PROGRESS TOWARDS THE 2030 GOAL: THE GLOBAL ELIMINATION OF HUMAN RABIES BY DOGS (GEHRD)

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Rabies: Introduction

- An acute, progressive encephalomyelitis\textsuperscript{1,2}
- Case to fatality rate is the highest of any conventional infectious disease\textsuperscript{1,3}
- One of the oldest described diseases\textsuperscript{3}
- The leading viral zoonosis in terms of global public health significance\textsuperscript{4}
- Unlike smallpox and rinderpest, not a candidate for true eradication
- Caused by diverse lyssaviruses

LYSSAVIRUS GENOME & ANTIGENS
(conservation of a monophyletic Genus)

Single-stranded, Negative-sense RNA

Five proteins:
*N (Nucleoprotein)
P (Phosphoprotein)
M (Matrix protein)
*G (Glycoprotein)
L (RNA-dependent polymerase)
LYSSAVIRUS DIFFERENTIATION

Gradual Refinement of Methods:

- Host species
- Fixed vs. street isolates
- Serology
- Antigenic variants
- Genetic sequencing
- NGS
Family Rhabdoviridae, Genus Lyssavirus: Associated Phylogeny

Regions where different lyssaviruses were found are colored and dates for initial isolations are shown. Banyard et al. Viruses. 2014 Aug; 6(8): 2974–2990.
Stealth: Lyssaviruses Are Quintessential Neurotropic Agents

Schnell et al., 2010

Green et al., 2006
**Extent: Global Burden**

- Tens of thousands of human rabies deaths estimated annually\(^1\)
- Most occur in developing countries\(^1,2\)
- Tens of millions of human exposures per year\(^2,3\)
- Outside the Americas, the dog is the single most important animal reservoir\(^2,3\)
- Wildlife are important reservoirs, especially in developed countries, such as those in Europe and North America\(^1,2,4\)

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HISTORICAL NERVE TISSUE VACCINES (NTV)

Used adult animal (or suckling mouse) CNS

Associated with higher adverse events

Modern cell culture products much safer

NTV no longer recommended by WHO (but still produced)
A Timeline of Rabies Virus Vaccine Development

1889 Pasteur’s dried spinal cord vaccine ~13 doses
1910 Fermi/Semple vaccine ~ 14-21 doses
1956 Fuenzalida/Palacios mouse CNS ~ 14-23 doses
1956 Duck Embryo ~ 14-23 doses
1973 HDCV ~ 6 doses
1980 HDCV ~ 5 doses
1984 HDCV, PCEC, FBKC ~ 4 doses: 2-1-1 schedule*

PAST, PV, PM, CVS
KISSLING
LEP, HEP
SAD, ERA, SAG, RV97
Nishigahara/NI-CE, RC-HL
CTN-181, pG/aG
MODERN RABIES PROPHYLAXIS

• Pre-exposure Vaccination

• Postexposure Prophylaxis (PEP)
PRE-EXPOSURE VACCINATION

• Provided to subjects at risk before occupational or vocational exposure to rabies
• Subjects include diagnosticians, laboratory & vaccine workers, veterinarians, cavers, etc.
• Simplifies postexposure management

POSTEXPOSURE PROPHYLAXIS

• Provided to subjects after rabies exposure
• Consists of wound care, rabies immune globulin, and vaccine
• If prompt and proper, survival virtually assured
RABIES BIOLOGICS

- Rabies Vaccines (for pre- and PEP)
- Rabies immune globulin (only in PEP)
Rabies Immune Globulin

- Homologous Human Rabies Immune Globulin (HRIG)
- Heterologous Equine Rabies Immune Globulin (ERIG)
- Infiltrated at site of bite during PEP
- Given at 20 IU/kg (HRIG) or 40 IU/kg (ERIG)
MODERN RABIES VACCINES

• Human Diploid Cell Vaccine (HDCV)

• Purified Chick Embryo Cell Vaccine (PCEC)

• Purified Vero Cell Vaccine (PVRV)

• Purified Duck Embryo Vaccine (PDEV)

• Veterinary Biologics include MLV, Inactivated, Adjuvanted, Recombinant (IM, SC, Oral)
RABIES VACCINE ADMINISTRATION

• Typically given IM (1.0 ml)

• Separate site and syringe from HRIG

• Typically use deltoids or anterior lateral thigh

• Intradermal route is dose sparing (0.1 ml) and more economical
PRE-EXPOSURE VACCINATION

• Vaccine given on days 0, 7, and 21 or 28

• Serology occurs every 6 months to 2 years (if remaining at risk)

• If antibody titer is not adequate, administer a single booster dose

• If ever exposed, administer a vaccine dose on days 0 and 3, regardless of titer
Postexposure Prophylaxis Considerations

- Balance of benefits and harm may differ between individuals based on risk of disease
- Rabies PEP recommendations are dependent upon associated risks:
  - Type of exposure
  - Animal rabies epidemiology
  - Circumstances of the exposure incident
  - Availability of exposing animal for observation
  - Prompt diagnostic testing
### Rabies Postexposure Prophylaxis Guide – United States

<table>
<thead>
<tr>
<th>Animal type</th>
<th>Evaluation and disposition of animal</th>
<th>Postexposure prophylaxis recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs, cats and ferrets</td>
<td>Healthy and available for 10 days observation.</td>
<td>Persons should not begin prophylaxis unless animal develops clinical signs of rabies.</td>
</tr>
<tr>
<td>Rabid or suspected rabid</td>
<td></td>
<td>Immediately vaccinate.</td>
</tr>
<tr>
<td>Unknown (e.g., escaped)</td>
<td></td>
<td>Consult public health officials.</td>
</tr>
<tr>
<td>Skunks, raccoons, foxes and most other carnivores; bats</td>
<td>Regarded as rabid unless animal prove negative by laboratory tests.</td>
<td>Consider immediate vaccination</td>
</tr>
<tr>
<td>Livestock, small rodents (rabbits and hares), large rodents (woodchucks and beavers), and other mammals</td>
<td>Consider individually.</td>
<td>Consult public health officials. Bites of squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, mice, other small rodents, rabbits, and hares almost never require antirabies PEP.</td>
</tr>
</tbody>
</table>
Why Do People Still Die Of Rabies?

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

- PEP not accessible or too expensive:
  - Rabies mostly affects poor, rural communities
  - Biologics often not available
  - Delays are dangerous and costly
    - Travel to urban centres
    - Delays because of need to raise money
    - Need to sell valuable food animals to buy live-saving vaccines

As development increases, bite victims are more likely to obtain PEP and thus NOT die of rabies

Hampson et al. 2015
Targeting Rabies Management:
Dynamics of Virus Transmission and Exposures

Vaccines can be used to interrupt transmission at any stage

U.S. Advisory Committee on Immunization Practices, Human Rabies Prevention
NASPHV Compendium of Animal Rabies Prevention & Control
A GLOBAL DIVERSITY OF RABIES VIRUS VARIANTS IN DOGS, WILD CARNIVORES AND BATS

Adapted from: Troupin et al. 2016
Historical Rabies in the United States: Impact of Animal Vaccination on Human Fatalities
Organization of veterinary public health services within countries

Rise of intersectorial collaboration among health and agriculture ministries with regular regional meetings (e.g. REDIPRA)

Enhanced social participation

Reduction of a concentration on culling animals

Promotion of animal health and environmental resources

Focus upon annual mass dog vaccination, initially in major urban centers

Application of lessons learned from North American rabies control, prevention and elimination

Increased laboratory-based vigilance, including viral characterization

Technical cooperation with the Pan American Health Organisation, with use of the revolving fund for purchases of biologics

Engagement with WHO CC (e.g., CDC, CFIA, etc.) and NGOs (e.g., RITA, NARMP, etc.)

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

PAHO Rabies Information System, SIRVERA (www.panaftosa.org.br).
Why Also Focus on Animal Management Versus Humans Alone?

- Worldwide >90% of rabies exposures are from dogs
- Worldwide >99% of human rabies deaths are via dogs
- Bite wounds, stress, and trauma from canine rabies
- Rabies control and elimination is possible in dogs (low R0)
- Community-infected dogs are not obstacles to success
- Animal rabies prevention is much more cost-effective

### Global Dog Rabies Elimination Pathway: phases for a dog rabies elimination program

<table>
<thead>
<tr>
<th>Implementation Phase:</th>
<th>Phase I: Preparation</th>
<th>Phase II: Scale-up dog vaccination</th>
<th>Phase III: Sustained 70% dog vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Program year</strong></td>
<td>1  2  3</td>
<td>4  5  6</td>
<td>7  8  9  10  11  12  13</td>
</tr>
<tr>
<td><strong>Expected dog vax coverage:</strong></td>
<td>&lt;18% (current rate)</td>
<td>18% - 35% 35% - 53% 53% - 70%</td>
<td>≥70%</td>
</tr>
<tr>
<td><strong>Activities achieved</strong></td>
<td>Field studies</td>
<td>Pilot implementation</td>
<td>Mass vaccination of dog</td>
</tr>
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<td></td>
<td>Workforce training</td>
<td>Scaling-up vaccination coverage</td>
<td>Surveillance to establish disease burden and assess progress</td>
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<td></td>
<td>Strengthening lab capacity</td>
<td>Logistical improvements</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Operational equipment</td>
<td></td>
</tr>
<tr>
<td><strong>Cost estimates:</strong></td>
<td>Current vaccination coverage</td>
<td>Expected vaccination coverage</td>
<td>Vaccination of 70% of the dog population</td>
</tr>
<tr>
<td></td>
<td>Infrastructure improvements*</td>
<td>Infrastructure improvements*</td>
<td></td>
</tr>
</tbody>
</table>

Wallace et al. Front Vet Sci. 2017
T’chad: cost trends of three different rabies control scenarios

- Scenario 1: PEP alone
- Scenario 2: PEP + dog vaccination
- Scenario 3: One Health

Cost of PEP for 100% human rabies prevention

Mindekem Front Vet Sci. 2017
GLOBAL FRAMEWORK FOR THE ELIMINATION OF DOG-MEDIATED HUMAN RABIES

Dog-mediated human rabies kills tens of thousands of people every year worldwide. Freedom from dog-mediated human rabies is a global public good and is feasible with currently available tools.

1. SOCIO-CULTURAL
   - Rabies control involves a wide range of stakeholders including the general public. The socio-cultural context influences rabies perceptions and dog-keeping practices at-risk populations. Understanding the context guides approaches to motivate behavioural change and plan feasible delivery of services.
   - Includes activities: Awareness; promote awareness of dog-mediated rabies as a preventable global public health problem including through participation in initiatives such as World Rabies Day.

2. TECHNICAL
   - Effective animal health and public health systems are required to eliminate dog-mediated human rabies. These systems must be strengthened and resources appropriately, and gaps identified and filled.
   - Includes activities: Vaccination; logistics; diagnostics; surveillance; technical support; community engagement.

3. ORGANIZATION
   - The One Health approach of close collaboration is applied. Leadership, partnership, and coordination for rabies elimination activities arise from the human health and animal health sectors and other stakeholders.
   - Includes activities: One Health approach; intersectoral coordination; harmonization; diagnostics; surveillance.

4. POLITICAL
   - Success depends on political will and support for elimination of dog-mediated human rabies. Political will results from recognition of rabies elimination as a national, regional, and global public good.
   - Includes activities: Political support; international support; legal frameworks; coordination.

5. RESOURCES
   - Rabies elimination activities frequently span several years and therefore require sustained, long-term support.
   - Includes activities: Case for investment; support for dog vaccination programmes; logistic support.

STRATEGIC VISION: zero human deaths from dog-mediated rabies by 2030 in participating countries.

Sufficient resources, logistics and infrastructure; sufficient supply of quality-assured rabies vaccines.
WHO Strategic Advisory Group of Experts (SAGE) on Immunization Rabies WG Terms of reference:

First rabies working group under SAGE, established in June 2016.
1. Assess evidence and country practices in the use of human rabies vaccine and RIG

2. Emphasize evidence of implementation of ID use of rabies vaccines

3. Reduced # of doses for PEP & PrEP (day 0 & 7) schedules

4. PrEP recommendations and the cost-effectiveness of the interventions

5. Revisit the WHO position for RIG and monoclonal antibody use to improve access to care/public health impact

6. Consider economic burden of rabies and cost-effectiveness of Vaccination, including modelling

7. Potential of new vaccines to improve delivery
New WHO position on rabies immunization (SAGE):

Safety - programmatic savings - feasibility

Topic: 2010 - 2018 (reduced duration, visits, doses)

**PEP regimen duration**
- 3-4 weeks: 1-2 weeks
- 4-5 visits: 3-4 visits

**Vaccine savings PEP**
- ID: 0.8 ml
  - -20% (0.6 ml)
- IM: 5 ml
  - -20% (4 ml)

**RIG infiltration mode**
- Wound + distant IM
- Wound only
  - -40% RIG vials
  - -80% RIG volume/person

**RIG allocation**
- All category III exposures
- High risk cat. III exposures
  - 60 to 90% need RIG

Source: Rabies vaccines: WHO position paper WER 16, 2018, 93
Integrated Program of Surveillance, Prevention & Management of Rabies

QUESTIONS?
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RABIES IN THE AMERICAS INTERNATIONAL CONFERENCE

RITA XXIX
Buenos Aires, Argentina
October 28-November 2, 2018
http://www.rabiesintheamericas.org/home