

“Rabies – “When The Bite is Worse Than The Bark”

WRAIR- GEIS 'Operational Clinical Infectious Disease' Course

WRAIR

Walter Reed Army
Institute of Research

Soldier Health • World Health



The Most Common Story ... A 3 Year Old Girl - Dog Bite:

Old Girl - Dog Bite:

- Out in yard with other children
- “Unknown” small dog approaches group
- Nips her palm, then runs off
- No one can identify dog’s location, after an extensive search...



The Military Relevant Story...A 40 yr old Master Sergeant Near Balad Iraq:

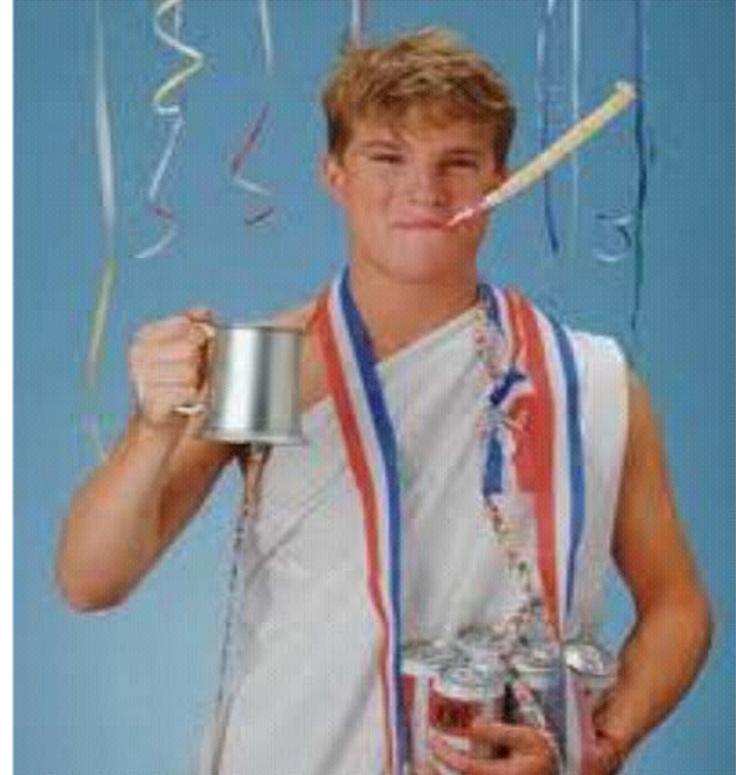
- Out in FOB with other NCO's
- "Unknown" small cat appears tangled in the camouflage netting
- He tries to free up this feral cat
- Cat bites his palm, then runs off
- No one can identify cat's location, after an extensive search...
- (Refused photograph)



The Plain Stupid Story... A 21 Year Old (ND)

Student:

- Out at a party with the other students – consuming large amounts of beer
- Fell asleep in a chair on the porch – intoxicated, with beer spilled on his bare feet
- Wakes to an “unknown” raccoon licking and chewing his toes
- Waits a week, then told his father
- No one can identify raccoon’s location, after an extensive search...



Post-Exposure Prophylaxis (PEP) for any or all 3 of These?

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search ID: bhon1327

*"We'll have to clean that out immediately...
there's nothing dirtier than a lawyer bite."*

The Incredibly Sad Story ...

- 24 year old Ft Drum Soldier deployed to Afghanistan as a cook, also duties with base dogs
- “Reportedly” Bit on hand by stray dog in Afghanistan in Jan, 2011:
- Soldier “reported” that the treatment was possibly incomplete (Partial PEP, expired vaccines, dog tested? – **all this is hearsay from family; quoted in the common press, all that is unofficial**)
- August 14, 2011 – weird tingling in left arm, followed by GI issues
- Aug 17 – trouble drinking
- Aug 18 – checked into Ft Drum
- Aug 19 – collapsed; immediate question of rabies – transfer to Syracuse, induced Coma, ECMO, experimental rabies protocol
- Aug 31 – brain hemorrhage and death
- Investigation – possible other exposures/other animal contact without PEP?

ALARACT/Facts - Army PHC: (All Army Activities ...)



- Follow General Order 1: **Do not keep mascots or pets** when deployed!
- Do **not** approach, feed, or **handle animals**.
- If bitten or if saliva contacts your broken skin, eyes or mouth, immediately wash the area with soap and water and **seek medical attention**
- **Report** animal exposures immediately.
- Rabies vaccines.... must be **stored and handled correctly**
- ... may include what is known as **post-exposure prophylaxis (PEP)**
- Should all deployed receive the primary (0-7-21/28) 3 dose rabies series?
 - Costs - \$600 for primary series
 - ***Not enough vaccine in the world***
 - Inflaming the “Anti-Immunization” press/league
- > 600 known bites per year in deployed – So, “Follow The Rules For PEP”
- Logistics of PEP are difficult for “select units” – consider for high risk groups (Current practices)

Rabies – Then ... and Now ...

1. Historical Overview
2. The Virus and regional patterns of disease – constant ecological evolution - distinct local vectors (animals)
3. Role of wound care
4. “PEP” post-exposure prophylaxis – changes in vaccine and antibody strategies over recent years
5. Can we “treat” rabies? The “Milwaukee protocol”



Rabies Background Quiz:

- How far back in history have we recorded rabies?
- When did they recognize the common modes of transmission?
- What are they?
- Any “good “ historic preventive medicine practices?
- Any favorite “quack” cures?
- How could they control rabies?

An Old, Old Disease ...

- Sanskrit “*rabhas*” = “to do violence”
- Latin “*rabere*” = to rage
- Greek “*lyssa*” = violence/madness
(Source of virus family)
- Mesopotamian “Laws of Eshnunna” - 2300 BC (4K ago)
 - North of Ur, near Diyala River, tributary of Tigris (Near Balad)
 - Fines for dog owners ***allowing spread of rabies by bites***



Bridges near
“FOB Warhorse”

Rabies – First Clean the Wound:

- **Aulus Cornelius Celsus (Not MD):**
 - Roman historian, 25 BC to 50 AD
 - “Rubor, Dolor, Calor, Turgor”
- ***Cleanliness and washing wounds with solutions such as vinegar***
- Hold the victim underwater to relieve thirst and cure rabies



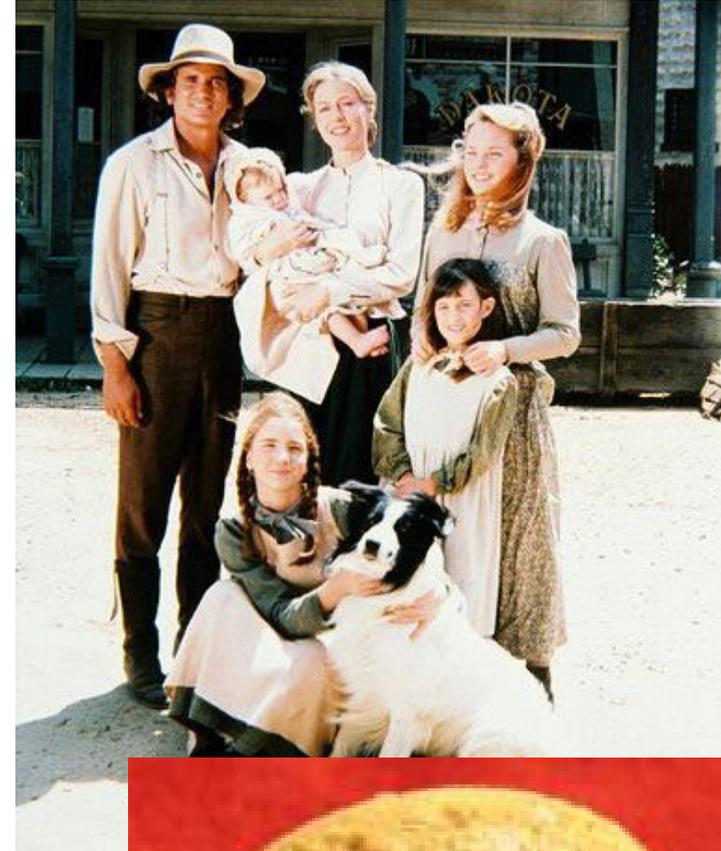
Middle Ages - St Hubert:

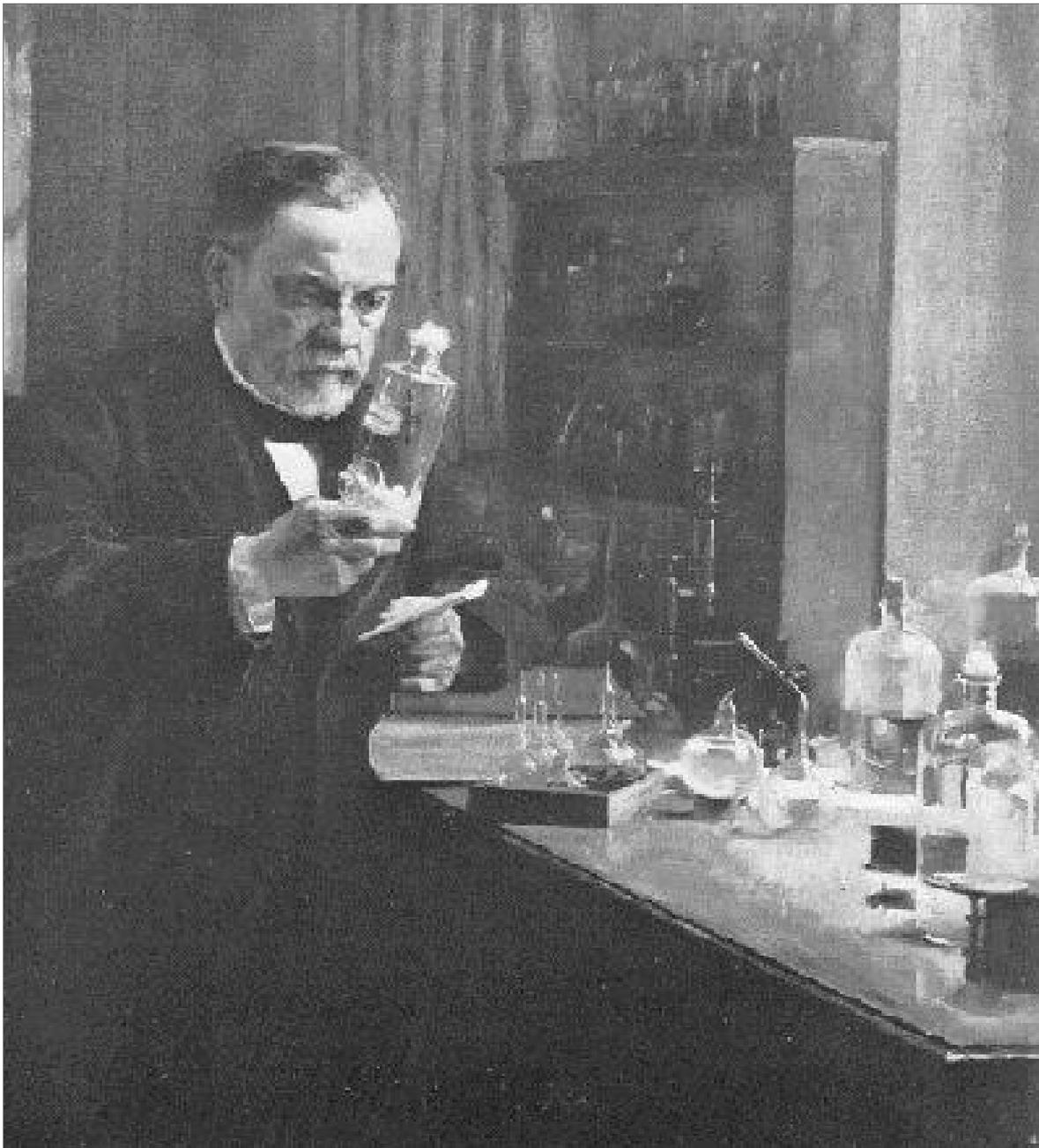
- 656-727 (est); Patron of the Hunter
- His wife died, depressed – he “escaped by hunting”
- Had a vision - a stag with a cross in its horns told him to “shape up!”
- He became the Bishop of Liege
- **Given a Metal Key by St Peter to “cauterize wounds and stop rabies”**
- Europeans traveled to his shrine at Liege, Belgium, to help cure rabies



Rupprecht – Rabies in the New World:

- “Bat related illness” in the tribal legends of the Pacific Northwest
- California, 1703 – Rabies reported by a Spanish priest
- Late 1700’s Rabies in the Colonies:
 - Fox hunting
 - Outbreaks in Virginia
- **Madstones** common in the Ozarks – 1860’s – lay against bites





Louis
Pasteur
1822-1895

Vaccines:

- **Dr. Emile Roux** –“killed” rabies vaccine
 - Desiccating the spinal cords of infected rabbits.
 - Tested only in eleven dogs
- **Joseph Meister:**
 - Age 9 in July 1885 - Mauled by a rabid dog - Alsatian region
- **Roux:** “the vaccine is not ready for humans”
- **Pasteur:** Go ahead – use it! (This was a big risk for Pasteur who was not a physician!)
- Professor Michel Peter complained: “M. Pasteur does not cure hydrophobia; he gives it!”
- Some unpleasant manipulation of results by all involved (Pro and anti-vaccine groups)



Within a few years ...

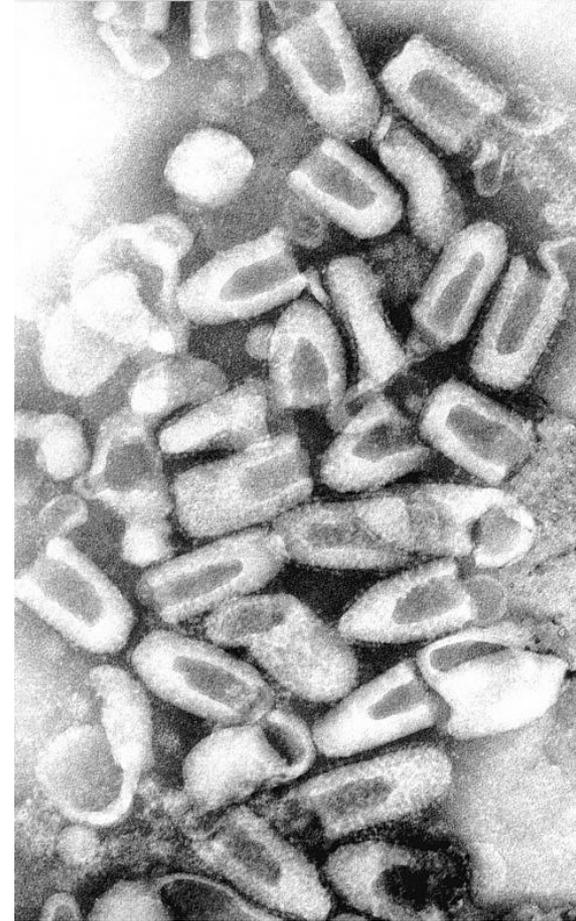
Parke-Davis – 1913 Catalogue - available:

- Pasteur desiccated spinal cord
- Cumming's modified "brain" preparation
- 21 daily doses for most bites; 14 for lower extremities
- 1950's: **wide use of RIG** to avert vaccine failure



Genera: Lyssavirus: “Rabies, and Rabies-like” viruses

- Bites are the **most common route** – virus in saliva
- Global: **dogs, dogs, dogs > bats > other mammals** (skunk, fox, raccoon)
- Peak in summer; # 1 young males
- No racial, genetic differences in susceptibility



Shaped like a bullet!

Human Rabies – March 15, 2013:

- (CNN) -- A Maryland man recently died of rabies that he contracted from a **tainted kidney he received in a transplant** operation a year and a half ago, the Centers for Disease Control and Prevention said Friday. (Raccoon Rabies - 18 Month incubation)
- Anti-rabies shots to three other patients who received organs from the same donor as the patient (per the CDC) **Good AB response in all 3 (kidney, heart, liver)**
- The Maryland man and three other people -- in Florida, Georgia and Illinois -- received organs from a person who died in Florida in 2011 – **thought to be Ciguatera toxin severe enteritis.**
- Coincidentally, both the donor and the recipient who died are members of the military. The donor was a 20-year-old airman who was training to be an aviation mechanic in Pensacola, and the recipient was a retired Army veteran, according to the Department of Defense.
- Doctors knew the donor had encephalitis, an inflammation of the brain, when they harvested the organs. However, no rabies test was done before the before the donor's kidneys, heart and liver were delivered for transplantation in September 2011, the CDC said.

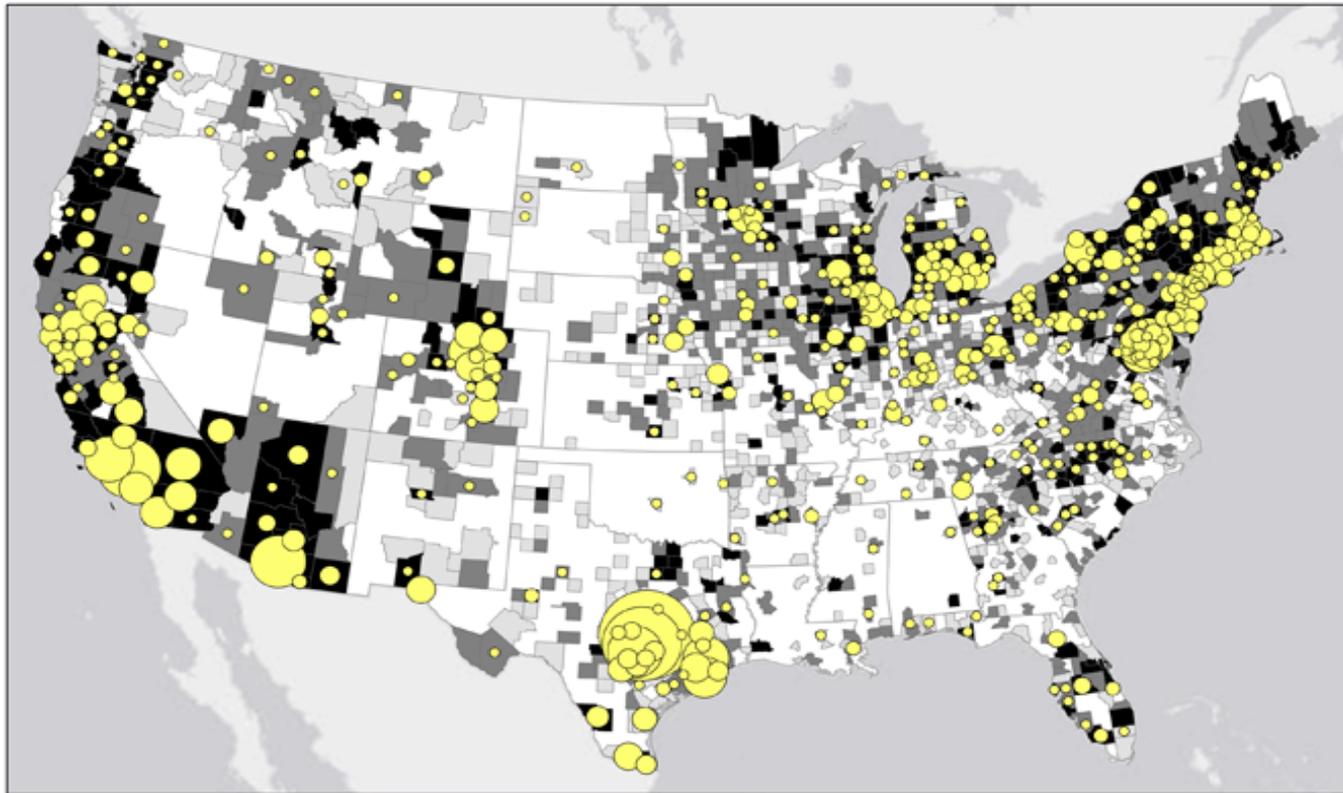
Human and Animals with Rabies - USA

	HUMAN	Total Animals	BATS	RACOONS	SKUNKS	FOXES	PETS
2013	3 (org. donor+ recip-raccoon); Guatemalan immigrant-dog	5,865	1,598 (27%)	1,898 (32%)	1,447 (25%)	344 (6%)	Cats – 247 (4%) Dogs – 89 (1.5%)
2012	1 California - bat	6,162	1,680 (27%)	1,953 (32%)	1,539 (25%)	340 (6%)	Cats-257 (4.2%) Dogs-84 (1.4%)
2011	6 immigrants, most dog	6,031	1,380 (23%)	1,981 (33%)	1,627 (27%)	427 (7%)	Cats-303 (5%) Dogs-70 (1.2%)
2010	2 bat (1 US, 1 vampire from S.America)	6,154	1,430 (23%)	2,246 (37%)	YEAR	429 (7%)	Cats-303 (5%) Dogs-69 (1.1%)
2009	4 (3 bat , 1 recovered); 1 immigrant-dog	6,690	1,625 (24%)	2,327 (35%)	1,603 (24%)	504 (8%)	Cats-300 (5%) Dogs-81 (1.2%)

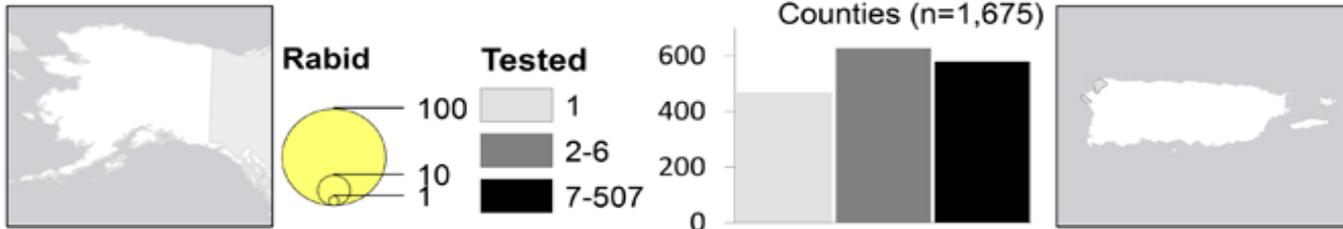
92% of rabies positive specimens were wildlife (Carnivora and Chiroptera) Bats = #1 animal submitted; #2 = Cats

J Am Vet Assoc, 2010-2014, Rupprecht et al.

Where are Rabid Bats Found?

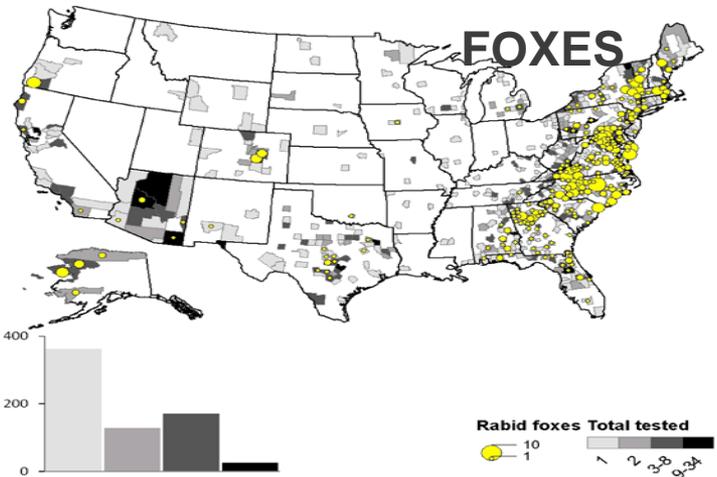
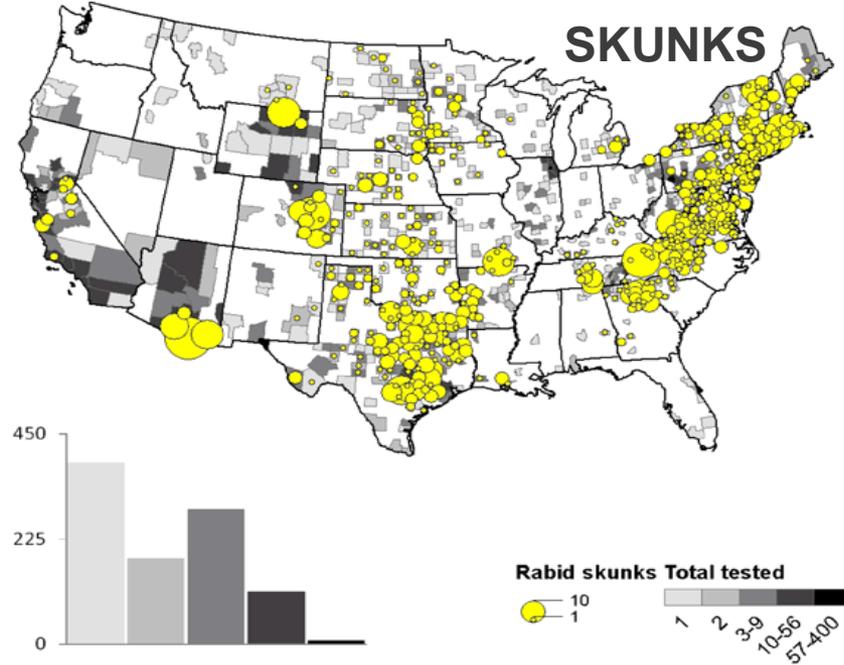
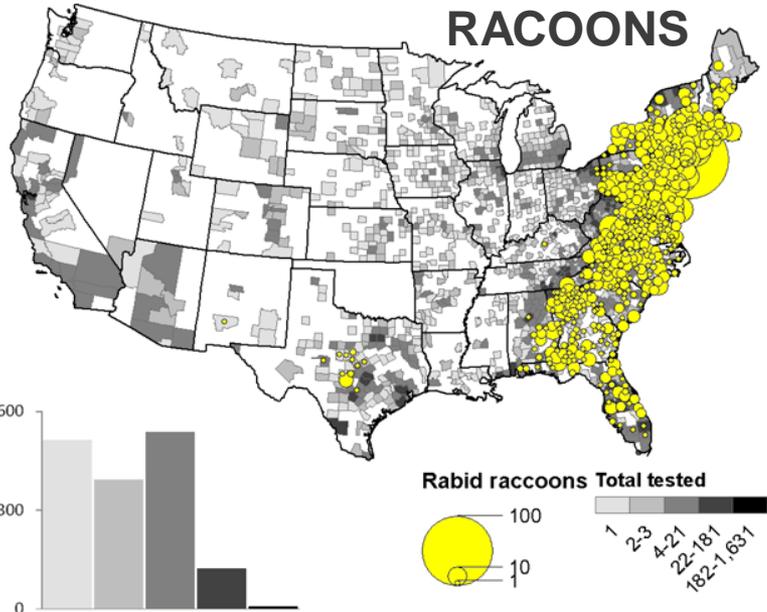


- 2011 -CDC
- RIG and 4 x immuniz. = \$ 1-2,000



<http://www.cdc.gov/rabies/location/usa/surveillance/index.html> "Rabies surveillance in the United States (CDC)"

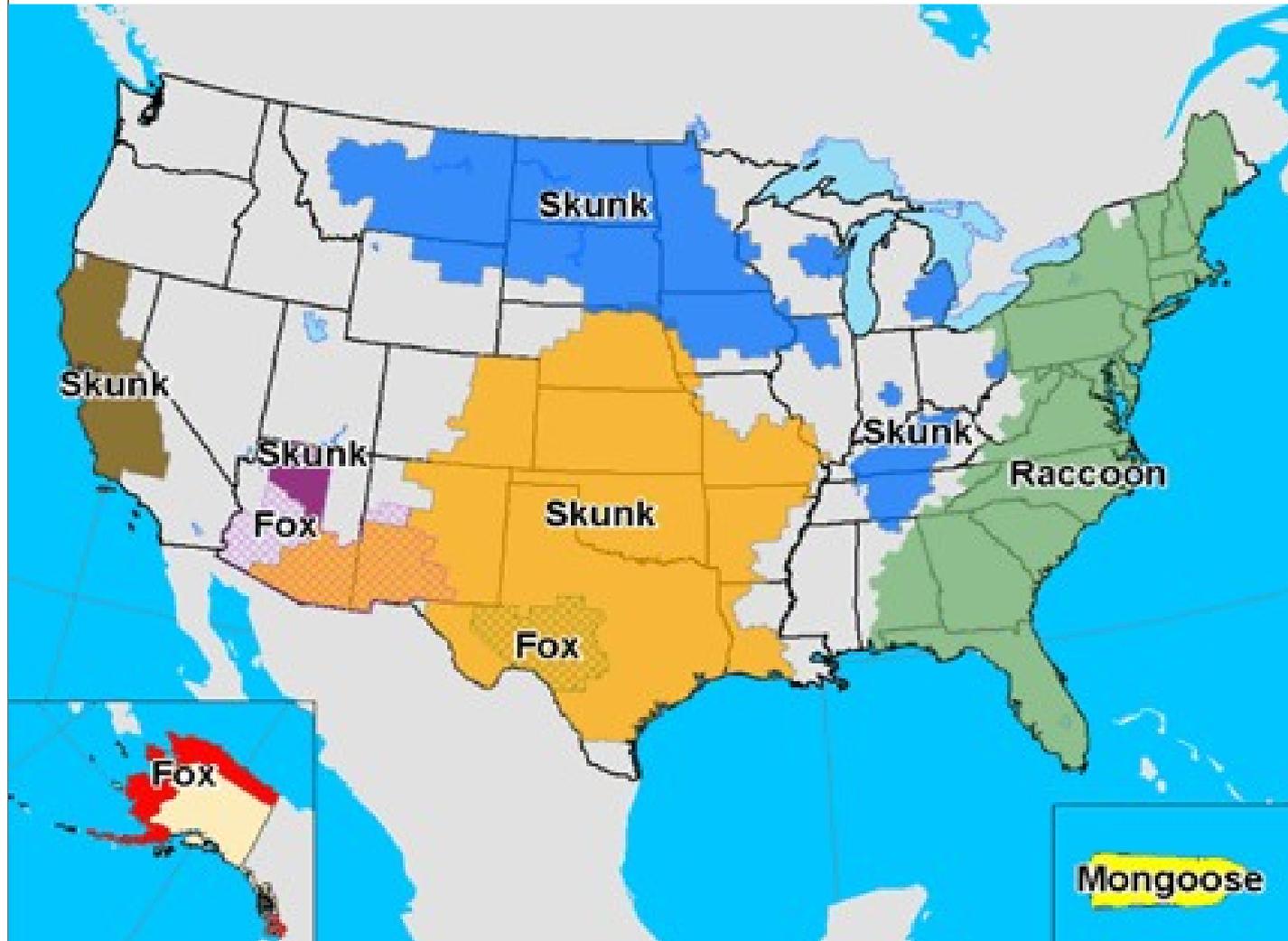
In Contrast:



<http://www.cdc.gov/rabies/location/usa/surveillance/index.html>

"Rabies surveillance in the United States (CDC)"

Know Your Region in the US by Mammalian Reservoir:



**Bat Rabies –
Virtually
Everywhere**

**Difficult
Question: Which
Rabies
Predominates in
Hawaii?**

A Few Bats = Most Rabies

- North American (Low birth rates, long lives):
 - *Pipistrellus subflavus* = Tri-color bat (black/brown/yellow)
 - Small, 4-10 g, 4 inch wingspan
 - Eastern ½ of US, and southwest
 - Low territory, dead trees, hurt by wind farms
 - *Lasiononycteris noctivagans* = Silver haired bats
 - Medium, 8 to 12 g – up to 1 foot wingspan
 - Most of US, South Canada, NW Mexico
 - Like deep old forests
 - *Tadarida brasiliensis* = Mexican free-tailed bats
- S. American – Vampire Bats – rising #'s:
 - *Desmodus rotundus*
 - 77% of Peru's rabies from 2002-2007 (EID, 2013)
 - 12 humans, 145 animals (Cattle #1).
 - Increased human contact, encroach on Amazon

Messenger et al, EID, 2003; Smithsonian - Nat History Museum



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Bats as a Reservoir for Rabies:

- 1953 – Florida – Identification of Human Rabies
- NOW = 2/3 of endogenous rabies - **BAT SEROTYPES**
- Transmission– **Still Mysterious ???**
 - Frequent “lack” of a significant (Bite or MM) exposure
 - **2 of 24** bat rabies cases (90-2001) had a **definitive bite**
 - Silver haired bats >>> brown bats
(Still, only 0.5-1%of bats test pos.)
- What explains “Bat to Human?”
Gibbons, RV (WRAIR), Ann Em Med, 2002



Bats to Humans – HOW?

1) Evidence for transmission by aerosol is weak:

- 56 yo veterinarian in 1972 blending rabid brains for vaccines
 - died of rabies (14 yr since last vaccine, no ABs)
- 32 yo immunized lab tech in 1977 “spraying” live rabies virus in a pharm machine; neurologically impaired
- Older cases:
 - 1956 entomologist died of rabies studying Frio Cave, TX
 - 1959 mining engineer visited Frio cave, TX, unknown cut on face, died of rabies (Frio Cave – 20,000,000 Mex. free-tail bats)
- 1960’s animals in cages in bat caves – some infection

1) Bat to other mammal, then human transmission:

Modest/Minimal Spillover: 1/261 cats and dogs with a bat variant (Higher for Vampire bats)

Gibbons, RV. WRAIR, Ann Emerg Med. 2002

Bat behavior = Risks

3) Risk of Cryptogenic Bites?

Colorado Study (1977-1996):

- If human, pet contact, or abnormal behavior **685 = 15% of 4,470** bats rabies positive (VS, 0.5% baseline)
- 69 of 233 that bit humans, were rabies + (**30%**)
- Big brown bats, hoary bats, ***silver-haired bats = 73%** (most common human rabies in USA from 1980 to 1997)

Pape WJ, et al. EID. 1999

Table 2. Circumstances in which humans encountered bats, Colorado, 1977–1996

Circumstances	Bat captured and tested		Bat not tested	All encounters
	Rabid	Not rabid		
Bat landed on person	17	2	27	46
Person picked up bat outdoors	24	5	15	44
Person awoke to find bat in room	17	4	14	35
Person tried to remove bat from indoors	5	2	17	24
Person inadvertently touched hidden bat	3	5	8	16
Person handled captured bat	12	0	1	13
Child found alone with bat	4	3	2	9
Person handled bat as part of job	6	1	1	8
Person stepped on bat	3	0	3	6
Person bitten while taking bat from pet	2	1	3	6
Person bitten by pet that had bat in mouth	1	4	1	6
Person attributed wound to bat they saw	0	2	0	2
Other circumstances	0	0	6	6
Unspecified in report	5	3	11	19
Total	99	32	109	240

Tlingit Indians and “First Peoples” of the Alaskan and Canadian Coast/NW:

Known for these:



And These:

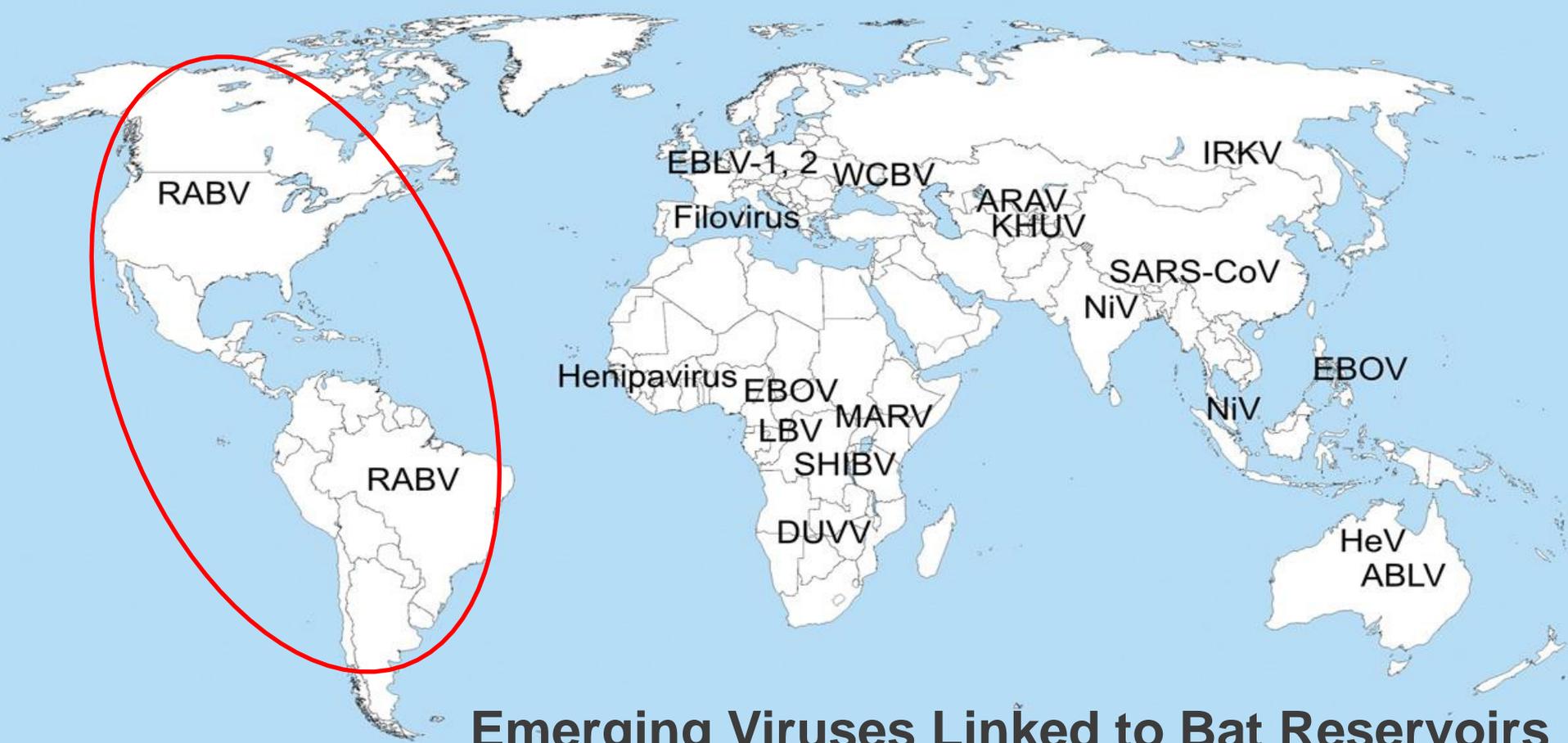


Also had a rich cultural history of variations of “Animism” – the role of the Raven, the Eagle, the Owl, and the Bat

Bats = underworld, death, cannibalism, madness

Helmet Carved Like a Bat





Emerging Viruses Linked to Bat Reservoirs

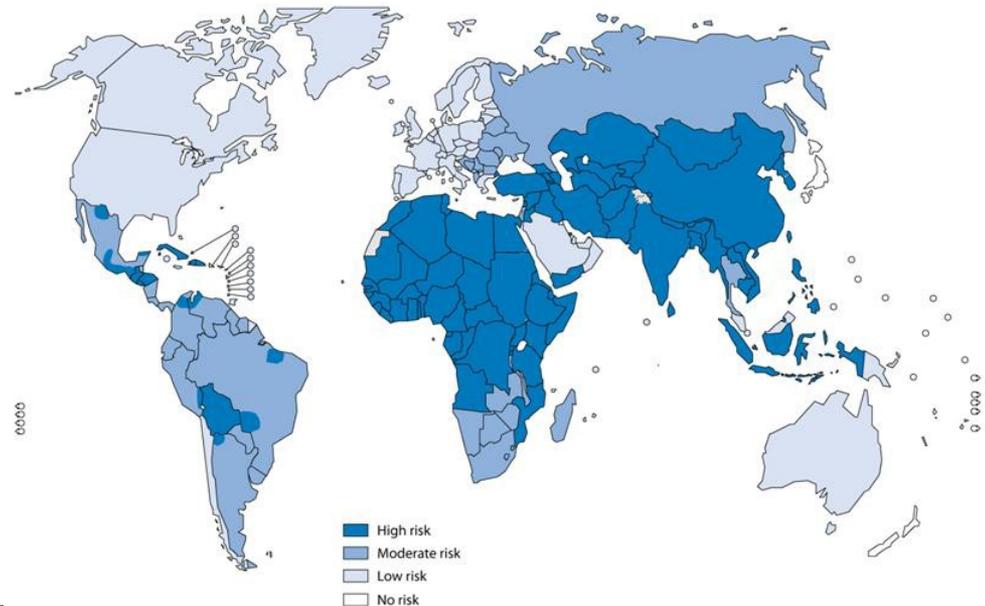
- Many “Emerging Viruses” in bat reservoirs, but ? “Spillover Mechanism” to Humans?
- Family *Rhabdoviridae*, **10 of 11 Lyssaviruses** are found in bat reservoirs
- Classic Rabies Virus (RABV) is in the Americas’ (Mexican/Brazilian free-tailed, Silver haired, Tri-colored, Vampire, Hoary bats, Big Brown bats)
- In **1911** – Association of vampire bats with spread and death in Brazilian Cattle
- in **1953** – Association of N. American bats with rabies in a young boy (Florida)

Kuzmin IV, et al. Emerg Health Threats J. 2011

Varied Practices/Environments - Result in Distinctly Regional Epidemiology

- Most rabies may have originated in **bats**, but, most human spillover occurs from intermediate mammalian reservoirs - **Dogs**
- **Worldwide ~40 – 60K human cases *reported*** to WHO annually
- Majority of cases are in the developing world –
 - India >30,000 cases/year (Population, unregulated mammals)
 - Often undiagnosed
- 10 million human PEP's yearly
 - 5 million in China
 - 1 million in India
 - 40-60,000 in N. America

Distribution of risk levels for humans contracting rabies, worldwide, 2009



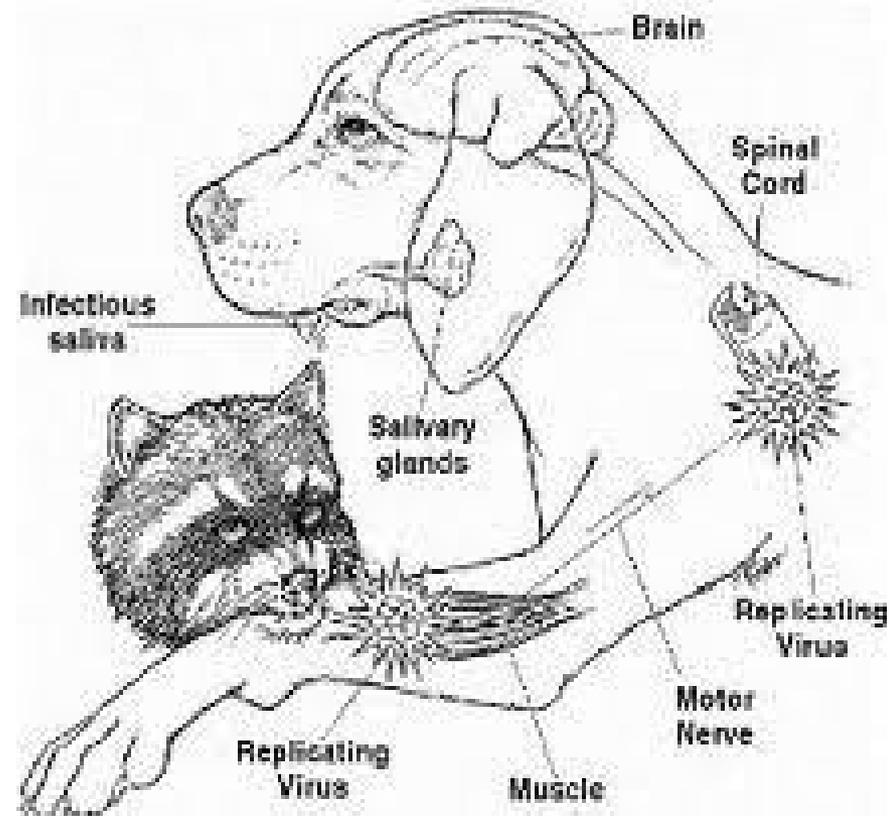
Clinical Rabies Quiz:

- What are the two forms of clinical mammalian rabies?
(Think Dogs)
- How does rabies go from the site of exposure to the CNS?
- When and how can we diagnose rabies in humans?
- What is the incubation period in humans?
- What is the standard Post-Exposure Prophylaxis?
- Can we cure rabies once established?
- Best ways to prevent rabies?

Understand Rabies: Pathogenesis

- After bite occurs:
 - virus localized in wound area ... then long latent period ... then **spread up neurons to CNS**
- After CNS - rapid spread
 - salivary glands infected shortly after CNS
 - Faster in dogs? Effective Transmitters

Russian Website: Russia-IC.com
LOCAL – NERVE – CNS - SALIVA



Understand Rabies: Incubation

- In humans, typically 1 – 3 months
 - 84% within 90 days, **99% < 1 year**
 - Wide range of 4 days to 19 years
 - Shorter period if bites to face/neck – close to brain (Virus travels up nerves)
- We try to give vaccine and RIG ASAP for head and neck bites!!



Human Rabies?

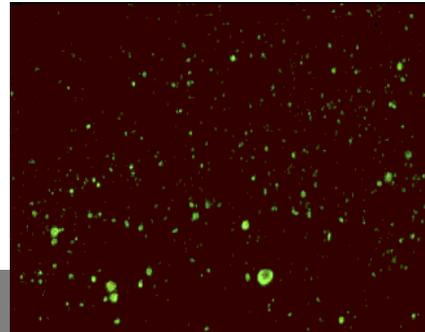
- “Hydrophobia” - Violent spasm of diaphragm and accessory muscles triggered by attempts to swallow
- Fever 100°F – 104°F, seizures, hallucinations
- Neurological deterioration to coma over days – week
- Cardiac or respiratory arrest (Parasympathetic instability) – 100% fatal
- Commonly “Misdiagnosed” prior to CNS infection
 - No antibody while “immunologically protected” at bite or in neurons
 - AB begins after CNS infection (Game is Over) avg. 6th day of illness
 - CSF Ab may not appear for another week (VERY SLOW)
 - Steroids, interferon may delay antibody development

4 sample sites required by CDC to Rule Out rabies (To prove you do NOT have rabies)

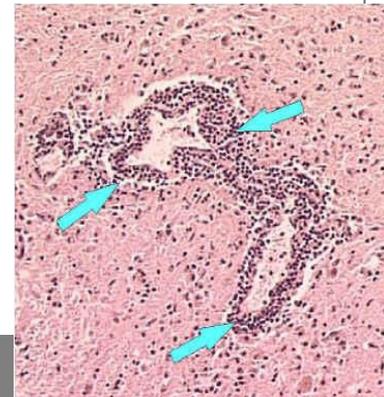
1. **Saliva for virus:** Collect with dropper and place in sterile container. Tracheal aspirates, sputa not suitable; Do **RT-PCR; Virus isolation**
 2. **Neck biopsy:** 5-6 mm diameter punch from nape; minimum 10 hair follicles- deep to include **cutaneous nerves** at base On moist sterile gauze; **RT-PCR** and fluorescent staining for viral Ag in frozen sections
- 3 & 4. Serum and CSF serology:**
- **FLUORESCENT FOCUS INHIBITION TEST (RFFIT) – WHO GOLD STANDARD = I N VITRO CELL CX**
 - **ASSAY THAT MEASURES NEUTRALIZING AB (HIGHLY SENSITIVE AND SPECIFIC)**
 - **RARE REPORTS OF UNIMMUNIZED HUMANS WITH AB**
 - **IF NO VACCINE OR RIG (NO PEP), SERUM RABIES AB MAKES DX, CSF TESTING UNNECESSARY**
 - **AB TO RABV IN CSF, REGARDLESS OF IMMUNIZATION HX, SUGGESTS RABIES INFECTION**

***Brain biopsy** – old histopathology for “Negri” bodies (1903 Pathologist) – very specific, lower sensitivity – cerebellum or basal ganglia (post mortem)

Rabies specimen submission form: www.cdc.gov/rabies/docs/ror_form.pdf



“Babes Node”
- focal demyelination
- lymphocyte collections

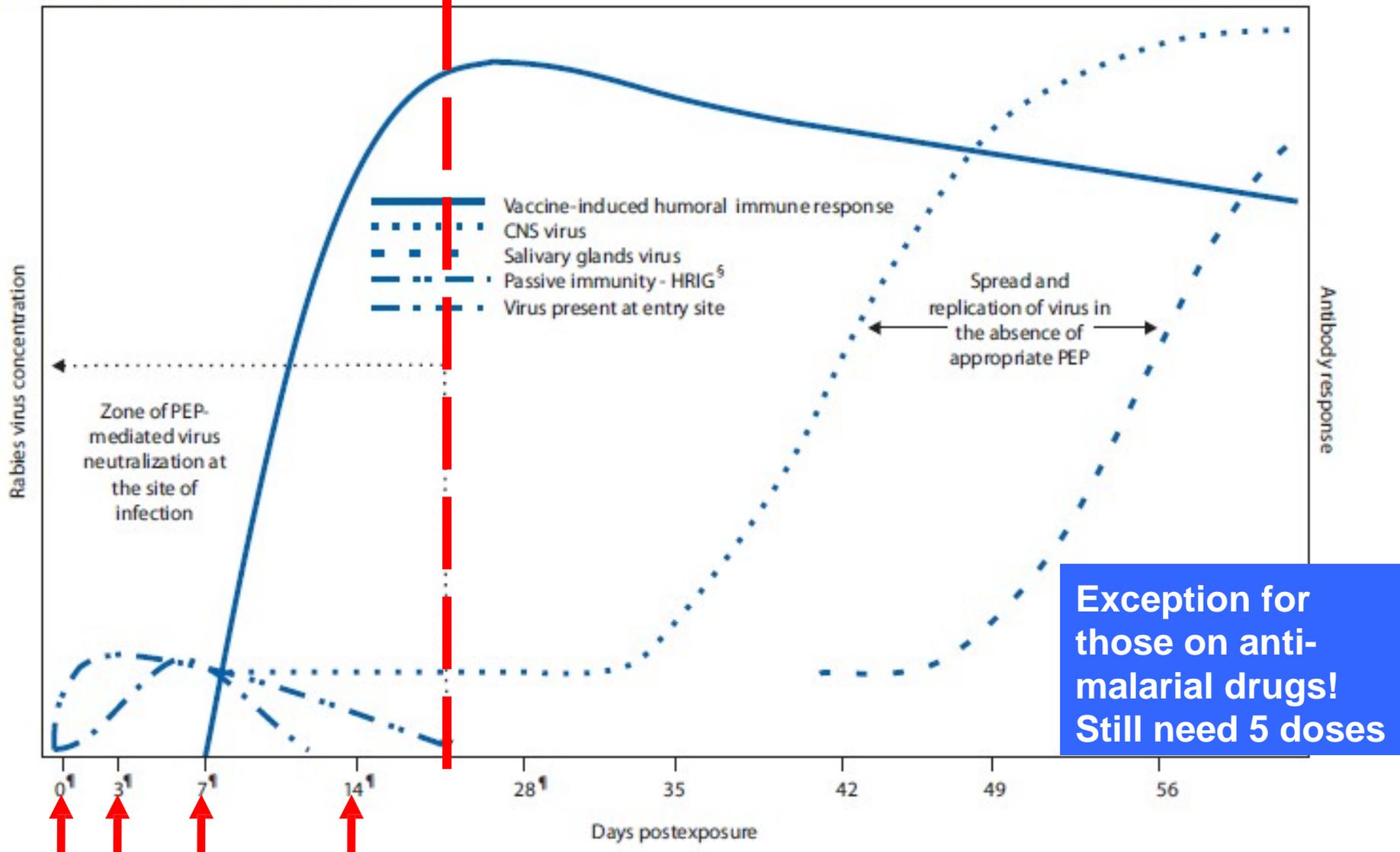


Back to the 3 Year Old Girl - Dog Bite:

- What are the common aspects of this case?
- Rabies Prophylaxis? – Y or N
- If so, what sequence (March, 2010, ACIP)
- 4 Doses of vaccine (HDCV or :
 - **Days 0 – 3 – 7 – 14**
 - Prior Vaccine – 2 doses; days 0, and 3 (no HBIG)
 - Plus **HRIG** (Days 0 to 7, if no prior immunizations) full dose around wound; NOT near 1st Vaccine
 - Plus **wound cleansing** (Don't underestimate this!)
- The 5th dose added “nothing” to protection (Critical 28 days), same antibody response
 - But, is given if Immunosuppressed; or “on anti-malarials”
- NO breakthroughs in the USA if at least 4 doses

Why 4 Shots?

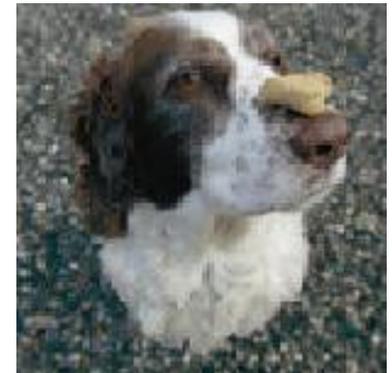
FIGURE 1. Schematic of dynamics of rabies virus pathogenesis* in the presence and absence of postexposure prophylaxis (PEP)-mediated immune responses†



Rabies prevention:

Post-Exposure Prophylaxis (PEP)

- **1st CLEANSE the WOUND (After Celsus)**
 - avoid the burnt head of a dog
- **Evaluate exposure -- assess risk:**
 - Can the animal's vaccination be verified?
 - Can the animal be watched for illness (if it was an extremity bite)?
 - Stray dog that ran away – Must Prophylax
 - Bat found flying clumsily in sleeping child's bedroom ?
..... More later
- **Post-exposure prophylaxis**
 - Initiate vaccination
 - Administer passive immunization: RIG



Rabies Vaccines:

- Schedule:
 - 40,000/yr in US receive 4 post-exposure vaccines (0, 3, 7, 14)
 - **Add day 28 if immune suppressed**
 - 18,000/yr in US receive 3 pre-exposure series (0, 7, 21/28)
 - If pre-vaccinated, 2 boosters (days 0 and 3) and **no HRIG**
 - **Booster every 2 years (High risk – check RFFIT titer Q-6 to 24 mo)**
- Contraindications:
 - History of reaction to vaccine - **weigh risk of death for PEP** (easy choice)
- Adverse effects:
 - occasional local reactions
 - hypersensitivity reactions
 - more frequent after booster doses
 - probably less with PCECV
 - occasionally anaphylactic
 - less likely than with older spinal/notocord vaccines
- Storage: 2 to 8 °C, 35 to 46 °F – do not freeze



RabAvert Manufacturer: Novartis

TABLE 1: RABIES PREEXPOSURE PROPHYLAXIS GUIDE – UNITED STATES, 1999

<u>Risk Category and Nature of Risk</u>	<u>Typical Populations</u>	<u>Preexposure Recommendations</u>
<u>Continuous</u> . Virus present continuously, often in high concentrations. Specific exposures likely to go unrecognized. Bite, nonbite or aerosol exposure.	Rabies research lab workers,* rabies biologics production workers.	Primary course. Serologic testing every 6 months; booster vaccination if antibody titer is below acceptable level.*
<u>Frequent</u> . Exposure usually episodic, with source recognized, but exposure might be unrecognized. Bite, nonbite or aerosol exposure.	Rabies diagnostic lab workers,* spelunkers, veterinarians and staff, and animal-control and wildlife workers in rabies enzootic areas.	Primary course. Serologic testing every 2 years; booster vaccination if antibody titer is below acceptable level.**
<u>Infrequent</u> (greater than population-at-large). Exposure nearly always episodic with source recognized. Bite or nonbite exposure.	Veterinarians and animal-control and wildlife workers in areas with low rabies rates. Veterinary students. Travelers visiting areas where rabies in enzootic and immediate access to appropriate medical care including biologics is limited.	Primary course. No serologic testing or booster vaccination.**
<u>Rare</u> (population-at-large). Exposures always episodic. with source recognized. Bite or nonbite exposure.	US population-at-large, including persons in rabies-epizootic areas.	No vaccination necessary.

Rabies Immune Globulin (HRIG):

- Historically: Used since mid-1950's
 - Extensive WHO studies in the Middle East
- All US/Western IG products are very safe!
 - HyperRab™; and Imogam®
- Covers the initial 7 days until patients develop their own immunity
- **Not used** if prior immunization
- Simple rules:
 - Give once
 - Within and including 7 days, ***then no benefit afterwards***
 - ***Do not overdose*** (may reduce vaccine efficacy)
 - 20 IU/Kg of body weight
 - All or most near the wound if possible, remainder IM deltoid or thigh – **NEVER IV**
 - ***Never anatomically close*** to the vaccine site



Best Approach = Avoid Bites and Decrease Rabies in Vectors:

- Immunize domestic animals by “shot” – pets, livestock (cattle, sheep, horses)
 - Oral immunization in the wild – ORV: Oral Rabies Vaccine = pox virus with rabies glycoprotein (antigen) – put into fishmeal
 - 10,000,000 baits per year in US/Canada
 - Utilize regional vaccines = raccoon, fox (Raccoon - #1)
 - Slow migration (Appalachian “fence”)
 - Working in Ohio, West Virginia, Canada
- *A few known human infections with bait



Oral Bait Vaccines

Travelers, Occupations, and Rabies

- Vaccine (pre-exposure) consider for travelers staying in rural areas for > 4 weeks, or with questionable access to medical attention
 - 6.8% of street dogs in Thailand are rabid
 - a dog lick was experienced by 8.9% and a dog bite by 1.3% of travelers visiting for average of 17 days
- Military units - ready access to vaccine if exposed?
- Veterinarians, wildlife experts, etc.



Understand Rabies Mortality

- Patients usually die of **respiratory arrest**
- ICUs duration from onset to death averages 25 days—
 - patient may survive in a coma for months
 - usual complications of ICU/ventilated patients
- Most uniformly fatal infection in humans – 100%
 - Yet, NO massive necrosis/NO dramatic inflammation; MILD changes in basal ganglia, caudate nuclei, cerebellum, brainstem (Awasthi, et al, AJNR, May, 2000)
 - If it is not so destructive, could people survive?
- And then....

Rabies Treatment: Case Report, 2004

October 2004: 15 year old female in Fond du Lac County, WI:

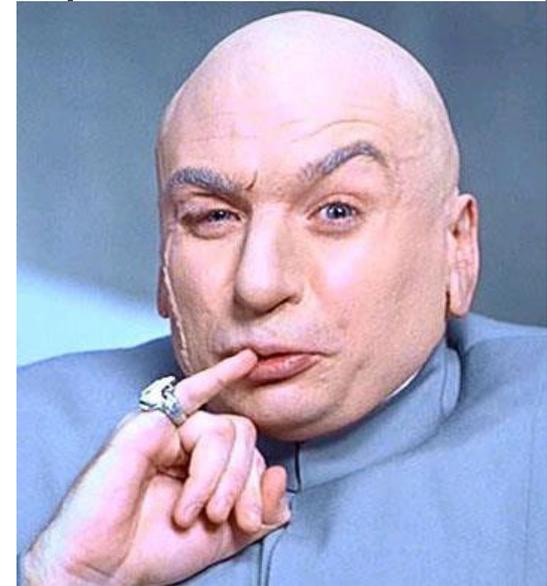
- “Fatigue, tingling and numbness (L) hand,” headache, diplopia, nausea and vomiting, and partial CN VI Palsy
- Brain MRI/MRA normal, sent home
- Admitted on day #4 LP: **Viral Meningitis?**
 - WBC = 23 cells/ μ L, 93% lymph
 - RBC = 3 cells/ μ L
 - Protein = 50 mg/dL (nl: 15-45)
 - Glucose = 58 mg/dL (nl: 40-70)
- Fever 102.9, tremors, deterioration



Jeanna Giese

Rabies Treatment: Case Report, 2004

- On illness day #6: a bat-bite history was now recalled:
 - 31 days prior, picked up a bat in church, bit on tip of left index finger, washed at home
- Dx studies: serum, CSF, nuchal skin, saliva
 - Rabies-specific Ab (+) in serum and CSF
 - **Game Over?**
 - DFA staining of nuchal skin biopsies negative
 - Rabies virus isolation from saliva negative
 - Rabies RNA not detected by RT-PCR
- Option of induced coma and drugs:



“it has never been done before, and he doesn't know if it will work or if I would come out brain dead.”

Rabies Treatment: Case Report, 2004

- Avoid respiratory complications, supportive care
 - “Neuroprotective Measures”: drug-induced coma - midazolam, phenobarbital
 - Initially IV ribavirin (IND protocol) plus amantadine
- CSF IgG increased from 1:32 to 1:2,048
- Coma for nearly 1 month, extubated on day #33, 2 months after bite; transferred to rehab

“I was slowly taken out of the coma. It was unknown whether I was actually alive, or if my soul had left my body.”



Case Report, 2004

- Was “No Vaccine” better than partial prophylaxis?
 - Less inflammation?
- Bit on **tip of finger** = better systemic immunity?
- **Weaker form of virus?** (bat viruses vary)
- Bit in church-**role of St Hubert!**
- **2nd survivor – 2009:**
 - 17 yo girl, aseptic meningitis months after visiting bat cave
 - Serum rabies IgG = 1:8,192



Summer of 2011 - Another Survivor:

- 8 yo Precious Reynolds
- Scratch by feral cat April 2011 (CA)
- Flu-like symptoms, abdominal complaints, then developed a “Polio-like” illness, muscle paresis, difficulty swallowing
- 2 wk ICU coma, long ward stay
- Minimal residual
- **Fatality drops from 100% to the high 99%’s**
 - 3 US survivors; a total of 7 global (15 yo in Brazil; an 8 yo in Columbia ..)
 - No reason to declare victory and go home...



Bats in the Bedroom! What do you do?

- 55 US/Canadian bat associated cases of human rabies in 2 generations (1950-2007):
 - 22 (39%) cases a bite was reported
 - 9 (16%) cases contact but no bite detected
 - 6 (11%) cases bats in the home but no known contact
 - **2 (4%) in their bedroom – PEP?**
 - 19 (34%) no history of any bat exposure – can't prevent
- Case: Bat found flying in upstairs
 - One room with sleeping 8 yo boy



Bats in the Bedroom! What do you do?

- Median incubation period 7 weeks
- If bat is available, send it for rabies testing
- **Consider PEP** if bat is unavailable, and persons were unaware that a bite or direct contact occurred
 - one decision factor: if sleeping in the room
 - But, **only 2 “probable” cases** in 20 years
 - Number needed to treat and cost benefit analysis ????



USAF Basic Trainees — TX, Jan. 2014

- 17 Jan one “Flight” (Dorm room) reported bats at night
 - Mexican free-tailed bats (*Tadarida brasiliensis*)
 - All 45 given PEP (3 days to get RIG)
 - Further investigation – 6 dorms exposed? (nearly 1,000 people)
- Used the “Kentucky” experience (2011-13) – and a similar “Kansas” experience for “RISK STRATIFICATION”
 - Interviewed 866, but since grouped in same rooms – each flight had **risk established for all as one unit**
 - 1 flight (Above) = **high risk** – >75% saw bats, > 2 days - **All PEP**
 - 3 flights = **moderate risk**; 1-75% saw bats > 1 night – **All PEP**
 - 14 = **low risk**, one bat sighting for a brief period not during sleep
 - Addit. 35 trainees moved (medical holds, etc.) – 9 Higher Risk
 - Total of 45 initial and additional 157 recommended for PEP

USAF Basic Trainees — Tx, Jan. 2014

- Lessons Learned:
 - 200 total recipients (\$400,000) of 922 trainees/instructors screened for “risks” were given PEP
 - 2 with urticaria, 6 with pruritis (all continued, with diphenhydramine, one received steroids)
- Extended investigation for 1 year prior – no further high risk identified
- **“Risk Based” stratification of groups** = High – Moderate – Low; helped sort a massive exposure
- Still huge \$\$\$ and logistics
- Single colony of 400-600 bats found in wall crevices: Dorms sealed, ceilings refurbished, one-way exclusion devices, etc.

SUMMARY

- Rabies Vaccine and RIG Works – must be used **exactly as recommended**
- Animal immunization programs – work, but expensive
- Bat Risk – Is the sleeping/bedroom risk exaggerated? What is the source of most exposures?
- Therapy – has “worked” a few times – are these unusual circumstances?
 - Still > 99% Fatal
- Prevention !!!

