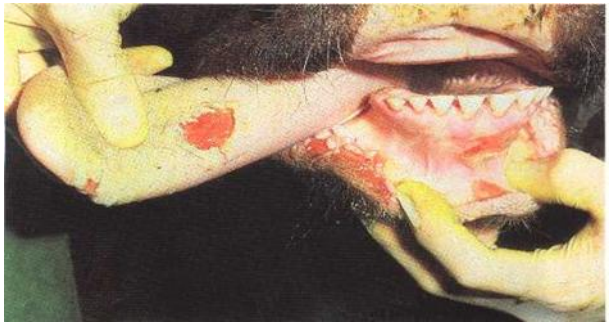
Host

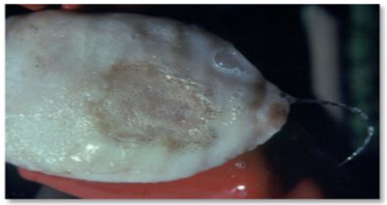
FMDV naturally infects and causes disease in cloven –hoofed animals (cattle, sheep, goat, pigs, deer and many wild ruminants

It has also been known to infect hedgehogs and elephants; whereas, llamas, and alpacas may develop mild symptoms, but are resistant to the disease and do not pass it on to others of the same species. In laboratory experiments, mice, rats, and chickens have been successfully infected by artificial means, but they are not believed to contract the disease under natural conditions. Humans are very rarely infected. Man is more important as a mechanical carrier of the virus.

Foot and mouth disease (FMD) is caused by viruses that belong to seven immunologically distinct serotypes of the genus Aphthovirus which is classified within the Picornaviridae family. The disease naturally affects cloven-hoofed animals although the severity of the resulting disease varies between different species. The virus causes a **high fever for two or three days**, followed by blisters inside the mouth and on the feet that may rupture and cause lameness.

The disease is characterized by the development of vesicles in the mucosa of the mouth (with the exception of the ventral surface of the tongue) and the skin of the coronets and interdigital spaces of the feet. Lesions may also occur on the muzzle/snout. In dairy cattle it may cause teat lesions and severe mastitis. FMDV rapidly replicates and spreads within the infected animal, among in-contact susceptible animals, and by aerosol. Disease signs can appear within 2 to 3 days after exposure and can last for 7 to 10 days.





A healed FMDV-induced tongue lesion showing the absence of regeneration of tongue papillae

Cows may develop vesicles and erosive / ulcerative lesions on the teats and udder

Foot-and-Mouth Disease

The disease is still a major global animal health problem, but its geographic distribution has been **shrinking** in recent years as control and elimination programs have been established in more and more countries.

Seven serotypes of foot-and-mouth disease virus have been identified by cross-protection and serologic tests; they are designated O, A, C, SAT 1, SAT 2, SAT 3, and Asia 1.

Clinical Features

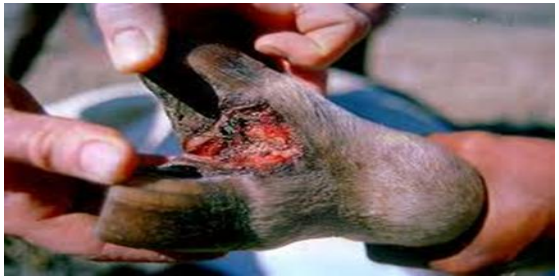
1-After an incubation period of 2 to 8 days.

2-There is high fever that declines rapidly after two or three days.

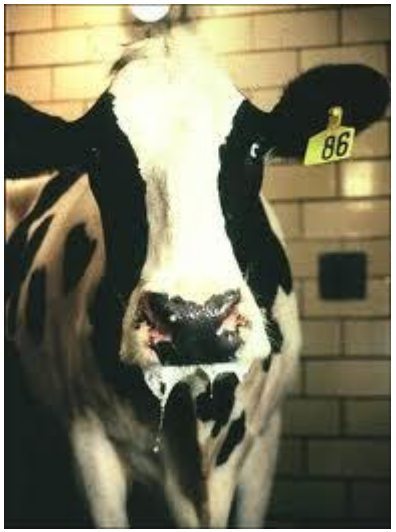
3- Within 24 hours, blisters inside the mouth developed that lead to excessive secretion of stringy or foamy saliva and to drooling, and blisters on the feet that may rupture and cause lameness.

4-The animal may open and close its mouth with a characteristic smacking sound.

5-Vesicles may also be found in the interdigital skin and coronary band of the feet and on the teats.



6-Adult animals may suffer from loss of appetite, depression, weight loss from which they do not recover for several months.
7-Swelling in the testicles of mature males,
8- Marked drop in milk production in cow.
Though most animals eventually recover from FMD, the disease can lead to myocarditis (inflammation of the heart muscle) and death, especially in newborn animals.
Some infected ruminants remain asymptomatic carriers, but they nonetheless carry FMDV and may be able to transmit it to others.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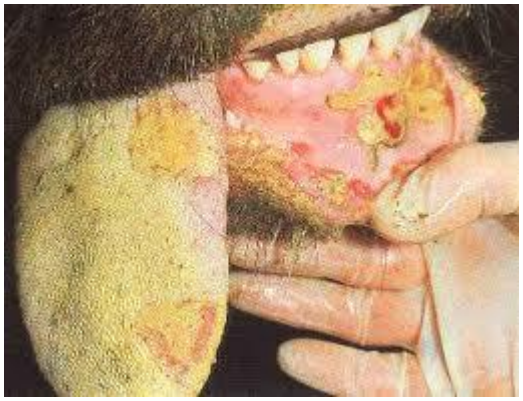
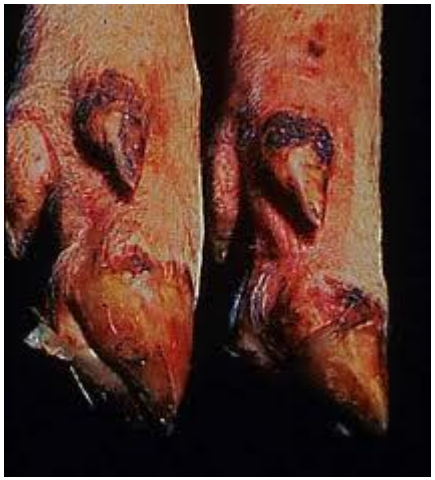




Pathogenesis

In cattle the tissues most consistently infected during the previraemic phase of the disease are the epithelia of the naso-pharynx and larynx.

It is therefore likely this is the primary replication site in ruminants.

The tissues of the naso-pharynx and FMD viruses have a complex relationship because not only does initial infection of ruminants take place there but the naso-pharynx is also the site of viral persistence in chronically infected animals (so-called carriers).

The main route of infection in ruminants is through the inhalation of droplets. Viral excretion commences about 24 hours prior to the onset of clinical disease and continues for several days.

Aerosols produced by infected animals contain large amounts of virus, particularly those produced by swine. Large amounts of virus are also excreted in the milk. The excretion of virus in high titer in droplets and in milk has epidemiologic significance and is important for the control of disease.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

1-Clinical signs & pathology

In cattle and pigs the clinical diagnosis of FMD is usually not difficult because the signs and lesions are characteristic and consistent. FMD is characterized by development of vesicles, which soon rupture leaving erosions, in the mouth, including the tongue (but not the ventral surface of the tongue), and at the skin-hoof junction of the feet.

2- Samples Collection

A- Usually samples include, vesicular fluid, epithelial tissue from edge of rupture vesicles, blood in anticoagulant serum and esophageal/ phalangeal fluid.

These samples are diluted immediately with an equal volume of tissue culture media containing 10% Fetal Calf Serum.

B- From dead animals, additional tissue samples may be collected from lymph nodes, thyroid and heart. Samples should be frozen atv-70^0C and immediately send to the laboratory.

C-In place where maintenance of the cold is difficult, duplicate samples should be collected and transported in glycerol buffer at PH 7.6.

3- A range of diagnostic tests is available like, ELISA, the test can be differentiated between the seven types of FMD.

4- Cell culture are generally used to isolate virus from other tissue, blood and esophageal or pharyngeal fluids. The isolated virus is identified by ELISA or neutralization test.

Transmission

The FMD virus can be transmitted in a number of ways:

1-Close-contact animal-to-animal spread, long-distance aerosol spread and fomites, or inanimate objects, typically fodder and motor vehicles.

2-The clothes and skin of animal handlers such as farmers, standing water, and uncooked food scraps and feed supplements containing infected animal products can harbor the virus, as well.

3-Cows can also catch FMD from the semen of infected bulls.

4-Humans may spread the disease by carrying the virus on their clothes and bodies, animals that are not susceptible to the disease may still aid in spreading it. This was the case in Canada in 1952, when an outbreak flared up again after dogs had carried off bones from dead animals

5-Wolves are thought to play a similar role in the former Soviet Union.

Prevention and Control

The accepted policy is to stamp it out by slaughtering all affected stock and any others which have been exposed to such risk of infection that it is reasonably certain that they would develop the disease if left alive. Compensation is paid for animals slaughtered.

The success of the slaughter policy depends on the prompt reporting of all suspected cases of disease. Delay allows the disease to get a start that is very difficult to overtake. Stock owners should therefore be constantly on the watch for any suspicious symptoms among their animals, even when the country is free from outbreaks of the disease.

No animals, vehicles, foodstuffs, milk etc., must be moved from the suspected premises and, if possible, no person should leave. Dogs, cats, and poultry must be shut in or tied up. Anyone leaving for some essential purpose must first thoroughly cleanse and disinfect his boots, wash his hands and if practicable, change his clothing before leaving the premises.

Vaccination

A decision to vaccinate can only be made by the Secretary of State once an outbreak has been confirmed using all the evidence available.

Like other viruses, the FMD virus continually evolves and mutates, thus one of the difficulties in vaccinating against it is the huge variation between, and even within, serotypes. **There is no cross-protection between serotypes (meaning that a vaccine for one serotype will not protect against any others).**

Vaccination only provides temporary immunity that lasts from months to years.

Many early vaccines used dead samples of FMDV to inoculate animals, but those early vaccines sometimes caused real outbreaks. In the 1970s, scientists discovered that a vaccine could be made using only a single key protein from the virus. The task was to produce enough quantities of the protein to be used in the vaccination.

Why is FMD such an important disease if it does not affect humans and is not generally a lethal infection of animals?

The answer to this question is subjective because it is often held that because the disease is **capable of rapid spread over long distances (highly contagious)** and, because of the diversity of FMD viruses with little or not cross protection, the disease is very difficult to manage under
intensive farming conditions that overcome in the developed world.

Therefore, North America, most of Europe and some Pacific Rim countries spent huge amounts of money, time and effort in eradicating FMD and go to great lengths to prevent its re-introduction.

On the other hand, in extensive farming regions, such as in most of sub-Saharan Africa, FMD often spreads slowly and has limited impact on either wild or domestic animals. These regions are **usually arid** and so the people there are very dependent on **livestock production** and export of live animals and meat. However, international trade regulations and conventions prohibit the
export of livestock and meat from FMD endemic areas to high value markets in North America,
Europe and Japan. Thus FMD has huge impact on the ability of developing countries to access markets where good prices can be obtained.

So the importance of FMD is largely determined by the reaction of governments and trading organizations to it rather than the direct effects of the disease.

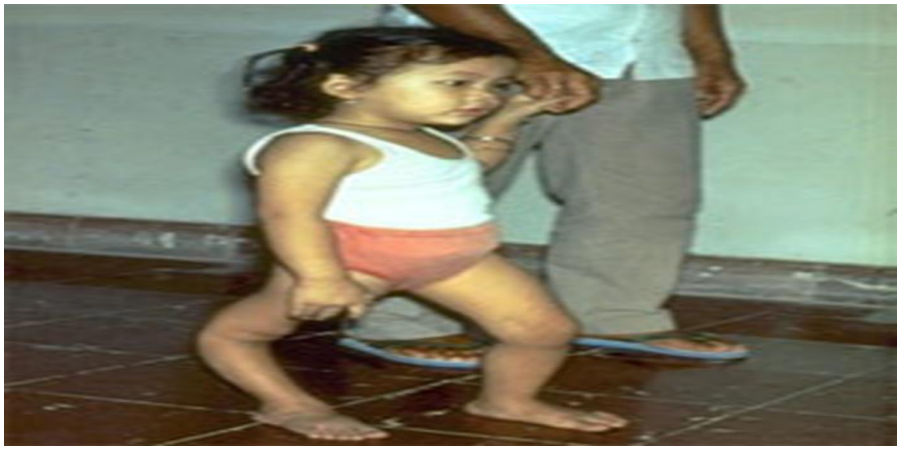
In other words, it’s not so much the disease that determines FMD’s importance but man-made rules that do not always make technical or economic sense.

Poliomalitis

often called **polio** or **infantile paralysis**, is an acute, viral, infectious disease spread from person to person, primarily via the fecal-oral route.

Poliomyelitis, literally meaning “gray spinal cord inflammation. Although approximately 90% of polio infections cause no symptoms at all, affected individuals can exhibit a range of symptoms if the virus enters the blood stream. The virus entry into mouth, replication in pharynx, GI tract, local lymphatics.

Hematologic spread to lymphatics and central nervous system, and the virus spread along nerve fibers lead to destruction of motor neurons. The destruction of motor neurons in the spinal cord results in flaccid paralysis (less than 0.1%). However, most poliovirus infections are subclinical.



- **Poliomyelitis**
- **Caused by polioviruses, three serotypes 1, 2 & 3 , type 1 is the most paralytogenic.**
- **They share 30-50% homology in the nucleotide sequences.**
- **They are enteroviruses.**
- **Transmitted by the fecal oral route.**
- **Humans are the only natural host for the virus.**
- **Poliomyelitis is a disease of infants and young children.**
- **Rapidly inactivated by heat, formaldehyde, chlorine, ultraviolet light**

- **Pathogenecity of poliomyelitis**
- After entry the virus replicates in the oropharyngeal and intestinal mucosa.
- The virus invades the sub-epithelial tissue and reaches local lymph nodes and blood stream.
- Primary and secondary viremia occurs.
- The virus reaches the CNS.
- Replication occurs in the grey matter particularly the anterior horns of the spinal cord and brain stem.
- Distinctive (plaques) produced in the grey matter.

Clinical Sings

-IP 7-14 days.

Clinically, the disease takes four forms.

1- Asymptomatic infection: About 95% of infected children develop no symptoms at all.

2- Minor illness (abortive polio) : about 4-8% of infected children develop fever, nausea, vomiting, malaise, headache and recover completely.

3- Aseptic meningitis: About 1 % of infected individuals will develop signs and symptoms of aseptic meningitis. Fever, headache, nausea, vomiting and stiffness of neck. Paralysis can occur in a small percentage of cases. Recovery is usual.

4- Paralytic polio: About 0.1 to o.5 % of the infected will suffer from paralytic polio (flaccid paralysis).

Flaccid paralysis results from viral damage to the motor neurons of the anterior horn of the spinal cord. If damage is severe the paralysis becomes irreversible. Involvement of the medulla may lead to respiratory paralysis and death.

Prevention

1- live attenuated vaccine(Sabin vaccine) Oral vaccine:

Contains the three polioviruses as attenuated strains.

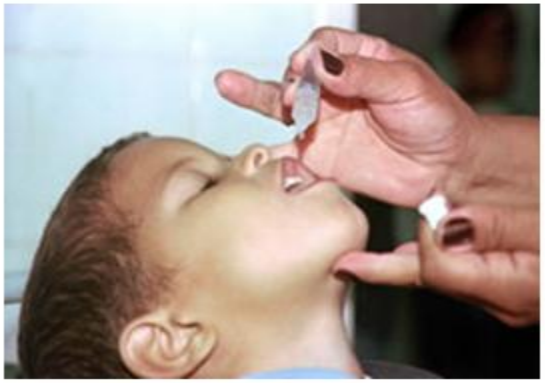
They have lost the ability to replicate in the CNS, but can replicate in the gut.

They have been attenuated by repeating passage of these viruses in monkey kidney tissue culture.

The vaccine is administered orally in 3 doses, along with the triple vaccine.

Vaccinated children are infectious to others, they shed vaccine strains in feces and saliva, so that vaccine strains circulate in the community.

OPV Rout



- **Advantages of the live attenuated vaccine**
- Induces long lasting immunity.
- Induces local immunity in the form of IgA production (gut immunity).
- Administered orally, without the need of sterile syringes.

- **Disadvantages of the live attenuated vaccine**

- The only disadvantage of this vaccine is the vaccine strain particular type 3 strain can reverts to virulence and cause paralysis in those who just been vaccinated.
- It is estimated that vaccine induced poliomyelitis is seen in rate of 1 in 3000,000 vaccinations.

2- Inactivated(killed) vaccine(Salk vaccine):

Contains the three polioviruses, which have been inactivated by formaldehyde.
The vaccine is given in three injections.

Advantages of IPV

- Effectiveness
- Good stability during transport and in storage
- Safe administration in immunodeficient patients
- No risk of vaccine-related disease

Disadvantages

- Lack of induction of local (gut) immunity
- Need for booster vaccine for lifelong immunity
- Fact that injection is more painful than oral administration
- Fact that higher community immunization levels are needed than with live vaccine

- Prevention (1)

No specific antiviral therapy is available. However the disease may be prevented through vaccination. There are two vaccines available.

- Intramuscular Poliovirus Vaccine (IPV)
  - consists of formalin inactivated virus of all 3 poliovirus serotypes.
  - Produces serum antibodies (IgG) only: does not induce local immunity (IgA) and thus will not prevent local infection of the gut.
  - However, it will prevent paralytic poliomyelitis since viremia is essential for the pathogenesis of the disease.
- Oral Poliovirus Vaccine (OPV)
  - Consists of live attenuated virus of all 3 serotypes.
  - Produces local immunity through the induction of an IgA response as well as systemic immunity.
  - Rarely causes paralytic poliomyelitis, around 1 in 3 million doses.

- **Prevention (2)**
- Most countries use OPV because of its ability to induce local immunity and also it is much cheaper to produce than IPV.
- The normal response rate to OPV is close to 100%.
- OPV is used for the WHO poliovirus eradication campaign.
- Because of the slight risk of paralytic poliomyelitis, some Scandinavian countries have reverted to using IPV. Because of the lack of local immunity, small community outbreaks of poliovirus infections have been reported.
- Poliovirus was targeted for eradication by the WHO by the end of year 2000 then 2005 and now ??.
- Poliovirus has been eradicated from most regions of the world except the Indian subcontinent and sub-Saharan Africa. It is possible that the WHO target may be achieved.