Togaviridae

VMC 321: Systematic Veterinary Virology

Dr Manoj Kumar

Assistant Professor

Department of Veterinary Microbiology

Bihar Animal Sciences University, Patna.

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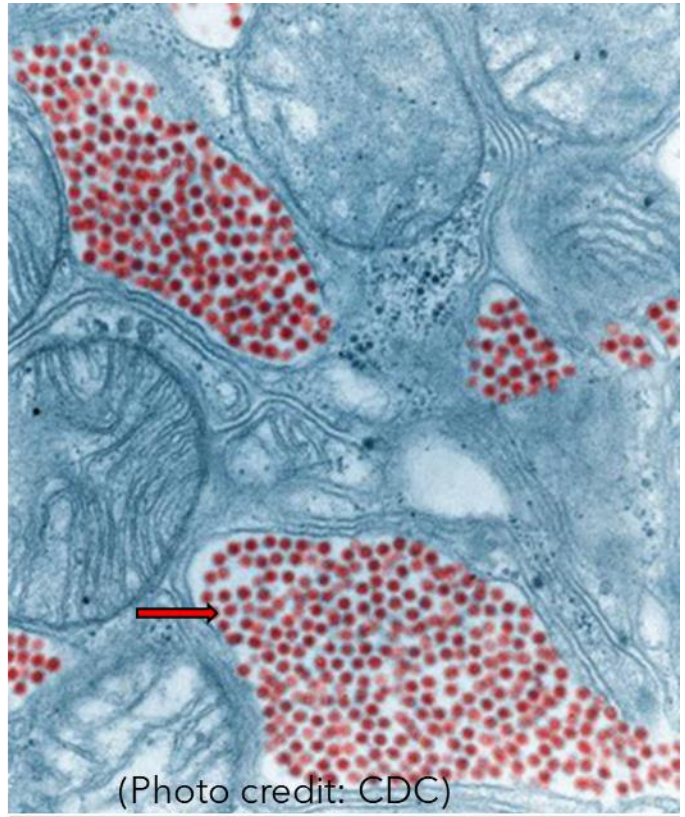
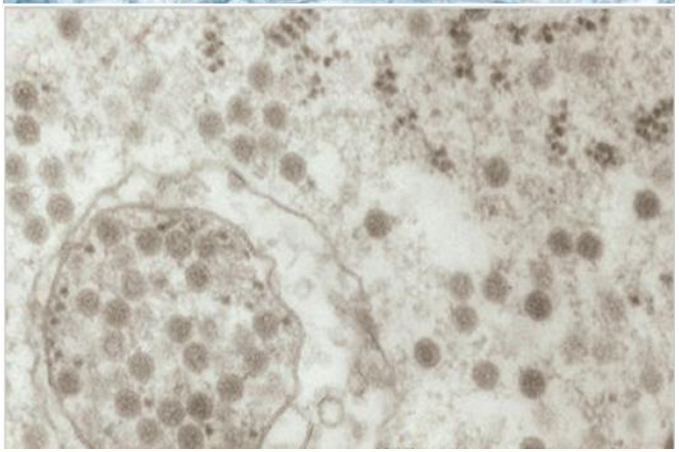
Baltimore Classification

- Group IV: (+) sense single-stranded RNA viruses

Family: *Togaviridae*

- *Togaviridae*
  - Genus :
    - *Alphavirus*
    - *Rubivirus*
  - *Species*
    - Eastern equine encephalitis virus (EEE virus)
    - Western equine encephalitis virus (WEE virus)
    - Venezuela equine encephalitis virus (VEE virus)


(Photo credit: CDC)



ICTV classification

- Family: *Togaviridae*
- Genus: *Alphavirus*
- Complex: New World

Arbovirus

- Arboviruses = arthropod-borne viruses
- Arboviruses are maintained in nature through biological transmission between susceptible vertebrate hosts by blood-feeding arthropods
- Vertebrate infection occurs when the infected arthropod takes a blood meal

Important species in the genus Alphavirus

Prototype virus: Sindbis virus (SINV),

Species	Host	Disease	Vector	Reservoir
Eastern equine encephalitis virus	Mammals,, Birds, Reptiles, amphibians	Encephalitis	*Aedes, Culex*	Birds
Western equine encephalitis virus	Humans , Horses, Birds	Encephalitis	*Culex tarsalis, Aedes*	Birds
Venezuelan equine encephalitis virus	Humans Horses, Birds	Encephalitis	*Aedes, Culex*	Horses
Chikungunya virus	Humans	Fever & arthritis	*Aedes aegypti*	Monkeys
Semliki Forest virus	Humans, mosquitoes, and animals, including wild birds, rodents, domestic animals and non-human primates	Fever & arthralgia	*Aedes*	Birds, rodents

Species	Host	Disease	Vector	Reservoir
Sindbis virus	Humans, mosquito and birds	Fever, Arthralgia, and rash,	Culex	Birds, mammals
Middelburg virus	Horses, Human			
Zikavirus	Human	Fever and arthritis	*Aedes aegypti*	
Japanese B encephalitis virus	Human	Encephalitis	*Culex tritaeniorhynchus*	Pigs, Birds
Dengue virus		*Hemorrhagic fever*	*Aedes aegypti*	Unknown

Morphology

- Virion appear round 65-70 nm in diameter
- Capid: 40 nm in diameter
- Capsid contains 42 capsomeres arranged in T4 symmetry
- Enveloped – consist of 240 copies of two virally encoded glycoproteins, E2 and E1
- Four nonstructural proteins nsP1, nsP2, nsP3, and nsP4 (viral RNA-dependent -RNA polymerase)

Alphaviruses: Protein Function

- E1and E2 glycoprotein heterodimers form trimers that appear as knobs on the surface of the virion
  - E1 – transmembrane glycoprotein with 2 to 3 N-linked glycosylation sites
  - E2 - glycoprotein with 1 to 2 N-linked glycosylation sites, contains short intracytoplasmic tail and hydrophobic stretch of amino acids that serves as the fusion peptide for viral entry
- Capsid protein has a conserved N-terminal region which binds RNA and a C-terminal region which interacts with the cytoplasmic tail of E2 as well as capsid proteins
- E3 and 6K proteins are signal sequences for E2 and E1, respectively, and are largely cleaved off from the mature virion

Genome organisation

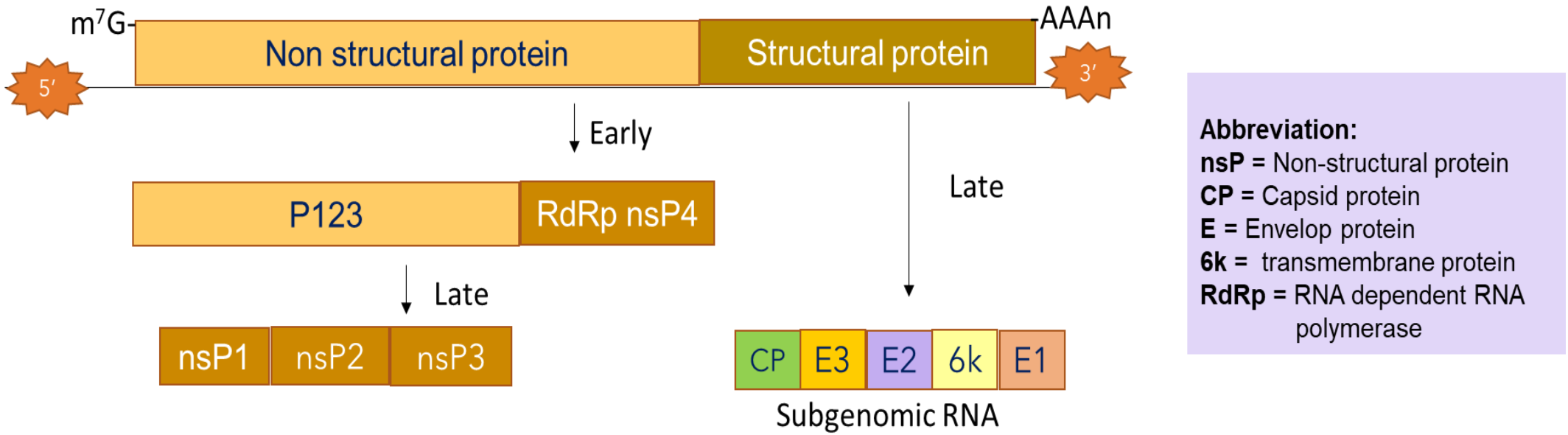
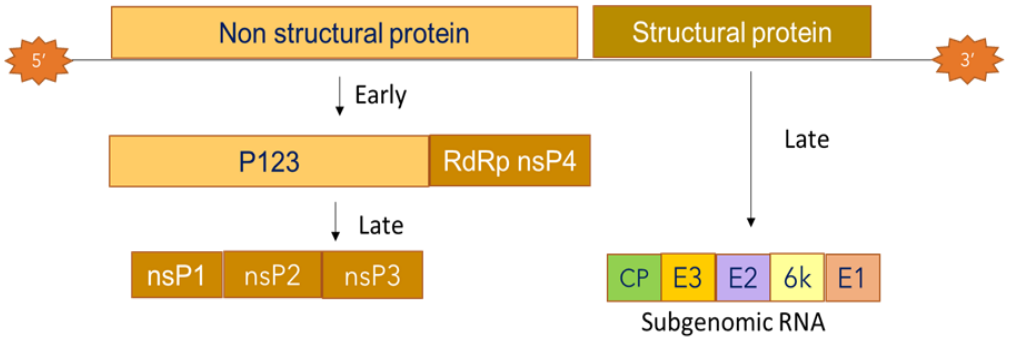


Figure: Genome organization of representative members of the *Togaviridae*

Viral Genome

- Genomic RNA (+ sense)
- Non-segmented - poly (A) tail
- Size ranges from
  - 9.7 to 11.8 kb for the Alphavirus
  - 9.8–10.0 kb for Rubivirus.



- RNA contains a 5′-terminal m7G cap and a 3′-terminal poly-A tail
- genome encodes non-structural proteins in a single ORF immediately after a 5′ non-coding region
  - Non structural proteins include-nsP1, nsP2 and nsP3
  - Structural proteins include the capsid (C/CP), E3, E2, 6K, and E1 proteins

Biological properties

- Alphaviruses are:
  - arthropod-borne viruses
  - replicate in invertebrate vectors and their vertebrate hosts.
  - cytopathic to vertebrate cells
- RUBV
  - only infect mammals
  - develop persistent infections.

Replication Cycle

- Proposed Model: E1 glycoprotein interacts with proteins on the cell surface. E2 binds to cellular proteins and receptor-mediated endocytosis takes place.
- In acidified endosomal compartment, glycoproteins fuse with membrane and the nucleocapsid is released.
- Virion RNA serves as mRNA, translation of non-structural proteins begins
- Structural proteins are transcribed as polyprotein
- E2 and E1 travel from ER to the Golgi
- At cellular membrane regions containing E1 and E2 heterodimers interact with nucleocapsids and viral particles bud from the cell surface

Disinfectants

- Chemical disinfectant:
  - effective disinfectants - 1% sodium hypochlorite and 70% ethanol
- Physical disinfectant:
  - Inactivated by UV light and at pH below 6.0

The Viruses

- EEE, WEE, and VEE viruses
  - Family Togaviridae
  - Genus *Alphavirus*
- Mosquito-borne
- Disease
  - Encephalitis in humans and horses
  - Other mammals and birds are occasionally affected

Equine Encephalitides: Classification and Distribution

	Family	Genus	Disease
1	*Togaviridae*	*Alphavirus*	EEE
2	*Togaviridae*	*Alphavirus*	WEE
3	*Togaviridae*	*Alphavirus*	VEE

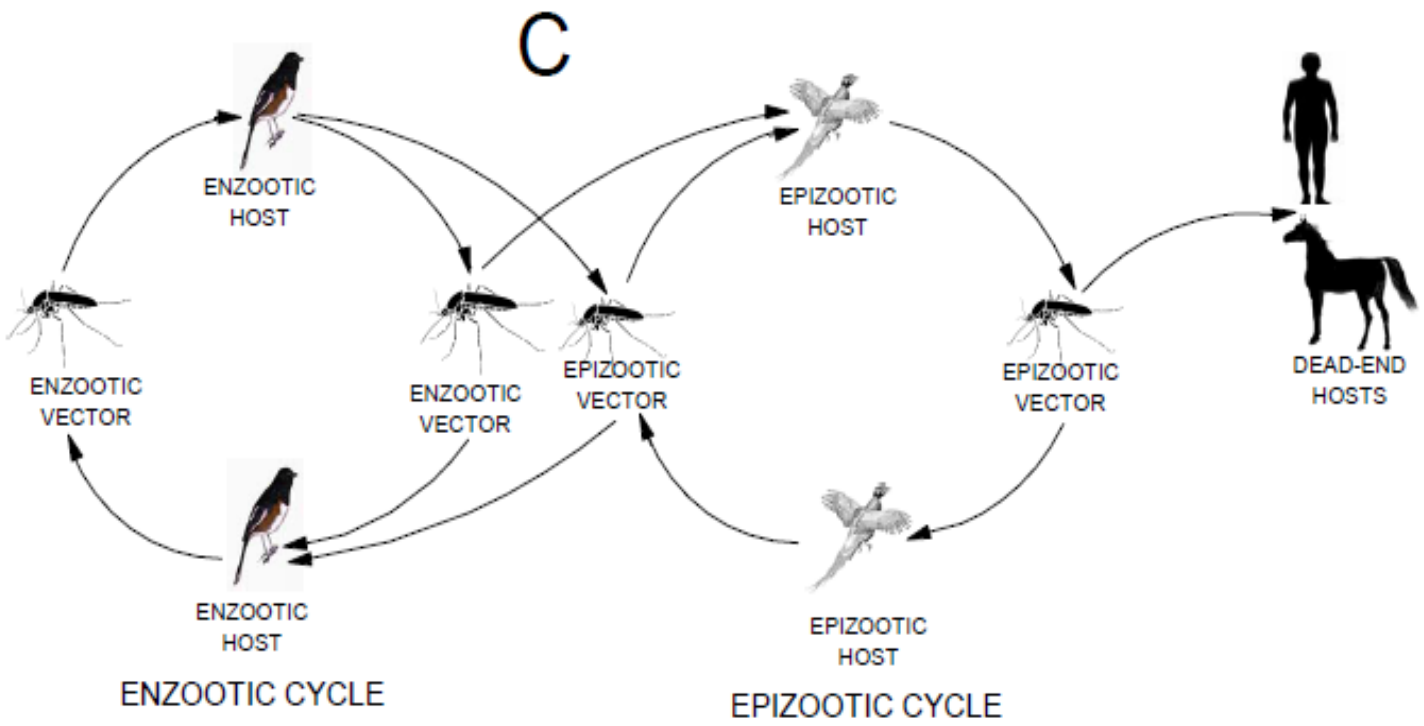
Togaviridae: Replication

- RNA is capped and polyadenylated
- serves as mRNA -> nonstructural proteins
- sense RNA -> antisense RNA
- Antisense RNA template for progeny RNA
- antisense RNA--> mRNA -> structural proteins
- mature at intracytoplasmic membranes

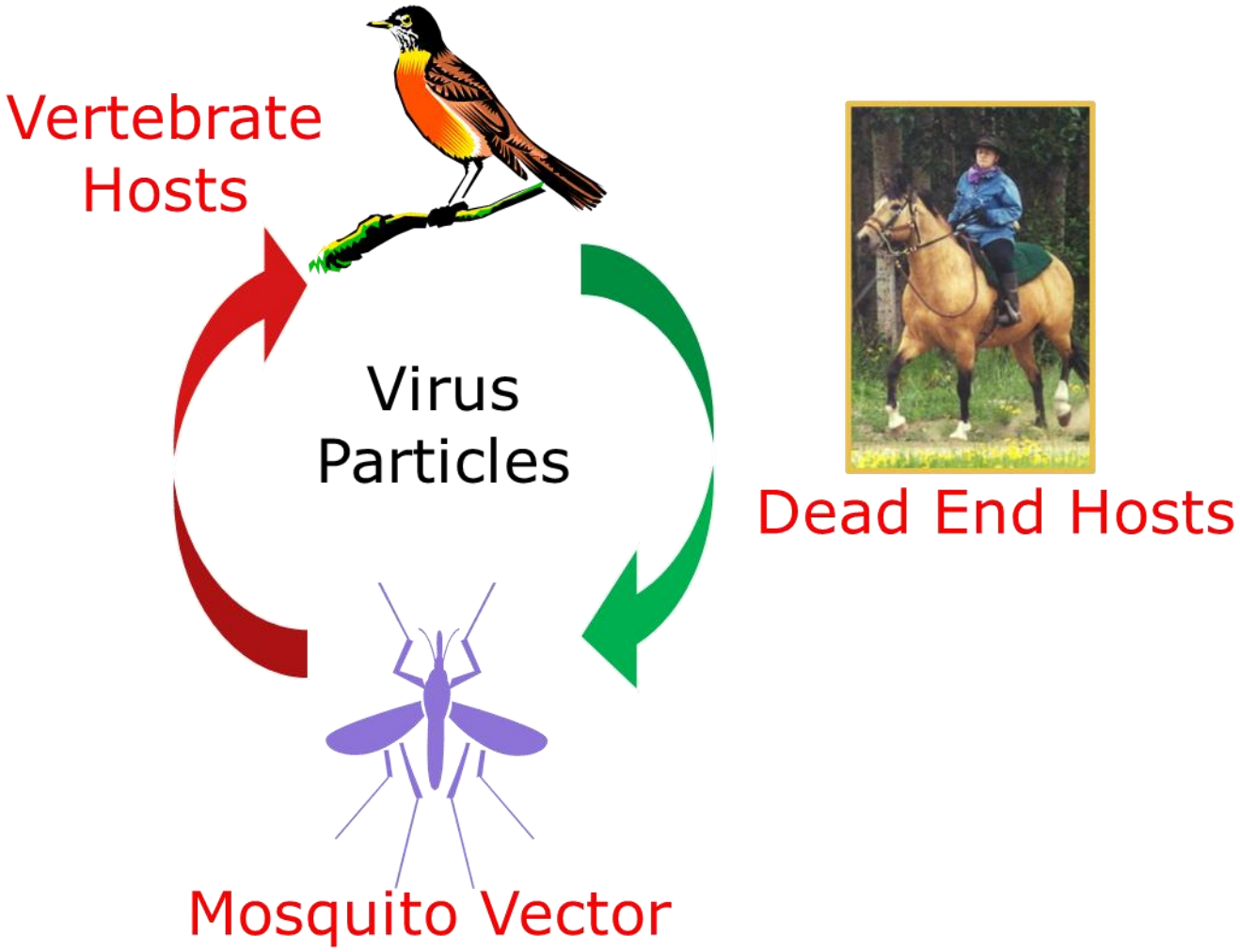

(Photo credit: CDC)

Transmission

Transmission



Transmission



Vectors of the Equine Encephalitides

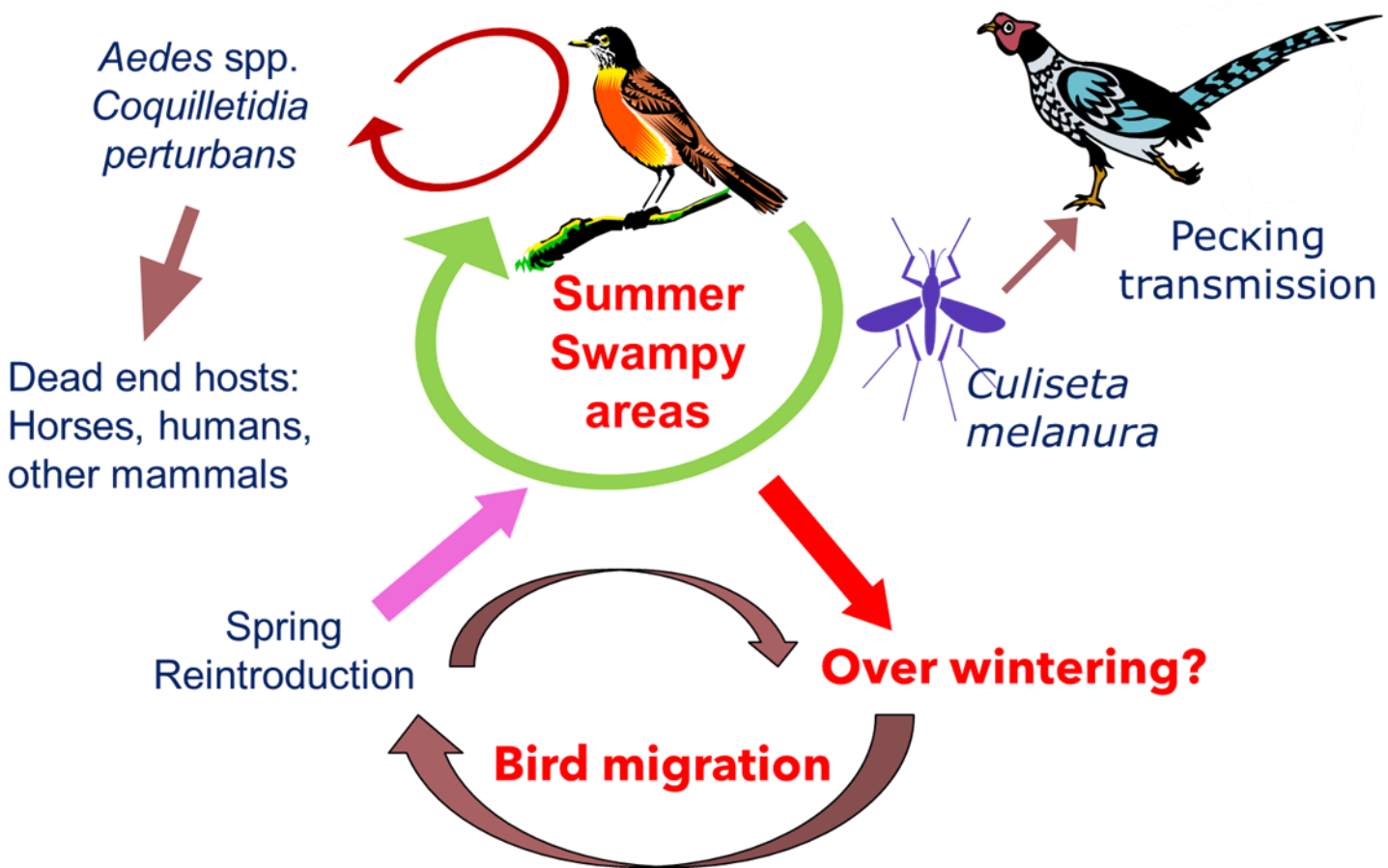
Disease	Mosquito Vector
EEE	*Culiseta melanura* *Aedes* spp. *Culex (Cx.) nigrapalpus, Coquilletidia* spp.
WEE	*Culex tarsalis* *Aedes melanimon* *Aedes dorsalis* *Aedes campestris*
VEE	*Culex* (*Melanoconion*) spp.

Summary of Equine Encephalitides

Distribution, Magnitude, and Outcomes

Eastern Equine Encephalitis

EEE Transmission



Wild-bird reservoir hosts and incidental hosts

- Wild-bird reservoir hosts and exposure of wild-bird reservoir hosts causes EEEV

EEE in Horses

- Incubation period: 5 to 14 days
- Clinical signs in horses
  - Fever, anorexia, depression
  - CNS signs
    - Hypersensitivity, aimless wandering, head pressing, circling, ataxia, paresis, paralysis
- Death may occur within days
- Asymptomatic or mild infections also occur
- Equine vaccine available

Clinical signs of EEE in a horse

Sleepy facial expression, the lax muzzle, and the abrasions between the eye and the base of the ear

EEE in Birds

- Asymptomatic in most bird species
- Clinical signs
  - Depression, tremors, leg paralysis, somnolence
  - Emus, ostriches
    - Hemorrhagic enteritis, emesis
  - Death 24 hours after onset
- Vaccination
  - Some birds are vaccinated for EEE

Diagnosis

- Ante mortem: serology
  - Virus neutralization
  - Hemagglutination inhibition test
  - Enzyme-linked immunosorbent assay (ELISA)
  - Complement fixation
  - Virus isolation
  - Immunofluorescence
  - Reverse Transcription Polymerase Chain Reaction (RT-PCR) assay
- Post mortem
  - Virus identification in tissues (brain)
  - Immunohistochemistry, ELISA, RT-PCR

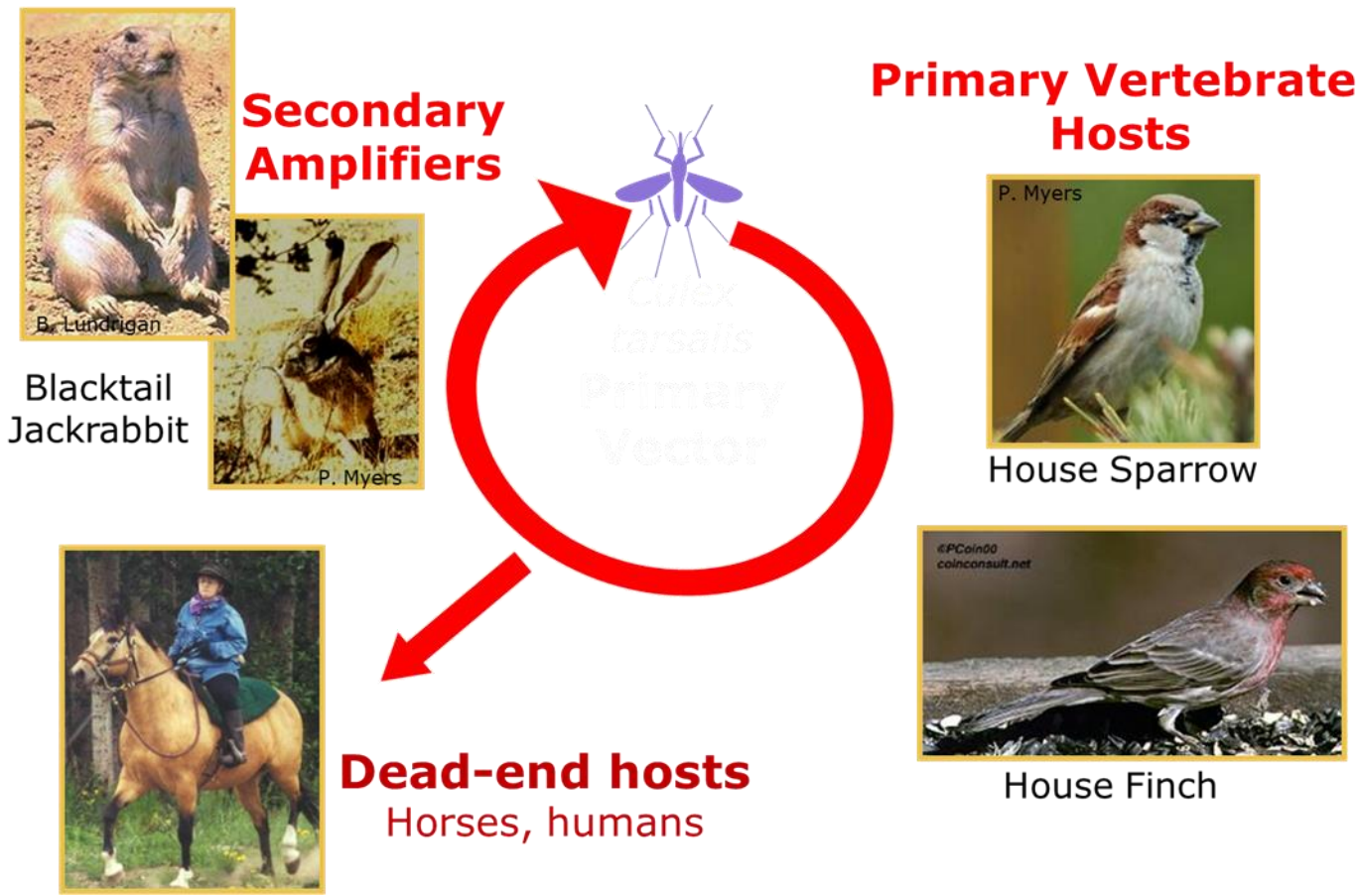
Diagnosis

- **Clinical diagnosis**
- – Fever
- **Laboratory conformation**

1. Probable case Detection of virus specific IgM antibodies in serum sample AND confirmation by neutralisation;.
2. Isolation of chikungunya virus from a clinical specimen;
3. Detection of chikungunya viral nucleic acid from a clinical specimen;
4. Detection of chikungunya specific IgM antibodies in a single serum sample

Western Equine Encephalitis

WEE Transmission



WEE in Animals

- Asymptomatic
  - Blacktail jackrabbit, kangaroo rat, Western gray squirrel, prairie dog, birds
- Horses with clinical signs
  - Fever, depression, altered mentation, head pressing, ataxia, dysphagia
  - Progress to paralysis, convulsions, death
  - Mortality rate <30%

WEE in Animals

- Diagnosis
  - Serology
    - Can differentiate EEE and WEE using the virus neutralization or ELISA tests
  - Post mortem
    - Immunohistochemistry, ELISA, RT-PCR
- Treatment is supportive care
- Vaccine available

Venezuelan Equine Encephalitis

VEE Viral Strains

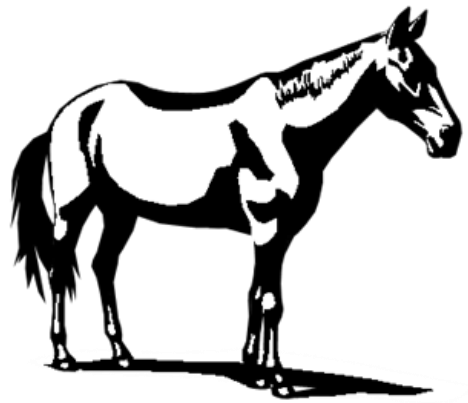
- Epizootic/Epidemic
  - I-A, I-B, and I-C
  - Disease in humans and horses
  - Transmission by many mosquito species
  - Natural reservoir unknown
  - Horses and donkeys act as amplifiers
- Enzootic/Endemic
  - Disease in humans
  - Transmission mainly by *Culex* (*Melanoconion*) species
  - Natural reservoir is rodents living in swamps and forests

VEE Epizootic Transmission

Primary Vector
multiple
mosquito species

Other species
naturally
infected but
not amplifiers

Dead-end hosts
Humans



Vertebrate Host
Horses

VEE Enzootic Transmission

Primary Vector
Culex
(Melanoconion)
species

Vertebrate Host
Rodents

Dead end hosts
Humans

VEE in Horses

- Incubation period: 1 to 5 days
- Horses most susceptible
  - Fever, anorexia, depression, flaccid lips, droopy eyelids and ears, incoordination, and blindness
  - Death 5 to 14 days after clinical onset
- Case-fatality rate: 50 to 90%
- In utero transmission results in abortion, stillbirth

VEE in Animals

- Most domestic animals do not show clinical signs or amplify the virus
- Experimentally
  - Infected rabbits and dogs die after inoculation
  - Laboratory animals susceptible
    - Act as sentinels
    - Guinea pigs, mice, hamsters
- Enzootic strains do not cause disease in animals

VEE in Animals

- Diagnosis
  - Virus isolation
  - Serology
    - Paired sera with rising titer
    - ELISA IgG or IgM
- Vaccine available for horses

Prevention and Control

Management of Mosquito-Borne Diseases

- Source reduction
- Surveillance
- Biological control
- Chemical control
  - Larvicide
  - Adulticide
- Educating the public
  - How to protect themselves

Biological Control

- Predators, natural and introduced, to eat larvae and pupae
  - Mosquito fish
    - *Gambusia affinis,*
      G. holbrooki
    - *Fundulus* spp.,
      Rivulus spp., killifish
- Other agents have been used but are not readily available
- Copepods

Chemical Control

- Essential when:
  - Source reduction not effective
  - Surveillance shows increased population of virus-carrying mosquitoes
- Requires properly trained personnel
- Larvicides, adulticides
- Toxic to many birds, fish, wildlife, aquatic invertebrates, honeybees
- Human exposure is uncommon

Chemical Control

- Federal Food Drug and Cosmetic Act limits the quantity of adulticide used
  - Due to wind drift onto agricultural crops
- Method used varies
  - Type of target mosquito
  - Type of targeted habitat
  - Aerial spraying covers wide area
- Funding provided by state or local government
  - Rarely federal

ACKNOWLEDGEMENT

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Thanks