Flaviviridae

Classical Swine Fever, BVDV-Mucosal Disease, Border Disease

"Latin flavus that means "yellow", consistent with the jaundice caused by yellow fever virus"

The Viral Most Wanted: The Flavivirus Family

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Historical aspects

Yellow fever virus-Flavivirus, was **the first human virus discovered**. In the course of investigating epidemic yellow fever in Havana in 1900, **Walter Reed, James Carrol**l, and colleagues showed that the etiologic agent was a "**filterable virus**“ and that it was transmitted by the mosquito *Aedes aegypti*.

Loeffler, Frosch, and Koch for their discovery of **the first virus of animals, foot-and-mouth disease virus**, and

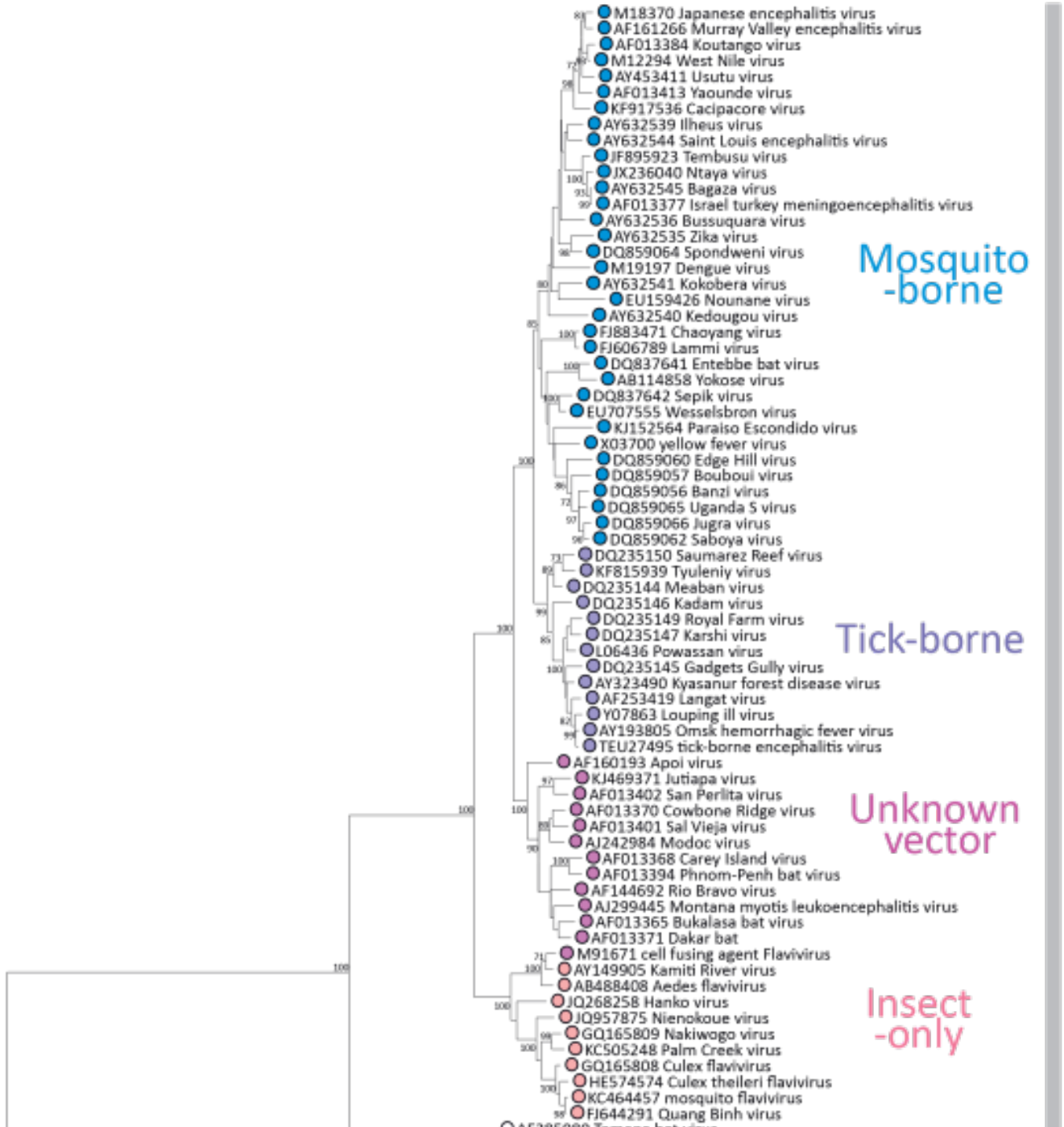
Salmon, Smith, Kilborne, and Curtice for their discovery that **arthropods can transmit infectious disease among animals** (the agent, *Babesia bigemina*, the etiologic agent of Texas fever of cattle; the vector, the tick *Boophilus annulatus*).

Family Flaviviridae

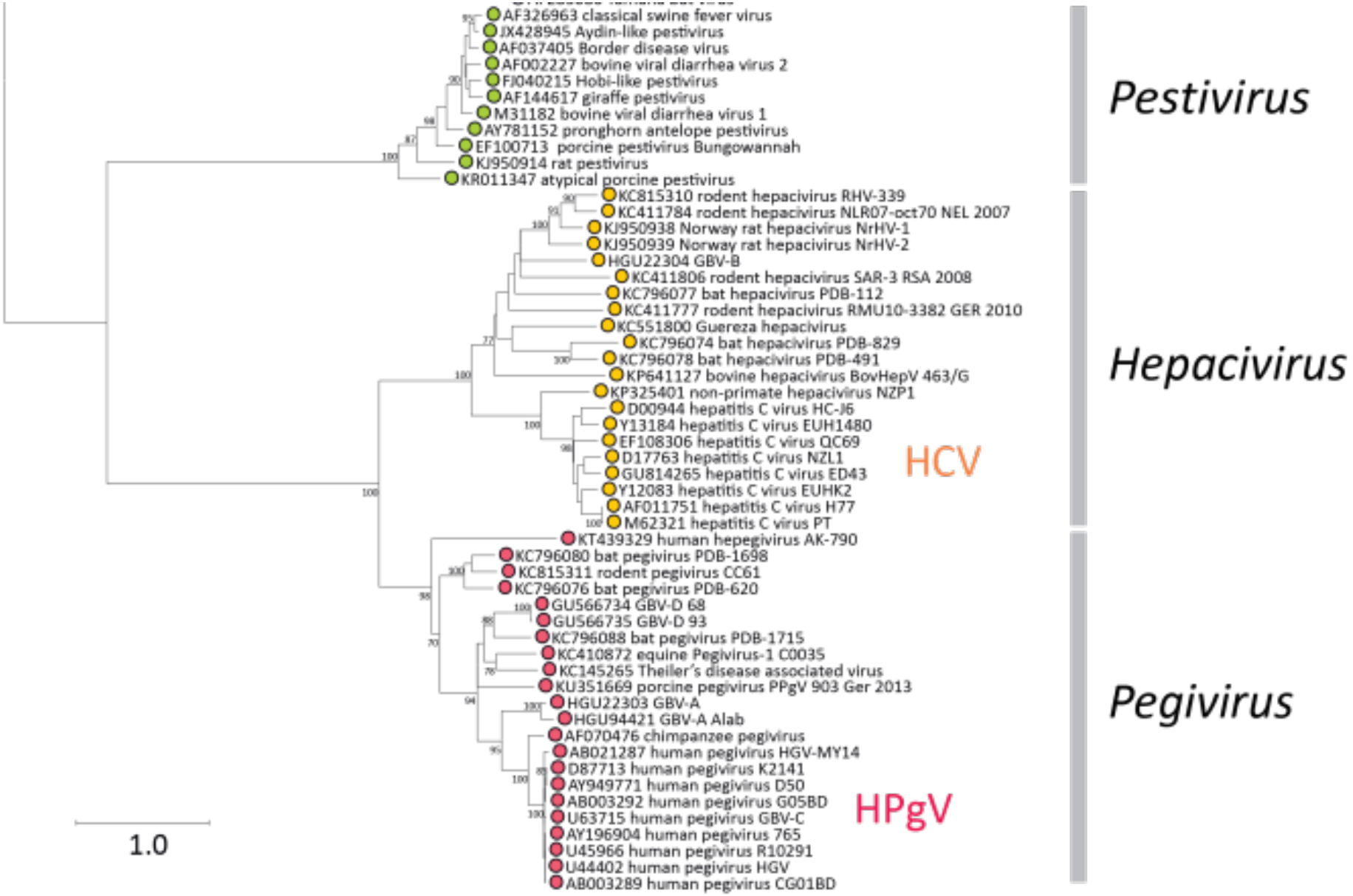
Group IV: ssRNA positive-strand viruses

Family:	***Flaviridae***
Genus:	*Orthoflavivirus* *Hepacivirus* *Pegivirus* *Pestivirus* Bovine V diarrhea virus BVDV-1 & 2, Classical swine fever virus Border disease virus (BDV) Giraffe-virus over HoBi-like viruses to recently discovered Bungowannah virus and atypical porcine pestivirus

The genus Flavivirus is composed of more than 70 recognized arthropod-borne viruses (or arboviruses) serologically related and broadly distributed



Orthoflavivirus


AF326963 classical swine fever virus
JX428945 Aydin-like pestivirus
AF037405 Border disease virus
AF002227 bovine viral diarrhea virus 2
FJ040215 Hobi-like pestivirus
AF144617 giraffe pestivirus
M31182 bovine viral diarrhea virus 1
AY781152 pronghorn antelope pestivirus
EF100713 porcine pestivirus Bungowannah
KJ950914 rat pestivirus
KR011347 atypical porcine pestivirus
KC815310 rodent hepacivirus RHV-339
KC411784 rodent hepacivirus NLR07-oct70 NEL 2007
KJ950938 Norway rat hepacivirus NrHV-1
KJ950939 Norway rat hepacivirus NrHV-2
HGU22304 GBV-B
KC411806 rodent hepacivirus SAR-3 RSA 2008
KC796077 bat hepacivirus PDB-112
KC411777 rodent hepacivirus RMU10-3382 GER 2010
KC551800 Guereza hepacivirus
KC796074 bat hepacivirus PDB-829
KC796078 bat hepacivirus PDB-491
KP641127 bovine hepacivirus BovHepV 463/G
KP325401 non-primate hepacivirus NZP1
D00944 hepatitis C virus HC-J6
Y13184 hepatitis C virus EUH1480
EF108306 hepatitis C virus QC69
D17763 hepatitis C virus NZL1
GU814265 hepatitis C virus ED43
Y12083 hepatitis C virus EUHK2
AF011751 hepatitis C virus H77
M62321 hepatitis C virus PT
KT439329 human hepegivirus AK-790
KC796080 bat pegivirus PDB-1698
KC815311 rodent pegivirus CC61
KC796076 bat pegivirus PDB-620
GU566734 GBV-D 68
GU566735 GBV-D 93
KC796088 bat pegivirus PDB-1715
KC410872 equine Pegivirus-1 C0035
KC145265 Theiler's disease associated virus
KU351669 porcine pegivirus PPgV 903 Ger 2013
HGU22303 GBV-A
HGU94421 GBV-A Alab
AF070476 chimpanzee pegivirus
AB021287 human pegivirus HGV-MY14
D87713 human pegivirus K2141
AY949771 human pegivirus D50
AB003292 human pegivirus G05BD
U63715 human pegivirus GBV-C
AY196904 human pegivirus 765
U45966 human pegivirus R10291
U44402 human pegivirus HGV
AB003289 human pegivirus CG01BD
HCV
HPgV
1.0
Pestivirus
Hepacivirus
Pegivirus

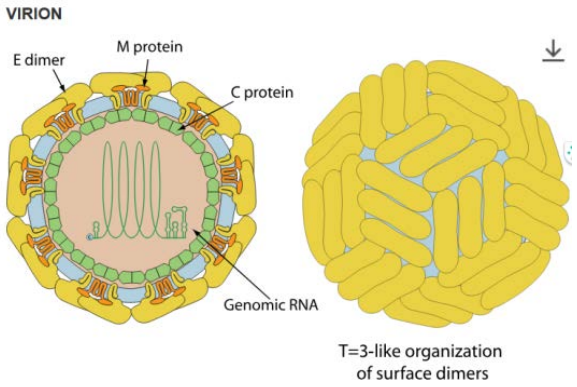
Flaviviridae

Classification	Virus	Host	eographical Distribution
Mosquito-borne flaviviruses	Yellow fever virus (YFV)	Primate populations and mosquito vectors (Aedes spp., Haemagogus spp., and Sabethes spp.	First discovered in Ghana; mostly in tropical Africa and tropical South America.
	Dengue virus (DENV)	Aedes mosquito and Ae. Albopictus mosquito	Tropical and subtropical areas.
	Japanese encephalitis virus (JEV)	Vertebrate, Culex tritaeniorhynchus mosquitoes	In northern temperate areas JE occurs in summer epidemics, whereas in southern tropical areas the disease is endemic and occurs year-round.
	West Nile virus (MNV)	Mosquitoes, birds, mammals and reptiles, human	First identified in Uganda in 1937, the virus is commonly found in Africa, West Asia, and the Middle East.
	St Louis encephalitis virus	Culex species mosquitoes, wild birds, human	Most cases occur in the eastern and central United States during the summer and early fall.
	Murray Valley encephalitis virus (MVEV)	waterbirds and Culex annulirostris mosquitoes, Aedes normanensis mosquitoes, human	endemic to Australia and New Guinea
	Zika virus (ZIKV)	Aedes spp. mosquitoes, non-human primates, and human	Isolated in 1947 in the Zika Forest in Uganda; Outbreaks did not occur outside of Africa until 2007, when it spread to the South Pacific.

Flaviviridae

Classification	Virus	Host	geographical Distribution
Tick-borne Flavivirus	Tick-borne Encephalitis virus (TBEV)	Ticks of the Ixodideae family and human	Endemic to Northern Eurasia and commonly seen across **Europe.**
	Powassan virus (POWV)	Ixodes scapularis and Ixodes cookei ticks, small or medium sized mammals, and human	First reported in 1958 in Powassan, Ontario; endemic in the northeast and upper mid-west of the United States, and cases have also been reported in **Far-Eastern Russia**. the only tick-borne flavivirus that is endemic in the western hemisphere
	Louping ill virus (LIV)	sheep or castor bean tick, Ixodes ricinus, human	Upland areas of the British Isles, particularly in Scotland, Cumbria, Wales, Devon and Ireland
	Omsk haemorrhagic fever virus (OHFV)	Dermacentor spp. ticks and small mammals, human	in forest-steppe zones of the Omsk, Novosibirsk, Kurgan, and Tyumen regions of western **Siberia**
	Kyasanur Forest disease virus	**Haemaphysalis** spp. Ticks, human	In the tropical deciduous forests of the **Karnataka State** in South India

Family Flaviviridae



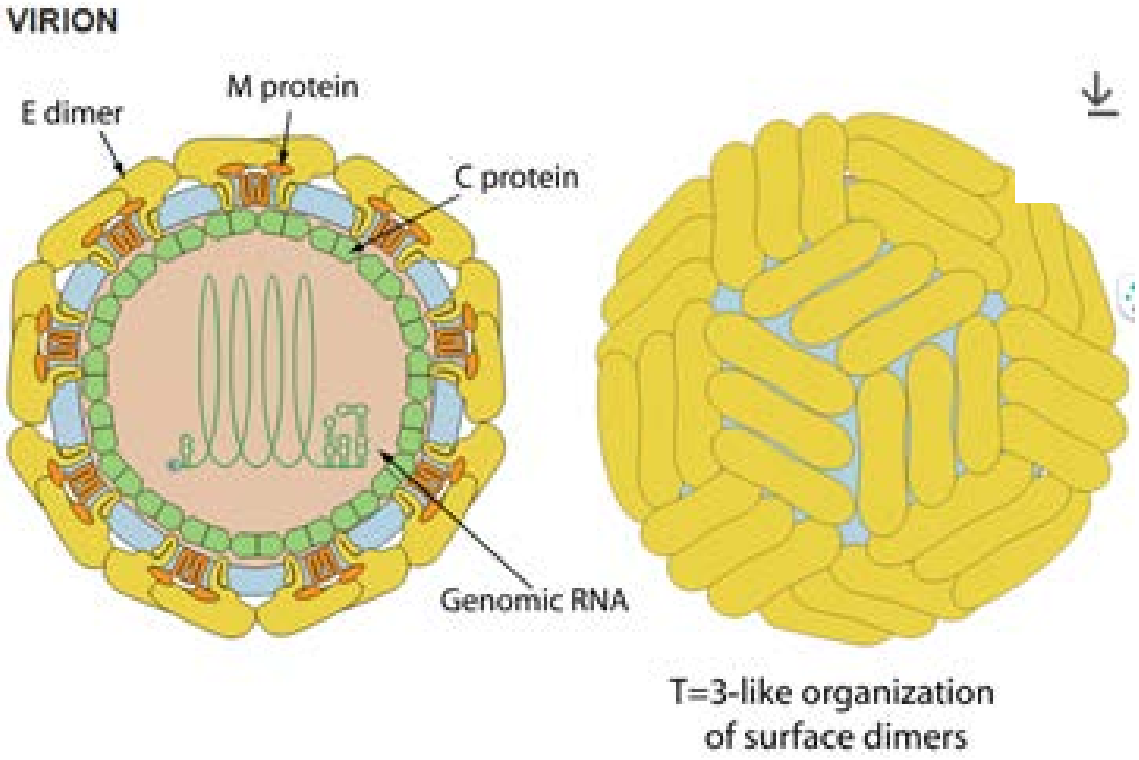
Virus Properties
Enveloped, spherical,
Size: 50 nm in diameter

Genera: **Flavivirus,** **mostly arthropod-borne viruses**; **Pesti-virus,** **nonarthropod-borne**, includes several veterinary pathogens; Hepacivirus, human hepatitis C virus

Genome is a **single molecule of linear positive-sense, single-stranded RNA**, 10.6-10.9 (flaviviruses), 12.5 (pestiviruses),or 9.5 (hepaciviruses) kb in size; 5' end capped, but 3' end usually is not polyadenylated.

Genomic RNA is infectious
Cytoplasmic replication; a single polyprotein is translated from genomic RNA; it is cleaved cotranslationally to yield nonstructural proteins and three or four structural proteins

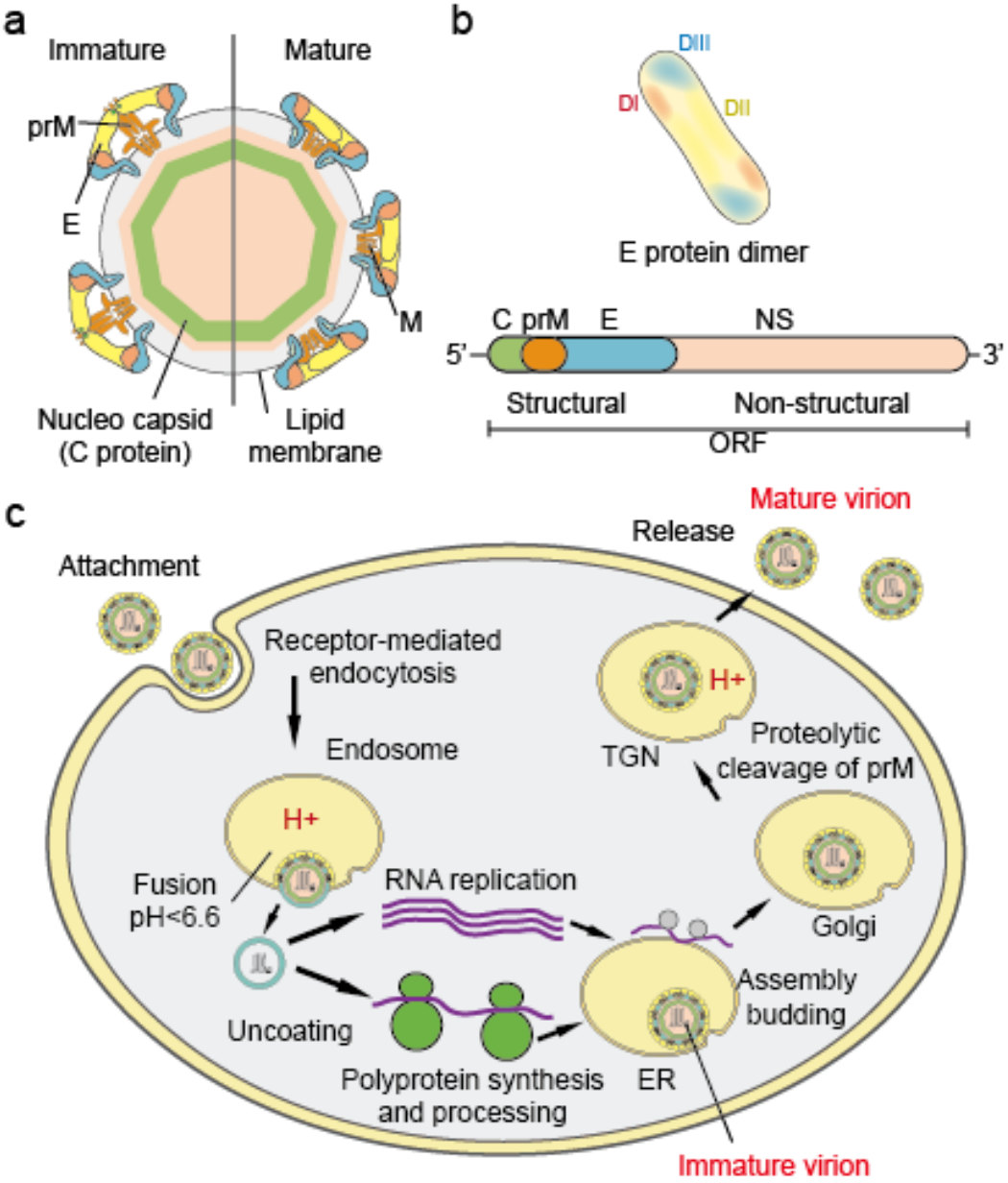
Family Flaviviridae



The enveloped viral particles consist of four structural proteins, namely the core protein (C), and envelope glycoproteins E1, E2, and Erns

Highly virulent CSFV strains such as “Margarita” or “Koslov” (the ones that are often used for vaccine testing)

Family Flaviviridae



The enveloped viral particles consist of four structural proteins, namely the core protein (C), and envelope glycoproteins E1, E2, and Erns

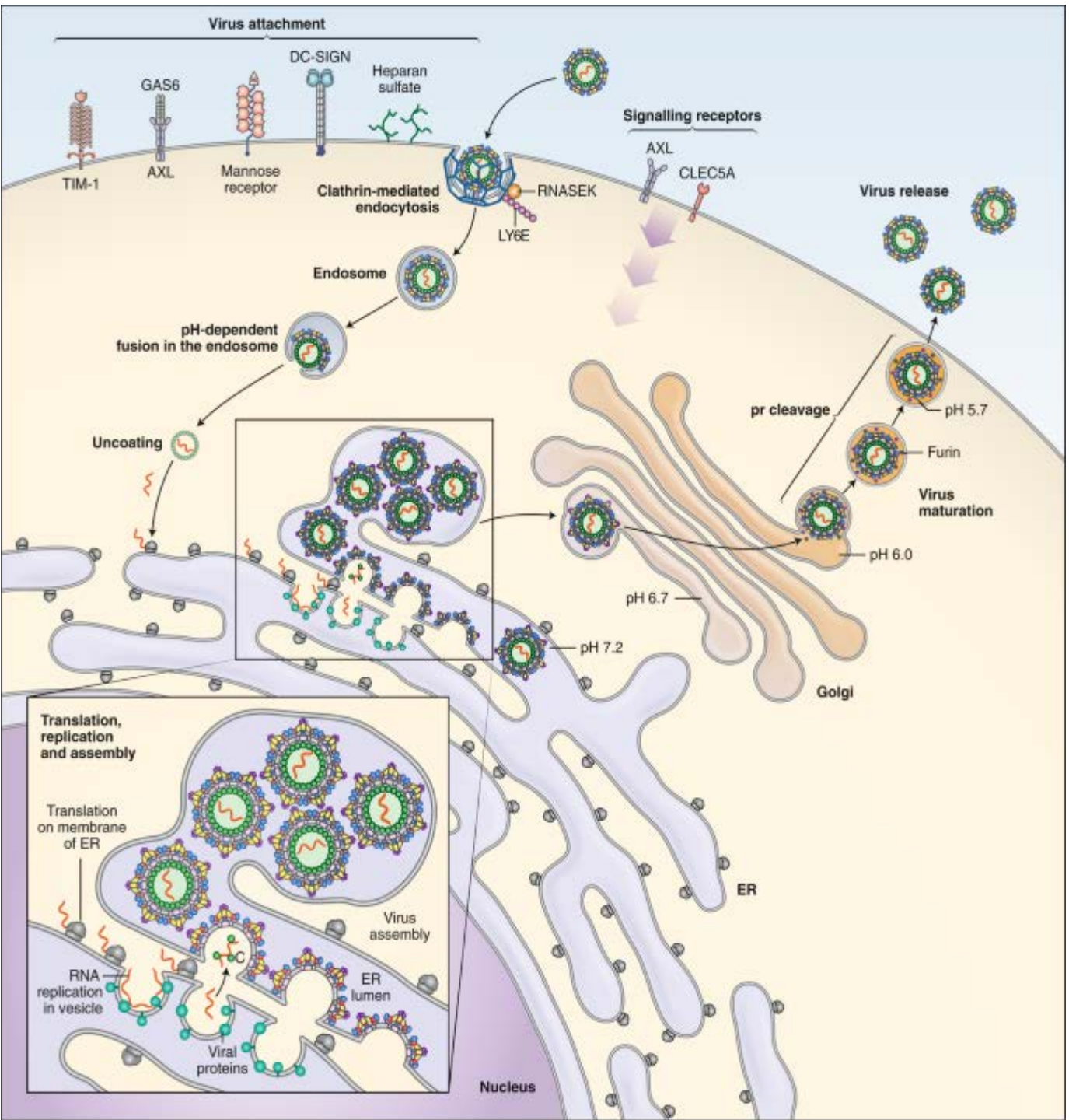
It codes for 3 structural proteins:
capsid (C protein),
membrane (M, which is expressed as prM, the precursor to M and
envelope (E protein) and
7 nonstructural proteins: NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5

Maturation occurs on intracytoplasmic membranes without evidence of budding

CSF-Virus replication

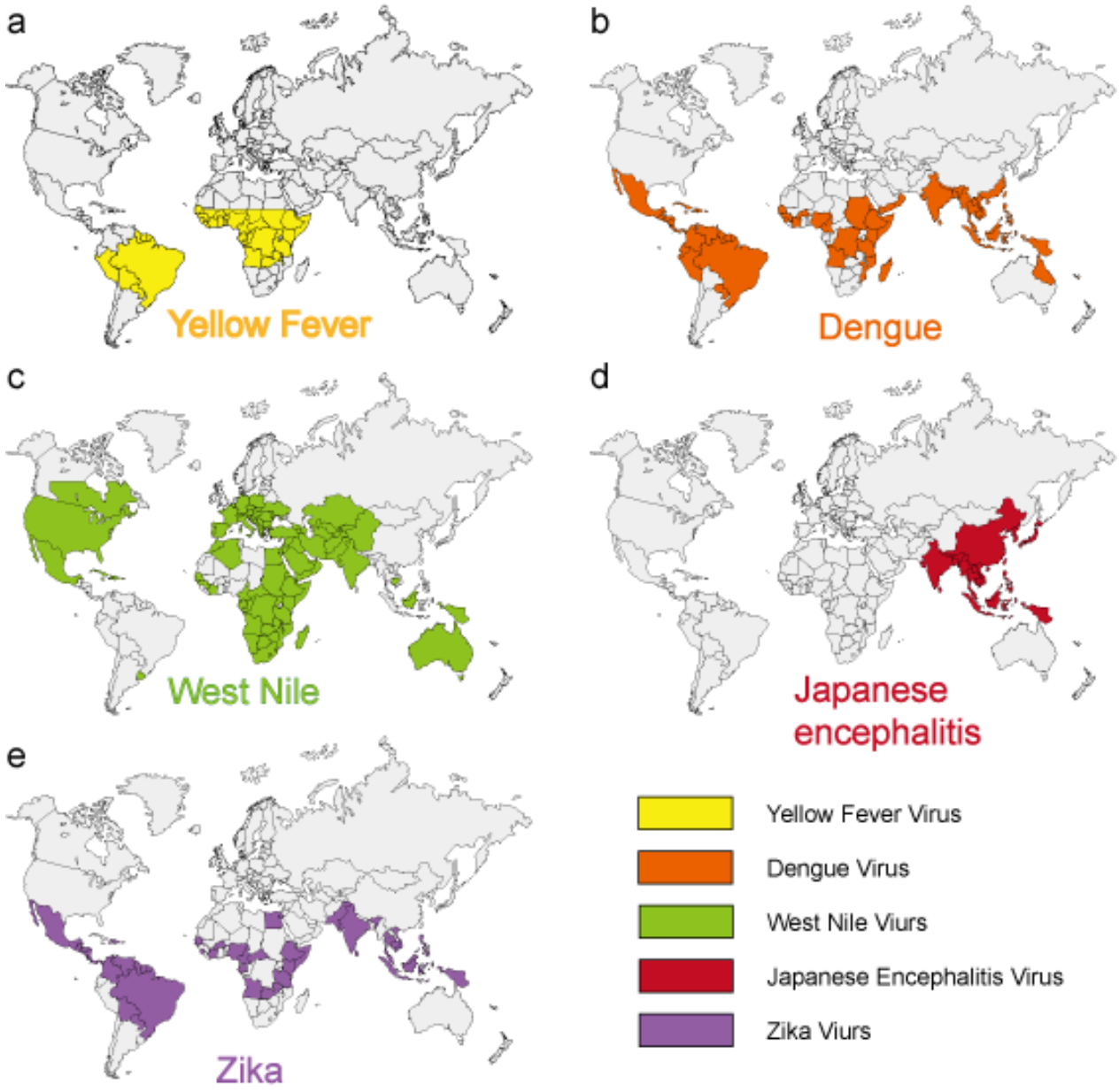
Virus replication takes place in the cytoplasm after receptor mediated endocytosis and does normally not lead to a cytopathic effect in cell culture (naturally occurring CSFV strains were found to be non-cytopathic).

A putative receptor is the porcine complement regulatory protein **cluster of differentiation (CD) 46** that was shown to play a major role in **CSFV attachment**, together with heparan sulfates.



CSF-Virus replication

Epidemic area of Flavivius



Classical swine fever

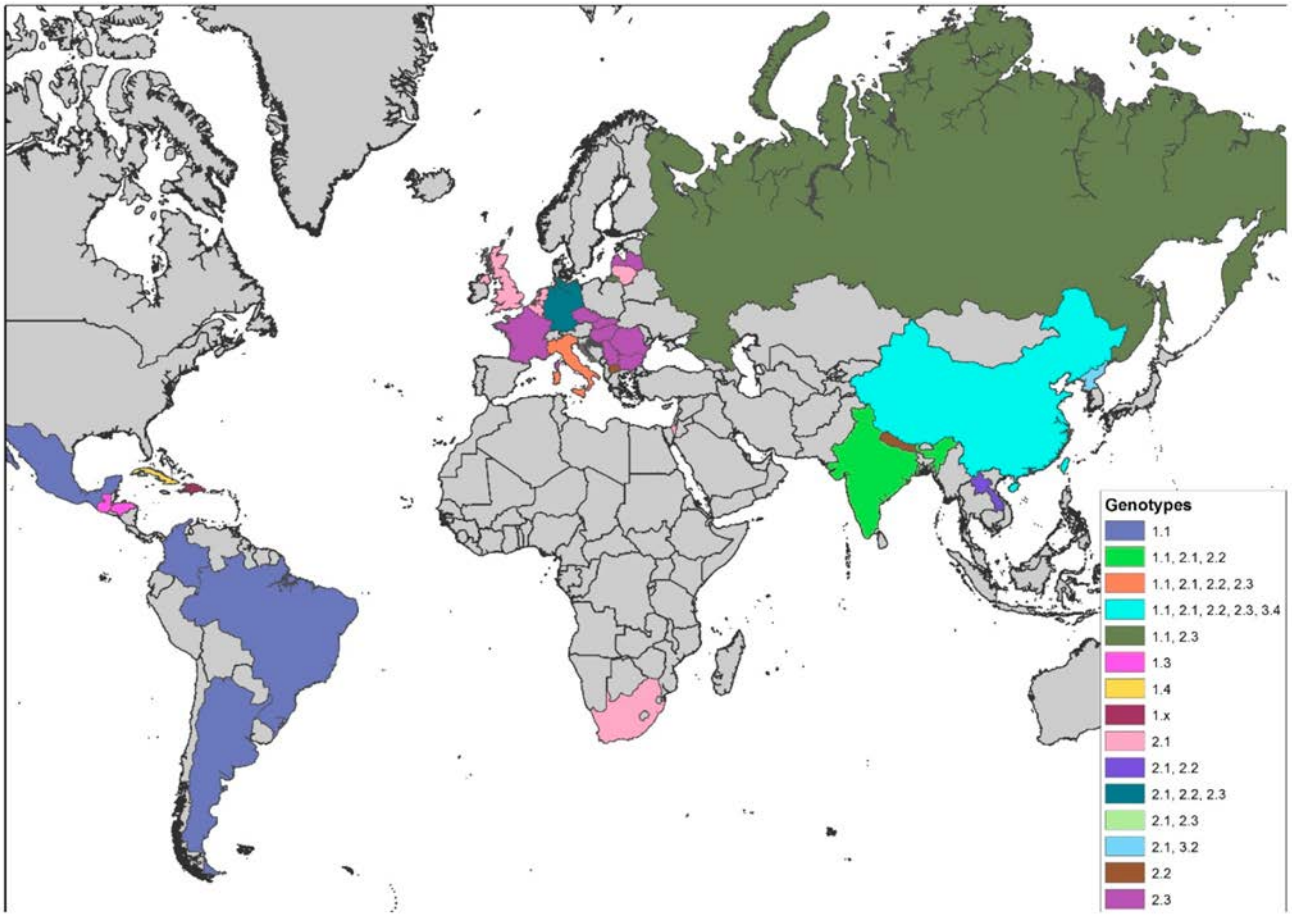
Classical swine fever (CSF), also known as **hog cholera**, is a **contagious viral disease** of domestic and wild swine. It is caused by a virus of the genus *Pestivirus* of the family *Flaviviridae*, which is closely related to the viruses that cause bovine viral diarrhoea in cattle and border disease in sheep.

There is **only one serotype of CSF virus** (CSFV).

CSF is a disease listed by the World Organisation for Animal Health (WOAH) and must be reported to the WOAH.

Geographical distribution

- CSF is found in **Central and South America, Europe, and Asia and parts of Africa**.
- North America, Australia and New Zealand are currently free of the disease.



Global distribution of classical swine fever virus (CSFV) sub-genotypes (map based on Global Administrative Areas (GADM database 2.8; November 2015).

Classical Swine Fever

Transmission and spread

- The most common method of transmission is through **direct contact between healthy swine and those infected** with CSF virus.
- The virus is shed in **saliva, nasal secretions, urine, and feces**. Contact with contaminated vehicles, pens, feed, or clothing may spread the disease. Animals that are chronic carriers of the disease (**persistently infected**) may show no clinical signs of illness but may shed the virus in their feces. Offspring of infected sows can become infected in the uterus, and can shed the virus for months.
- CSF virus can survive in pork and processed pork products for months when meat is refrigerated and for years when it is frozen. Pigs can become infected by eating CSF-infected pork meat or products.
- It has been proven that in parts of Europe, the wild boar population may play a role in the epidemiology of the disease.
- The disease has been spread through legal and illegal transport of animals, and by feeding swill containing infective tissues to pigs.

Persistent Infection Vs Latent Infection

Persistent infections are where the viruses are continually present in the body.

In a latent viral infection the virus remains in equilibrium with the host for long periods of time before symptoms again appear, but the actual viruses cannot be detected until reactivation of the disease occurs.

Clinical signs

Incubation period is variable : 5-14 days

- The disease has acute and chronic forms, and can range from severe, with high mortality, to mild or even unapparent.
- In the acute form of the disease, in all age groups, there is **fever, huddling of sick animals, loss of appetite, dullness, weakness, conjunctivitis, constipation followed by diarrhoea, and an unsteady gait**.
- Several days after the onset of clinical signs, **the ears, abdomen and inner thighs may show a purple discoloration**.
- Animals with acute disease die within 1-2 weeks. Severe cases of the disease appear very similar to African swine fever.
- With low virulence strains, the only expression may be **poor reproductive performance** and the birth of piglets with **neurologic defects such as congenital tremor**.

Classical swine fever is a highly contagious, viral disease of swine that in its most virulent form causes **morbidity and mortality approaching 100%**

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Classical Swine Fever

Pinpoint or petechial hemorrhages in the sub capsular region of the kidneys resembling 'Turkey egg kidney'.

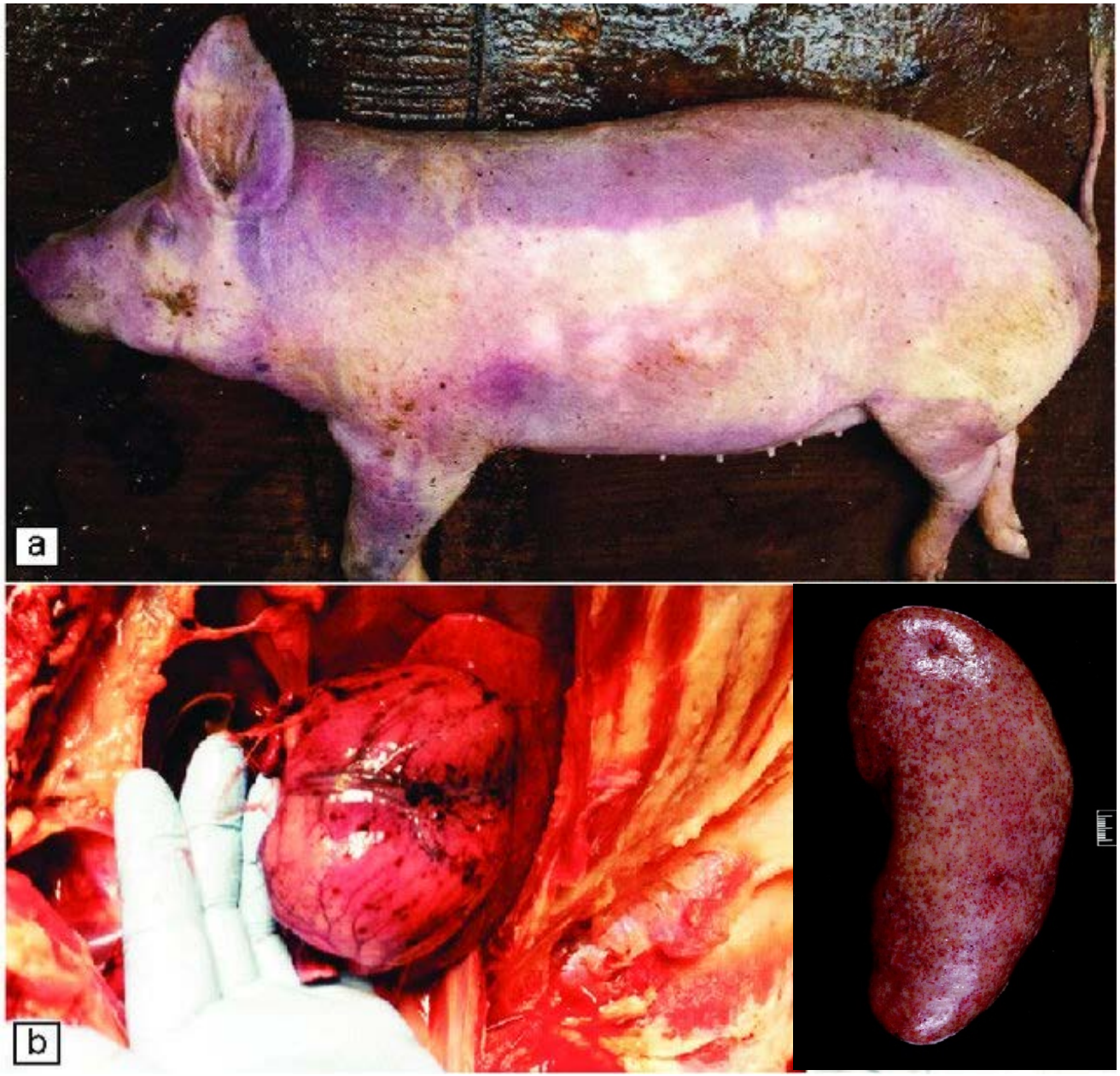
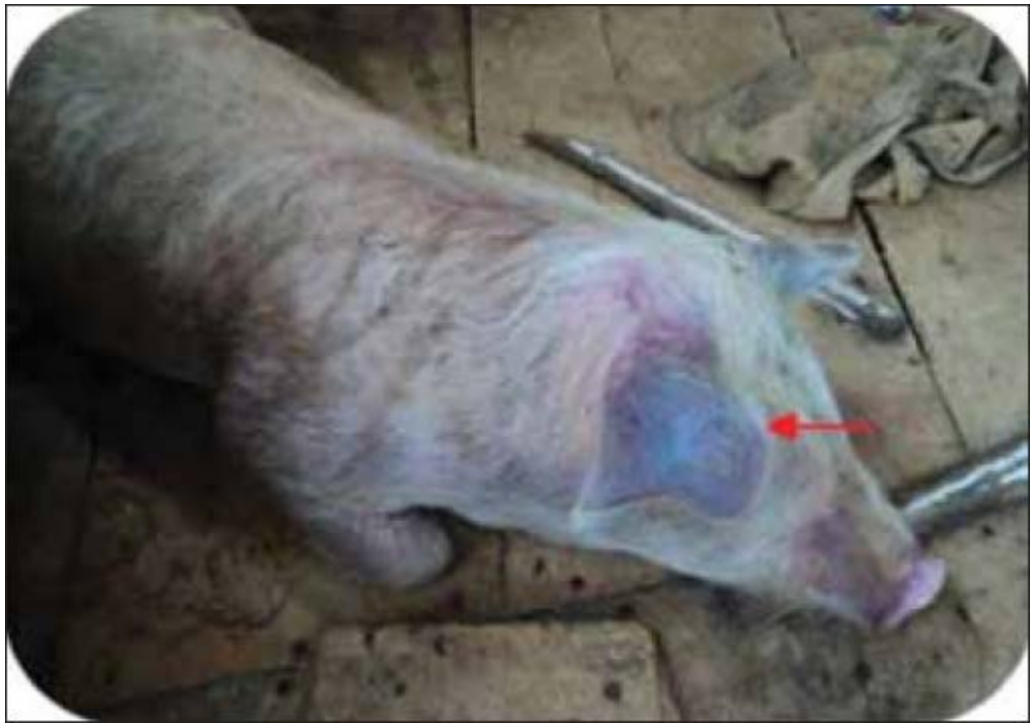


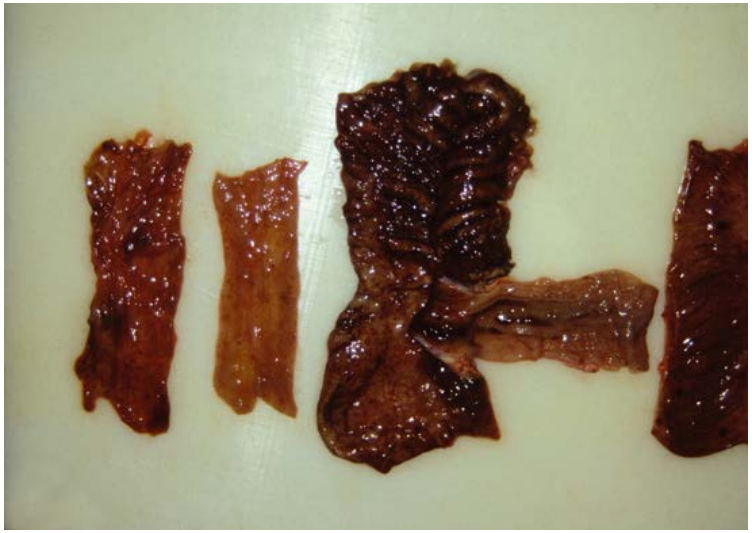
Fig. Gross examination of pig affected with classical swine fever. (a) Purple discolouration of skin; (b) Epicardial haemorrhages; (c) Petechial haemorrhages on kidney

Classical Swine Fever



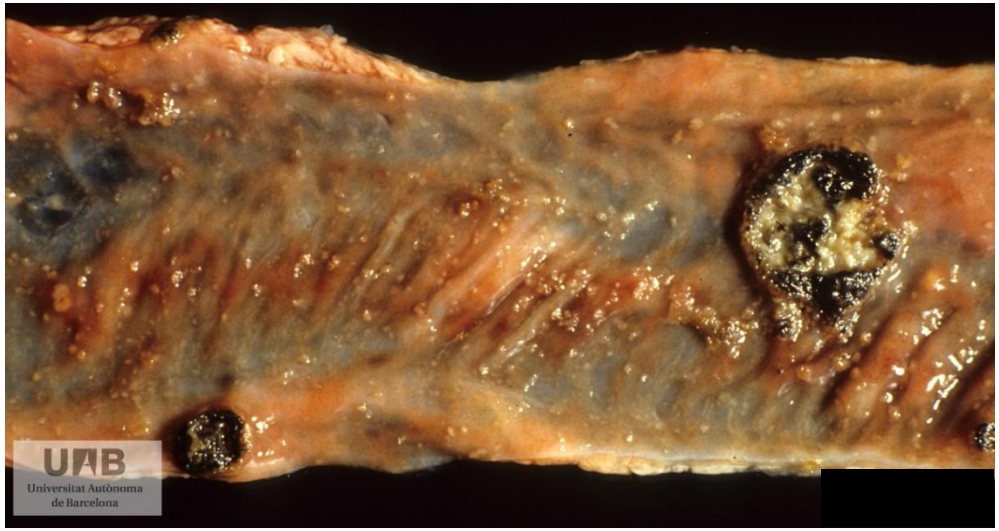
Purple discoloration of skin at the tip of the ears in pigs suffered from acute classical swine fever

Classical Swine Fever



Haemorrhagic to fibrinous Enteritis in small and large intestine from a fattening pig experimentally infected with hog cholera virus: small intestine at the right side, parts of ileum, caecum, and colon in the middle, and 2 colonic samples at the left side.

J. Pohlenz
https://www.thepigsite.com/publications/2/ileitis/78/445-classical-swine-fever-csf-hog-cholera



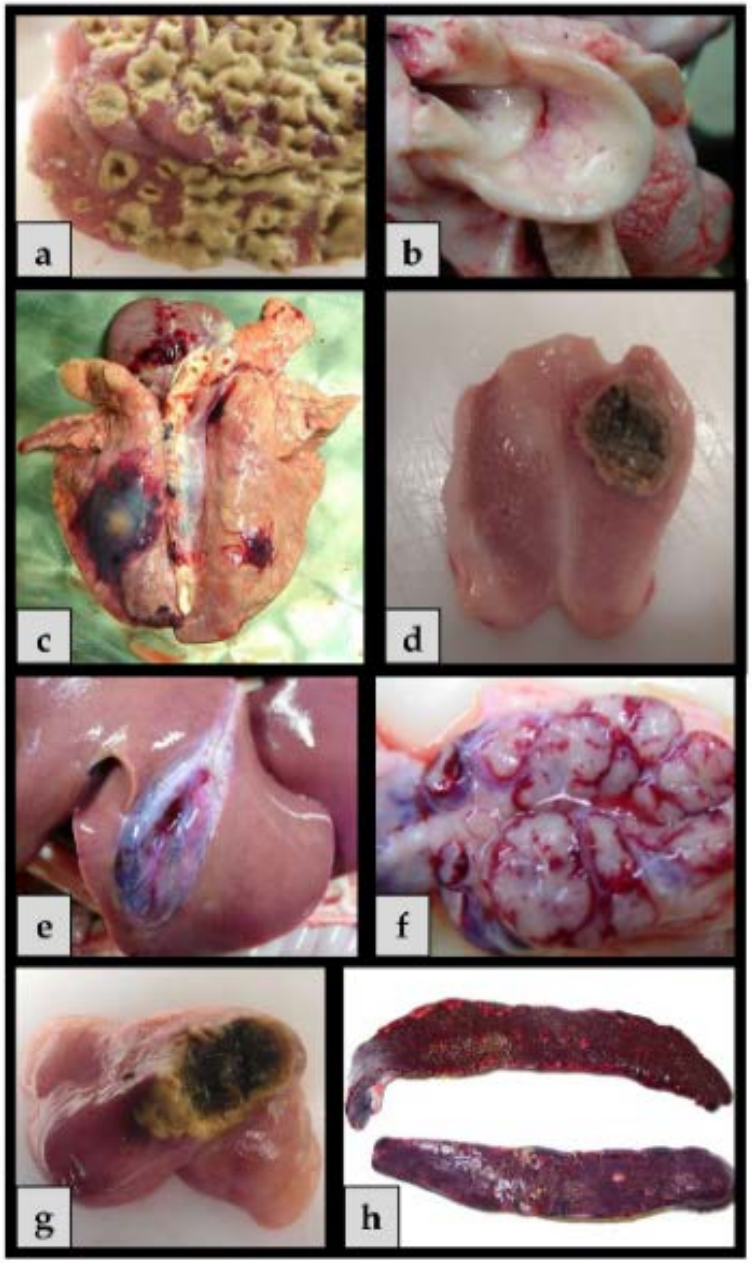
Button shaped ulcer in the colon of a CSF field case

Lesions of classical swine fever infection

Gastrointestinal/Oral:
Necrotic foci (button ulcers) of intestinal mucosa
Necrotizing enteritis
Necrotic, ulcerative ileocecal valve
Tonsillitis

Thoracic and Abdominal:
Cavities:
Pleural effusion
Ascites
Gallbladder edema

Hemorrhages/Petechiae:
Skin
Lymph nodes
Kidney
Bladder
Larynx
Epiglottis
Trachea
Intestines
Spleen (infarcts)
Lungs
Epicardium

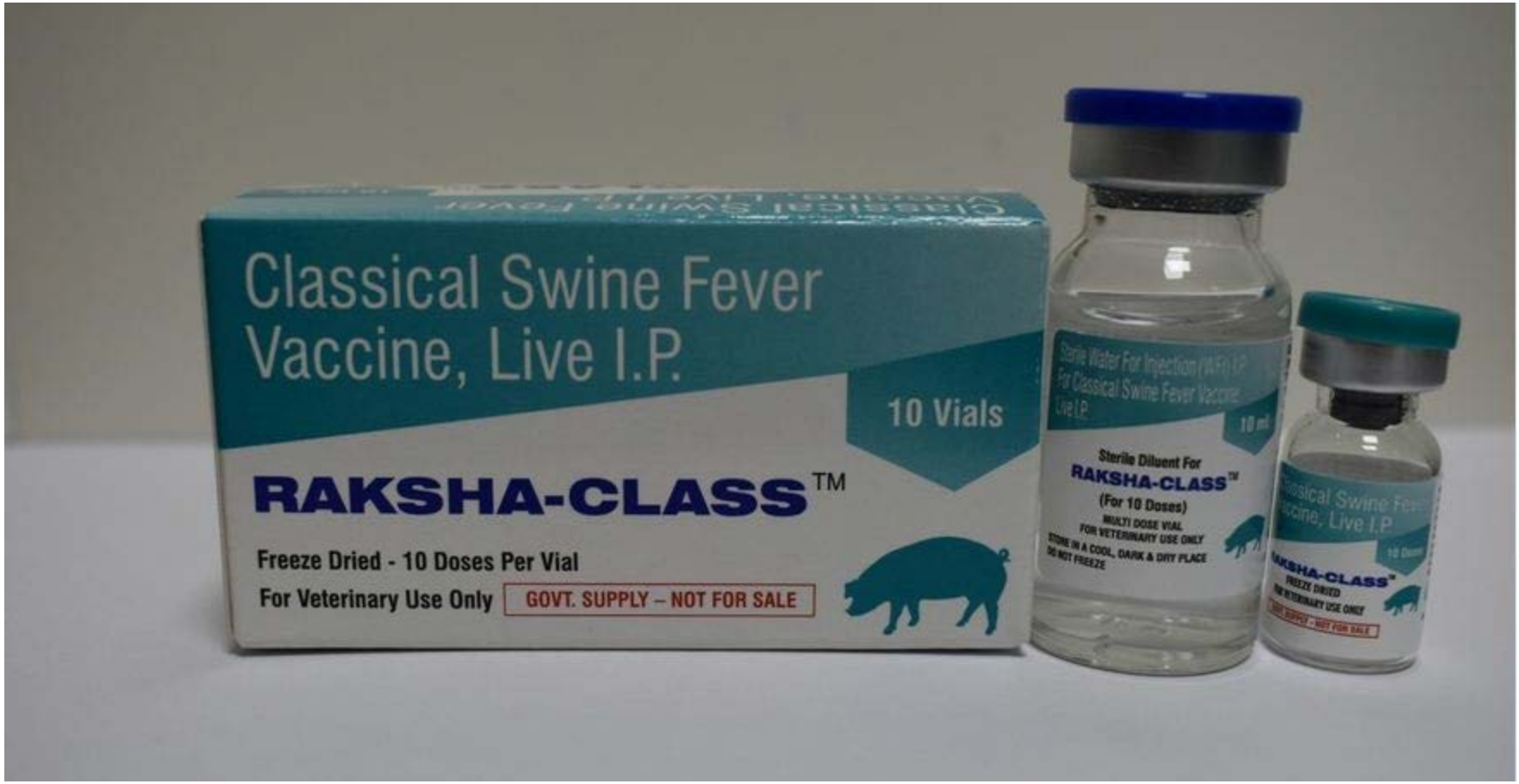


CSF related lesions: (a) Diphtheroid-necrotizing enteritis; (b) **hemorrhages on the epiglottis**; (c) severe secondary infections of the lung (Actinobacillus pleuropneumoniae); (d) **necrotic tonsillitis with an ulcer**; (e) gallbladder edema; (f) **hemorrhagic lymph node**; (g) **necrotizing ileocecal valve**; and (h) **splenic infarcts**.

Immunity to CSF

Despite the immunopathogenesis of most CSF-related lesions, pigs recovering from CSFV infection mount an effective immune response with E2-specific antibodies detectable after 10–14 days . The E2 antibodies are able to neutralize CSFV in vitro and induce protective immune responses. These **antibodies and protection against re-infection persist probably livelong**.

Classical Swine Fever



Indian Immunologicals launches classical swine fever vaccine
Called 'Raksha Class', this vaccine has been developed in collaboration with Indian Veterinary Research Institute (IVRI), Bareilly

Classical Swine Fever

Vaccination

Swine fever vaccine (lapinized swine fever vaccine)
Dose: 1ml, S/C or I/M
Primary vaccination: After weaning (weaning at 45 days)
First booster: 30 days after first vaccination.
Second booster: After 6 months of first booster.
Revaccinate at 6 months interval.
In case of tissue culture vaccine dose and route of administration is same as lapinised vaccine but it gives longer duration of immunity

Lapinized -attenuated by passage through rabbits

Classical Swine Fever

Diagnosis

- Isolation of Virus: **PK-15 cells**
- RT-PCR
- ELISA
- VNT

Bovine Viral Diarrhoea / Mucosal Disease

Bovine viral diarrhea (BVD) is a pestivirus infection affecting cattle and some other ruminant species.

Clinical disease associated with BVD virus infection is most common in young cattle (6–24 months old). The clinical presentation can range from inapparent or subclinical infection to acute and severe enteric disease.

Mucosal disease (MD)

Is an uncommon but highly fatal form of BVD occurring in persistently infected (PI) cattle and can have an acute or chronic presentation.

Mucosal Disease (MD) is usually sporadic, progressive and fatal.

It would seem to occur in a small number of congenitally infected animals which are immunotolerant and harbor virus in all their tissues without showing any clinical symptoms.

Bovine Viral Diarrhoea / Mucosal Disease

- Bovine Virus Diarrhea and mucosal disease are clinically dissimilar disease syndromes, and were originally described as separate diseases.
- But they are now known to have a common viral etiology.

BVD Etiology

- Caused by Pestivirus of Flaviviridae family.
- Virus is grouped into 2 genotypes, **BVDV Type 1 and Type 2**, based on genomic characteristics and the severity of disease they produce in cattle.
- Each genotype, 1 and 2, are divided into two biotypes- **cytopathic** (cp) and **non-cytopathic** (ncp) based on how they replicate in cell culture.
- Cytopathogenicity does not correlate with the severity of disease in vivo (high and low virulence strains) Some cp strains are recovered from animals with mucosal disease (MD), but most of the time ncp isolates are recovered from infected animals.

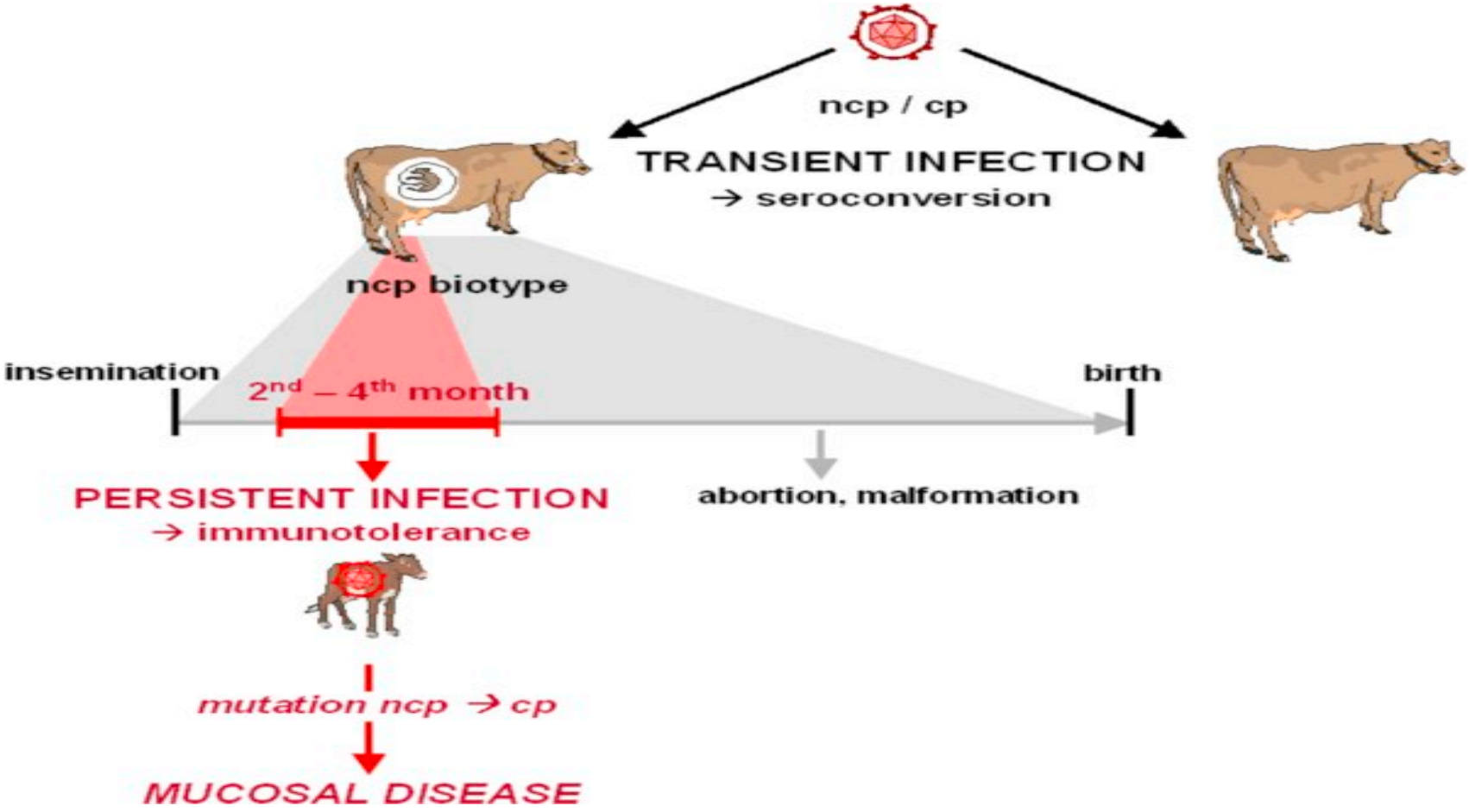
- The **classic virus is ncp**; cp isolates are generated by mutations or genome rearrangements in the original/parental ncp strain.
- **Most (>95%) of the field isolates are ncp**.
- Young calf persistently infected with BVD compared to similarly- aged normal herd mate.

Epidemiology

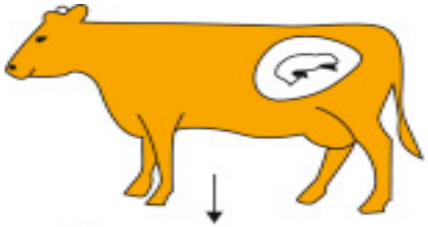
- It is **normally an infection of cattle**, but it has the ability to cause infections in pigs, sheep, goats,, deer, reindeer, bison and other wild ruminants.
- The virus may be present in various **secretions and semen**.
- Spread is by direct and indirect contact.
- The mode of infection is by ingestion and inhalation.
- Transplacental infections are frequent and result in serious consequences for the embryo/fetus.
- **Bulls may be persistently infected and the virus in semen is spread by coitus an artificial insemination**.
- **BVD seen predominantly in 6-18 month old cattle as a primary infection**.

Pathogenesis

- Infection is via the oropharyngeal route with **primary replication in the epithelium of the oropharynx**
- Rapid uptake into the drainage lymph nodes.
- **Viremia involves infection of lymphocytes** giving rise to a **leucopenia**,
- Spreads to other lymphoid tissues, particularly Peyer's patches.
- **Concurrent replication in the epithelium of the alimentary tract** results in discrete erosions.
- which in the oral cavity cause excessive salivation, and in the small and large intestine induce diarrhea.
- Lesions in the nasal cavity and conjunctiva may also occur and be associated with discharges.

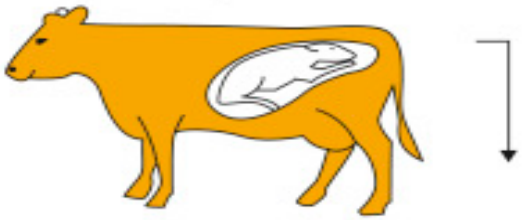

ncp / cp
TRANSIENT INFECTION
→ seroconversion
ncp biotype
insemination
2nd – 4th month
birth
PERSISTENT INFECTION
→ immunotolerance
abortion, malformation
mutation ncp → cp
MUCOSAL DISEASE

(A)



Cow and fetus infected with noncytopathic bovine viral diarrhea virus in early pregnancy

(B)



Cow becomes immune. Fetus becomes tolerant and unable to make antibody

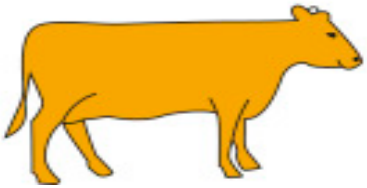
(C)

Calf remains infected with virus for life

(D)

Mutation of virus to cytopathic form may occur

(E)



(F)

Superinfection of this and other viremic animals with cytopathic virus causes fatal mucosal disease

Clinical signs

- BVDV infection can result in a wide spectrum of clinical disease varying from sub-clinical infection to fatal disease.
- Different clinical signs can be seen simultaneously in a herd.
- The most common clinical signs are:
  Infertility or abortion – foetal abnormalities can occur with infections later in pregnancy resulting in brain abnormalities.
- Calf with **cerebellar hypoplasia** unable to stand and **"stargazing"**
- Diarrhoea

Incubation period is 9-10 days.

BVD

- Mucosal disease – a condition that can vary in severity from mild to severe.
- Signs include ill-thrift, diarrhoea, ulceration in mouth and gastro-intestinal tract and lameness (from ulceration of feet).
- Death can ensue after a variable period of time.
  - Failure to conceive
  - Early embryonic death / abortion / congenital deformity
  - Foetal loss
  - Persistently infected calves

Mucosal Disease

Diagnosis

- Diagnosed in laboratories via serology, antigen detection assays, virus isolation, and by viral RNA amplification such as polymerase chain reaction (PCR).
- Sample from Buffy coat or nasal swab immunohistochemistry, and antigen-capture ELISA assays.
- Serological evaluation of acute BVDV infection is most commonly performed via serum neutralization in paired sera.

Treatment

- Currently, there is no treatment available to cure BVD Virus.
- Antibiotics for Secondary Infections Pneumonia etc.
- If the animal develops Mucosal Disease, there are treatments to alleviate the symptoms, but the animal will eventually die.
- IV fluids and electrolyte for diarrhea and water loss.
- PI's should be euthanized to prevent further contamination and potential infection to the rest of the herd.

Prevention and control

- Vaccination does not provide complete protection against BVDV infection.
- It can help to reduce the number of infections
- Vaccination is not long lasting.
- Regular booster shots should be kept up to date according to label
- Vaccinated cattle can thus become infected and show some symptoms but death will not occur.
- Pregnant cattle that are vaccinated have less chance if infection and transmission of the virus to the fetus.
- There is still a chance of abortions in those cattle that are vaccinated.
-

THANKS

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