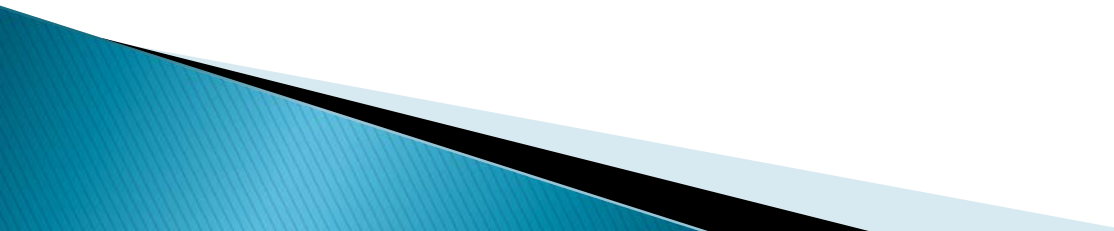


Human Rabies Pre-exposure Vaccination & Post-exposure Prophylaxis

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Human Rabies Pre-exposure Vaccination & Post-exposure Prophylaxis

- ▶ Wake AHEC requires all speakers to disclose any relevant financial conflicts of interest.
 - ▶ Carl Williams has no relevant financial conflicts of interest to disclose.
 - ▶ Jodi Reber has no relevant financial conflicts of interest to disclose.
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Prevention of Rabies

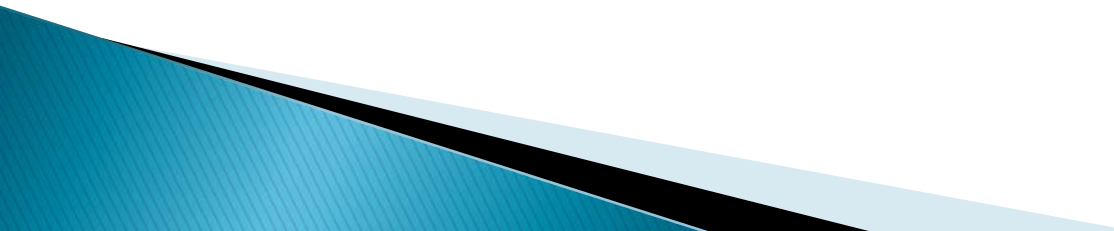
▶ Medical Intervention

- pre exposure vaccination
 - human
 - pet animal
- post exposure management
 - human
 - pet animal
- vaccination of wildlife

▶ Behavior Modification

- knowledge
- caution
- common sense

Objectives

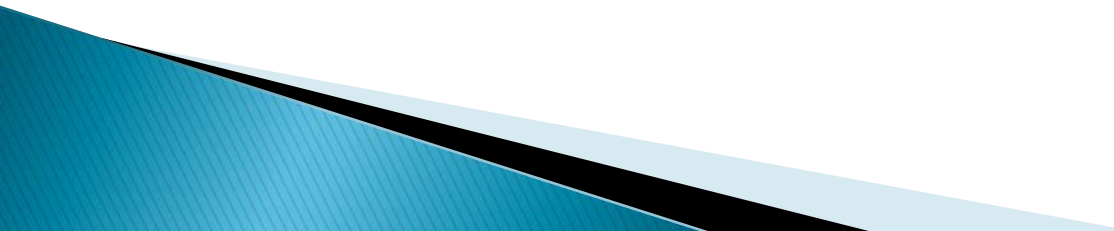
- ▶ Understand the need for pre-exposure prophylaxis
 - ▶ Gain familiarity with risk assessments for post-exposure prophylaxis
 - ▶ Learn the biologicals used
 - ▶ Know the difference between CDC / WHO / PHAC recommendations
- 

Who should receive *Pre-exposure* Vaccination?

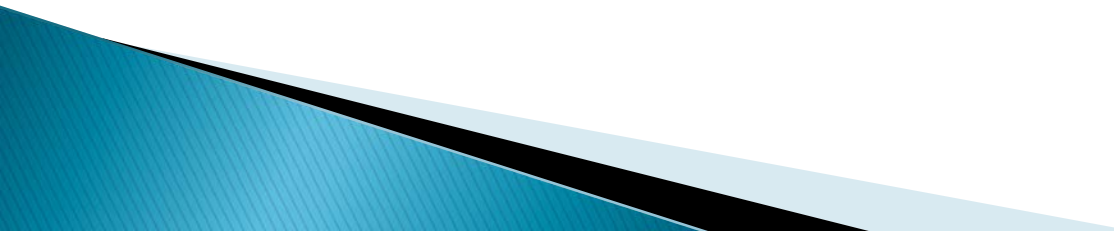
- Veterinarians and staff
- Laboratory workers
- Animal control officers
- Wildlife workers
- Travelers to rabies endemic countries; at risk

<http://www.cdc.gov/rabies/news/RabVaxupdate.html>

Pre-exposure Vaccines for People at risk for Rabies Exposure

- ▶ 3 Vaccines
 - ▶ Days 0, 7, and 21 or 28
 - ▶ Local Health Department or Private Physician
- 

Rabies Titers

- ▶ Used to assess response to vaccination only!
 - ▶ Presence of an adequate titer does not obviate the need for PEP if indicated!
 - ▶ Requesting titer testing for persons exposed to rabies is inappropriate!
- 

Rabies Titers

Use to assess vaccine response in select occupational groups

- ▶ RFFIT – gold standard
 - Rapid focus fluorescent inhibition test
 - A virus neutralization assay
- ▶ Performed by
 - Kansas State University (785–532–4483)
 - <http://www.vet.ksu.edu/depts/dmp/service/rabies/index.htm>
 - Atlanta Health Associates (800–717–5612)
 - <http://www.atlantahealth.net/>

Rationale for Rabies Pre Exposure Immunization for People

- ▶ It may provide protection to persons with inapparent exposure to rabies
- ▶ It may protect persons whose post exposure therapy is expected to be delayed
- ▶ In the event of an exposure to rabies it simplifies therapy by
 - Eliminating need for HRIG
 - Decreasing number of vaccine doses required

Human Rabies Prevention — United States, 2008, Recommendations of the Advisory Committee on Immunization Practices, MMWR May 23, 2008 / Vol. 57 / No. RR-3

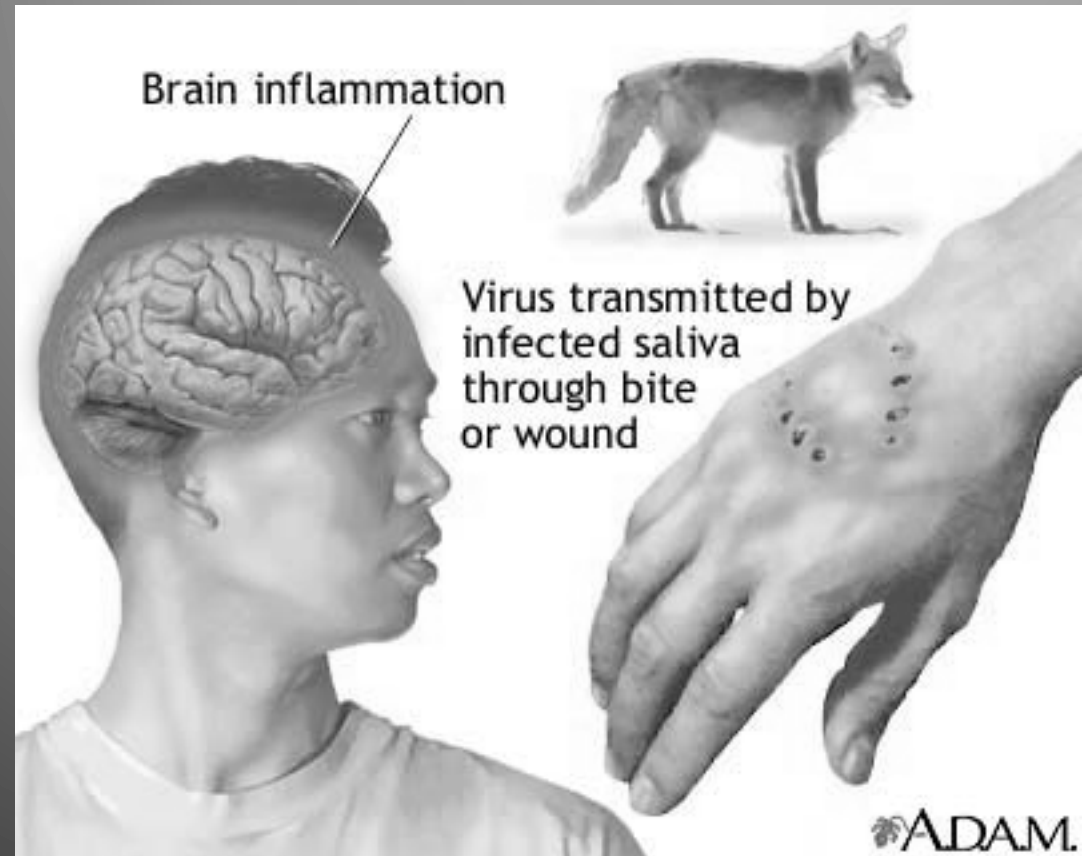
Rabies Exposure and Post-exposure Prophylaxis

- ▶ Administration of PEP is a medical urgency, not a medical emergency
 - Consult with colleagues, and PH officials when needed
- ▶ Type of exposure
 - Rabies is transmitted when the virus is introduced into bite wounds or open cuts in skin, or onto mucous membranes
 - **If no exposure has occurred, no PEP is required**
- ▶ Three major categories of exposure
 - Bite
 - Nonbite
 - Bat

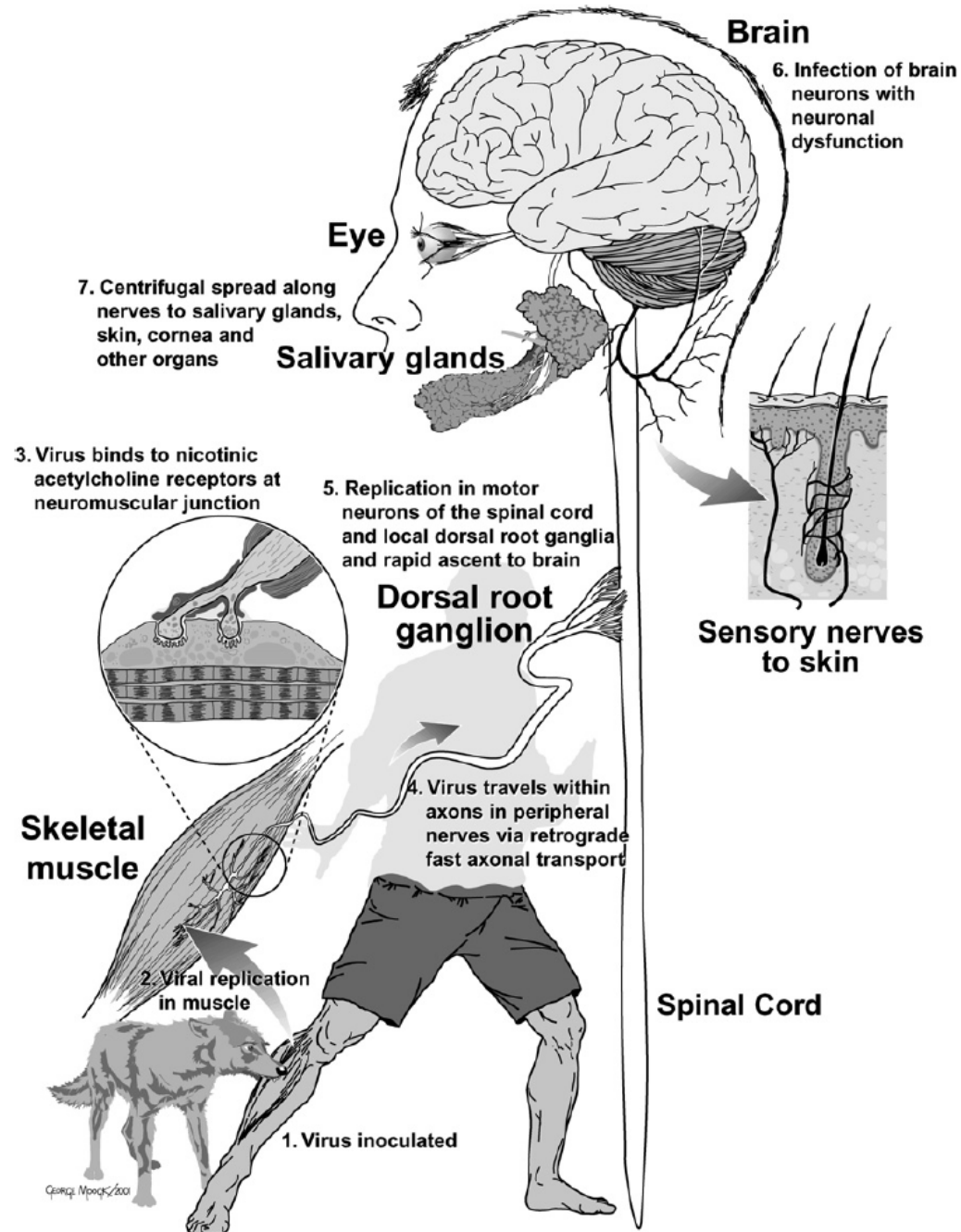
Rabies Exposure

▶ Bite

- Any penetration of the skin by teeth constitutes exposure
- It is assumed that all bite exposures result in contamination of the wound with saliva



Rabies Virus Pathway



Jackson. Rabies.

Neurol Clin 26 (2008) 717-726

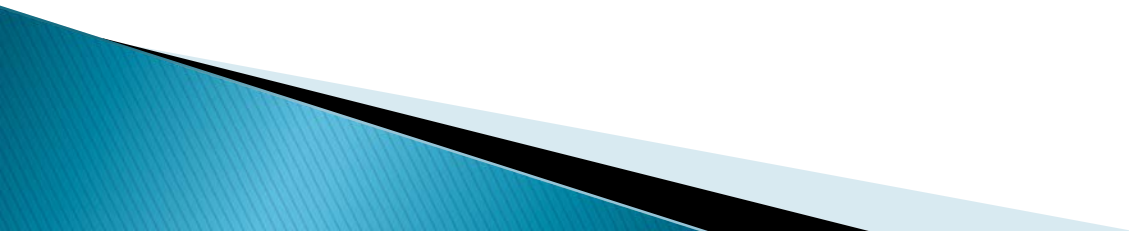
Rationale for Rabies Vaccination

- ▶ Following inoculation of rabies virus into a human by a rabid animal, the virus replicates locally before invading the nervous system
- ▶ This delay provides an opportunity to neutralize the virus
- ▶ Once virus has gained access to the nervous system, it is beyond immune attack and agonizing death is virtually inevitable

Don't Always Rush to Administer PEP

Scenario 1

What course of action is
required here?



Dogs and Cats

- ▶ It is estimated that each year in the US
 - 4.5 million people are bitten by dogs
 - Resulting in 316,000 ED visits and 9,500 hospital stays in 2008
- ▶ In the state of Victoria, Australia, 1998–2004
 - 12,982 bites occurred
 - 79.6% due to dogs
 - 8.7% due to humans!!
 - 7.2% due to cats

Holmquist. ED Visits and Inpatient Stays Involving Dog Bites, 2008. AHRQ/HCUP Statistical Brief 101. November, 2010

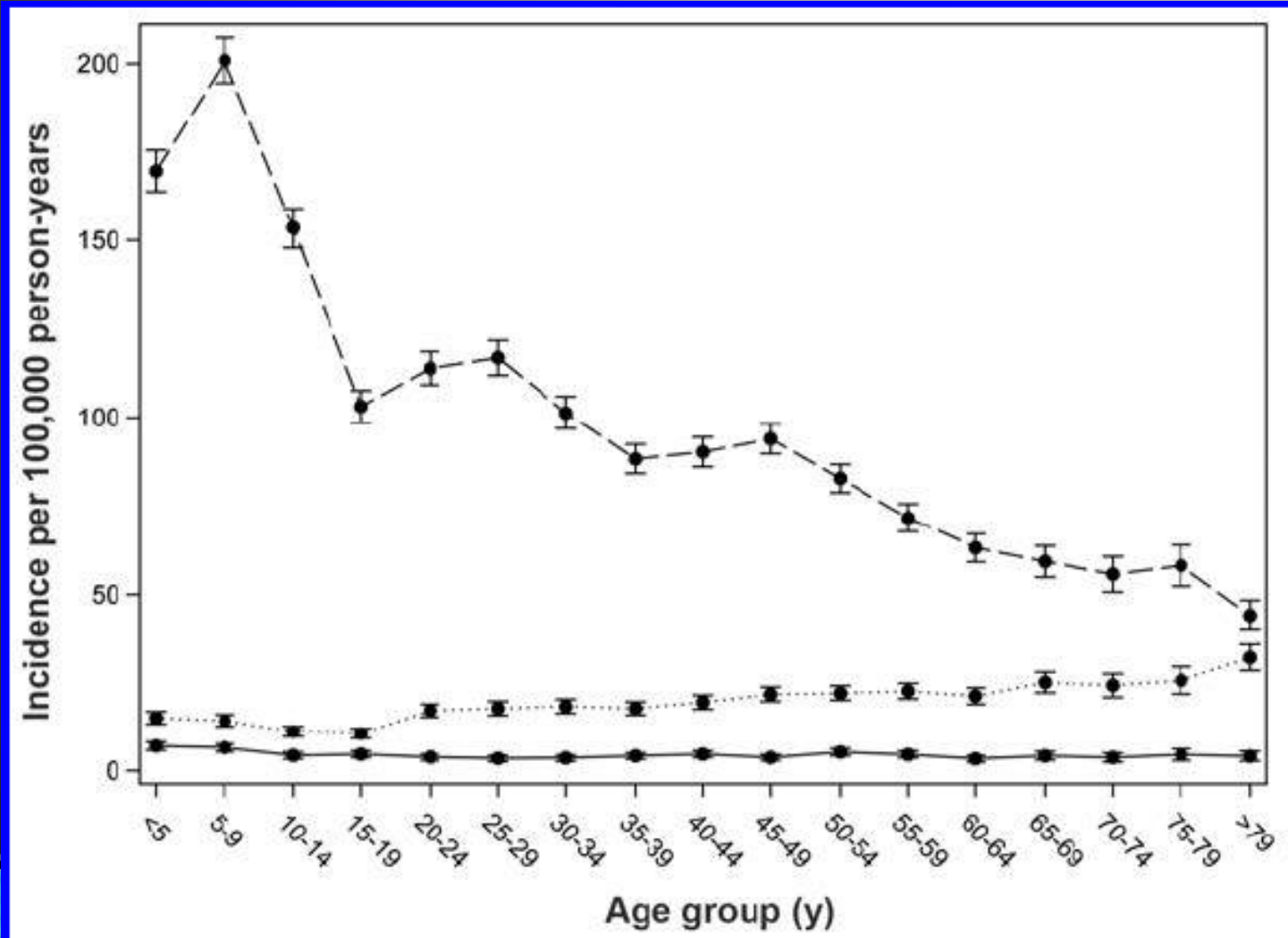
Mac Bean, et. al. Animal and human bite injuries in victoria, 1998-2004. MJA. 2007, 186(1). 38-40.

NC Data, 2008–2010

- ▶ ~14 million ED visits
 - 38,971 Animal bite or scratch related
 - 29,586 dog bites, 5,314 cat bite scratch
 - Rabies PEP initiated for
 - 839 / 29,586 dog bites (2.8%)
 - 379 / 5,314 cat bites / scratches (7.1%)

Rhea, et. al. Use of statewide emergency department surveillance data to assess incidence of animal bite injuries among humans in North Carolina. JAVMA, Vol 244, No. 5, March 1, 2014

Incidence rates for animal bite-related emergency department visits among humans in North Carolina by patient age group and biting animal species

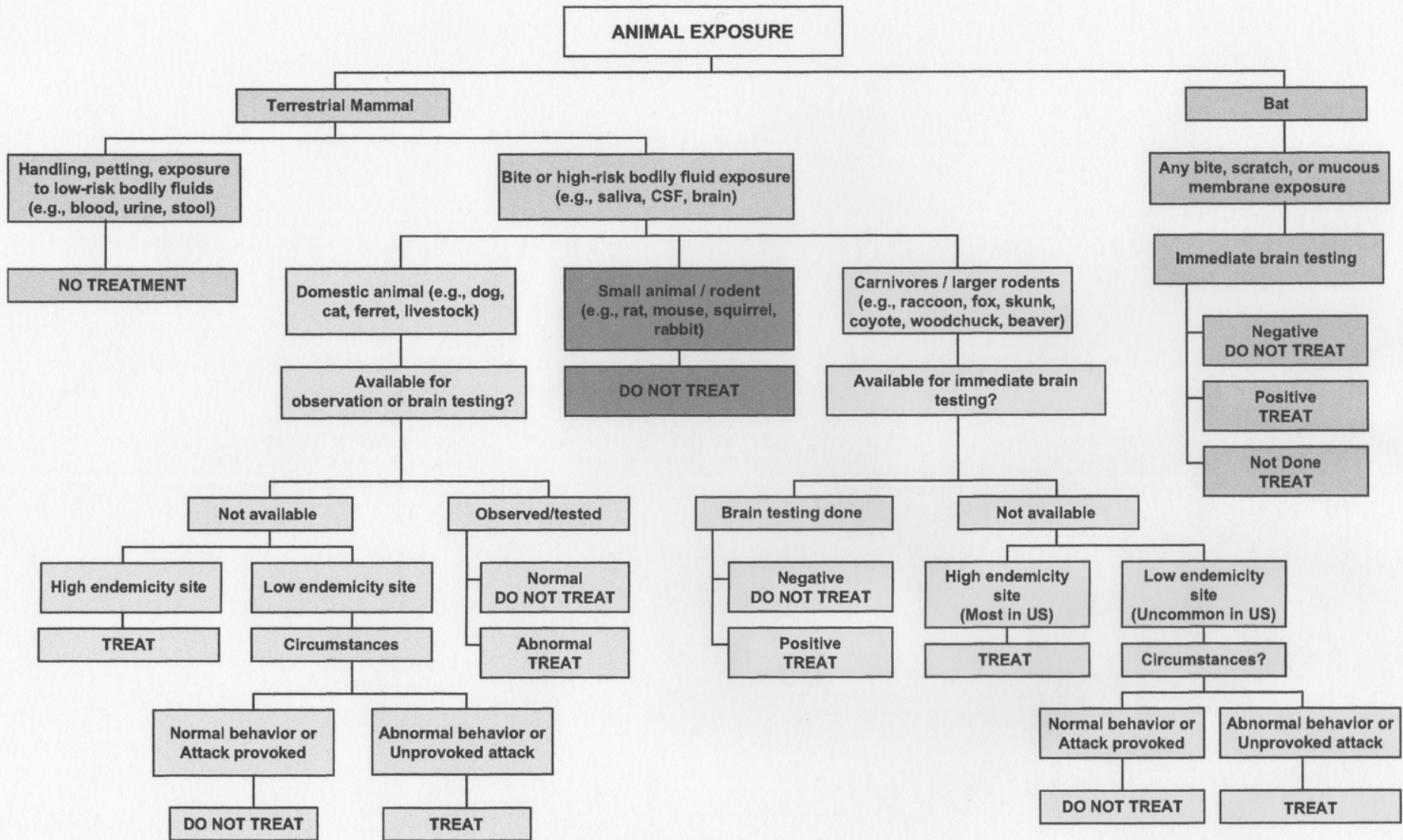


Millions of Bites, Thousands of ED Visits

What do these patients really need?

- ▶ Wound care
- ▶ Antibiotic therapy
- ▶ Tetanus Booster or TIG administration¹
 - Many immigrants not adequately vaccinated against tetanus, thorough history needed
- ▶ Rabies specific risk assessment
 - Most dog/cat bites do not require rabies PEP

¹ Talan DA, Abrahamian FM, Moran GJ, et al. Tetanus immunity and physician compliance with tetanus prophylaxis practices among emergency department patients presenting with wounds. *Ann Emerg Med.* 2004;43:305-314.

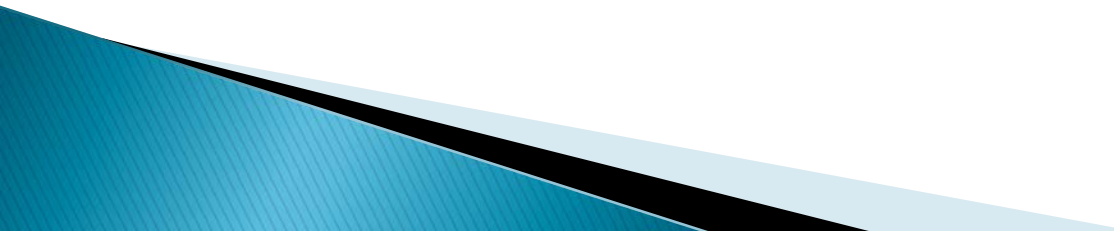


Moran, et. al. Antimicrobial Prophylaxis for Wounds and Procedures in the Emergency Department. Infect Dis Clin N Am 22 (2008) 117–143

Animal Type	Evaluation & Disposition of Animal	PEP Recommendations
Dog/Cat/Ferret	Healthy & available for 10 day observation	No PEP unless animal shows clinical signs of rabies*
	Rabid or suspected rabid	Begin PEP
	Unknown	Consult PH

*If animal develops signs of rabies, euthanize and submit for testing, begin PEP

“Shedding” period

- ▶ “Shedding” of virus occurs when rabies virus is excreted in the saliva
 - ▶ We know the shedding period for dogs, cats and ferrets; it does not exceed 10 days.
 - ▶ We don’t know the shedding period for other species.
- 

Observation/Testing vs. PEP Administration

- ▶ Healthy People 2000 noted a goal of
 - Reduce post exposure rabies treatments to no more than 9,000 per year
 - PEP goals not stated in HP 2010 or 2020
- ▶ In one study of PEP administration, it was given inappropriately (given when not necessary) 40% of the time
- ▶ Supplies of Rabies Biologicals are not unlimited

: <http://www.cdc.gov/nchs/data/hp2000/hp2k01.pdf>

Moran. Appropriateness of Rabies Postexposure Prophylaxis Treatment for Animal Exposures. JAMA 284(8). 2000. pp. 1001-1007

Cost Effectiveness of Rabies PEP

- ▶ There is concern that the costly rabies PEP treatment is over utilized, resulting in financial burden on healthcare systems and periodic shortages of the biologics
- ▶ When the risk of a patient getting rabies is deemed greater than 0.7%, then giving PEP will be cost saving (societal perspective)
- ▶ Median risk of rabies transmission after bite from a dog in US has been estimated to be 0.00001

Dhankar. Cost effectiveness of rabies post exposure prophylaxis in the United States. *Vaccine* 26. 2008. pp 4251–4255

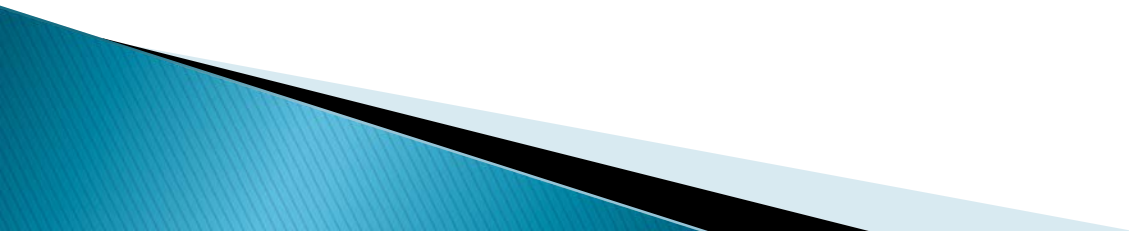
Vaidya. Estimating the risk of rabies transmission to humans in the U.S.: a delphi analysis. *BMC Public Health* 10 (278). 2010.

Sometimes PEP Administration is
More Urgent

Scenario 2



What course of action is
required here?



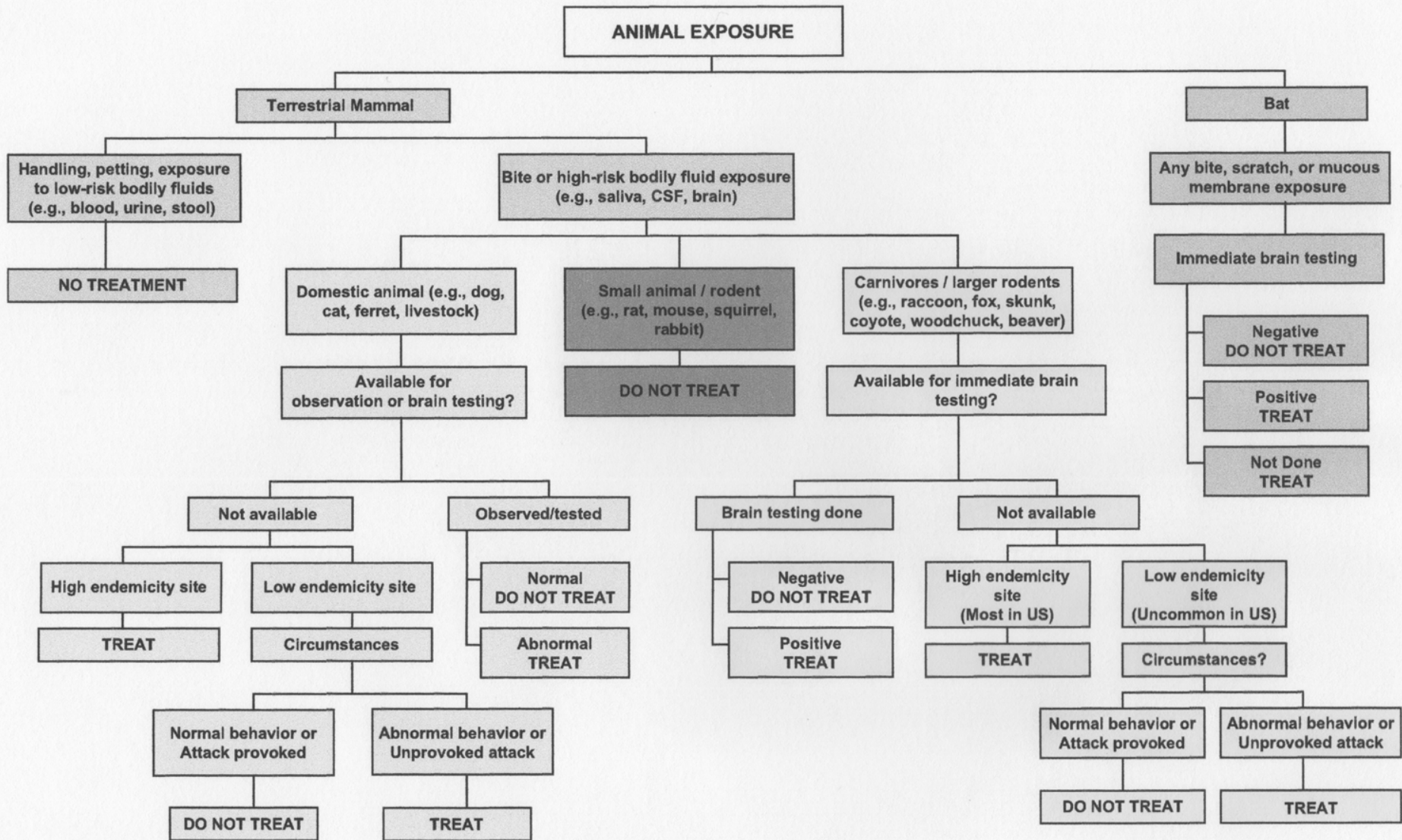
“Substantial delays between exposure and initiation of prophylaxis are of concern, especially with severe wounds to the face and head, which might provide access to the central nervous system through rapid viral neurotropism.”

Human Rabies Prevention --- United States, 2008 Recommendations of the Advisory Committee on Immunization Practices

Risk of Rabies Without PEP After Exposure to Rabid Animal

Multiple severe bites around face	80 – 100%
Single bite	15 – 40%
Superficial bite(s) on an extremity	5 – 10%
Contamination of open wound by saliva	0.1%
Transmission via fomites (tree branch)	No cases reported
Indirect transmission (raccoon saliva on dog)	No cases reported

Bruner, Counselman. Revisiting Rabies. *Emerg Med* 39(8):30, 2007



Moran, et. al. Antimicrobial Prophylaxis for Wounds and Procedures in the Emergency Department. Infect Dis Clin N Am 22 (2008) 117–143

Human Rabies PEP IF previously vaccinated; 2 doses, 2 visits*



1 ml (IM) into deltoid (adults) or into anterolateral area of thigh (children)

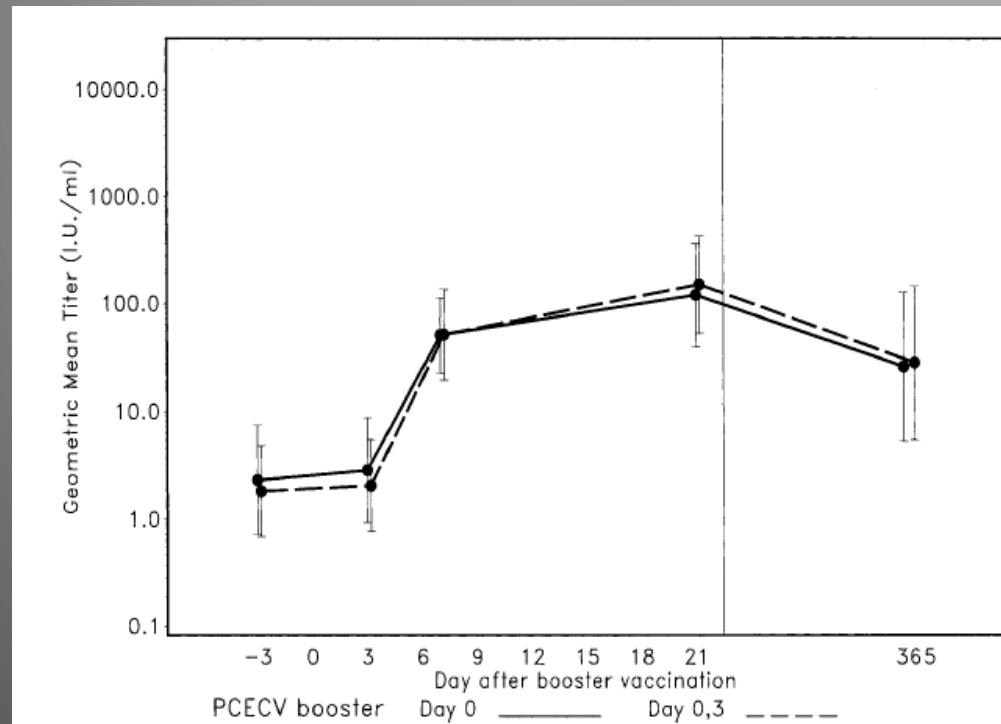


D 0 D 3
x 1 x 1

D 0
Wound Cleansing

Human Rabies PEP if previously vaccinated

- ▶ **IF** previously vaccinated against rabies
 - Wound cleansing
 - 1.0 mL IM only, HDCV or PCEC
 - days 0, 3
 - HRIG is NOT administered



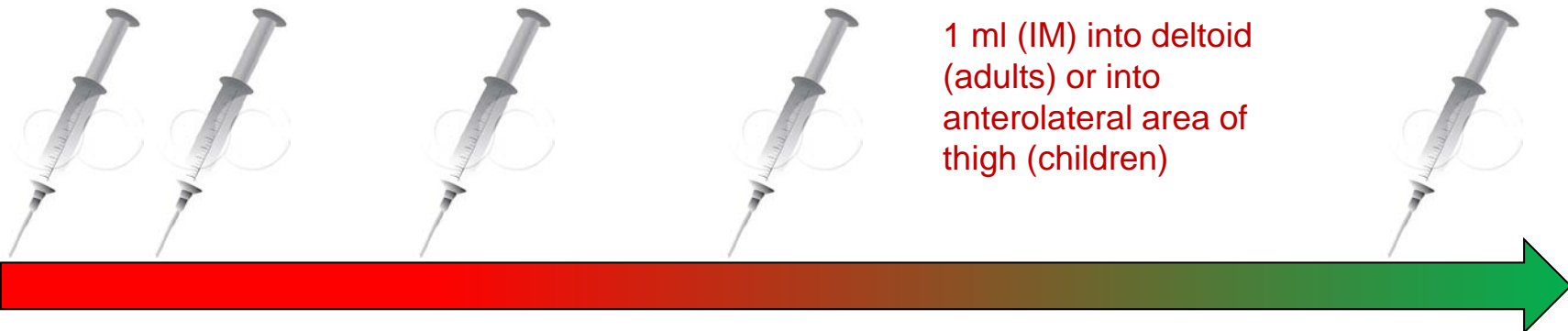
Briggs, et. al., Purified Chick Embryo Cell Culture Rabies Vaccine: interchangeability with Human Diploid Cell Culture Rabies Vaccine and comparison of one versus two-dose post-exposure booster regimen for previously immunized persons. *Vaccine* 19 (2001) 1055–1060

What Constitutes Previous Vaccination?

- ▶ Persons who have ever previously received
 - complete vaccination regimens (pre-exposure or postexposure) with a cell culture vaccine or
 - persons who have been vaccinated with other types of vaccines and have previously had a documented rabies virus neutralizing antibody titer

Essen Schedule; 5 doses, 5 visits*

PEP for those persons not previously vaccinated



D 0 D 3 D 7 D 14 D 28
x 1 x 1 x 1 x 1 x 1

D 0
HRIG 20 IU/kg

D 0
Wound Cleansing

ACIP Modified Essen Schedule; 4 doses, 4 visits*



1 ml (IM) into deltoid
(adults) or into
anterolateral area of
thigh (children)

D 0 D 3 D 7 D 14
x 1 x 1 x 1 x 1

D 0
HRIG 20 IU/kg

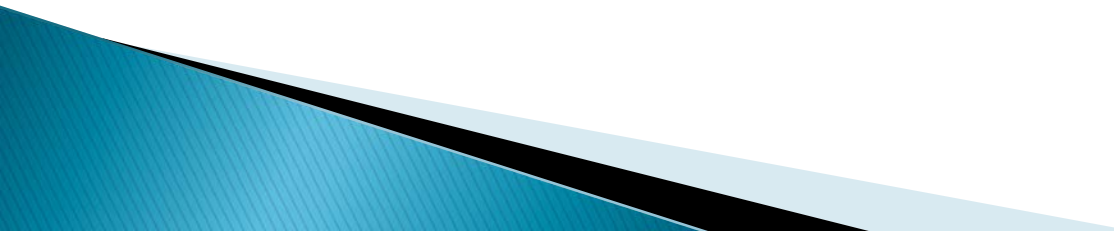
D 0
Wound Cleansing

* Use of a Reduced (4-Dose) Vaccine Schedule for Post exposure Prophylaxis to Prevent Human Rabies. **March 19, 2010 / 59(RR02);1-9**

JUNE 2009 ACIP reduced the number of rabies vaccine doses for postexposure prophylaxis (PEP), from 5 doses as recommended in the 2008 ACIP document on Human Rabies Prevention, to 4 doses administered on days 0, 3, 7 and 14.

Day →	0	3	7	14	28
2008 ACIP	1.0 ml vaccine* IM (deltoid) & 20 IU/kg HRIG	1.0 ml vaccine IM (deltoid)	1.0 ml vaccine IM (deltoid)	1.0 ml vaccine IM (deltoid)	1.0 ml vaccine IM (deltoid)
2010 ACIP	1.0 ml vaccine IM (deltoid) & 20 IU/kg HRIG	1.0 ml vaccine IM (deltoid)	1.0 ml vaccine IM (deltoid)	1.0 ml vaccine IM (deltoid)	No vaccine given

Notes on HRIG Administration

- ▶ If anatomically feasible, the full dose of Rabies Immune Globulin (Human) (HRIG) should be thoroughly infiltrated in the area around and into the wounds.
 - ▶ Any remaining volume should be injected intramuscularly, using a separate needle, at a site distant from vaccine administration
- 

Notes on HRIG Administration

- ▶ Immunization with live vaccines should not be given within 3 months of Imogam or Hyperrab S/D administration* **
- ▶ The gluteal region should not be used as an injection site because of the risk of injury to the sciatic nerve**

Animal Type	Evaluation & Disposition of Animal	PEP Recommendations
Dog/Cat/Ferret	Healthy & available for 10 day observation	No PEP unless animal shows clinical signs of rabies*
	Rabid or suspected rabid	Begin PEP
	Unknown	Consult PH

Remember to Follow ACIP!

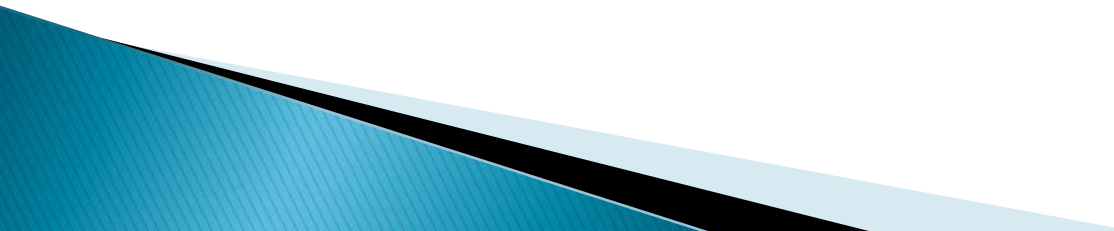
	ACIP	WHO
Previously Vaccinated	2x IM CCV (No RIG)	2x IM CCV (No RIG)
Immunologically naive	4x IM CCV (+ RIG)*	4x or 5x IM CCV or ID CCV (No RIG)**
		4x or 5x IM CCV or ID CCV (+ RIG)***

* 5x IM CCV if immunocompromised

** nibbling of uncovered skin, minor scratches or abrasions without bleeding, licks on broken skin

***single or multiple transdermal bites or scratches, contamination of mucous membrane with saliva from licks; exposure to bat bites or scratches

Follow ACIP Guidelines

- ▶ WHO guidelines are very informative and educational but ultimately do not apply
 - ▶ ACIP is the standard of care
- 

Rabies Biologicals – CCV

▶ Human Diploid Cell Vaccine (HDCV)

◦ Imovax; Sanofi Pasteur, SA, License #1724

- Wiktor et. al. Development and clinical trials of the new human Rabies vaccine of tissue culture (human diploid cell) origin. Dev Biol Stand 1978; 40: 3–9.
- Anderson et. al. Postexposure trial of a Human Diploid Cell Strain Rabies Vaccine. J. Inf. Dis 1980; 142(2): 133–138.

▶ Purified Chick Embryo Cell Vaccine (PCECV)

◦ Rabavert; Novartis Vaccines and Diagnostics, License #1754

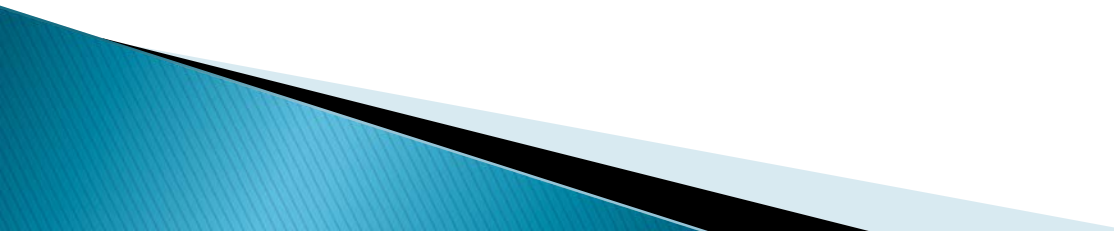
- Barth et. al. Purified Chicken Embryo Cell Rabies Vaccine For Human Use. Lancet 1983; March 26: 700
- Dreesen et. al. Two-year comparative trial on the immunogenicity and adverse effects of purified chick embryo cell rabies vaccine for pre-exposure immunization. Vaccine 1989; 7:397–400.

Rabies Biologicals – HRIG

- ▶ HyperRAB S/D; Grifols Therapeutics, License # 1871
- ▶ Imogam Rabies HT; Sanofi Pasteur, SA, License #1724
 - Loofbourow et. al. Rabies immune globulin (human): clinical trials and dose determination. *JAMA*. 1971;217:1825–1831.
 - Lang et al. Evaluation of the safety and immunogenicity of a new, heat-treated human rabies immune globulin using a sham, post-exposure prophylaxis of rabies. *Biologicals*. 1998;26:7–15.

Small Rodents Present a low Risk of Transmission

Scenario 3

- ▶ Bites from rabbits, squirrels, chipmunks, rats and mice seldom, if ever, call for rabies prophylaxis
 - ▶ Only an unprovoked, aggressive, attack by a small rodent or rabbit should be considered for rabies prophylaxis
 - ▶ Domesticated rodents purchased from pet shops, raised in controlled environments, and never exposed to carnivorous animals or bats pose not risk of rabies by biting
- 

IS INJECTING A FINGER WITH RABIES IMMUNOGLOBULIN DANGEROUS?

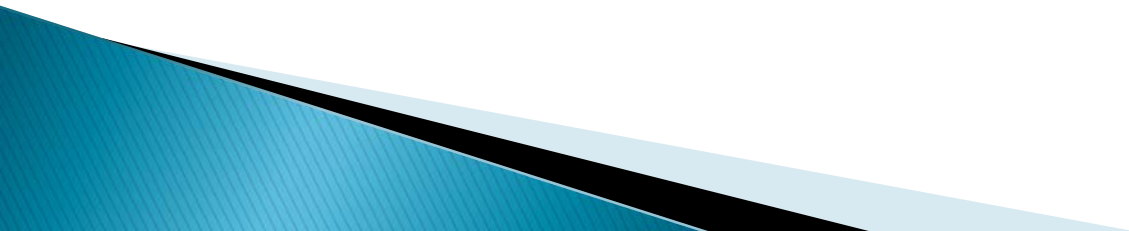
- ▶ Almost all body sites, except fingers, toes, the bridge of the nose, and ear lobes, have ample space for retaining immunoglobulin without compromising circulation. However, injecting the tip of a finger or toe is not only a painful procedure but is also one that can be technically difficult.
- ▶ It is a safe procedure if carried out with care by experienced staff.
 - Suwansrinon, et. al. SHORT REPORT: IS INJECTING A FINGER WITH RABIES IMMUNOGLOBULIN DANGEROUS? *Am. J. Trop. Med. Hyg.*, 75(2), 2006, pp. 363–364

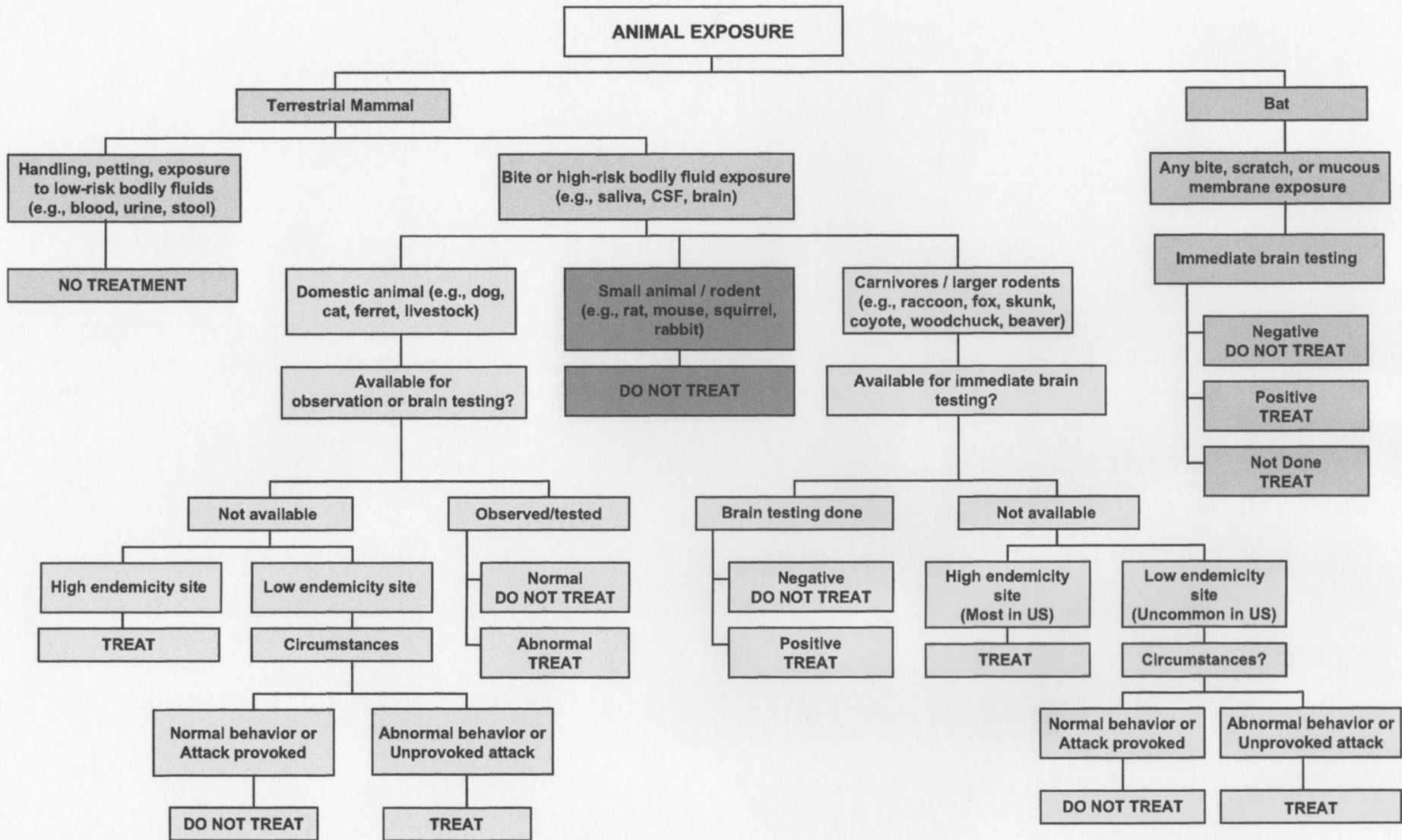


Wild Carnivores Present a High Risk of Transmission

Scenario 4

What course of action is
required here?





Moran, et. al. Antimicrobial Prophylaxis for Wounds and Procedures in the Emergency Department. Infect Dis Clin N Am 22 (2008) 117–143

Access to Biologicals; PAPs

- ▶ Programs for uninsured or underinsured patients
 - http://www.cdc.gov/rabies/medical_care/programs.html
- ▶ NC Indigent rabies vaccine program
 - <http://epi.publichealth.nc.gov/cd/rabies/docs/AffidavitFreePEP.pdf>

What About Opossums?

Scenario 5

- ▶ Opossums are relatively resistant to infection with rabies and are considered a low risk for infection
- ▶ The viral dose required to infect opossums is 80,000 times that required to infect a fox
 -
- ▶ Rabies virus binds to nAChR in skeletal muscle
- ▶ A high content of receptors in muscle of red fox makes them susceptible
- ▶ Low content of receptors in muscle of opossums makes them resistant

-

Mechanical Transmission of Raccoon Saliva

Scenario 6



For the child / dog, what
course of action is required
here?

Rabies Exposure

▶ Nonbite

- Rarely does this constitute exposure
- The contamination of open wounds, abrasions, mucous membranes and scratches with saliva or OPIM (nervous tissue) could theoretically constitute an exposure

Risk of Rabies Without PEP After Exposure to Rabid Animal

Multiple severe bites around face	80 – 100%
Single bite	15 – 40%
Superficial bite(s) on an extremity	5 – 10%
Contamination of open wound by saliva	0.1%
Transmission via fomites (tree branch)	No cases reported
Indirect transmission (raccoon saliva on dog)	No cases reported

Bruner, Counselman. Revisiting Rabies. *Emerg Med* 39(8):30, 2007

