Updates in rabies vaccine protocols and diagnostic techniques used globally and nationally

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WHO-OIE-FAO-GARC: ZERO BY 30

• Why?
  – Rabies kills
  – Rabies is preventable
  – Rabies affects the most vulnerable populations in the world
  – Eliminating rabies strengthens health systems
  – Eliminating rabies is a model for One Health collaboration
  – Because the world wants to end neglect and inequality
Why now?

- Because much progress has been made
- Because the mechanisms are in place
- Because for the first time in history we are united to succeed.

Proof of concept programs: it is possible

- 99% of human rabies is transmitted by bites of rabid dogs: dog & human rabies cases are closely linked

Dog vaccination stops rabies transmission from dogs to humans

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A PHASED APPROACH TO ELIMINATION

We propose a pragmatic, three-phase approach to achieve the shared goal of Zero by 30:

**Phase 1: START UP**
- 2018-2020
- 29 countries

**Phase 2: SCALE UP**
- 2021-2025
- +52 countries

**Phase 3: MOP UP**
- 2026-2030
- +19 countries

**Phase 1: START UP**
We will build a strong foundation for rabies elimination by preparing and improving normative tools and structures to catalyse action. Core activities include supporting countries to prepare robust, budgeted, effective and sustainable national rabies elimination plans following a One Health approach; and facilitating the coalescence of these plans into a coordinated regional effort.

**Phase 2: SCALE UP**
We will engage with and involve 52 more countries in rabies elimination, to give a total of 81 out of 100 endemic countries. Using the strong foundation established in Phase 1, refined and improved with learning and experience, we will expand our efforts and truly go global.

**Phase 3: MOP UP**
We will engage the remaining endemic countries in the fight to eliminate rabies, and continue to support country efforts as communities, nations and regions advance to reach Zero by 30. Phase 3 is the last mile.
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
The Burden of Rabies

Endemicity of dog and human rabies, 2016

- + +: Endemic dog and human rabies
- + 0: Endemic dog rabies
- +/-: Sporadic dog-transmitted rabies
- +/0: Controlled dog rabies
- 0 0: No dog rabies nor human rabies
- No information

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Cost of rabies post-exposure prophylaxis and dog vaccination

**Indicative rabies treatment costs per patient in rabies endemic countries**

- Up to 80% savings with intradermal PEP regimens \(^a\)
- RIG is recommended for severe category III exposures \(^b\)

- Up to 99% of bite victims survive with prompt wound washing & vaccine without RIG

**Mass dog vaccination cost per dog**

- Average costs: US$ 4.03 (min: US$ 1.56 – max: US$ 11.33)
- n=10 published studies

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\(^a\) Full vaccine course at a medical centre consisting of four consultations and four vaccine vials administered through intramuscular injection (IM); 41 rabies endemic countries where data are available were used.

\(^b\) Single or multiple transdermal bites or scratches, licks on broken skin, contamination of mucous membrane with saliva from licks and exposure to bats.
“Sustained commitment drives progress”
WHO Strategic Advisory Group of Experts on Immunization – Terms of Reference

1. Assess evidence and country practices in the use of human rabies vaccine and RIG, including that of targeted vaccination of high risk communities in rural settings;

2. Review the new evidence on the need for PrEP booster doses and the cost-effectiveness of the interventions;

3. Assess the most recent evidence on the potential shortening of PEP schedules and new regimens;

4. Review the evidence and revisit the current WHO position for RIG and monoclonal antibody use with the view to improve access to care and increase public health impact;

5. Assess the implementation and evidence of the current recommendation on ID use of cell culture-derived vaccines (CCV);

6. Economic burden of rabies and cost-effectiveness of vaccination as well as modelling data should be assessed to inform rabies vaccination strategies (including vaccination in the context of other control strategies);

7. Consideration should be given to new vaccines in different phases of clinical trials or in the process of obtaining WHO prequalification and/or national market authorization by mid/end 2016.

The new WHO recommendations for rabies immunization supersede the 2010 WHO position on pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) for rabies. These updated recommendations are based on new evidence and directed by public health needs that are cost-, dose- and time-sparing, while assuring safety and clinical effectiveness. In addition, new guidance on prudent use of rabies immunoglobulins (RIG) is provided.

The following sections summarize the main points of the updated WHO position as endorsed by the Strategic Advisory Group of Experts on Immunization (SAGE) at its meeting in October 2017. The full version of the WHO position on rabies vaccines and immunoglobulins will be published in the Weekly Epidemiological Record in April 2018.

Rabies prevention involves two main strategies: (i) dog vaccination to interrupt virus transmission to humans; and (ii) human vaccination as a series of vaccine administrations before or after an exposure. Currently, rabies vaccines made from inactivated cell cultures are extremely well tolerated and have no contraindications.
WHO Vaccine and RIG update: **Post exposure prophylaxis (PEP)** for those not previously vaccinated:

**Vaccination:**

Route-either intradermal (ID) (0.1 mL) or intramuscular (IM) (entire vial)

*WHO option-ID promoted-low dose, dose sparing, cost effective: 2-site on day 0, 3 and 7*

Previous WHO recommended regimens are still valid, regimen chosen should be based on clinical setting and patient preference

**Rabies Immunoglobulin (RIG) administration:**

HRIG and **ERIG** are equivalent

Where RIG is *limited in supply* only given to category III exposures with the following: multiple bites, deep wounds, bites to highly innervated tissues, patient with immunodeficiency, bitten by a dog with rabies signs, exposure to a rabies positive bat.

Amount not given into wound *does not need to be injected at a distant site.*
WHO Vaccine and RIG update: Pre exposure prophylaxis (PrEP)

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

New: recommended for sub-populations in remote rabies endemic settings considering: (i) timely access to rabies biologicals; (ii) access to rabies serological testing; (iii) requirements for booster vaccination; and (iv) presence of rabies in wildlife reservoirs.

PrEP regimens for individuals of all ages are:
--- 2-site ID vaccine administrations on days 0 and 7
--- 1-site IM vaccine administrations on days 0 and 7
WHO Vaccine and RIG update: **Post exposure prophylaxis (PEP)** for those who can document PEP or PrEP previously

Either route, ID or IM acceptable

No changes to regimen (two doses at day 0 and 3, no HRIG or ERIG required).

*Added: if repeat exposure is within 3 months no booster doses required.*
In the United States human rabies vaccination (PEP and PrEP): Advisory Committee on Immunization Practices (ACIP)

• Last update was in 2010, which reduced the 5 vaccination regimen for PEP to 4 vaccinations (no more day 28)
• The ACIP committee will meet soon to update the recommendations.
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)
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

• RIG and 1st vaccine given on day 0, followed by vaccination at days 3, 7, and 14.
• 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>
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<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>
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<tr>
<td></td>
<td>Rabid or suspected rabid</td>
<td>Immediately vaccinate.</td>
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<tr>
<td></td>
<td>Unknown (e.g., escaped)</td>
<td>Consult public health officials.</td>
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<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>
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</tbody>
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Targeting Rabies Management: Dynamics of Virus Transmission and Exposures

Transmission pathways:
- 1-way
- 2-way
- Circulating
Rabies in Skunks - Kansas 1995-2017

Rabies positive skunks  Total skunks  % positive skunks

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Rabies in Kansas

Number of Rabies Positives

2011: 24
2012: 34
2013: 38
2014: 48
2015: 66
2016: 33
2017: 26
2018: 18

- Bovine
- Feline
- Equine
- Bats
- Other
- Skunk
Rabies Diagnostics Update
Rabies Guidelines - Global

Laboratory Techniques in rabies (2018)
Description of recommended rabies diagnostic techniques and vaccine production – Update to be published soon.

WHO Expert consultation on Rabies (2018)
International group of experts provide WHO with the latest scientific and technical advice on rabies

Standards for laboratory diagnostic methods and requirements for the production and control of vaccines
Guidance procedures

- Standard case definition
  - Presence of viral antigens
  - Virus isolation in cell culture or in laboratory animals
  - Presence of virus-specific antibodies in the CSF or the serum of an unvaccinated person
  - Presence of viral nucleic acids detected by molecular methods
Diagnostic Samples

• Collection
  – Described in the WHO and OIE manuals
  – On-line videos

• Newer methods—brain tissue or serum on filter paper

• Shipment
  – Refrigerated preferred
  – Other preservation methods possible depending on method for antigen detection
Virus Detection
Classically applied to brain tissue

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<tr>
<th>Antigen Detection</th>
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<tbody>
<tr>
<td>• FAT (DFA)</td>
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<tr>
<td>• Immunoperoxidase methods (DRIT and IRIT)</td>
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<tr>
<td>• Rapid immunodiagnostic test (RIDT)*</td>
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<table>
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<tr>
<th>Molecular techniques</th>
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<tbody>
<tr>
<td>• RT-PCR</td>
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<td>• PCR-ELISA</td>
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<td>• Real-time PCR</td>
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<tr>
<th>Virus replication</th>
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<tbody>
<tr>
<td>• Cell culture</td>
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<tr>
<td>• Mouse inoculation</td>
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*RIDT: Rapid immunodiagnostic test
Antibody Detection
Classically applied serum

Neutralizing antibodies

- RFFIT
- FAVN
- Modifications

Binding antibodies

- Competitive ELISA kits
- Indirect ELISA kits
- Immunochromatographic test
Tools

- Test results provide data
- Reliability
  - Sample
  - Method
    - Reagents and equipment
    - Technician training and competency
    - Quality Assurance
- Ideal test is sensitive, specific, rapid, affordable, and available
- Validation standards: OIE, WHO, ICH, FDA, etc.
Challenges

• Poor resourcing and training of laboratory staff in all regions
  – Test should be flexible to allow for decentralization
• Guidelines should outline which tests are most appropriate for which purpose
  – ‘Fit for purpose’
  – Differentiation between routine and confirmatory tests
  – Hierarchy of tests based on the evolution of surveillance in the region
Specific issues

- Brain stem sampling is sufficient—removal of whole brain is not necessary, can use straw technique.
- Antibody monitoring—what level is significant
- Need for clear guidelines for ELISA kits in monitoring:
  - canine vaccine coverage,
  - wildlife oral vaccination coverage,
  - human antibody response to vaccination
  - human diagnostic samples
- Use of RIDT for surveillance
- Methods described in the WHO and OIE manuals ideally should be consistent
WHO: Future initiatives

- Updating the WHO Laboratory Manual every 5 years
- Availability of the WHO Laboratory Manual on-line or E-book format with videos and other media
- Development of a ‘biological bank’ concept for laboratory reagents
- Pre-approved list of diagnostic kits as per vaccines
Rabies Diagnostics in the United States

- In 1999, National Working Group on Rabies Prevention and Control determined there was a need for a minimum national standard for the laboratory diagnosis of rabies (Hanlon et al., JAVMA, 215:1444-1446, 1999). In response to this recommendation, a committee was formed from representatives of national and state public health laboratories.
The dRIT demonstrates sensitivity and specificity equivalent to those of the DFA. The test is simple, requires no specialized equipment or infrastructure, and can be successfully performed on samples preserved in glycerol solution for 15 months or frozen for 24 months and in variable conditions of preservation. These qualities make it ideal for testing under field conditions and in developing countries.
Updates

• Recently scientists at CDC have developed molecular test: LN34
  – Currently, it is under evaluation by American Public Health Laboratory (APHL) Workgroup to develop a minimum standard protocol for validation and use.
• Another APHL workgroup is reviewing the minimum standard protocol for the DFA and establishing guidelines for the use of LN34 as an adjunct for the DFA.
• LN34 Advantages:
  – High sensitivity
  – Applicable to deteriorated samples
  – Does not require high quality antibody conjugates, a skilled technician, a fluorescence microscope and diagnostic specimen of sufficient quality
• The publication “Multi-site evaluation of the LN34 pan-lyssavirus real-time RT-PCR assay for post-mortem rabies diagnostics” concluded the assay is robust and reliable, and is expected to play a role in improving rabies diagnostics and surveillance.
RFFIT/FAVN Automation for high throughput at KSU

- KSU currently
  - Automated serum dilution
  - Automated plate washing with robotics for plate handling
  - Automated reading with robotics for plate handling
  - Automated electronic interpretation/reporting

- In planning
  - Automated addition of virus dose and cell culture cells
Contrasting realities: Rabies in Developing versus Developed Countries
Rabies fear through history

"Rabies has symptoms strikingly similar to the traits ascribed to vampires"
SPANISH neurologist, Dr Juan Gomez-Alonso of Xeral Hospital in Vigo, has suggested rabies may have inspired the early vampire legends. His thesis can be found in the Sept 98 edition of the journal Neurology. Watching an old vampire film, he was struck by the "obvious similarities between vampires and what happened in rabies, such as aggressiveness and hypersexuality".

“I came across St Hubert his grave
Without stick or without stave
Evil dog, stand still:
It is St Huber’s will”

“The most common way in which someone contracts the disease rabies is by being bitten by an infected animal (like werewolf stories). Usually, they are bitten by a dog that had contracted the virus from a wild animal. An animal with the virus will suddenly become insane, incredibly aggressive and savage, acting much like a demon.”
Differences in rabies in developed and developing countries

- Incidence of Human Rabies
- Primary reservoirs
- Availability of rabies vaccine and biologics
- Accessibility to rabies diagnostic services
- Ease of travel
- Ability to cover the costs of PEP and PrEP

• AWARENESS
We are victims of our own success

- Rabies awareness is a key component of rabies prevention and control
- As cases go down, awareness goes down