

**NEARLY DOG-GONE BUT
NOT FORGOTTEN:
RARE BUT DEADLY CASES OF
RABIES STILL OCCUR IN THE U.S.**

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OBJECTIVES:

- Describe the transmission and pathogenicity of the rabies virus.
- Discuss diagnosis and treatment of rabies.
- List current methods of rabies prevention.

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IN THE NEWS: SEPTEMBER 2021

- The Illinois Department of Public Health reported the first human case of rabies in Illinois since 1954. Testing at the CDC confirmed the diagnosis.
- In mid-August, an 80-year-old male in northeast Illinois awoke to a bat on his neck. The bat was captured and tested positive for rabies, but the patient declined postexposure rabies treatment, not recalling having been bitten.
- One month later, he began experiencing neck pain, headache, difficulty controlling his arms, numbness in his fingers, and difficulty speaking. He subsequently died.
- Wildlife experts found a bat colony in the man's home.
- People who had contact with secretions from the patient were assessed and given rabies preventive treatment as needed.
- Approximately 3% of bats tested for rabies in Illinois are positive.

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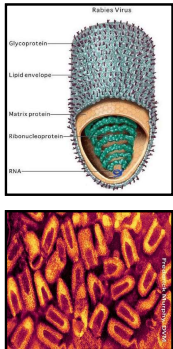
IN THE NEWS: NOVEMBER 2021

- The Idaho Department of Health and Welfare reported the first human case of rabies and subsequent death in the state since 1978. Testing at the CDC confirmed the diagnosis.
- In late August, a Boise county man encountered a bat on his property. It flew near him and became caught in his clothing, but he did not believe he had been bitten or scratched.
- In October, he fell ill and was hospitalized, and he subsequently died.
- It was not until after the investigation into his illness began that the bat exposure was discovered.
- Those who had contact with the patient's secretions are being assessed and will be given preventive treatment as needed.
- Approximately 11% of bats tested for rabies in Idaho are positive.

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RABIES VIRUS

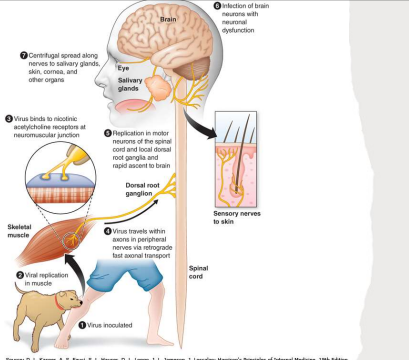
- One of the most ancient and deadly human infectious diseases
- Member of the Rhabdovirus family that causes disease in humans and other mammals
- Single-stranded RNA virus with a bullet shaped envelope that may be identified by electron microscopy, fluorescent antibody staining or RT-PCR of infected cells or tissue
- Transmitted primarily by the saliva of infected dogs
- Causes almost 100% fatal encephalomyelitis
- Causes ~60,000 deaths/year worldwide despite highly effective vaccines and treatments



The diagram shows a cross-section of a Rabies Virus particle. It has a bullet-shaped envelope with a lipid bilayer. Inside, there is a matrix protein layer, a ribonucleoprotein core, and a single strand of RNA. Below the diagram is an electron micrograph showing multiple bullet-shaped virus particles.

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PATHOGENESIS OF RABIES

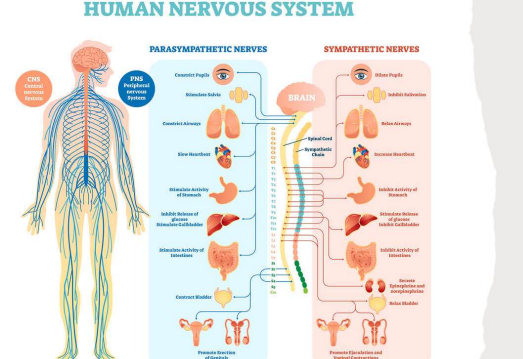


The diagram illustrates the pathogenesis of rabies in a human. It shows a dog biting a person's arm. The virus enters through the wound and travels through the peripheral nervous system. Key steps include:

1. Virus inoculation at the bite site.
2. Viral replication in skeletal muscle.
3. Virus binds to nicotinic acetylcholine receptors at the neuromuscular junction.
4. Virus travels with axons in peripheral nerves via retrograde fast axonal transport to the spinal cord.
5. Proliferation in motor neurons of the spinal cord and local dorsal root ganglia and rapid ascent to brain.
6. Contingent spread along nerves to salivary glands, skin, cornea, and other organs.
7. Infection of brain neurons with neuronal dysfunction.

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HUMAN NERVOUS SYSTEM



The diagram shows the human nervous system with the brain at the top. It is divided into two main branches:

- PARASYMPATHETIC NERVES:** These nerves originate from the brainstem and sacral region of the spinal cord. They are responsible for 'rest and digest' functions, such as stimulating salivary glands, inhibiting heart rate, stimulating digestion, and promoting urination.
- SYMPATHETIC NERVES:** These nerves originate from the thoracic and lumbar regions of the spinal cord. They are responsible for 'fight or flight' functions, such as dilating pupils, inhibiting digestion, stimulating heart rate, and promoting urination.

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CLINICAL MANIFESTATIONS

- **Incubation period**
 - The time between the bite/exposure and the appearance of symptoms
 - In humans is typically 1-3 months, but may be as short as one week or over a year
 - Length of time depends on number of nerves in bitten area
 - Dose of virus
 - Severity of wounds
 - Distance from the bite wound to the CNS
- **Three phases of clinical symptoms:**
 1. Prodromal phase – early nonspecific symptoms
 2. Excitation phase – acute neurologic symptoms
 3. Paralytic phase – death

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PRODROMAL PHASE



- Initial symptomatic phase lasting from 2-10 days
- Non-specific symptoms:
 - Fever
 - Malaise
 - Sore throat
 - Nausea and vomiting
 - Headache
 - Mild photophobia

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EXCITATION PHASE

- Acute neurologic phase
- Lasts 2-7 days
- Signs of nervous dysfunction:
 - Nervousness
 - Apprehension
 - Hallucinations
 - Bizarre behaviors like hydrophobia, aerophobia
- Overactivity of the nervous system:
 - Increased tear, saliva and sweat production
 - Muscle spasms, especially of throat
 - Pupillary dilation
 - Priapism
 - Hypersexuality



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PARALYTIC PHASE

- Convulsive seizures
- Coma
- Death, often due to cardiorespiratory arrest



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TWO DIFFERENT PRESENTATIONS OF RABIES: FURIOUS VS. DUMB

- **Furious rabies**
 - 80% of all cases
 - Onset signaled by hyperactivity, hydrophobia, severe or uncontrollable anxiety
 - Intermittent "furious" episodes occur, usually lasting five minutes or less
 - Death due to cardiorespiratory failure, simple exhaustion, seizures of extensive paralysis
- **Dumb rabies**
 - 20% of cases
 - Patient is characteristically quiet and lucid throughout
 - Course of illness is a bit more prolonged, beginning with paralysis of the bitten limb
 - Headaches and fever first, then paralysis that leads to quadriplegia
 - Death due to respiratory weakening and arrest of breathing
- Cause of difference in presentation remains unclear

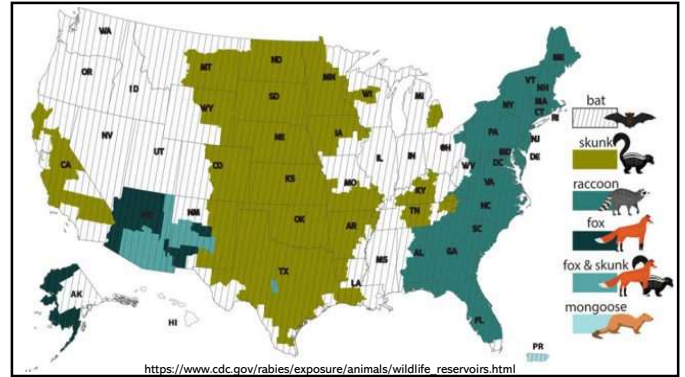
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RABIES TRANSMISSION

- Can affect any mammal but only a few serve as important reservoirs
- Humans are dead-end hosts
- Exposure to rabid dogs is the cause of nearly all human rabies deaths worldwide
- 90% of U.S. cases in animals occur in wildlife: raccoons, skunks, bats, and foxes
- Contact with infected bats is the leading cause of rabies deaths in the United States
- In the United States, only 1 to 3 cases reported annually, but ~55,000 Americans get post-exposure treatment each year to prevent potential infection

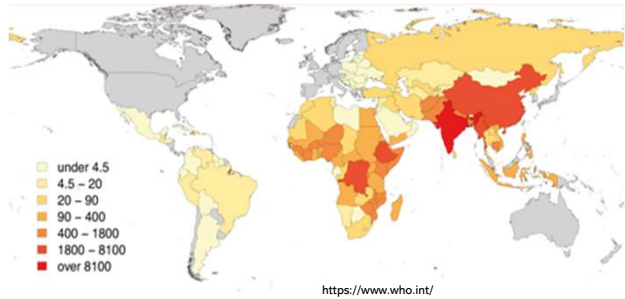


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NUMBER OF HUMAN DEATHS WORLDWIDE - 2017



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EVEN RARER STILL: RABIES FROM ORGAN TRANSPLANT

- ROTA – Rabies from organs or tissues allotransplantation
- 13 cases reported worldwide from 1978 to 2017
 - Cornea
 - Heart
 - Liver
 - Kidney
 - Heart valve
- Rabies screening among donors not currently required
- Long incubation period of rabies may prevent detection in donors

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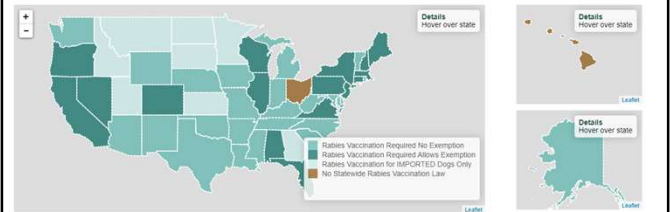
RABIES CONTROL IN THE U.S.

- *Estimated to be \$250-500 million annually*
- U.S. canine rabies control efforts began in earnest in the early 1940s
- U.S. officially declared *canine* rabies-free in 2007
- Number of rabies-related human deaths in the U.S. declined during the 20th century, from more than 100/year in the early 1900s to just one or two per year since 1960
- U.S. rabies prevention mechanisms:
 - Mandatory vaccination of common pets
 - Successful animal control programs
 - Public health surveillance and testing
 - Availability of post-exposure prophylaxis (PEP) for rabies
 - Rabies vaccines available to people at risk of rabies
- Vaccine baits
- Ban on imported dogs

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MANDATORY U.S. PET VACCINATION

- Varies from state to state
- Animals that require vaccination also vary
- <https://www.animallaw.info/content/rabies-vaccination-and-exemption-laws-dogs>



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RABIES POST-EXPOSURE PROPHYLAXIS (PEP)

- *About 55,000 Americans get PEP each year*
- Developed in the late 1800s
- Human rabies immune globulin (HRIG) on day 0
- Multiple doses of rabies vaccine on days 0, 3, 7 and 14
- (A previously vaccinated person only needs two doses of the vaccine, and not HRIG)
- Combination is recommended for bite and non-bite exposures
- Adverse reactions to PEP are not common: mild, local reactions such as pain, redness, swelling, or itching at the injection site
- Cost of PEP in the U.S.: \$10,000+
- Government programs for uninsured or underinsured are available: https://www.cdc.gov/rabies/medical_care/programs.html

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RABIES VACCINE

- Pasteur – dried spinal columns of infected rabbits to attenuate/weaken
- In modern times, repeated culture passages of the virus in special media are used to weaken it
- A regimen of four 1-mL doses of vaccines should be administered intramuscularly to previously unvaccinated persons, on days 3, 7, and 14 after the first vaccination.
- Adults: deltoid area of the arm
- Children: thigh is acceptable (never gluteal area)
- Average cost in the U.S.: ~\$400, often considered elective by insurance companies
- *Not cost effective or feasible for most countries and warrants development of new, safe, CHEAP, single-dose vaccines*

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PRE-EXPOSURE RECOMMENDATIONS

Risk Category	Nature of Risk	Typical Population	Pre-exposure Recommendations
Continuous	Virus present continuously, often in high concentrations. Specific exposures likely to go unrecognized. Bite, nonbite, or aerosol exposure.	Rabies research laboratory workers; rabies biologics production workers.	Primary course. Serologic testing every 6 months; booster vaccination if antibody titer is below acceptable level.
Frequent	Exposure usually episodic, with source recognized, but exposure also 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. All persons who frequently handle bats.	Primary course. Serologic testing every 2 years; booster vaccination if antibody titer is below acceptable level.
Infrequent	Exposure nearly always episodic with source recognized. Bite or nonbite exposure.	Veterinarians and terrestrial animal-control workers in areas where rabies is uncommon to rare. Veterinary students. Travelers visiting areas where rabies is enzootic and immediate access to appropriate medical care including biologics is limited.	Primary course. No serologic testing or booster vaccination.
Rare (population at large)	Exposure always episodic with source recognized. Bite or nonbite exposure.	U.S. population at large, including persons in rabies-enzootic areas.	No vaccination necessary.

https://www.cdc.gov/rabies/specific_groups/travelers/pre-exposure_vaccinations.htm

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RABIES CONTROL, CONT.



- Vaccine baits
 - In use in the U.S. since 1990, in Canada since 1985, and in Europe since 1980
 - Oral vaccine pellets distributed by air and by hand based on likely animal reservoirs in an area
 - Matchbox-size plastic packet containing oral rabies vaccine coated or encased in fishmeal
 - Sachet ruptures when animal bites into it, allowing oral vaccination
 - Increased number of vaccinated animals in the wild stops the spread to other animals and people
- Current temporary ban on imported dogs in the U.S.
 - About 1 million dogs are imported each year.
 - Due to a sharp increase in the number of puppies imported with fraudulent rabies vaccine certificates
 - Pandemic prompted a surge of pet adoptions
 - Banned importation from 113 countries considered high risk including Kenya, Uganda, Brazil, Colombia, Russia, Vietnam, North Korea, Nepal, China and Syria

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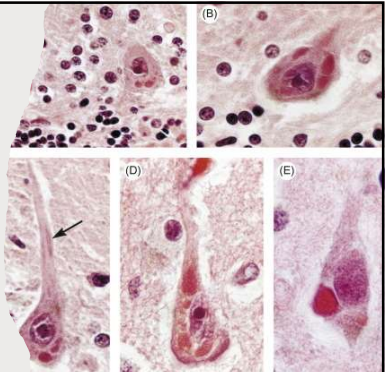
DIAGNOSIS OF RABIES

- May take months or longer to have symptoms
- Once symptoms manifest, infection is nearly always fatal
- Rabies evades the immune system
 - Kills protective migrating T cells
 - Sneaks into nervous system without triggering an immune response or destroying neuronal cells
 - CNS is an immune privileged site
- Lab testing not sensitive until after symptoms manifest or post-mortem
 - Biopsies of skin at hairline on back of neck, corneal samples
 - RT-PCR
 - Viral antigen detection in tissues or fluids
 - Antibodies in blood
 - Negri bodies in brain tissue post mortem
- Can perform testing on euthanized animal if captured

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NEGRI BODIES

- Eosinophilic inclusions
- Comprised of proteins produced by virus
- Pathognomic for rabies



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RARE CASES OF RABIES SURVIVAL WITHOUT PRE- OR POST-EXPOSURE PROPHYLAXIS TREATMENT (PEP)

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JEANNA GIECE

- In October 2004, a previously healthy female aged 15 years in Wisconsin received a diagnosis of rabies after being bitten by a bat approximately 1 month before symptom onset.
- While attending a church service in September, the girl picked up a bat after she saw it fall to the floor. As she took the bat outside to release it, it bit her on her left index finger. The bat was not captured for rabies testing.
- The wound was approximately 5 mm in length with some blood present at the margins; it was cleaned with hydrogen peroxide. Medical attention was not sought, and rabies PEP was not administered.
- A month later, symptoms began: tingling and numbness of left hand, double vision, nausea and vomiting. She was referred to a neurologist as her symptoms progressed.
- The bat bite was then reported, and blood, CSF, saliva and skin samples were submitted to the CDC for rabies testing.
- Clinical management from team of specialists consisted of supportive care and neuroprotective measures, including a drug-induced coma for seven days and ventilator support for 33 days.

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MILWAUKEE PROTOCOL

- Dr. Rodney Willoughby, pediatric infectious disease specialist
- Attempted a new rabies treatment protocol for patients without PEP: infusion of anesthetics, sedatives, and antivirals
- Based on the (controversial) concept that rabies does not cause inflammation or destruction in the brain; it interferes with how the brain communicates with other parts of the body
- Also based on the idea that the immune system can mount an effective response to rabies if given enough time
- A medically induced coma might suppress brain activity, while allowing her respiration and circulation to be controlled, allowing time for antibodies to be produced
- Remains highly controversial as to whether it is truly successful

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PRECIOUS REYNOLDS

- In May 2011, a girl aged 8 years from a rural county in California was brought to a local emergency department (ED) with a 1-week history of progressive sore throat, difficulty swallowing, and weakness.
- After she developed flaccid paralysis and encephalitis, blood, CSF, saliva and skin samples were submitted to the CDC for rabies testing.
- rabies was diagnosed based on detection of rabies virus-specific antibodies in serum and cerebrospinal fluid (CSF); a compatible clinical syndrome in the patient, and absence of a likely alternative diagnosis.
- The patient received advanced supportive care, including treatment with therapeutic coma.
- She was successfully extubated after 15 days and discharged from the hospital 37 days later to continue rehabilitation therapy as an outpatient. The public health investigation identified contact with free-roaming, unvaccinated cats at the patient's school as a possible source of infection.

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WHEN TO SEEK RABIES TREATMENT

- If you've been in contact with any wildlife or unfamiliar animals, particularly if you've been bitten or scratched
 - Note: bats have small teeth and it can be difficult to tell whether you were bitten
 - If a wound is present, clean the wound and see a health care provider immediately regardless of vaccination status
- If you wake up to find a bat on you or in the same room with you, try to safely capture the bat for testing
- If a bat is seen in a room with an unattended child, or a mentally impaired or intoxicated person
- *It is critical to seek treatment BEFORE symptoms start*

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PEP – THE HIGH COST OF SURVIVING RABIES

- More feasible in the U.S. to treat after exposure rather than vaccinate everyone
- For those potentially exposed, seeking PEP may be financially burdensome
- Programs for un/der-insured often not well known
- Insured may face repeated co-pays or only partial coverage
- Costly PEP also given to those in contact with infected patient



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THE RISING PRICE OF RABIES TREATMENT



Year	Brand: HyperRAB	Brand: Imogam
2007	\$756.00	\$749.30
2008	\$1,571.70	N/A
2009	\$1,497.40	\$1,495.00
2010	\$1,867.20	N/A
2011	\$2,347.20	\$1,644.50
2012	\$2,362.00	\$1,882.10
2013	\$2,480.30	\$2,051.50
2014	\$2,728.20	\$2,348.00
2015	\$3,001.60	\$2,789.20
2016	\$3,301.10	\$3,318.40
2017	\$3,550.60	\$3,612.70
Total Increase	370%	388%

Prices are per 10 milliliters, the standard dose for an adult weighing between 134 and 166 pounds.

- To make human rabies Ig, drug companies must recruit and immunize donors with the rabies vaccine
- Rabies treatment only offered via hospital EDs in most states
- High treatment costs in the U.S. sometimes offset discounted drug costs in countries where rabies is more common
- High cost may cause some to hesitate in getting treatment

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SHOULD YOU GET VACCINATED?



- People at high risk of exposure:
 - Veterinarians, animal handlers, or veterinary students
 - Rabies laboratory workers
 - Spelunkers (people who explore caves)
 - Persons who work with live vaccine to produce rabies vaccine and rabies immune globulin
- People whose activities bring them into frequent contact with rabies virus or with possibly rabid animals
- International travelers who are likely to come in contact with animals in parts of the world where rabies is common and immediate access to appropriate care is limited
- *People who live in rabies-endemic areas*

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VACCINATE YOUR PETS!




- Cost of rabies vaccine for animals: ~\$15-30—CHEAP
- It's the law!
- If a wild animal bites your pet, it should be captured if possible and submitted immediately for testing.
- If the wild animal is not captured and the pet is **unvaccinated**, the wild animal is assumed to be rabid and the pet should either be euthanized immediately or kept in strict isolation for 6 months and vaccinated one month prior to release.
- If the pet is **vaccinated**, it should be kept under observation for 45 days.
- If a pet bites someone and there's no documentation of it having been vaccinated...

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CHARACTERIZATION OF RABIES IN DOGS


- Clinical manifestations, including changes to normal behavior such as:
 - Restlessness and withdrawal
 - Aggression – biting without provocation
 - Lack of fear
 - Eating abnormal items such as sticks, nails, feces, etc.
 - Running for no apparent reason
 - Vocal changes (e.g. hoarse barking and growling) or inability to produce sounds
 - Excessive salivation or foaming from the mouth
 - Inability to swallow
 - Dilated pupils
 - Seizures
 - Paralysis



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A BIT ABOUT BATS

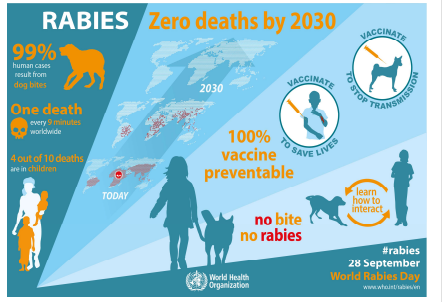
- 1,400+ species of bats worldwide; ~45 in U.S. and Canada
- What good are bats?
- Most bats don't have rabies, but true confirmation can only be made in a laboratory
- Rabid bats may exhibit abnormal behaviors:
 - Active by day
 - Difficulty flying, disoriented
 - Present in unusual areas
- Can you exterminate bats?
- Preserve habitats so bats are less likely to come into contact with humans



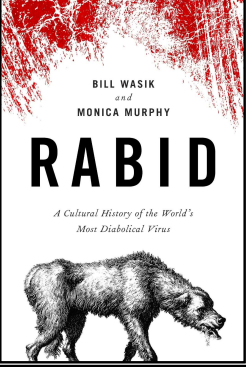
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WORLDWIDE RABIES PREVENTION AND MANAGEMENT

- Coordinated response between animal and health systems for:
 - Awareness
 - Treatment
 - Vaccination




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BILL WASIK
and
MONICA MURPHY

RABID

*A Cultural History of the World's
Most Diabolical Virus*



- Rabies history over thousands of years
- Cultural mythology
 - Vampires
 - Werewolves
 - Zombies
- Literary and cinematic references
- History of vaccine and treatment developments – Louis Pasteur

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THANK YOU FOR LISTENING!

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