RABIES: A NEGLECTED, RE-EMERGING ZOONOSIS

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National Center for Emerging and Zoonotic Infectious Diseases
Centers for Disease Control and Prevention
Myths about Rabies

Rabies is rare
Rabies is not widespread
Nothing can be done to make an impact towards rabies elimination
Rabies 101

- An acute, progressive viral encephalomyelitis
- The highest case fatality rate of any conventional etiological agent
- Leading viral zoonosis
  - International burden
  - Veterinary and public health significance
- Distributed on all continents but Antarctica
- One of the oldest described infectious diseases, known for more than 4 thousand years

Rabies: An Ancient Disease

- **2300 BC**
  - Dog owners in Babylon fined heavily for deaths caused by their dogs biting people

- **800–700 BC**
  - Homer likens Hector to a “raging dog” in *The Iliad*

- **1271**
  - 1st large rabies outbreak reported (Germany)

- **1703**
  - 1st case of rabies reported in the Americas by a priest in Mexico

Rabies: Etiology

RNA viruses in the family *Rhabdoviridae*, genus *Lyssavirus*

- The type species of the genus is Rabies Virus
- Historically, at least 6 other lyssavirus species cause rabies, some lacking cross reactivity to commercial biologics
- Recently, the International Committee on Virus Taxonomy ratified 4 new lyssavirus species from Eurasian bats
- Additional pathogen discovery is expected

All mammals appear susceptible; major reservoirs

- Carnivora: Dogs, foxes, raccoons, skunks, etc.
- Chiroptera: Insectivorous, hematophagous, and frugivorous bats

RNA, Ribonucleic acid
Rabies: Pathogenesis

- Transmission primarily via bite
- Viruses are highly neurotropic
  - Enter peripheral nerves
  - Centripetal travel by retrograde flow in axoplasm of nerves
  - Replicate in CNS
  - Centrifugal flow to innervated organs, including the primary portal of exit, the salivary glands
- Viral excretion in saliva

CNS, Central nervous system
Rabies virus concentration

Antibody response

Days post-exposure

- Virus present at entry site
- Zone of PEP mediated virus neutralization at the site of infection
- Vaccine induced humoral immune response
- Spread and replication of virus in the absence of appropriate PEP

Infection

<table>
<thead>
<tr>
<th>Incubation period (5 days to &gt; 2 years)</th>
<th>Prodrome (0-10 days)</th>
<th>Acute neurologic period (2-7 days)</th>
<th>Coma (5-14 days)</th>
<th>Death</th>
</tr>
</thead>
</table>

- US median incubation period is ~35 days
- Passive immunity - HRIG

Prodrome (0-10 days)
- Acute neurologic period (2-7 days)
- Coma (5-14 days)
- Death

Vaccine induced humoral immune response

CNS virus

Salivary glands virus

Incubation period (5 days to > 2 years)

Prodrome (0-10 days)

Acute neurologic period (2-7 days)

Coma (5-14 days)

Death

US median incubation period is ~35 days

Vaccine induced humoral immune response
Rabies: Clinical Stages

- **Incubation period**
  - Range: 6 days to >2 years
  - Average: 4–6 weeks

- **Prodromal stage**
  - Nonspecific signs

- **Acute neurologic phase**

- **Coma**

- **Death**
  - Vs. extremely rare reports of experimental treatment and recovery from rabies after the onset of clinical signs

Rabies: Diagnosis

- History of animal exposure and typical neurologic clinical signs

- Laboratory diagnosis
  - Gold standard: Postmortem demonstration of viral antigens in CNS by DFA
  - National laboratory protocol in 2000
  - In humans, antemortem detection of virus or viral amplicons, antibodies, or antigens (sera, CSF, saliva, nuchal biopsy)

CNS, Central nervous system
DFA, Direct fluorescent antibody
Rabies: Global Burden

- Human rabies exposures/year: Tens of millions
- Estimated human rabies deaths/year: >55,000
  - Africa (rural): 3.6/100,000
  - India (rural): 2.5/100,000
  - Pakistan: 1.2/100,000
  - China: 0.2/100,000
- Most cases occur in Africa and Asia, and in children
- Reservoirs
  - Domestic dog: Single most important animal reservoir
  - Wildlife important, especially in developed countries of Europe and North America

Rabies in the United States

- **Human rabies:** Uncommon
  - 20,000–40,000 exposures/year
  - 1–8 cases/year

- **Animal rabies**
  - 7,000 –10,000 cases/year
  - Dog rabies transmission eliminated
  - Wildlife hosts include raccoons, skunks, foxes, mongooses (Puerto Rico), and bats
  - Distributed in every state but Hawaii

Why Focus on Dogs?

- Worldwide >90% of rabies exposures are from dogs
- Worldwide >99% of human rabies deaths are via dogs
- Bite wounds, stress, and trauma from dogs rabies
- Rabies control and elimination is possible in dogs
- Roaming infected dogs are obstacles to success
- Oral Rabies Vaccination (ORV) and contraception hold promise to enhance rabies control
Rabies in the United States: Effect of Animal Control on Human Fatalities

Number of human rabies cases

Number of canine rabies cases

Human Rabies

Rabid Dogs
Rabies: Foundations of Prevention and Control

- Dog rabies vaccination, *en masse*
- Minimization of human exposures to infected animals
- Prompt wound care and prophylaxis with vaccine and rabies immune globulin after exposure
- Regulations to support the disease-free status of many localities, due to the introduction of rabid animals (e.g., Bali)

Goals Towards Global Rabies Prevention and Control in the 21st Century

- Counter viral emergence from wildlife reservoirs
- Develop humane methods for population management of free-ranging animals
- Translate progress in canine rabies elimination
  - From developed to developing countries
  - On a realistic, sustainable, regional basis
  - Based upon ideal models
- Create of new international advocacy and effective blueprints for rabies prevention and control
- Establish dynamic, multidisciplinary partnerships via renewed intersectoral cooperation
RABIES MANAGEMENT AT THE HUMAN–ANIMAL INTERFACE

Dennis Slate, MS, PhD
National Rabies Management Coordinator
US Department of Agriculture
Animal and Planet Health Inspection Service
Wildlife Services
Impact of Dog Rabies on Humans

- Worldwide, 90% of rabies exposures are from dogs
- Worldwide, 99% of human rabies deaths are from dogs
- Bite wounds, stress, and trauma from dogs rabies

- Burden of coexistence with dog rabies
- Rabies transmission at the dog–wildlife interface
Dog Subpopulations: A Challenge to Achieving Control of Dog Rabies

Home-Owned Pet

- Specific owner: 72 million dogs in the US (2007)
- Generally accessible for vaccination by injection

Feral Roaming Street Community

- No specific owner
- Not easily accessible for vaccination by injection
Dog Rabies: Dynamics of Virus Transmission and Exposure

Transmission pathways:
- 1-way
- 2-way
- Circulating
Challenges for Control of Dog Rabies

- Achieving adequate immunity in owned-dog population (50-70% level)
- Vaccination of free-roaming dogs
- Dog overpopulation may impede or prevent rabies control success
- Virus spillover at the dog-wildlife interface may confound success of dog and wildlife rabies control
## Dog-Wildlife Interface

### Achieving objectives of dog and wild carnivore rabies control

**Profound conservation impacts**

<table>
<thead>
<tr>
<th>Species</th>
<th>Interface Event</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>*African wild dog</td>
<td>Spillover of canine variant into African wild dog</td>
<td>Threatens local extirpation</td>
</tr>
<tr>
<td>*Ethiopian wolf</td>
<td>Spillover of canine variant into Ethiopian wolf</td>
<td>Threatens species extinction</td>
</tr>
<tr>
<td>Coyote</td>
<td>Spillover of canine variant from Mexico into coyote</td>
<td>Creates a public health emergency in south Texas</td>
</tr>
<tr>
<td>Gray fox</td>
<td>Spillover of gray fox variant into dog</td>
<td>Confounds success of ORV in gray foxes</td>
</tr>
</tbody>
</table>

* Endangered species
Effective Control of Dog Rabies May Require Integration of Additional Tools

- Education
- Quarantine
- Injectable vaccination campaigns
- Oral Rabies Vaccination (ORV)
- Contraception

Compendium of Animal Rabies Prevention and Control, 2008*
National Association of State Public Health Veterinarians, Inc. (NASPHV)
Oral Rabies Vaccination Basics

- Delivering a vaccine-bait to a target species for consumption to create herd immunity
- Canada, Europe, and the United States are primary users
  - 42,166,134 ORV doses in 2009
- Cost is a potential limiting factor ($1.23/dose)
- Led to elimination of specific rabies variants at the landscape scale

ORV, Oral rabies vaccination
Canine variant rabies cases in south Texas: 1988-2010.

Canine rabies spillover into coyotes
Integration of ORV contributed to canine rabies elimination
US declared free of canine rabies in 2007

ORV, Oral rabies vaccination
Enhanced Rabies Surveillance
dRIT- direct Rapid Immunohistochemistry Test

Road kill sample

Collecting brainstem sample

Slide preparation

Test determination via light microscope

negative

positive

Inexpensive, quick and accurate test for detecting rabies
Used in the US to enhance rabies surveillance to support ORV

ORV, Oral rabies vaccination
ORV Handout Trails to Vaccinate Free-ranging Dogs on Navajo Lands, Arizona 2006

- 373 dogs hand baited with Raboral V-RG
- 33/104 dogs tested had rabies virus neutralizing antibodies
Current and Future Contraceptive Approaches

- **Surgery**
  - Intrusive, expensive, time-consuming, postoperative infections
  - High efficacy

- **Injectable EsterilSol™ (zinc gluconate)**
  - Males only, anesthetic to inject testicles, permanent contraceptive
  - Currently not licensed in the United States

- **Injectable GonaCon™ (GnRH vaccine)**
  - Immunocontraceptive effect persists 3–4 years in some species
  - Effective in males and females for population control effects
  - Captive dog trials underway with new formulation to evaluate adverse local immune reactions (e.g., granulomas)

GonaCon, EPA. Reg. No. 56228-40 for use in deer only in US
North American Rabies Management Plan
International Collaboration and Coordination

- Information transfer
- Surveillance and monitoring
- Rabies control
- Research

Environment
Public Health
Agriculture
Wildlife
Successful Dog Rabies Control

- Injectable vaccination campaigns for companion dogs
  - Integrates:
    - Contraception to reduce dog fecundity
    - ORV targeting free roaming dogs and wildlife
NEW APPROACHES TO RABIES ELIMINATION IN LATIN AMERICA

Luis Fernando Leanes, MVD, MSc
Regional Advisor
Zoonosis Diseases – Veterinary Public Health
Pan American Health Organization (PAHO)
World Health Organization
<table>
<thead>
<tr>
<th>Country</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anguilla</td>
<td>Cayman Islands</td>
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<tr>
<td>Antigua and Barbuda</td>
<td>Chile</td>
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<tr>
<td>Argentina</td>
<td>Colombia</td>
</tr>
<tr>
<td>Aruba</td>
<td>Costa Rica</td>
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<td>Bahamas</td>
<td>Cuba</td>
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<tr>
<td>Barbados</td>
<td>Dominica</td>
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<td>Belize</td>
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<td>Bermuda</td>
<td>El Salvador</td>
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<tr>
<td>Bolivia</td>
<td>Ecuador</td>
</tr>
<tr>
<td>Brazil</td>
<td>US/MEX Border</td>
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<tr>
<td>British Virgin Islands</td>
<td>French Guiana</td>
</tr>
<tr>
<td>Canada</td>
<td>Grenada</td>
</tr>
<tr>
<td>Guadalupe</td>
<td>Paraguay</td>
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<tr>
<td>Guatemala</td>
<td>Peru</td>
</tr>
<tr>
<td>Guyana</td>
<td>Puerto Rico</td>
</tr>
<tr>
<td>Haiti</td>
<td>Saint Kitts and Nevis</td>
</tr>
<tr>
<td>Honduras</td>
<td>Saint Lucia</td>
</tr>
<tr>
<td>Jamaica</td>
<td>Saint Vincent and the Grenadines</td>
</tr>
<tr>
<td>Martinique</td>
<td>Suriname</td>
</tr>
<tr>
<td>Mexico</td>
<td>Trinidad and Tobago</td>
</tr>
<tr>
<td>Montserrat</td>
<td>Turks and Caicos Islands</td>
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<tr>
<td>Netherlands Antilles</td>
<td>Uruguay</td>
</tr>
<tr>
<td>Nicaragua</td>
<td>US</td>
</tr>
<tr>
<td>Panama</td>
<td>Venezuela</td>
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Overview

- Political decisions and mandates
- Epidemiological trends and progress made
- Remaining challenges
- Strategy for elimination and prevention of human rabies
Political Decision and Mandates

- 1983: 3rd Ministries of Health and Agriculture and PAHO Directive Council
  - Launched rabies elimination initiative fostering National Plans
- 2008: PAHO Directing Council
  - Elimination of human rabies transmitted by dogs by 2012
- 2010: Regional Meeting of the National Directors of Rabies Control Programs in Latin America (REDIPRA)
  - Follow up of National Plans through 13 PAHO-sponsored meetings of National Rabies Directors with OIE, WSPA, GARC, and CDC

OIE, World Organization for Animal Health
WSPA, World Society for Protection of Animals
GARC, Global Alliance for Rabies Control
CDC, Centers for Disease Control and Prevention
National Plans

- Surveillance
- Pre- and post-exposure prophylaxis
- Veterinary vaccination schemes and dog population control
Epidemiological Trends of Human and Canine Rabies Cases (N=7,228)
Latin America, 1970–2009

1984: >300 human cases
2009: 19 human cases; 95% reduction of human and dog cases

Epidemiological Trends: Human Rabies Cases Transmitted by Dogs (N=239)
Latin America, 2000–2009

Circulation of Rabies among Dogs
Latin America, 2010

Areas of low risk:
Achieved interruption of circulation of rabies among dogs

Areas of moderate risk:
Non sustained circulation of rabies among dogs

Areas of high risk for human rabies:
Sustained circulation of rabies among dogs

Remaining Challenges: Human Rabies Transmitted by Dogs

- Inadequate supply for canine vaccination
  ELS, HON, DOR, HAI, CUB, BOL

- Limited capacities for PEP
  GUT, ARG, DOR

- Coordination at local level
  GUT, MEX, VEN, BRA

- Coordination at borders
  ELS-HON, HAI-DOR, ARG-BOL, PER-BRA
## Remaining Challenges: Wild Reservoirs – Human Cases
Latin America, 2000–2009

<table>
<thead>
<tr>
<th>Transmission by</th>
<th>Mexico</th>
<th>Cent.-Am</th>
<th>Andean</th>
<th>Caribbean</th>
<th>Brasil</th>
<th>South-Cone</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>Dogs</td>
<td>5</td>
<td>37</td>
<td>61</td>
<td>54</td>
<td>76</td>
<td>6</td>
<td>239</td>
</tr>
<tr>
<td>Vampire bats</td>
<td>4</td>
<td>3</td>
<td>69</td>
<td>0</td>
<td>73</td>
<td>0</td>
<td>149</td>
</tr>
<tr>
<td>Non-haematophagous bats</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Non-specified bats</td>
<td>10</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Cats</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Cattle and horses</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Wild carnivora</td>
<td>8</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Not specified</td>
<td>0</td>
<td>4</td>
<td>10</td>
<td>2</td>
<td>8</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td><strong>Grand Total</strong></td>
<td><strong>35</strong></td>
<td><strong>47</strong></td>
<td><strong>147</strong></td>
<td><strong>61</strong></td>
<td><strong>163</strong></td>
<td><strong>9</strong></td>
<td><strong>462</strong></td>
</tr>
</tbody>
</table>

REDIPRA Strategies to Prevent Human Rabies

- Avoid relaxation when there are no human cases
- Manage urban transformations
  - Stray dogs and migration
- Prevent circulation of rabies among dogs and wild Carnivora
- Ensure access to health care and human pos- and pre-exposure prophylaxis
One Health Approach

- Veterinary vaccination schemes
- Diagnostic surveillance based on CDC monoclonal antibodies and molecular typing
- Animal control and welfare
- Post-exposure and pre-exposure prophylaxis

Interdisciplinary collaborations in all aspects of health care for humans, animals and the environment

http://onehealthinitiative.com
RENEWED ADVOCACY AND EFFECTIVE PARTNERSHIPS FOR RABIES PREVENTION AT THE COMMUNITY LEVEL

Deborah J. Briggs, PhD
Director
Global Alliance for Rabies Control
Why Do People Still Die of Rabies?

- Lack of awareness on all levels about
  - Responsible pet ownership – vaccinating pets
  - Need for post-exposure prophylaxis (PEP)
  - Primary wound care

- Rabies immunoglobulin (RIG) not available

- Rabies vaccines not available
  - Greater cost of travel
  - Increased risk of rabies onset

- Rabies vaccines are too expensive
  - Likelihood of giving up
  - Delays because of need to raise money
Overview

- Global partnerships and efforts for rabies prevention
- From blueprint to local implementation

NGOs, Nongovernmental organizations
Recent Examples of Innovative Programs for Global Rabies Prevention and Control

- **World Rabies Day, launched 2007**
  - Focal point for increasing global awareness

- **Global Alliance for Rabies Control, established 2007**
  - Registered 501 c3 in US; registered charity in Scotland

- **Partners for Rabies Prevention, established 2008**
  - Informal group of global stakeholders
  - Public, private, NGOs, funding organizations

- **E-global communications**
  - Bank of free educational materials

- **Pilot projects for One Health rabies control**
  - Example: Bohol Philippines, 2007–2011
World Rabies Day
September 28

Since September 2007...

- 135 participating countries
- 150+ participating schools of public health, veterinary and medical colleges have hosted one or more ‘rabies-awareness’ events
- ~300K Web visitors, 214 countries/territories

www.worldrabiesday.org
Impact of World Rabies Days

- **Since September 2007…**
  - >1,200 reported events
  - 4.6 million animals vaccinated
  - 150 million people educated

Children bringing pets to be vaccinated in Napak, Uganda during WRD 2010
Photo: Dr Inangolet Francis Olaki
Impact of World Rabies Days

- New animal vaccination programs in endemic countries
- New and invigorated educational programs
- Global community networks
- Listed on UN website of globally observed health days

Classroom education in Iraq

Vaccination clinic in Mozambique
Impact of World Rabies Day: Mozambique

Prior to World Rabies Day 2007
- Dogs unvaccinated due to local superstition
- Lack of support from government
- Basic educational materials not available

As of World Rabies Day 2010
- Partnership between veterinary clinics and Maputo Veterinary University
- Multiple vaccination clinics held throughout Mozambique
- National government funding rabies vaccinations on WRD
- Education of locals; construction of animal record database
The World Rabies Days: Evaluation of the Impact

- Continuous evaluation of global programs
- Annual evaluation of World Rabies Day campaign
- In 2010, questions about the effort as a whole were included
  - 213 surveys returned: English, French, Portuguese, and Spanish
  - 96.3%: “Rabies Education Programs Are Saving Lives”
  - 89.6%: “World Rabies Day Is Making a Difference”
  - 95.0%: “Will Host a World Rabies Day Event in 2011”
Partners for Rabies Prevention (PRP)

- **Informal group of stakeholders**
  - Public and private: Bring time, talent, treasure to table
  - GARC, CDC, FAO, OIE, PAHO/WHO, WSPA, etc.
  - Discuss common strategies
  - Evaluate needs, timelines, deliverables

- **Secretariat: Global Alliance for Rabies Control (GARC)**

- **Activities**
  - Road map: 2008
  - Blueprint for Canine Rabies Control: 2009–2010
  - Next step: Evaluate the global burden of rabies
- Free access on line
- Examples of ongoing programs
- Links to documents
- Information on
  - Cost
  - Planning
  - Funding
Blueprint: The Concept

- Aimed at assisting and guiding individual countries on implementation of canine rabies control programs
  - If rabies is present
  - If rabies is reintroduced after a period of absence
- New concept – not meant to replace existing documents
Global partnerships and efforts for rabies prevention

From blueprint to local implementation

- Istanbul and India: International workshops on development and implementation of the communications plan delineated in the Blueprint
- India: The Blueprint is a source of reference for human rabies prevention
- West Africa: The Blueprint used to improve communications networking and to set up dog vaccination programs
- Requests for translation into several different languages
Bohol, Philippines: Controlling Canine Rabies and Preventing Human Deaths

- Partnership with government and the Global Alliance for Rabies Control
- Additional funds from WHO and other NGOs
- Initiated in 2007
- Cost
  - Estimated $2.5 million/year in cost-savings by eliminating dog rabies in Philippines
  - Costs would be repaid in 4–11 years

WHO, World Health Organization
NGOs, Non government organizations
Bohol Philippines: Controlling Canine Rabies and Preventing Human Deaths

- **Community mobilization**
  - 140 to >15,000 persons involved in program

- **Vaccination**
  - 70% of dog population

- **Increased access to postexposure prophylaxis (PEP)**
  - New clinics
  - Expanded training

- **Integration of rabies education into school curriculum**
  - 182,000 children educated

- **CDC training of direct Rapid Immunohistochemical Test (dRIT) and evaluation of diagnostics**
No human or dog rabies deaths reported since Oct 2008

- In 2 prior years 10 cases/year reported

Currently undergoing evaluation by the Philippine Ministry of Health for rabies-free status
Lessons Learned

- Rabies prevention is possible
  - Need support from multiple sectors
  - Public/private partnerships are critical – pooling of resources

- Communication networks are powerful
  - World Rabies Day
  - First global webinar included >2,000 participants from 34 countries

- Many tools are already in place
  - Vaccines, reduced regimens, dRIT, websites, etc.

dRIT, direct Rapid Immunochistochemical Test
Needs, Challenges, and Way Forward

- **Investment in new tools (dog population control)**
- **Shorter pre-exposure vaccination regimens**
  - Especially important to vulnerable or isolated populations e.g., Amazonia
- **Improved global and national surveillance**
- **Reassessment of global burden to fully understand burden of rabies and to develop impact models that assess strategic interventions**
- **Novel strategies and methods to ensure sustainability to prevent reintroduction**