Rabies:
Overview and Perspectives

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Summary

- Why is rabies important?
- Why has rabies not yet been eliminated?
- The role of science and research in policy
- Importance of data sharing and collaboration

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EURL for Rabies

IP
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Biological Engagement Program

EU FP7 (ANTIGONE)

DEFRA

Research at the School of Veterinary Medicine

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Background:

UK's eighth vet school	Second to be opened in last 50 years	7 student applications for every place	International demand for vets in the areas of livestock, research & pathology

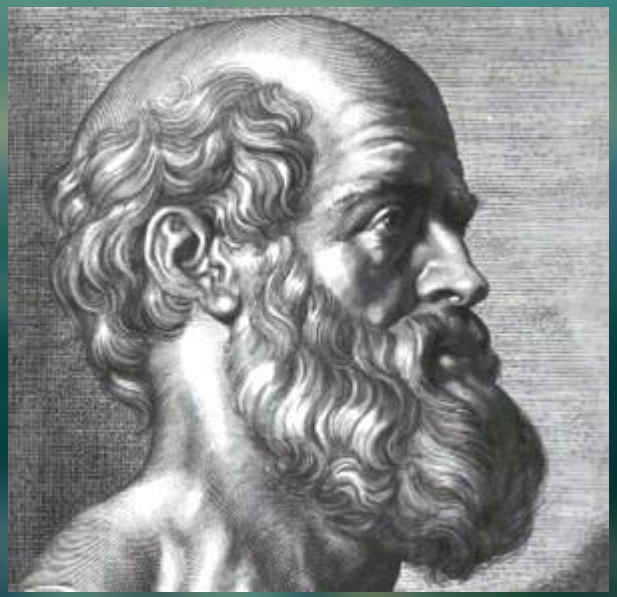
Timeline:

- First cohort of 48 students **2014**
- 120 students per year from **2015**
- RCVS Accreditation **2019**

Mission: Inspire and educate veterinary professionals who will advance veterinary medicine to meet the needs of a changing world

‘public health depends on a clean environment’

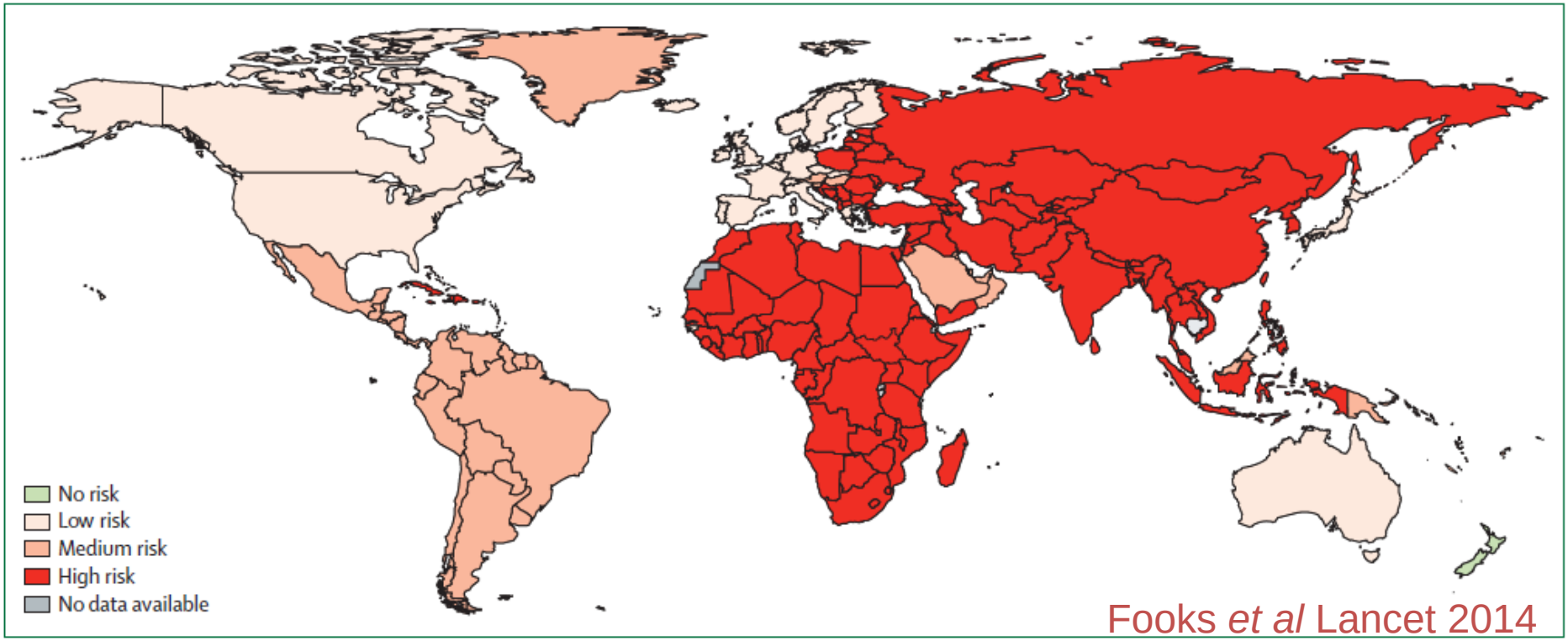
Hippocrates. circa 400 BC (reviewed in W. H. S. Jones. Cambridge. Harvard University Press. 1868)



Global impact: Why is rabies important?

- Kills an estimated 100 children each day
- Kills 25-159,000 people annually
- Impacts animal AND human health and welfare
- Is entirely preventable through vaccination
- Elimination of dog-to-dog transmission of rabies is possible

Global rabies risk map



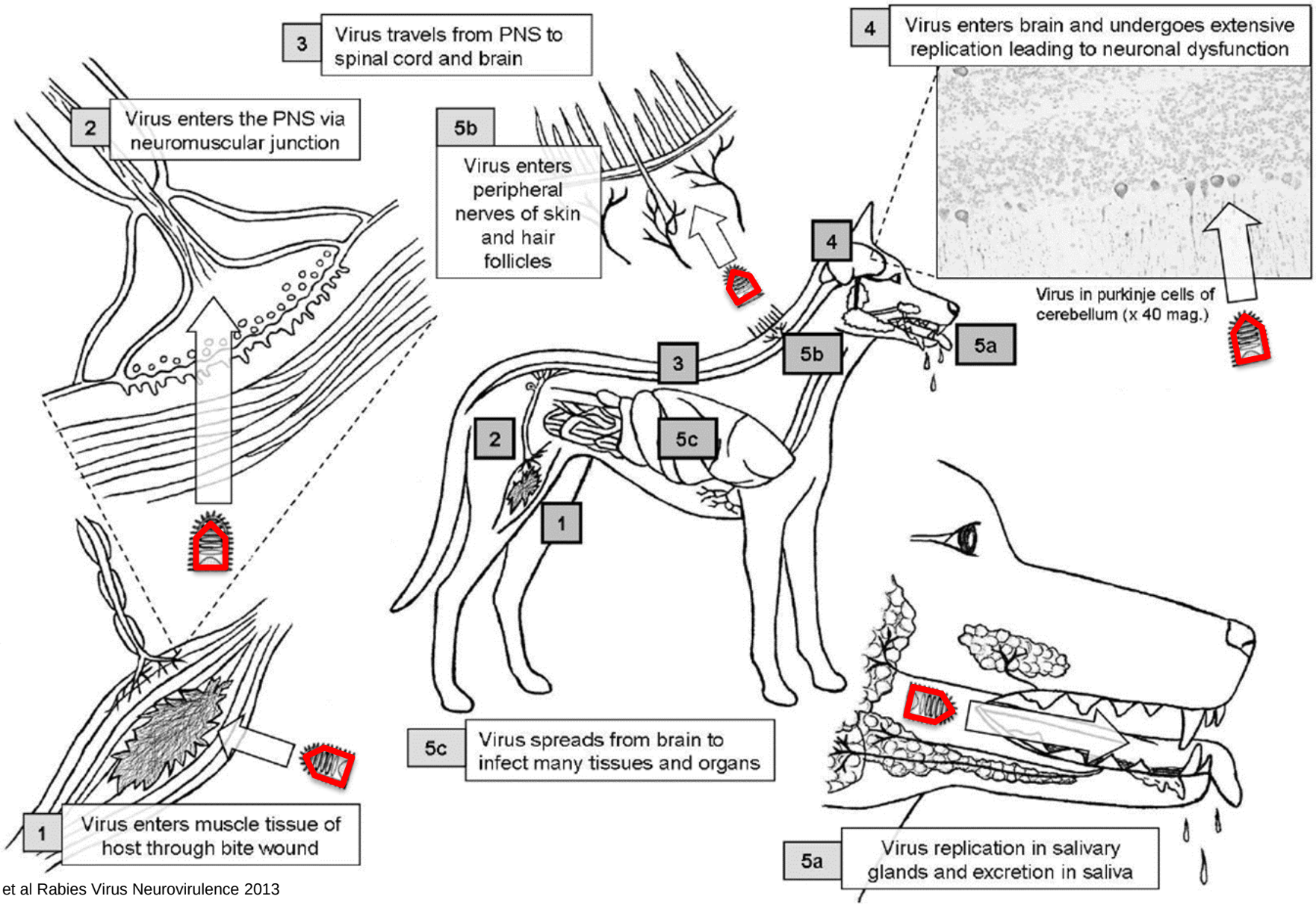
Fooks *et al* Lancet 2014

Cost in numbers:

- **25-159,000 human deaths per year**
- **Countless more animal deaths**
- **8.6 billion USD losses annually**

Hampson *et al* PlosNTD 2015

Rabies pathogenesis



Jeffries et al Rabies Virus Neurovirulence 2013

Diagnosis is difficult

Direct fluorescent antibody (DFA) on acetone fixed brain smears

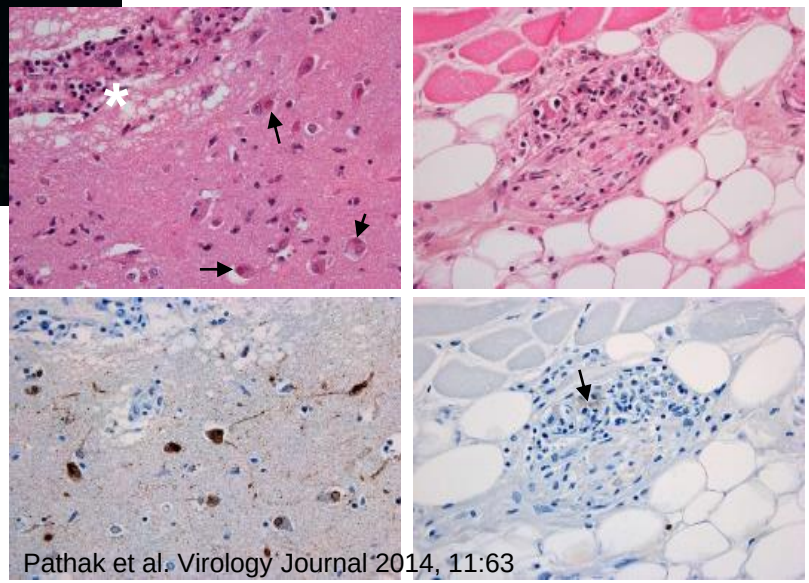
- Gold standard for animal rabies diagnosis
- **Post mortem**
- Trained personnel
- Expensive reagents and equipment

Virus isolation – Bioassay or Cell culture

Immunohistochemistry, DRIT

Serology- virus neutralisation test

RT-PCR, sequencing and virus typing



Pathak et al. Virology Journal 2014, 11:63

Diqqət! Diqqət! Diqqət!

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BU HEYVANLAR QUDUZLUQ XƏSTƏLİYİ TÖRƏDƏ BİLƏR!

QUDUZLUĞUN ƏLAMƏTLƏRİ: AĞIZIN SULANMASI, AQRESSİVLİK VƏ YA SAKİTLİK, ANORMAL DAVRANIŞ

ƏGƏR SİZ QUDUZLUQDAN ŞÜBHƏLƏNİRSİNİZSƏ, DƏRHAL SAHƏ BAYTAR HƏKİMİ VƏ YA RAYON BAYTARLIQ İDARƏSİNƏ XƏBƏR VERİN

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Reducing dog rabies reduces human cases

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Casos de rabia en Humanos

Casos de rabia en Caninos

Años

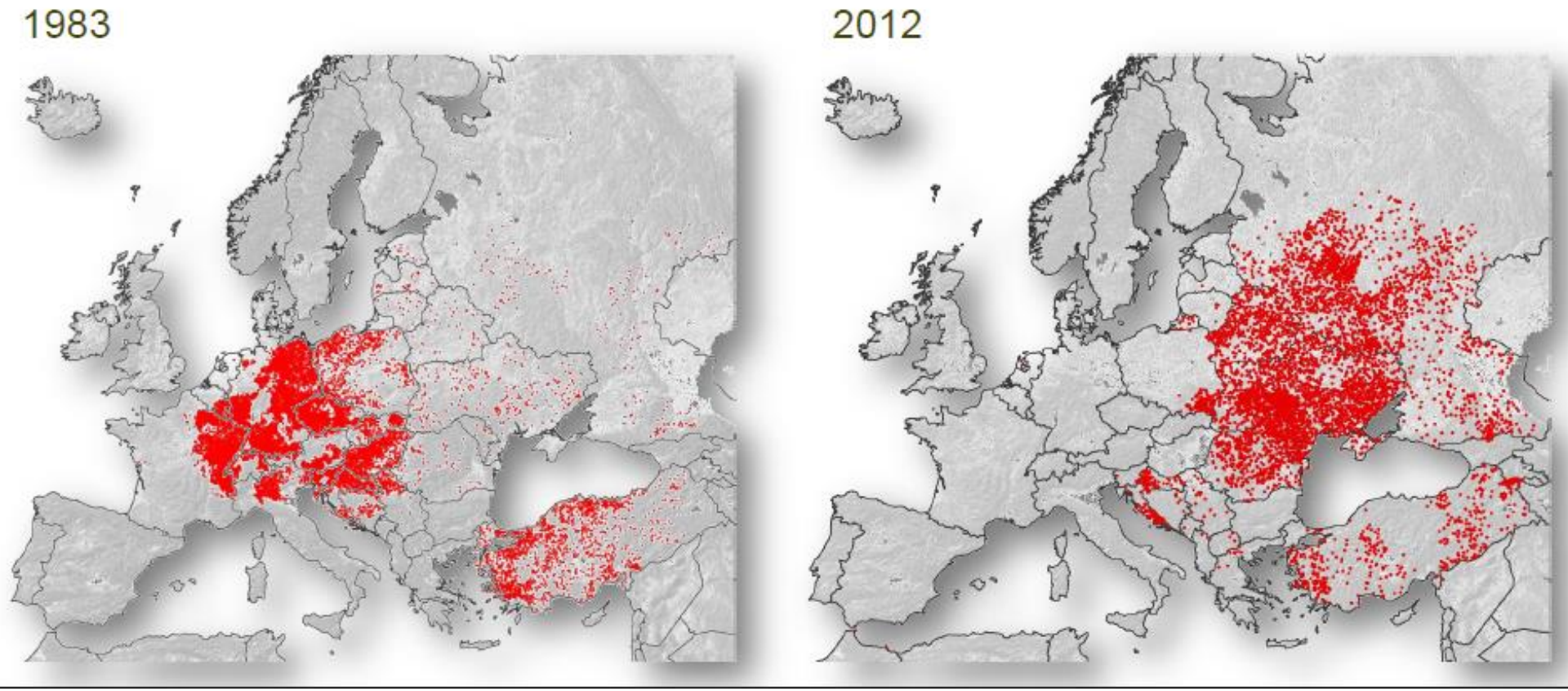
PANAFTOSA
Centro Panamericano de Fiebre Aftosa
Salud Pública Veterinaria

Humans cases by dogs

Humans cases by vampire bat

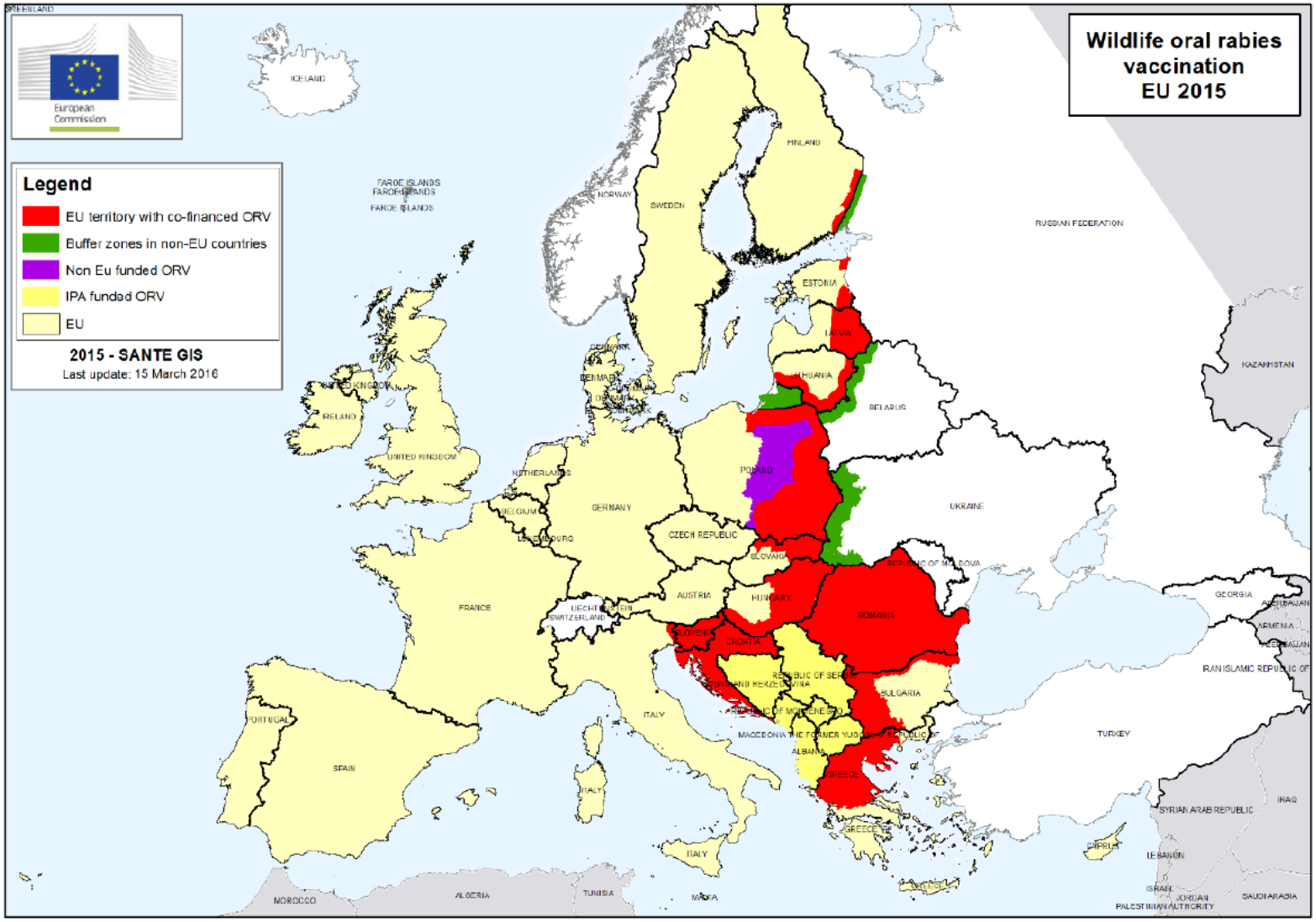
Canine cases

Rabies vaccination in wildlife



Data: Rabies bulletin Europe

Expensive



20-27 Million EURO per year 2012-2016 (European Union, 2017)

Rabies in the Middle East and Central Asia

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- Challenges
  - Culturally and geographically diverse
  - Multiple borders and trade routes
  - Burden of rabies not easy to quantify
    - Reported incidence of ranges from 0.2 to 10/100,000 in humans*
    - Incidence in animals unknown

(* Multiple data sources)

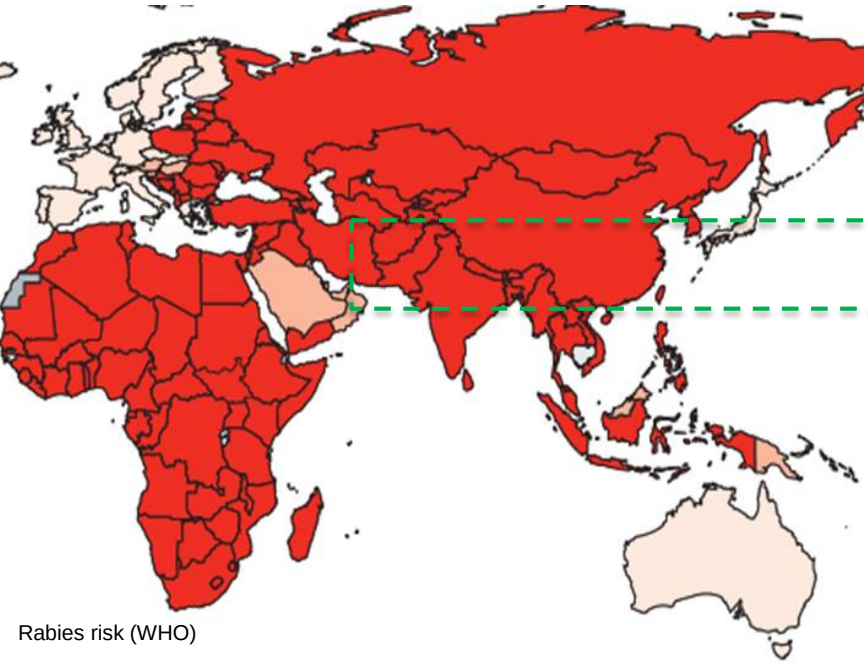
Questions:

Where and when is rabies spreading?

What is the reservoir (source) of human rabies?

Where and when is rabies spreading?

Use virus genomes to reconstruct evolutionary history

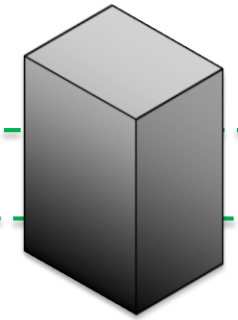


Rabies risk (WHO)

180 samples over 40 years

FTA™ cards

Policy-relevant risk assessment



Bayesian phylogenetics

Partial N gene sequences

Horton et al. (2015)

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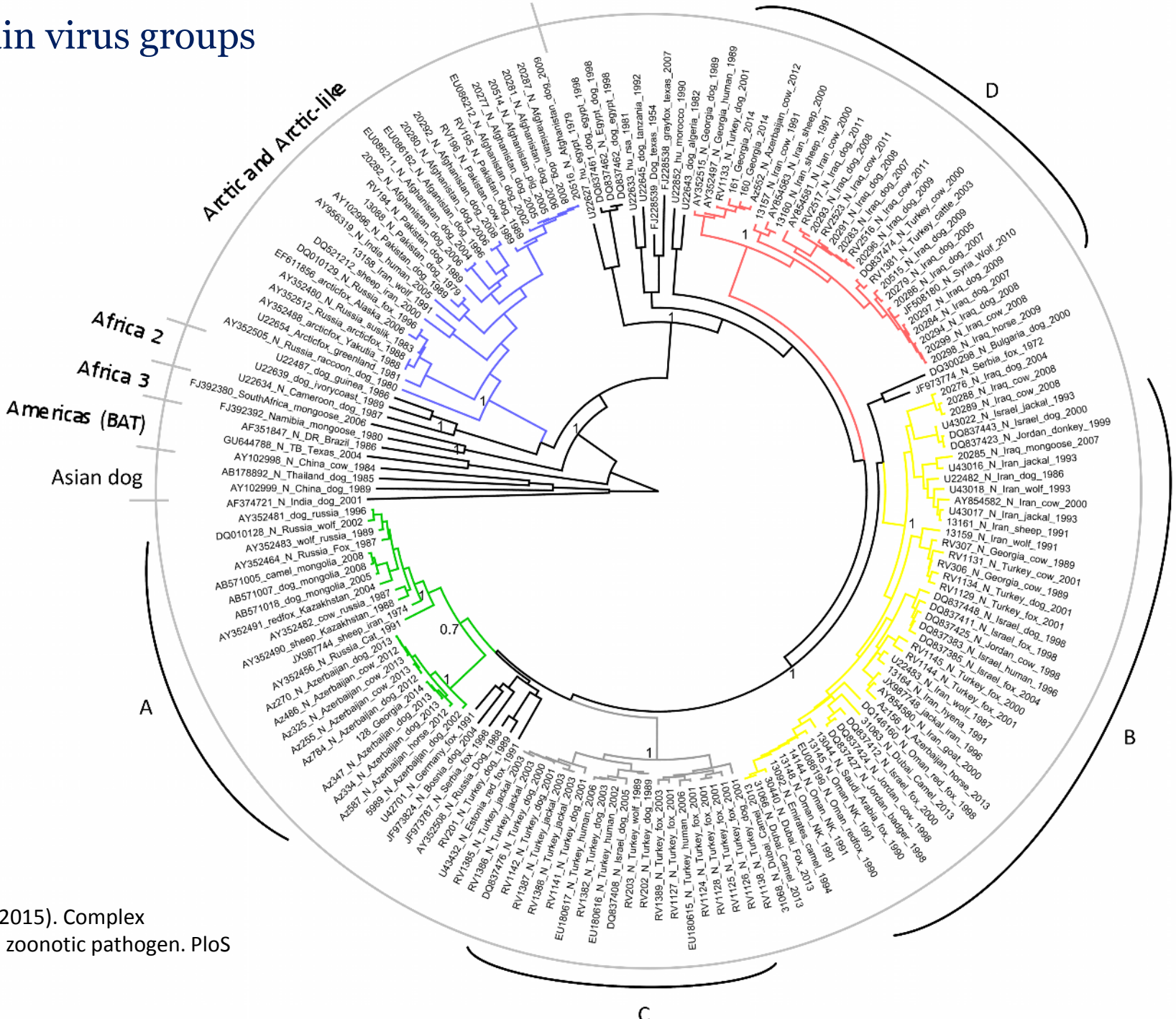
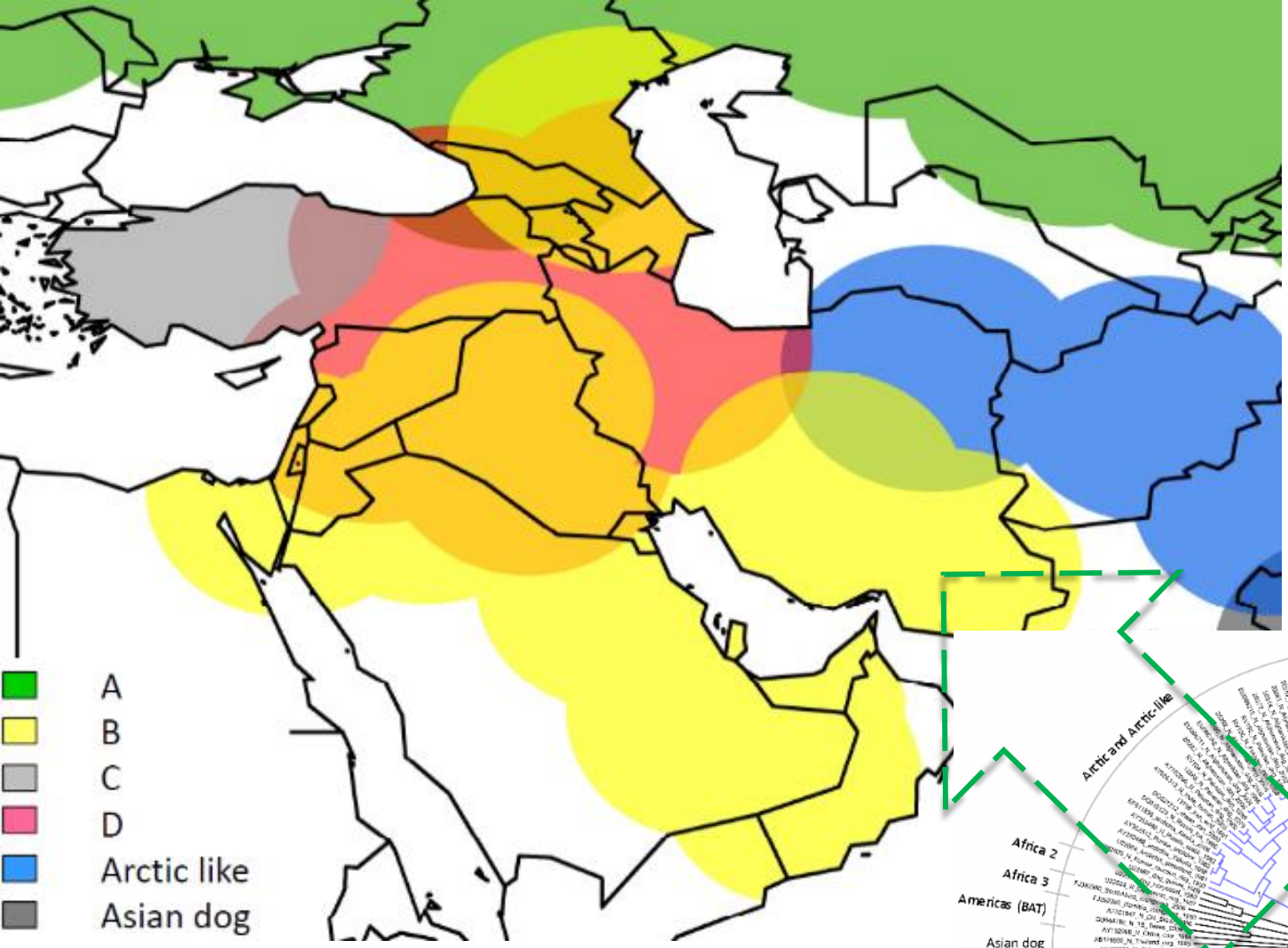
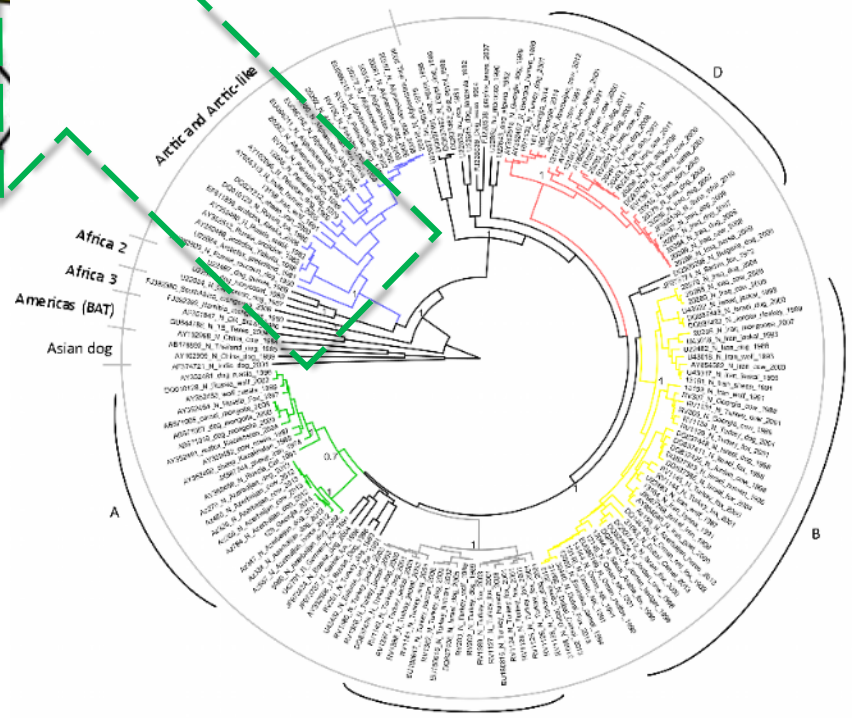
=Four main virus groups

So what?



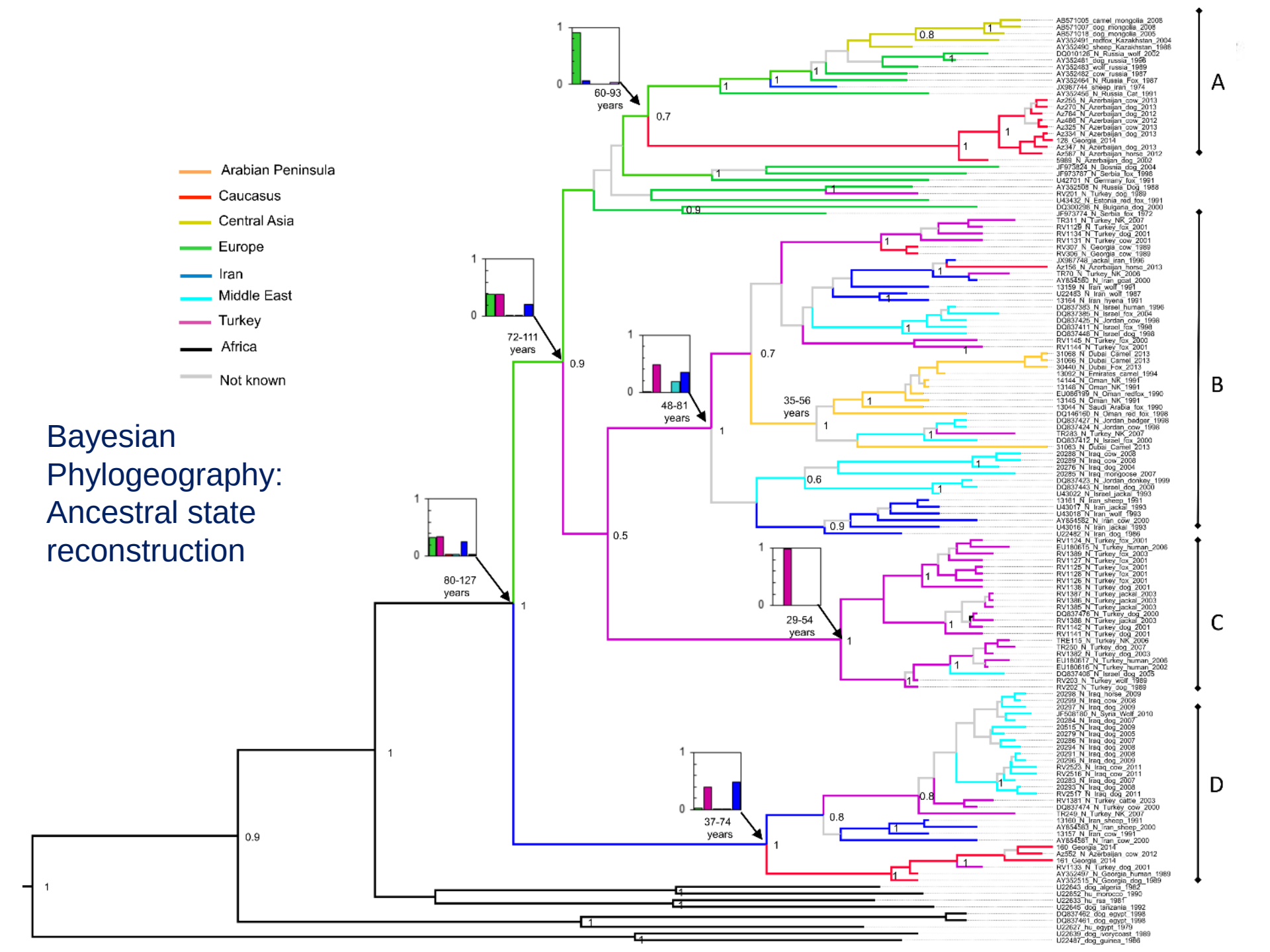
Horton DL, et al. (2015). Complex Epidemiology of a zoonotic pathogen. PloS NTD

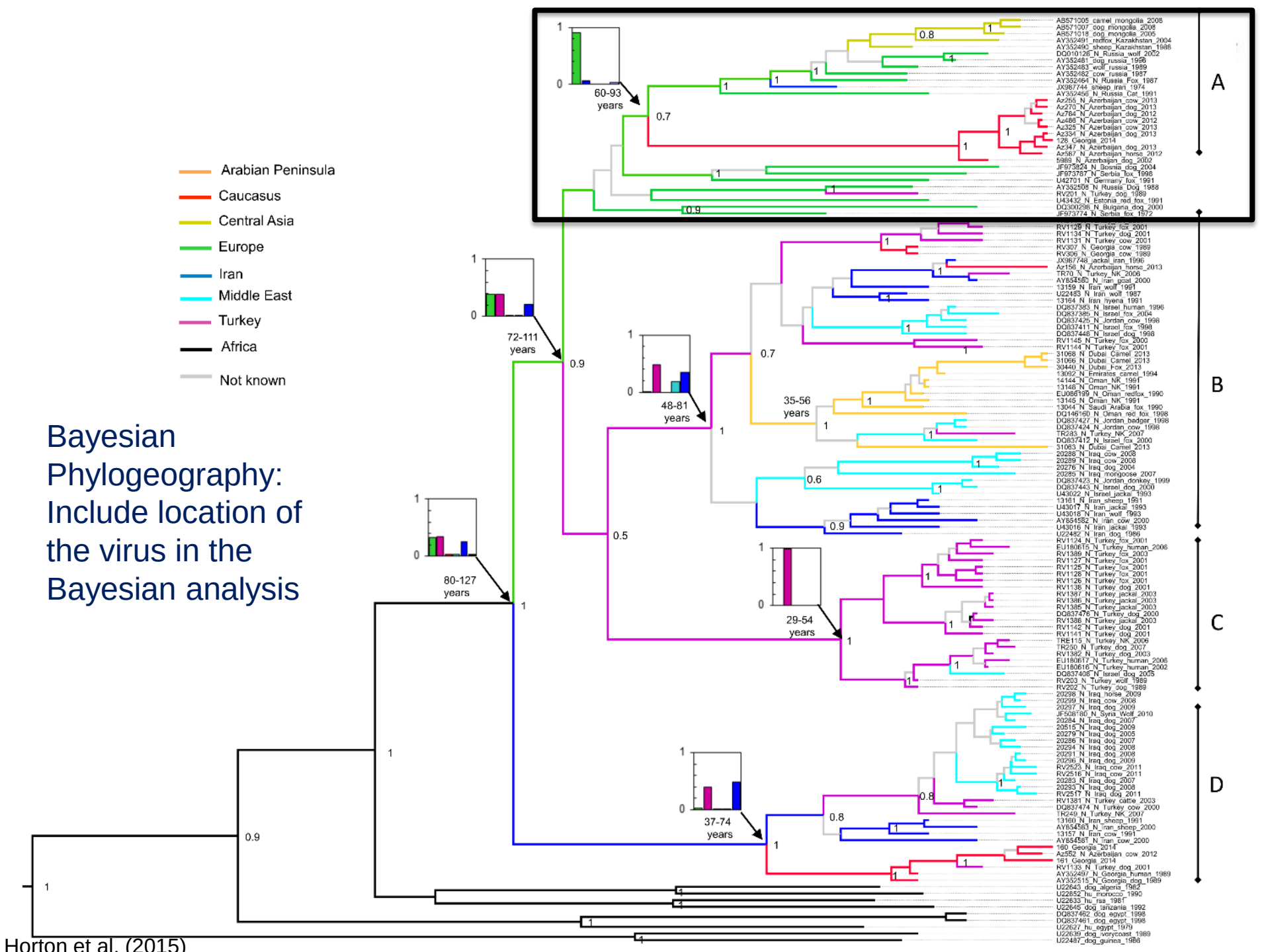




-Mapping the distribution of existing clades

-In some areas three clades circulating at the same time

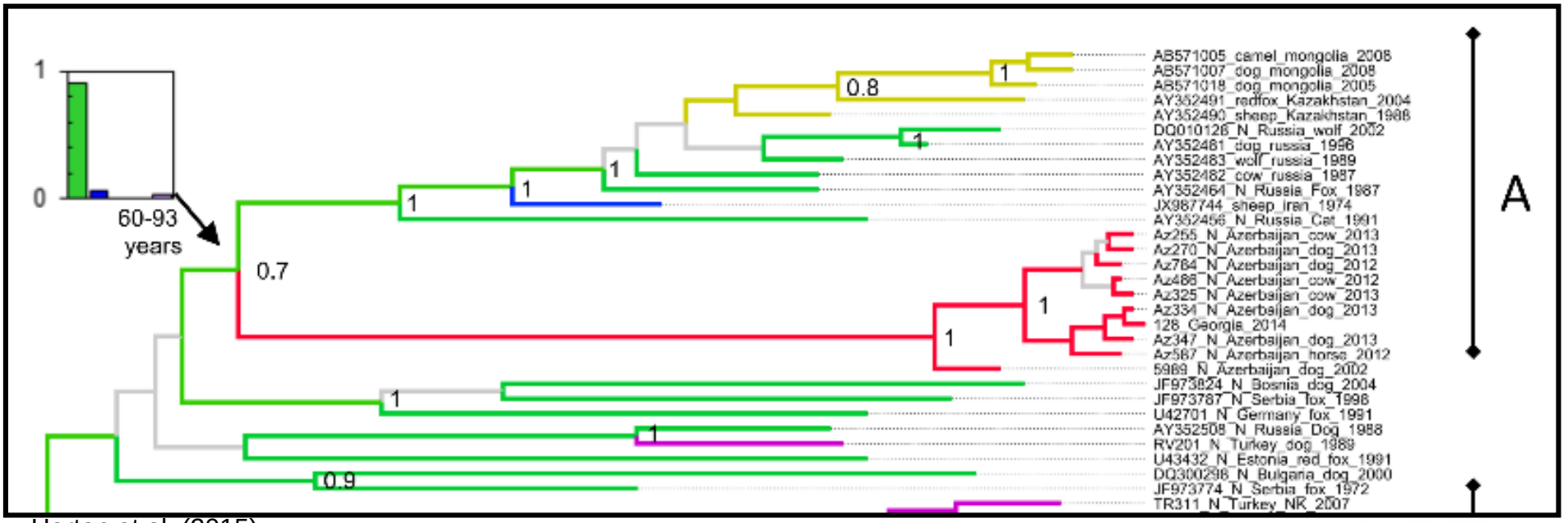

Arabian Peninsula
Caucasus
Central Asia
Europe
Iran
Middle East
Turkey
Africa
Not known
Bayesian Phylogeography: Ancestral state reconstruction
60-93 years
72-111 years
48-81 years
35-56 years
80-127 years
29-54 years
37-74 years
A
B
C
D



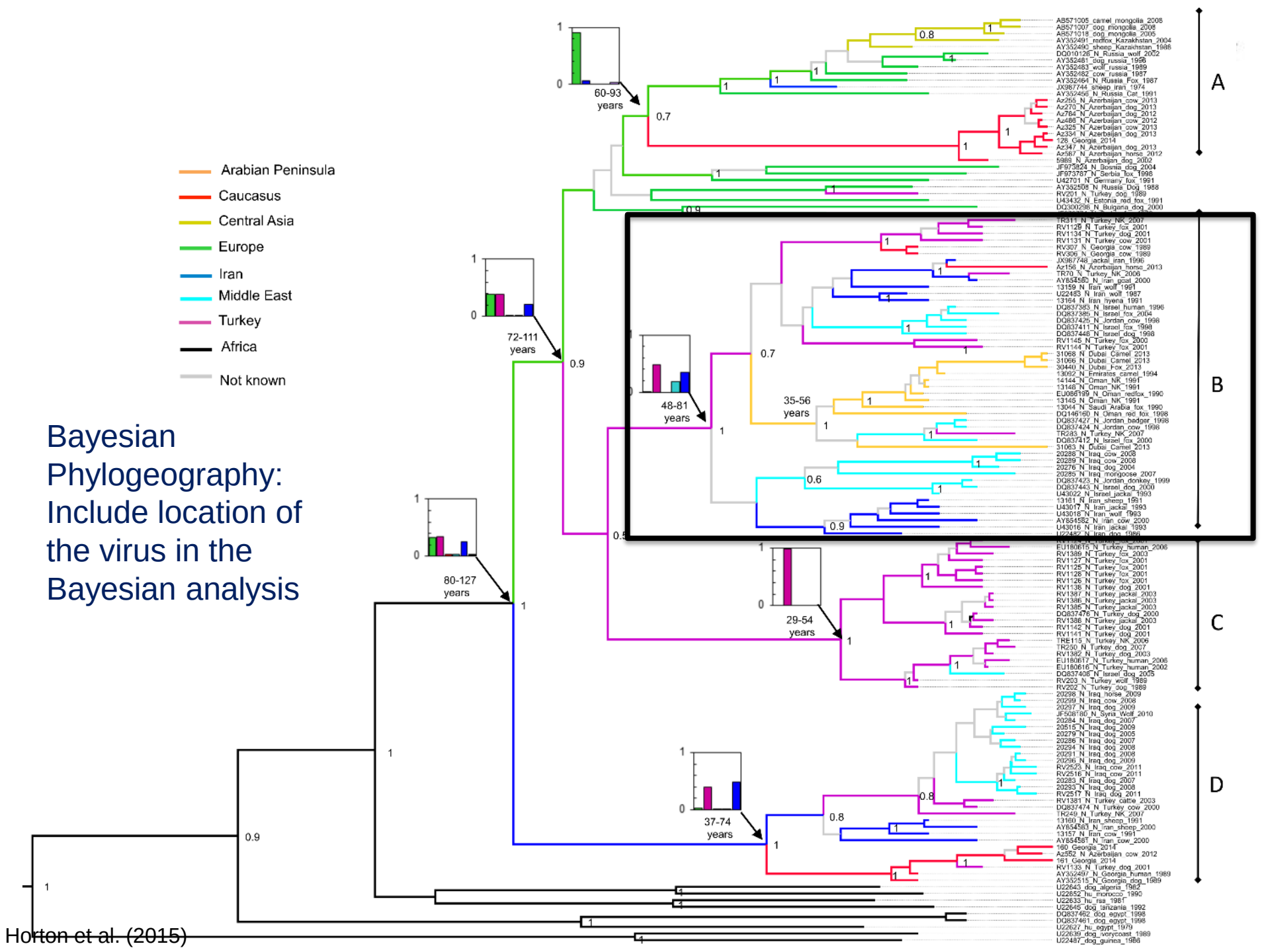
Bayesian Phylogeography: Include location of the virus in the Bayesian analysis

Horton et al. (2015)

- Clade A (currently circulating in the Caucasus)
- >90% probability that ancestor occurred in Europe



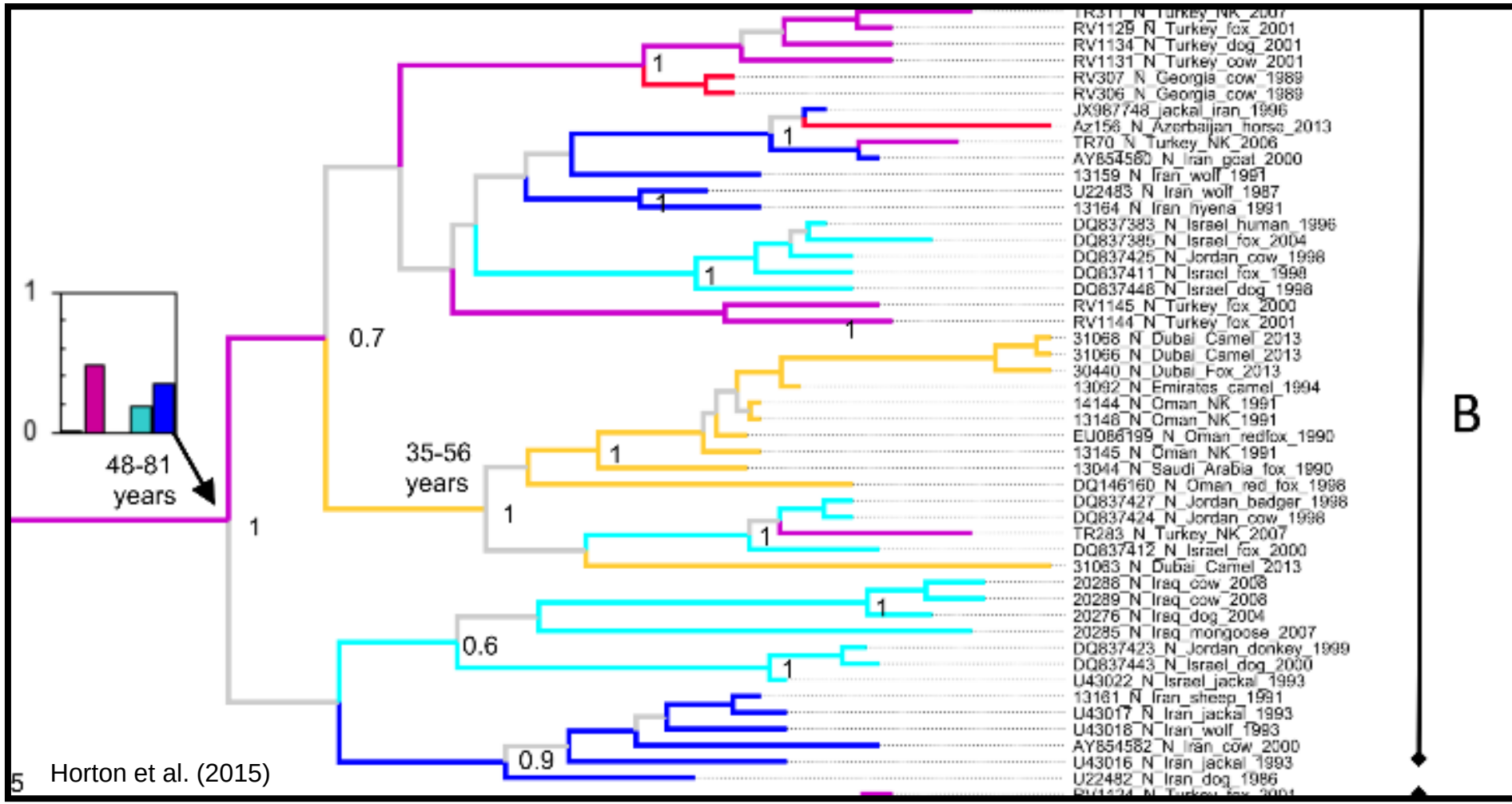
Horton et al. (2015)



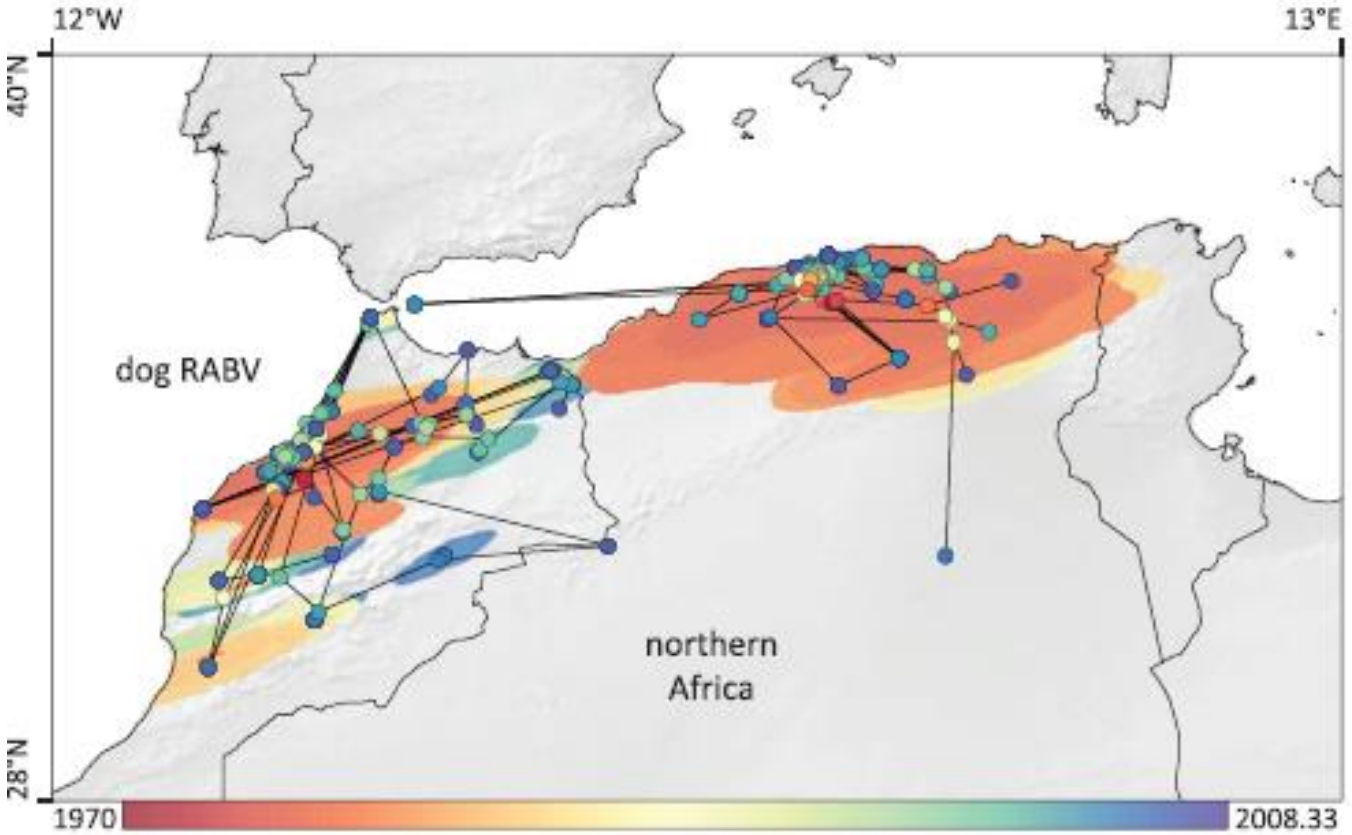
Bayesian Phylogeography: Include location of the virus in the Bayesian analysis

Horton et al. (2015)

Clade B in multiple countries- Caucasus, Middle East, Arabian Peninsula
The origin is more uncertain



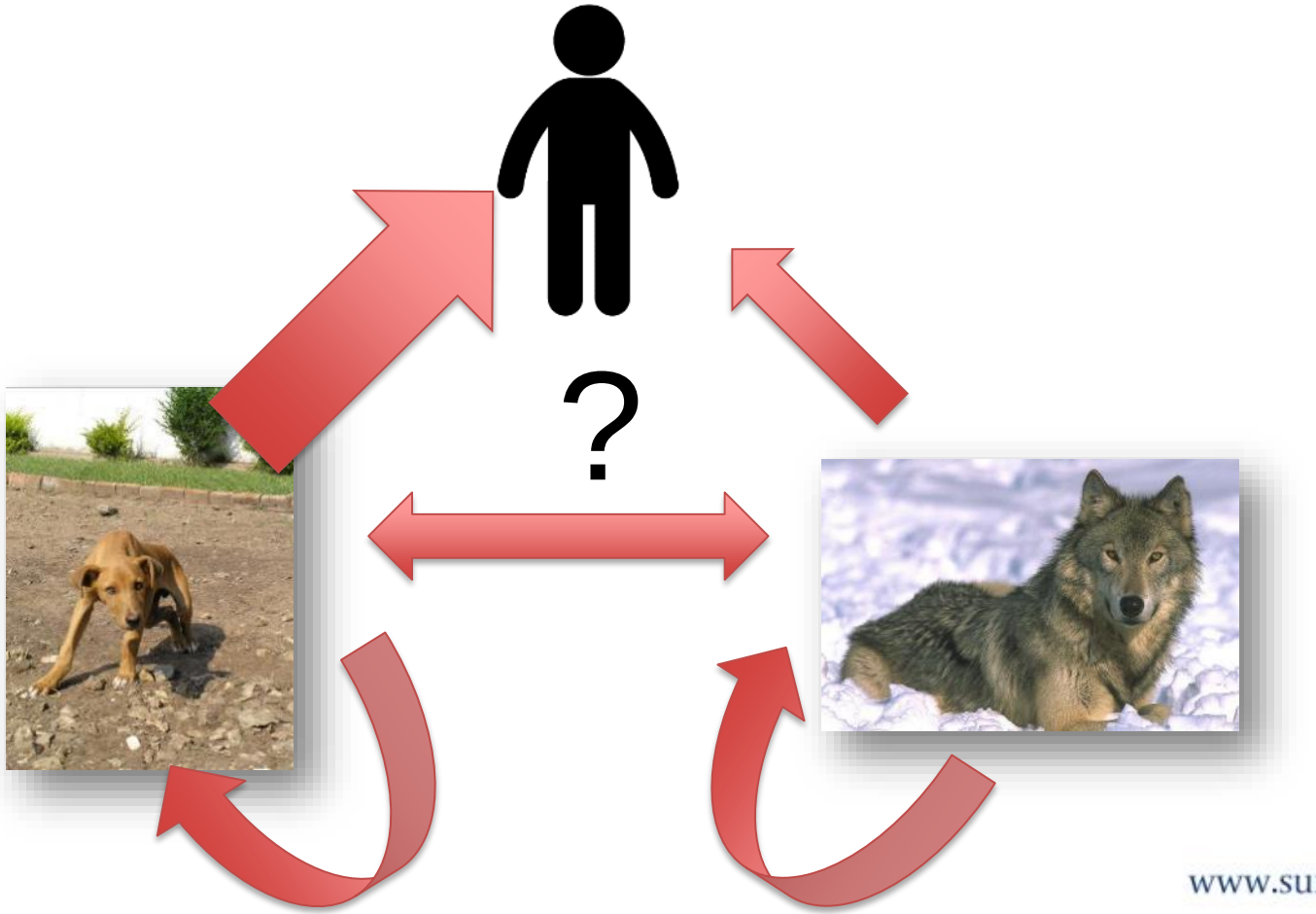
Horton et al. (2015)



- Measure the effect of environmental and human factors on speed of spread (Dellicour *et. al. MBE* 2017)

- Rabies occurs in urban (dog) or sylvatic (wildlife) cycles

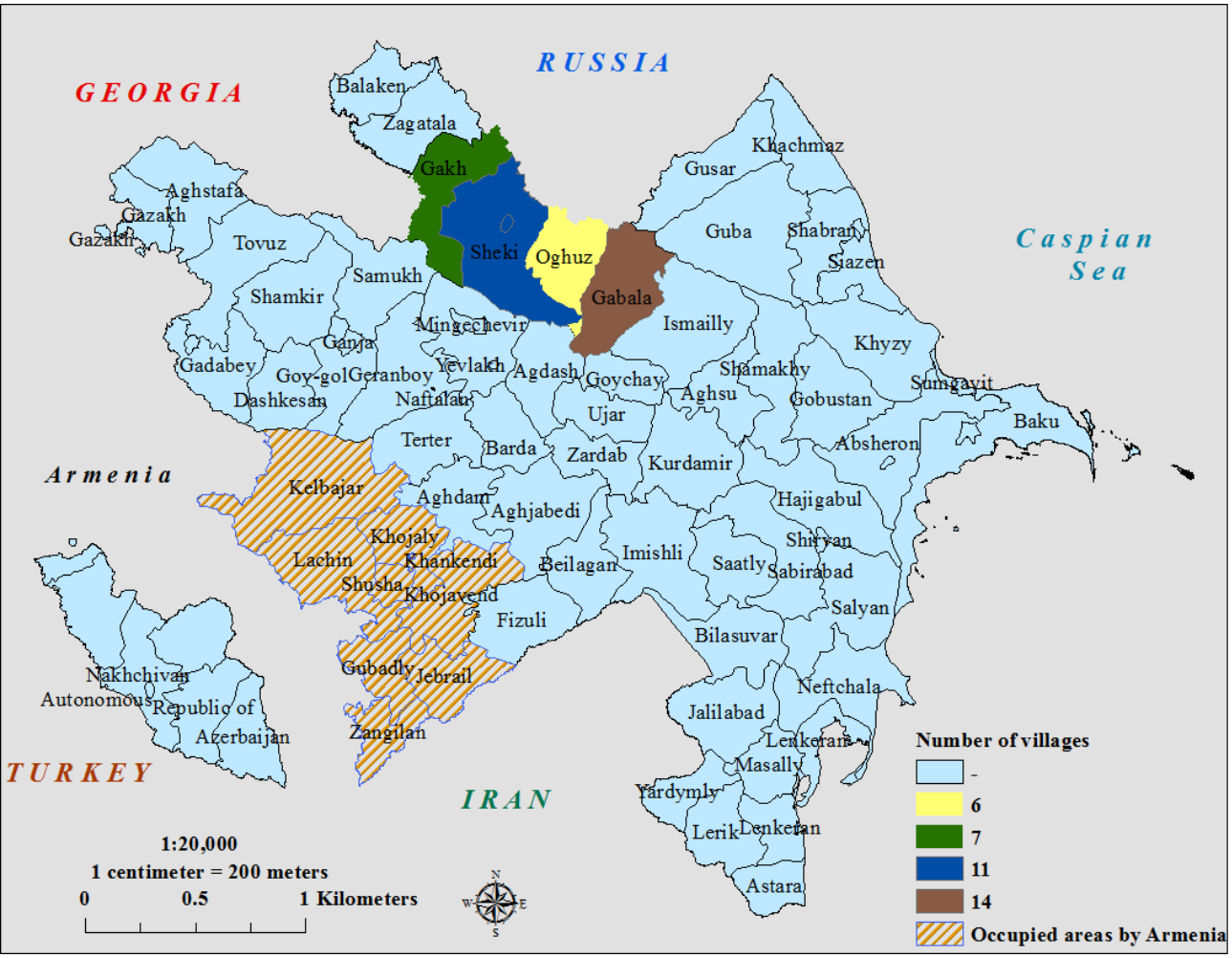
Is rabies in the Middle East wildlife or dog rabies (or both)?



Knowledge, Attitudes and Practices: Example from Azerbaijan

- Increasing surveillance and public awareness
- Laboratory and biosafety training
- Proficiency testing
- Molecular epidemiology

Assessing a Public Awareness Campaign in Azerbaijan



- 600 respondents from 38 towns
- Four Rayons- matched for population demographics
- Two had traditional leaflet/poster based awareness campaign, two had nothing

(CDC FELTP)

Public awareness in animals- key results

1. The awareness campaign group had better knowledge of rabies symptoms (PRR=1.3; 95% CI 1.1-1.5) and vaccination schedules PRR=1.3 (95% CI 1.1 - 1.4).
2. **Awareness campaign group were also 1.4 times more likely to have vaccinated their dogs and cats (RR-1.4 95% CI 1.1-1.7)**

An example (Azerbaijan 2000-2010)
Perception of wildlife rabies , but dog samples predominate

Year	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	Sub total	Total
Dog	n.d	7	15	9	14	9	9	13	7	17	11	111	
Cattle	n.d	4	5	4	3	4	1	5	9	8	15	58	
Sheep	n.d	0	0	0	0	0	1	1	0	1	0	3	
Horse	n.d	0	0	0	2	0	1	0	1	2	0	6	
Other	n.d	2	4	1	2	4	2	3	7	6	7	38	
Total Positive	0	13	24	14	21	17	14	22	24	34	33		216
Negative	9	10	5	4	3	10	3	0	8	6	17		75
Untestable	6	7	3	1	3	2	1	7	2	1	2		35
Total submitted	15	30	32	19	27	29	18	29	34	41	52		326

n.d=no data

What is the reservoir host?
Try using Bayesian phylogenetics:

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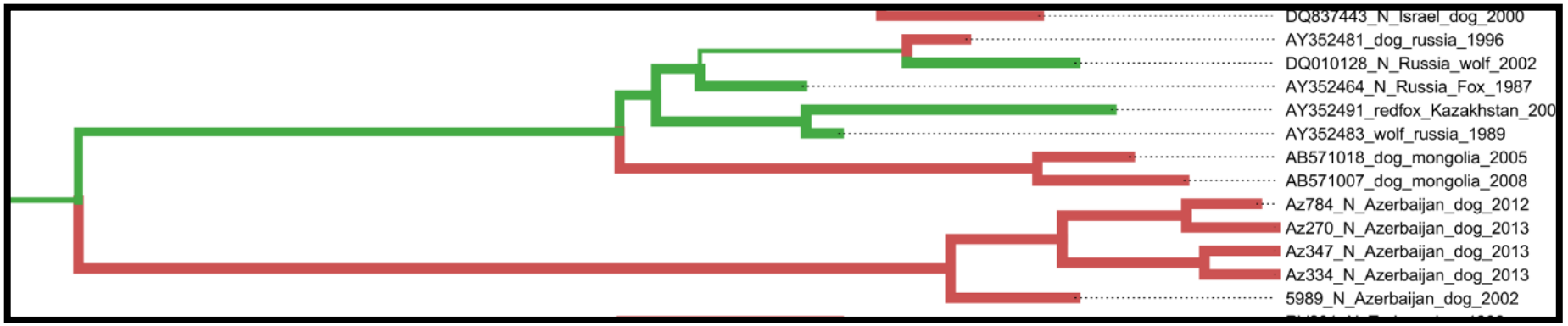
What is the reservoir host?

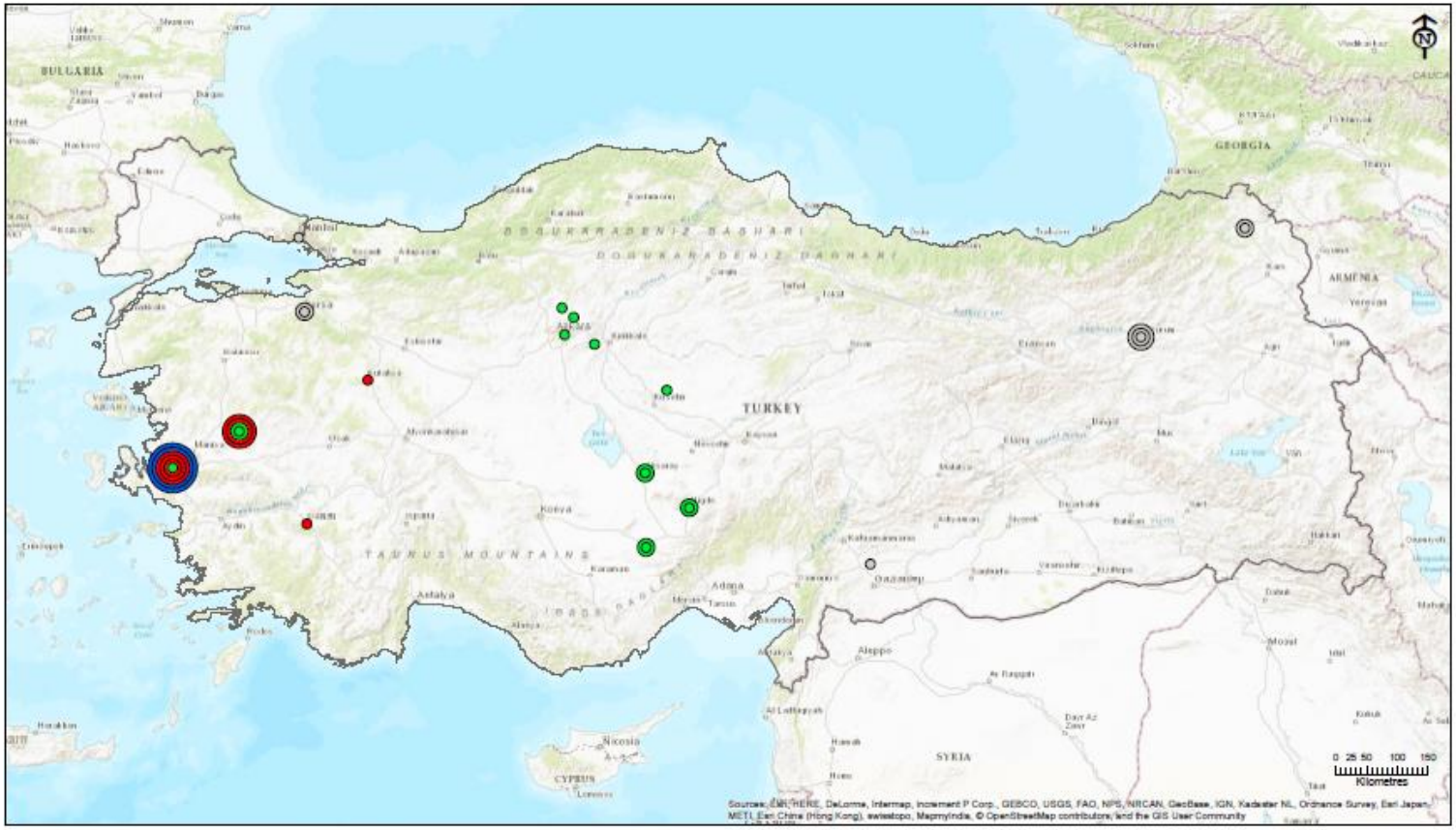
What is the reservoir host?

70% probability of
a wildlife ancestor

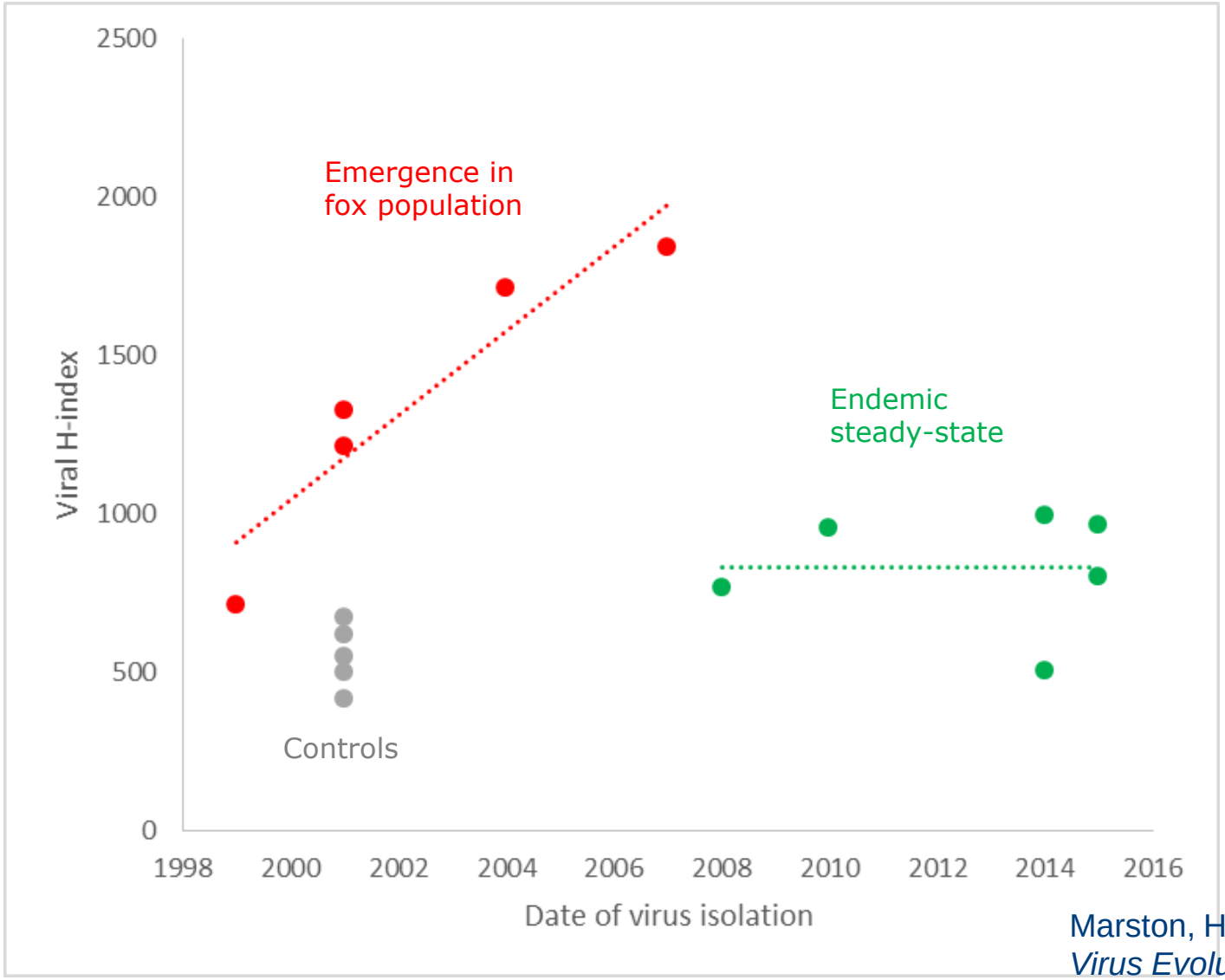


Viral heterogeneity

- Deep sequencing of 30 viruses from an outbreak in Turkey
- Known DOG---FOX cross species transmission event
- Calculated heterogeneity (H-index number of variants within a sample, controlled for depth of coverage)



Viral heterogeneity

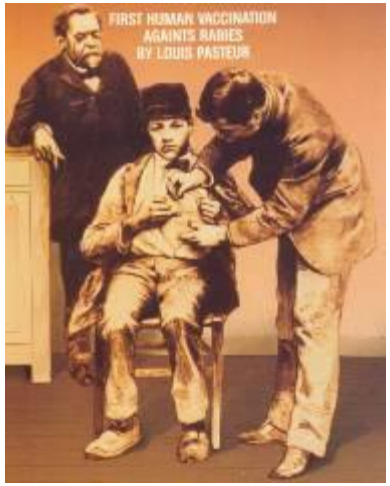


Marston, Horton et al
Virus Evolution 2017

Wider context

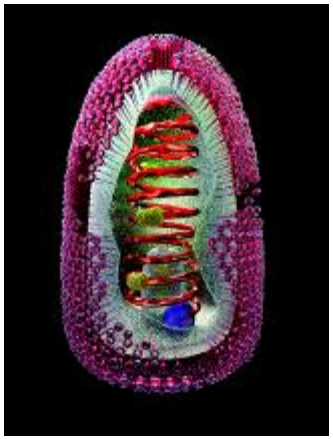
Family *Rhabdoviridae*: Genus Lyssavirus

1885



- Classical rabies virus
- Lagos bat
- Mokola
- Duvenhage
- European bat lyssavirus 1
- European bat lyssavirus 2
- Australian bat lyssavirus
- Aravan virus
- Khujand virus
- Irkut virus
- West Caucasian bat virus
- Shimoni bat lyssavirus
- Bokeloh bat lyssavirus (Germany) - 2011
- Ikoma lyssavirus (Tanzania) – 2012
- (Lleida bat lyssavirus (Spain)- 2013)
- Gannoruwa Bat Lyssavirus (2016)

2018



Food for thought- potential emergence of new lyssaviruses


New York Times