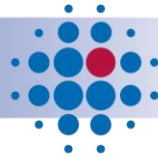


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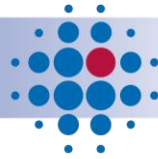


LYSSAVIRUSES

A potential re-emerging public health threat

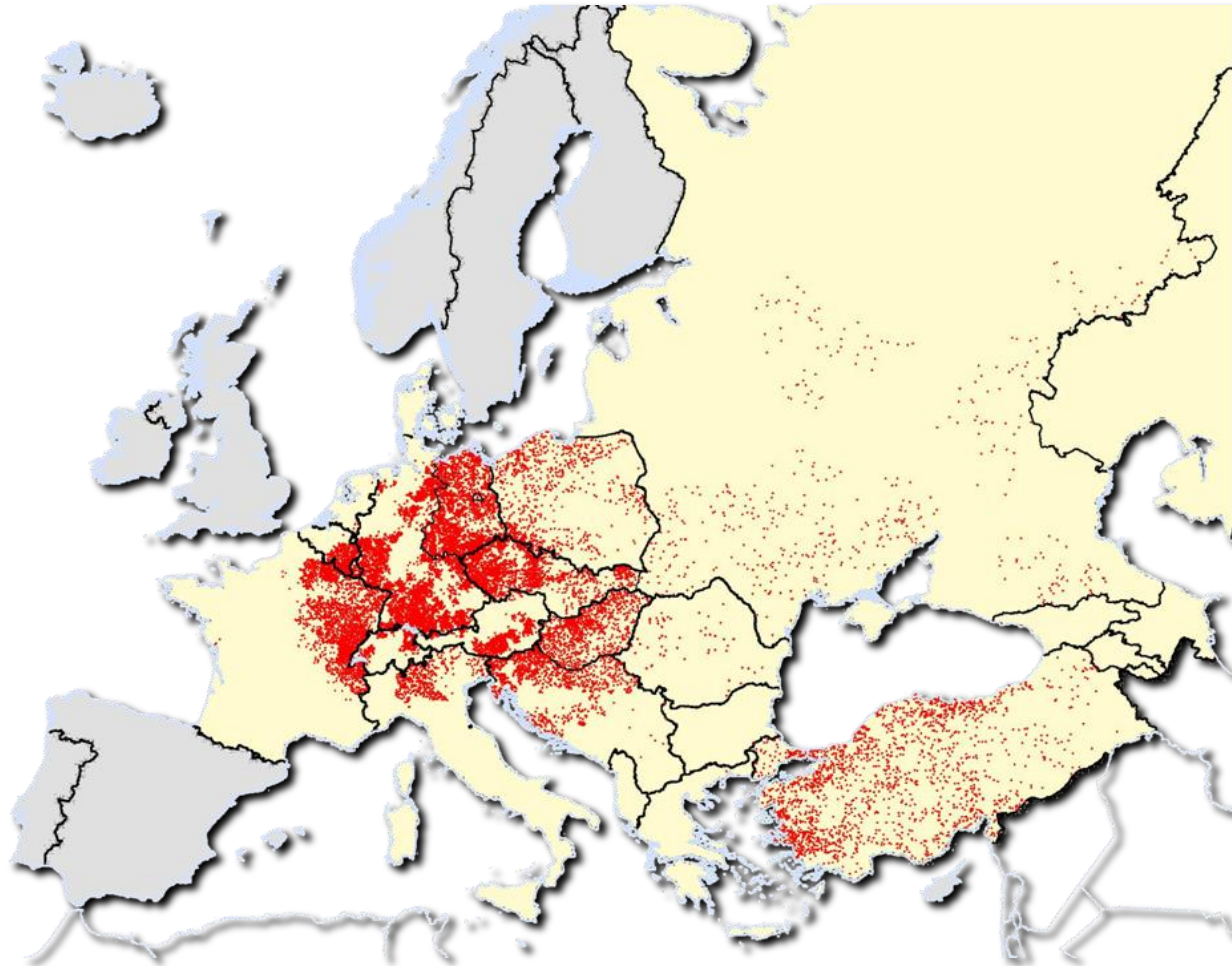
Müller T, Freuling C, Hoffmann B, Vos A, Finke S, Conzelmann KK, Höper B, Köllner B, Drosten C, Ross S,
Beer M, Mettenleiter TC

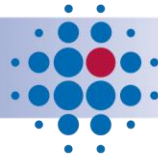




Rabies in Europe 1983

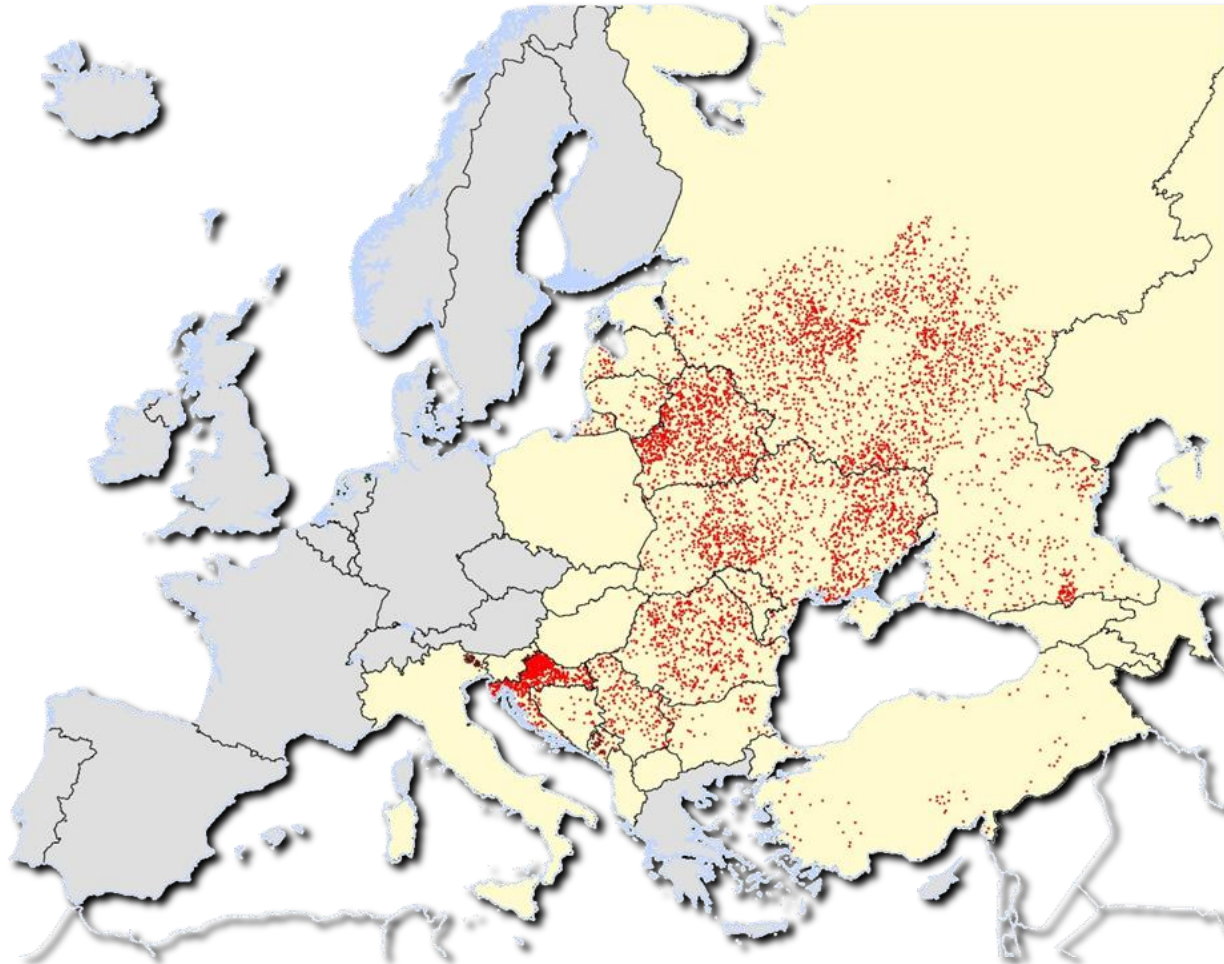
after 30 y of conventional rabies control

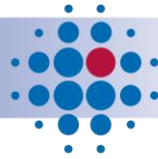




Rabies in Europe 2009

27 y of oral vaccination of foxes



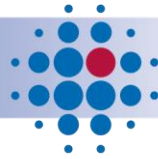


Rabies control in Europe

How was this success achieved?

- Strong long term political commitment, legal basis
- Adequate strategy, surveillance & diagnostics
- Support of European Union:
 - 50% co-financing of ORV campaigns
 - Pet Travel scheme
- Commitments of WHO / OIE
 - Exchange of information - Rabies Bulletin Europe
 - Informal WHO meetings on rabies control
 - Scientific conferences
- Bilateral meetings with neighbouring countries
- Involvement of all stakeholders

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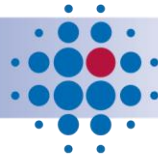
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So what is the problem with rabies?

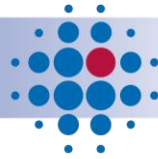


Rabies

Do you know?

- Epidemiological peculiarities & differences
- thousands of human death annually
- 90% of rabies deaths occur in Asia and Africa
- 50% of rabies death occur in children <15 years
- Neglected disease of poverty
- World's poorest countries affected
- Highest burden in developing countries





Large variety of reservoir species

Rabies cannot be eradicated!



Canine Rabies

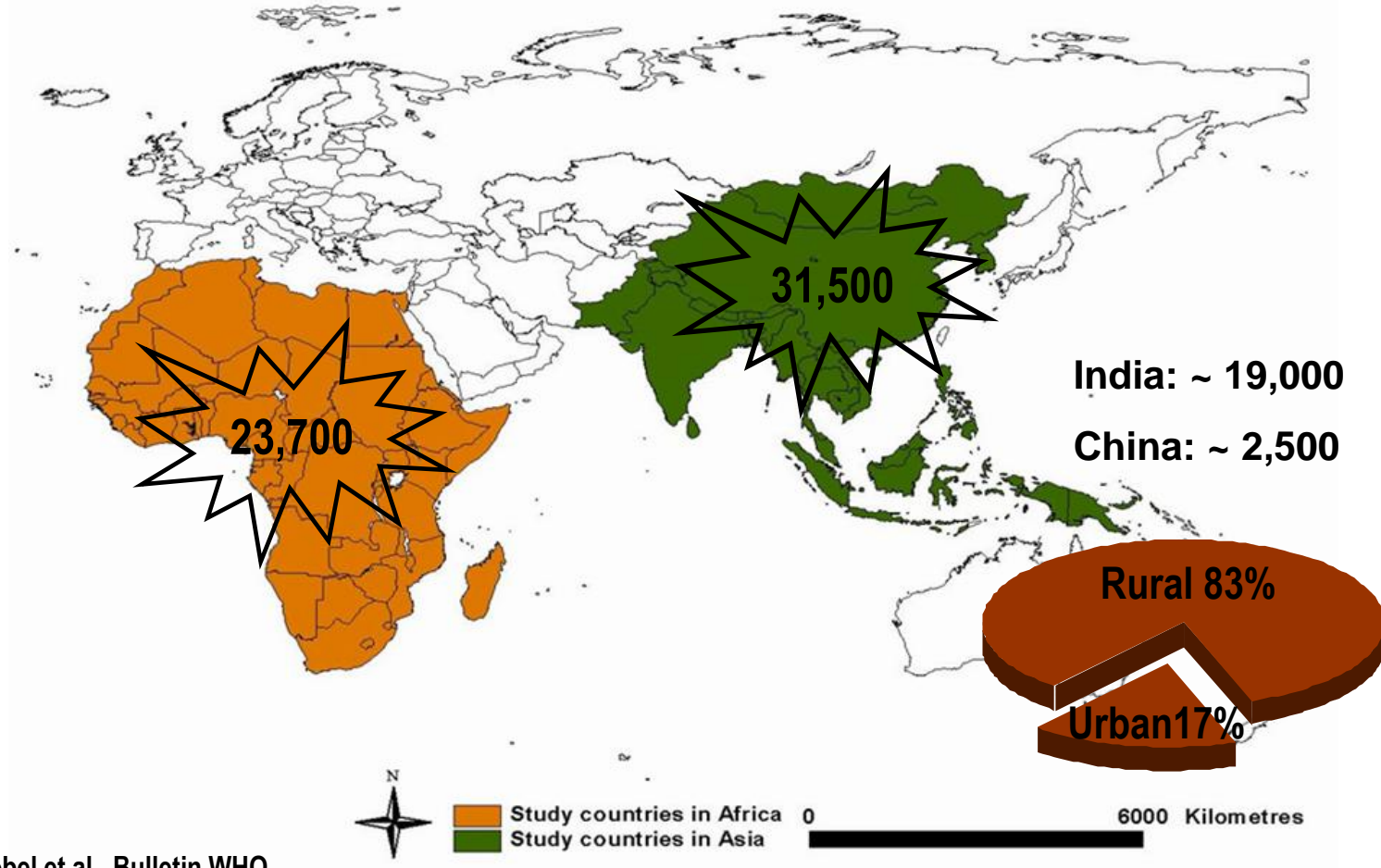
Rabies exposures

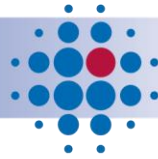
- 98% of human rabies deaths come from bites of rabid dog
- Many children (Ø 50%) who come face to face with them



Estimated Annual Human Rabies Death

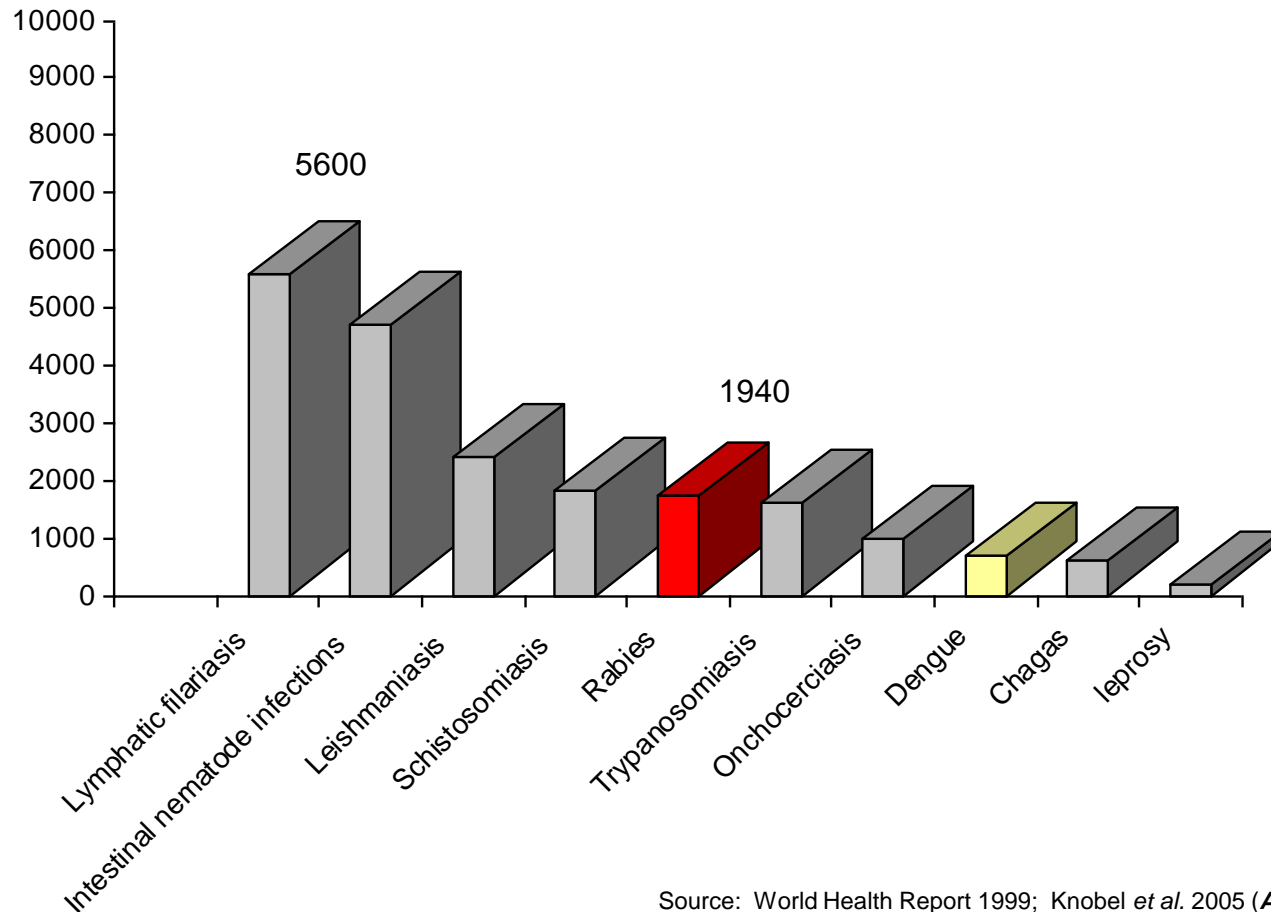
Africa and Asia





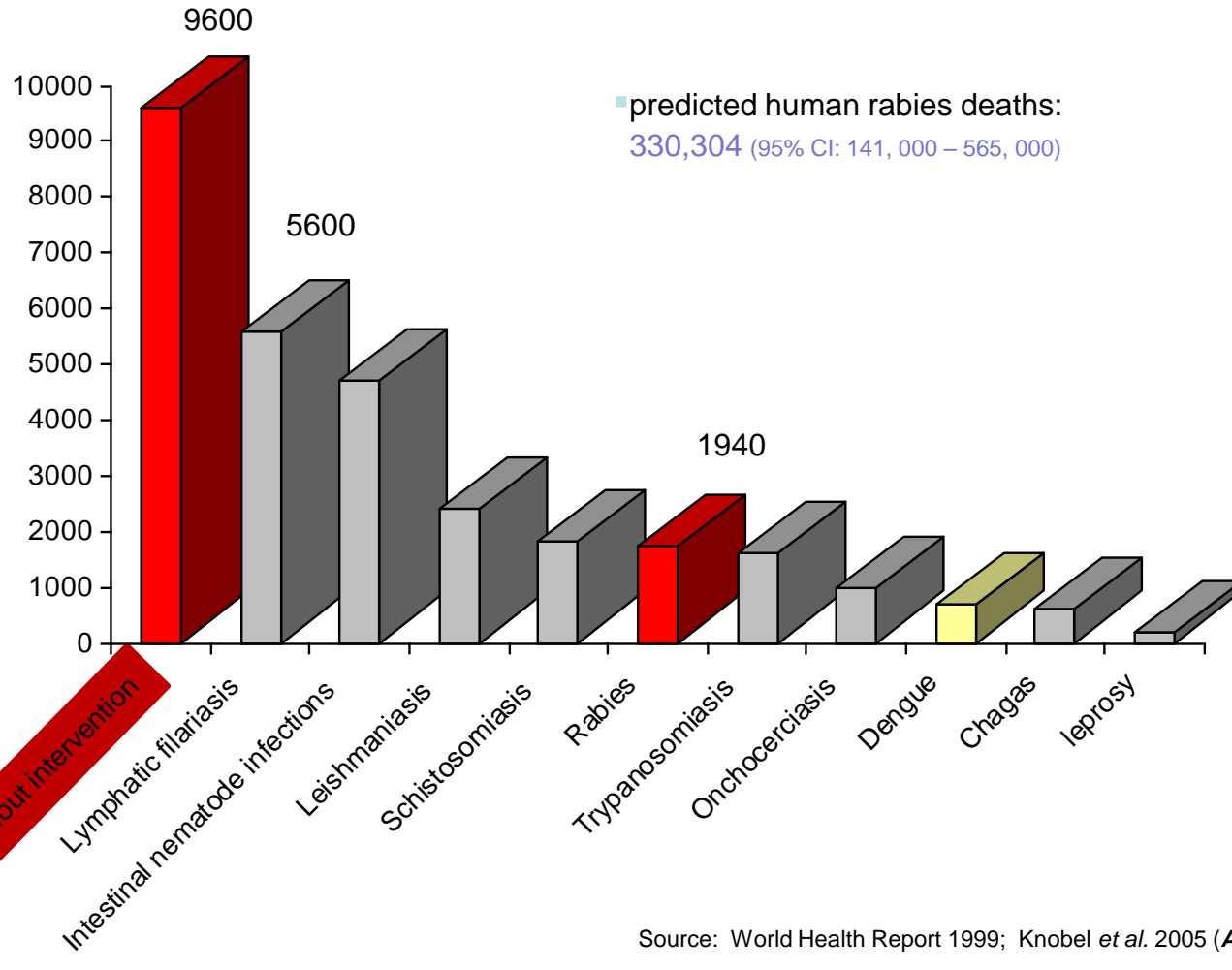
WHO: Burden of “neglected diseases”

DALY scores x 1000



WHO: Burden of “neglected diseases”

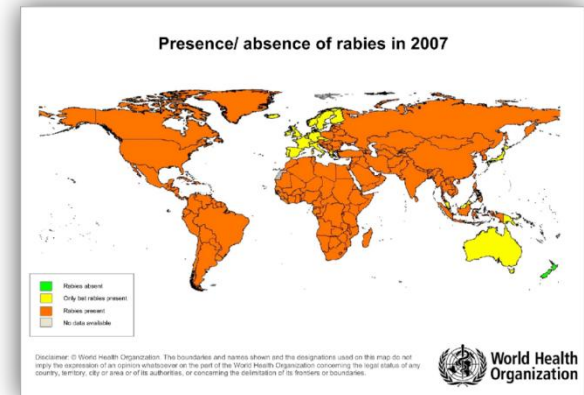
DALY scores x 1000



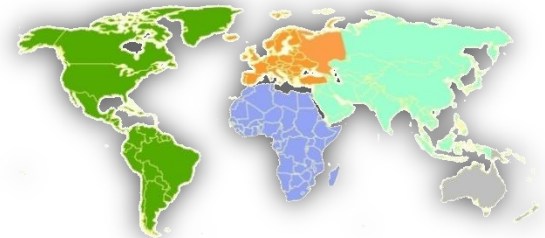
Rabies

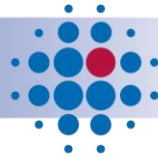
12 Species of Lyssaviruses - Rhabdoviridae

Virus	Genotype	Spread	Reservoirs
RABV	I	worldwide	mammals chiroptera
LGBV	II	Africa	chiroptera
MOKV	III	Africa	???
DUVV	IV	Africa	chiroptera
EBLV 1	V	Europe	chiroptera
EBLV 2	VI	Europe	chiroptera
ABLV	VII	Australia	chiroptera
ARAV	?	Asia	chiroptera
KHUV	?	Asia	chiroptera
IRKV	?	Asia	chiroptera
WCBV	?	Asia	chiroptera
SBV	?	Africa	chiroptera

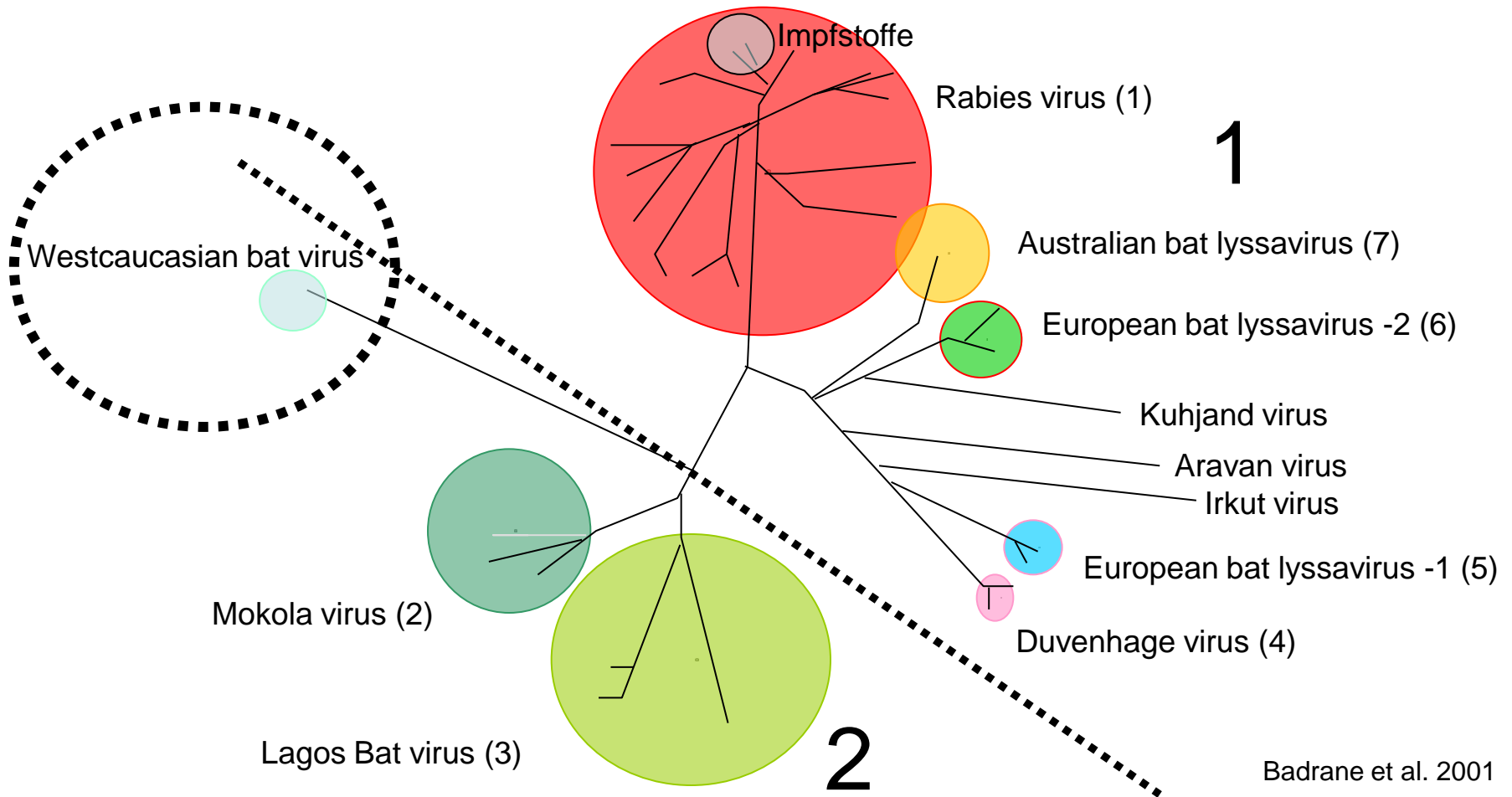


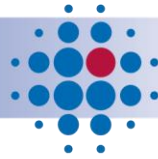
Bat lyssaviruses





Lyssaviren - Phylogruppen






Bat lyssaviruses - Spillovers

terrestrial animals & humans

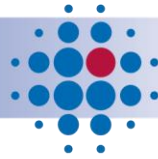
	Genotype	Animals *		Humans**	
		No.	<i>Spp.</i>	No.	<i>Spp.</i>
North America	RABV	221	12	50	12
Central America	RABV	147	7	137	1
South America	RABV	329	9	334	7
Africa	LBV, DUVV	18	3	2	?
Europe	EBLV-1, -2	5	2	5	2
Australia	ABLV	-	-	2	1
Asia	-	-	-	1	-

Source: * literature search 1982-2006 ** Brass (1994) + CDC Atlanta

 Underreporting

 vampire bat-related cases

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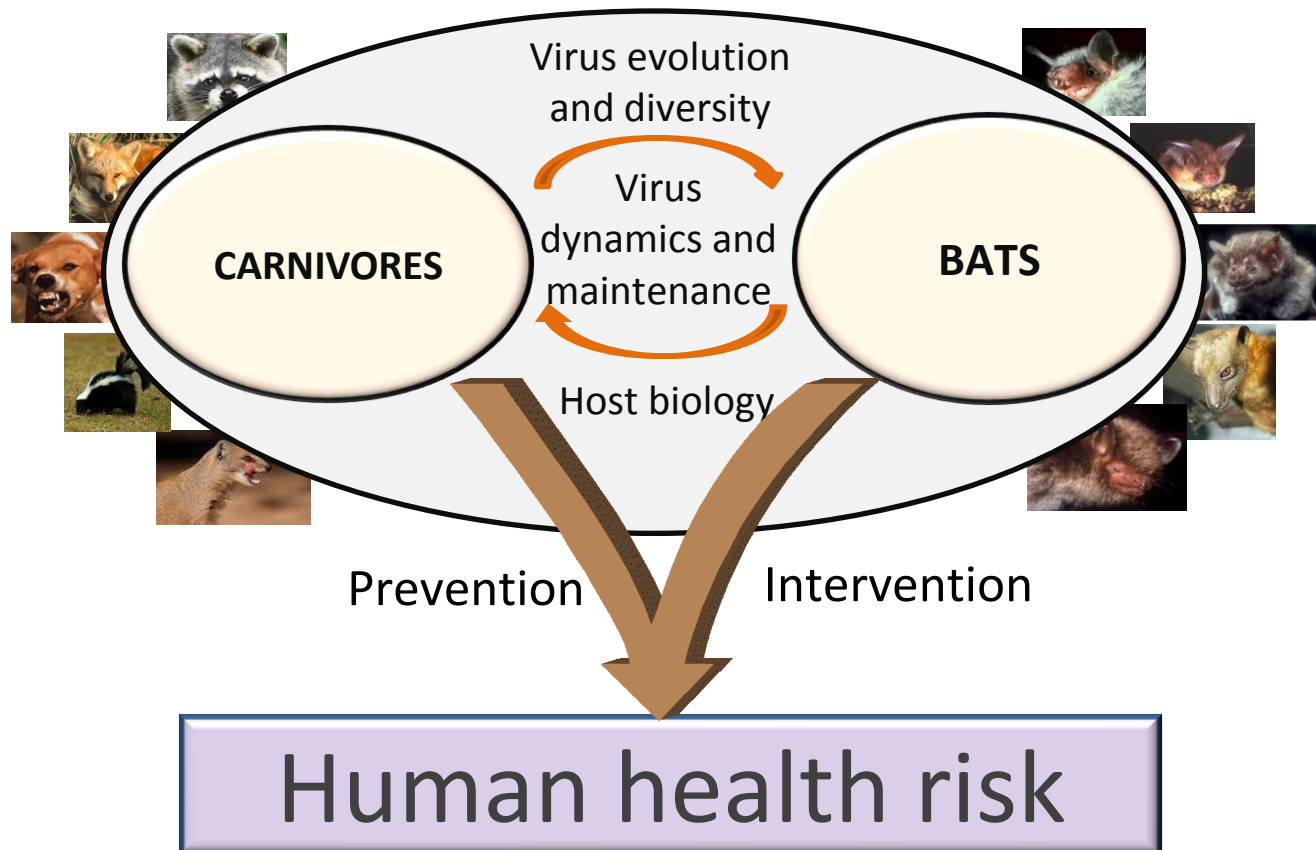
Networks for zoonotic infectious diseases

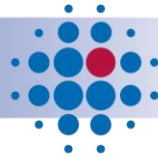
LYSSAVIRUSES -

A potential re-emerging public health threat

Hypothesis driven research concept

Lyssaviruses

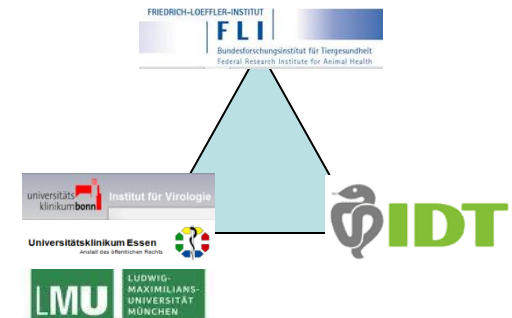


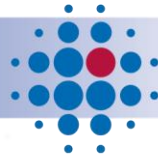


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individual projects

- Virus maintenance, evolution, and diversity
 - P6 surveillance Europe, America
 - P7 surveillance Africa, America, host ecology
 - P4 partial & full sequencing
- Host biology
 - P1 envelope proteins and host barrier (reverse genetics)
 - P2 innate immunity and host barrier
 - P5 adaptive immune system in bat reservoirs
- Intervention and prevention
 - P3 potential emerging hosts (raccoon)
 - P8 potential public health threat
- P9 technology platform

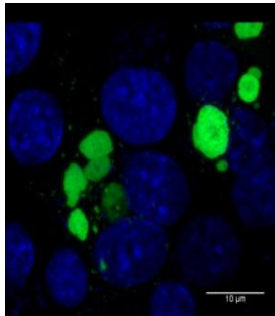




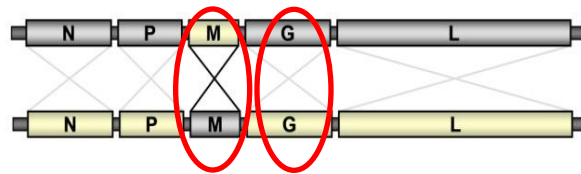
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Project 1

Lyssaviral envelope proteins and their contribution to host range and pathogenicity



RABV backbone

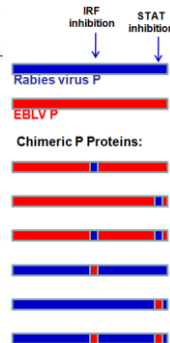
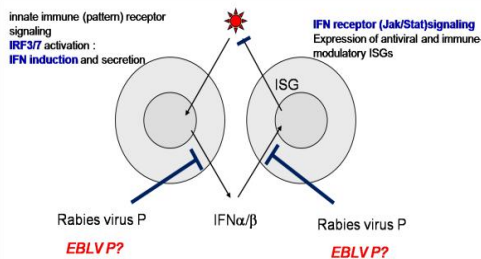


- contribution of M and G to host tropism, pathogenicity & transmission
- envelope-switched chimeras
- correlation to fatal dead end spill-overs
- highly cross-protective LV vaccines



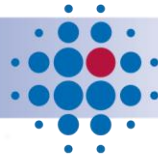
Project 2

The phosphoprotein – a key virulence and host range factor of rabies-like viruses



IRF and STAT domain mutations

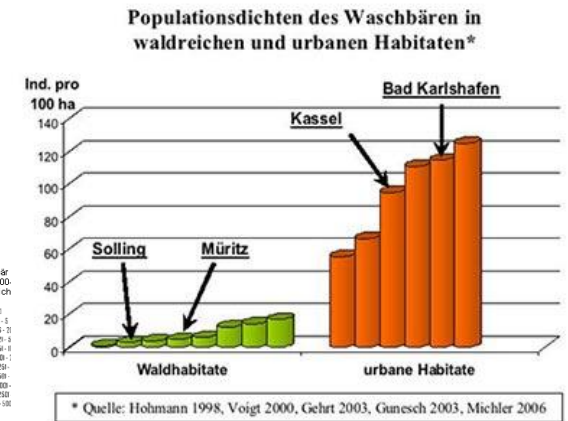
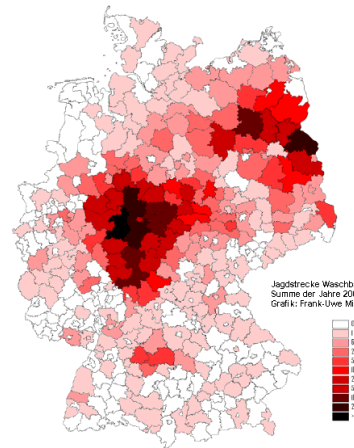
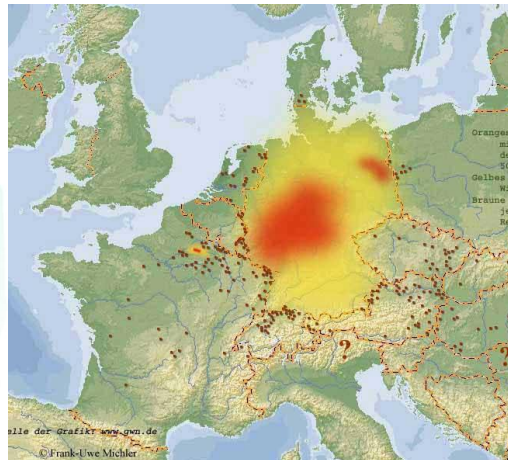
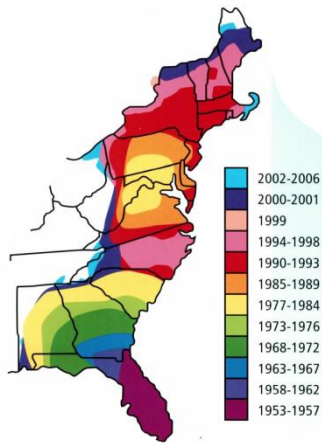
- P is rabies virus IFN antagonist
- Are bat LV P adapted to bat IFN pathways?
- individual functions & interactions of LV Ps
- mutations of IRF and STAT domains “towards” prototype RABV



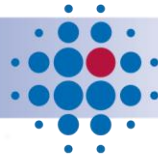
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Project 3

Potential emerging rabies hosts - raccoon



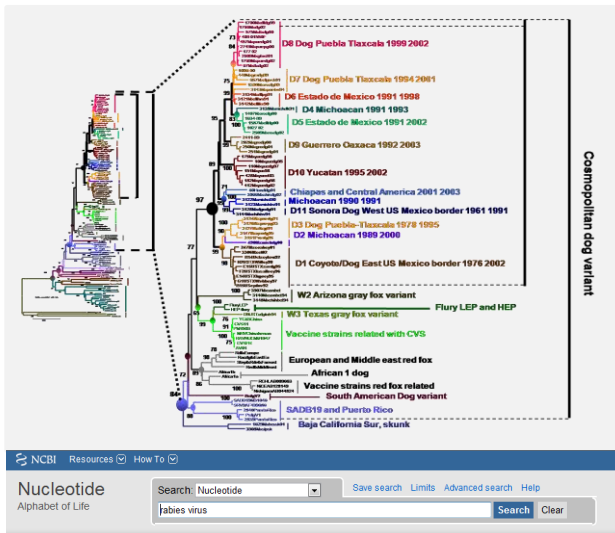
- Susceptibility studies (RABV, EBLV-1, -2)
- Efficacy studies
 - 1 - Commercial oral rabies vaccines
 - 2 - reverse genetic vaccine candidates
 - 3 - new recombinant vaccine candidates
 - 4 - bait development



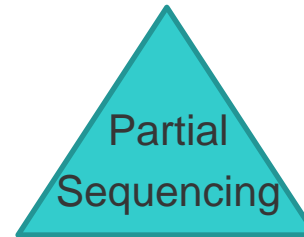
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Project 4

Whole genome sequencing, virus-host adaptation, and molecular epidemiological analyses of lyssaviruses



Selective full genome sequencing



In vitro
Quasi species

Literature re-review &
Screening of sequence datenbanks

NCBI Resources How To

Nucleotide
Alphabet of Life

Search: Nucleotide Save search Limits Advanced search Help

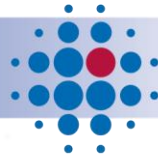
rabies virus Search Clear

Display Settings Summary, 20 per page, Sorted by None

Found 11298 nucleotide sequences. Nucleotide (11297) EST (1)

Results: 1 to 20 of 11297

- Rabies virus strain_4102Cl08.glycoprotein (G) gene, partial cds, and G-L intergenic spacer, partial sequence
1,305 bp linear cRNA
GU123662.1 | GI:262480439
[Related sequences](#)
- Rabies virus strain_7579Cl05.glycoprotein (G) gene, partial cds, and G-L intergenic spacer, partial sequence
1,305 bp linear cRNA
GU123661.1 | GI:262480437
[Related sequences](#)
- Rabies virus strain_6979Cl05.glycoprotein (G) gene, partial cds, and G-L intergenic spacer, partial sequence
1,305 bp linear cRNA
GU123660.1 | GI:262480435
[Related sequences](#)



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Project 5

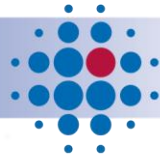
Humoral and cellular adaptive immune reactions of raccoons & European bats against „emerging viruses“



Poly- and monoclonal antibodies specific to immunoglobulines from

- serological assays (ELISA; IF & IB assays)
- Main immunoregulatory molecules (leukocyte receptors, humoral factors etc.) involved in anti-viral immune responses
- real-time-PCR based analysis of immune response after viral infection of bats
- Comparison of parameters of anti rabies immune response in bats and mouse



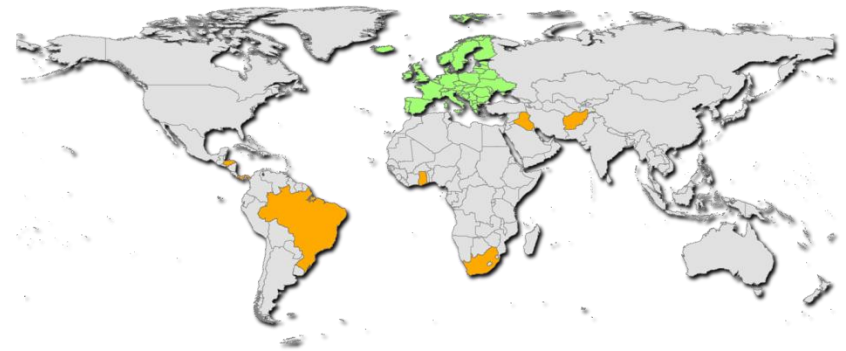


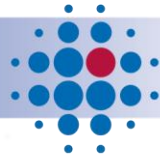
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Project 6

Bat-borne Lyssaviruses as neglected causes of viral encephalitis in Africa and Brazil

- ecological and virological species barriers
- prevalence of LVs in fruit-eating bats
- organ tropism and patterns of virus excretion of LVs in *E. helvum*
- Generation of bat cell lines from *E. helvum*
- transmissibility to humans and livestock by cell culture models
- induction of interferon by Lyssa- and Henipaviruses in human versus bat cells.



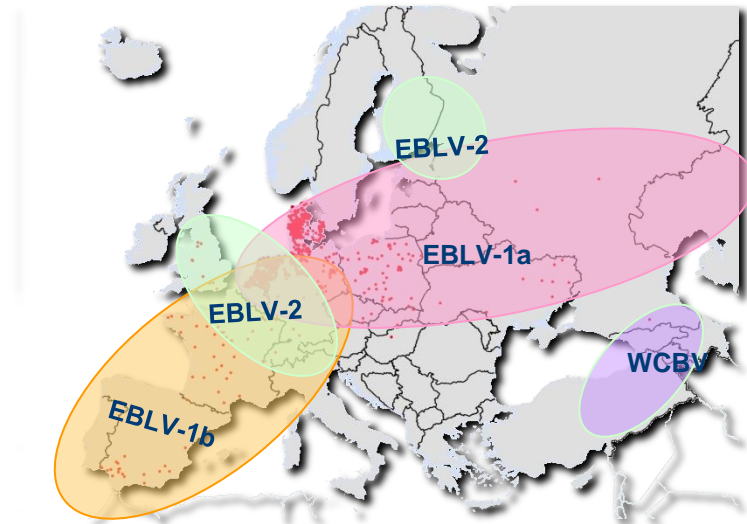


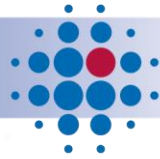
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Project 7

Establishing passive and active surveillance of bat related lyssaviruses in indigenous bat species in Europe

- improvement of routine surveillance (RBE)
- additional passive surveillance of bats (collections / archives)
- retrospective testing of archived specimens
- active surveillance (high-risk bat colonies)
- genetic fingerprinting (species identification)
- factors influencing the spread of EBLVs
- species-specific sera for development of anti-species conjugates

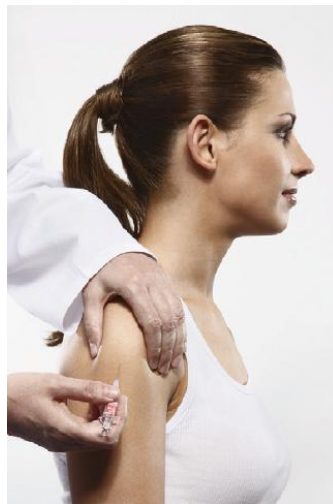




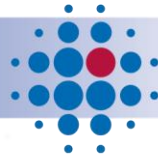
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Project 8

The potential public health hazard of rabies – perception by the general population & the medical community in Germany



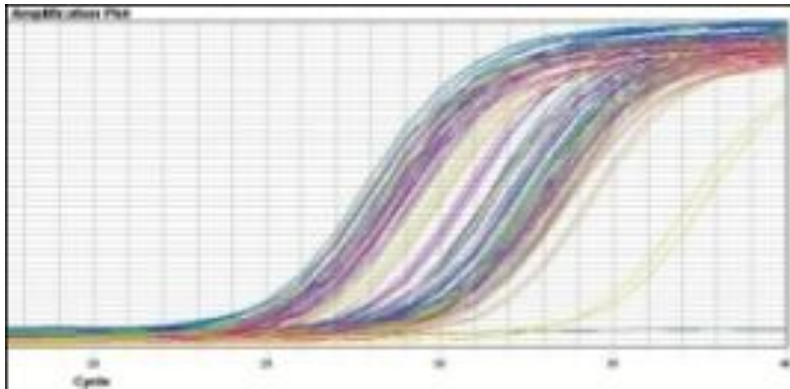
- Rabies risk assessment Germany
 - Risk of re-introduction of rabies
 - Perception of autochthonous and travel associated rabies risk in human PEP
 - Deficit analysis
 - Re-consideration of current guidelines
- one health aspect (synergies human & veterinary medicine)
- Tools from social science
 - „focus group discussion“, „Expert discussion“, Risk maps (bat rabies)



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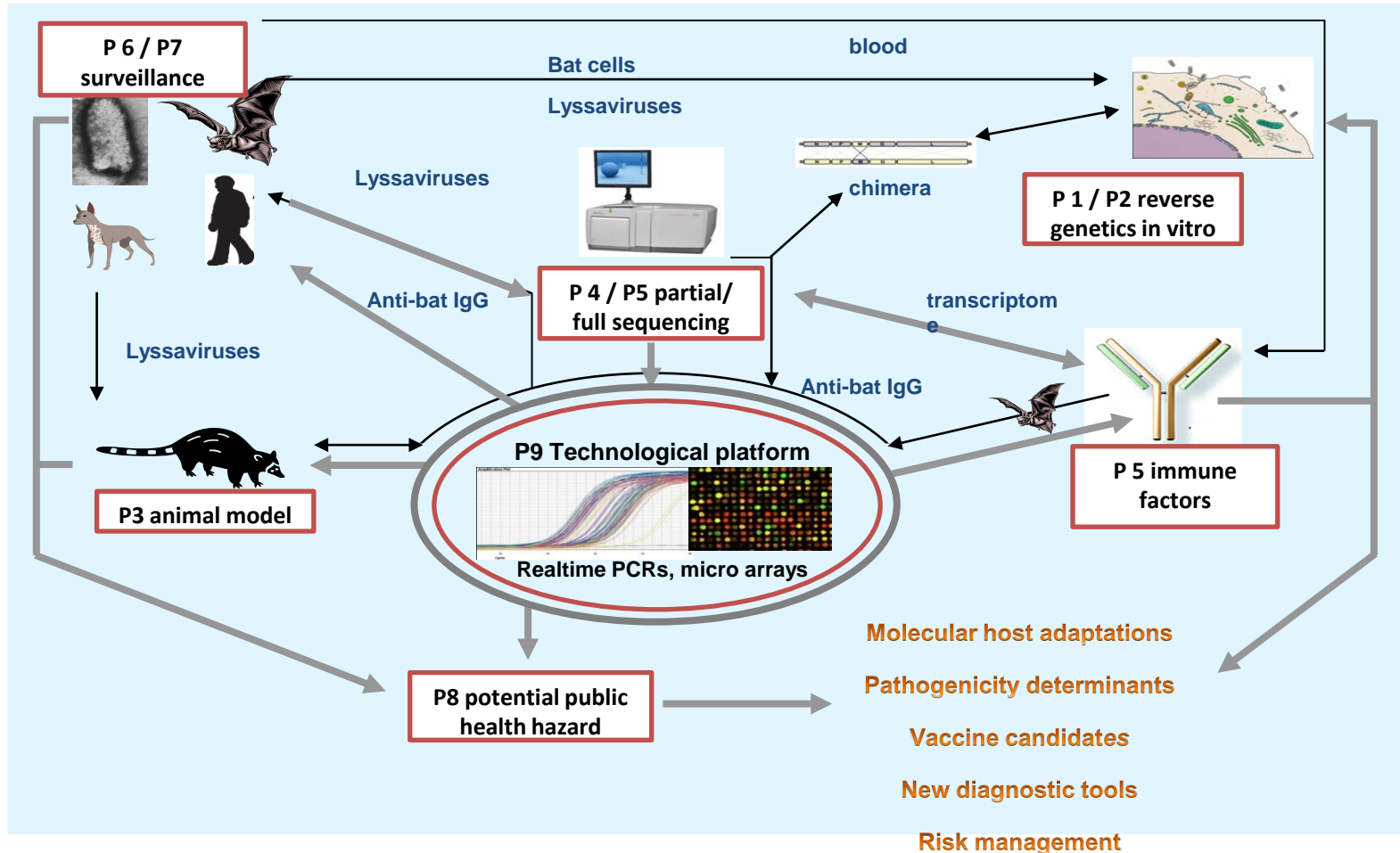
Technology platform 9

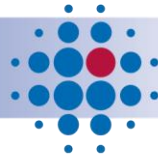
Development and validation of molecular methods for genome detection and characterization of all lyssaviruses



- Development of sensitive, specific and reliable lyssavirus diagnostics of clinical samples from both humans and animals
- Development and establishment of fully validated, standardized and applicable real-time RT-PCR and microarray systems
- Technology transfer to developing countries

Mehrwert & Produkte





WORLD RABIES DAY

September 28, 2010

Working Together to Make Rabies History!



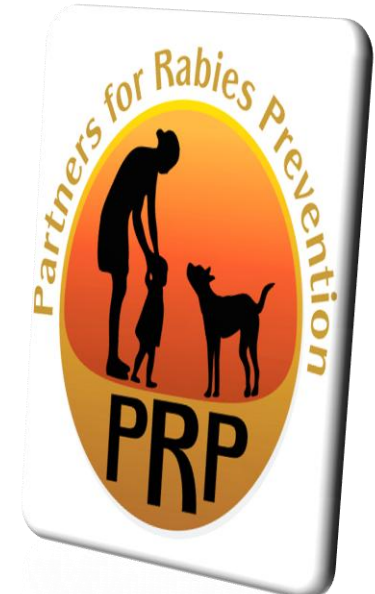
ALLIANCE
FOR
RABIES CONTROL



Alliance
for Rabies
Control



WORLD RABIES DAY
SEPTEMBER 28



Partners for Rabies Prevention
PRP

Make a difference!
Get involved!