Rabies!!!

Tom DeLoughery, MD MACP FAWM @bloodman

Oregon Health and Sciences University

Knight Cancer Institute
at Oregon Health & Science University

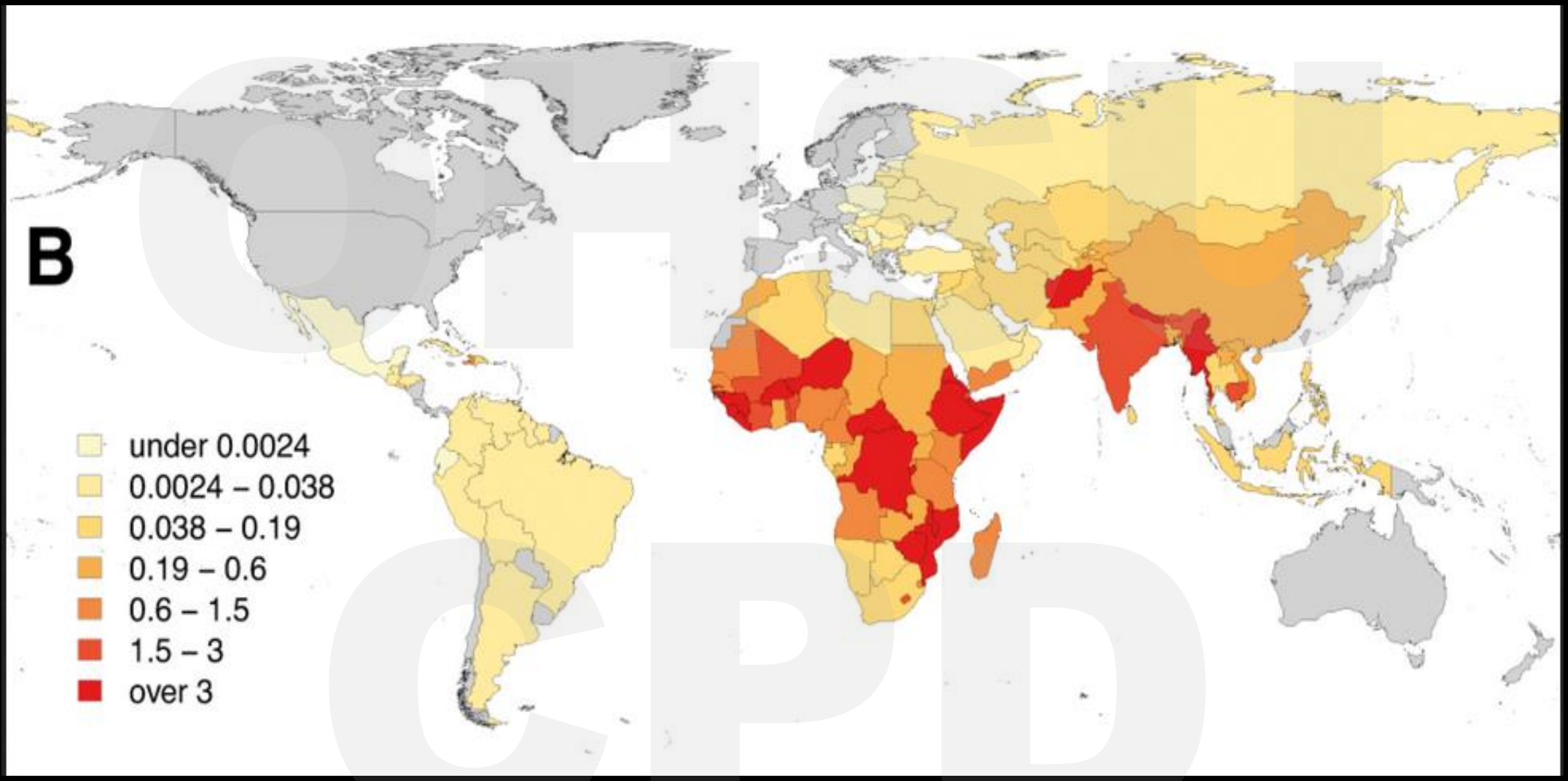
DISCLOSURE

Relevant Financial Relationship(s)

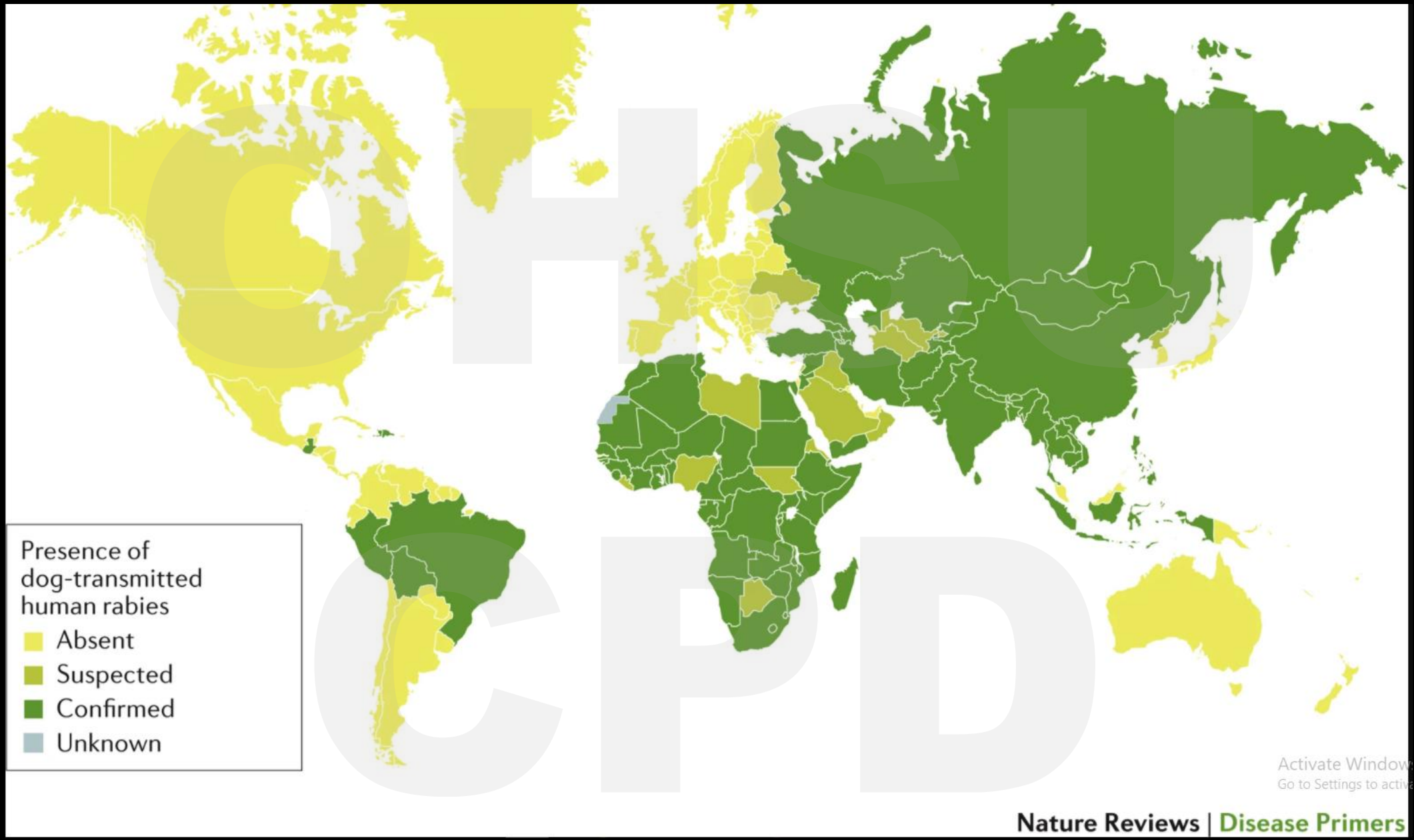
None

Rabies: Epidemiology

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

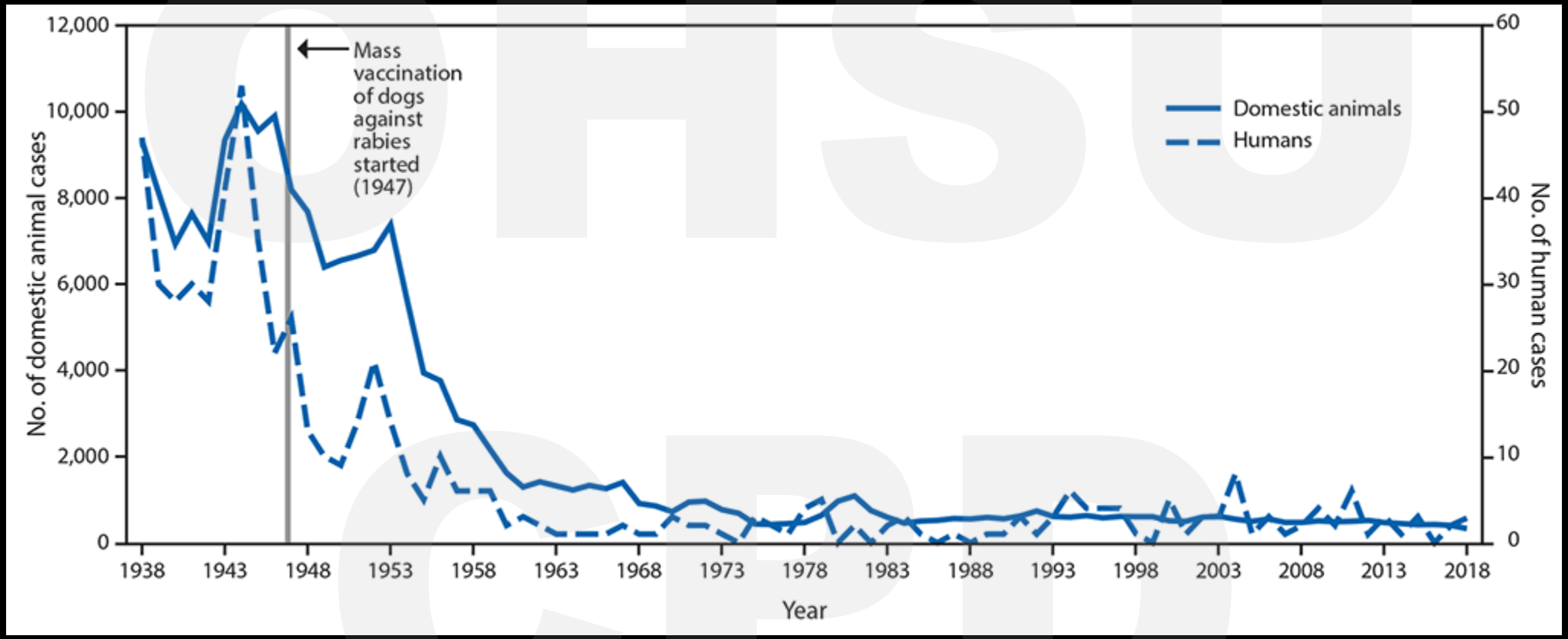


Deaths per capita WHO


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

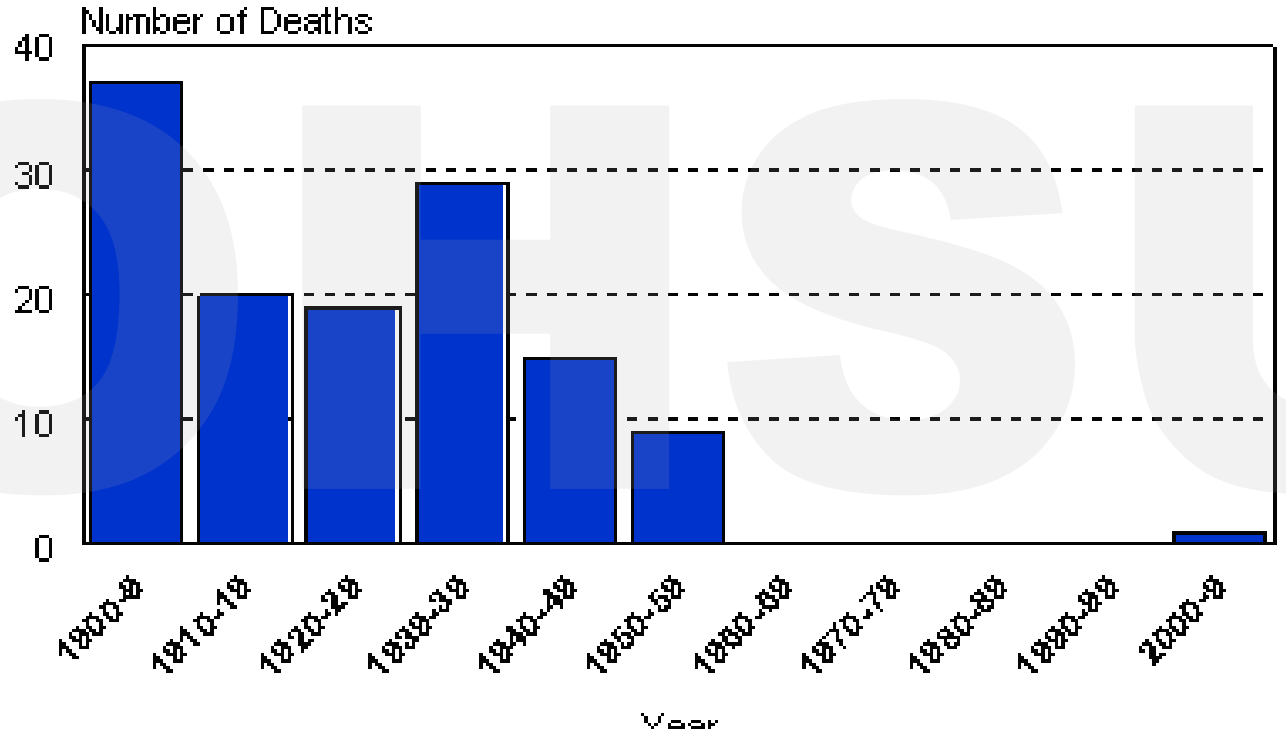
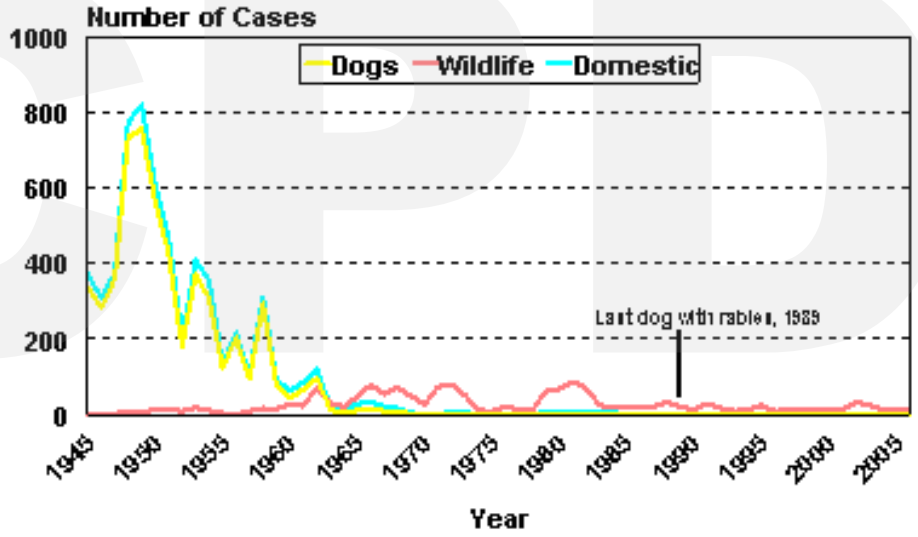


Figure 3. Animal Rabies, Indiana,1945-2006



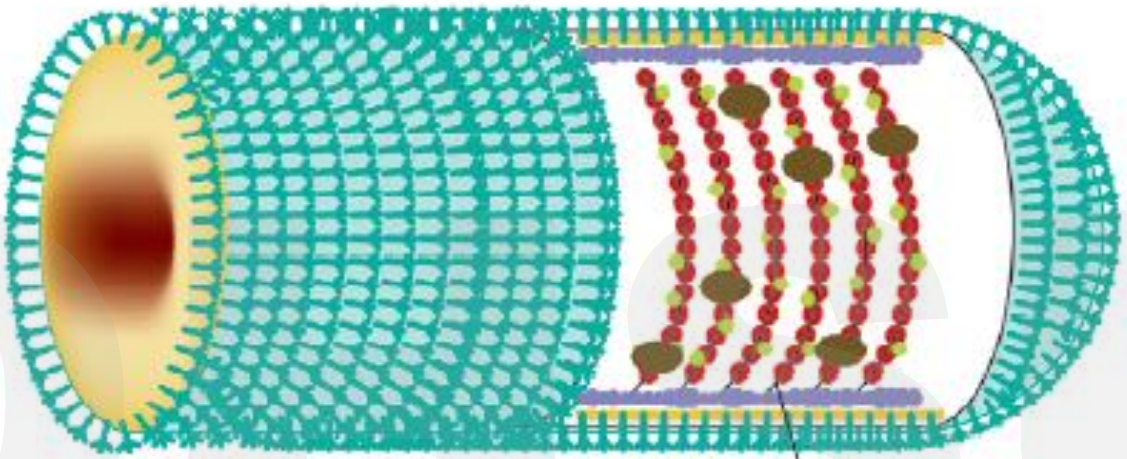
Rabies: Travelers

- 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

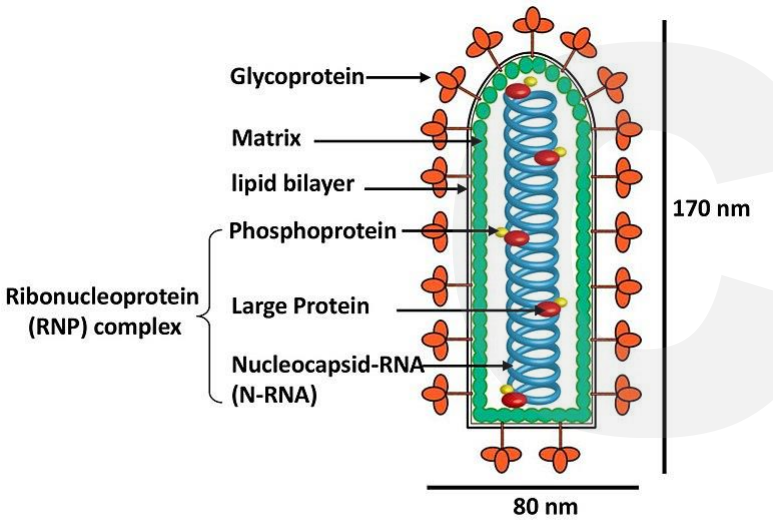


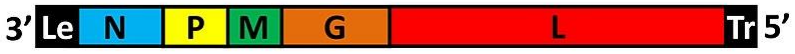
Matrix protein

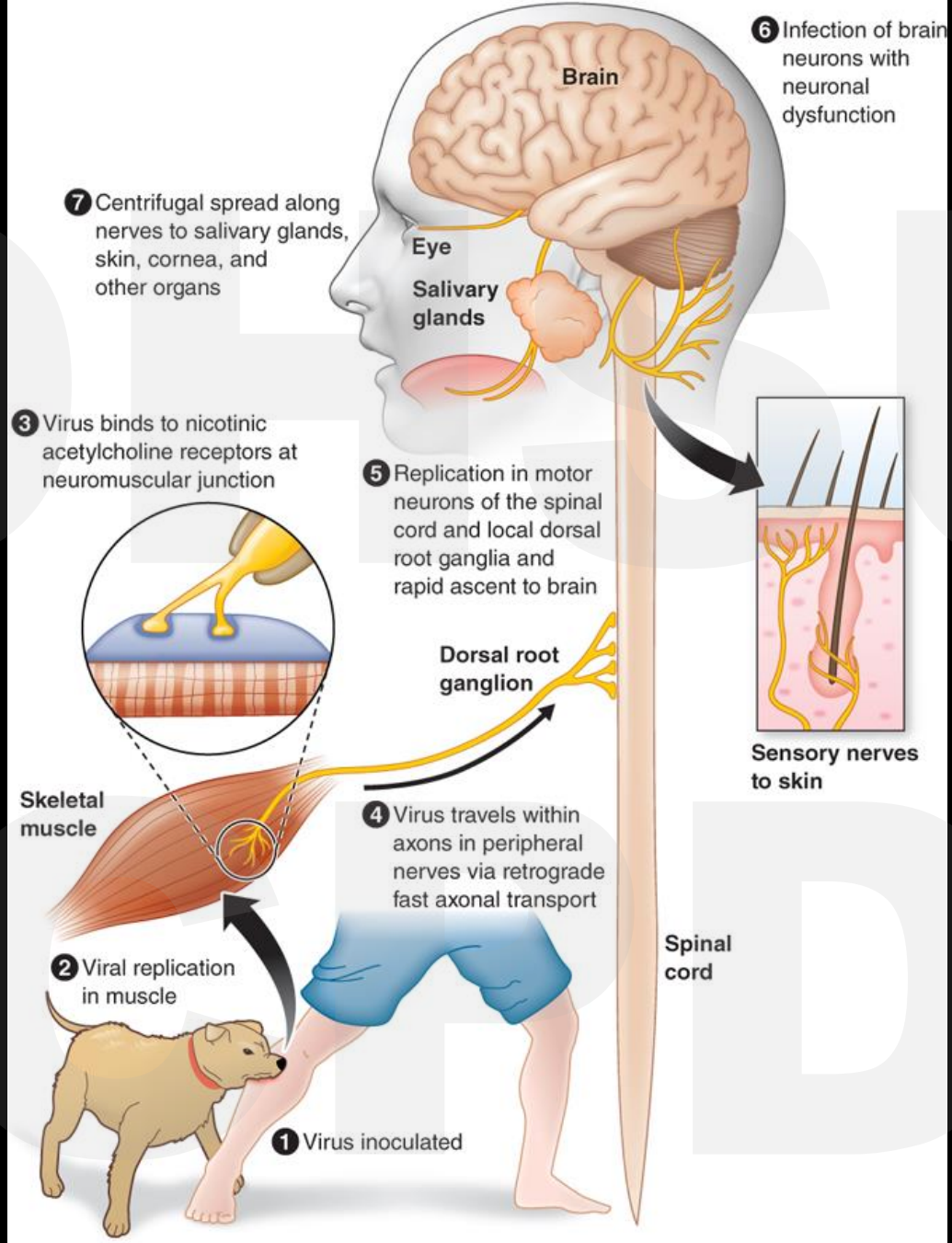
Envelope
- Host-derived lipid membrane
- Glycoprotein

RNA genome helical coil

Ribonucleoprotein complex or nucleocapsid
- Nucleoprotein
- Phosphoprotein
- RNA polymerase



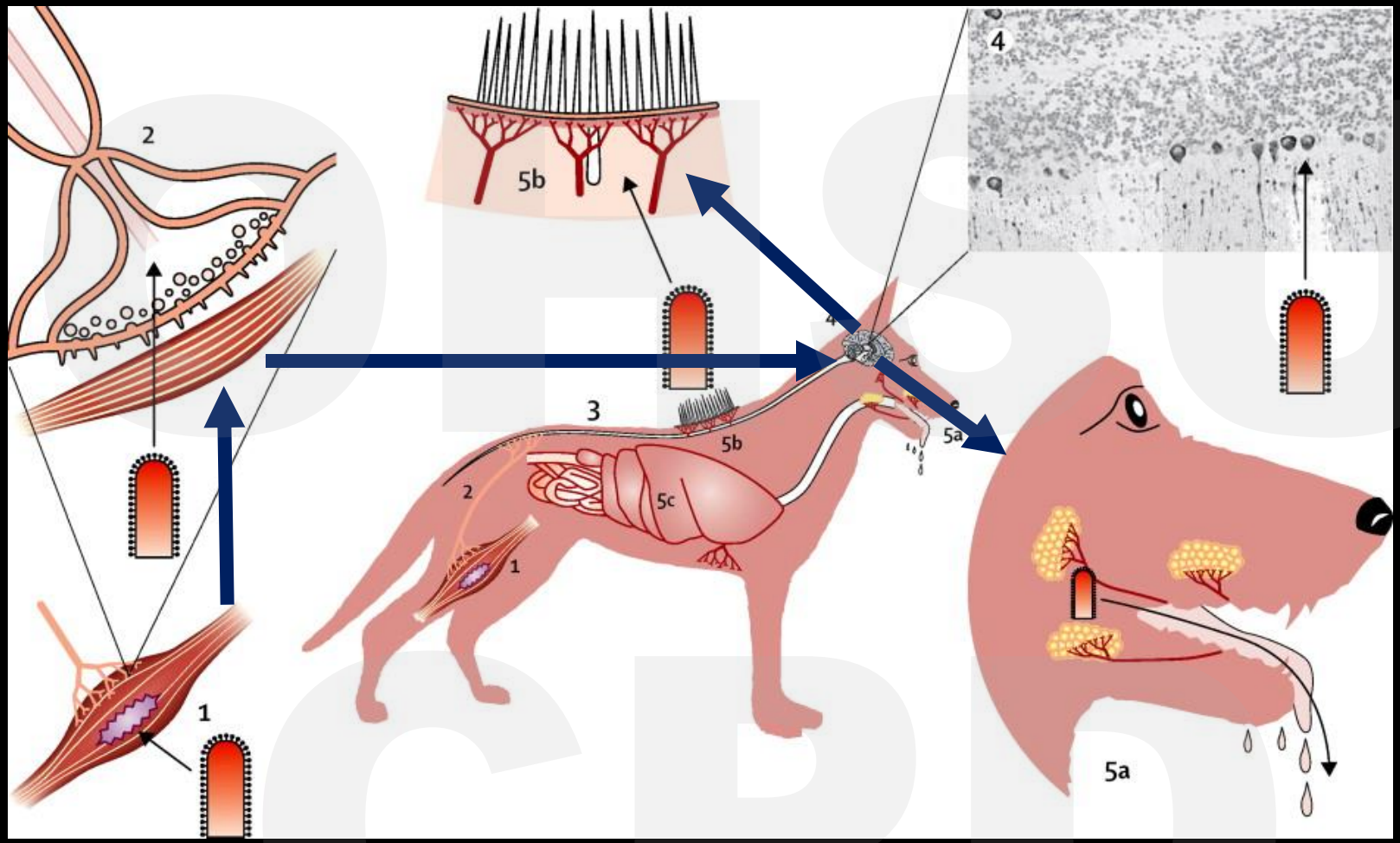




Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

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

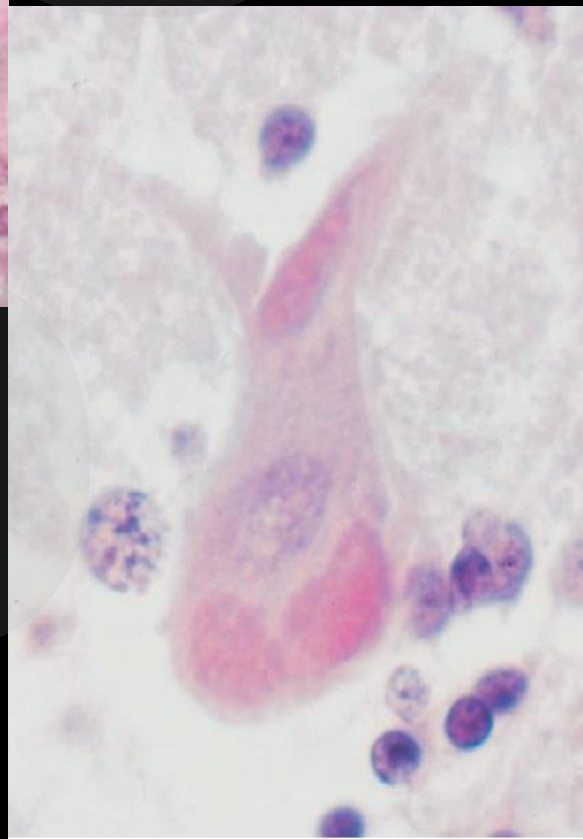

2
5b
4
3
5b
5a
2
5c
1
1
5a

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

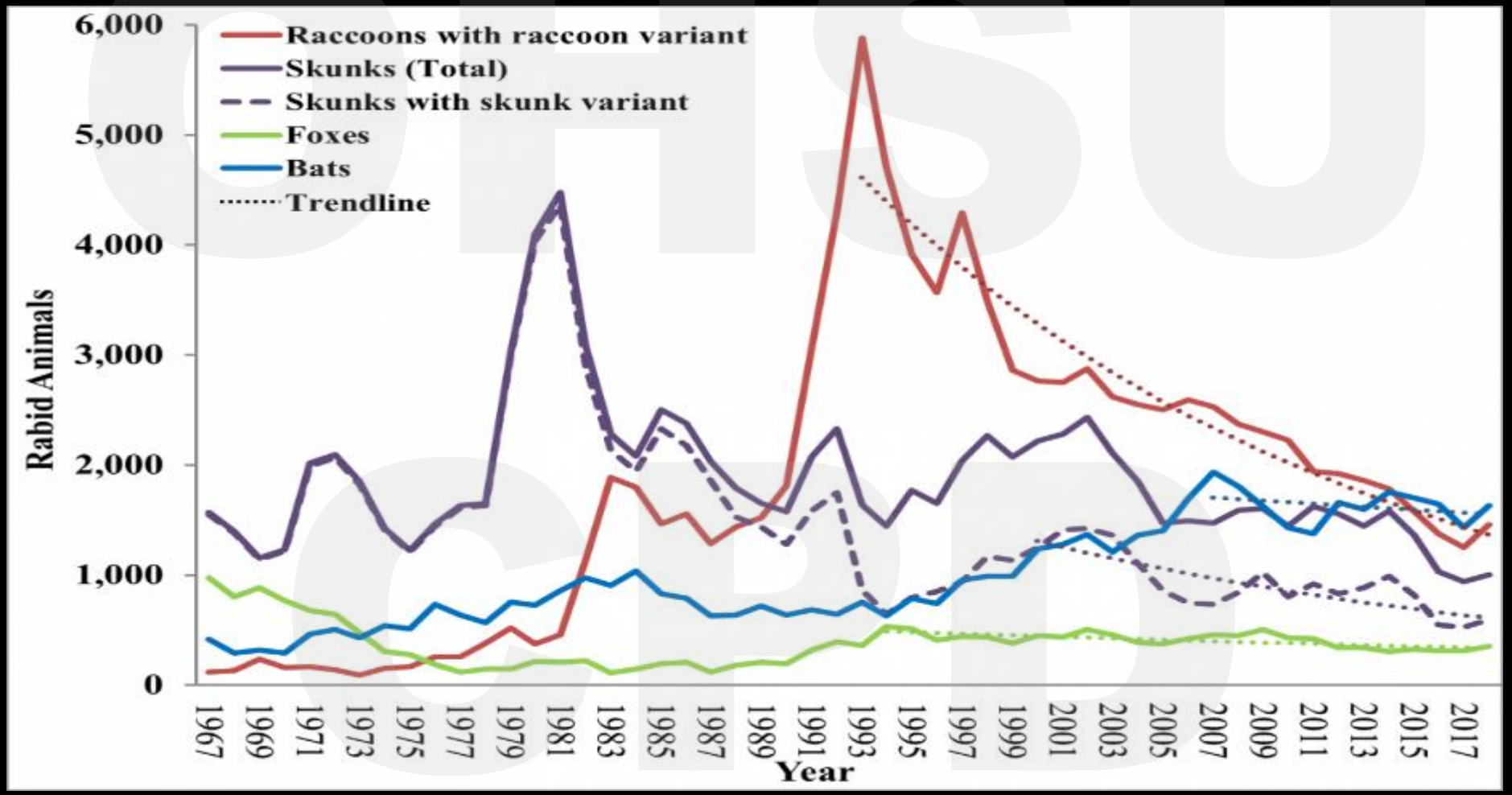


What Animals Get Rabies?

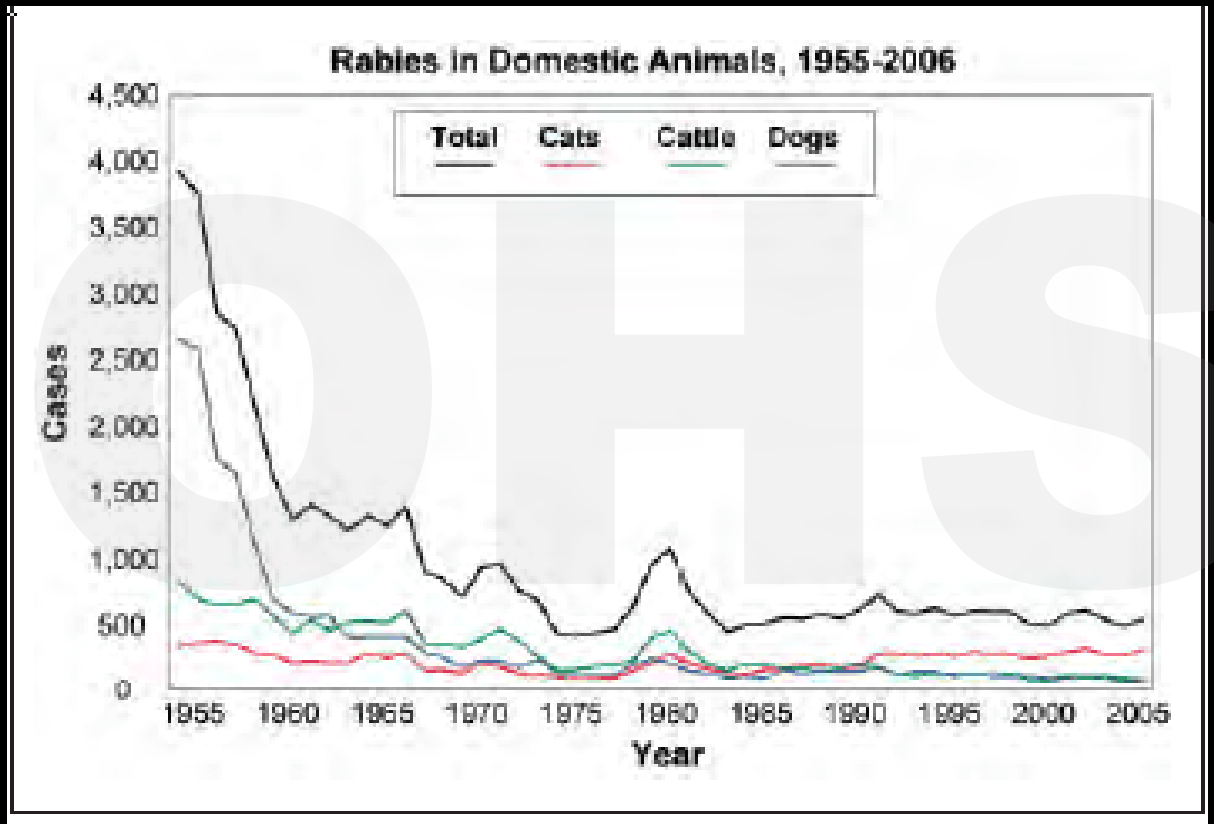
USA

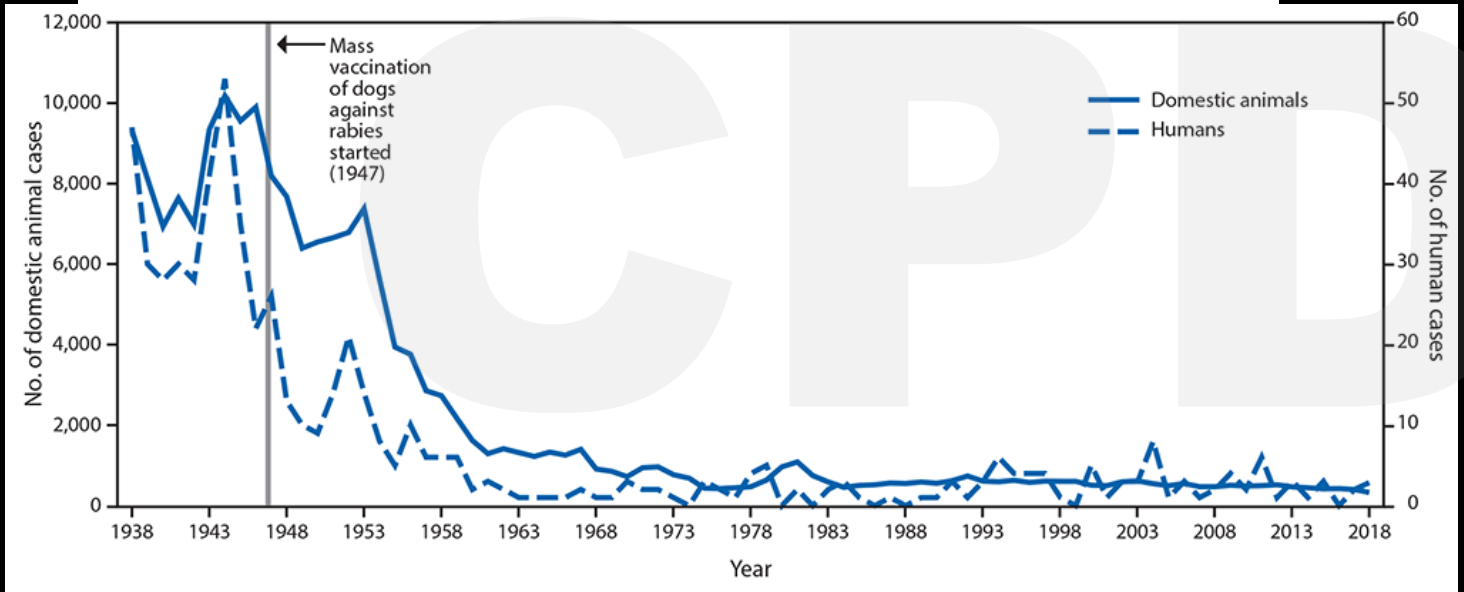
- More rabid cats then dogs in USA
- Dogs biggest threat world-wide
  - Also foxes, mongooses, raccoons, jackals, and wolves

USA Animals



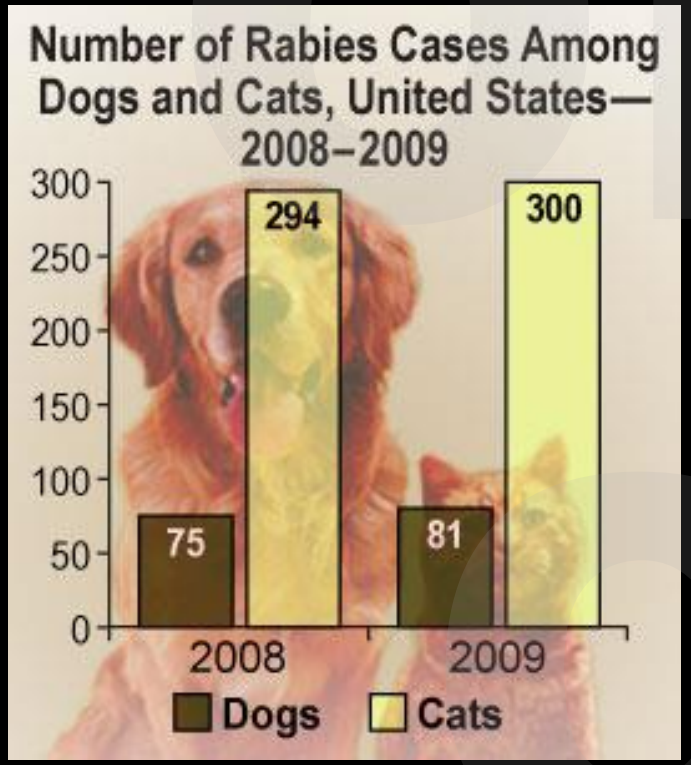
CDC

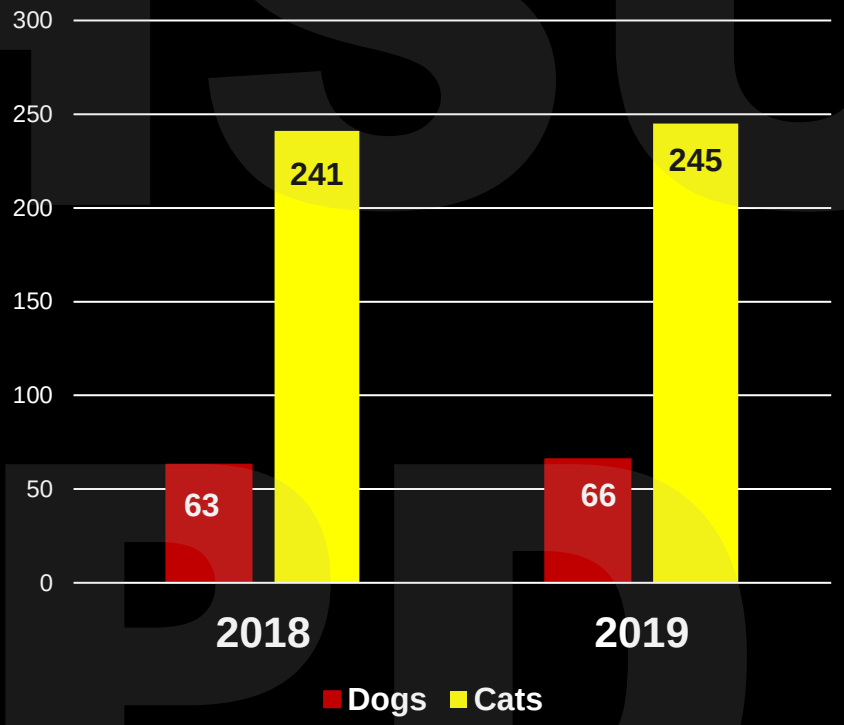

Rabies in Domestic Animals, 1955-2006
Total
Cats
Cattle
Dogs
Cases
4,500
4,000
3,500
3,000
2,500
2,000
1,500
1,000
500
0
1955
1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
Year


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

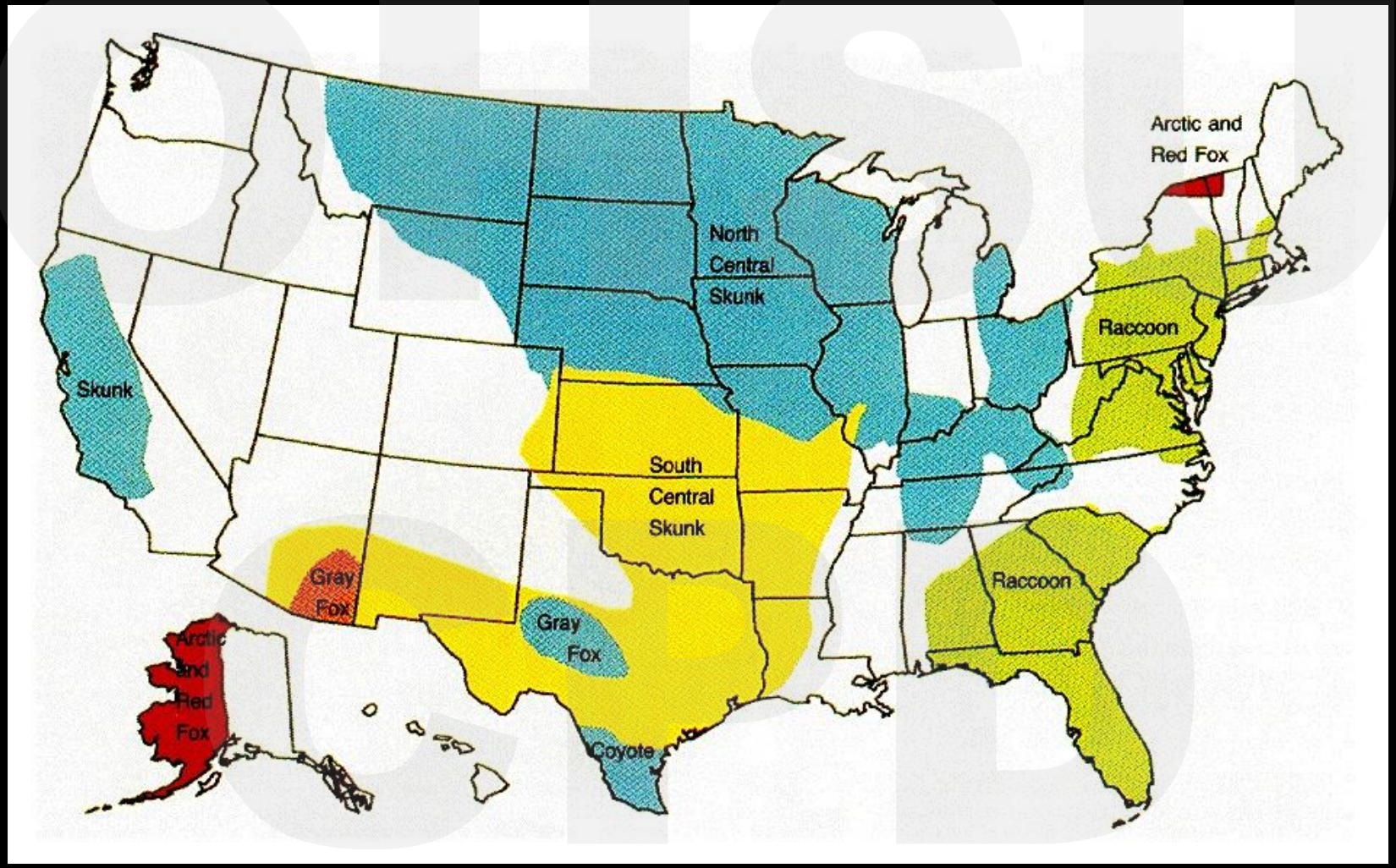
CDC

Dogs and Cats





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

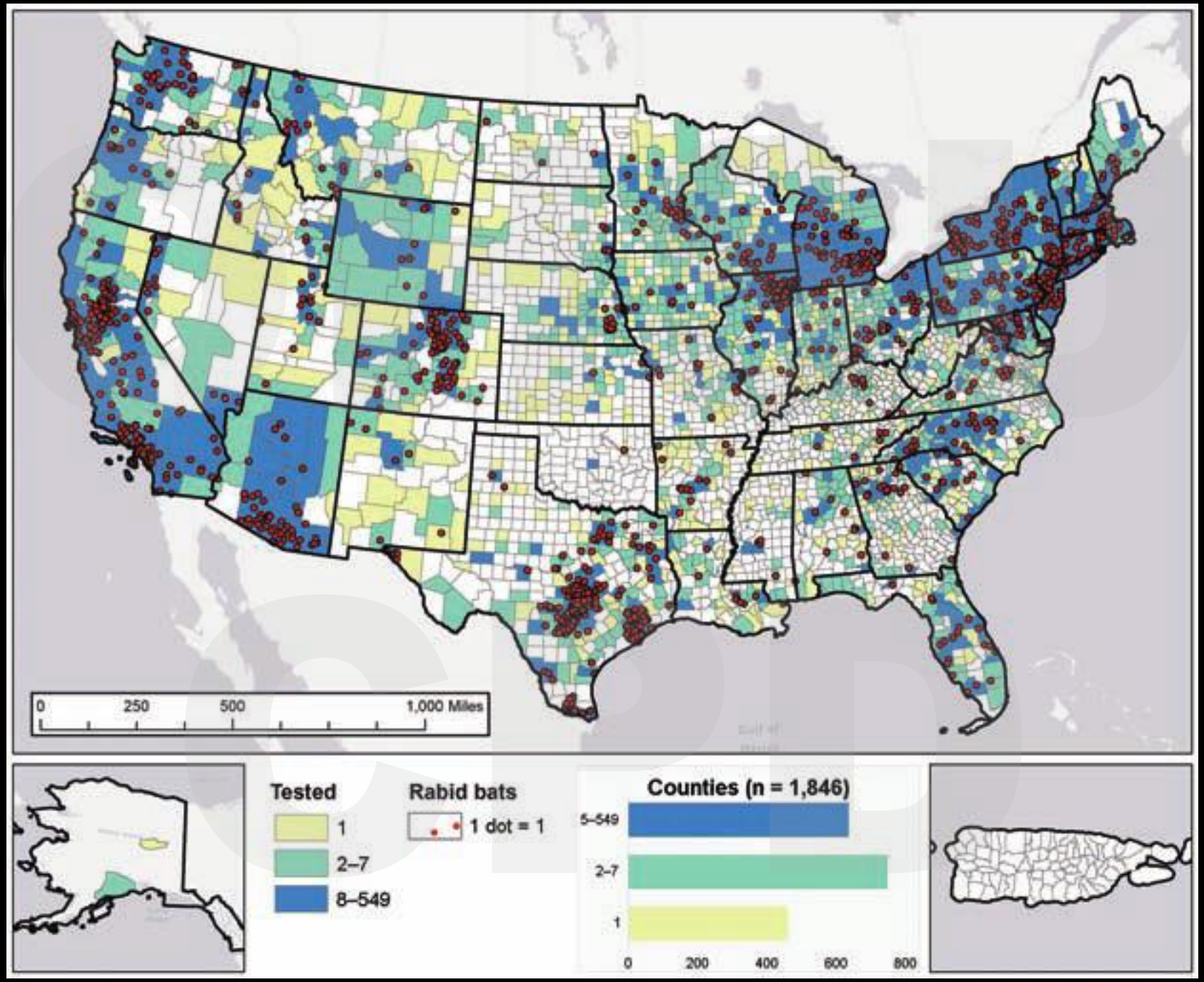


Fishbein DB, Robinson LE. N Engl J Med 1993;329:1632-1638.

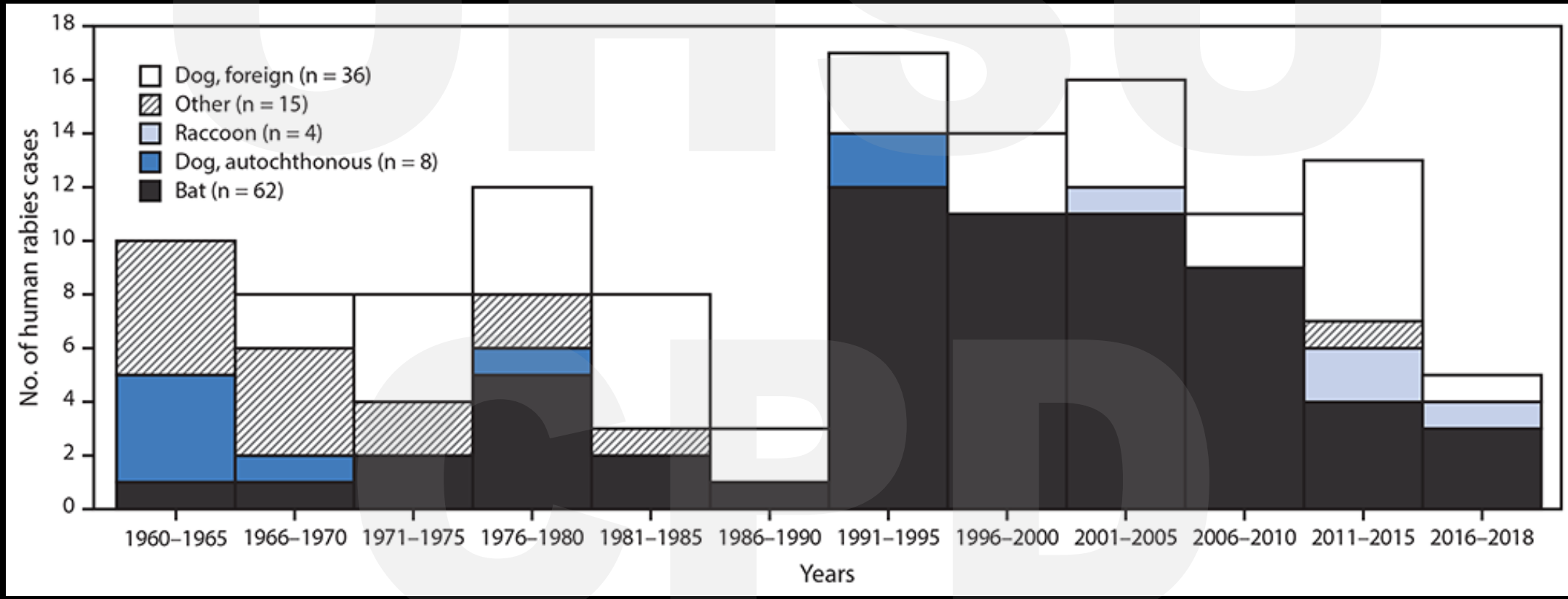
Other Animals

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

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

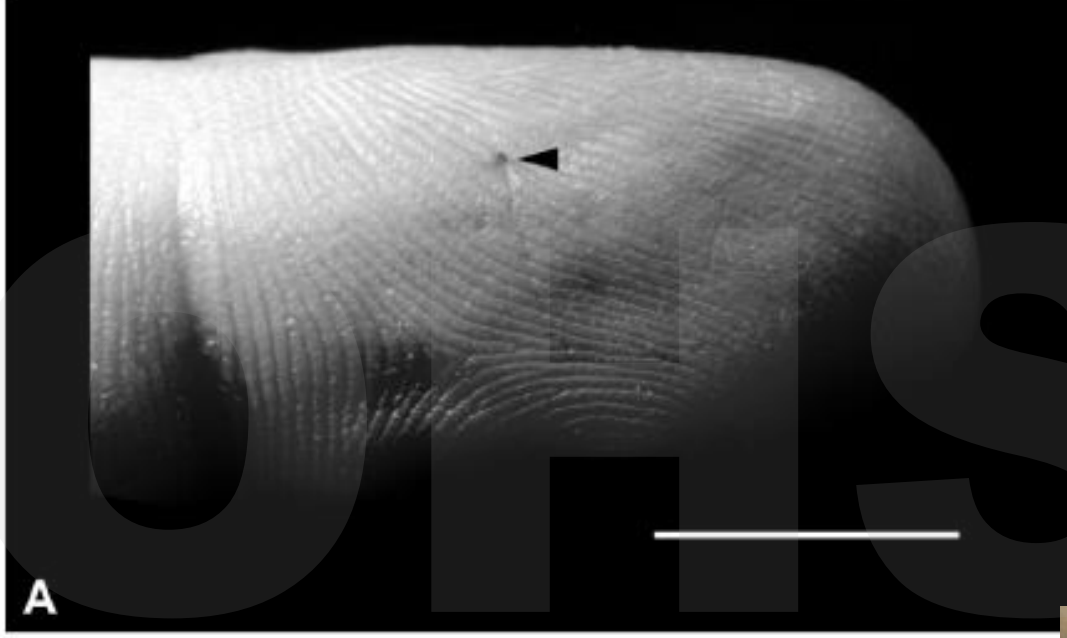
NW Rabies

- Oregon: 20 year data
  - 258 bats
  - 2 cats no dogs
  - 27 foxes
  - 3 coyotes, 1 skunk and 1 goat
- Washington: 30 year
  - 542 bats
  - 2 cats no dogs
  - 1 horse, 1 llama

Bats

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


OHSU
CPD



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

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

OHSU

CPD

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?

The Grim Reality

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

Prophylaxis/Prevention

- 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

Rabies Immune Globulin

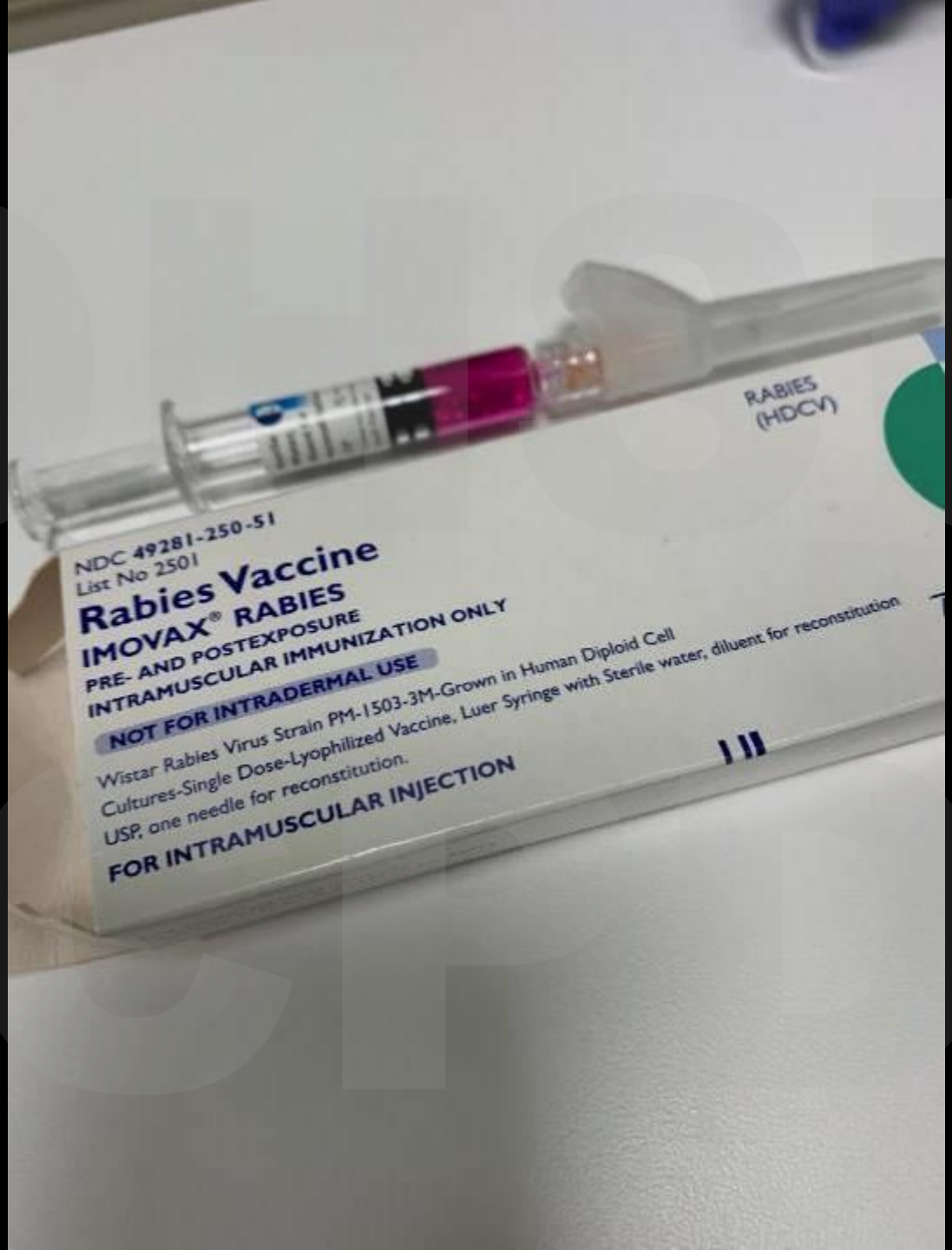
- Humans (horses)
- 20 IU/KG
  - Infiltrated around wound
  - Rest gluteal
- Monoclonal antibodies in development

Pre-exposure Prophylaxis

- Occupational risk
- Travel to high risk areas
- Vaccine days 0, 7

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

Risk Assessment

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

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

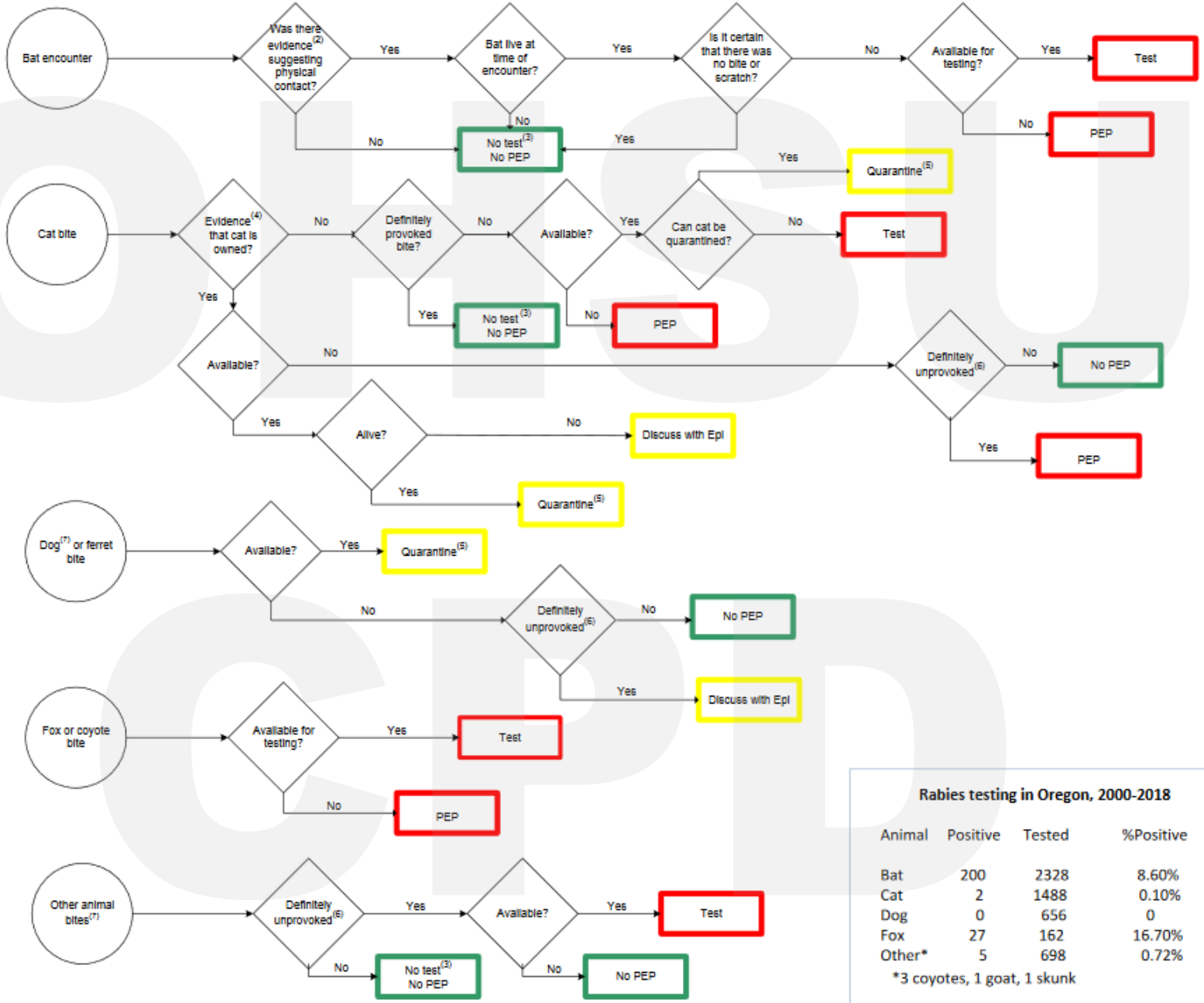
Small Pets/Livestock

- 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

The Future

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