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
Acknowledgements

University of Surrey
Victor Del Rio Vilas
Yasaman Kalantar-Motamedi
Roberto La Ragione
Martha Betson

APHA, UK
Professor Tony Fooks
Denise Marston
Lorraine McElhinney
Ash Banyard
Nick Johnson
Wildlife Zoonoses and
Vector Borne Diseases group
Andrew Breed

FLI, Germany
Thomas Muller
Conrad Freuling

Turkey
Hikmet Un
Orhan Aylan

Iraq
Mashair Zaki

Azerbaijan
Shalala Zeynalova
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

Fooks et al Lancet 2014
Hampson et al PlosNTD 2015
Rabies pathogenesis

1. Virus enters muscle tissue of host through bite wound

2. Virus enters the PNS via neuromuscular junction

3. Virus travels from PNS to spinal cord and brain

4. Virus enters brain and undergoes extensive replication leading to neuronal dysfunction

5a. Virus replication in salivary glands and excretion in saliva

5b. Virus enters peripheral nerves of skin and hair follicles

5c. Virus spreads from brain to infect many tissues and organs

Virus in Purkinje cells of cerebellum (x 40 mag.)
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!

BU HEYVANLAR QUDUZLUQ XƏSTƏLİYİ TƏRƏFƏ BİLƏR!

QUDUZLUQÜN ƏLƏMƏTLƏRİ:
AĞIZIN SULANMASI,
AQRESSİVLİK VƏ YA
SAKİTLIĞ, ANORMAL
DAVRANIŞ

ƏGƏR SİZ QUDUZLUQDAN
ŞÜBƏLƏNİRSLİNZƏ,
DƏRHAL SƏHƏ BAYTAR
HƏKİMİ VƏ YA RAYON
BAYTARLIQ İDARƏSİNƏ
XƏƏR VERİN

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Reducing dog rabies reduces human cases

- **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

- 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

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)

Partial N gene sequences

Policy-relevant risk assessment

Bayesian phylogenetics

Partial N gene sequences

FTA™ cards

180 samples over 40 years

Horton et al. (2015)

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Four main virus groups

So what?

- Mapping the distribution of existing clades

- In some areas three clades circulating at the same time
Bayesian Phylogeography: Ancestral state reconstruction
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

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n.d=no data
What is the reservoir host?

Try using Bayesian phylogenetics:
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

Emergence in fox population

Endemic steady-state

Marston, Horton et al
Virus Evolution 2017
Family *Rhabdoviridae*: Genus Lyssavirus

- 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)
Food for thought - potential emergence of new lyssaviruses