

Rabies: Slaying a mad dog. Credit: Wellcome Collection. CC BY

Lecture 18: Rhabdoviridae and Pneumoviridae

Russ Fraser, Fall 2023

Rhabdoviridae: general

Size	100 – 430 nm
Morphology	Enveloped
	• Helical symmetry • Bullet shaped
Genome	linear, ssRNA, 11-15 kbp
Site of Replication	• Cytoplasm
Properties	• Eosinophilic intracytoplasmic inclusions (Negri bodies in rabies) • Buds from plasma membrane

Rhabdoviridae

- One of the most diverse groups of known viruses

- Vesiculovirus
  - Vesicular stomatitis New Jersey virus
  - Vesicular stomatitis Indiana virus (Indiana-1)
  - Vesicular stomatitis Cocal virus (Indiana-2)
  - Vesicular stomatitis Alagoas virus (Indiana-3)
  - Piry virus
  - Maraba virus
  - Chandipura virus
  - Carajas virus
  - Isfahan virus

- Lyssavirus (in 3 phylogroups)
  - Rabies virus (genotype 1)
  - Duvenhage virus (genotype 4)
  - European bat lyssavirus 1 (genotype 5)
  - European bat lyssavirus 2 (genotype 6)
  - Australian bat lyssavirus (genotype 7)
  - Bokeloh bat lyssavirus (genotype ?) (new)

  - Lagos bat virus (genotype 2)
  - Mokola virus (genotype 3)
  - Shimoni bat virus (genotype ????) (new)

  - Ikoma lyssavirus (genotype ??) (new)
  - West Caucasian bat virus (genotype ???) (new)

- Ephemerovirus
  - Bovine ephemeral fever virus
  - Berrimah virus
  - Adelaide river virus
  - Kotonkan virus (new)
  - Obodhiang virus (new)

- Novirhabdovirus – in fish
  - Viral haemorrhagic septicaemia, VHS, virus
  - Infectious haematopoetic necrosis, IHN, virus
  - Snakehead virus
  - Hirame rhabdovirus

- Perhabdovirus – in fish
  - Perch rhabdovirus
  - Anguillid rhabdovirus (eel virus)
  - Sea trout rhabdovirus

- Tibrovirus – in cattle
  - Tibrogargan virus
  - Coastal plains virus

- Sprivivirus – in fish
  - Spring viraemia of carp virus
  - Pike fry rhabdovirus

- Tupavirus – in birds
  - Durham virus
  - Tupaia virus

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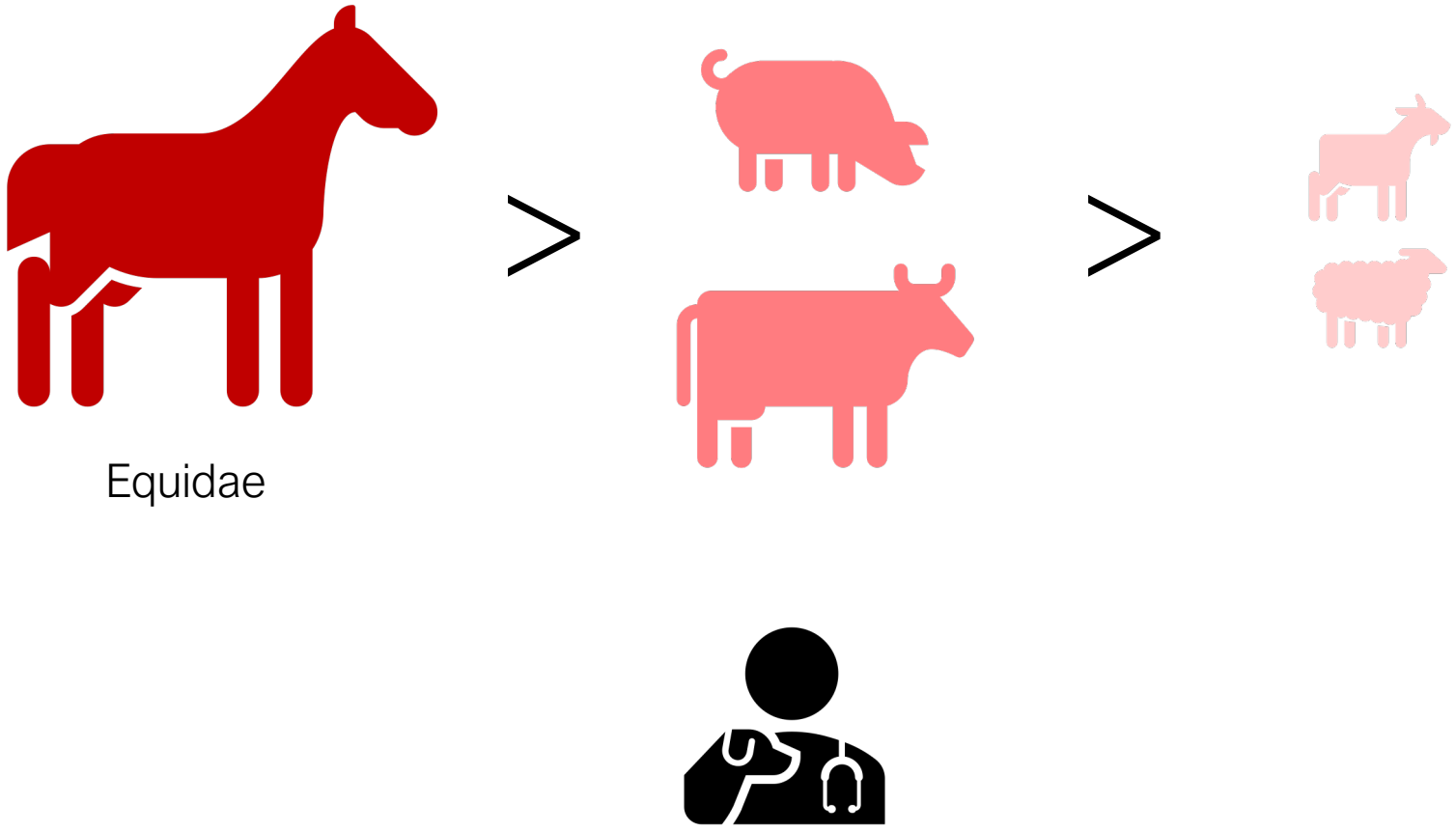
Vesicular stomatitis virus

Vesicular stomatitis virus: general

- Is exotic to Canada (last outbreak here was 1949)
  - Outbreak of FMD in 1952 was originally believed to be VS
- It is reportable
- Caused by 4 antigenically distinct rhabdoviruses (collectively referred to as vesicular stomatitis viruses)
  - VSV New Jersey
  - VSV Alagoas
  - VSV Indiana
  - Cocal virus



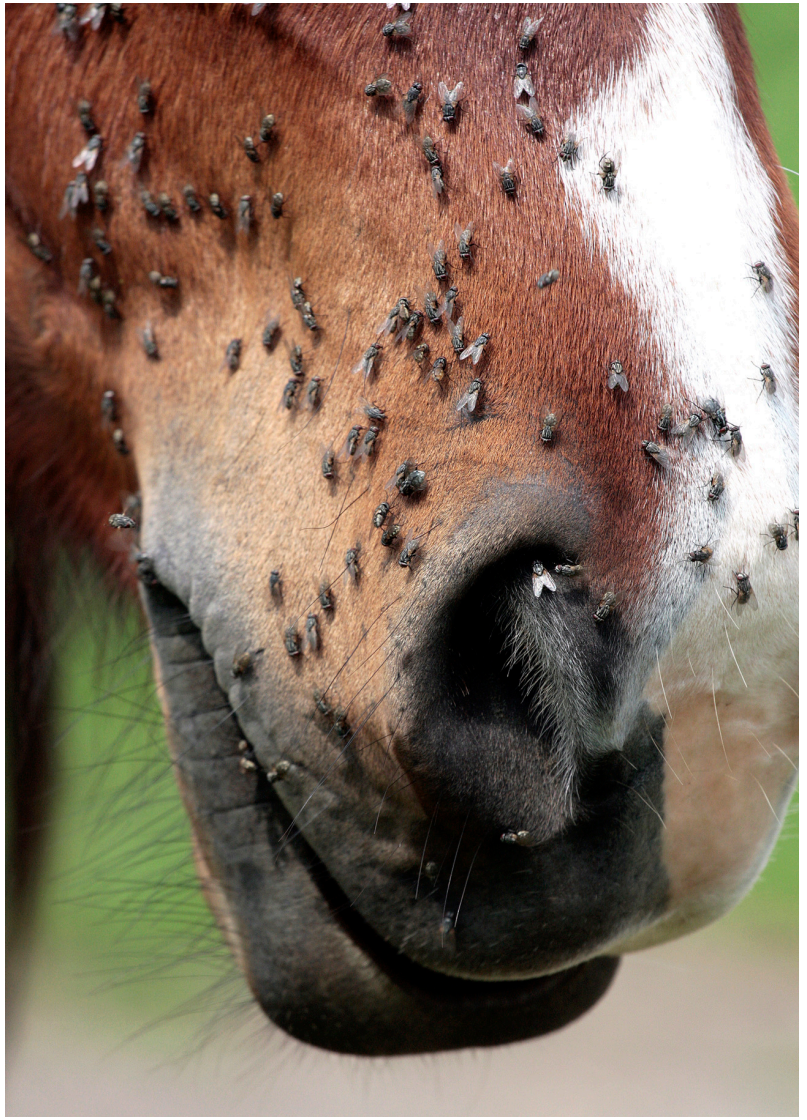
Vesicular stomatitis virus: host range



Equidae

Vesicular stomatitis virus: transmission

- Spread and transmission is not fully understood
  - Introduction to herd by biting insects or infected animals
  - Spread within herd by direct contact between infected animals
  - Contaminated fomites & environment
  - Consumption of contaminated meat



Vesicular stomatitis virus: pathogenesis

Entry through breaks in mucosa or skin

↓

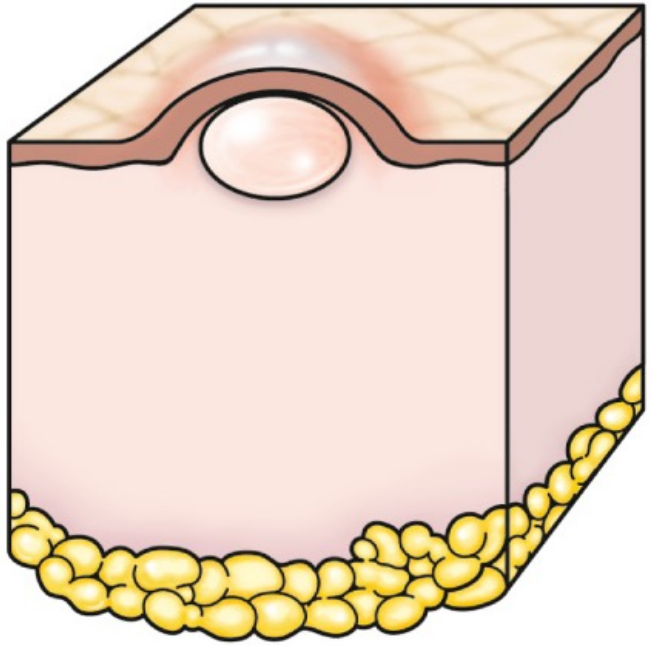
Localized infection of epithelium

↓

Vesicles that ulcerate

↓

Ulcers, erosions, crusts



Vesicle is a *fluid-filled blister* <1.0 cm in diameter (can be epidermal or dermal).

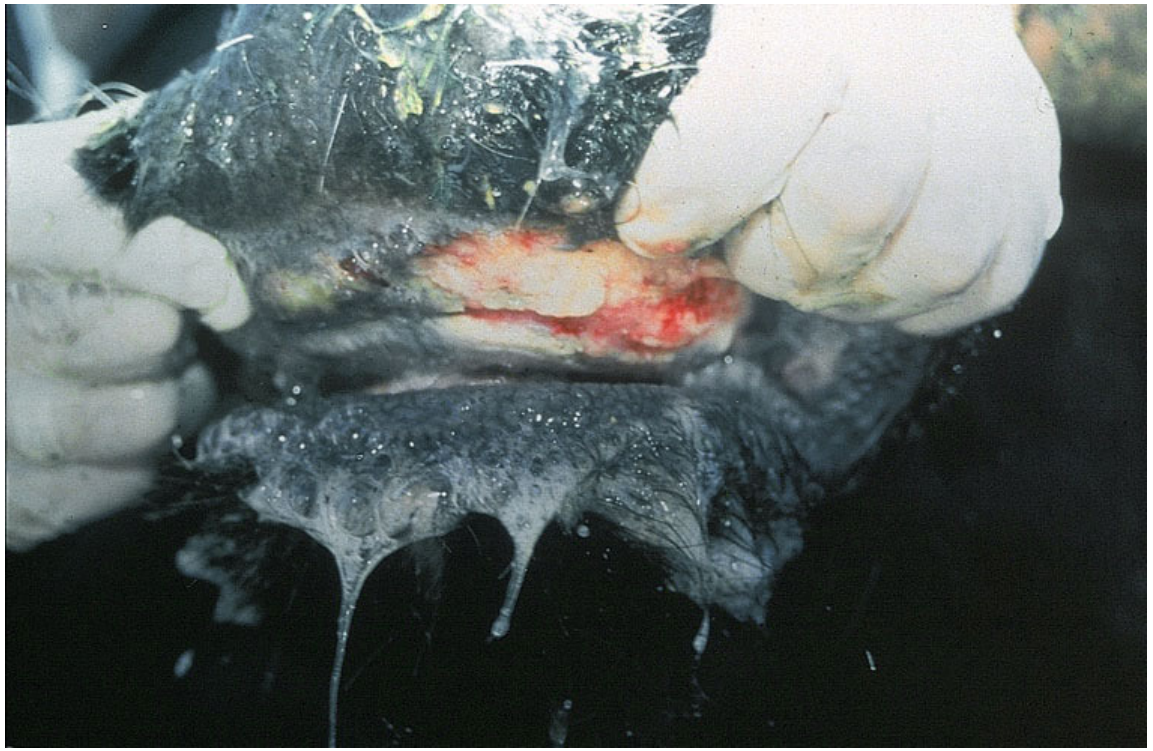
Vesicular stomatitis virus: clinical signs

- Subclinical >> more severe
- Excess salivation/drooling
- Difficulty eating
- Lameness
- Weight loss

- Cattle
  - Mastitis
  - ↓↓↓ milk production

- Humans
  - Influenza like symptoms

- Recovery in 2-3 weeks
  - Does not prevent infection with another VSV species



Vesicular stomatitis virus: gross lesions

- Vesicles → ulcers → crusts
  - Lips, gums, tongue, dental pad
  - Teats
  - Coronary bands
  - Prepuce, vulva



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Vesicular stomatitis virus

- VSV is one of the “vesicular diseases”
- These are a big deal.

Foot and mouth disease virus	Vesicular stomatitis virus
Vesicular exanthema virus	Swine vesicular disease virus

Vesicular stomatitis virus

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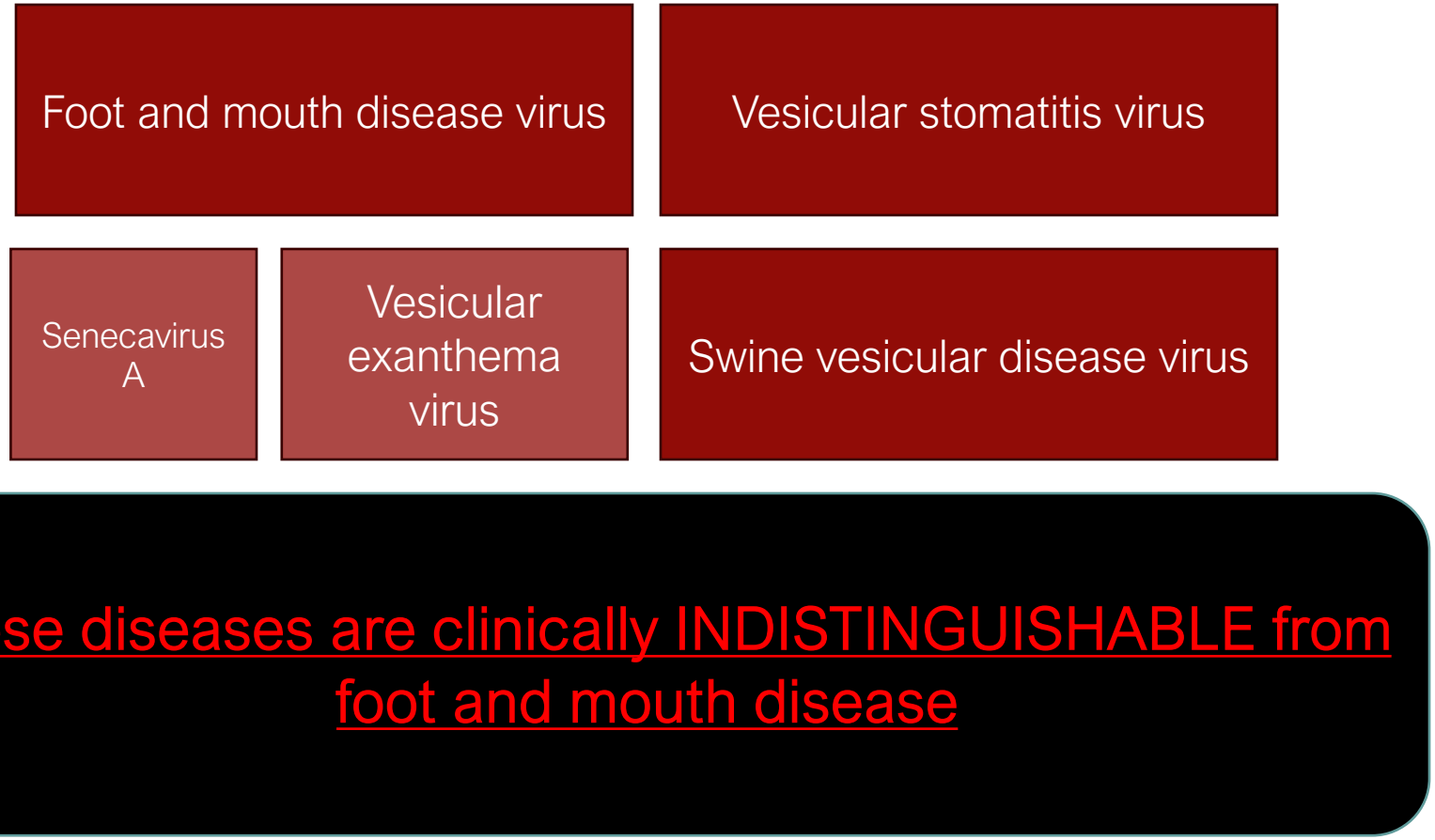
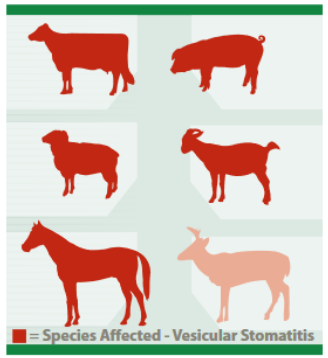


Characteristics that differentiate VSV from FMDV

	Vesicular stomatitis	Foot-and-mouth disease
Horses	affected	not affected
Incidence in herd	sporadic	epidemic
Animals with lesions at more than one anatomical site	small percentage	large percentage
Rumen & heart lesions	absent	present (heart lesions in calves <6 months old)
Disease in young animals	not severe	severe





Diagnosis of VSV

- DDx:
  - In horses: VSV is the only vesicular disease of Equidae
  - In pigs: other vesicular diseases including FMDV
  - In cattle: FMDV, MCF, BHV-1, BVDV, bluetongue, (Rinderpest)

- Accurate lab diagnosis is critical for the differentiation of VSV and FMDV

- Laboratory confirmation must be performed by federal lab:
  - PCR
  - Virus isolation

Control of VSV

- In case of a disease outbreak:
  - Restriction on animal movement until 30 days after last lesion found, has healed (or up to 6 months for exports)
  - Implement insect control program on farm
  - Avoid human exposure to this disease.

- Vaccines are not much used because:
  - Disease outbreaks are infrequent & unpredictable;
  - Outbreaks may involve several virus species which do not cross-protect.

- Public health significance:
  - Virus is zoonotic (occupational disease), but not a major human health issue.
  - Disease in humans resembles acute influenza, with recovery in 7-10 days.



Rabies virus

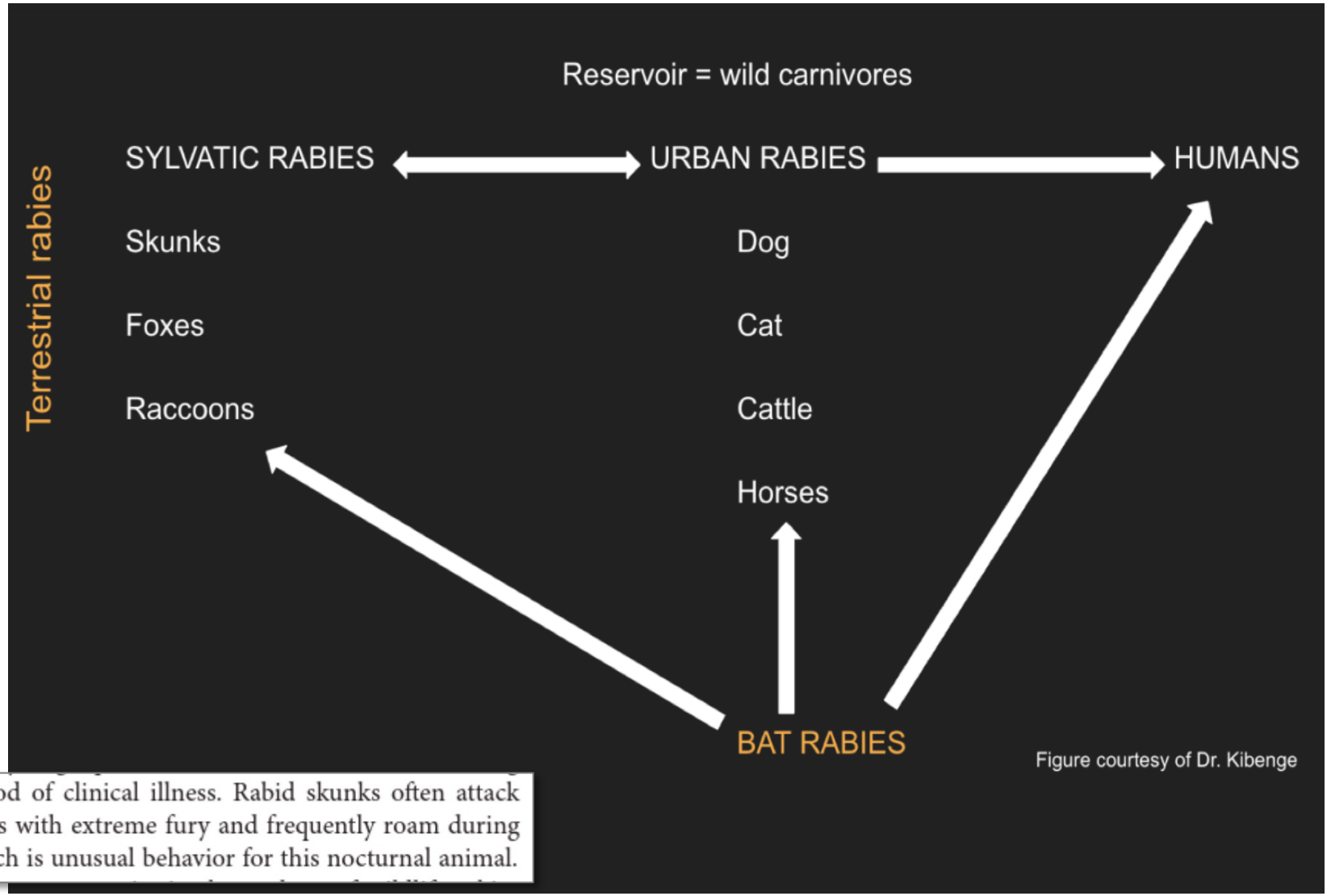
Rabies virus

- See tutorial presentations for general info
- Reportable
- Zoonotic
- 100% fatal





Rabies virus



the prolonged period of clinical illness. Rabid skunks often attack anything that moves with extreme fury and frequently roam during daylight hours, which is unusual behavior for this nocturnal animal.

Bat rabies

- Bat rabies is epidemiologically distinct from terrestrial rabies maintained by wild carnivores
  - insectivorous bats are involved in USA & Canada.

- 12 different variants of bat rabies in USA & Canada (not in Alaska or Hawaii). (This is also Rabies virus – Genotype 1).

- Account for most of the recent human infections in USA;
  - Often, there is no history of bite (i.e., cryptic). From 1990 to 2006, 74% of the 32 human cases of rabies were associated with bat rabies, but history of bite was established in only 2 cases.

- Vampire bat rabies is a problem for livestock & humans.

Rabies virus: transmission

- Host range:
  - All warm blooded animals.
  - Outcome of infection is almost always fatal.

- Transmission:
  - Bite/scratch of rabid animal (or in the absence of a bite, virus shed in saliva - contaminating an open wound or contact with mucosal membranes) or exposure to nervous tissue of an infected animal (e.g., corneal transplant or transplant of other tissues).

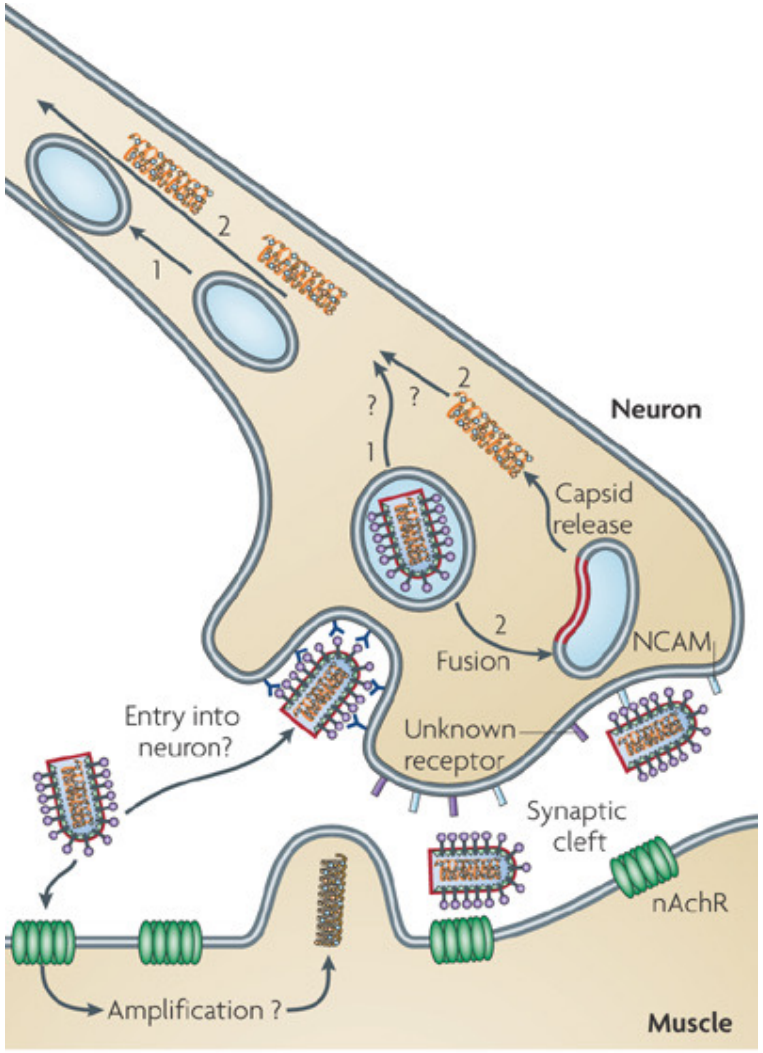
  - Aerosol transmission in bat caves & in research labs (contaminating mucous membranes of eyes, nose, & mouth)

  - Cryptic rabies (where clear history of exposure to rabies virus cannot be documented); most are due to bat rabies (i.e., contact with bats).





Rabies virus: transmission



The nicotinic acetylcholine receptor (nAchR) is located at the postsynaptic muscle membrane (neuromuscular junction). It has been suggested that nAchR enriches rabies virus at the neuromuscular junction or synaptic cleft, enabling more efficient infection of the connected motor neurons. Other research suggests that **initial rabies virus replication is in muscle cells, indicating that the nAchRs might be used to infect muscle cells. Virus can remain here for up to several months, replicating in muscle cells.**

Rabies virus enters the neurons using **neural cell adhesion molecule** (NCAM) or another, unknown receptor.

Two different mechanisms have been proposed for the transport of rabies virus through the axon to the cell body: the transport of either the rabies virus capsid or the whole rabies virus virion within the vesicle. The evidence favours the transport of intact virions.

Matthias *et al.,* 2010, *Nature Reviews Microbiology* 8:51-61.

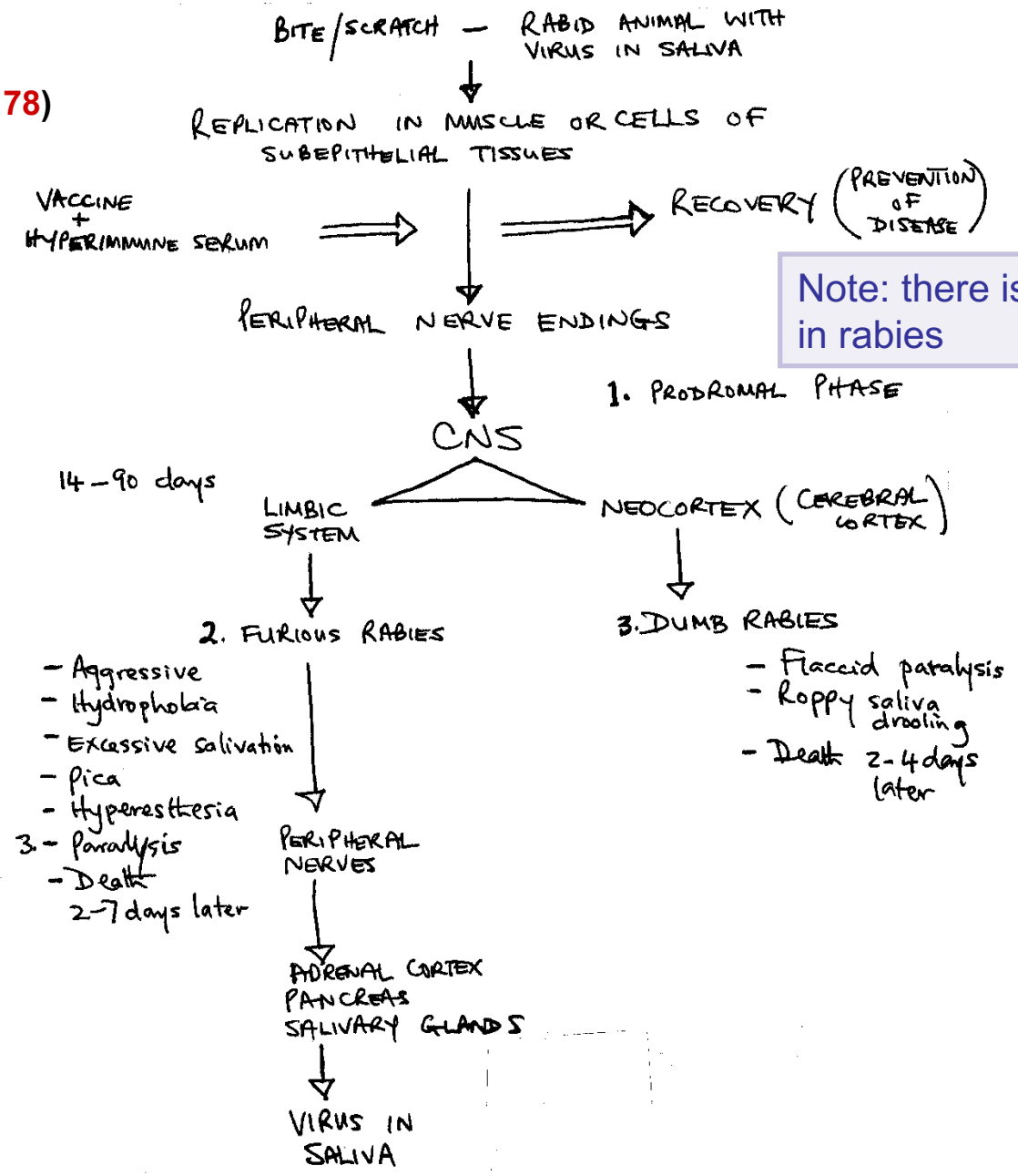
Rabies virus

- Incubation period is variable
  - Depends to some degree of anatomical location of inoculation
  - Virus thought to replicate in muscle, move centripetally along nerves to CNS
- Clinical signs are variable
  - Changes in behavior
  - Furious and dumb

Pathogenesis of rabies (pages 177-178)



Behavioral derangement



Note: there is no viraemia in rabies

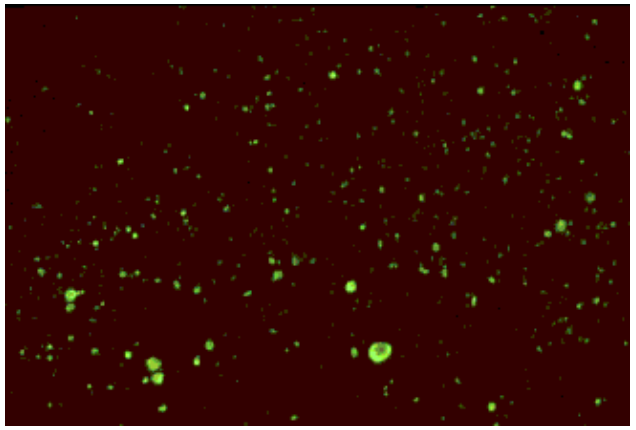
Rabies diagnosis

- Head from suspected case is submitted to Federal laboratory for testing.

However, effective April 1, 2014, the CFIA will no longer:

- collect and submit samples for rabies testing;
- investigate or quarantine domestic animals suspected of having rabies; or
- pay an indemnity for livestock that die due to rabies.

- Direct fluorescent antibody (FA) test on touch impressions of brain tissue
  - Gold standard test for rabies
  - Rapid
  - Is highly accurate.

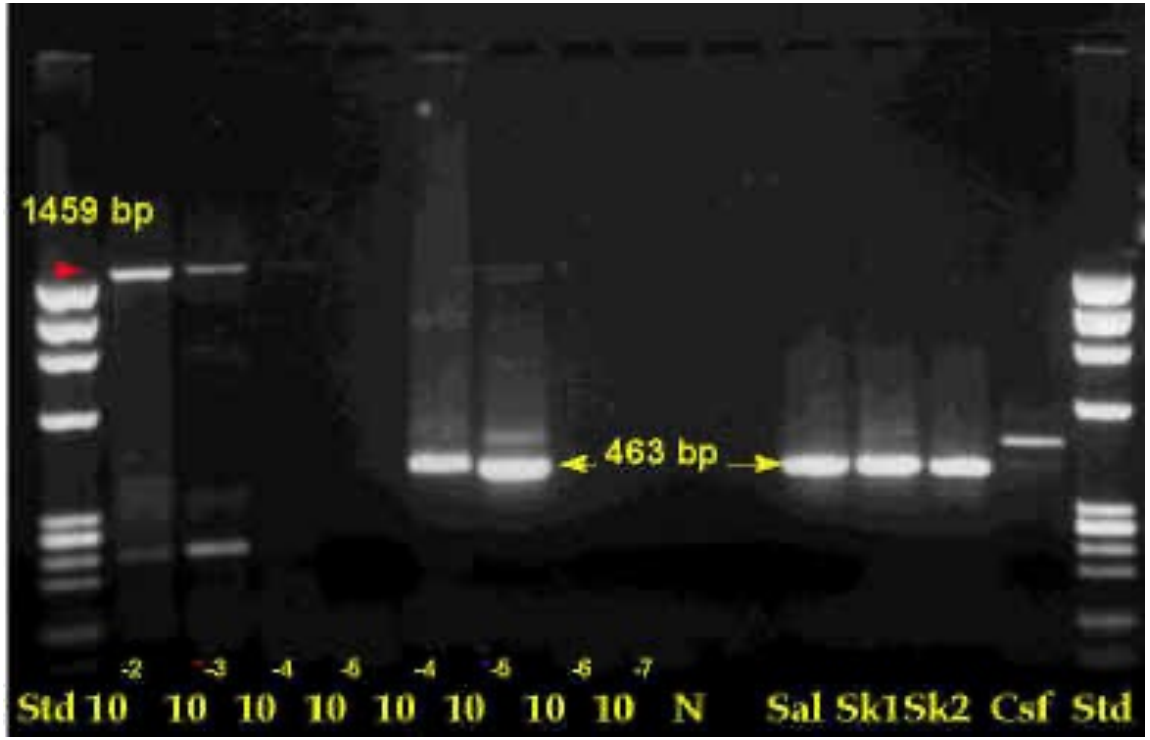


Positive test



Good negative reaction

Rabies diagnosis



- Reverse transcription-polymerase chain reaction (RT-PCR) to amplify rabies virus RNA as DNA copies
  - Is theoretically very accurate
  - Rapid
  - Can confirm FA results (its 100-1,000x more sensitive)
  - Can detect virus in saliva & skin biopsy samples (in humans).
  - Is useful when samples are unsuitable for other testing, for example when the suspect animal was buried & then exhumed or is decomposed.

Rabies virus: prevention and control

- The "Compendium of Animal Rabies Prevention and Control" is published every few years and is an excellent source of information on post-exposure planning.

- Rabies is a core vaccine for dogs, cats, and horses.
  - Administered at 3 months to dogs and cats, and again after 1 yr.
  - The booster vaccine is important: a single vaccine does not produce a lasting Ab titre in a significant portion of dogs
  - Foals: 6 months (if mare was vaccinated); 3-4 months if not. Boost according to label directions.

Rabies: prevention and control

TABLE 20-2

Recommendations for Rabies Vaccination of Animals and Humans in the United States[a]

Animal Exposed	Recommendation
PREEXPOSURE	
Dogs and cats	Vaccinate at 3 months of age; revaccinate 1 year later and every 1 or 3 years thereafter, depending on product recommendations
Ferrets	May be vaccinated at 3 months of age and revaccinated annually with an approved vaccine
Wildlife	Discourage ownership; no parenteral vaccine is approved for use; oral vaccination in government programs
Humans	Three doses of an FDA-approved vaccine given as 1 mL IM, based on manufacturer's recommendation, in the upper deltoid on days 0, 7, and 21 or 28; booster based on risk group
POSTEXPOSURE	
Dogs and cats	Previously unvaccinated: euthanize immediately or quarantine in secure enclosure for 6 months; vaccinate 1 month before release Vaccination not current: evaluate on case-by-case basis Vaccination current: revaccinate immediately and keep under owners' control for 45 days
Ferrets	Euthanize if not vaccinated; if vaccinated with an approved vaccine and vaccine is current, revaccinate immediately and place in strict isolation for 45 days
Wildlife	Regard as rabid and euthanize for examination
Humans	Previously unvaccinated: H-RIG[b], 20 IU/kg, infiltrated at site of bite once on day 0–7; FDA-approved cell culture-based vaccines[c] given at recommended dose IM in the upper deltoid on days 0, 3, 7, and 14; ID use not appropriate Previously vaccinated: three doses of an approved vaccine at recommended dose IM in upper deltoid on days 0, 7, and 21 or 28 days postexposure with no H-RIG. With serologic evidence of an adequate titer or previous full PEP series, only two doses are needed on days 0 and 3 with no H-RIG.

Greene's Infectious Disease of the Dog and Cat

Rabies: prevention and control

TABLE 21.4 Procedures Required by Public Health Officials for Prevention of Rabies According to the Compendium of Animal Rabies Prevention and Control[42]

Situation	Rabies Vaccination History	Procedure	Rationale
Dog or cat exposed[a] to a rabid wild animal or wild animal that is unavailable for testing	Unvaccinated, dog or cat	Euthanize immediately or place in strict isolation for 6 months. Administer rabies vaccine on isolation or up to 28 days before release.	The quarantine period is based on the known incubation period for rabies. Animals that develop signs consistent with rabies during quarantine should be euthanized and tested for rabies.
	Not up to date with booster vaccinations (no proof of prior vaccination for dogs or cats). Not up to date for ferrets.	Contact public health authorities who decide procedures (revaccination or euthanasia) based on biting species, local prevalence of rabies, timing of previous vaccinations.	
	Vaccinated, dog or cat Or not up-to-date with booster vaccinations, but proof of prior vaccination.	Revaccinate, and keep under owner's control and observation for 45 days.	
Human bitten by a healthy dog or cat	Any	Confine animal and observe daily for 10 days; report illness that develops immediately to public health authorities. If signs of rabies develop, euthanize and test for rabies. Vaccination should not be performed until after the isolation period is complete.	Dogs and cats shedding rabies virus within the saliva will develop illness and die within the 10-day quarantine period.
Human bitten by a stray or unwanted dog or cat		Euthanize biting animal immediately and submit for rabies testing.	
Human bitten by a known rabid animal	Vaccinated, human	Vaccinate (1 mL) on day 0 and day 3 intramuscularly, in the upper deltoid muscle.	
	Unvaccinated, human	Postexposure prophylaxis: injection of human rabies immune globulin infiltrated at the bite site, followed by vaccination (1 mL) on days 0, 3, 7 and 14 (and 28 only for immunocompromised persons)	

[a]Exposure for rabies constitutes introduction of the virus into bite wounds, open cuts in skin, or onto mucous membranes from saliva or other potentially infectious material such as neural tissue.
Compendium updates are available online at http://www.nasphv.org/documentsCompendia.html.
Modified from Brown CM, Slavinski S, Ettestad P, Sidwa TJ, Sorhage FE. Compendium of Animal Rabies Prevention and Control, 2016. *J Am Vet Med Assoc.* 2016;248:505–517.

Greene's Infectious Disease of the Dog and Cat

Rabies: prevention and control

Horses exposed* to a confirmed rabid animal:

Horse currently vaccinated against rabies *by a licensed veterinarian with proof of administration of a USDA-approved rabies vaccine:* Immediate revaccination by a licensed veterinarian and observation for number of days as directed by state public health officials.

Unvaccinated horse: Contact your state's public health officials immediately as they will have established requirements and conditions for the monitoring and/or disposition of exposed, unvaccinated animals. These officials will dictate what options are available for the exposed horse. These options may include isolation for up to six (6) months and immediate post-exposure immunization of the horse. Alternatively, the horse can be euthanatized immediately.

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https://aaep.org/guidelines/vaccination-guidelines/core-vaccination-guidelines/rabies



Pneumoviridae

Bovine respiratory syncytial virus

Bovine respiratory syncytial virus (BRSV)

- Virus belongs to genus Orthopneumovirus
- Causes important respiratory disease of recently weaned calves & young cattle kept in closely confined conditions.
  - There are also respiratory syncytial viruses of sheep & goats (with pathology in the respective hosts very similar to that of BRSV in cattle).
- Transmission: droplet infection.
- Host range: cattle & sheep
- Virus infection may predispose to “shipping fever” or bovine respiratory disease complex (together with other viruses… PI-3, IBR, BVDV, bovine coronavirus) and bacteria
  - Mixed infections are common.
- Clinical disease is characterized by:
  - Fever, rhinitis, cough, bronchiolitis & multifocal interstitial pneumonia
  - Secondary bacterial infections are common.

Bovine respiratory syncytial virus

- Characteristic pathology: syncytia with inclusion bodies in lungs (hence name of virus).
- There are several viruses that may predispose to shipping fever, and mixed infections are common:
  - PCR
  - FA detection of antigen in lung tissue from early cases of disease is sensitive & reliable
- Control:
  - An attenuated vaccine is available for use in cattle.
- Public health significance: none.
  - BRSV is very similar to HRSV but does not infect humans.

