Rabies!!!

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at Oregon Health & Science University

DISCLOSURE

Relevant Financial Relationship(s)

None

Case Study 1

- Faculty member enjoying a tropical vacation
- Masseuse notices small wounds near ankles

Cast Study 2

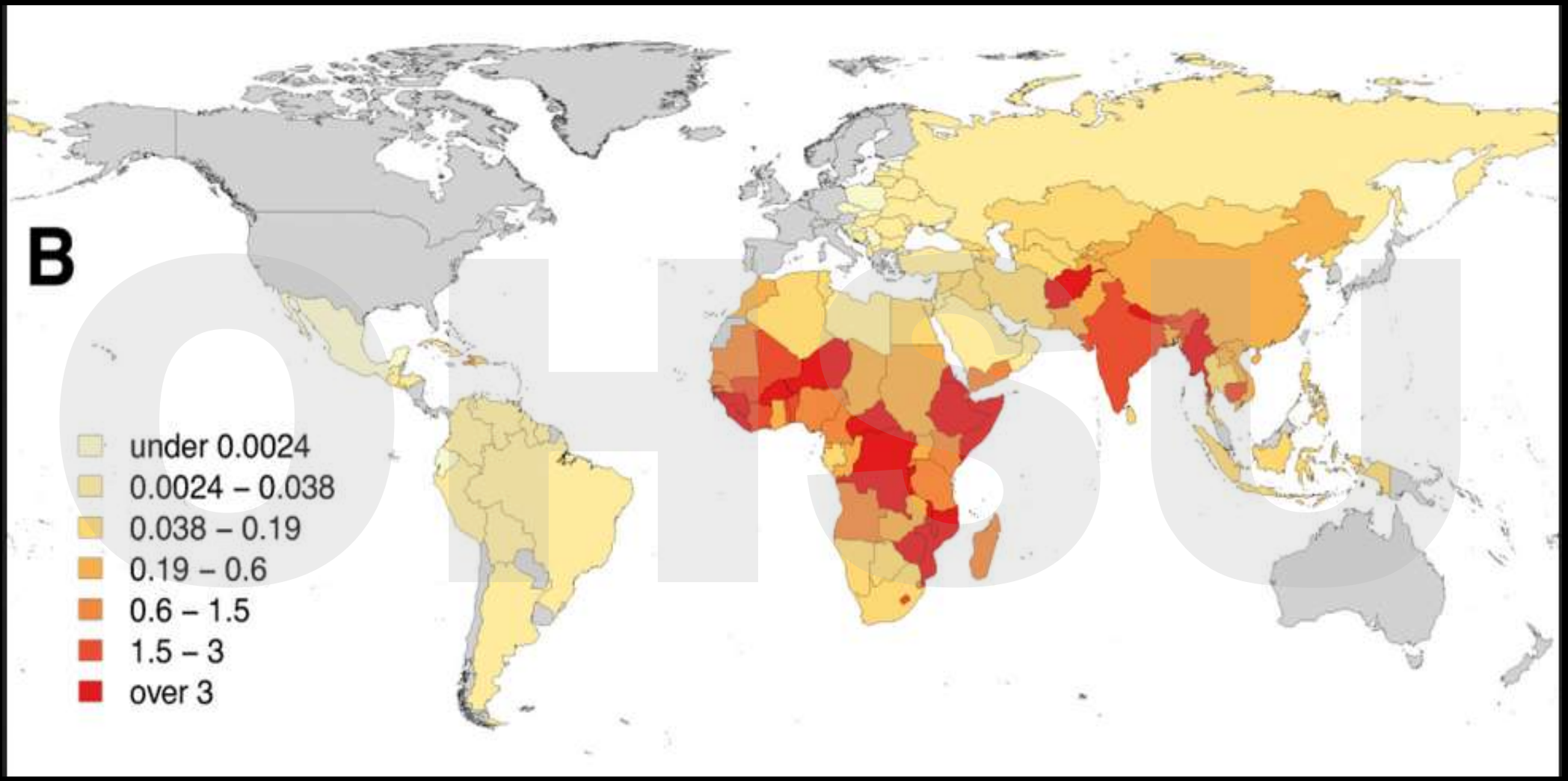
- You get a call from one of your co-workers
- While riding a bike, a dog runs across field, lunges at him and bite his legs and runs off….

Rabies: History

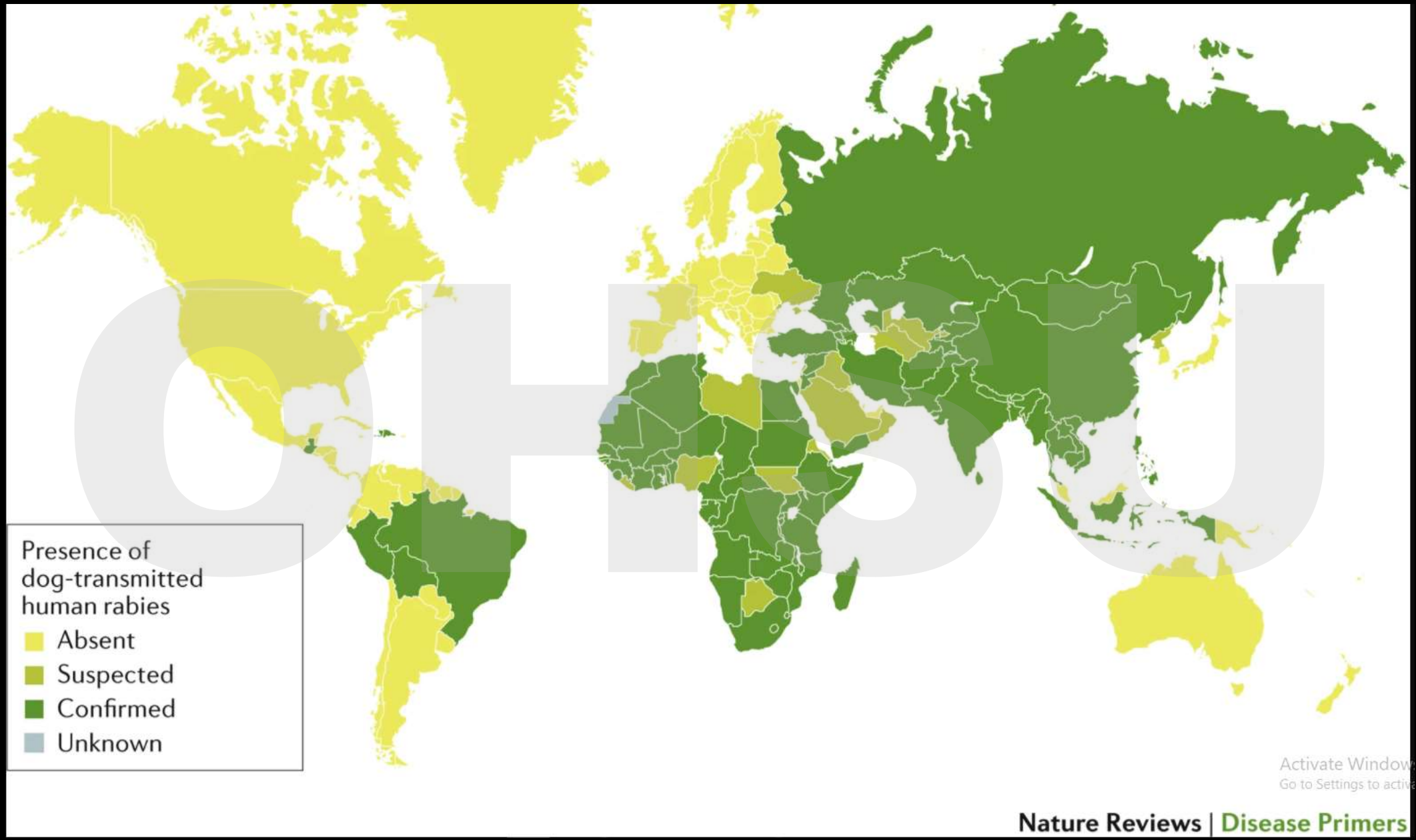
- Known for thousands of years
- Babylon legal code 2300BC – paid fine if your dog gave someone rabies
- Recognized by Aristotle
- “Rabere” Latin “to be mad”
- Pasteur created vaccine
- 1940-50 – dog rabies eliminated US

Rabies: Epidemiology

- Still terrible problem world-wide
- ~ 60,000/deaths
- Mainly via dogs
- 95% Africa/Asia

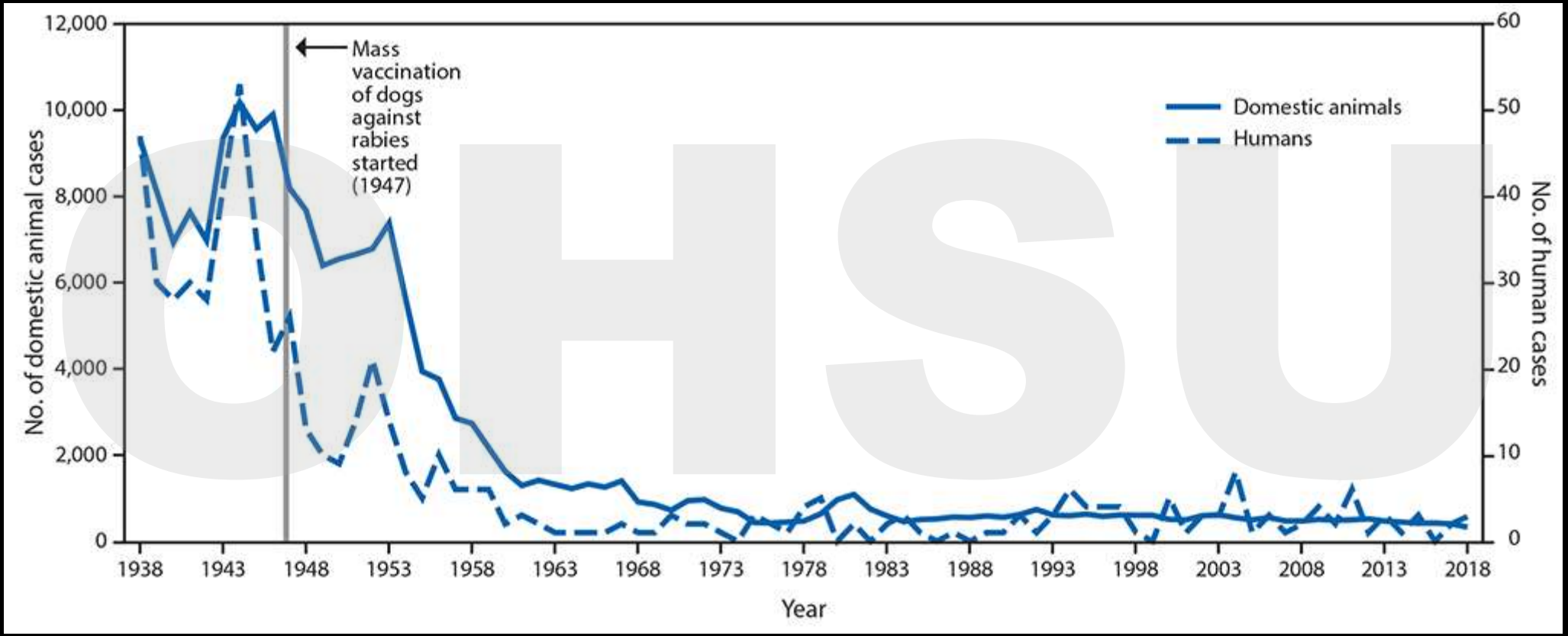


Deaths per capita WHO


Presence of dog-transmitted human rabies
Absent
Suspected
Confirmed
Unknown
Nature Reviews | Disease Primers

Rabies: USA

- Last century 30-50 case/yr
- Currently ~ 2 deaths/yr
- Dog rabies almost eliminated
- Most cases bats or “imported”



https://www.cdc.gov/mmwr/volumes/68/wr/figures/mm6823e1-F1.gif

Figure 1. Human Rabies Deaths in Indiana, 1900-2006

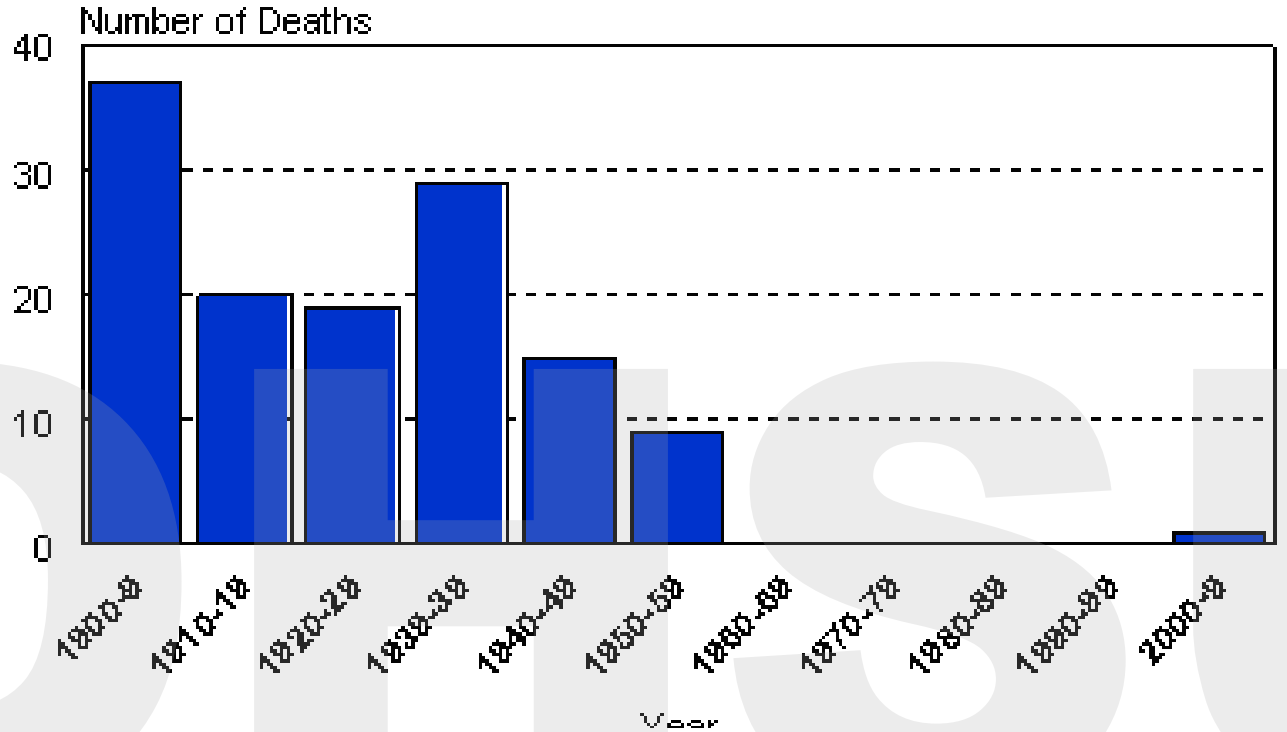
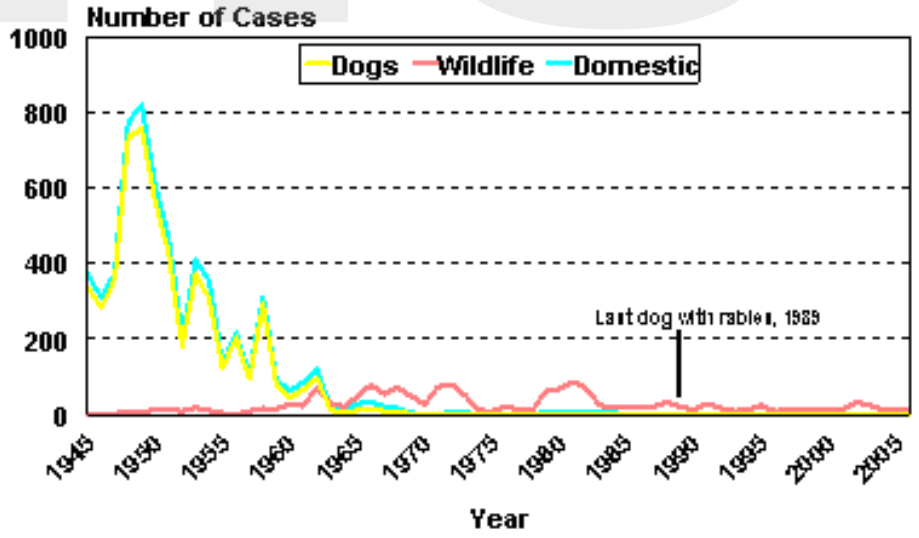


Figure 3. Animal Rabies, Indiana,1945-2006



Rabies: Travelers

- 30 years review
- 52% Asia
- 50% Visiting home
- 75% Male
- 81% Dogs

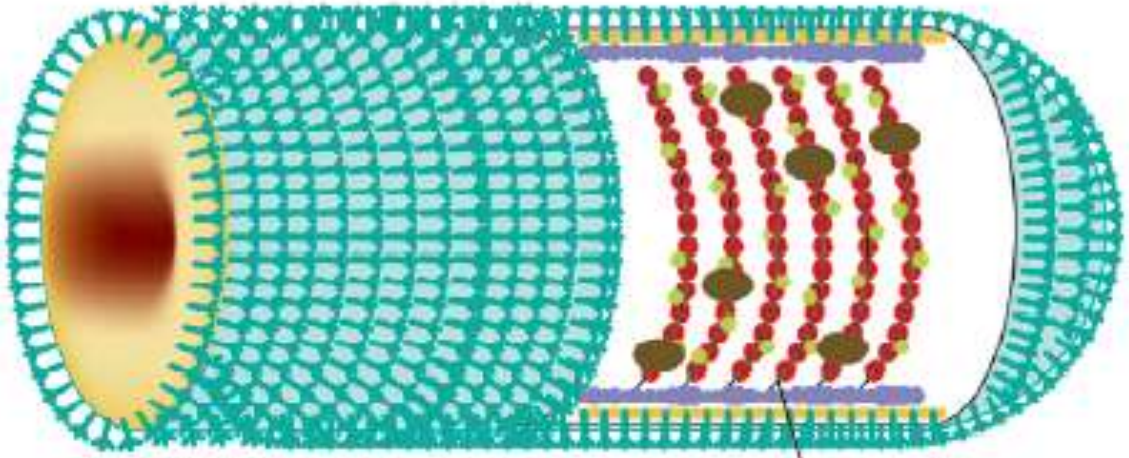
- Travel med ID 2020

The Virus

- Lyssavirus
  - Lyssa: the goddess of rage
- Member of Rhabdoviridae family
- Negative stranded RNA virus
- Very labile!
  - Inactivated by sunlight, heat, desiccation

The Virus

- Bullet shaped 200 nm x 80
- 5 proteins
  - Nucleoprotein
  - Phosphoprotein
  - Matrix protein
  - Glycoprotein
  - (L)Polymerase

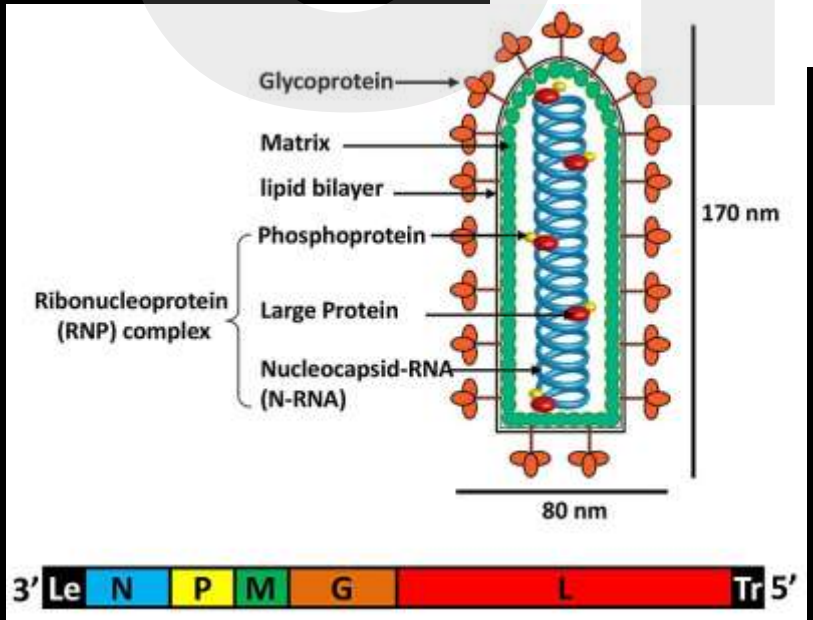


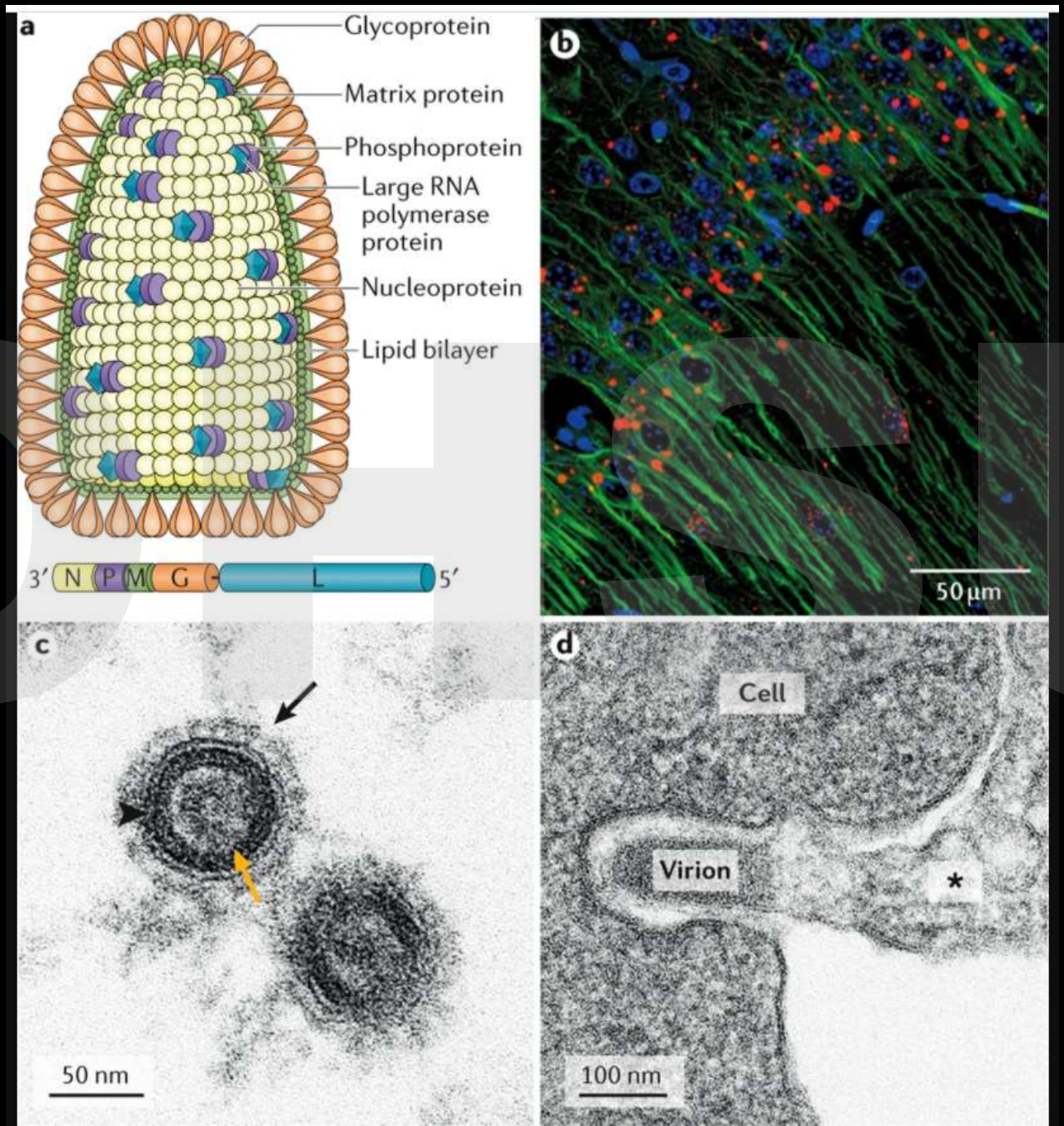
Matrix protein

Envelope
- Host-derived lipid membrane
- Glycoprotein

RNA genome helical coil

Ribonucleoprotein complex or nucleocapsid
- Nucleoprotein
- Phosphoprotein
- RNA polymerase




a
Glycoprotein
Matrix protein
Phosphoprotein
Large RNA polymerase protein
Nucleoprotein
Lipid bilayer
3′ N P M G L 5′
b
50 µm
c
50 nm
d
Cell
Virion
*
100 nm

How do we get Rabies?

- Bites
- Inhalation
- Scratched/licking
- Transplantation

Bites

- Rate of infection 5-80%
- Most common mode of transmission
- Deep crushing wounds highest rates
  - Rabies “injected” into muscle

Scratches

- Bats
  - Lick claws
  - Licks opened wounds
  - Scratches skin
  - ~ 0.1-1%

Inhalation

- One documented laboratory case
- Controversial spelunker cases
  - Unnoticed bat bites?

Transplant

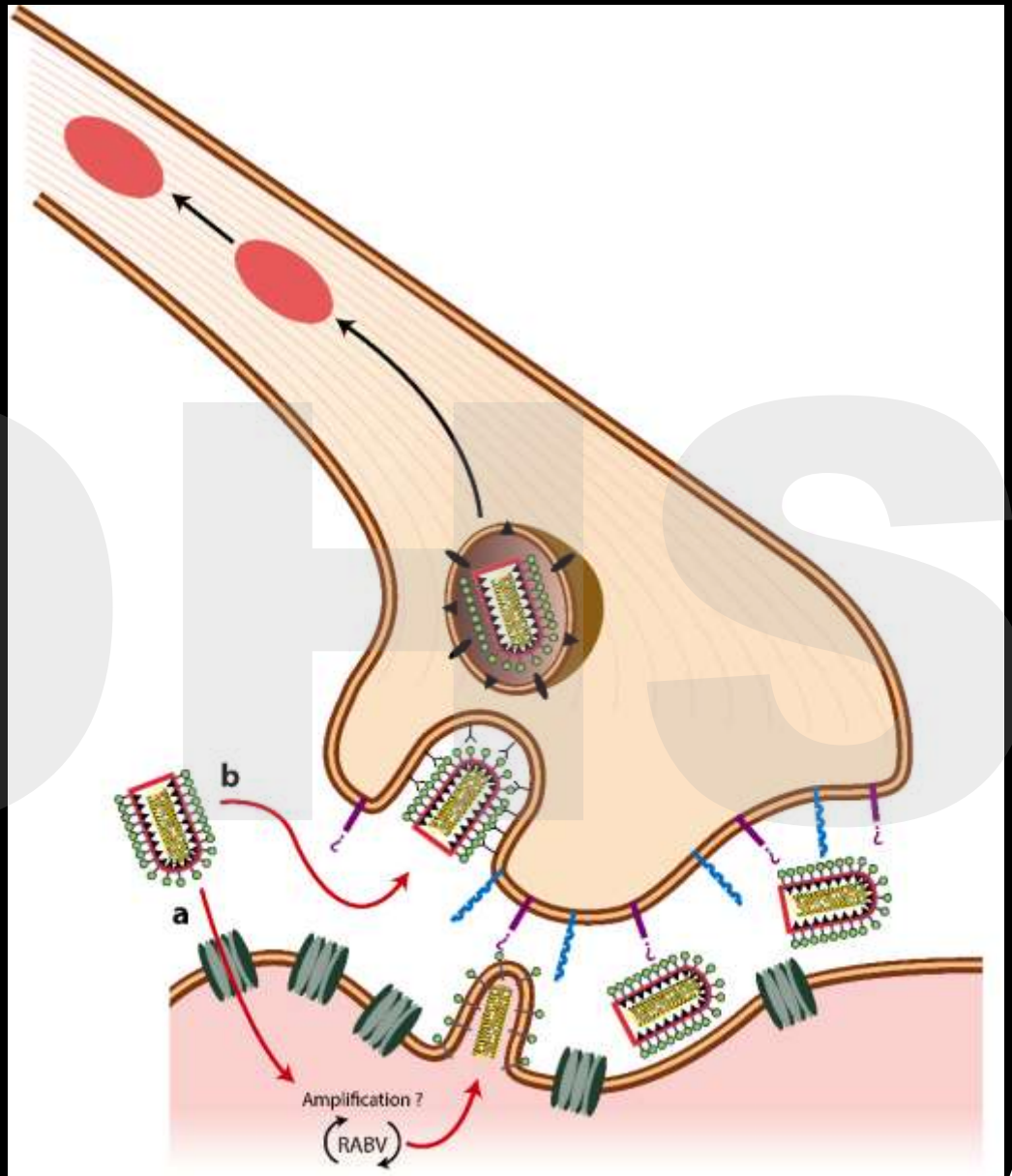
- Rare reports of organs spreading rabies
- Corneas most common
- Solid organs twice in USA
  - 2004, 2013

Pathophysiology: Overview

- Virus replicates in muscle cells
- Ascends peripheral nerves
- CNS: Massive replication
- Transmitted via efferent nerves
- Viral replication salivary glands

Post-Bite

- Virus replicates in muscle
  - Can take time
- Uptake by motor endplates
- Higher risk of infection in deep muscle wounds



Annual Reviews

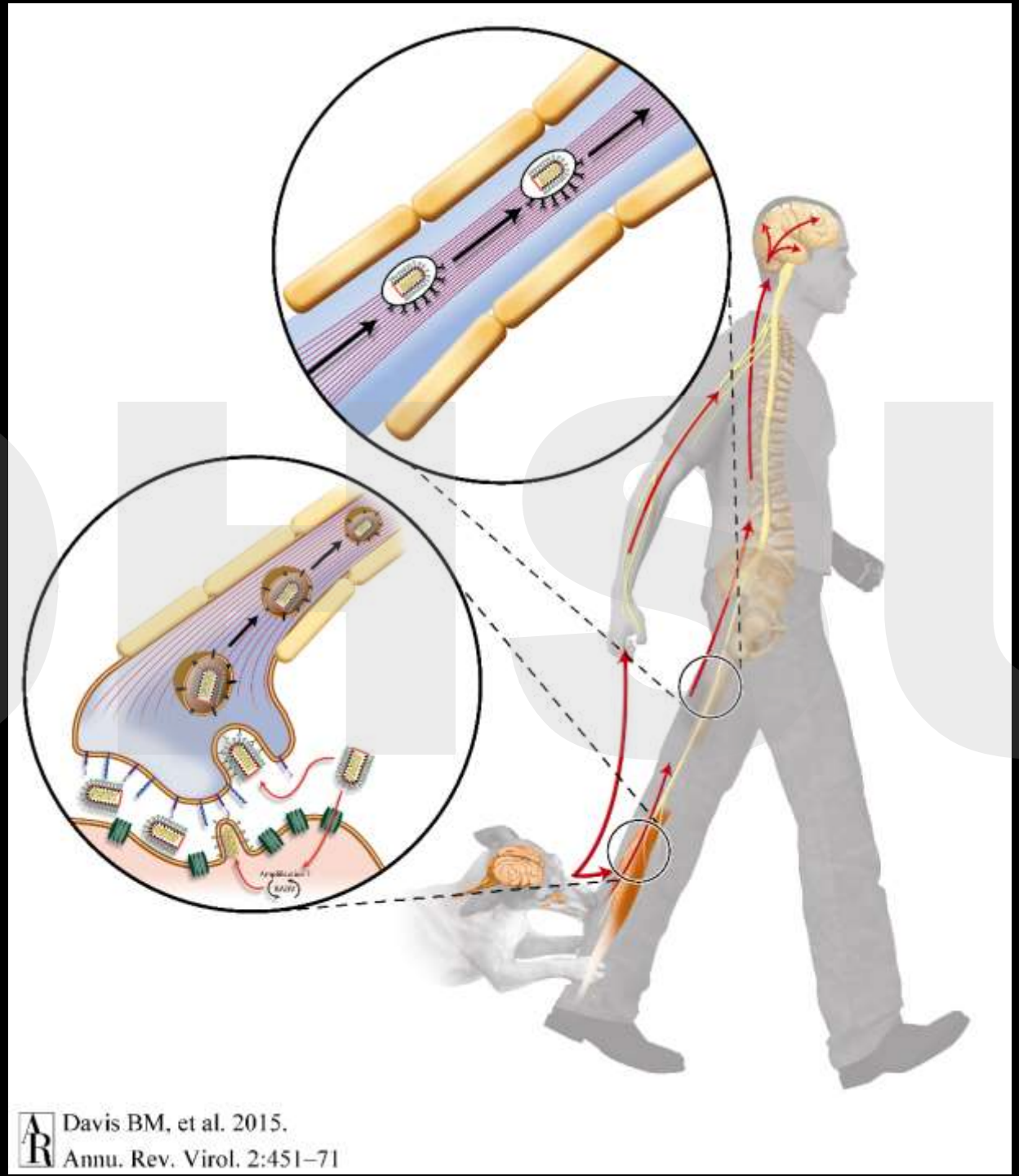
Davis BM, et al. 2015.
Annu. Rev. Virol. 2:451–71

Neuron Uptake

- Via virus G protein
  - Acetylcholine receptor
  - NCAM (CD56)
  - TNFRSF16

Axonal Travel

- Virus buds from muscle cells into the clefts of the NMJ
- Retrograde axonal transport
- Mainly motor neurons
- ~ One synapse every 12 hours
- 50-100 mm/day



Davis BM, et al. 2015.
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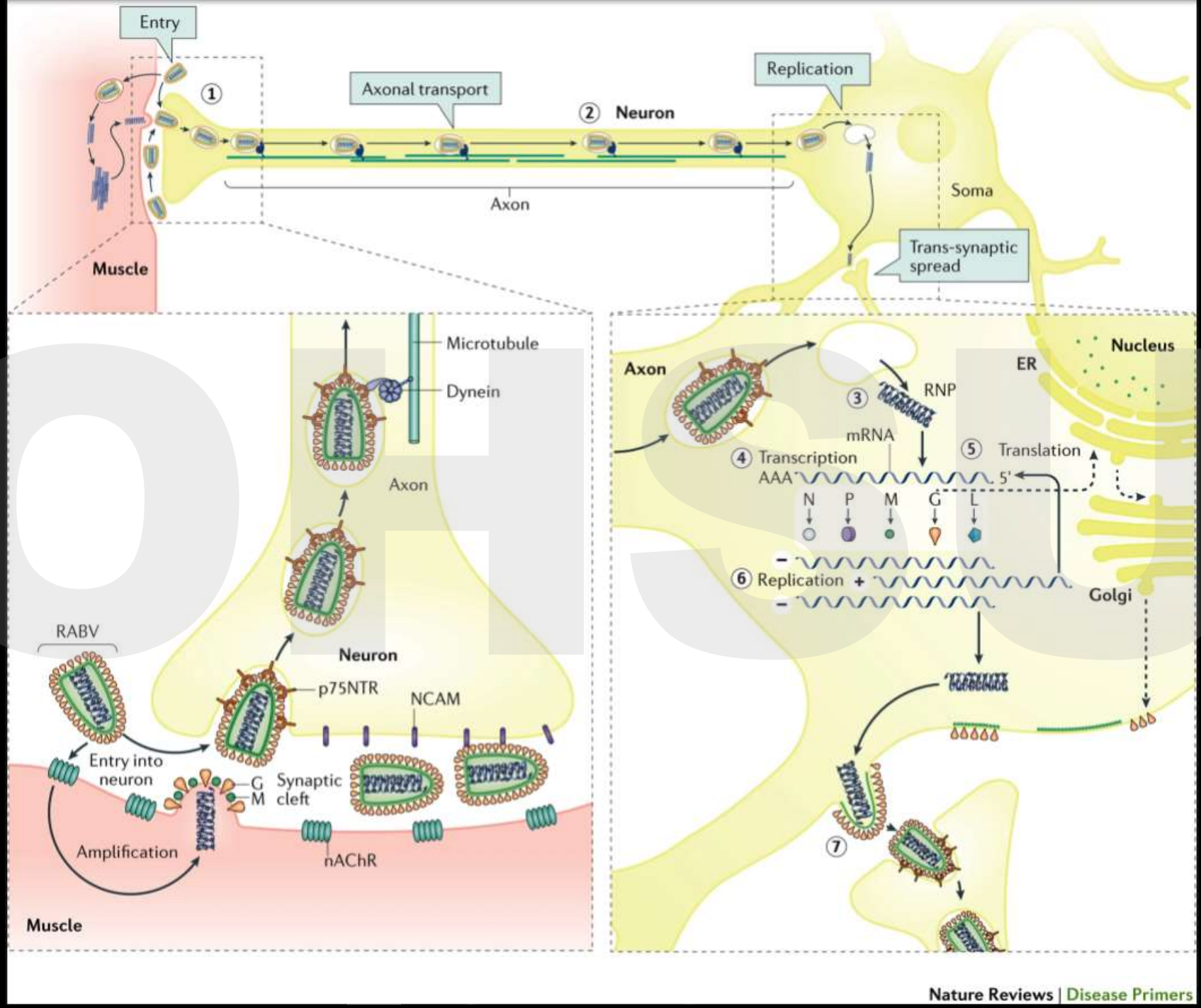
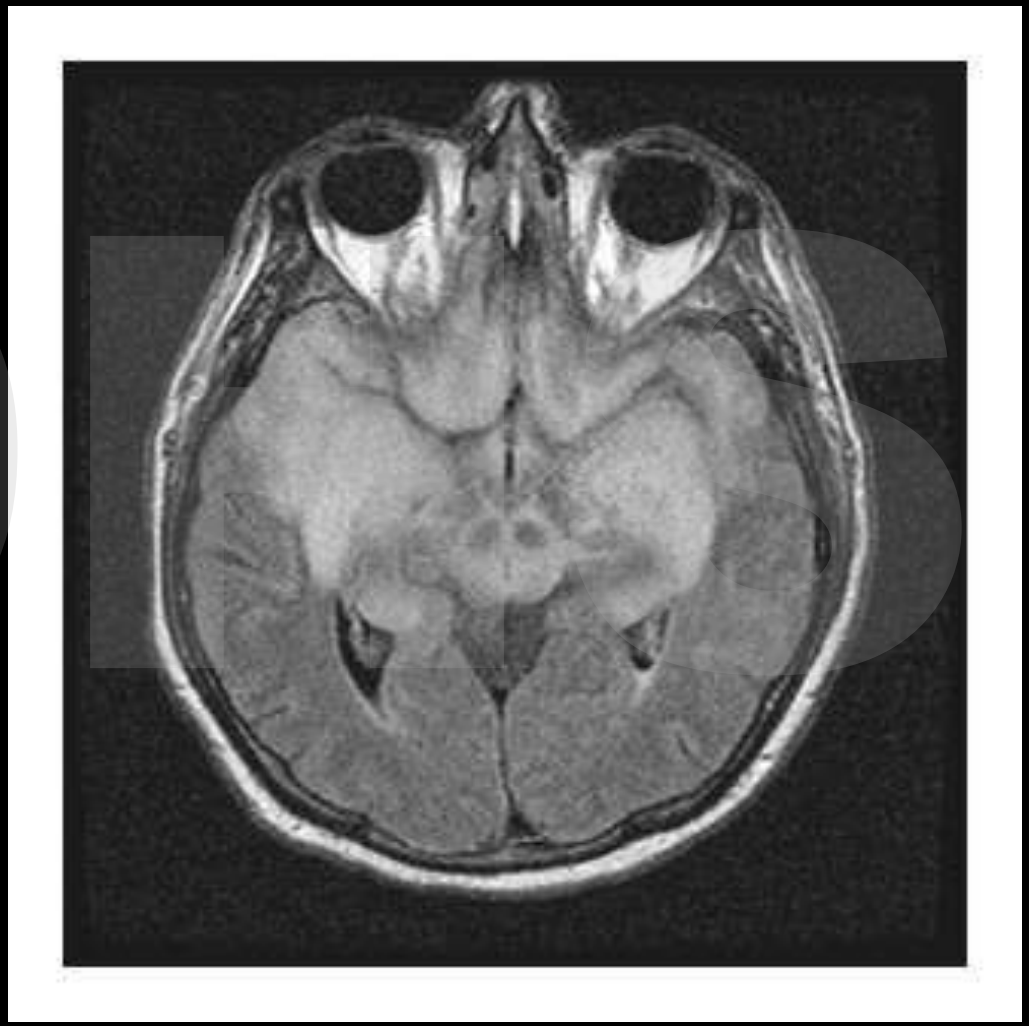

Entry
1
Axonal transport
2 Neuron
Replication
Soma
Axon
Muscle
Trans-synaptic spread
Microtubule
Dynein
Axon
Neuron
RABV
p75NTR
NCAM
Entry into neuron
G
M
Synaptic cleft
Amplification
nAChR
Muscle
Axon
3 RNP
mRNA
4 Transcription
AAA
5 Translation
5'
N
P
M
G
L
6 Replication
ER
Nucleus
Golgi
7

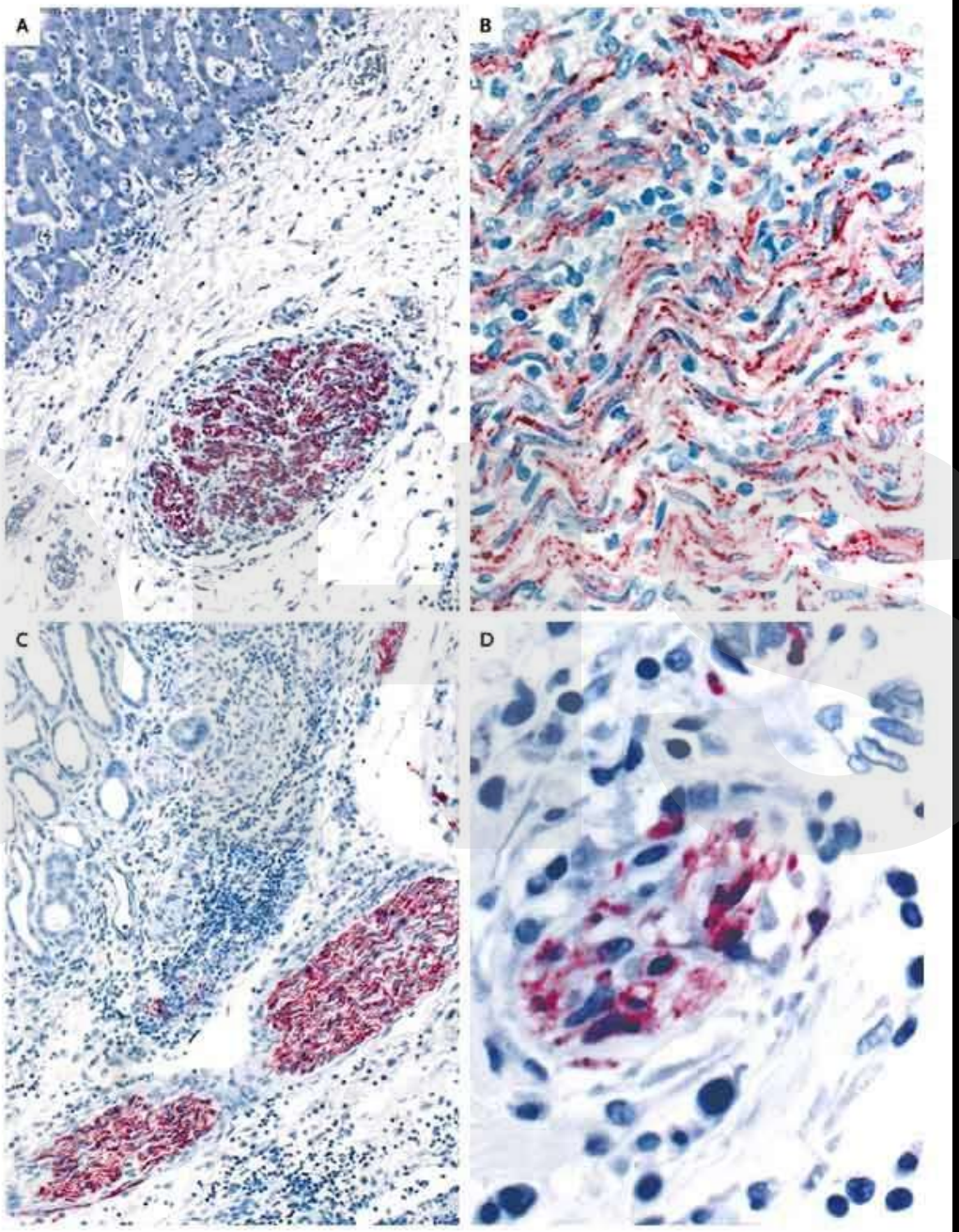
CNS

- When virus reaches CNS massive replication
- Spreads “centrifugally” through all nerves
- Leads to behavioral changes
  - Key to “spreading” virus
- Salivary glands high innervated
  - Virus shed in saliva

Axial Fluid-Attenuated Inversion Recovery MRI Scan Showing Profound Signal Abnormalities within the Bilateral Frontal and Temporal Lobes, Hippocampi, Basal Ganglia, and Medulla in Patient 2.



Srinivasan A et al. N Engl J Med 2005;352:1103-1111.



Srinivasan A et al. N Engl J Med 2005;352:1103-1111.

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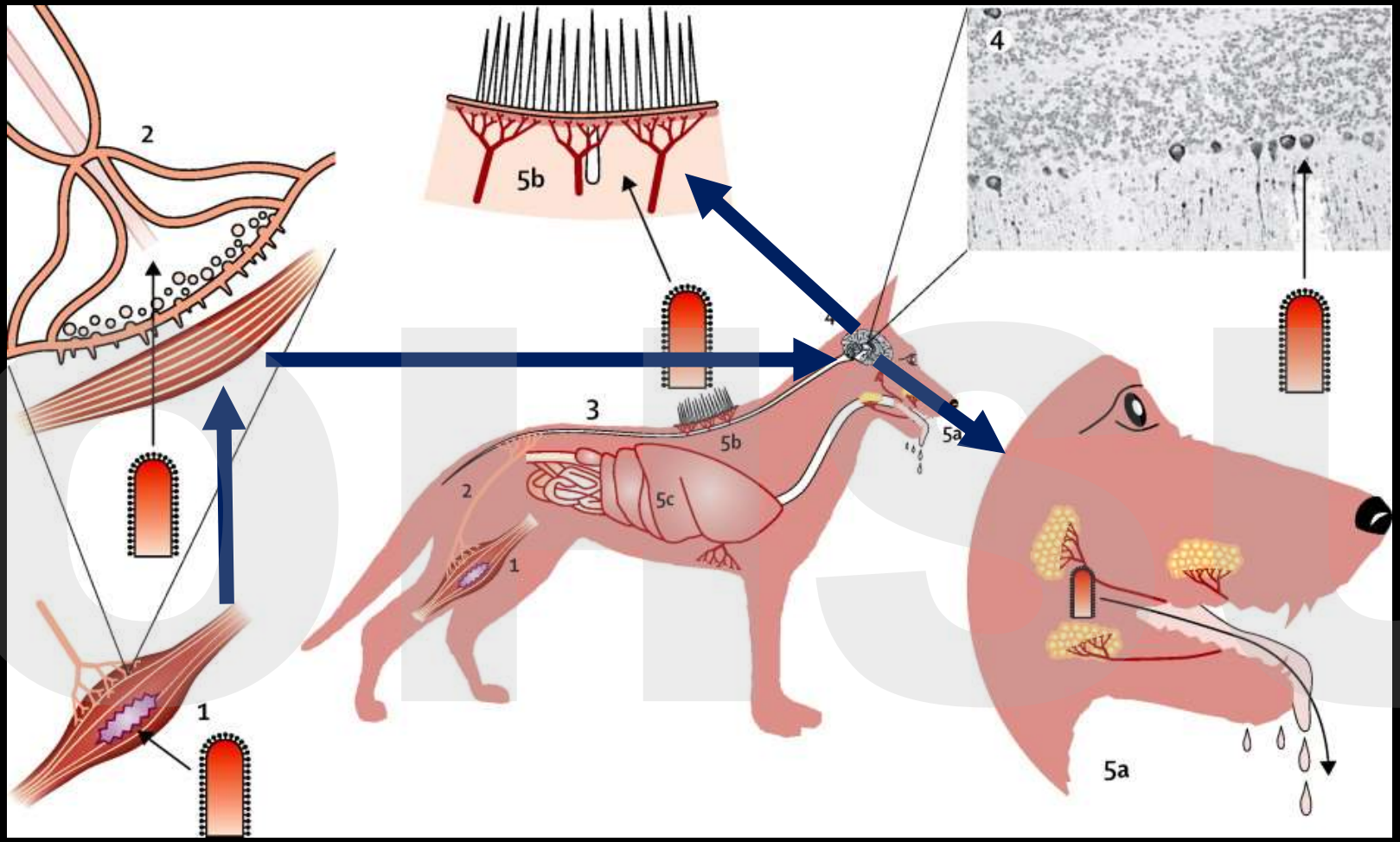
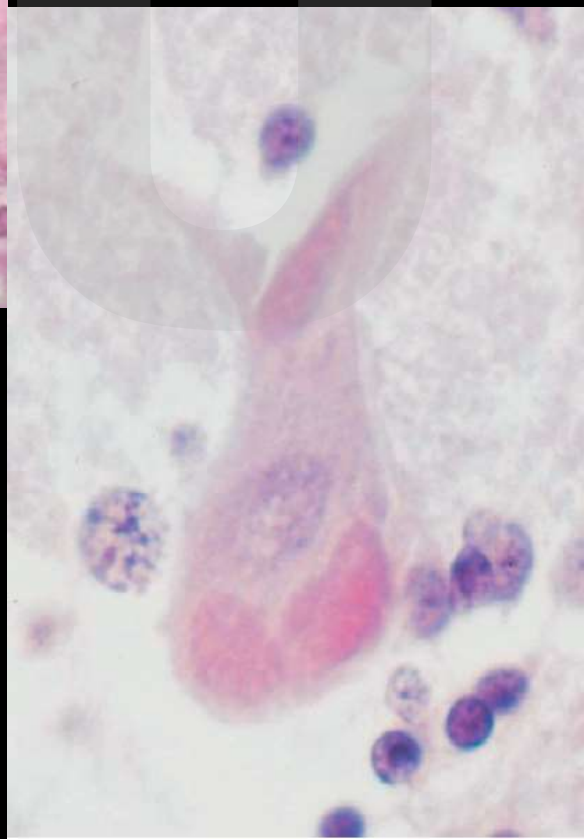

2
5b
4
3
5b
5a
2
5c
1
1
5a

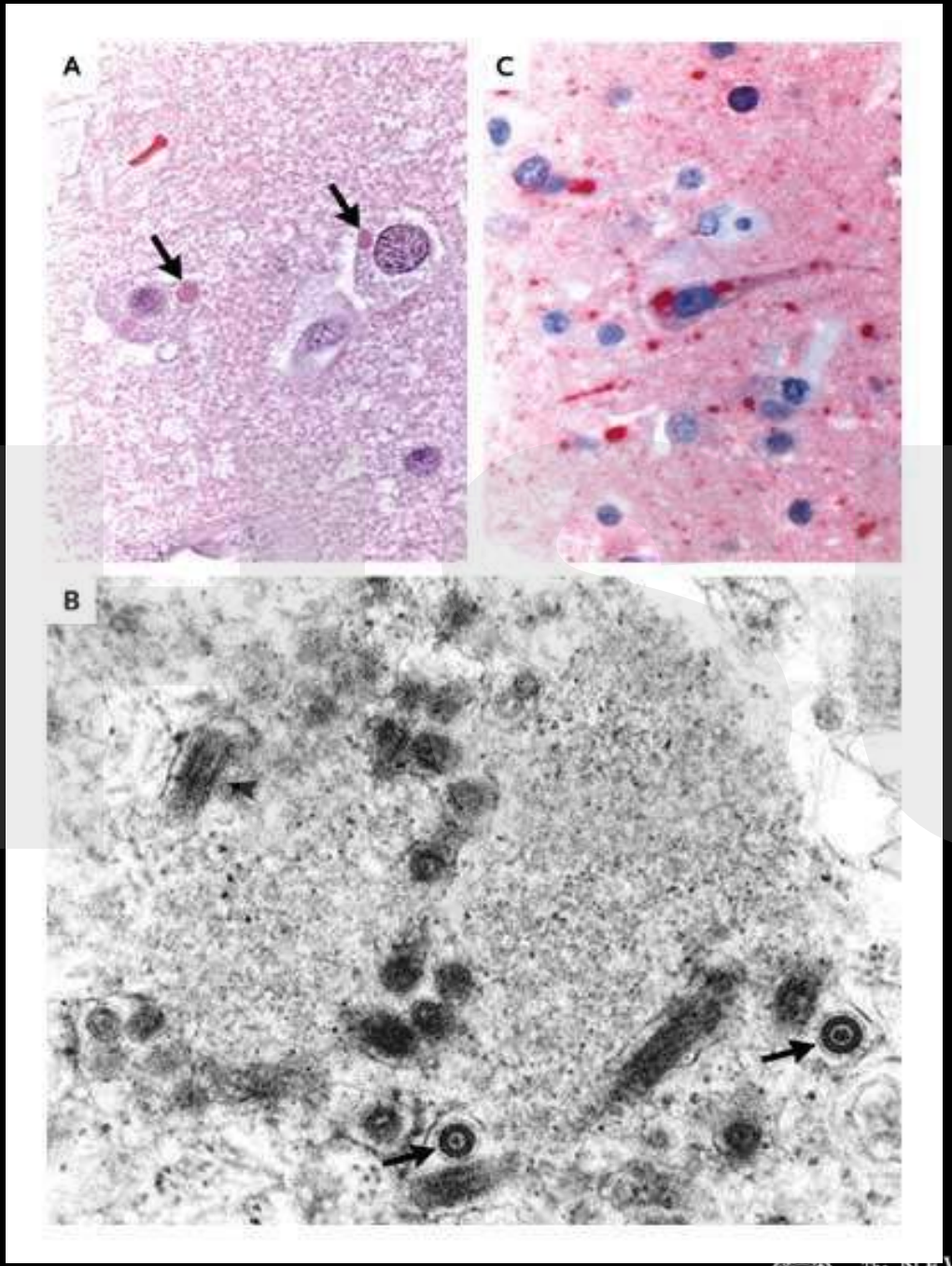
Lack of Immune Response

- In CNS rabies evades immune response
- Does not stimulate interferon or other antiviral response
- Can see antibody production in clinical infection

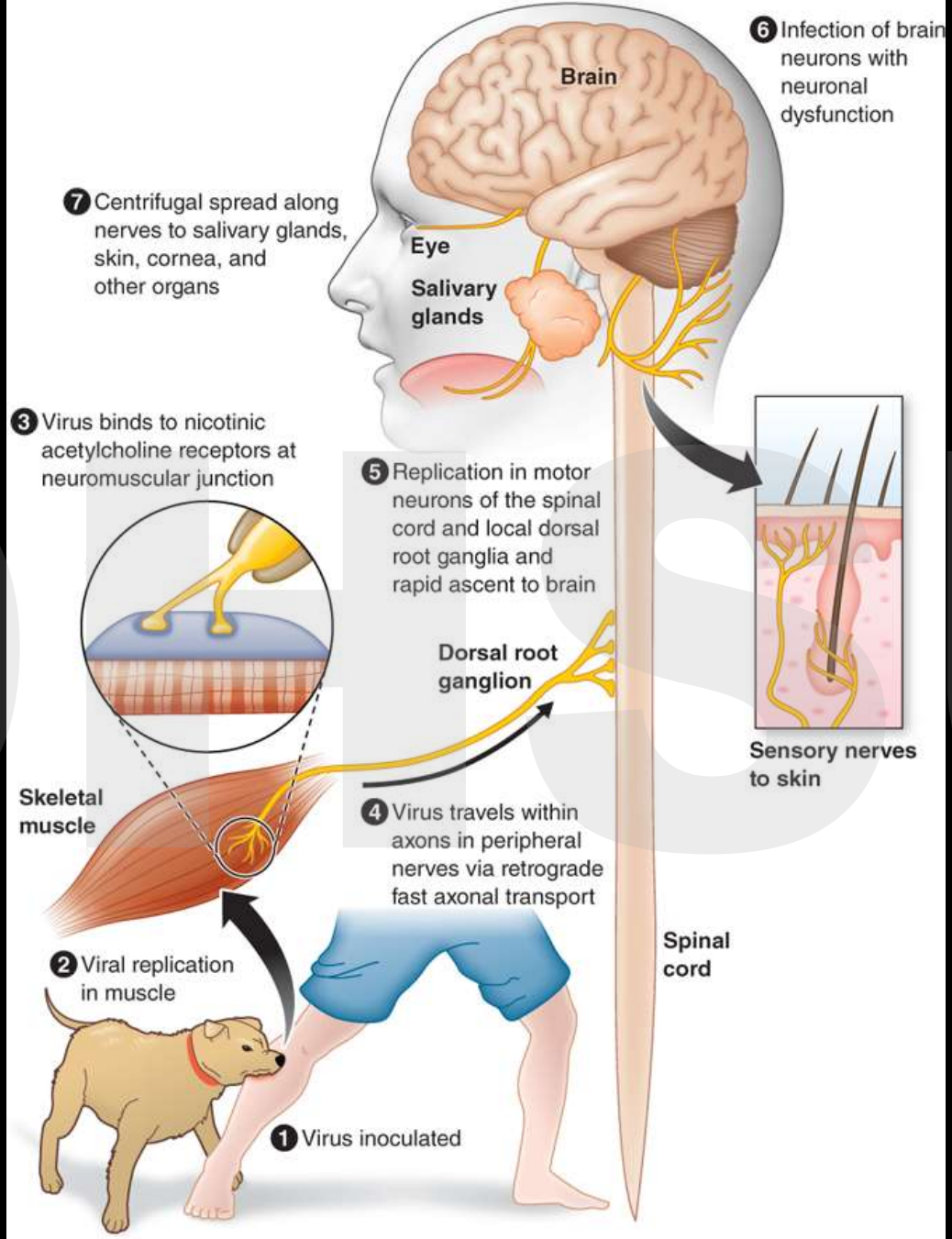
Pathology

- Only mild changes seen in the CNS!
  - Negri bodys: Viral replication (50%)
- No inflammatory response
- “Need” intact nervous system to spread virus





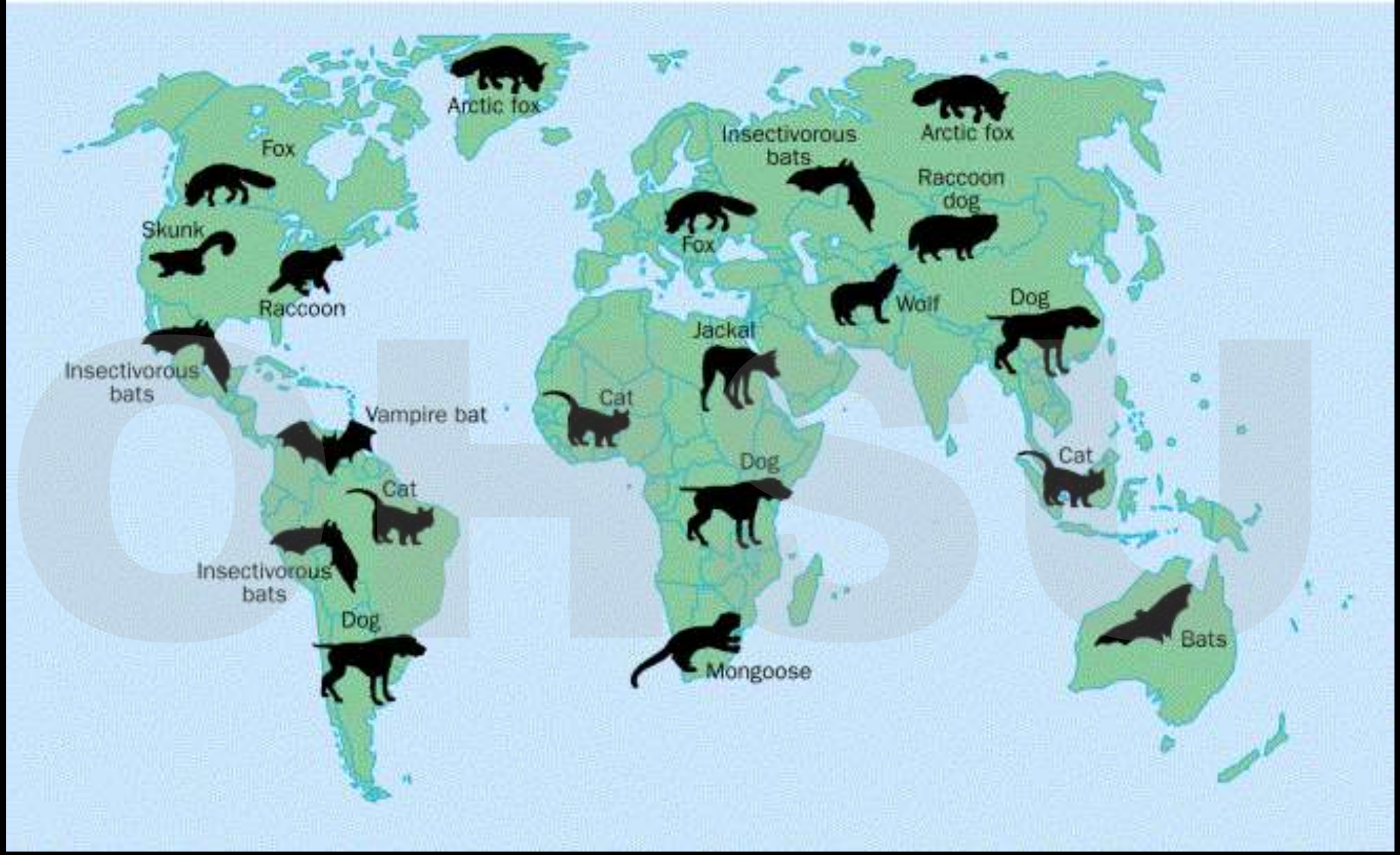
Srinivasan A et al. N Engl J Med 2005;352:1103-1111.



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

What Animals Get Rabies?

OHSU



Global distribution of mammalian rabies reservoirs and vectors

Rupprecht CE. The Lancet Infectious Diseases. 2002

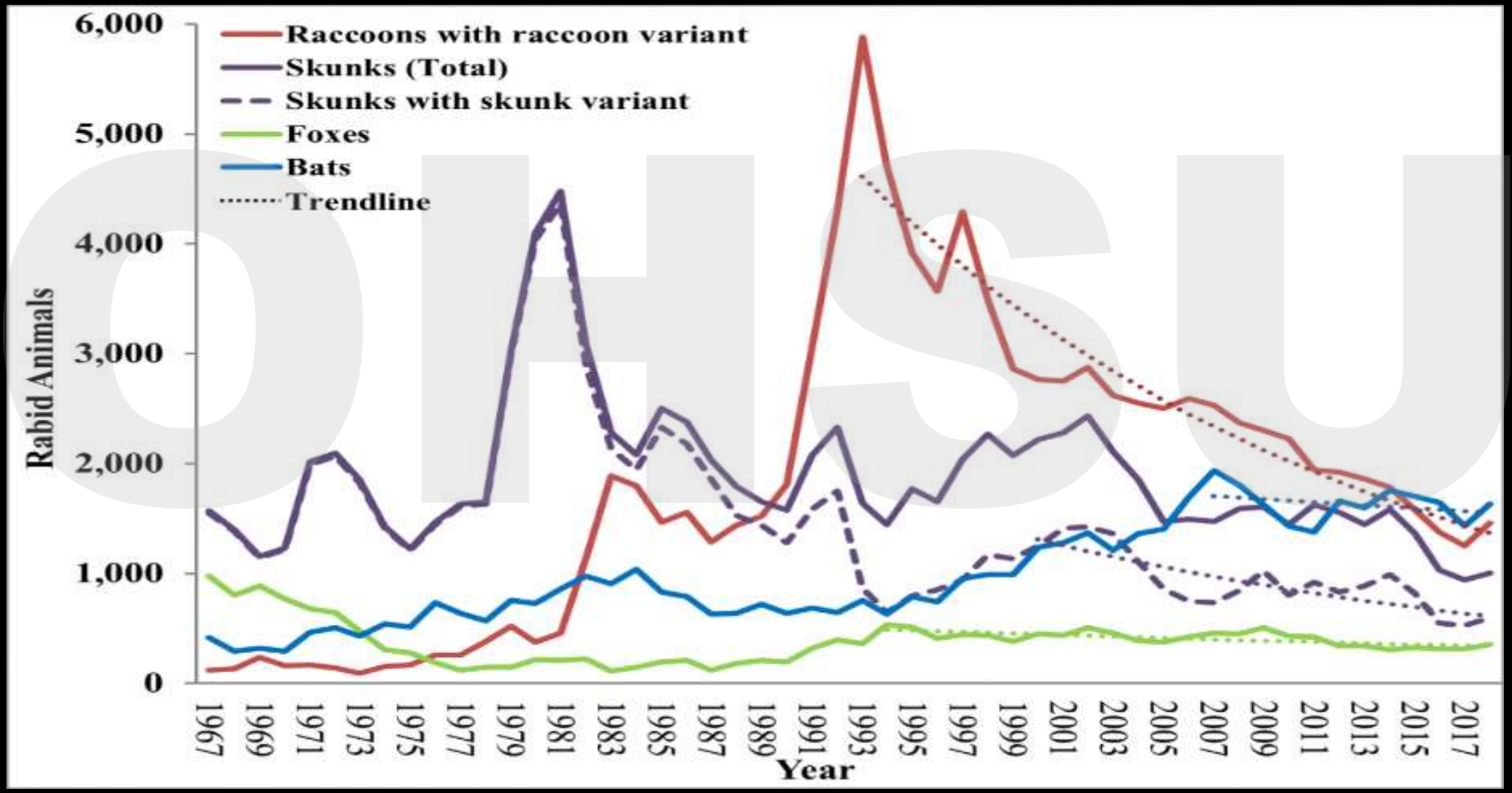
USA

- More rabid cats then dogs in USA
- Dogs biggest threat world-wide
  - Also foxes, mongooses, raccoons, jackals, and wolves

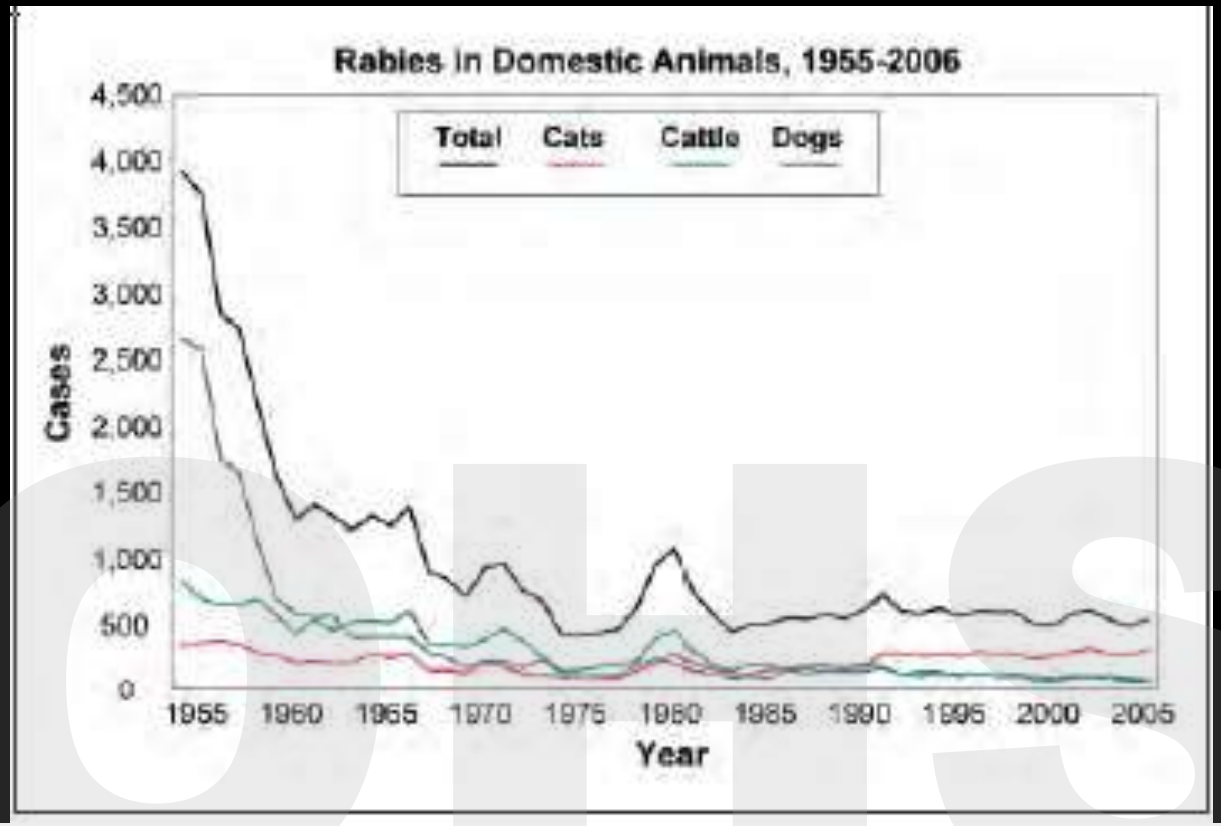
European Vectors

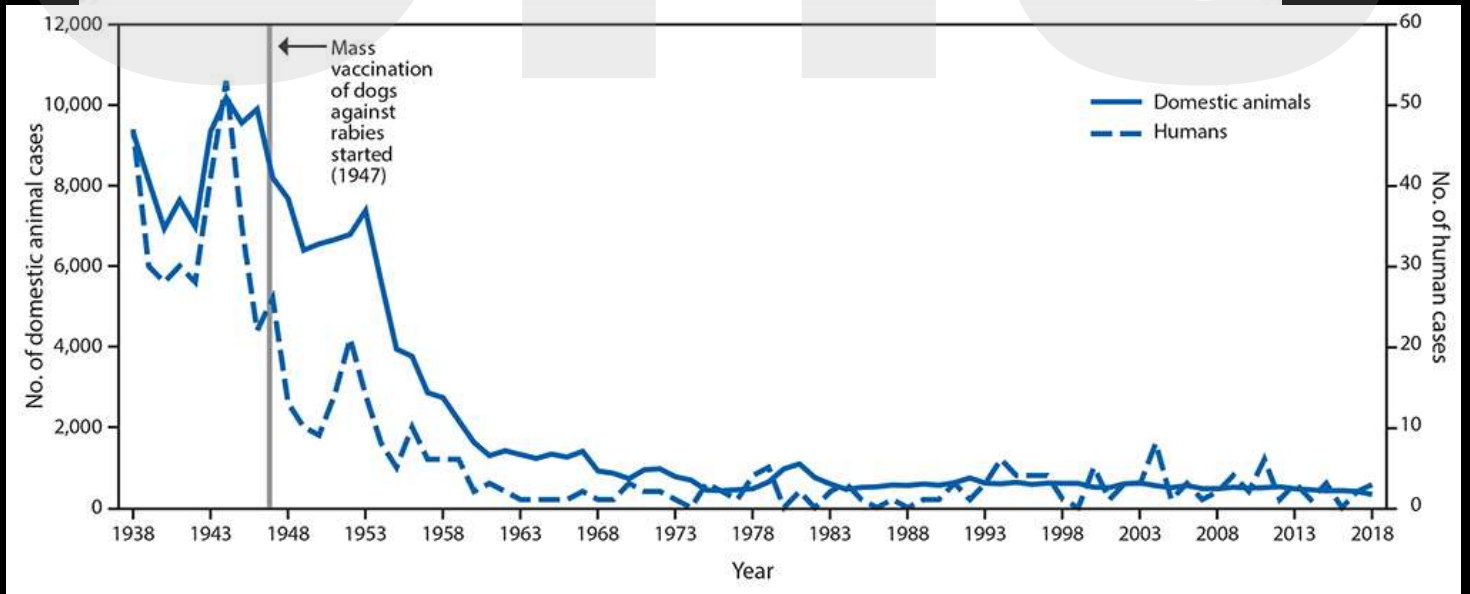
- Dog rabies also eliminated
- Red fox biggest reservoir
- Bats not rabid
  - Have rabies like viruses

USA Animals



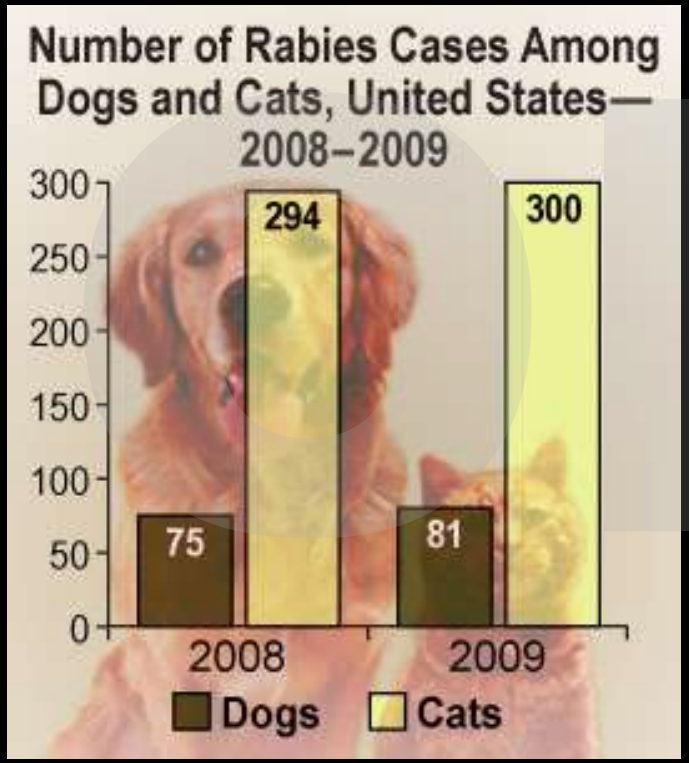
CDC

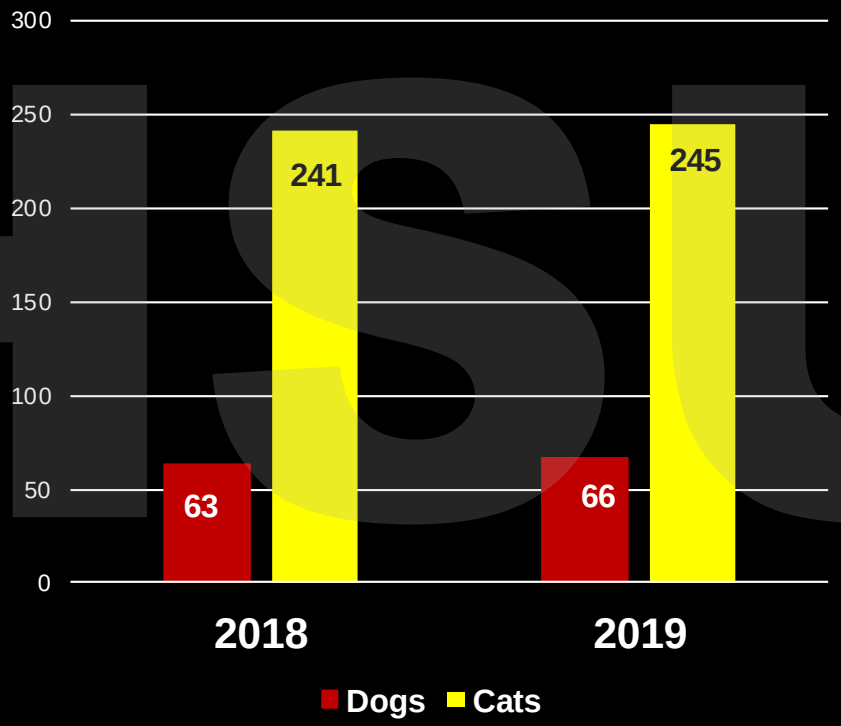

Rabies in Domestic Animals, 1955-2006
Total
Cats
Cattle
Dogs
Cases
4,500
4,000
3,500
3,000
2,500
2,000
1,500
1,000
500
0
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
Year


Mass vaccination of dogs against rabies started (1947)
Domestic animals
Humans
No. of domestic animal cases
No. of human cases
12,000
10,000
8,000
6,000
4,000
2,000
0
60
50
40
30
20
10
0
1938
1943
1948
1953
1958
1963
1968
1973
1978
1983
1988
1993
1998
2003
2008
2013
2018
Year

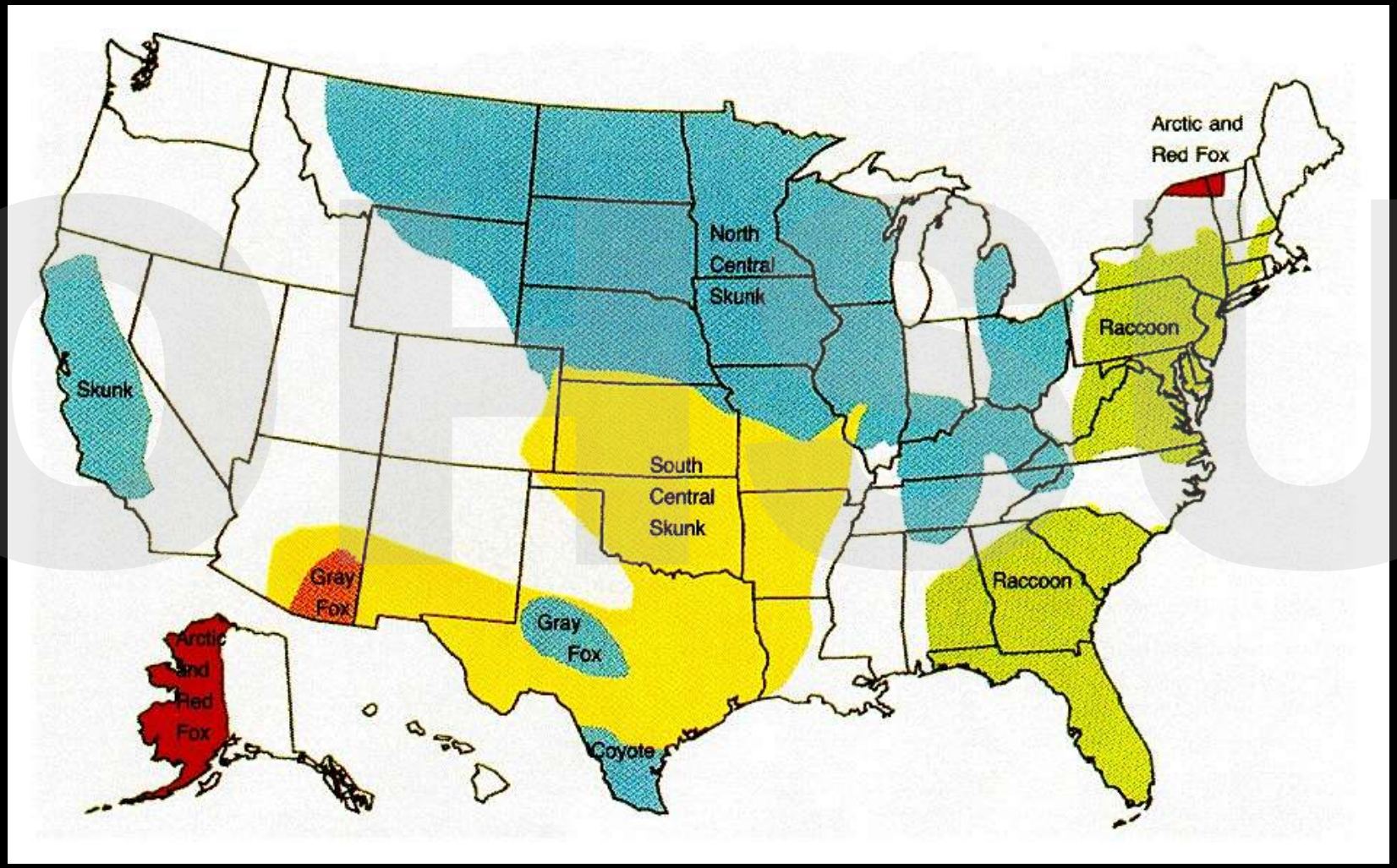
CDC

Dogs and Cats





Five Antigenically Distinct Strains of Rabies Virus and Predominant Species of Wildlife Affected in the United States in 1992.



Fishbein DB, Robinson LE. N Engl J Med 1993;329:1632-1638.

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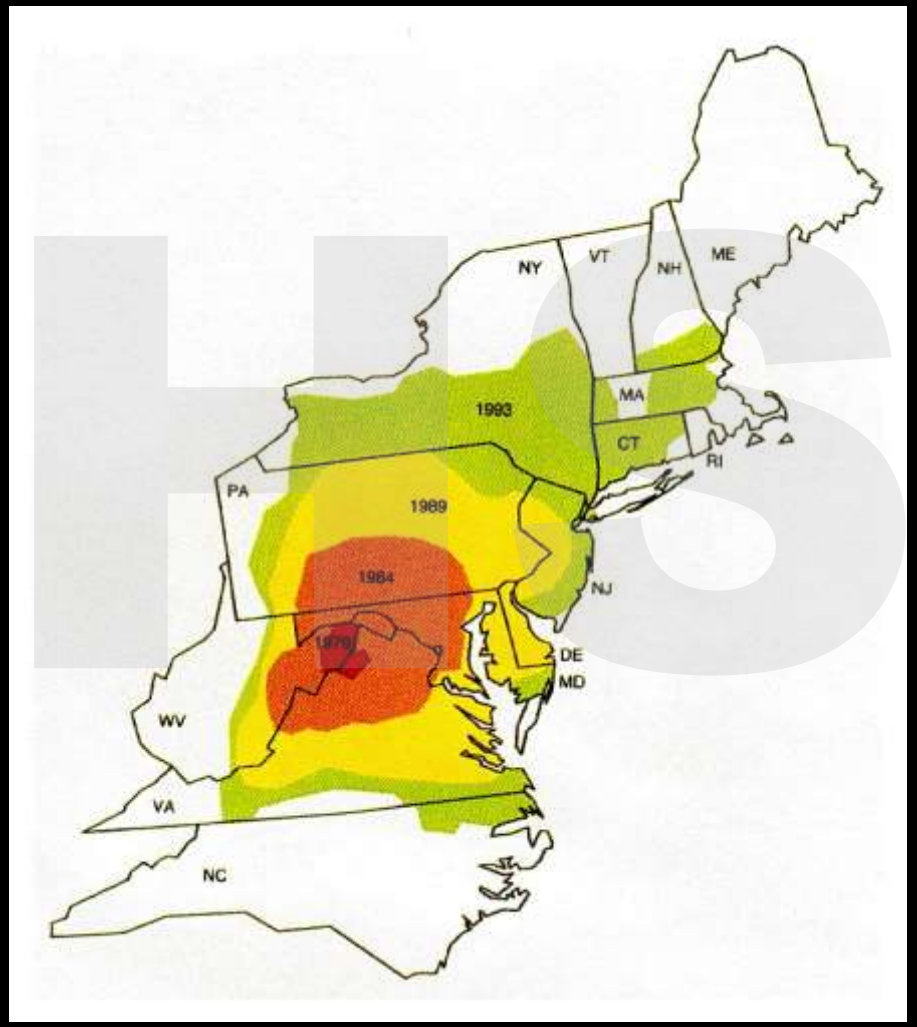
Spread of the Mid-Atlantic Rabies Epizootic among Raccoons from 1977 to 1993.



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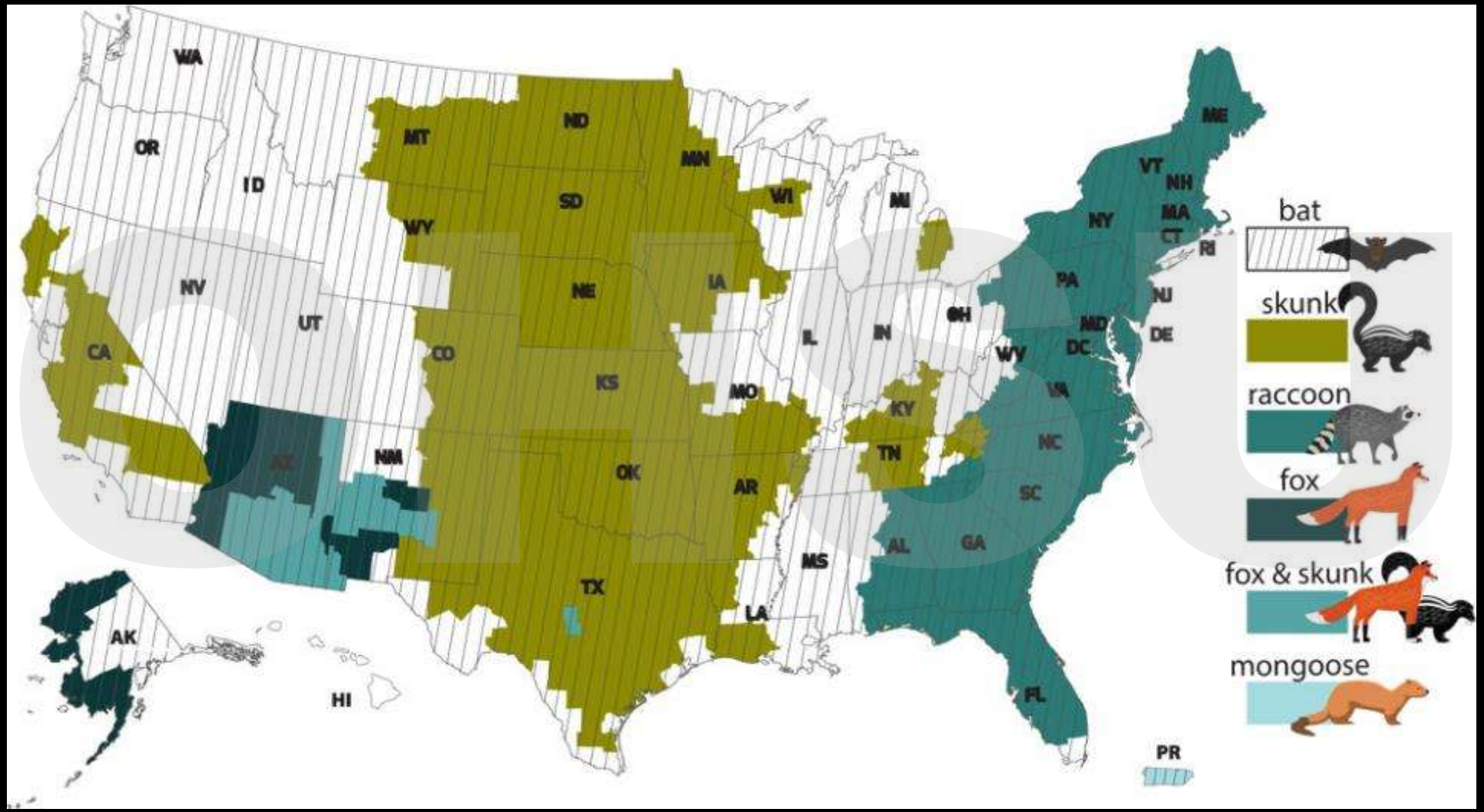
WA
OR
CA
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NV
MT
WY
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CO
NM
ND
SD
NE
KS
OK
TX
MN
IA
MO
AR
LA
WI
IL
MS
MI
IN
KY
TN
AL
OH
WV
GA
FL
SC
NC
VA
PA
NY
MD
DC
DE
NJ
CT
RI
MA
VT
NH
ME
AK
HI
PR
bat
skunk
raccoon
fox
fox & skunk
mongoose

Other Animals

- Carnivores – 2-20%
- Rodents/rabbits – very rare
  - Exception groundhog

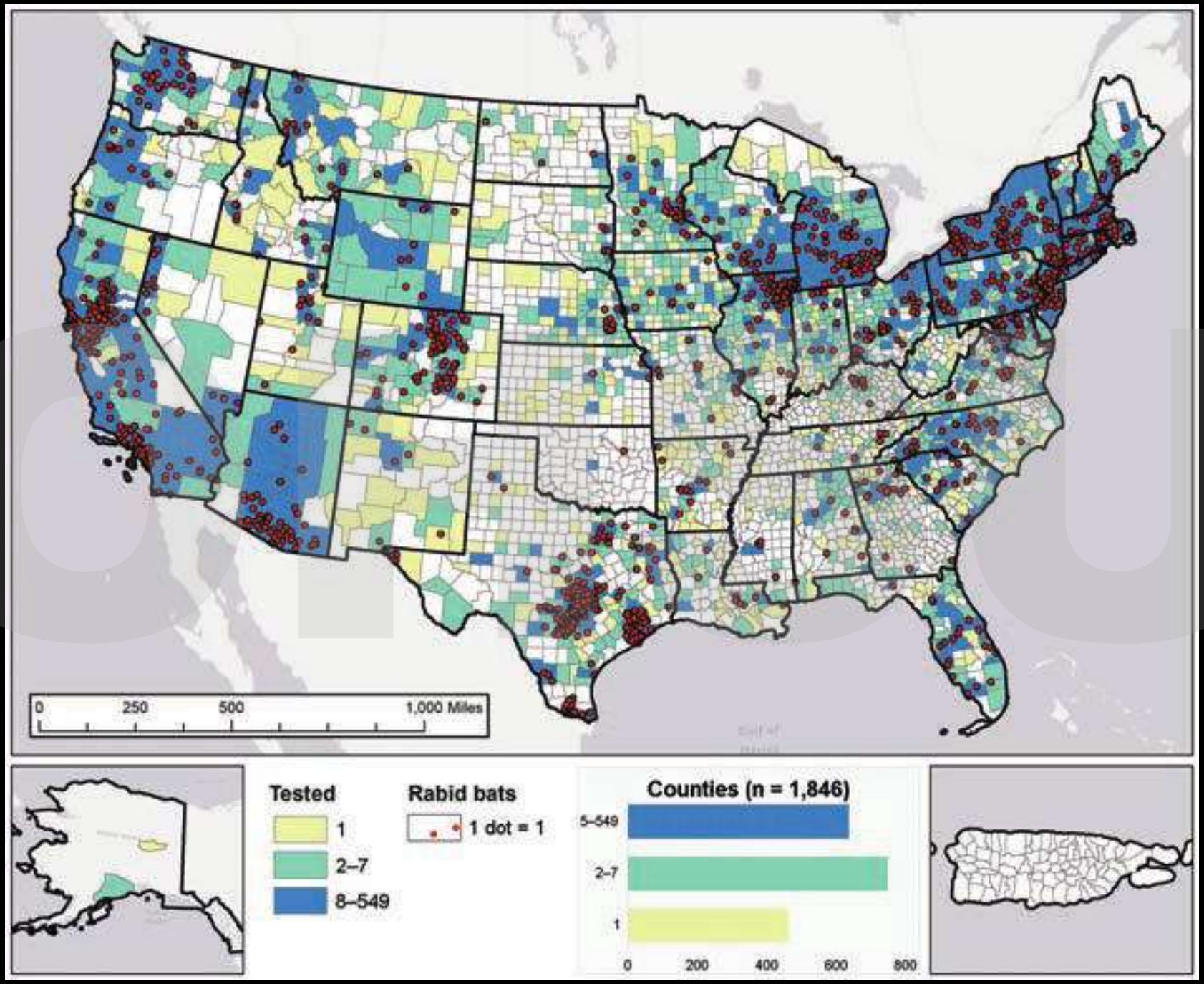
for rabies that yielded positive results for 2014 through 2019.

Table 2—Number of animals reported to be rabid in the United States, including Puerto Rico, and percentages of samples tested

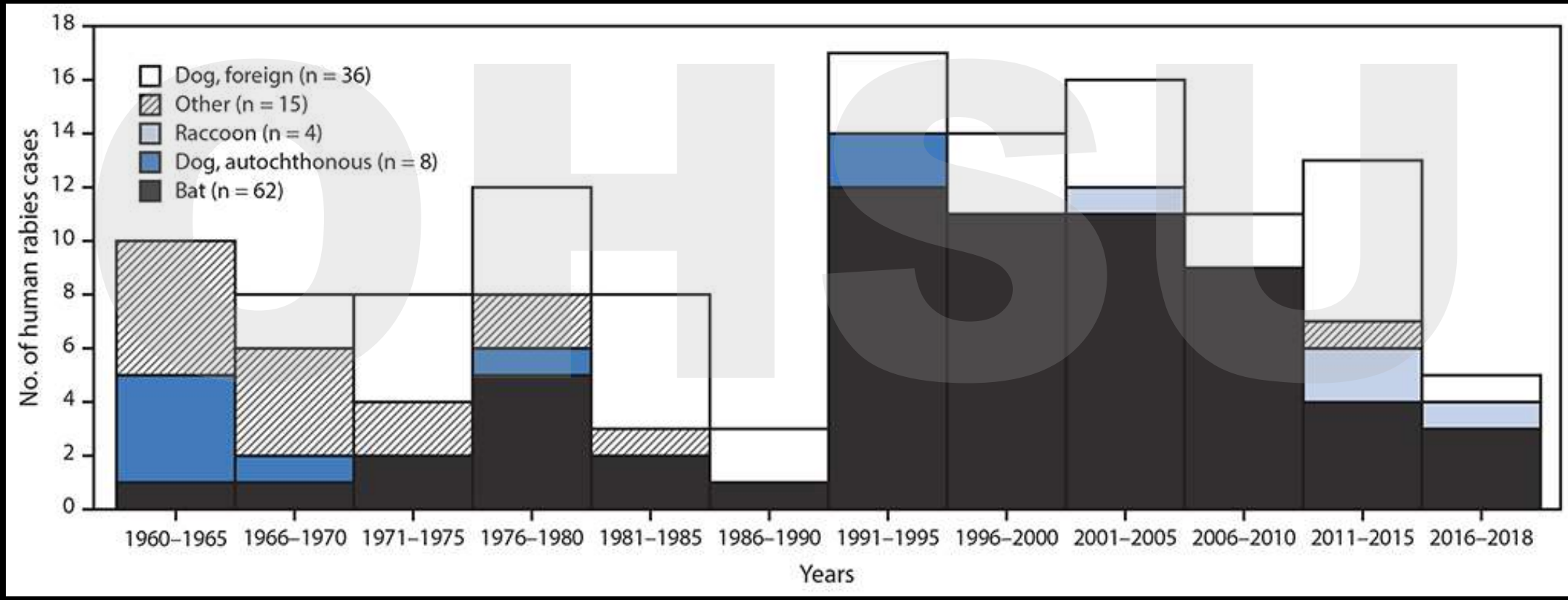
Animals	2019			2014–2018			
	No. of rabid animals	No. of animals tested with positive or negative result	Percentage of samples with positive result	No. of rabid animals		Percentage of samples with positive result	
				Mean	95% CI	Mean	95% CI
Domestic animals							
Cats	245	21,169	1.2	258	238–278	1.2	1.0–1.3
Cattle	39	985	4.0	60	30–91	5.0	3.0–7.0
Dogs	66	22,472	0.3	62	57–66	0.3	0.3–0.3
Horses and donkeys	22	777	2.8	18	10–25	2.4	1.4–3.3
Sheep and goats	10	624	1.6	10	8–13	1.7	1.2–2.2
Wildlife							
Bats	1,387*	25,327	5.5*	1,635	1,482–1,787	6.3	5.8–6.8
Raccoons	1,545	13,171	11.7	1,524	1,264–1,783	12.2	9.9–14.5
Skunks	915	3,796	24.1	1,185	839–1,532	26.3	21.9–30.7
Foxes	361*	1,854	19.5	324	300–348	18.8	16.9–20.6
All domestic animals	385	46,230	0.8	410	371–449	0.9	0.8–0.9
All wildlife	4,305	48,540	8.9	4,761	4,028–5,494	9.7	8.5–10.8
All animals	4,690	94,770	4.9	5,171	4,414–5,928	5.3	4.8–5.8

*Significantly different from mean value for 2014 through 2018.

Bats!


0
250
500
1,000 Miles
Tested
1
2–7
8–549
Rabid bats
1 dot = 1
Counties (n = 1,846)
5–549
2–7
1
0
200
400
600
800

Human Cases


Dog, foreign (n = 36)
Other (n = 15)
Raccoon (n = 4)
Dog, autochthonous (n = 8)
Bat (n = 62)
No. of human rabies cases
0
2
4
6
8
10
12
14
16
18
1960–1965
1966–1970
1971–1975
1976–1980
1981–1985
1986–1990
1991–1995
1996–2000
2001–2005
2006–2010
2011–2015
2016–2018
Years

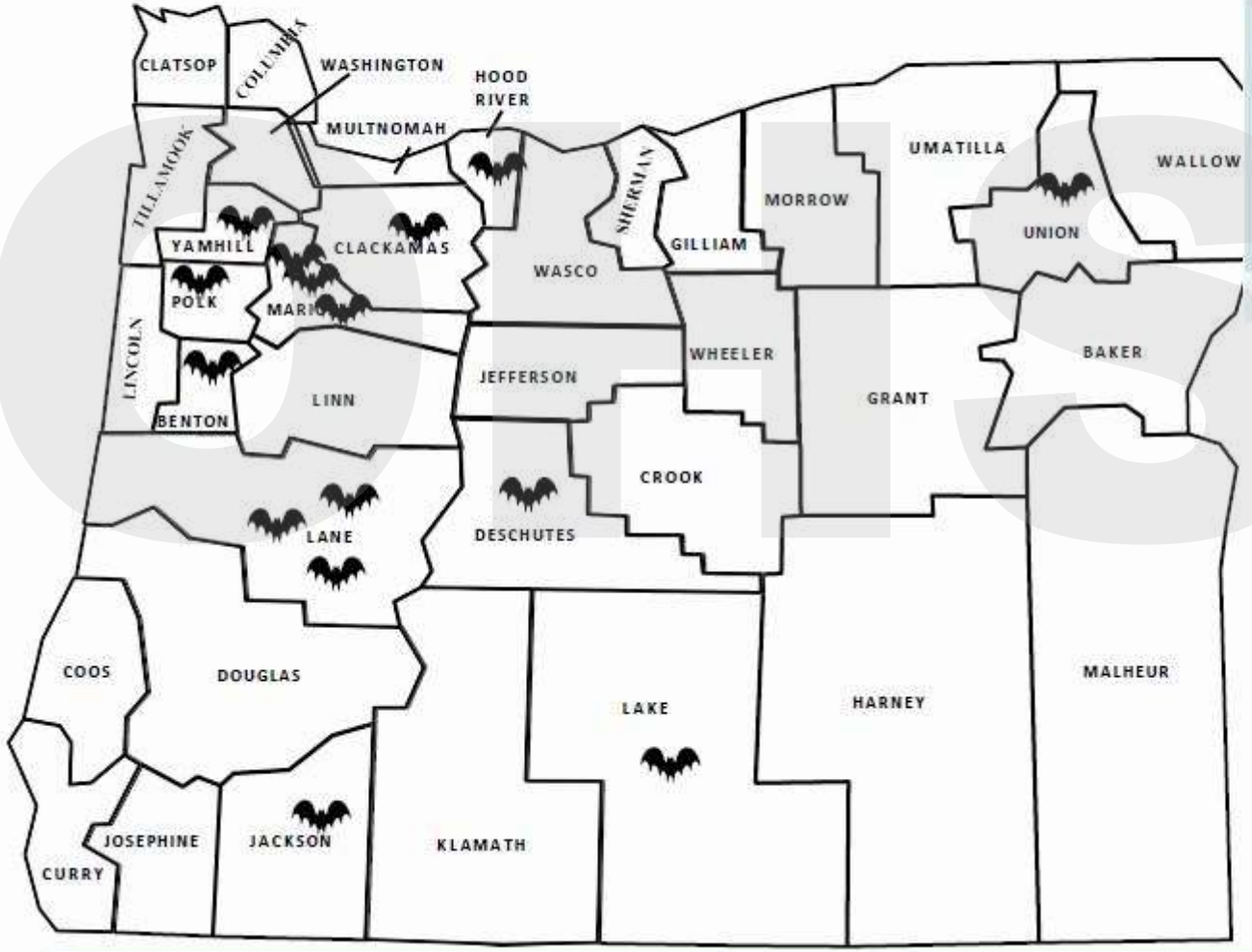
Date of onset	Date of death	Reporting state	Age (y)	Sex	Exposure*	Rabies virus variant†
16-Oct-18	4-Nov-18	UT	55	M	Contact	Bat, Tb
15-Jul-18	23-Aug-18	DE	69	F	Unknown	Raccoon, eastern United States
28-Dec-17	14-Jan-18	FL	6	M	Bite	Bat, Tb
6-Oct-17	21-Oct-17	FL	56	F	Bite	Bat, Tb
5-May-17	21-May-17	VA	65	F	Bite	Dog, India
25-Nov-15	1-Dec-15	PR	54	M	Bite	Dog-mongoose, Caribbean
17-Sep-15	3-Oct-15	WY	77	F	Contact	Bat, Ln
30-Jul-15	24-Aug-15	MA	65	M	Bite, Philippines	Dog, Philippines
12-Sep-14	26-Sep-14	MO	52	M	Unknown	Bat, Ps
16-May-13	11-Jun-13	TX	28	M	Unknown, Guatemala	Dog, Guatemala
31-Jan-13	27-Feb-13	MD	49	M	Kidney transplant	Raccoon, eastern United States
6-Jul-12	31-Jul-12	CA	34	M	Bite	Bat,Tb
22-Dec-11	23-Jan-12	MA	63	M	Contact	Bat, My sp
3-Dec-11	19-Dec-11	SC	46	F	Unknown	Bat,Tb
1-Sep-11	14-Oct-11	MA	40	M	Contact, Brazil	Dog, Brazil
21-Aug-11	1-Sep-11	NC	20	M	Unknown (organ donor)§	Raccoon, eastern United States
14-Aug-11	31-Aug-11	NY	25	M	Contact, Afghanistan	Dog, Afghanistan
30-Jun-11	20-Jul-11	NJ	73	F	Bite, Haiti	Dog, Haiti
30-Apr-11	Survived	CA	8	F	Unknown	Unknown
24-Dec-10	10-Jan-11	WI	70	M	Unknown	Bat, Ps
2-Aug-10	21-Aug-10	LA	19	M	Bite, Mexico	Bat, Dr
23-Oct-09	20-Nov-09	VA	42	M	Contact, India	Dog, India
20-Oct-09	11-Nov-09	MI	55	M	Contact	Bat, Ln
5-Oct-09	20-Oct-09	IN	43	M	Unknown	Bat, Ps
25-Feb-09	Survived	TX	17	F	Contact	Bat, unknown

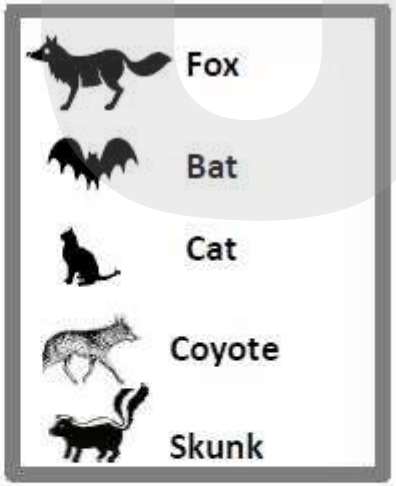
Oregon 2000-19

- Cat: 0.12% (2)
- Dog: 0.0%
- Fox: 16% (27)
- Bats 8.3% (226)
- Other: 3 coyote, 1 goat and 1 skunk

Rabies-positive Animals
Oregon, 2020

Month	County	Species
May	Lane	Bat
June	Marion	Bat
	Benton	Bat
	Clackamas	Bat
July	Hood River	Bat
August	Deschutes	Bat
September	Marion	Bat
	Jackson	Bat
	Marion	Bat
	Yamhill	Bat
	Lake	Bat
	Union	Bat
	Lane	Bat
	Lane	Bat
October	Polk	Bat



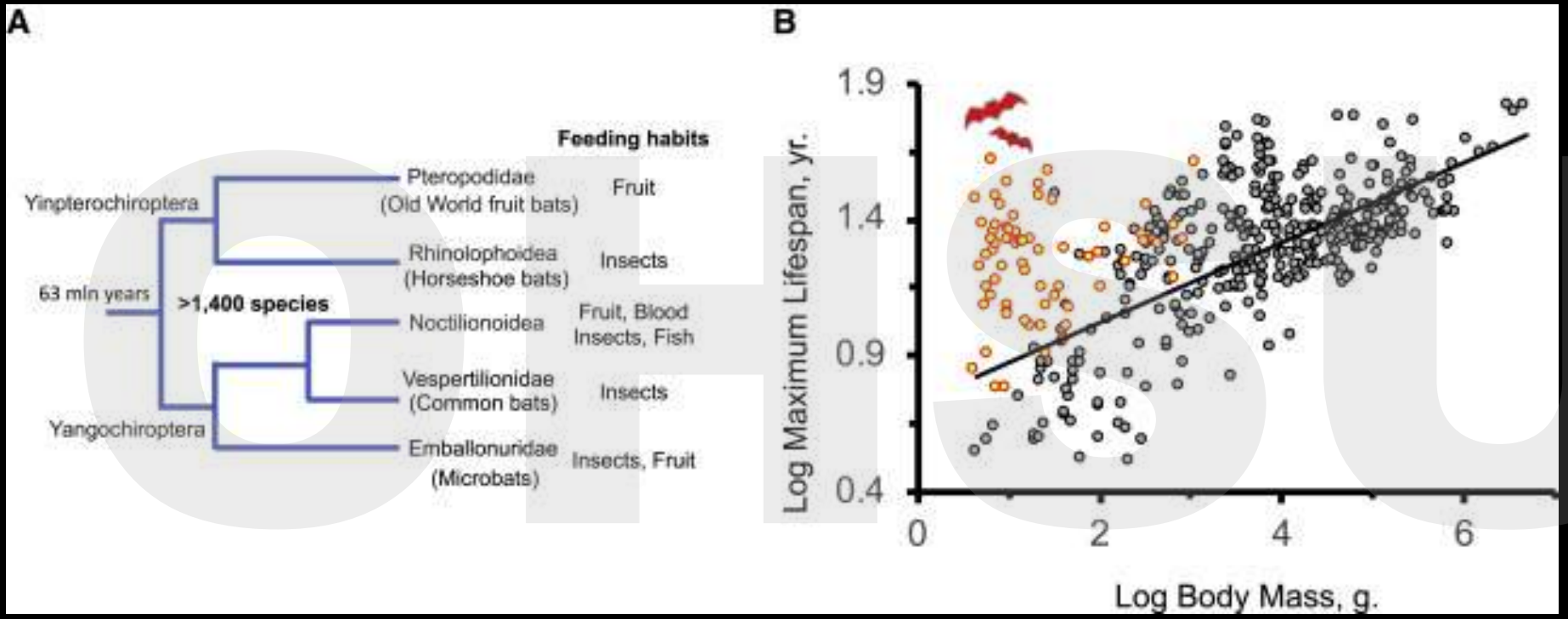


Updated: December 2020

Oregon Health Authority

Bats!

- 1,400 species
- Only flying mammal
- Can reach 100 mph
- Very longed lived!
  - 20-40 years


A
Feeding habits
Yinpterochiroptera
Pteropodidae
(Old World fruit bats)
Fruit
Rhinolophoidea
(Horseshoe bats)
Insects
63 mln years
>1,400 species
Noctilionoidea
Fruit, Blood
Insects, Fish
Vespertilionidae
(Common bats)
Insects
Yangochiroptera
Emballonuridae
(Microbats)
Insects, Fruit
B
Log Maximum Lifespan, yr.
1.9
1.4
0.9
0.4
0
2
4
6
Log Body Mass, g.

Bats

- Resistant to viruses
  - Rabies
  - Ebola
  - Marburg
  - MERS
  - SARS
  - COVID

Bats

- Downregulated immune response
  - Decreased inflammasomes
  - Decrease recognition of DNA
- Why?
  - Flight can induce inflammation
  - Bats live in huge colonies

Bats

- Very effective transmitter of rabies
- Sharp little teeth
- Lick claws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A
B

Bat Rabies

- Bat rabies variant
  - More efficient at infecting epithelial cells
  - More efficient at slightly lower temperatures
- Better able to replicate in skin
- Small bites effective

Clinical Rabies

- Incubation
- Prodrome
- Acute neurologic syndrome
- Coma
- Death

Incubation

- Varies!
- Range 12 days – 10 years!
- Median 80 days
- Faster if
  - Bite head/neck
  - Deep wounds

Prodrome

- Wound site
  - Paresthesia, itching, pain
- Limb
  - Radiculopathy
  - Myoclonic jerks
  - Percussion myoedema
  - Choreiform movements
- Viral prodrome
- NPR Radiolab “Rodney vs Death”

Furious Rabies

- Irritability
- Agitation
- Hyperesthesia
- Autonomic disturbances
  - Hypersalivation
  - Sweating
  - Blood pressure swings

Furious Rabies

- Dysautonomia
  - Priapism, cathecholamine surges
- Orofacial dyskinesia
- Can have periods of complete normalcy!

Hydrophobia

- Triad
  - Inspiratory muscle spasm
  - Painful laryngospasm
  - Terror of drinking
- Aerophobia
- Extension arms/legs
- Seizure/cardiac arrest

Paralytic Rabies

- ~ 20%
- More common:
  - Vampire bats bites
  - Incomplete vaccination
- Flaccid paralysis
- Dead due to respiratory arrest

What Kills People in Rabies?

- Mystery!
- Asphyxiation
- Respiratory arrest
- Seizures
- Myocarditis

Differential

- Furious rabies
  - Delirium tremors
  - Drugs
  - Tetanus
    - Shorter incubation
    - No encephalitis

Differential

- Paralytic
  - Guillain-Barre
  - Arbovirus
  - Herpetic simiae (monkey bite)

Diagnosis

- Suspicion!
  - 1/3 diagnosed at autopsy
- Skin biopsy (nape of neck)
  - Immunofluorescence most sensitive
  - PCR being used more now
- CDC
  - Saliva for PCR/viral culture
  - Skin biopsy for PCR/IF
  - CSF for PCR/viral culture

Treatment

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Traditional

- Madstones
- Herbal remedies
- Put between two mattresses
- Rooster anus
- Prevention
  - Cauterization
  - Amputation

THE TERRE HAUTE MADSTONE

MARCH 24, 2015 STEPHEN J. TAYLOR

APPLYING THE MADSTONE TO ARM OF A GIRL WHO WAS BITTEN BY A RABID DOG.

Modern Treatment

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Treatment

- Palliative Care
  - Sedation/quiet room
  - Benzodiazepines
  - Morphine
  - Anticholinergics

Treatment: Milwaukee Protocol

- 2004 survival unvaccinated patient
- Protocol
  - Therapeutic coma
  - NMDA antagonistic
- Probably never worked again
- Now abandoned

Treatment

- ICU care
- Vaccination
- Antivirals
  - Interferon (IT)
  - Ribavirin
  - Amantadine
- Hypothermia?

“Better” Prognosis

- Young age
- Any type of vaccination
- Mild disease at onset
- Bat variant

The Grim Reality

- 28 survivors
- 5 with no/mild sequelae
- 18 with profound deficits

Prophylaxis

- 16-39,000 people in USA get prophylaxis

Wound Cleaning

- Vigorous wound cleansing with soup and water crucial first step
- HRIG -> vaccinations
- If previous vaccination no HRIG

Local Therapy

Treatment	Infection	%
Tap water	1/19	5.3
20% soap	2/19	10.5
Ivory soap	2/20	10
Benzalkonium	2/20	10
Ivory soap/serum	2/20	10
Control	18/20	90

Bull Wld Hth Org 28:477, 1963

Risk Assessment of Bite

- Deep wounds high risk
  - Especially if into muscle
- Face/neck/head wounds
  - Short latent periods

Rabies Immune Globulin

- Humans (horses)
- 20 IU/KG
  - Infiltrated around wound
  - Rest gluteal
- Monoclonal antibodies in development

Vaccination History

- Pasteur – air dried rabbit spinal cords
- Phenol treated spinal cords
  - Large volume shots 10ml
  - Abdomen 14-23 injections
- Human diploid cells

Rabies Vaccine

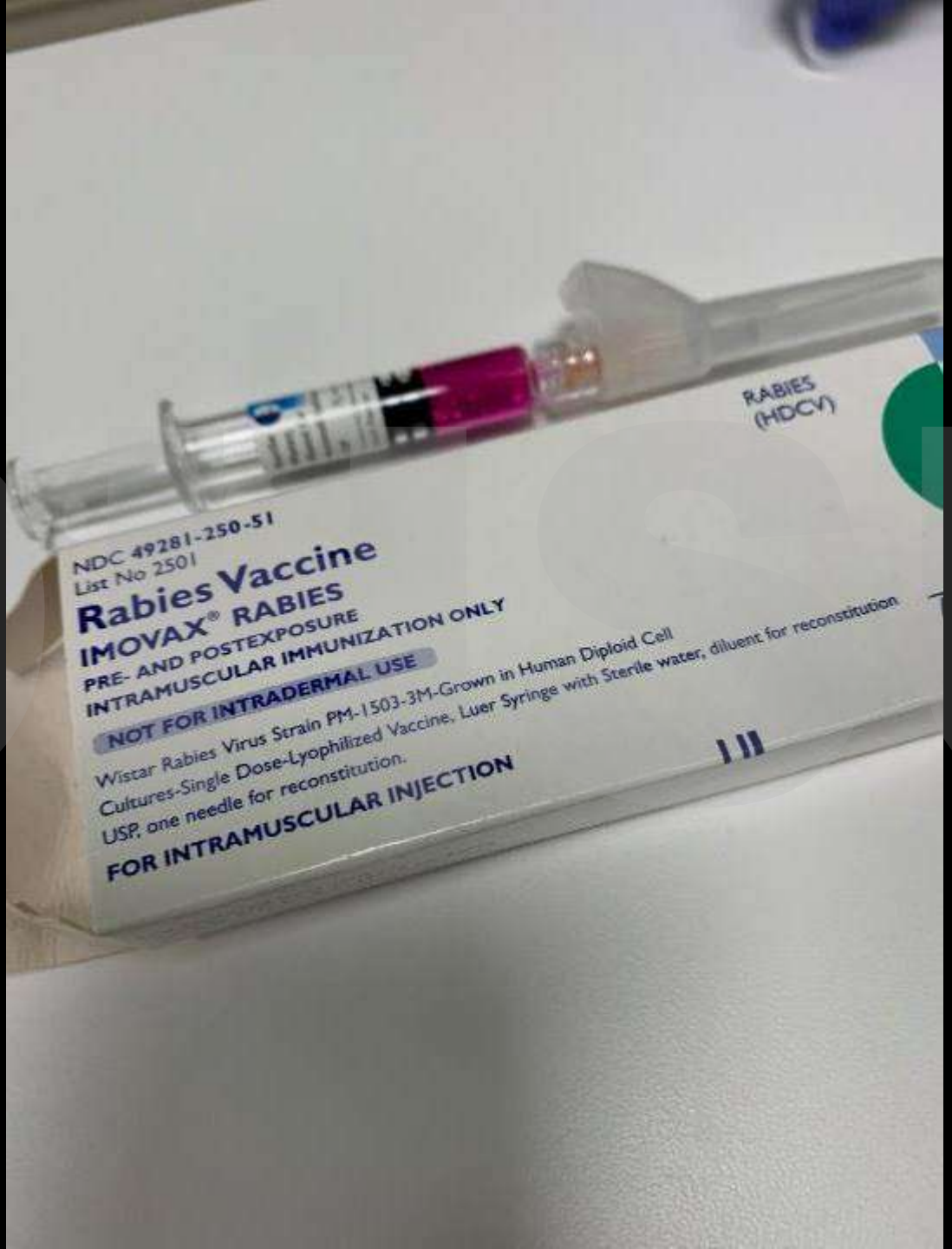
- Sources
  - Human diploid cell lines
  - Chick embryo cells
  - Vero cell
  - Duck embryo cells
- IM deltoid region
- NEVER gluteal
- mRNA vaccine in development

Pre-exposure Prophylaxis

- Occupational risk
- Travel to high risk areas
- Vaccine days 0, 3, 28

Post-Exposure Prophylaxis

- Human rabies immunoglobulin (HRIG)
  - Inject around wound
  - Rest buttocks
- Vaccination
  - Days 0, 3, 7, 14


RABIES
(HDCV)
NDC 49281-250-51
List No 2501
Rabies Vaccine
IMOVAX® RABIES
PRE- AND POSTEXPOSURE
INTRAMUSCULAR IMMUNIZATION ONLY
NOT FOR INTRADERMAL USE
Wistar Rabies Virus Strain PM-1503-3M-Grown in Human Diploid Cell
Cultures-Single Dose-Lyophilized Vaccine, Luer Syringe with Sterile water, diluent for reconstitution
USP, one needle for reconstitution.
FOR INTRAMUSCULAR INJECTION

When to Prophylaxes

- Bite by wild creature
  - Exception: lagomorphs/small rodents
- Unprovoked pet bites
  - Watch animal for 10 days

Prophylaxis Failure

- Improper wound cleaning
- Inadequate/counterfeit RIG
- Absence of RIG infiltration
- Counterfeit RIG/vaccine
- Vaccine into gluteal region

Risk Assessment

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Did Animal Exposure Occur?

- Was there a mammal bite?
- Open wound exposure to salvia
- Bats
  - Bite
  - Crawl/lick scratches

Bats Exposure

- Any bat exposure is suspect
  - Any contact
    - Bite, scratch, mucous membrane exposure
  - Same room as bat
    - Sleeping
    - Unattended child
    - Disable/intoxicated person

Transplant

- Corneal transplant
  - Stricter guidelines
- Solid organ transplant
  - Prophylaxis can be effective

Low Risk Wild Animal

- Small rodents, rabbits
- Very rare to have rabies
  - Usually killed by infected larger animal

High Risk

- Bat, raccoon, skunk, woodchuck, coyote, fox
- Test animal
- If not possible prophylaxis

Dog, Cat, Ferret (Pets)

- Healthy
  - 10 day quarantine
    - Gets sick prophylaxis
- Can't catch
  - Prophylaxis

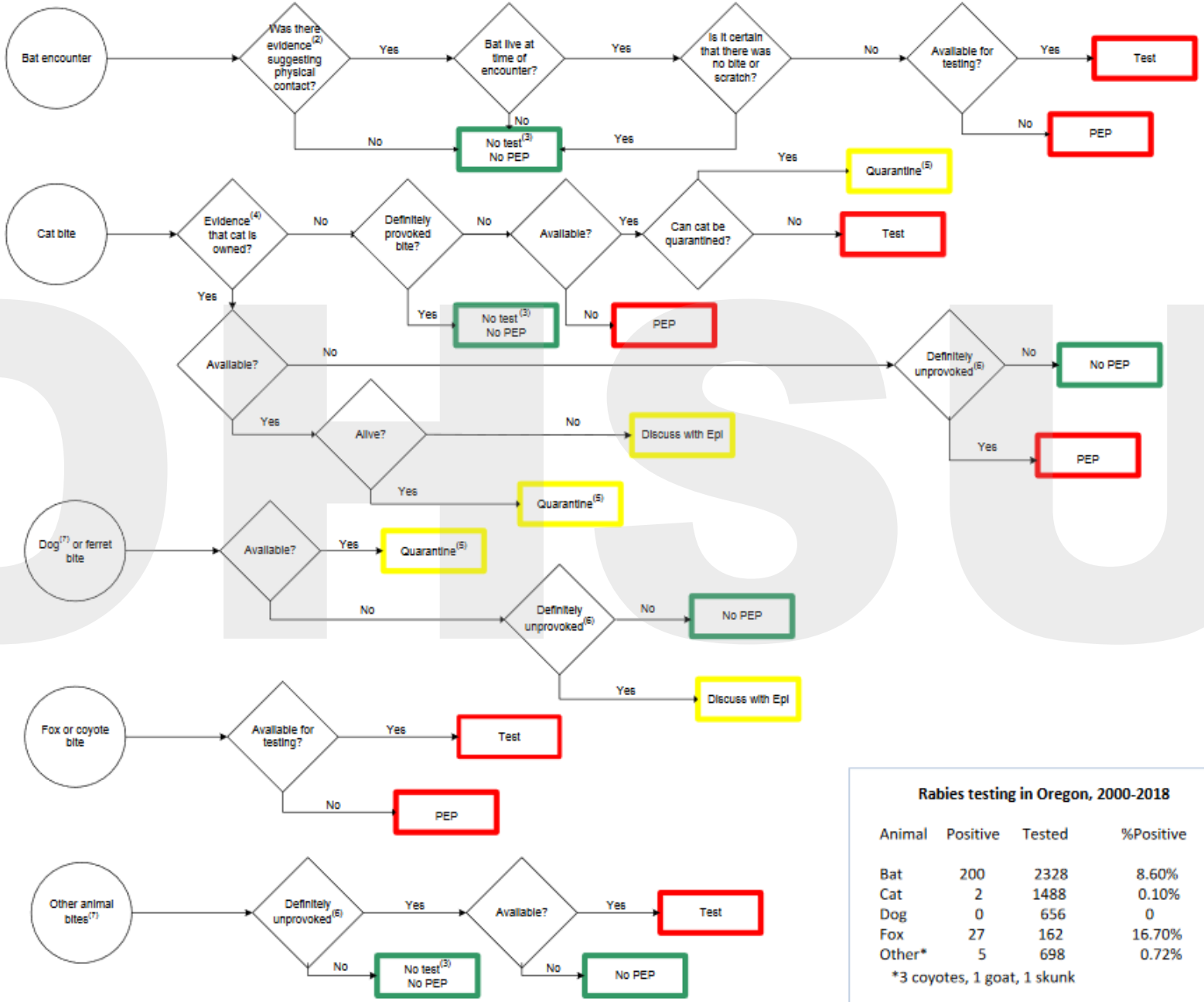
Small Pets/Livestock

- Always indoors
  - No
- Sometimes outdoors
  - Case by case
- Livestock
  - Case by case

Unprovoked Attack

- Always suspicious!
- Doing dumb things to animals is provocation

Algorithm for Prevention of Rabies After Animal Encounters in Oregon [1]



Rabies testing in Oregon, 2000-2018

Animal	Positive	Tested	%Positive
Bat	200	2328	8.60%
Cat	2	1488	0.10%
Dog	0	656	0
Fox	27	162	16.70%
Other*	5	698	0.72%

*3 coyotes, 1 goat, 1 skunk

Is Rabies more Common?

- 1/3 diagnosed post-mortem
- Cases missed?
- Epidemiology studies suggest higher infection rate

Non-Lethal Rabies?

- Studies showing both animals and humans with anti-rabies antibodies
  - Nonspecific antibodies
  - Subclinical infection
    - Cleared before CNS invasion
  - Recovery
  - Carrier state
  - Latent period

The Future

- Better antiviral therapy
- Need to understand pathophysiology
- mRNA vaccines

Case Study 1

- Faculty member enjoying a tropical vacation
- Masseuse notices small wounds near ankles
-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Cast Study 2

- You get a call from one of your co-workers
- While riding a bike, a dog runs across field, lunges at him and bite his legs and runs off….

Rabies

- Terrible way to die!
- Rabies a concern with any mammal bite
- Bats always a concern!
- Wound cleaning key
- Proper prophylaxis