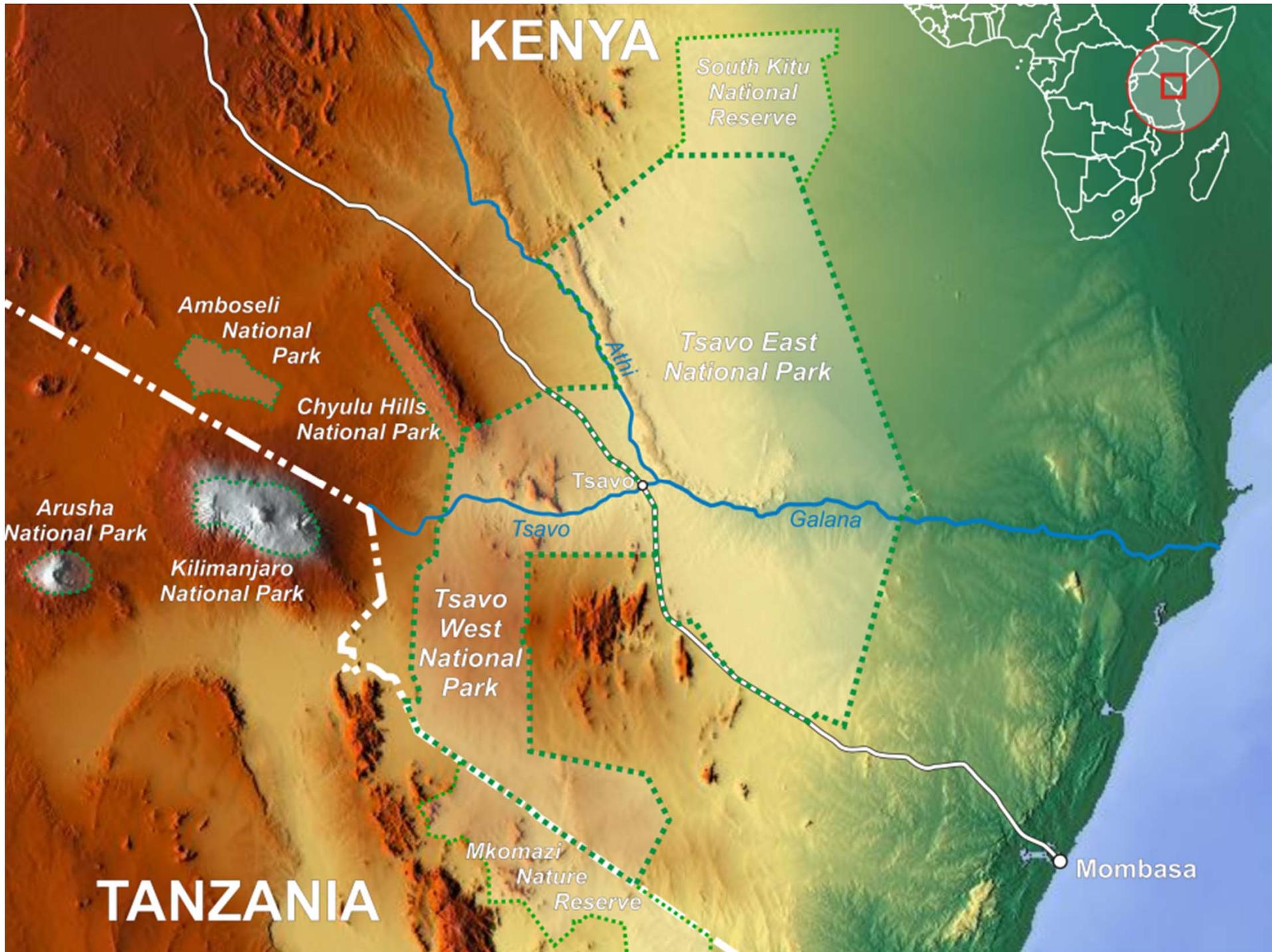


Rabies: the classic
zoonosis still unconquered

David A.
Warrell

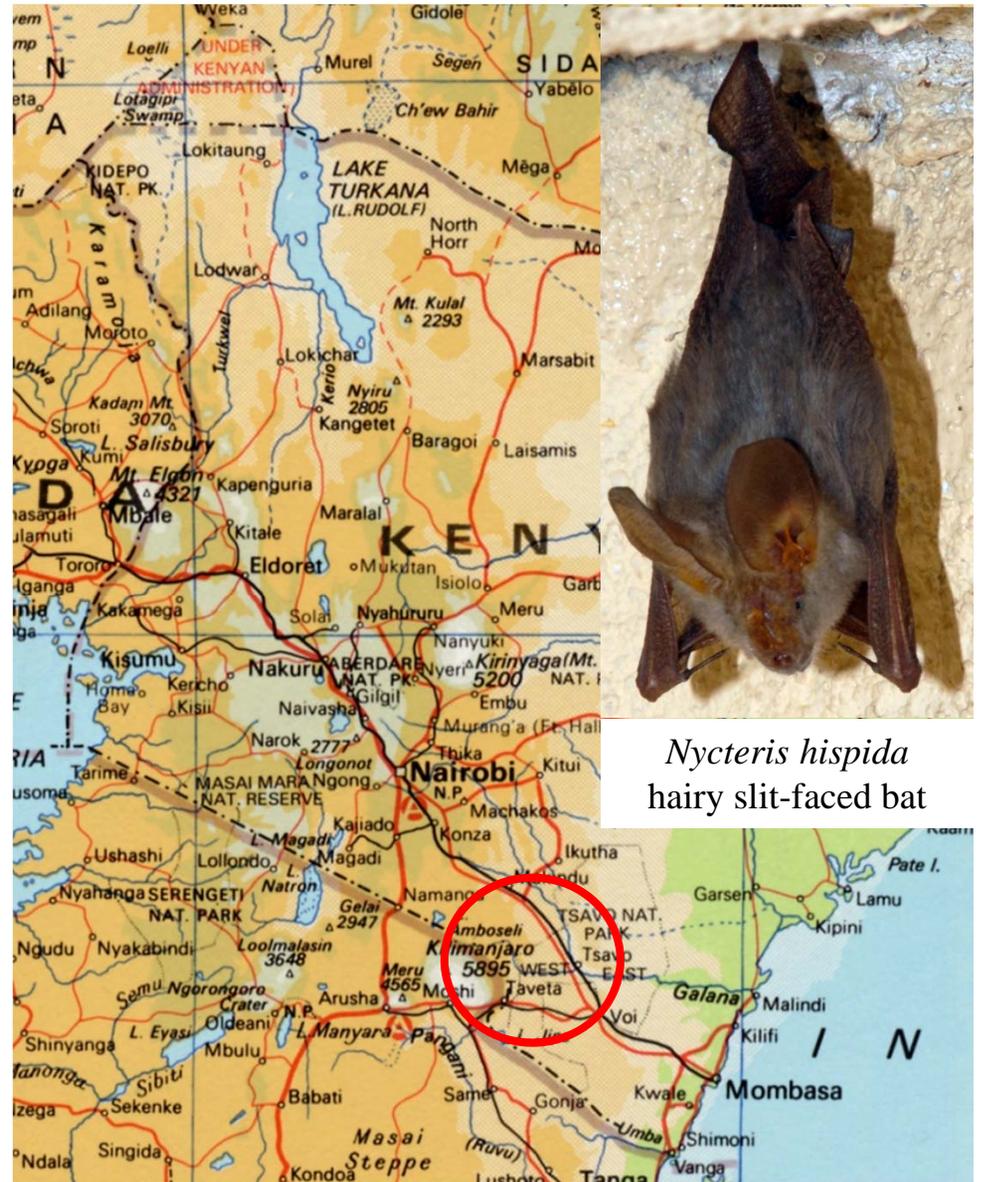
Nuffield Department of Clinical Medicine
University of Oxford
MMA Yangon 20-01-18





34-year-old Dutch lady doctor

- Camping holiday with husband in Tsavo West National Park, Kenya
- At dusk, small bat flew into the tent and brushed against her face inflicting two tiny scratches on her nose
- Washed bleeding wounds with soap and water - applied alcohol
- Next day: reassured by park and health facility staff that there was no rabies in bats in Kenya
- No further action recommended (she had not had pre-exposure rabies prophylaxis)



Nycteris hispida
hairy slit-faced bat

34F

Back in Amsterdam

- +23 days: malaise, dizziness, myalgia, headache
- +25 days: difficulty speaking, swallowing hyperesthesia of cheeks, unsteady, vomited
- +26 days: hospital - diplopia - neurologists' diagnosis: "hysterical conversion syndrome"
R_x tranquillisers
- +27 days: generalised convulsion, incontinence, aspiration, hypoxia, cyanosis – transferred to ITU

34F

- +33 days: R_x “Milwaukee treatment protocol”
- Diagnosis: Duvenhage virus (African rabies-related virus) encephalitis
- +45 days: died (+23 days after start of illness)

van Thiel et al. Fatal Human Rabies due to Duvenhage Virus from a Bat in Kenya: Failure of Treatment with Coma-Induction, Ketamine, and Antiviral Drugs. PLoS Negl Trop Dis. 2009 Jul 28;3(7):e428.

What can be learned from this tragedy?

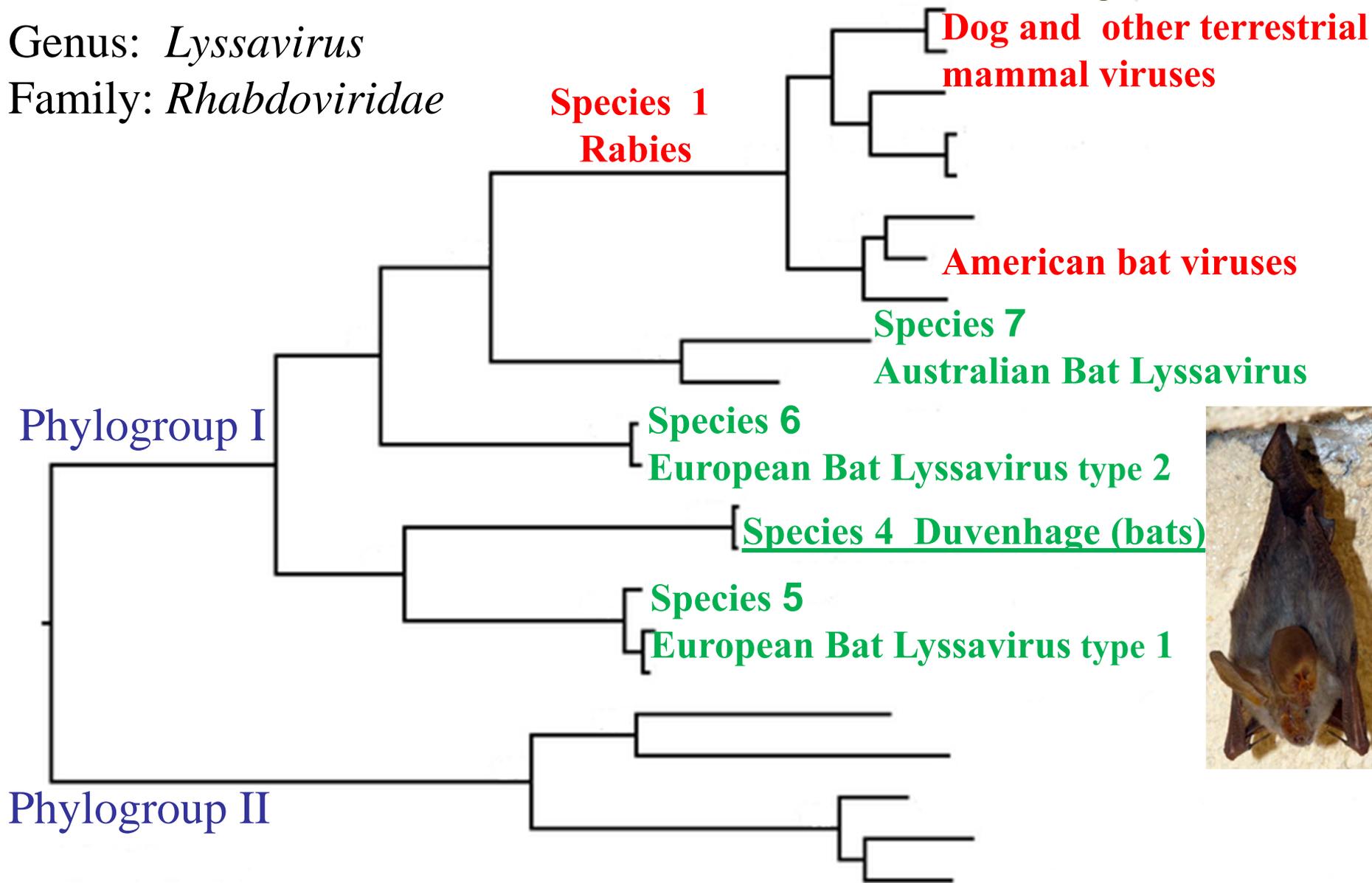
It was preventable!

- Educate travellers about risk of wild mammal bites **especially bats** in rabies endemic areas
- Encourage pre-exposure rabies vaccination
- Reservoir species of sylvatic rabies are unknown in many countries; the role of bats is becoming apparent in several emerging zoonoses
- Well-intentioned local advice about need for post-exposure prophylaxis (PEP) is often inconsistent with WHO/CDC/HPA guidelines
- It is worth breaking even a “holiday of a lifetime” to achieve urgent PEP!

Rabies and **rabies-related bat viruses** (5 among 15 Lyssavirus species)
known to cause clinical rabies in human beings

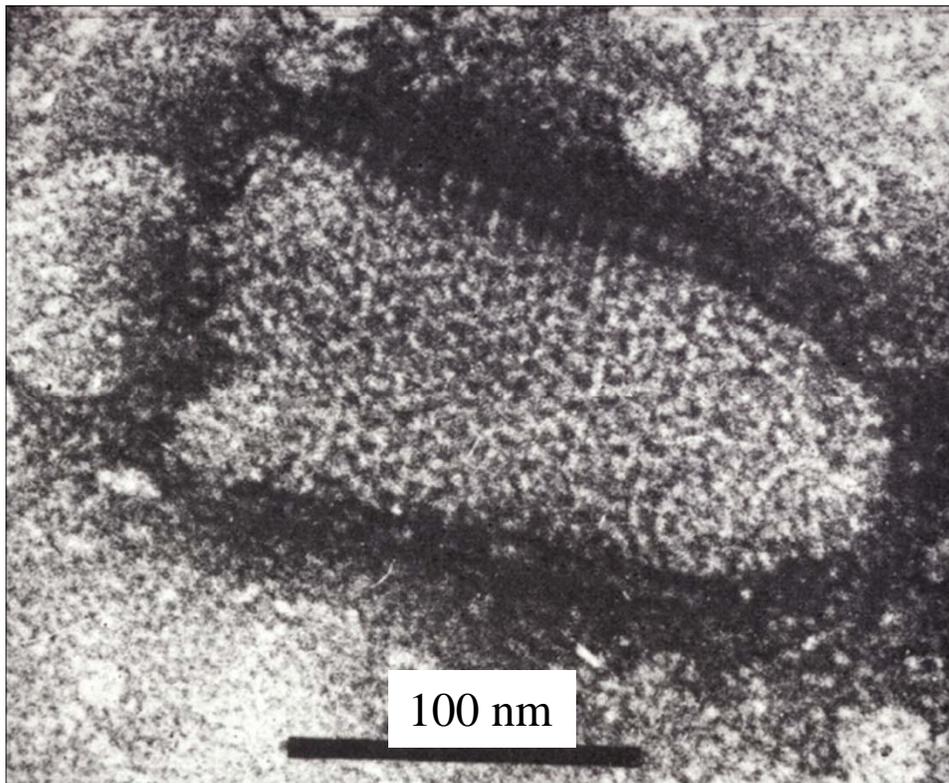
Genus: *Lyssavirus*

Family: *Rhabdoviridae*

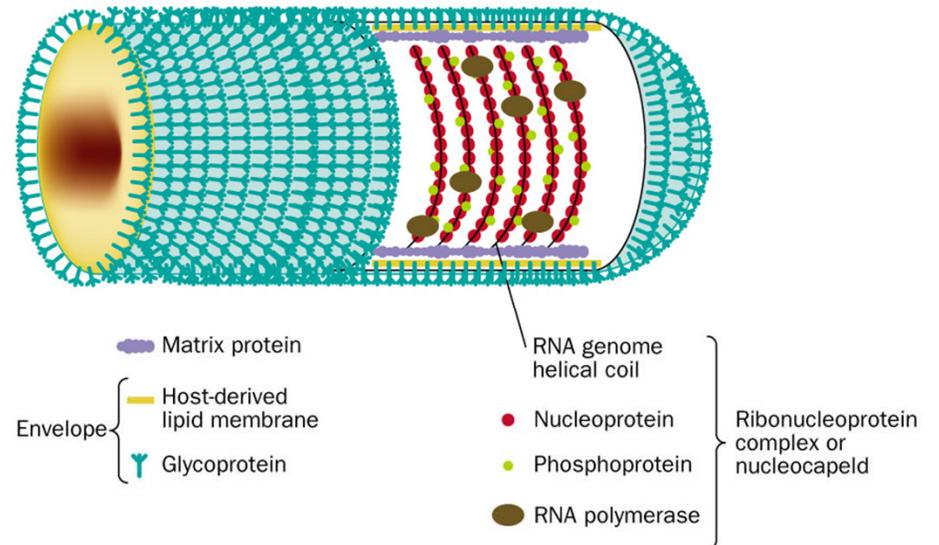


Rabies (Lyssa) viruses “rabies-related viruses”

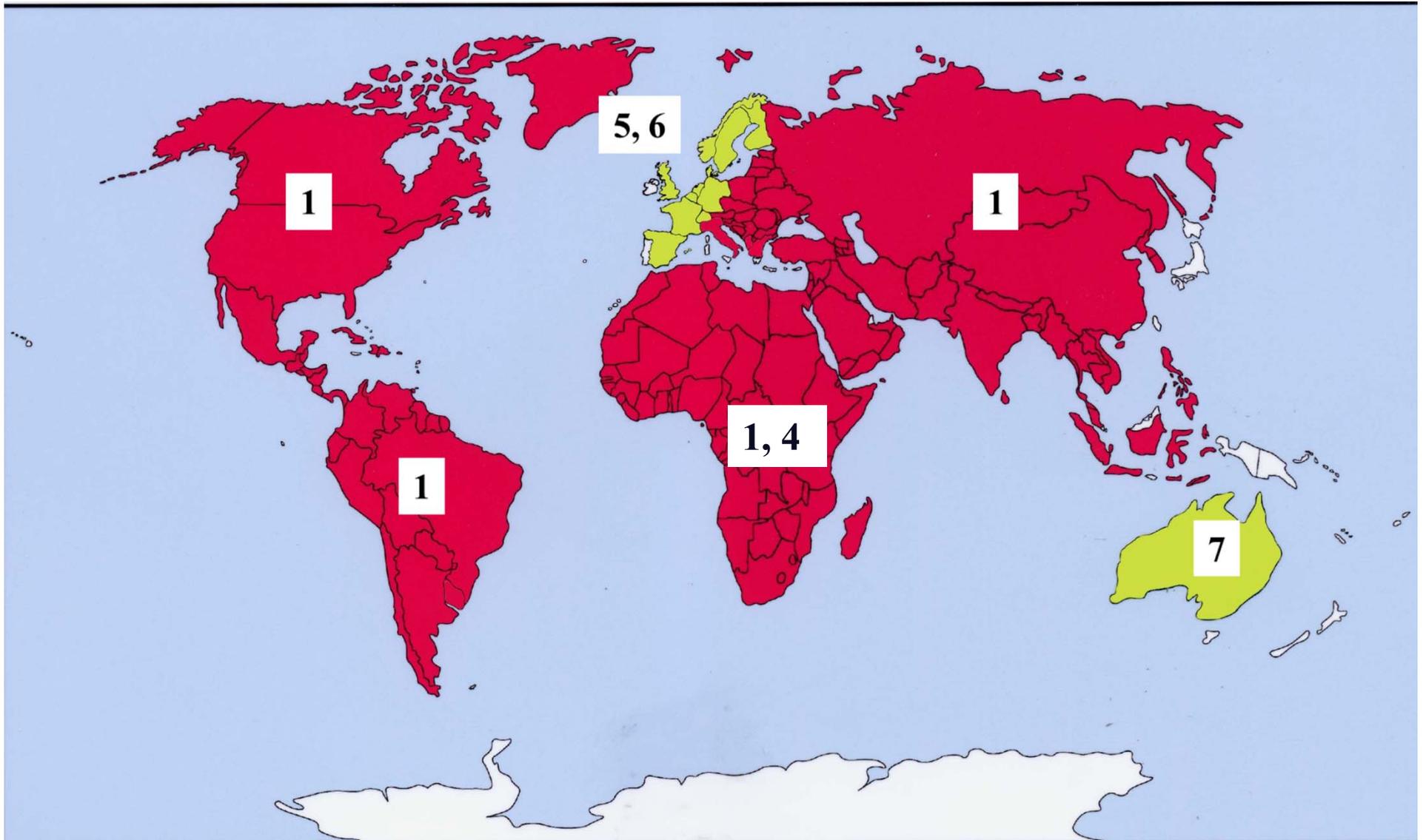
Five rabies (Lyssavirus) species can cause clinical rabies in human beings



Rabies virion (180×75 nm)



Distribution of **terrestrial rabies** and **rabies related bat viruses**





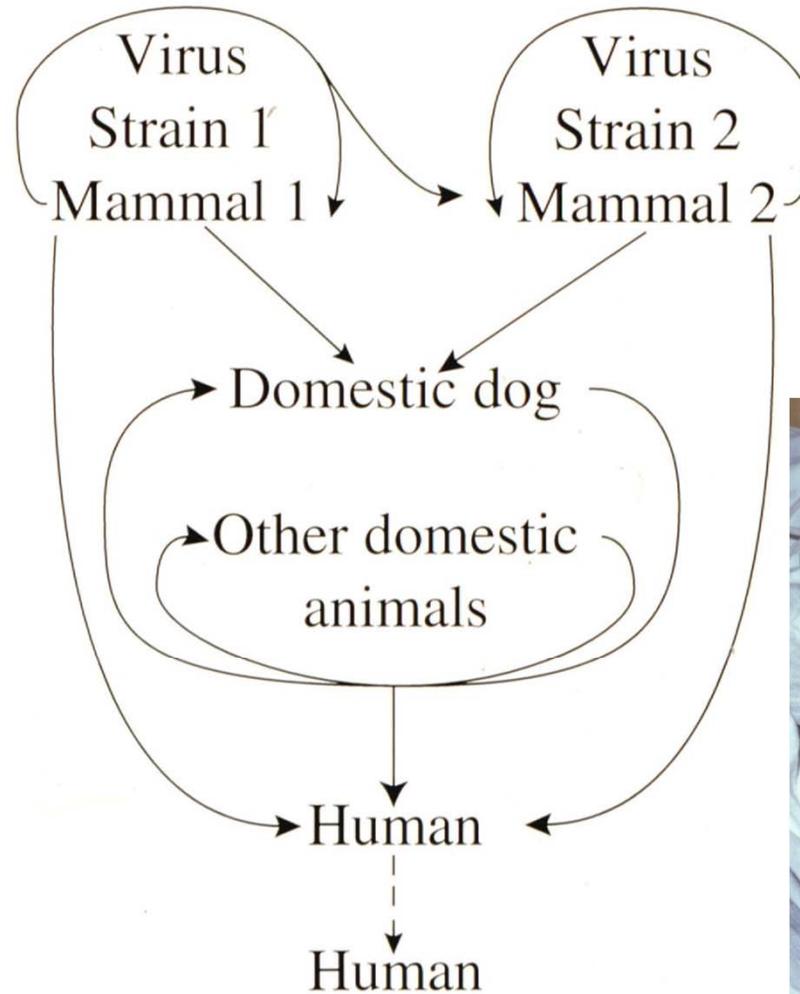
Sylvatic
(wildlife)



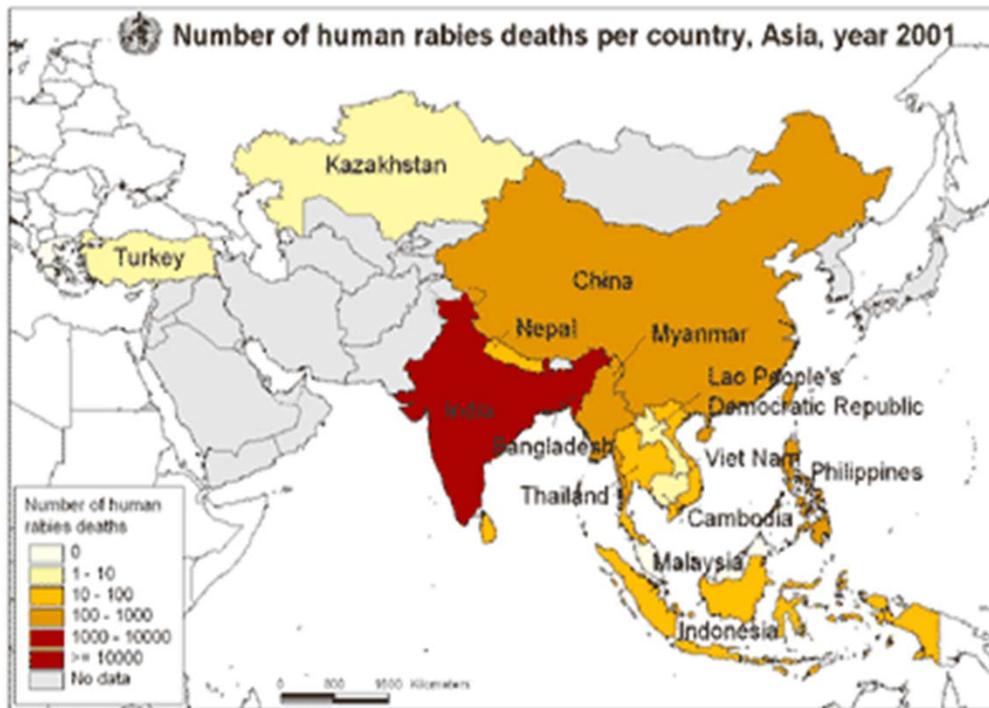
Urban
(domestic
dog)



Epidemiology of rabies



India: human rabies in 2005



- 16 million (dog) bites/year
- ?20,000 human deaths/year (12,000 “furious”)
- 4 million post-exposure prophylaxis courses/year

Australian Bat Lyssavirus



UK apparently free of
indigenous rabies since 1902

Myotis daubentonii



Since 1996, many EBLV-2a-
infected Daubenton's bats (*Myotis
daubentonii*) found in UK

- 2003: human death from EBVL-
2a rabies in Scotland

Rabies in Europe 2016

(virus isolation, many more sero-positive)

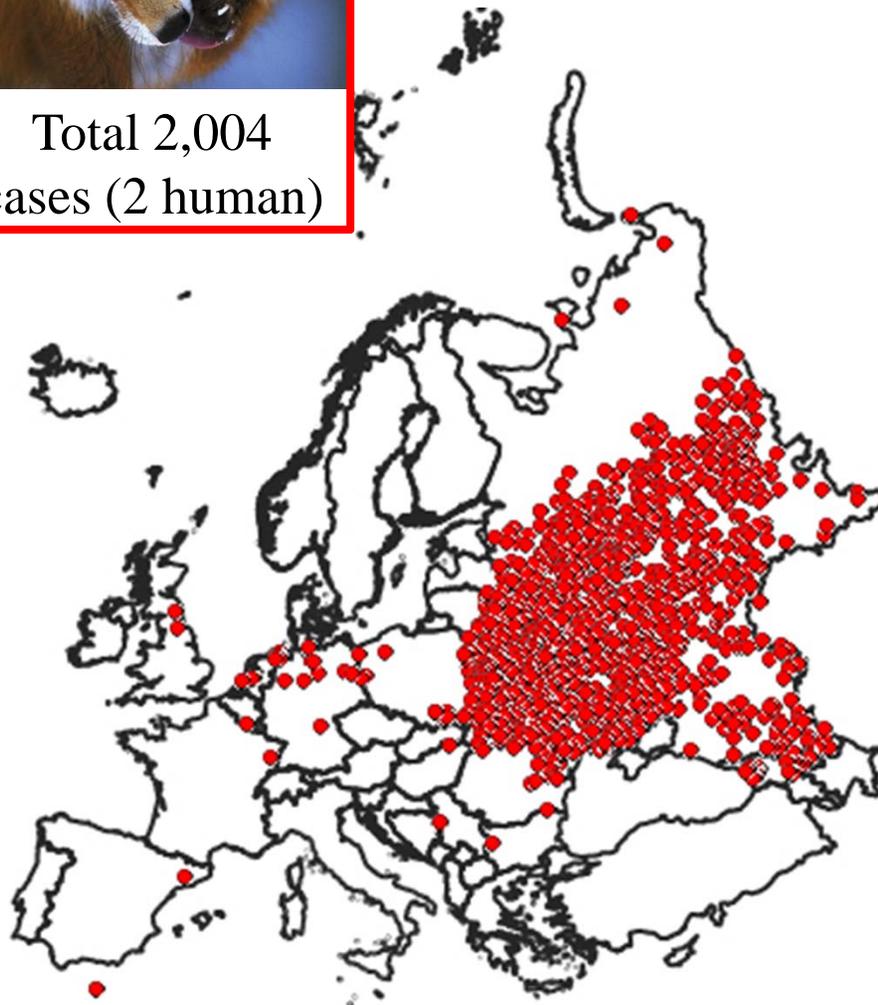
<http://www.who-rabies-bulletin.org>



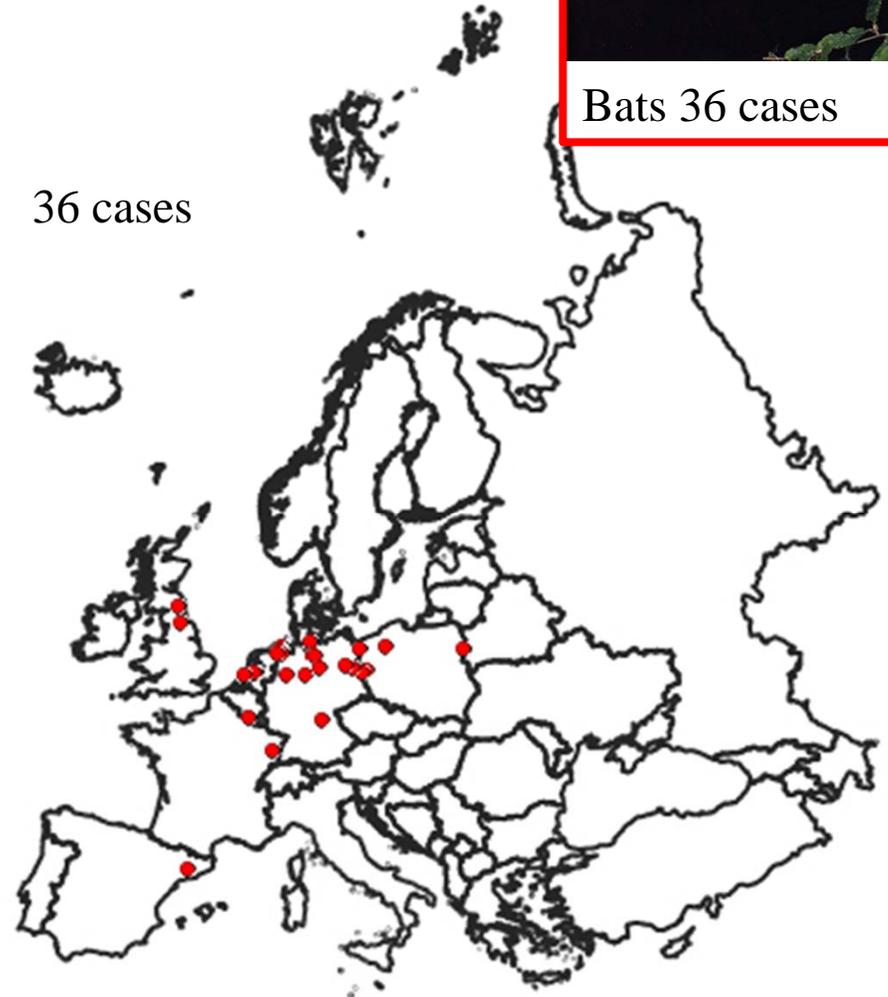
Total 2,004
cases (2 human)



Bats 36 cases



36 cases





United States



Eastern pipistrelle
Pipistrellus subflavus

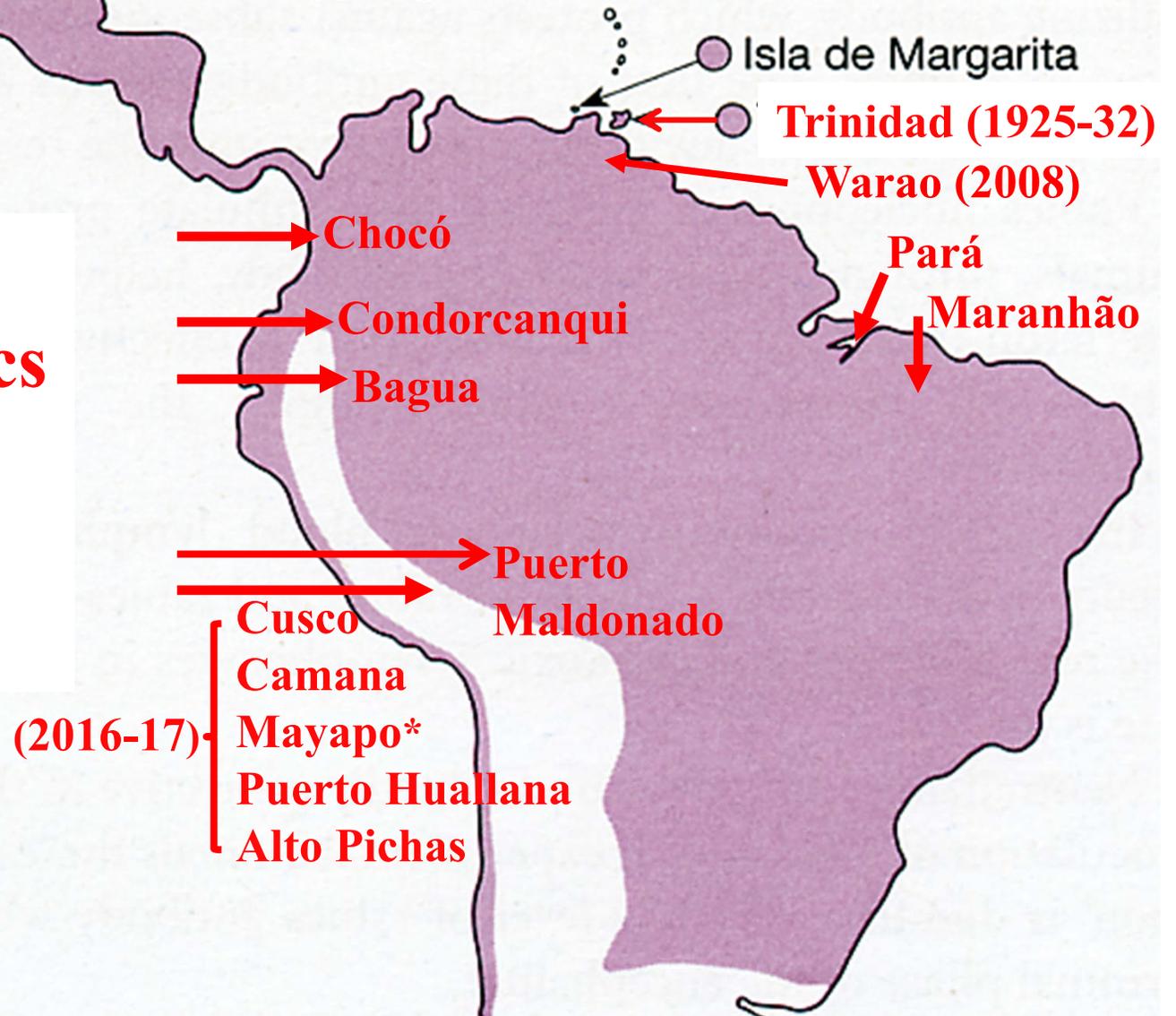
silver-haired bat
Lasionycteris noctivagans





Epizootic vampire bat rabies

Recent epizootics causing human deaths

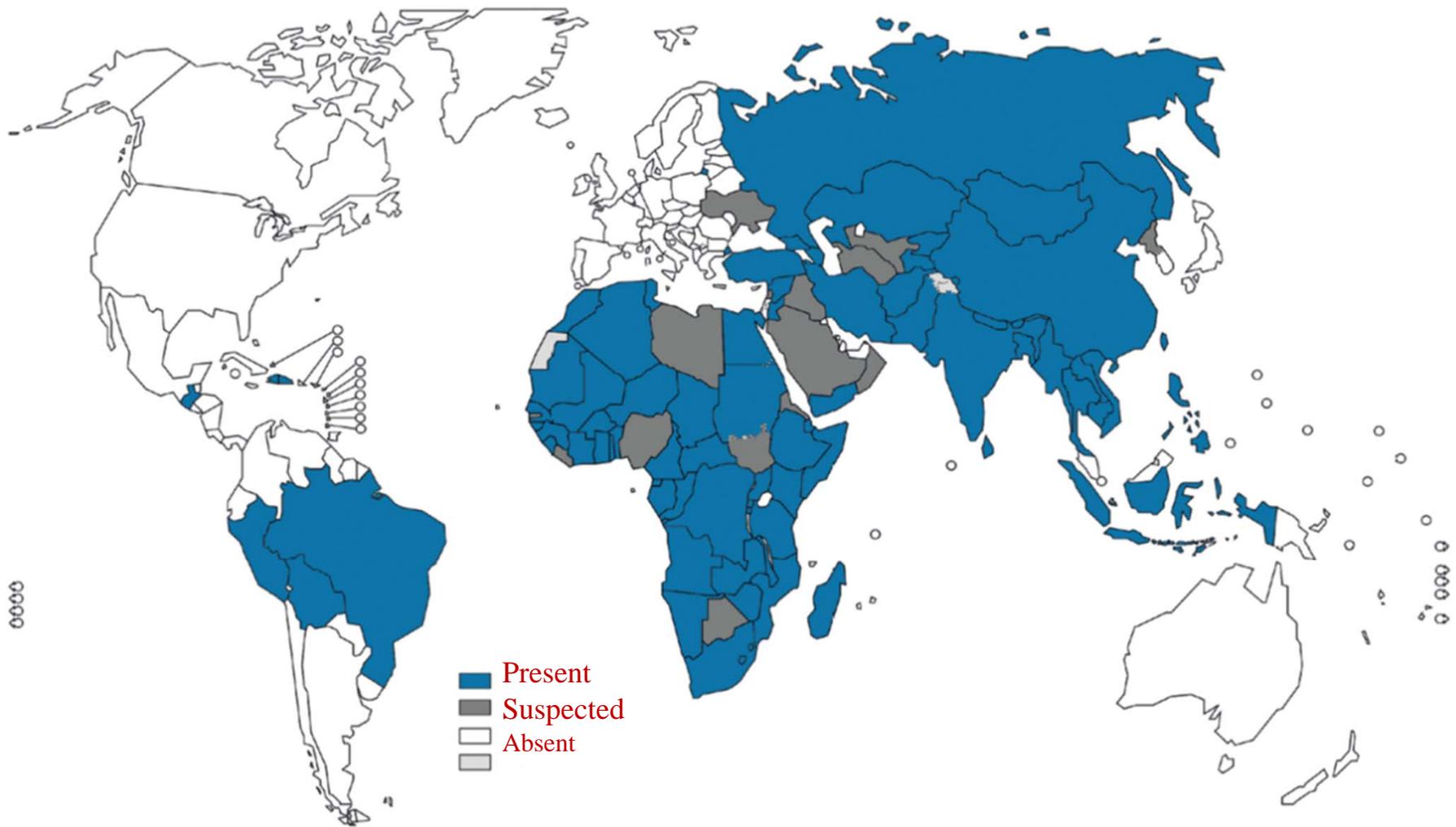


Do Myanmar bats carry rabies viruses, like those in Thailand, China, India, Philippine etc.?

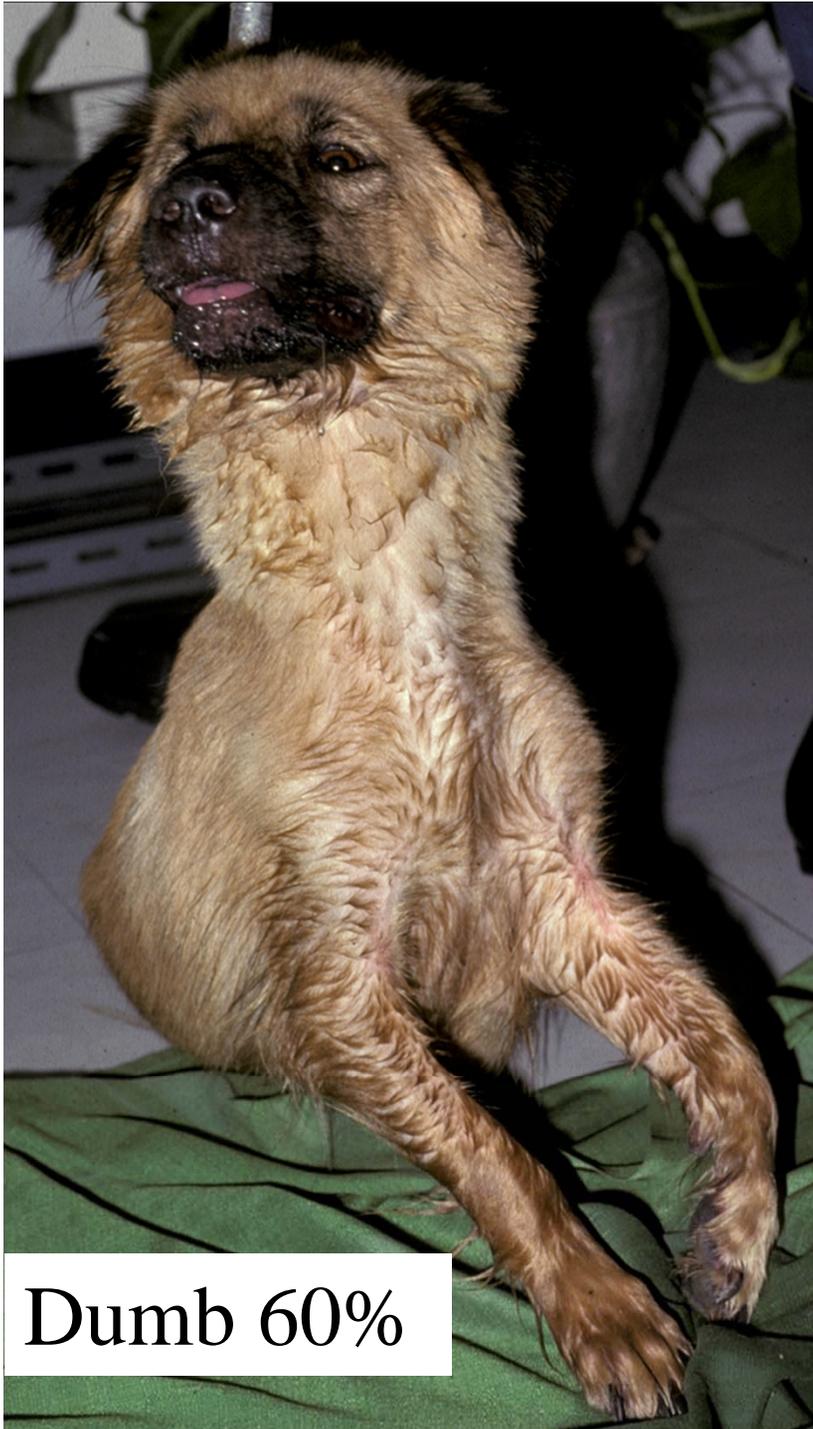


Than Lwin Bridge, Hpa An, Kayin

PRESENCE OF DOG-TRANSMITTED HUMAN RABIES 2010–2014



WHO (WER 2; 2016)



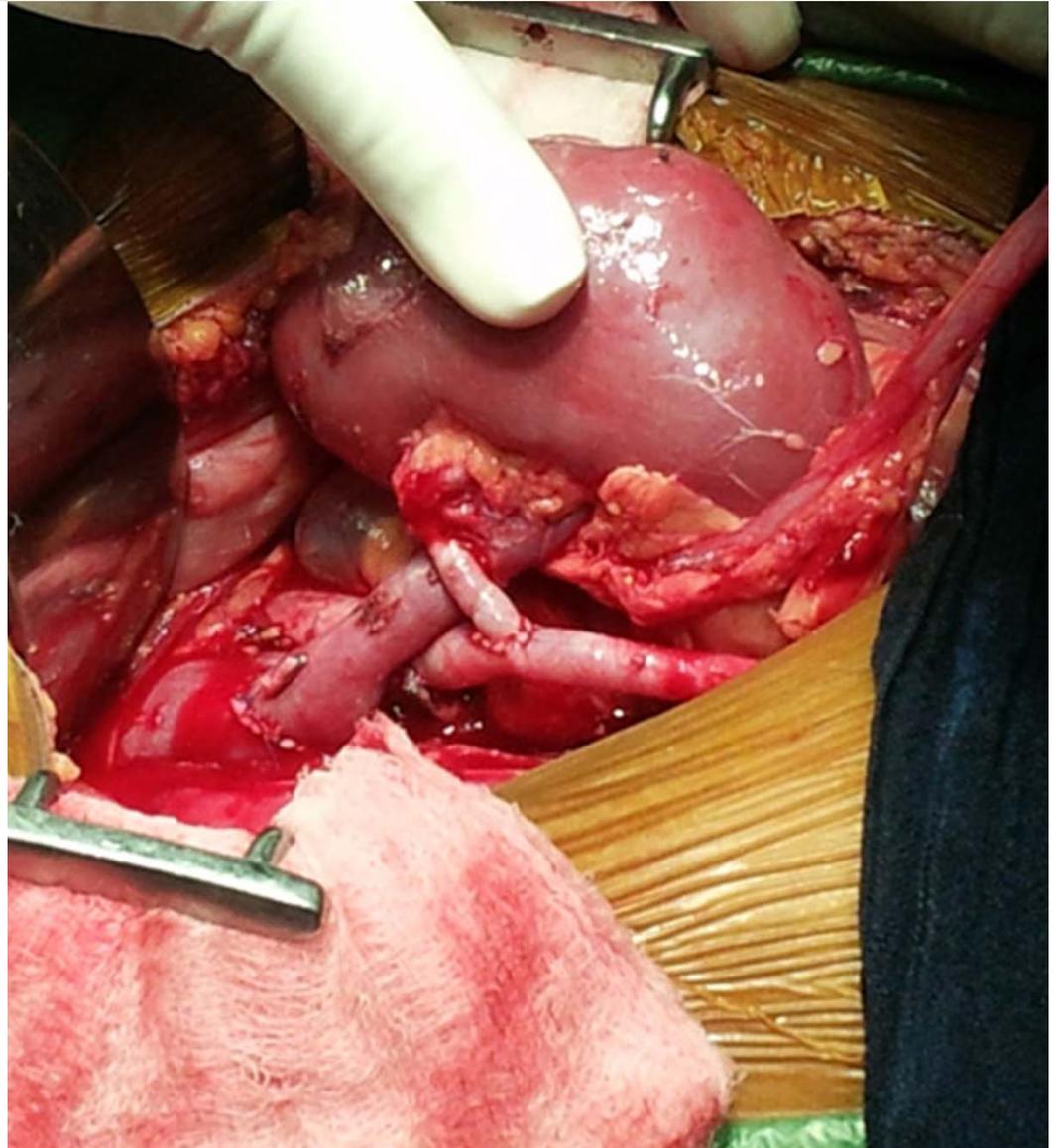
Dumb 60%



Furious 40%

Rabies: human-to-human transmission after tissue/organ transplantation

- Recipients of corneal and solid organ (liver, kidney, iliac artery) grafts died of rabies
- Most recent July 2015: 6M in Guangxi died of “viral encephalitis” 2 recipients of his kidneys died of rabies; 2 recipients of his corneas given post-exposure prophylaxis
- All donors had died of un-/mis- diagnosed neurological illnesses



Infection | **Incubation period** | **Disease** Rabies encephalomyelitis
trans-synaptic spread

20-90 days

Centripetal
Transport in
Axoplasm

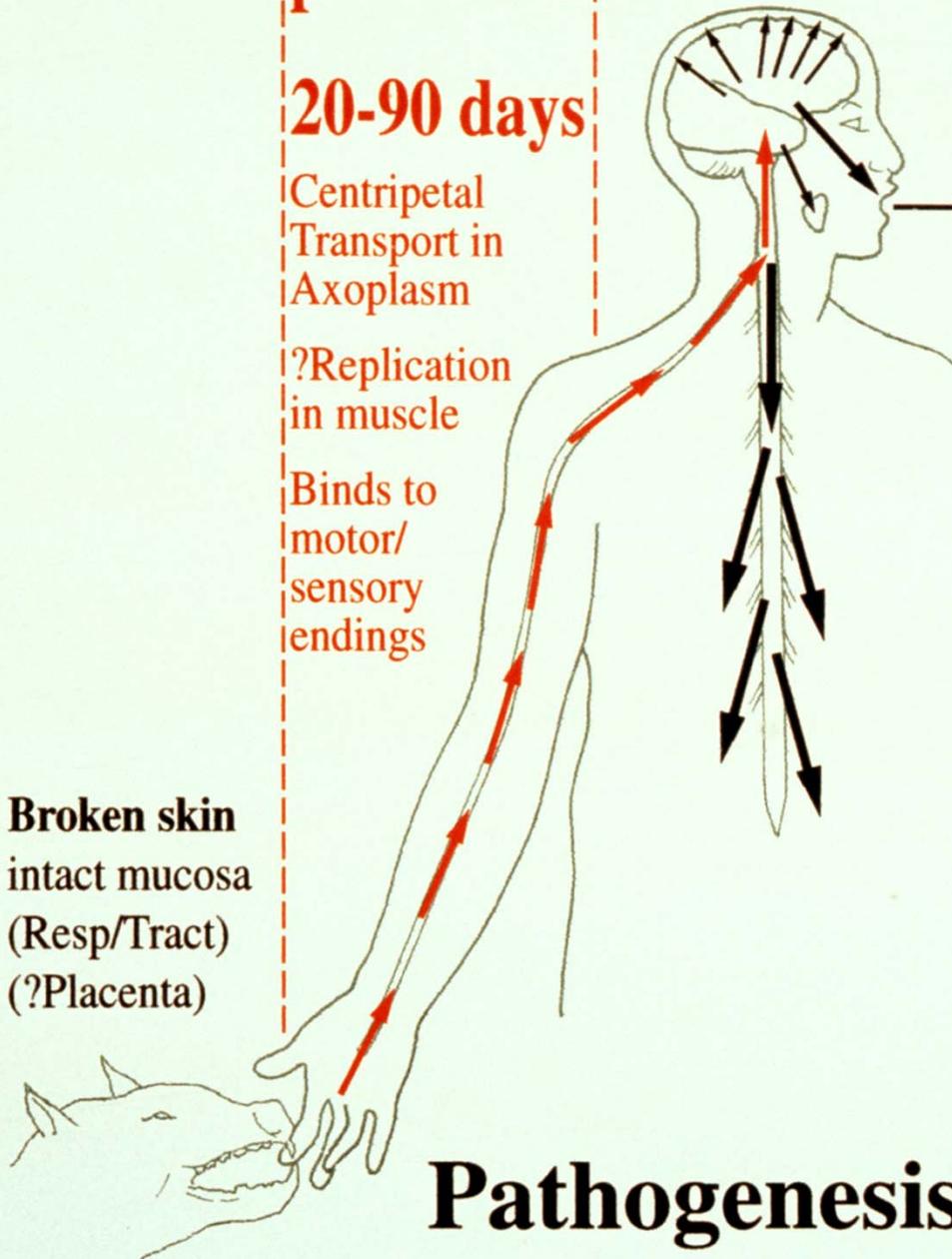
?Replication
in muscle

Binds to
motor/
sensory
endings

Centrifugal transport
Productive infection of
salivary glands

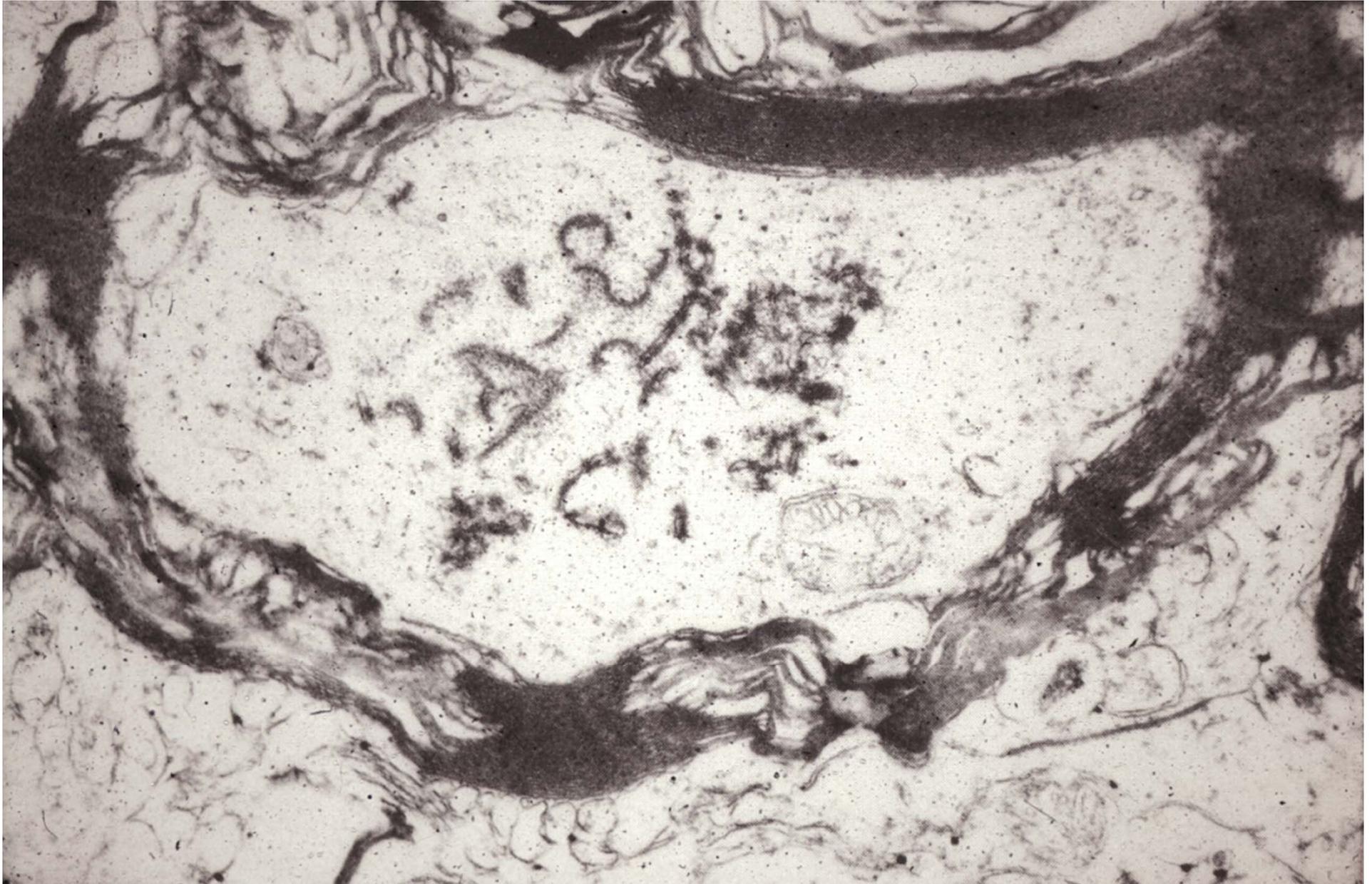
Lacrimal glands
Skin
Heart
Lung etc.

Broken skin
intact mucosa
(Resp/Tract)
(?Placenta)



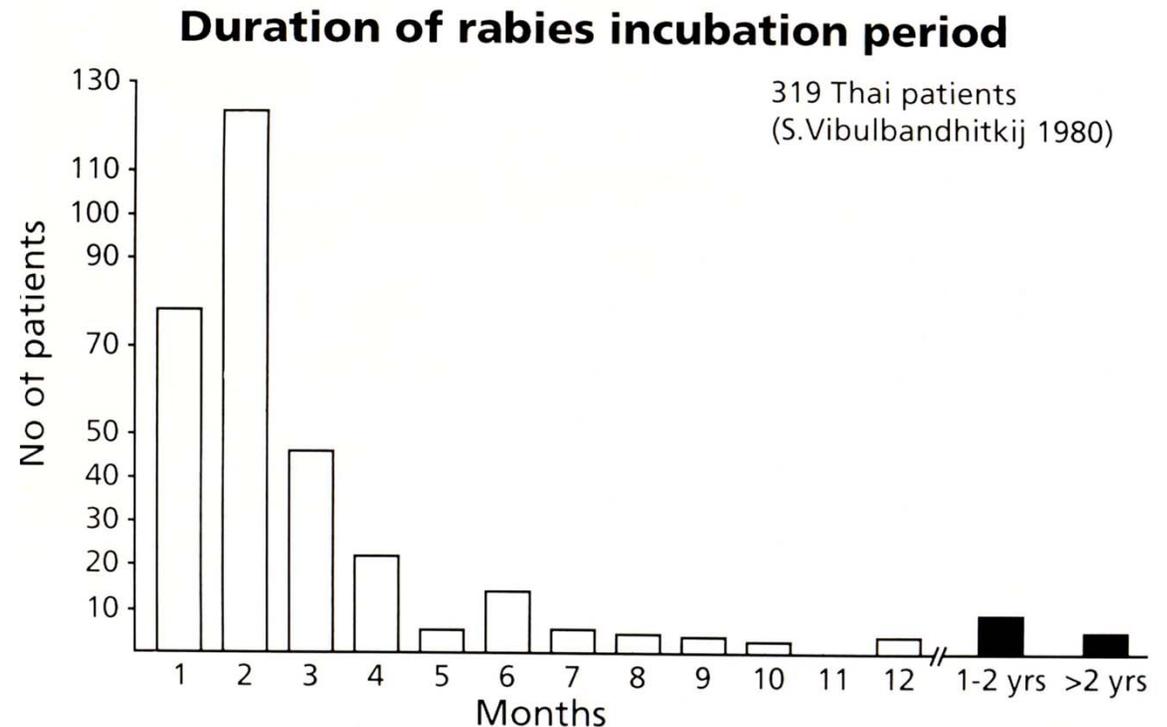
Pathogenesis of Rabies

Fast axonal transport system



Rabies encephalomyelitis

- Incubation period variable (usually few months)
- Earliest symptom – itching of healed bite wounds



Rabies encephalomyelitis

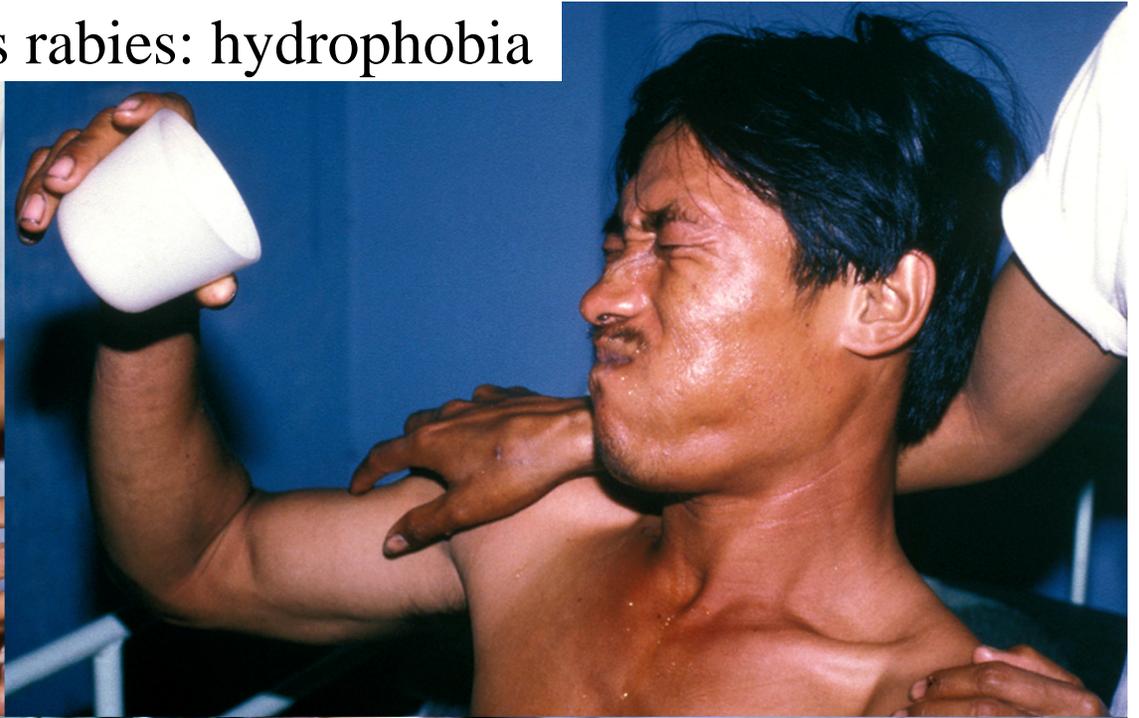
- After a few days prodromal symptoms
- Furious rabies: hydrophobic spasms, autonomic over-activity, rapid deterioration into coma
- Paralytic (“dumb”) rabies: ascending flaccid paralysis, longer survival



Furious rabies: hydrophobic spasm



Furious rabies: hydrophobia



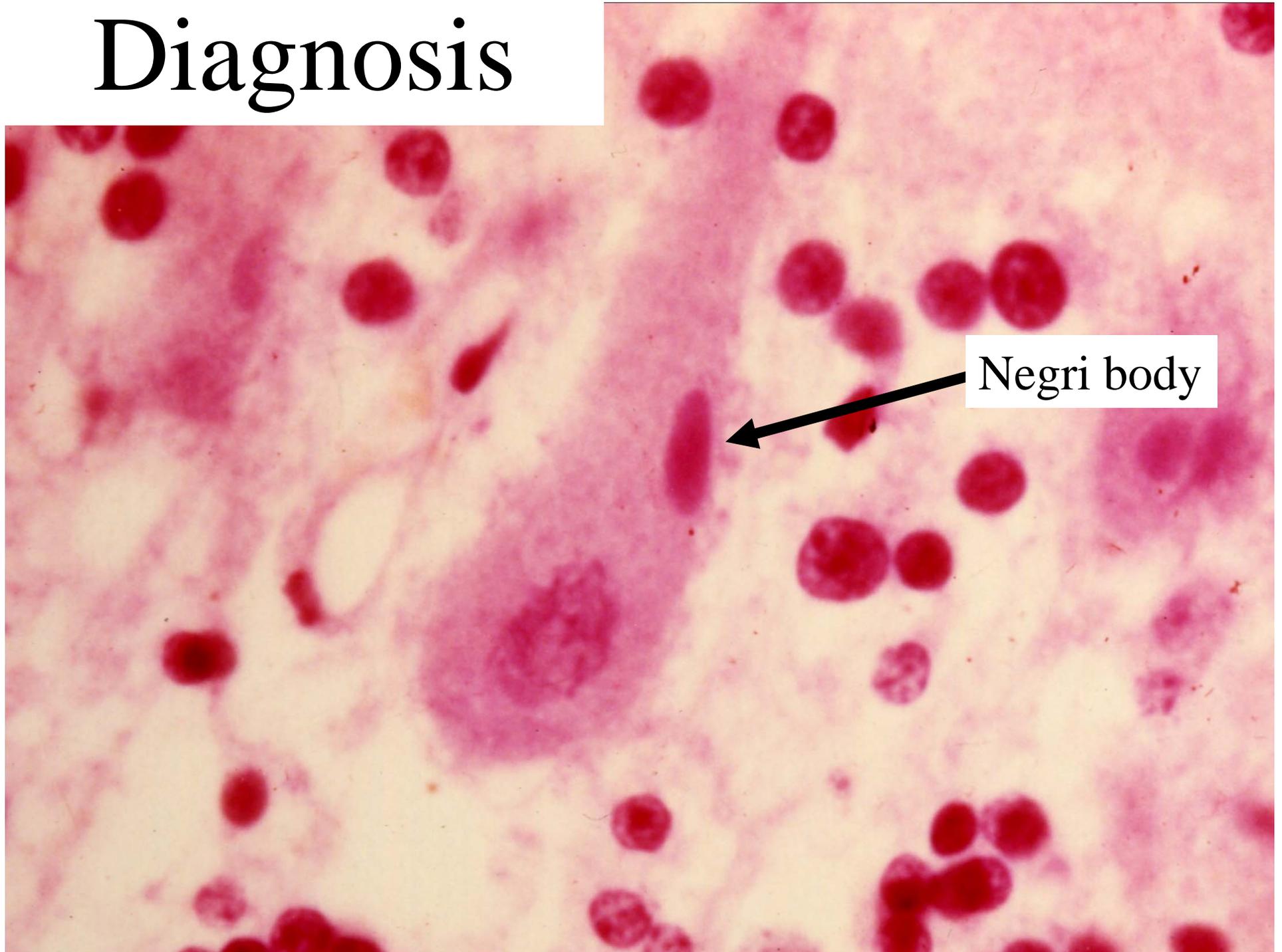
Furious rabies



Paralytic rabies



Diagnosis



16 patients reported as rabies survivors mostly diagnosed by antibody detection

- 2 Received vaccine after exposure but developed encephalitis, complete **recovery** - USA bat, Turkey dog
- 11 Incompletely vaccinated, survived but with severe sequelae
 - India 7, South Africa, Mexico, Brazil, USA, Peru
- 2 Vaccinated, survived with moderate sequelae
 - Argentina, Chile
- 1 Unvaccinated, developed encephalitis, R_x Milwaukee protocol ITU, therapeutic coma, **recovery** with mild sequelae, normal life USA

Since rabies can only very rarely be cured, emphasis must be on prevention

Prevention of human rabies: two strategies

1- Post-exposure prophylaxis



bite

POST-EXPOSURE

Vaccine + rabies immune globulin (RIG)



A few deaths

2- Pre-exposure + post-exposure booster



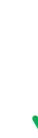
bite

POST-EXPOSURE

Booster vaccine only

PRE-EXPOSURE

Rabies vaccine



No deaths reported

Warrell MJ. Current rabies vaccines and prophylaxis schedules: Preventing rabies before and after exposure. *Travel Med Infect Dis.* 2012 Jan;10(1):1-15.

Primary post-exposure prophylaxis

Medical emergency!

- Thorough wound cleaning (iodine, alcohol)
- Passive immunisation (rabies immune globulin - RIG) infiltrated around wound
- Active Immunisation (tissue culture vaccine)



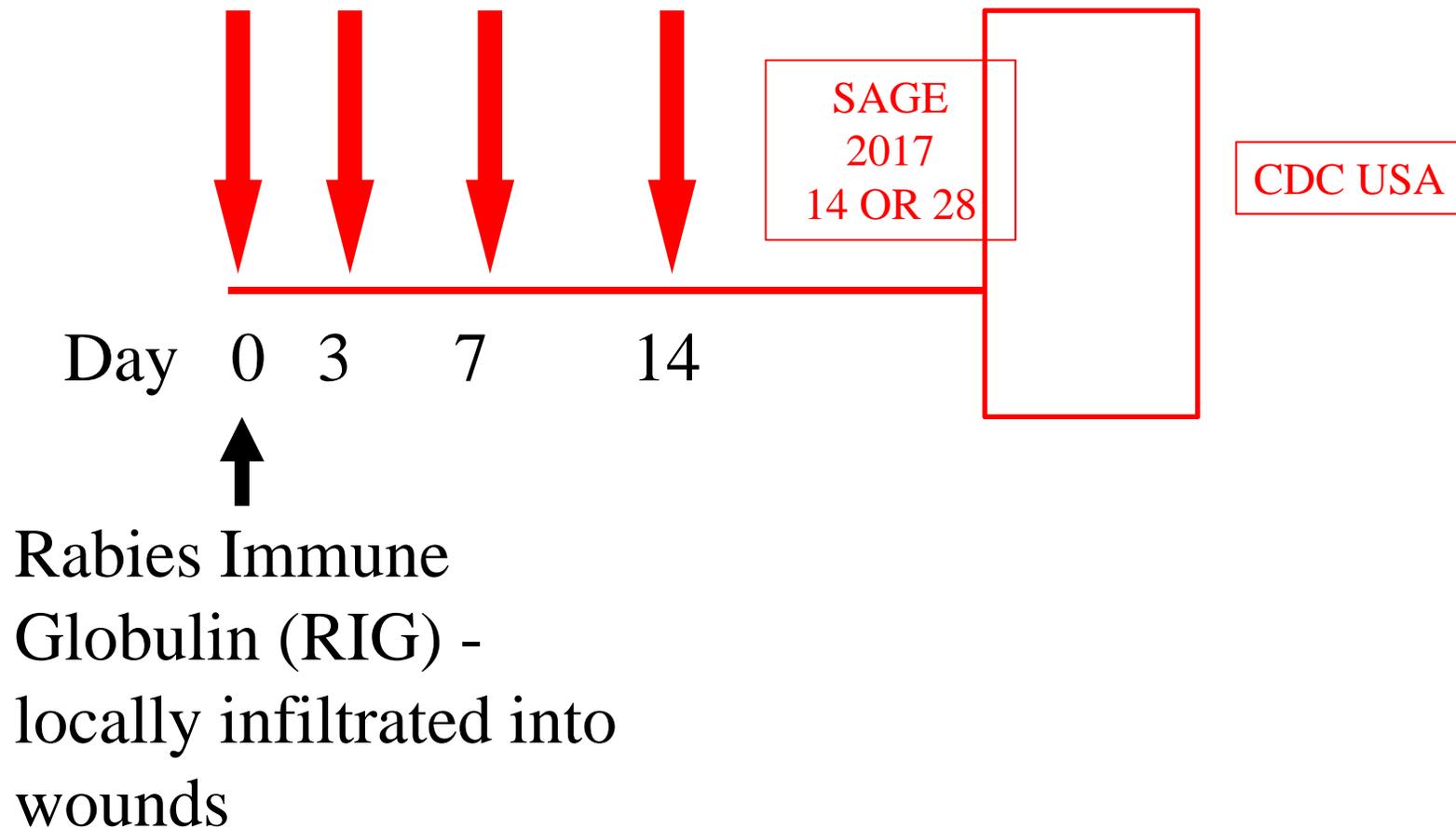
WHO Strategic Advisory Group of Experts (SAGE) on Immunization 2017

Trying to shorten all vaccination
regimens

Active immunisation with tissue culture rabies vaccine

Standard “Essen” IM rabies post-exposure vaccine regimen

IM 1-1-1-1-1 1.0 ml x 5 doses **TOO EXPENSIVE!**



Post-exposure prophylaxis in the developing world where 99% of human rabies deaths occur: need for economical regimens

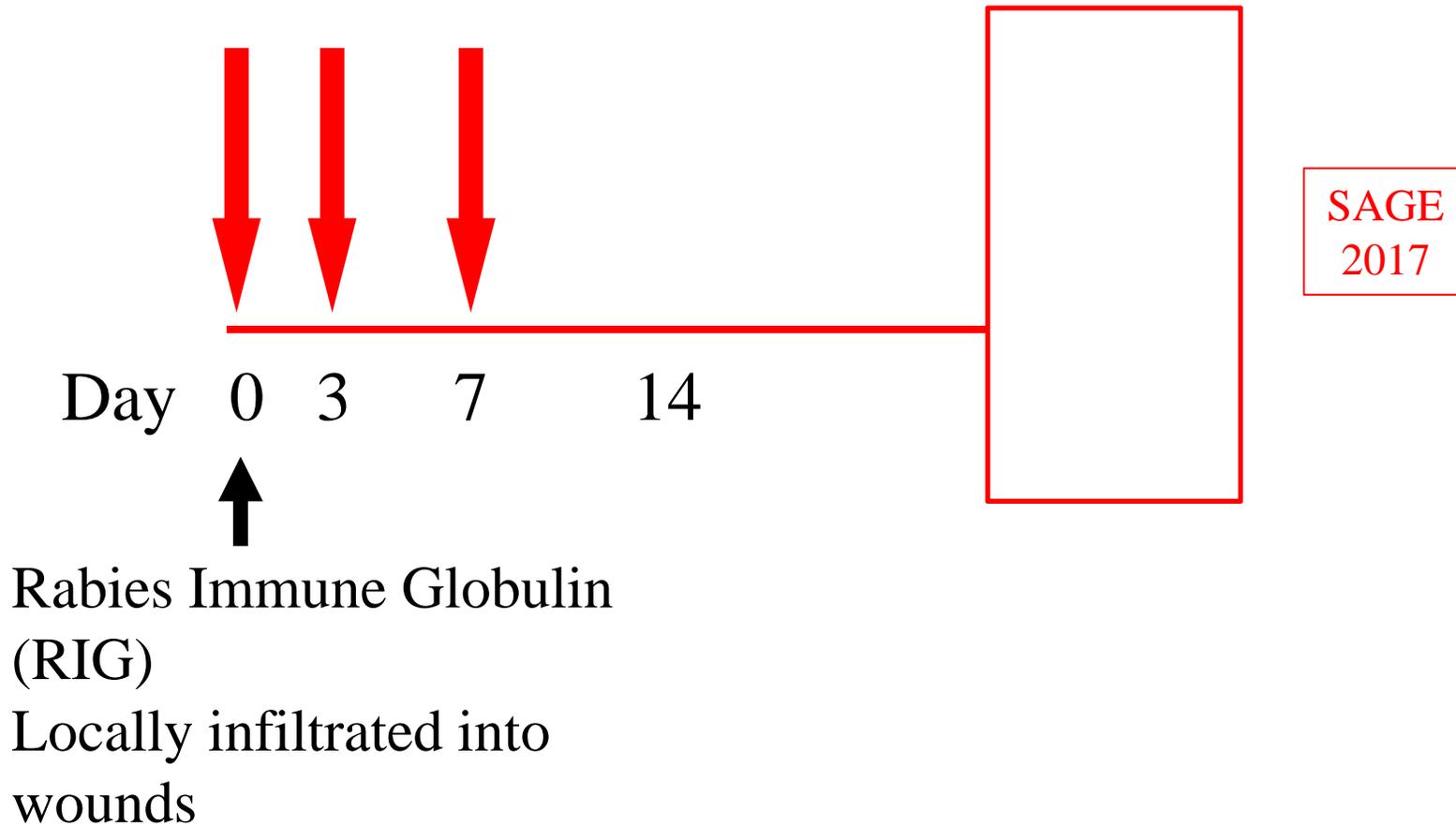
- Reduce cost while maintaining full immunogenicity
- Induce rapid immunity especially when RIG is not available
- Multi-site intra-dermal immunisation proved effective:
- “TRC” 2-site **[SAGE 2017 ID 2-2-2]**
- 8-site and 4-site regimens [days 0, 7, 14, 28]



Active immunisation with tissue culture rabies vaccine

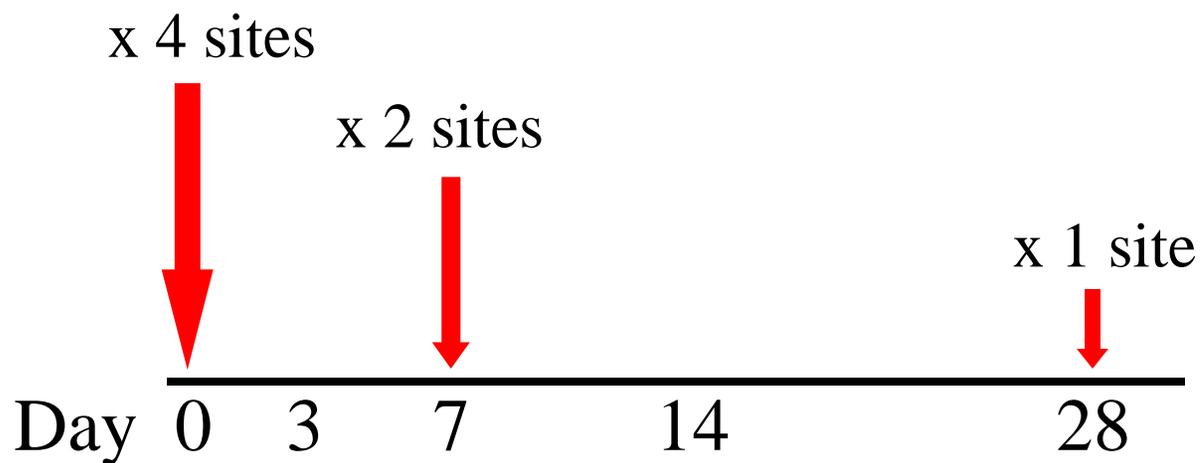
“Thai Red Cross (TRC)” ID rabies post-exposure vaccine regimen

2 x 0.1 ml ID 2-2-2-0-2



4-site ID rabies post-exposure vaccine regimen

ID 4-0-2-0-1

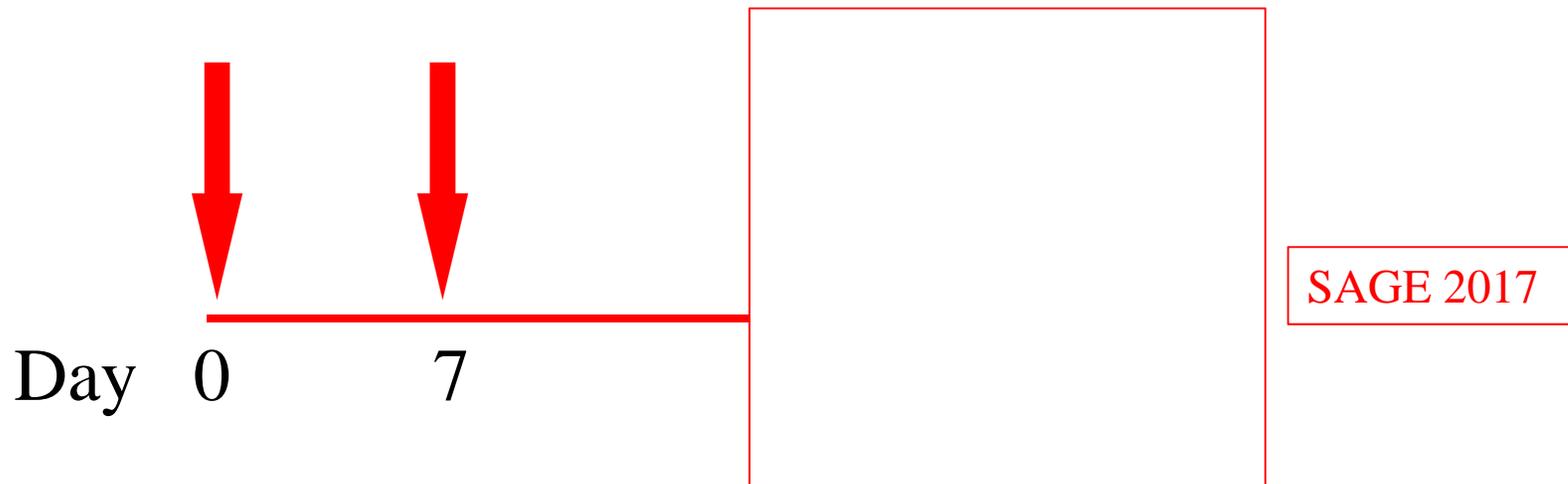


- Most economical regimen for rural areas, using <2 vials and requiring only 3 visits

Pre-exposure rabies prophylaxis

(laboratory workers, animal handlers, hospital staff, travellers to/residents of dog rabies enzootic areas, ?EPI)

1 dose IM or 2 x 0.1 ml ID on days 0, 7, 28-21

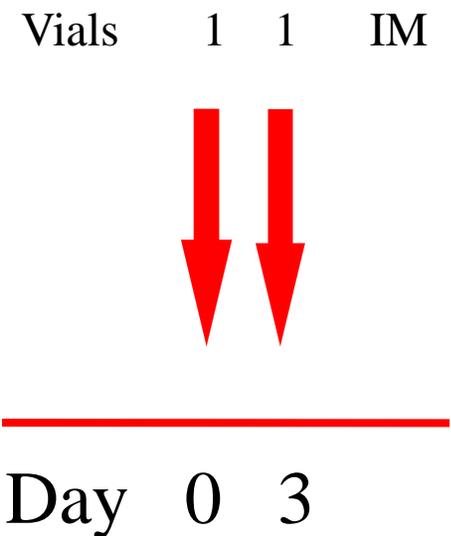


- If immuno-suppressed check neut. antibody ≥ 0.5 IU/ml

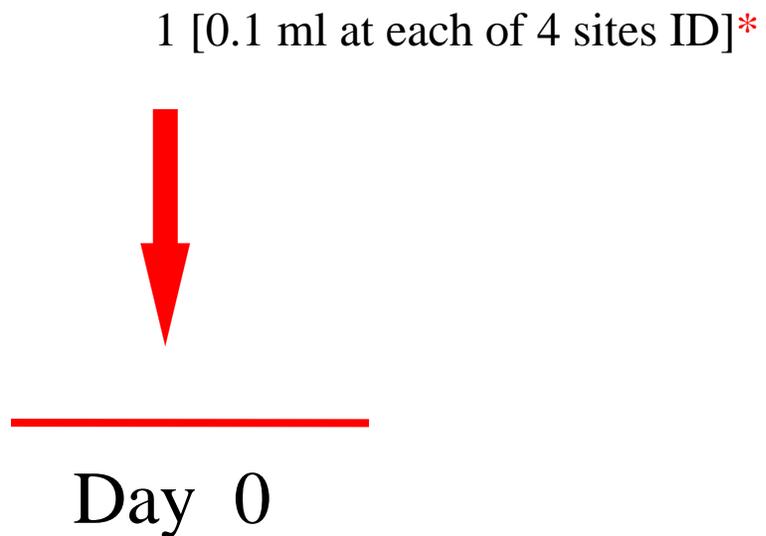
KEEP RECORD OF IMMUNISATION

Post-exposure boosting of those previously-vaccinated: two recommended regimens

The more immunogenic regimen



OR



No RIG needed

Why is human rabies “Unconquered”?

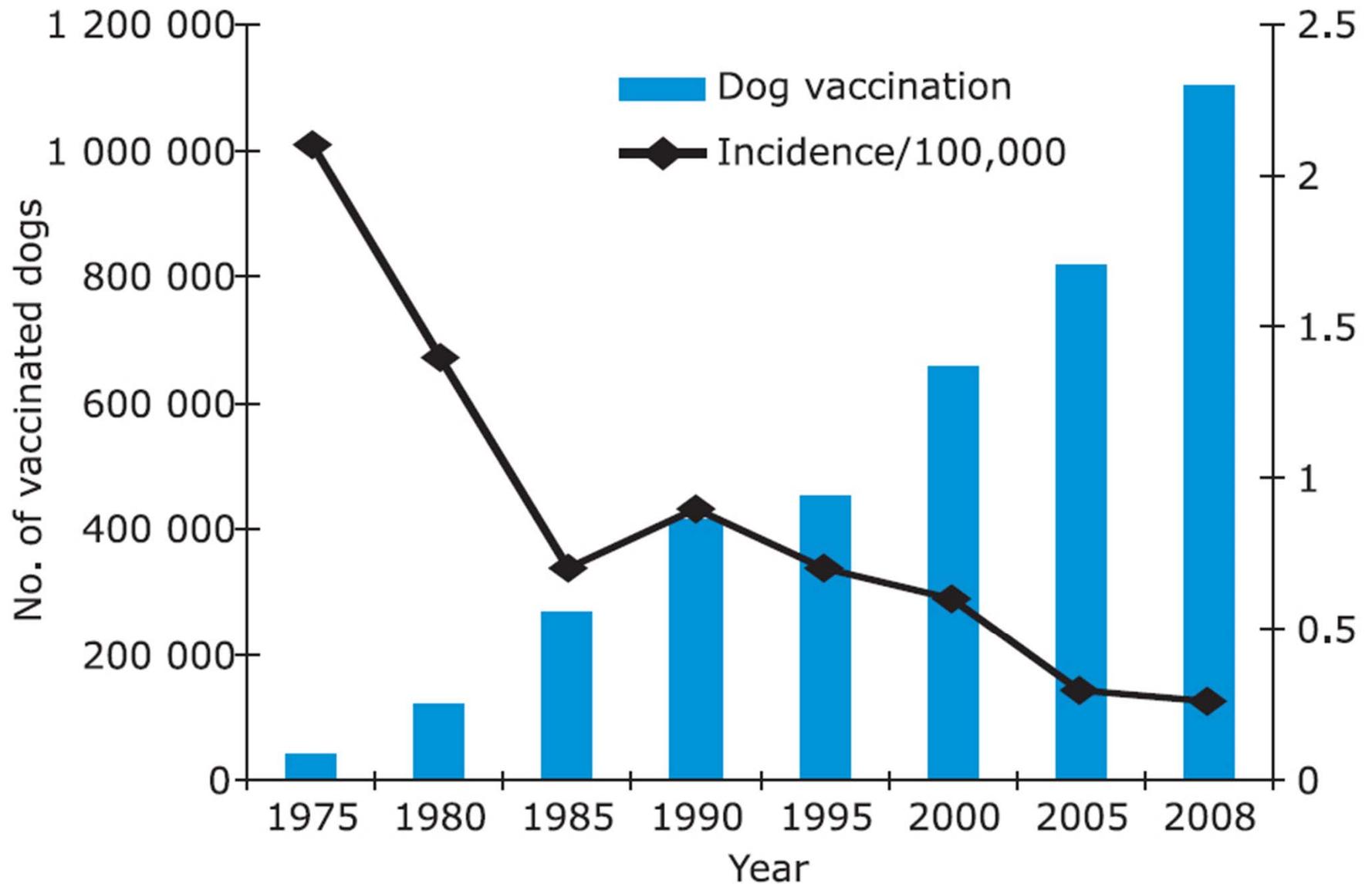


Failure of dog vaccination

Controlling rabies in domestic and wild mammals



Fig. 1: Impact of mass dog vaccination campaign on human rabies incidence, Sri Lanka, 1975-2005



Rabies: conclusions:

- **Untreatable but preventable and controllable**
- **Modern tissue/cell culture vaccines for pre- and post-exposure prophylaxis are potent and safe**
- **Multi-site id administration is effective and economical**
- **RIG is recommended but unavailable/unaffordable in developing countries**
- **Control of canine rabies is the most economical method of preventing human rabies**

