

Rabies:

Overview and Perspectives

Dr Daniel L Horton MA VetMB MSc PhD MRCVS Dip ECZM
School of Veterinary Medicine, University of Surrey

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

Acknowledgements



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Eldar Hasanov
Marika (Mariam) Geleishvili

Austria

Norbert Novotny

EURL for Rabies

IP

Noel Tordo



Biological Engagement Program

EU FP7 (ANTIGONE)

DEFRA



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

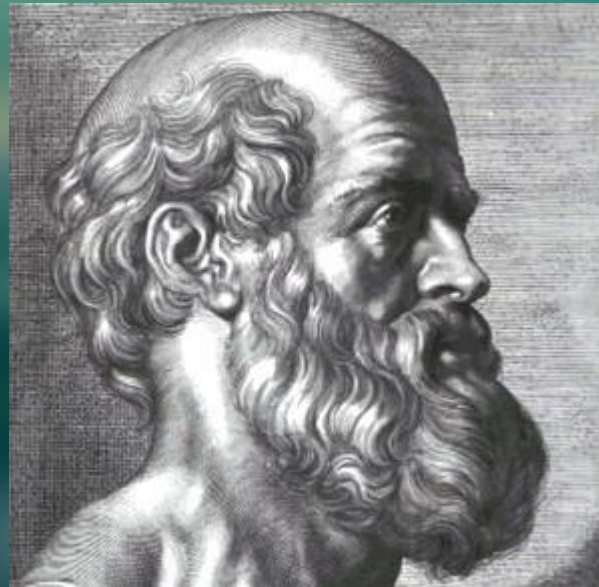
120
students
per year
from
2015

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)

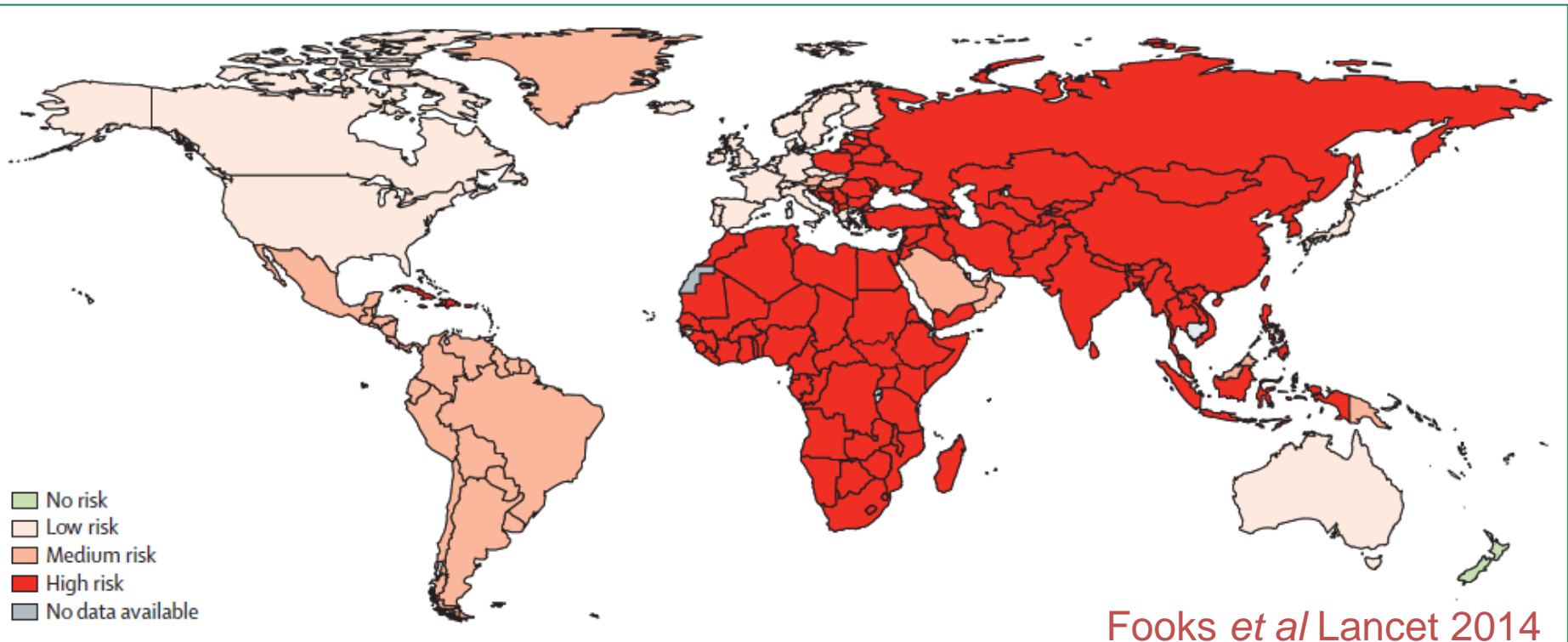


Global impact: Why is rabies important?

- 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

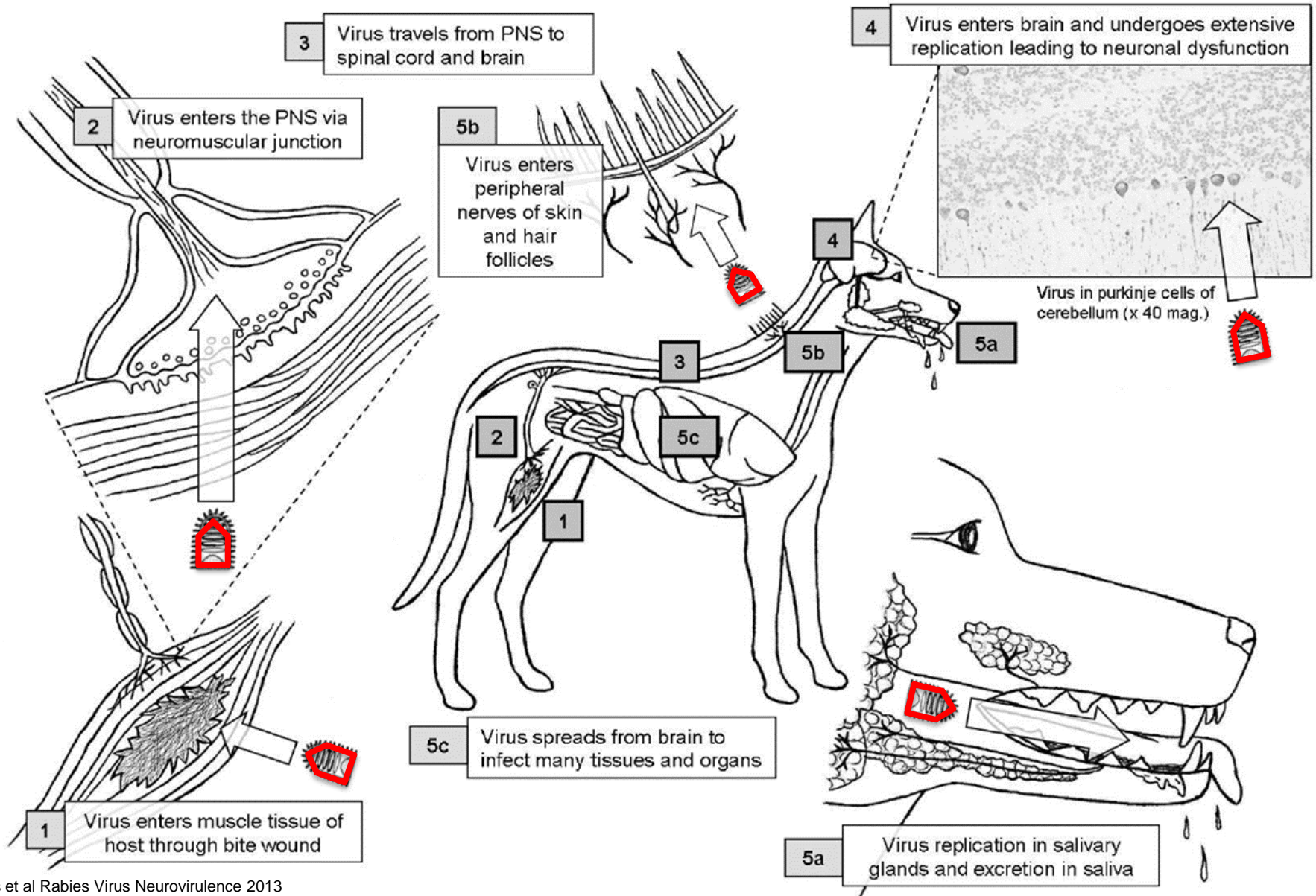


Cost in numbers:

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

Hampson *et al* PlosNTD 2015

Rabies pathogenesis

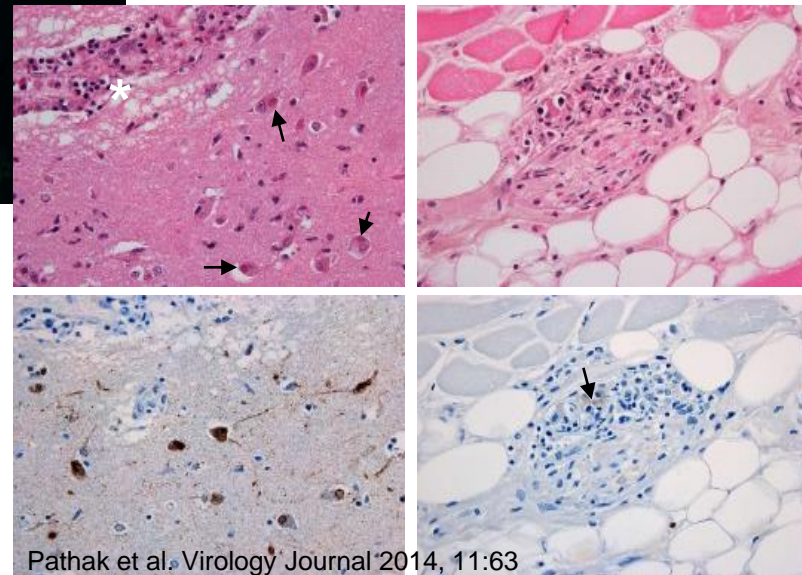


Diagnosis is difficult

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



Diqqət! Diqqət! Diqqət!



QUDUZLUĞUN
ƏLAMƏTLƏRİ:
AĞIZIN SULANMASI,
AQRƏSSİVLİK VƏ YA
SAKITLIK, ANORMAL
DAVRANIŞ

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

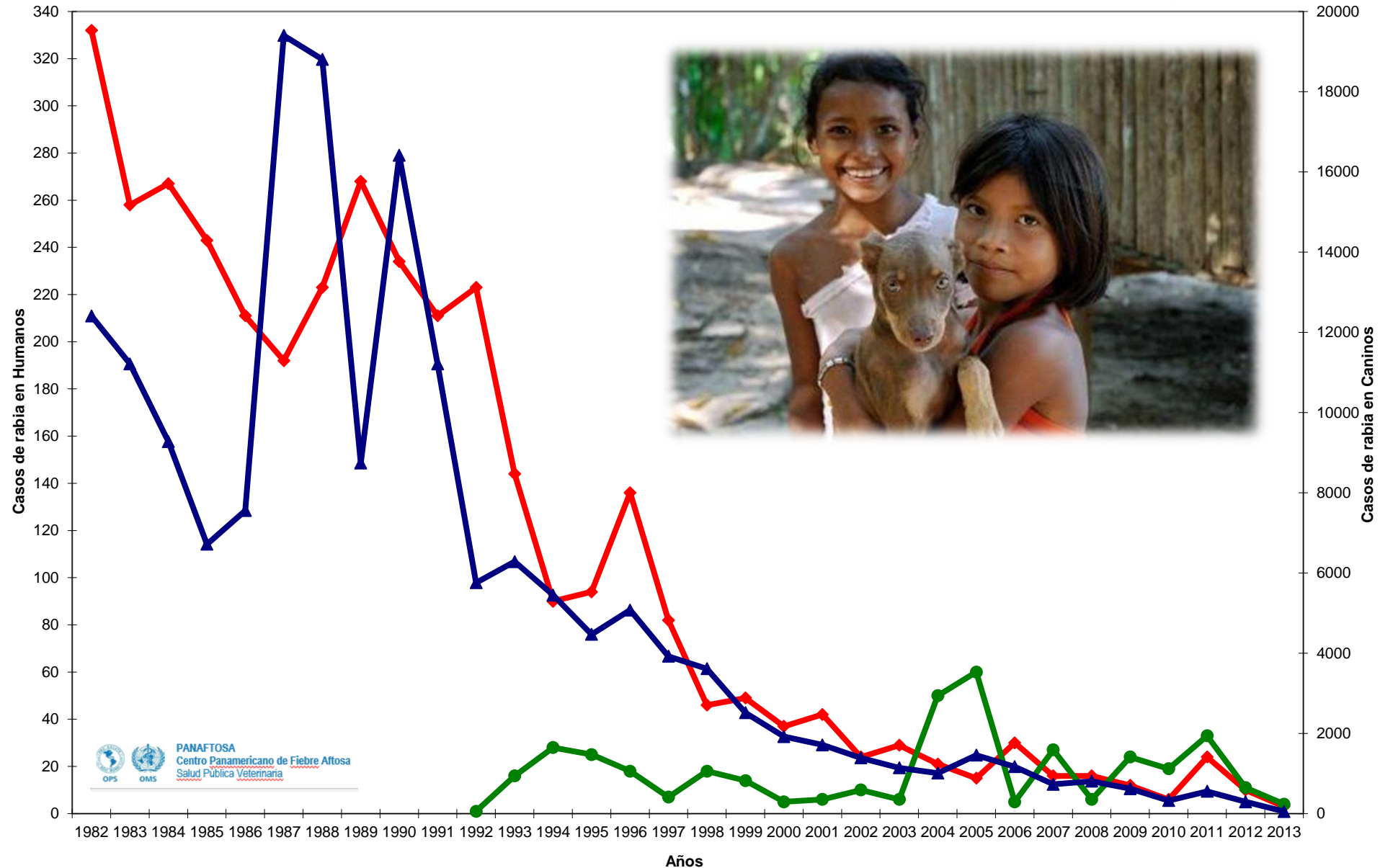


QDSB-nin əlaqə
nömrələri:
Ağ-1115, Əlaqə mərkəzi,
Daxili nömrə-3123
Tel: 994 12 96276 faks: 994 12 562 66 32

QDSB-nin QAYNAR SƏTTİ: 963 6006



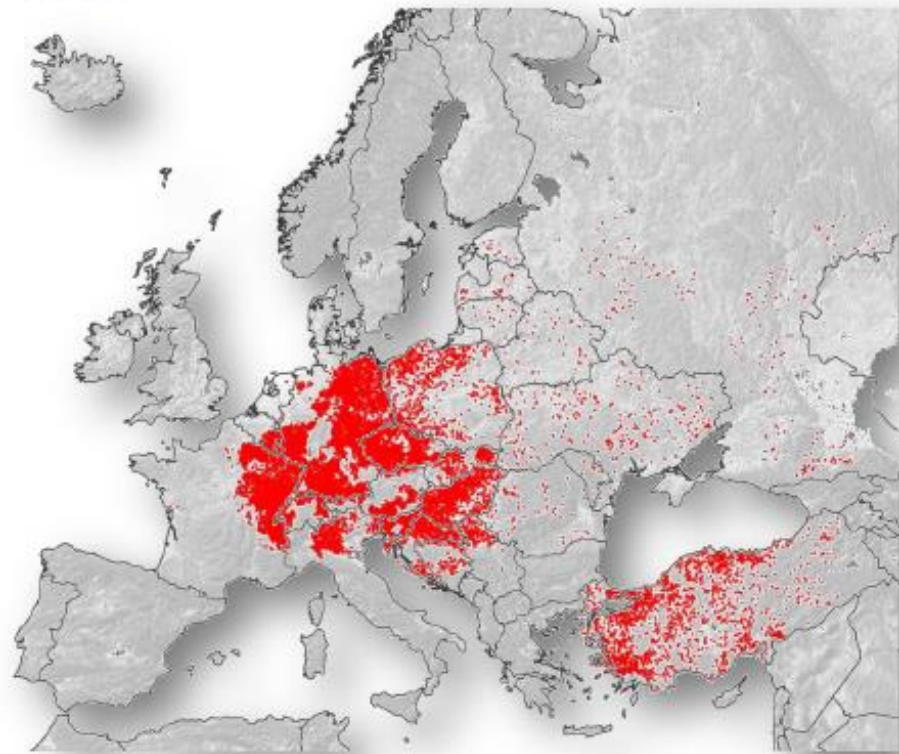
Reducing dog rabies reduces human cases



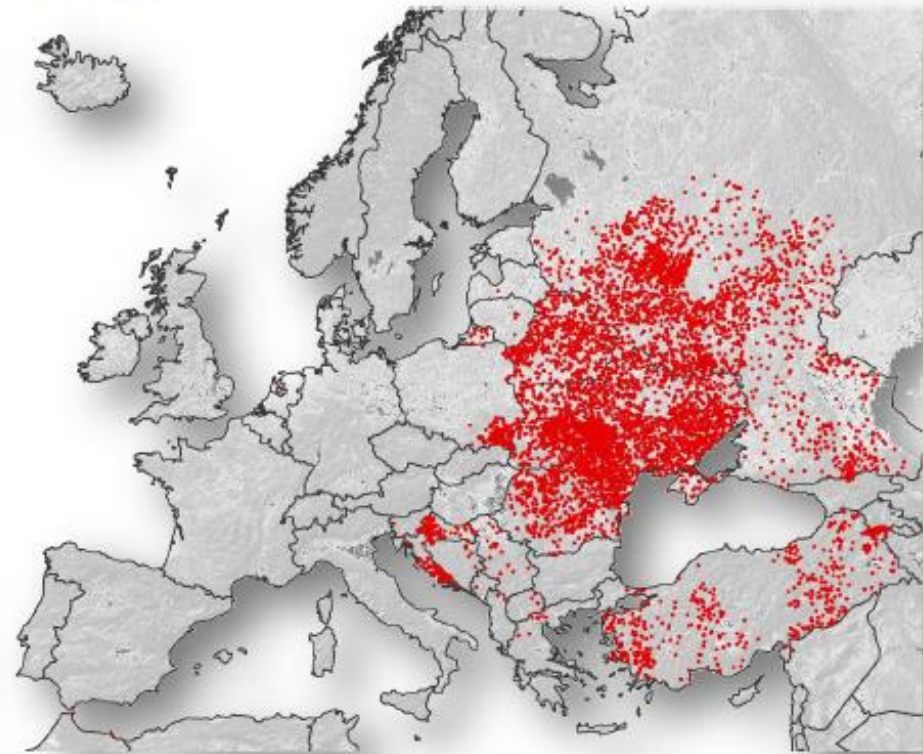
◆ Humans cases by dogs
 ● Humans cases by vampire bat
 ▲ Canine cases

Rabies vaccination in wildlife

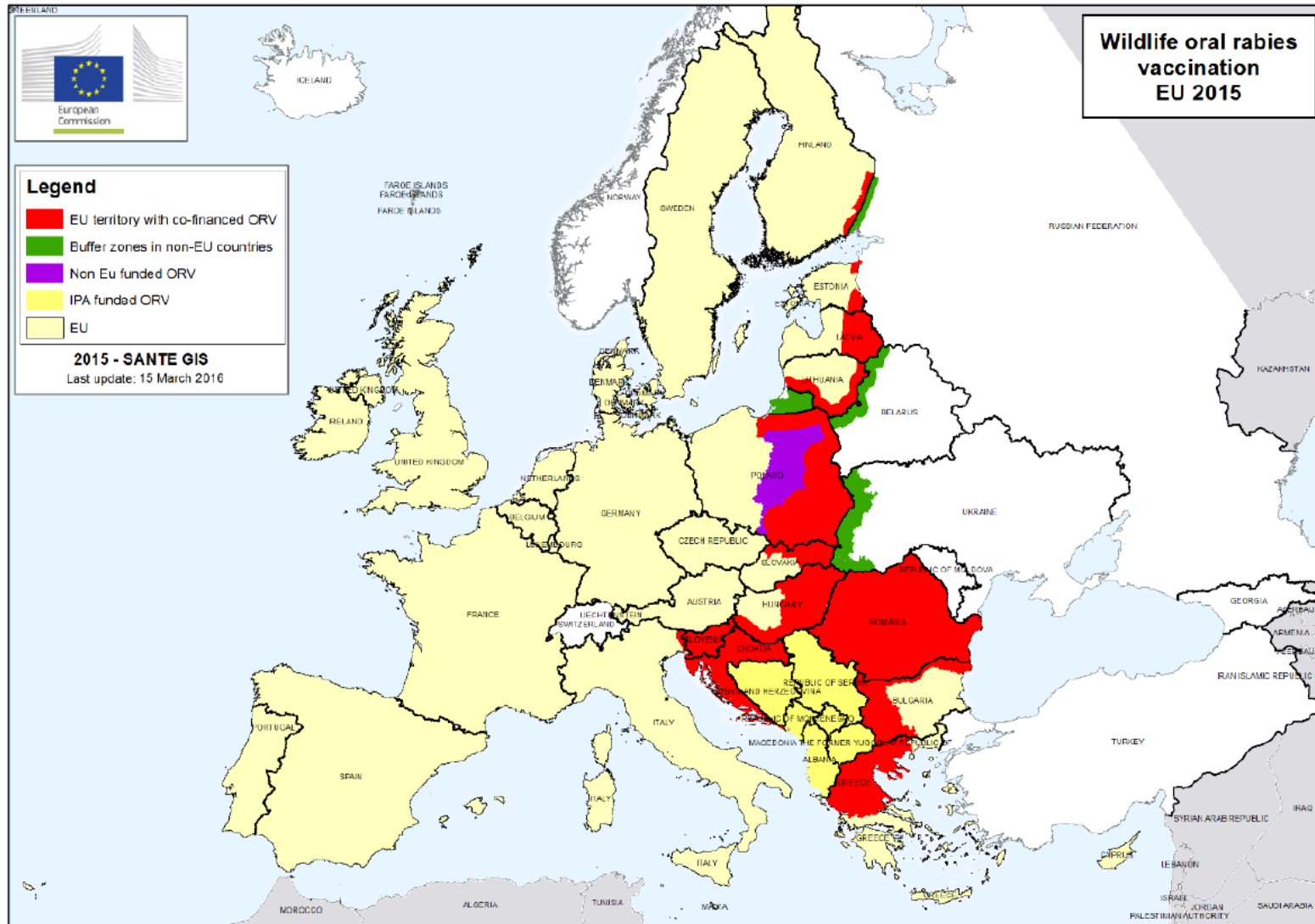
1983



2012



Data: Rabies bulletin Europe



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

Rabies in the Middle East and Central Asia

- 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?

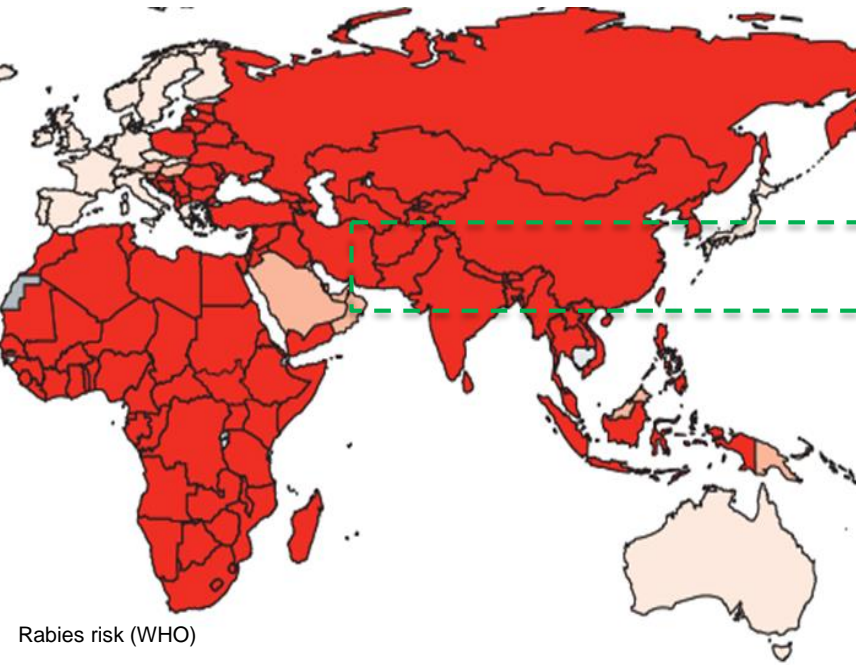
What is the reservoir (source) of human rabies?

Where and when
is rabies spreading?



Use virus genomes
to reconstruct
evolutionary history

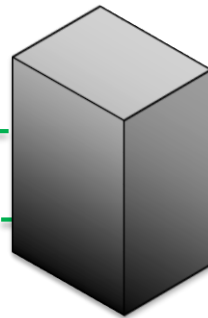




180 samples over 40 years



Policy-relevant
risk assessment



Bayesian
phylogenetics



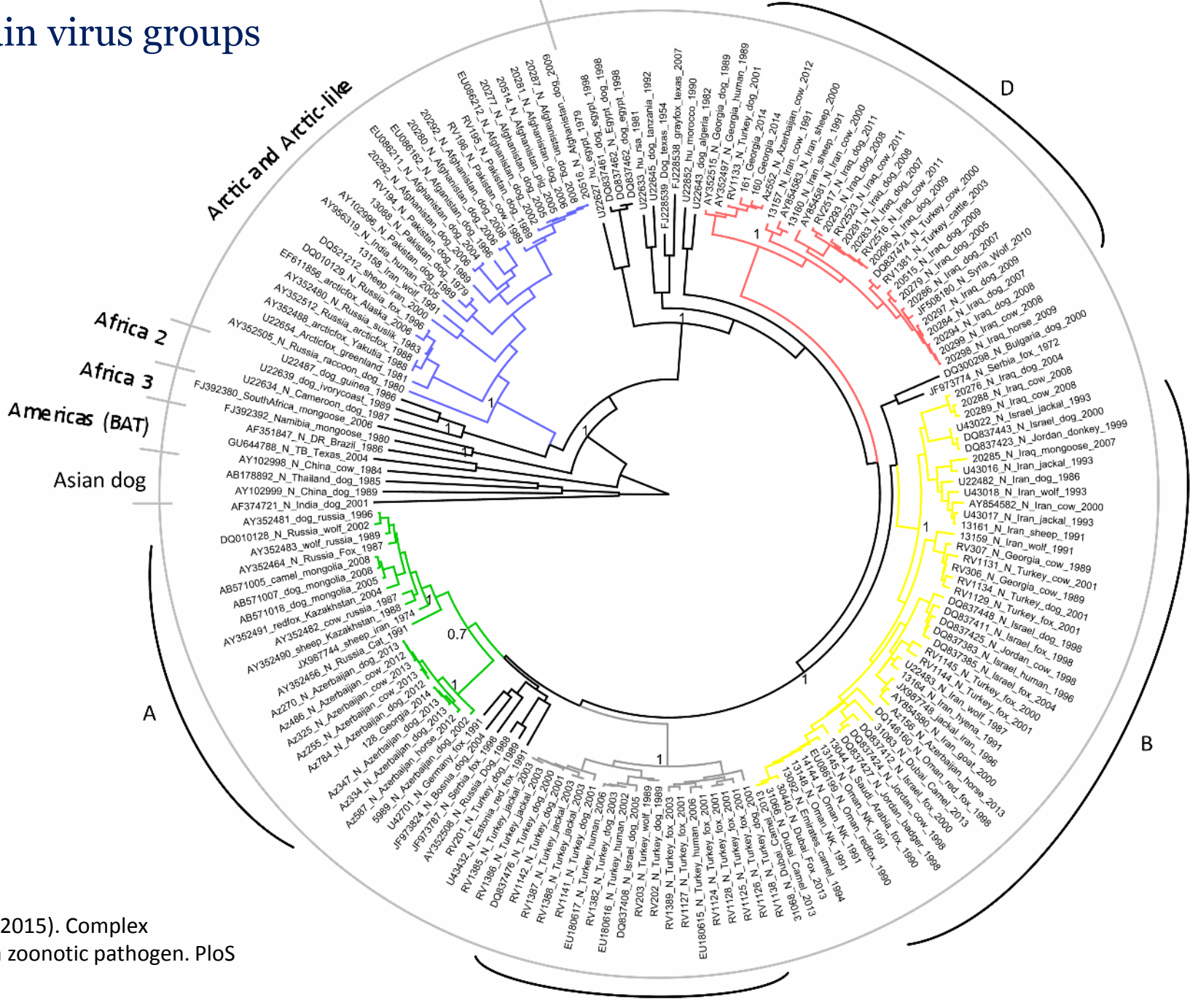
Partial N gene
sequences



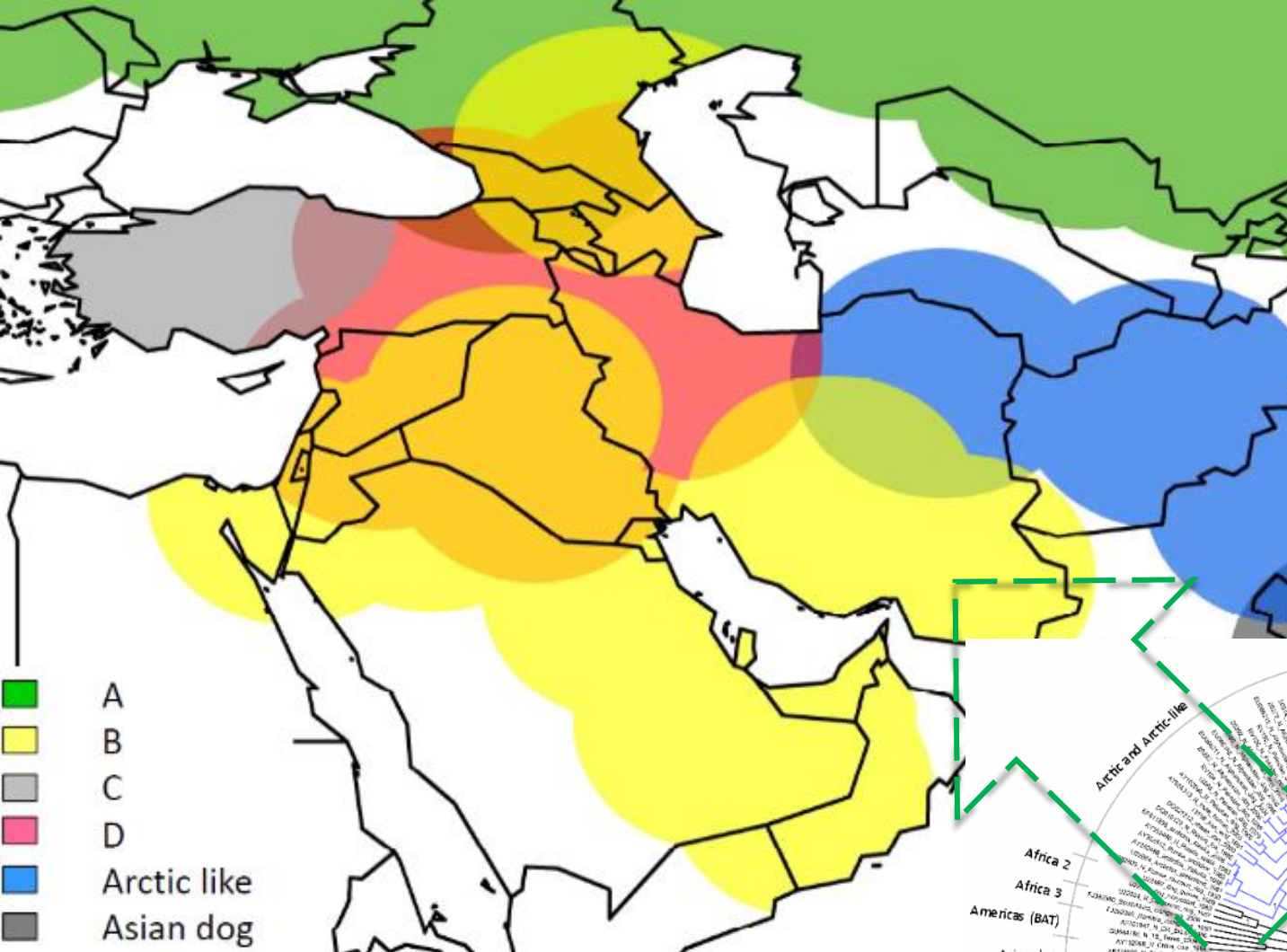
FTA™ cards

=Four main virus groups

So what?

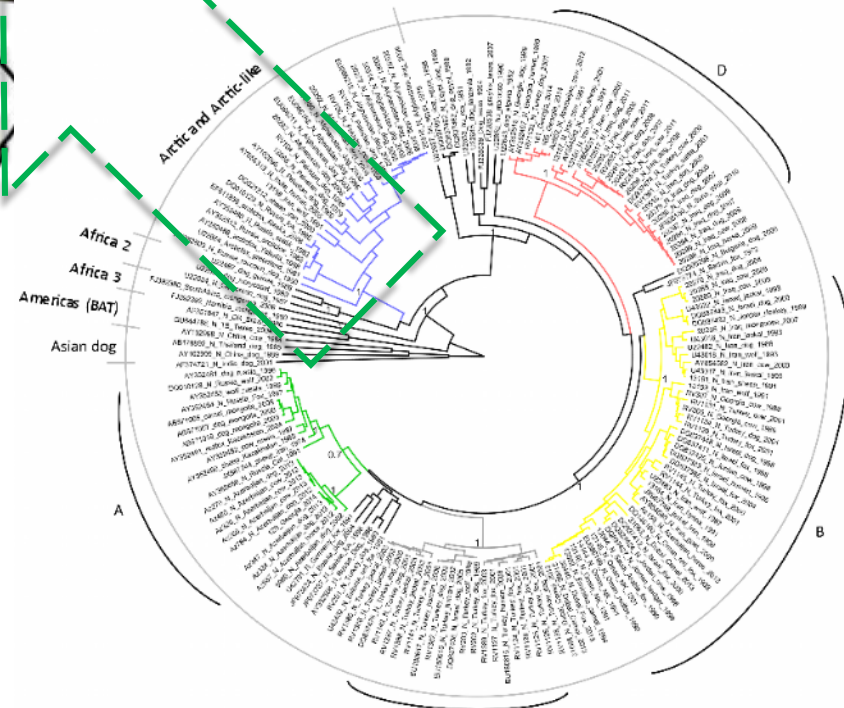


Horton DL, et al. (2015). Complex Epidemiology of a zoonotic pathogen. PLoS NTD



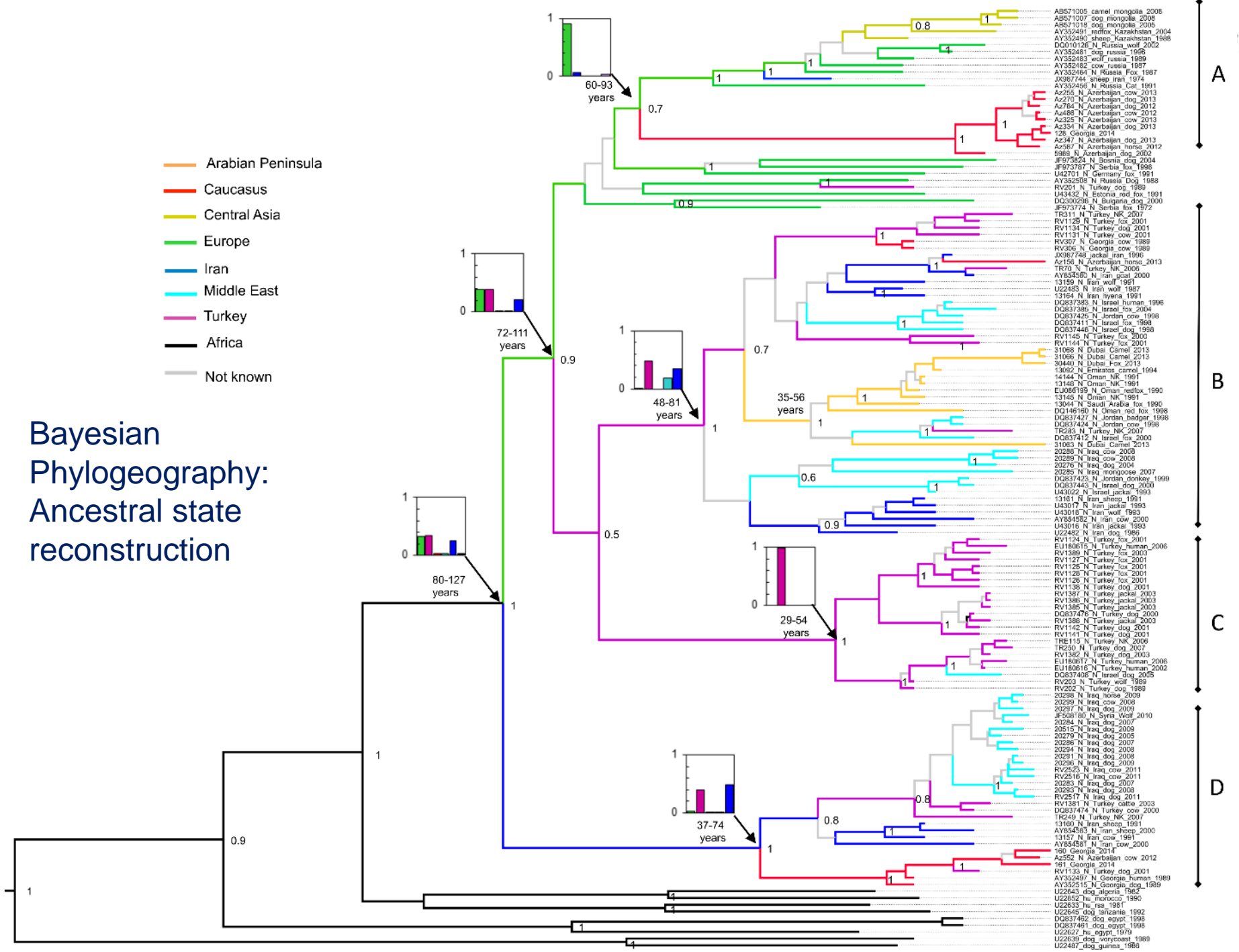
-Mapping the distribution of existing clades

-In some areas three clades circulating at the same time



Bayesian Phylogeography: Ancestral state reconstruction

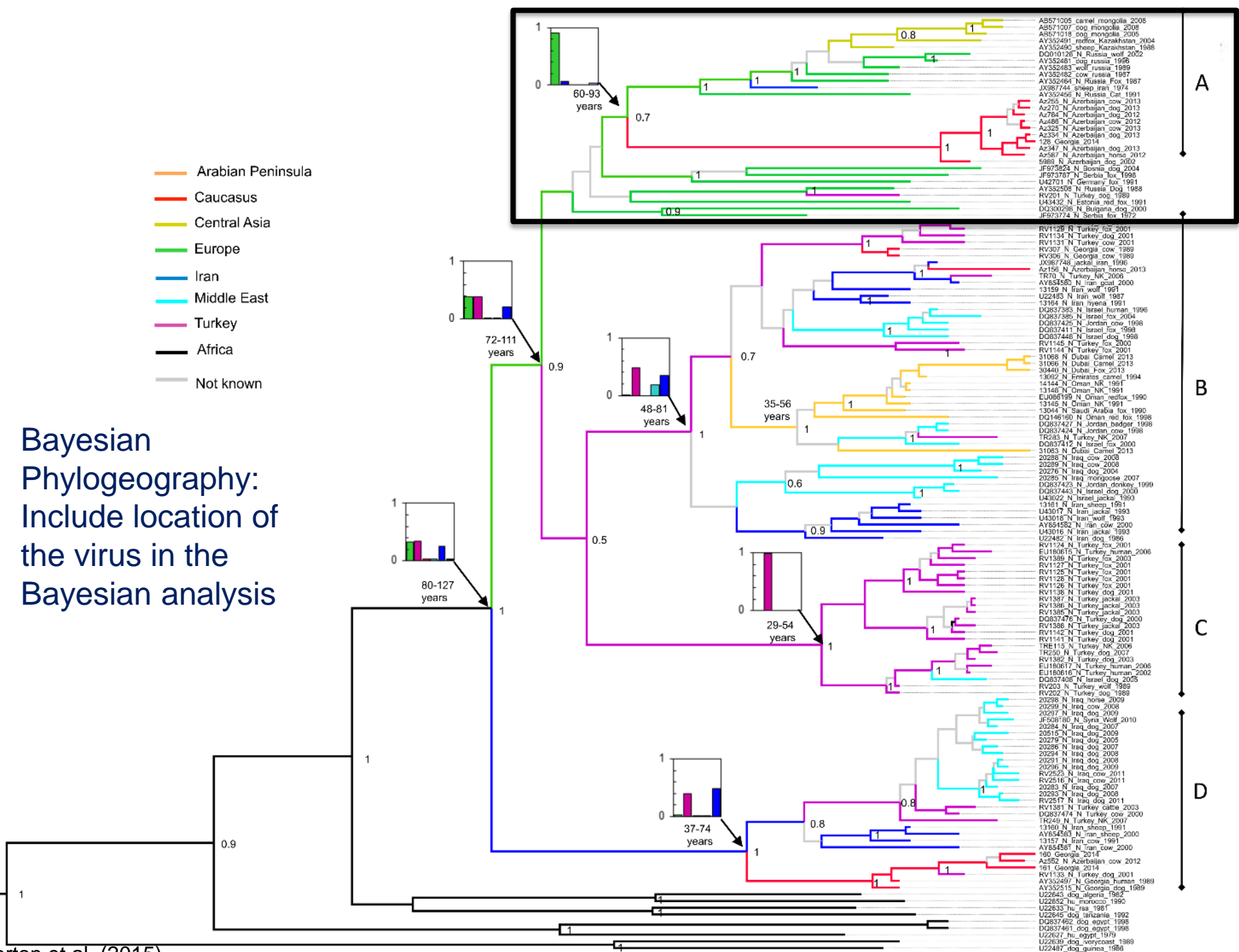
- Arabian Peninsula
- Caucasus
- Central Asia
- Europe
- Iran
- Middle East
- Turkey
- Africa
- Not known



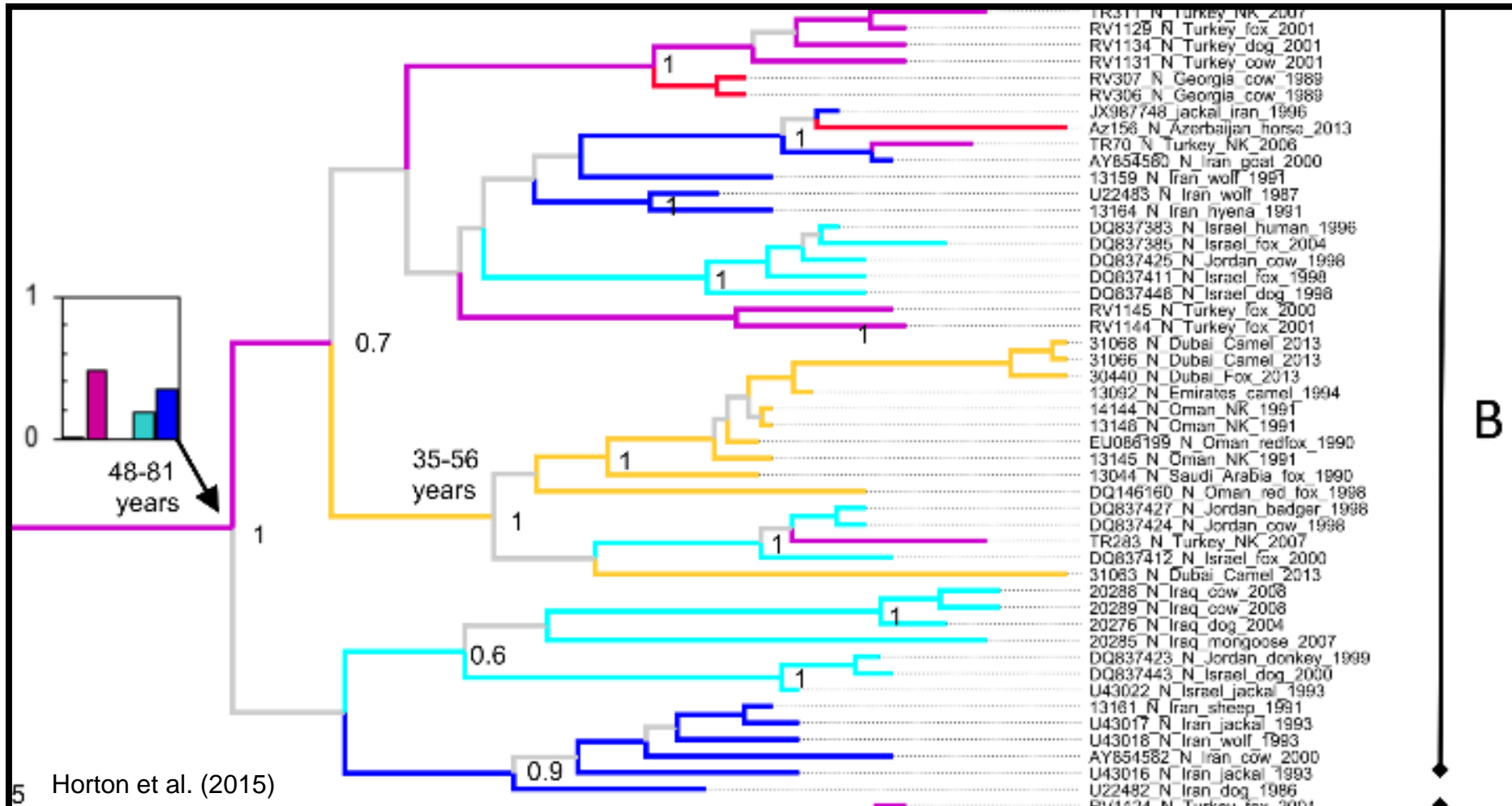
AB571005 camel_mongolia_2008
 AB571007 dog_mongolia_2008
 AB571018 dog_mongolia_2008
 AY324911 refox_Kazakhstan
 AY324903 sheep_Kazakhstan_1988
 D00101262_N_Russia_wolf_2002
 AY324881 cow_Russia_1989
 AY324883 wolf_Russia_1989
 AY324882 cow_Russia_1987
 AY324864 N_Russia_Fox_1987
 JX987444 sheep_Iran_1974
 AY324865 N_Russia_Cat_1991
 Az265 N_Azerbaijan_cow_2013
 Az270 N_Azerbaijan_dog_2013
 Az276 N_Azerbaijan_dog_2012
 Az468 N_Azerbaijan_cow_2012
 Az334 N_Azerbaijan_cow_2013
 Az334 N_Azerbaijan_dog_2013
 128_Georgia_2014
 Az347 N_Azerbaijan_dog_2013
 Az367 N_Azerbaijan_horse_2012
 5986 N_Azerbaijan_dog_2002
 JF578253 N_Georgia_dog_2004
 JF973707 N_Serbia_fox_1998
 U42701 N_Germany_fox_1981
 AY324808 N_Russia_Dog_1988
 RV201 N_Turkey_dog_1989
 U43432 N_Estonia_red_fox_1991
 DQ300296 N_Bulgaria_dog_2000
 JF93774 N_Serbia_fox_1972
 RV111 N_Turkey_NK_2007
 RV1128 N_Turkey_fox_2001
 RV1134 N_Turkey_dog_2001
 RV1131 N_Turkey_cow_2001
 RV307 N_Georgia_cow_1989
 RV306 N_Georgia_cow_1989
 JX987448 jackal_Iran_1996
 Az176 N_Azerbaijan_horse_2013
 RT01 N_Turkey_NK_2008
 AY854560 N_Iran_goat_2000
 13159 N_Iran_wolf_1995
 U22485 N_Iran_wolf_1987
 13184 N_Iran_hyena_1981
 DQ837583 N_Israel_human_1996
 DQ837386 N_Israel_fox_2004
 DQ837426 N_Jordan_cow_1998
 DQ837411 N_Israel_dog_1998
 DQ837446 N_Israel_dog_1998
 RV1145 N_Turkey_fox_2000
 RV1144 N_Turkey_cow_2001
 31088 N_Dubai_Camel_2013
 31086 N_Dubai_Camel_2013
 30440 N_Dubai_fox_2013
 13092 N_Emirates_camel_1994
 14144 N_Oman_NK_1991
 13146 N_Oman_NK_1991
 EU086199 N_Oman_refox_1990
 13165 N_Oman_NK_1991
 13044 N_Saudi_Arabia_fox_1990
 DQ146160 N_Oman_red_fox_1998
 DQ837427 N_Jordan_badger_1998
 DQ837444 N_Jordan_cow_1998
 TR285 N_Turkey_NK_2007
 DQ837412 N_Israel_fox_2000
 31083 N_Dubai_Camel_2013
 20286 N_Iraq_cow_2008
 20289 N_Iraq_cow_2008
 20276 N_Iraq_dog_2004
 20285 N_Iraq_monococoon_2007
 DQ837423 N_Jordan_donkey_1999
 DQ837443 N_Israel_dog_2000
 U43022 N_Israel_jackal_1993
 13161 N_Iran_sheep_1991
 U43017 N_Iran_jackal_1993
 U43018 N_Iran_wolf_1993
 AY854582 N_Iran_cow_2000
 U43016 N_Iran_jackal_1993
 U22482 N_Iran_dog_1986
 RV1124 N_Turkey_fox_2001
 EU180876 N_Turkey_human_2006
 RV11389 N_Turkey_fox_2003
 RV1127 N_Turkey_fox_2001
 RV1125 N_Turkey_fox_2001
 RV1126 N_Turkey_fox_2001
 RV1126 N_Turkey_fox_2001
 RV1138 N_Turkey_dog_2001
 RV1137 N_Turkey_jackal_2003
 RV1136 N_Turkey_jackal_2003
 RV1135 N_Turkey_dog_2000
 DQ837476 N_Turkey_dog_2003
 RV1138 N_Turkey_dog_2001
 RV1142 N_Turkey_dog_2001
 RV1141 N_Turkey_dog_2001
 TR115 N_Turkey_NK_2006
 TR230 N_Turkey_dog_2007
 RV1130 N_Turkey_dog_2003
 EU180817 N_Turkey_human_2006
 EU180816 N_Turkey_human_2002
 DQ837406 N_Israel_dog_2005
 RV203 N_Turkey_wolf_1989
 RV202 N_Turkey_cow_1989
 20288 N_Iraq_horse_2009
 20299 N_Iraq_cow_2008
 20297 N_Iraq_dog_2009
 JF508180 N_Syria_Wolf_2010
 20298 N_Iraq_dog_2005
 20295 N_Iraq_dog_2003
 20279 N_Iraq_dog_2005
 20286 N_Iraq_dog_2007
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 20291 N_Iraq_dog_2008
 20296 N_Iraq_dog_2009
 RV2523 N_Iraq_cow_2011
 RV2516 N_Iraq_cow_2011
 20289 N_Iraq_dog_2007
 20285 N_Iraq_dog_2008
 RV2517 N_Iraq_dog_2001
 RV1181 N_Turkey_cat_2003
 DQ837474 N_Turkey_cow_2000
 RV249 N_Turkey_NK_2001
 13180 N_Iran_sheep_1991
 AY854583 N_Iran_sheep_2000
 13157 N_Iran_cow_1991
 AY854581 N_Iran_cow_2000
 180_Georgia_2014
 Az252 N_Azerbaijan_cow_2012
 181_Georgia_2014
 RV1133 N_Turkey_dog_2001
 AY324909 N_Georgia_human_1989
 AY324915 N_Georgia_dog_1989
 U22843 dog_algeria_1982
 U22652 hu_morocco_1990
 U22633 hu_rsa_1987
 U22645 dog_sarania_1992
 DQ837482 dog_egypt_1988
 DQ837461 dog_egypt_1986
 U22627 hu_egypt_1979
 U22639 dog_voryneast_1986
 U22487 dog_guinea_1986

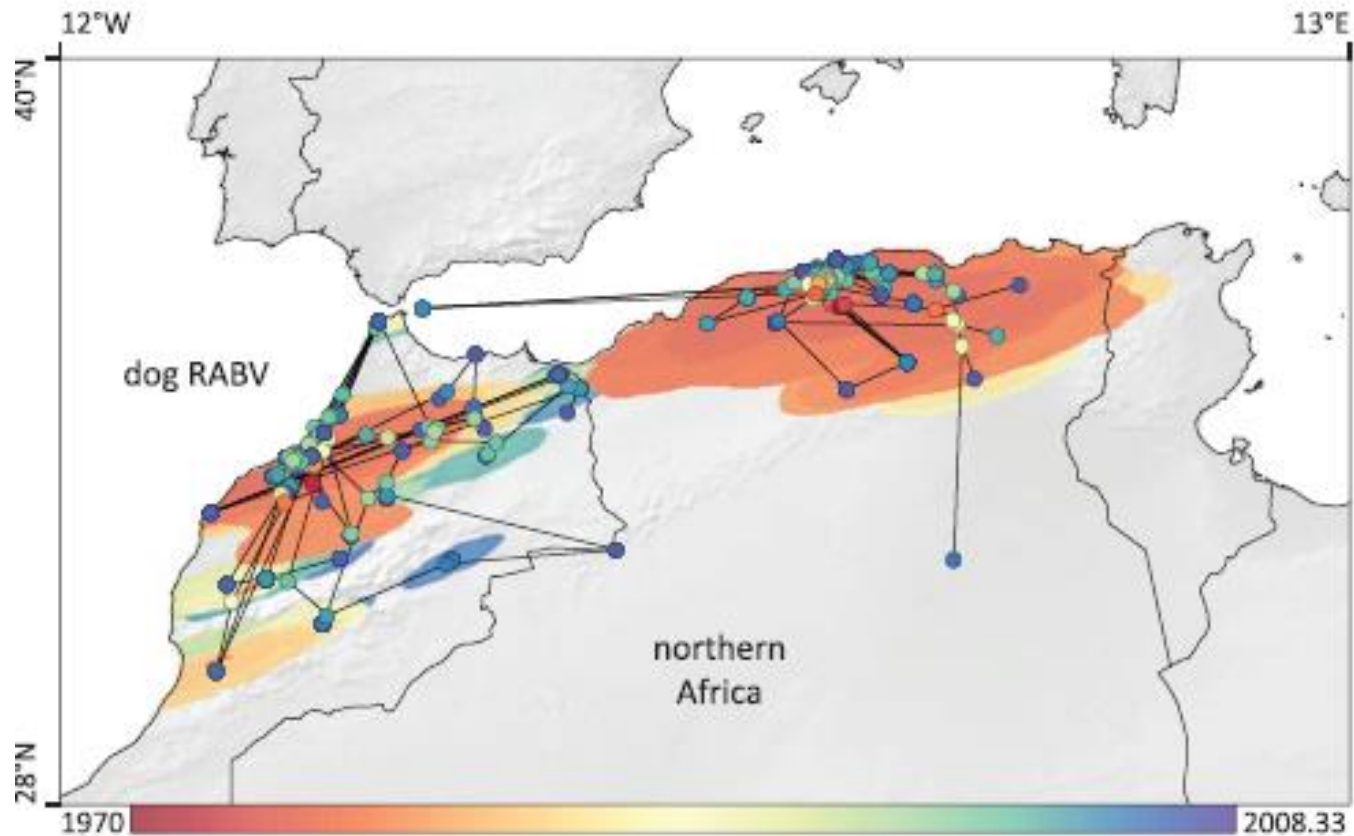
Bayesian Phylogeography: Include location of the virus in the Bayesian analysis

- Arabian Peninsula
- Caucasus
- Central Asia
- Europe
- Iran
- Middle East
- Turkey
- Africa
- Not known



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

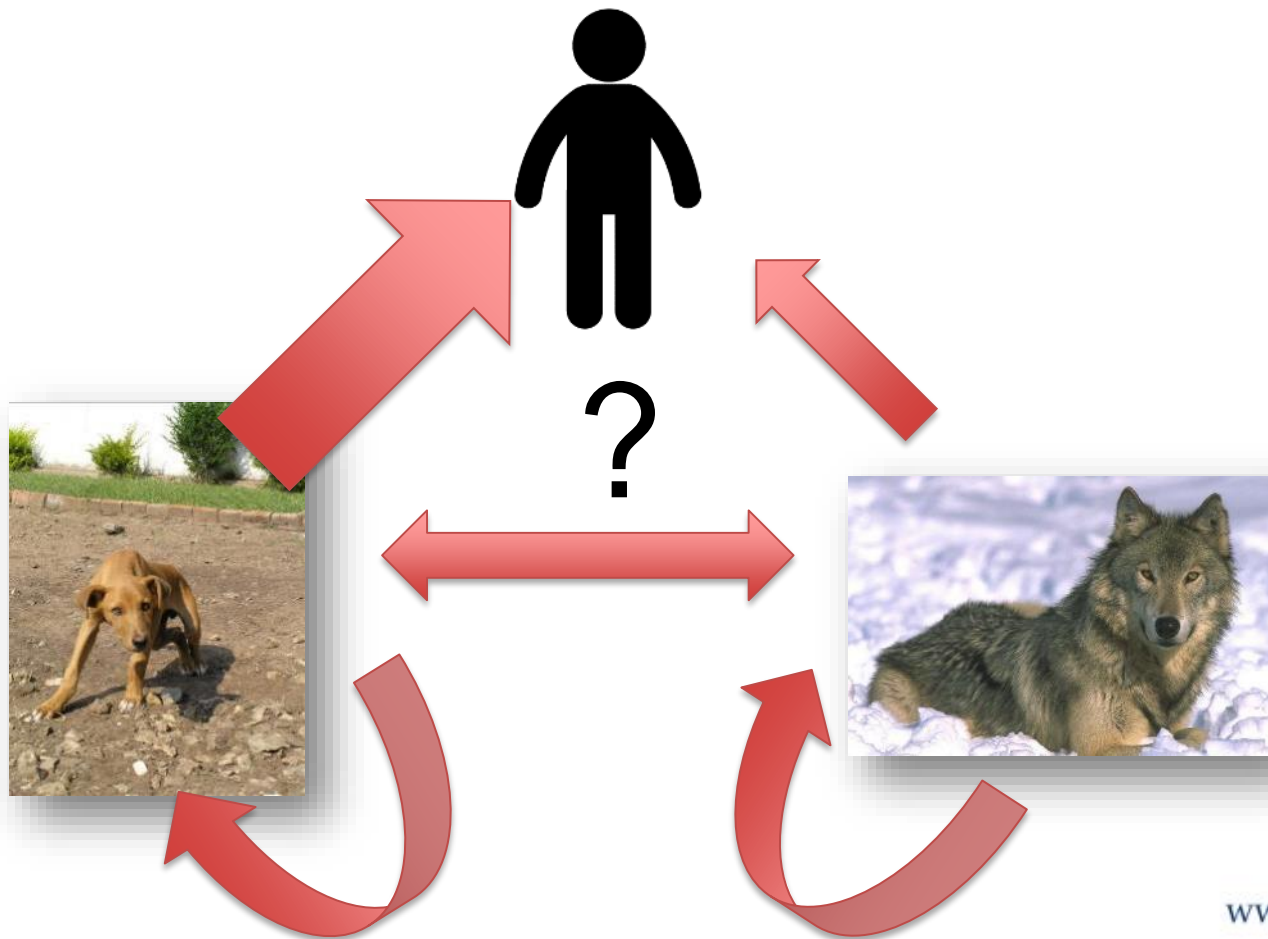




- Measure the effect of environmental and human factors on speed of spread (Dellicour *et. al. MBE* 2017)

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

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

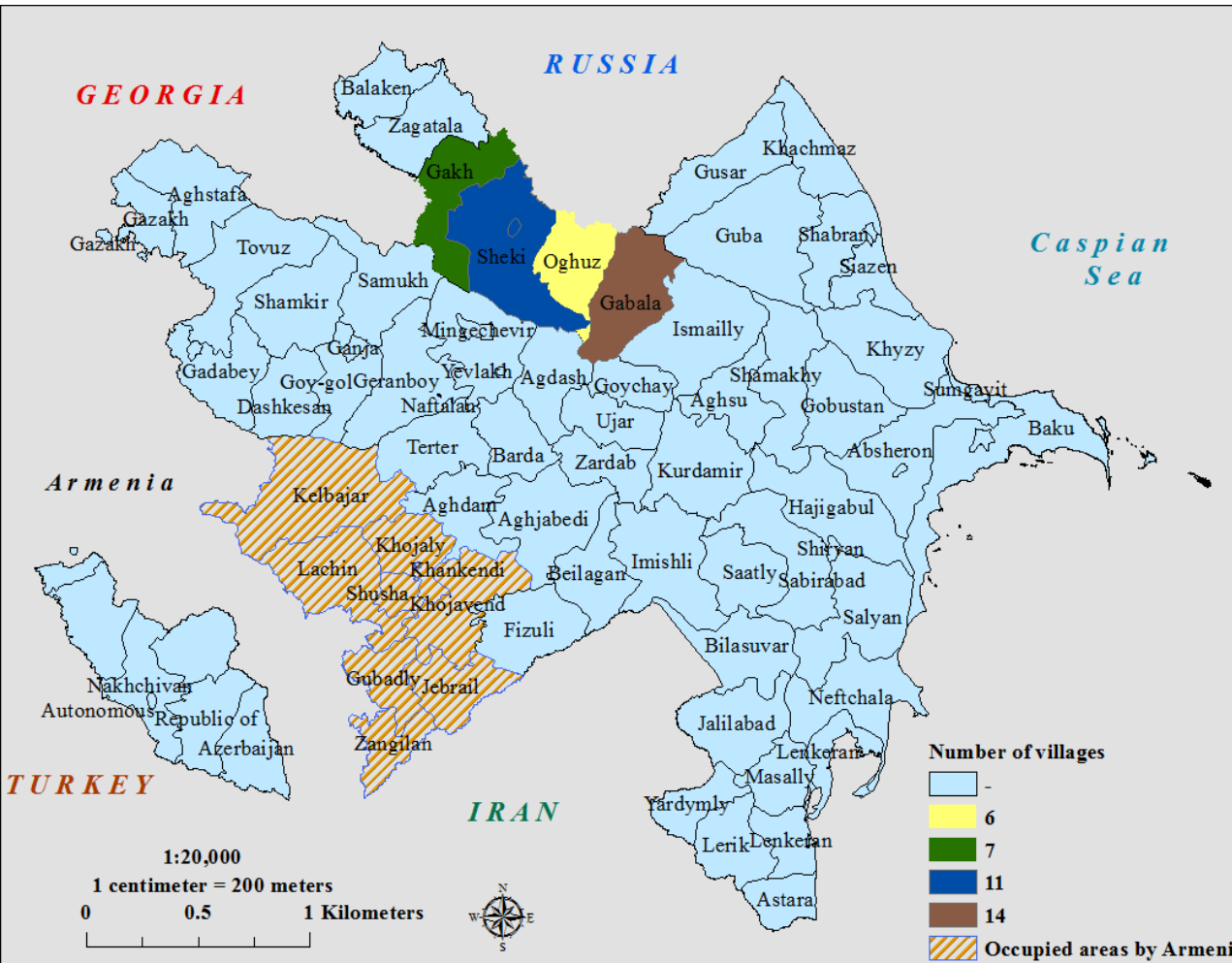


Knowledge, Attitudes and Practices: Example from Azerbaijan

- 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)

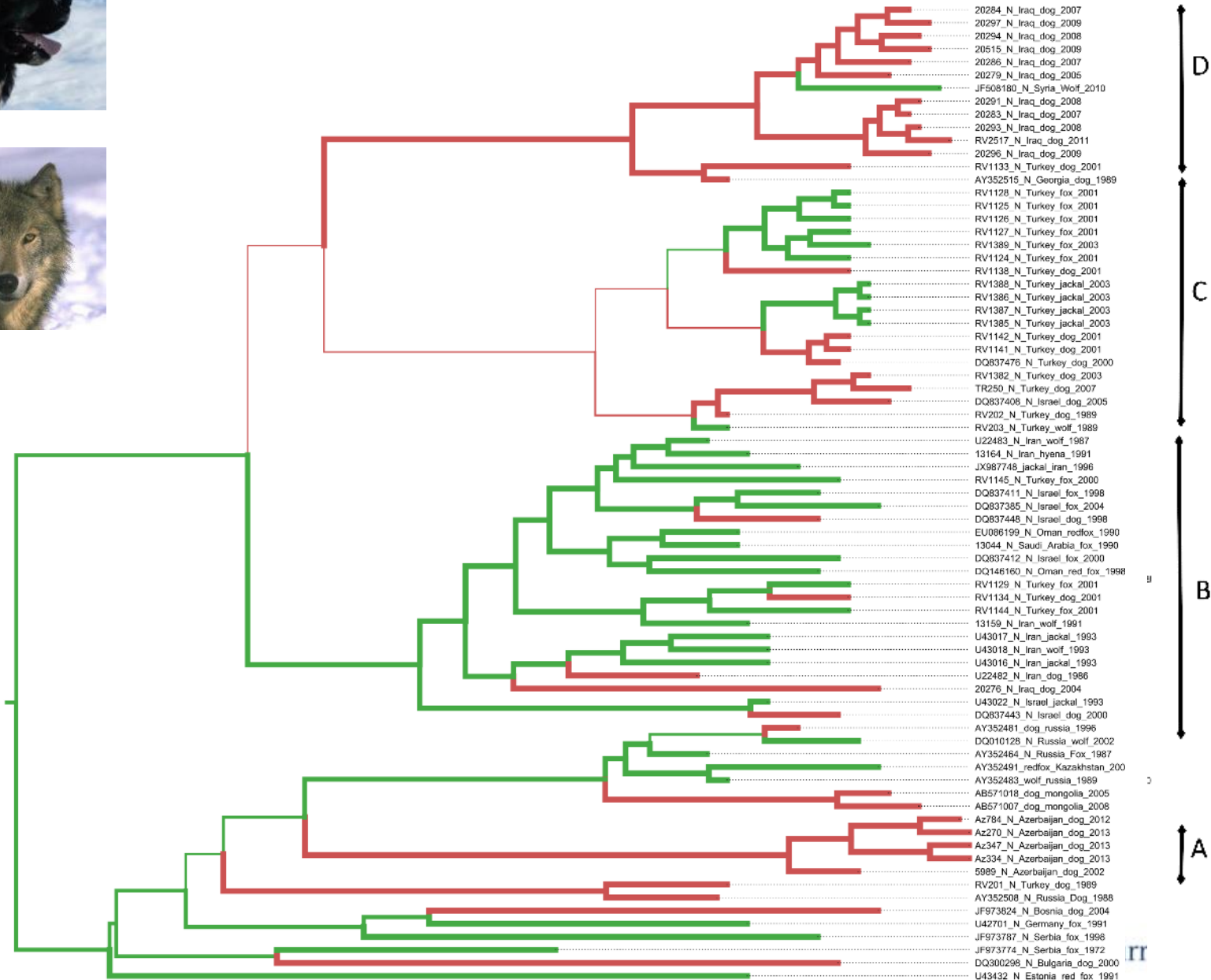
Perception of wildlife rabies , but dog samples predominate

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

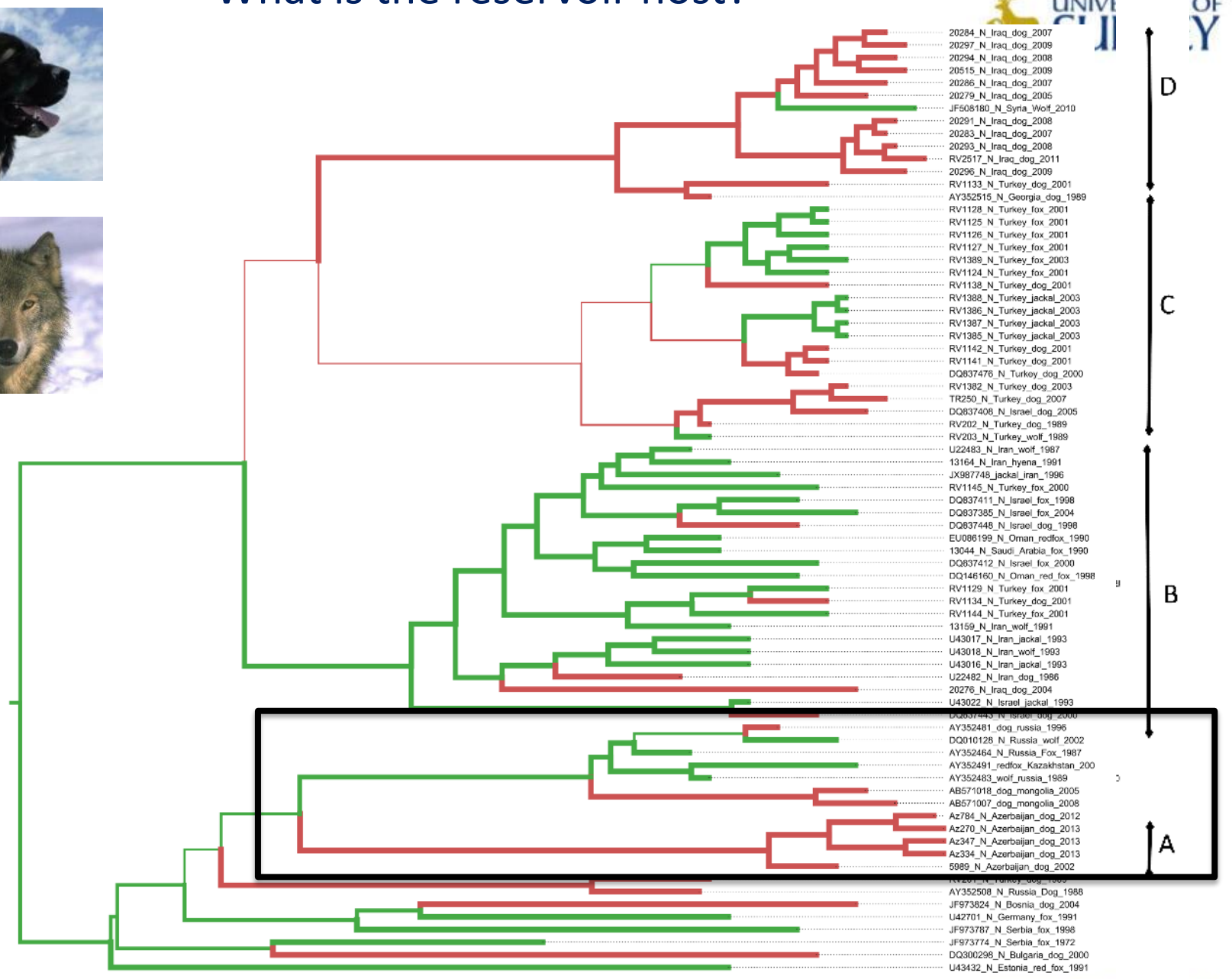
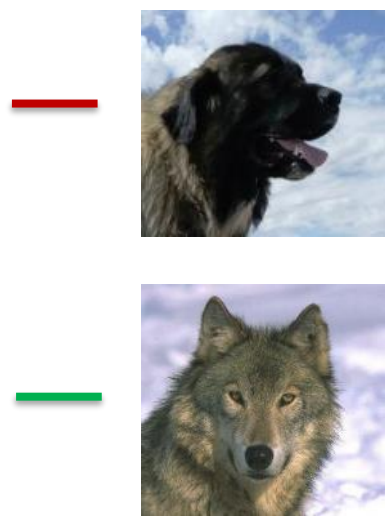
n.d=no data

What is the reservoir host?

Try using Bayesian phylogenetics:



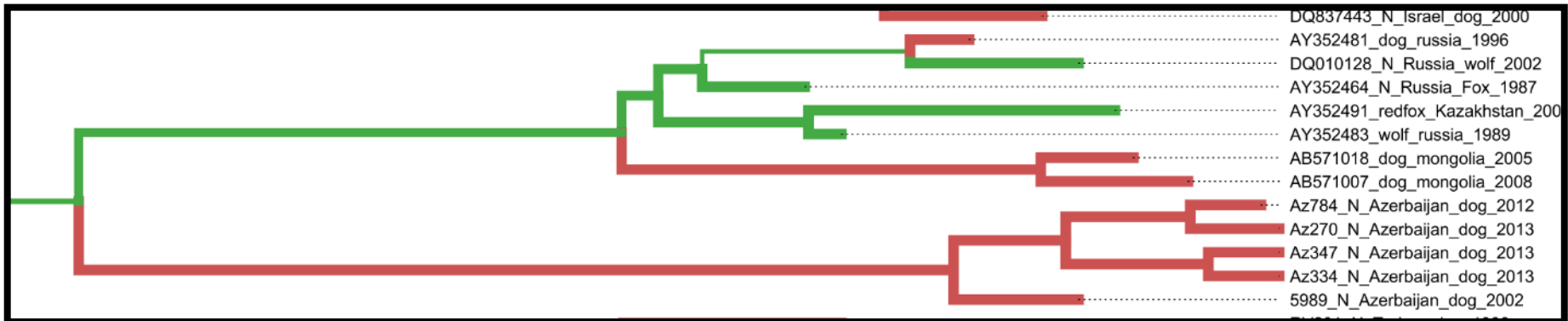
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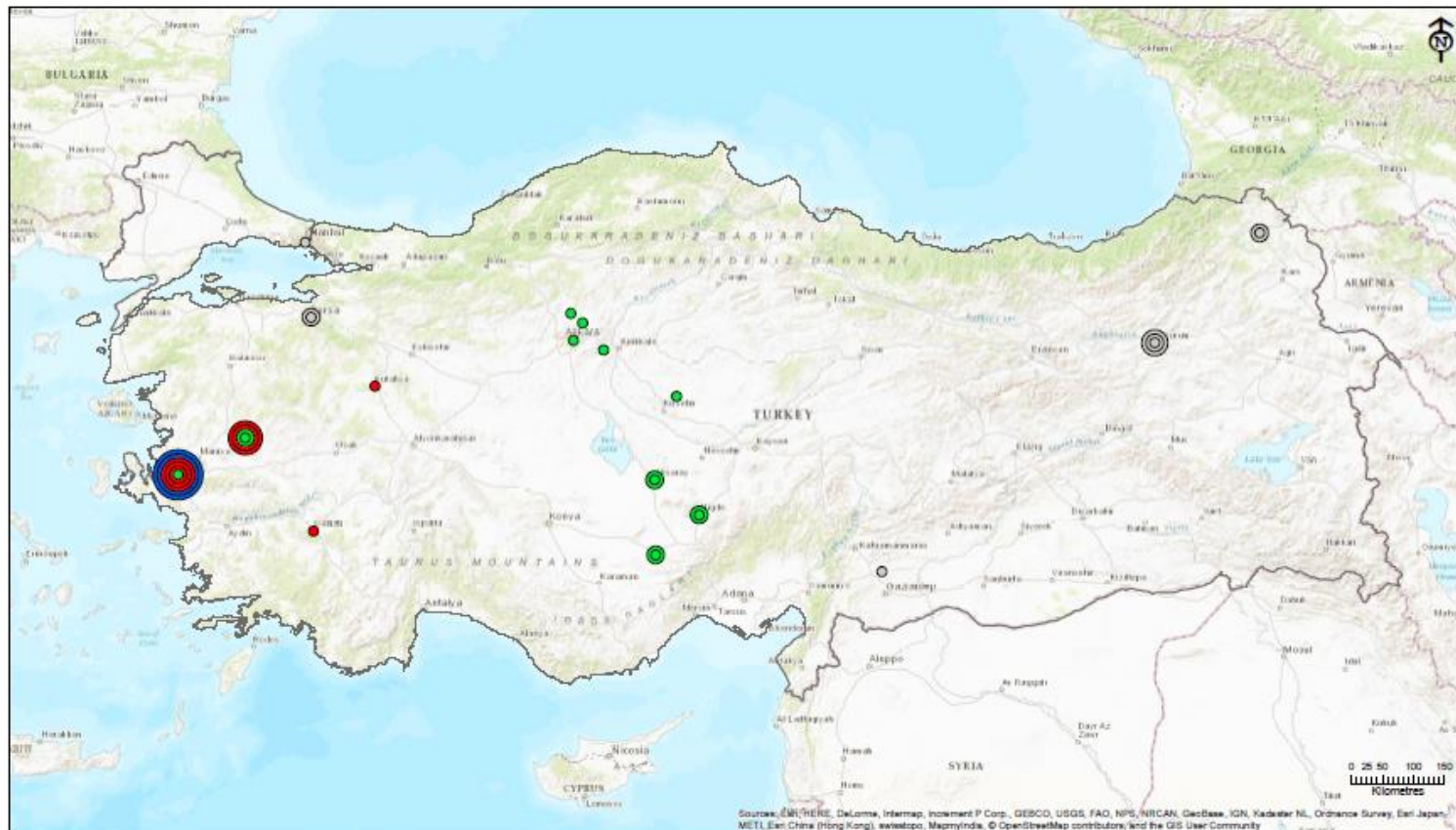
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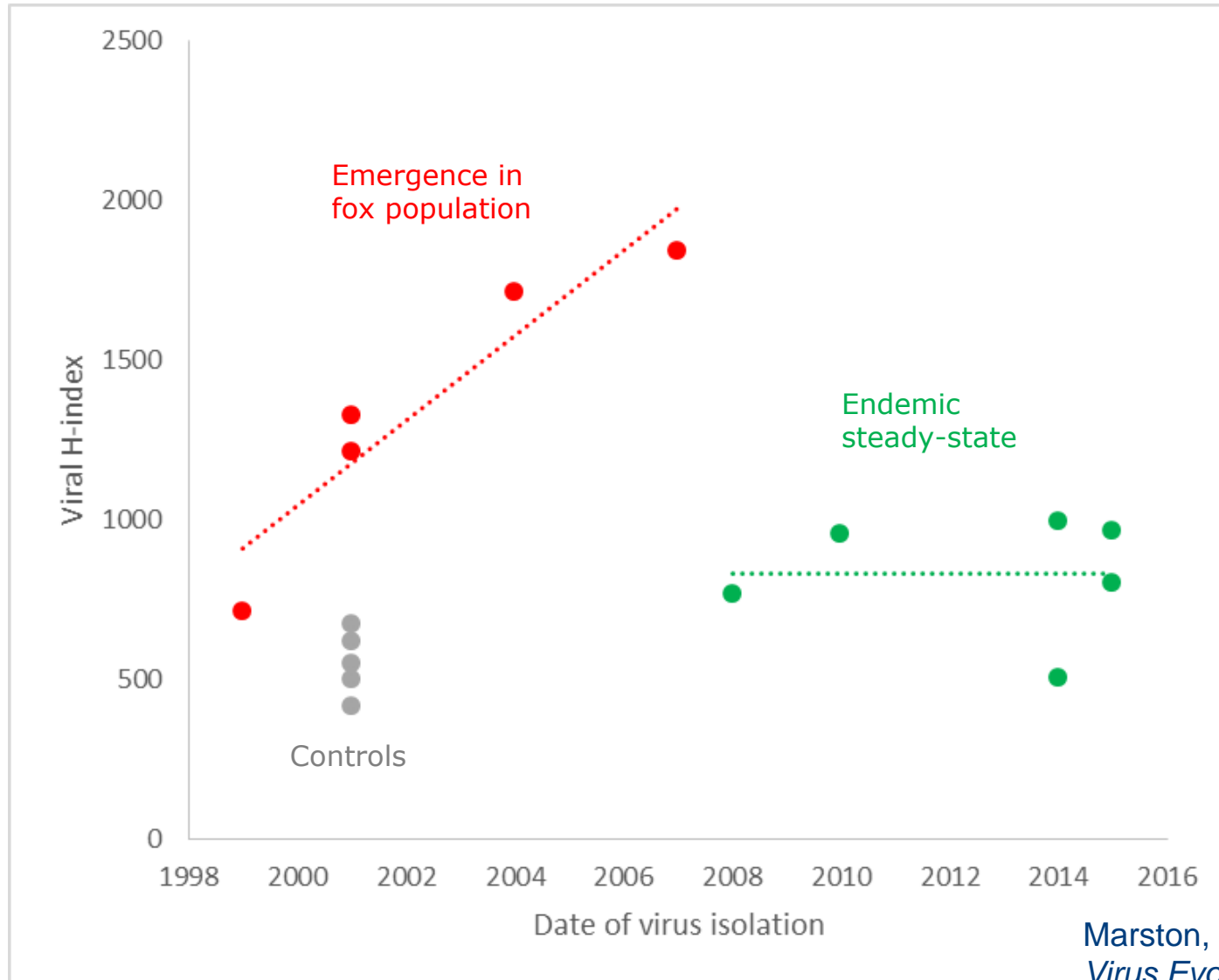
70% probability of
a wildlife ancestor



- 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)



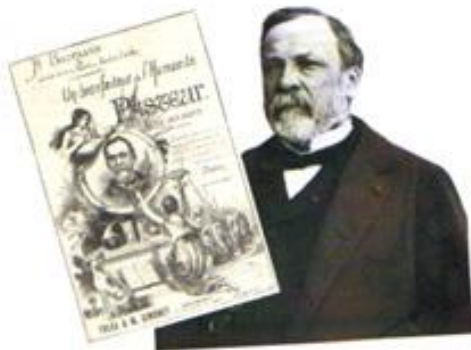
Viral heterogeneity



Wider context

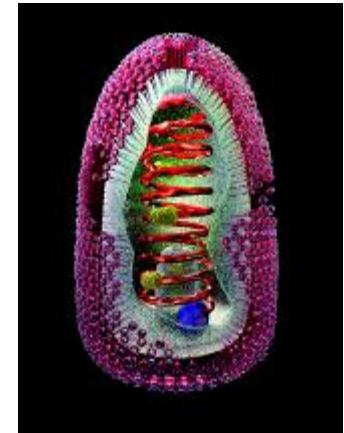
Family *Rhabdoviridae*: Genus *Lyssavirus*

1885

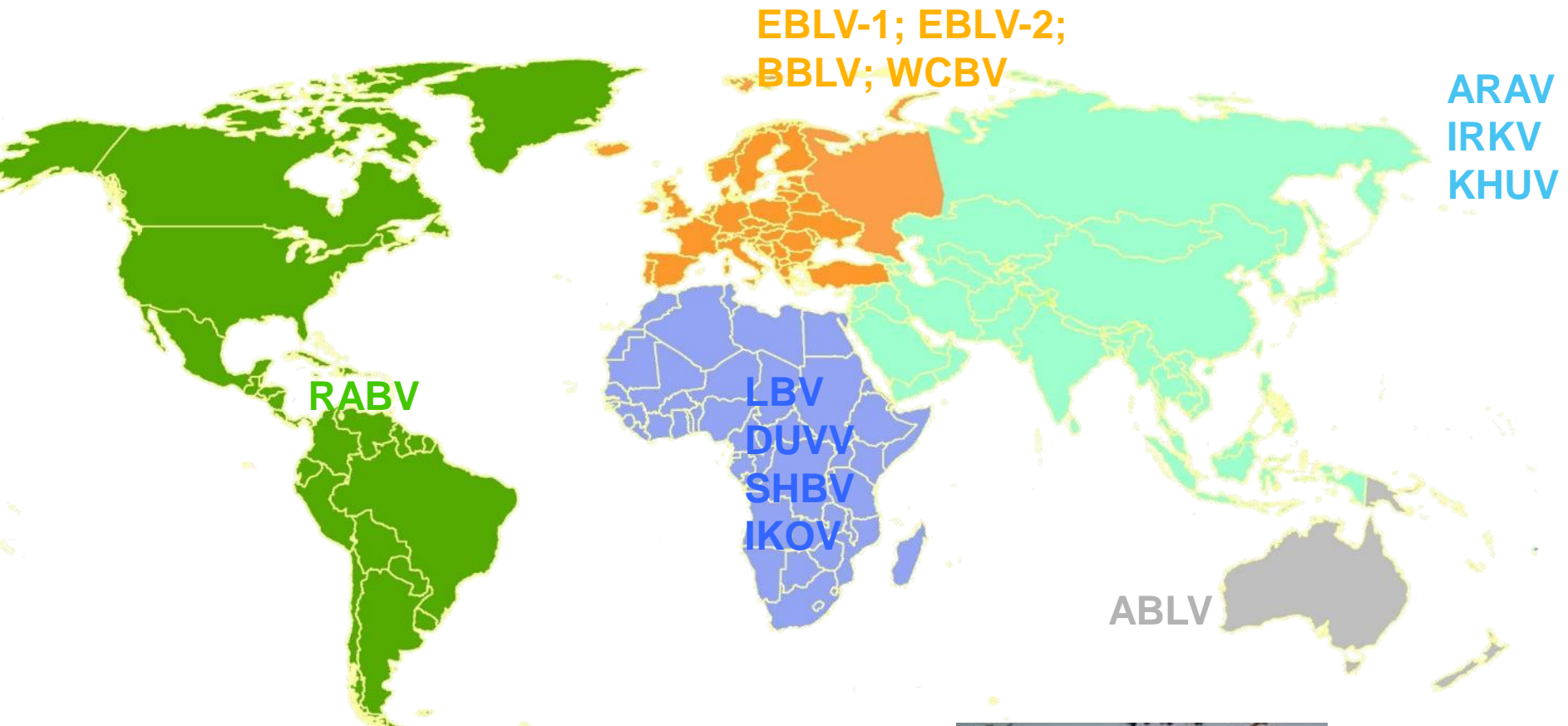


- Classical rabies virus
- Lagos bat
- Mokola
- Duvenhage
- European bat lyssavirus 1
- European bat lyssavirus 2
- Australian bat lyssavirus
- Aravan virus
- Khujand virus
- Irkut virus
- West Caucasian bat virus
- Shimoni bat lyssavirus
- Bokeloh bat lyssavirus (Germany) - 2011
- Ikoma lyssavirus (Tanzania)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

2018



Food for thought- potential emergence of new lyssaviruses





New York Times