Evaluating Rabies Pre-exposure Prophylaxis Vaccination Schedules:

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Background

Rabies PreEP: prospective studies
Rabies PreEP: retrospective studies
Discussion
Conclusion

Background

Rabies causes fatal encephalitis
- an estimated 59,000 - 70,000 human deaths every year in endemic regions
- estimated risk for an animal bite in travellers:
  calculated 0.4 % per month staying in an endemic country
  3 deaths per year in travellers

Disclosures
No disclosures
Norwegian woman dies from rabies after Philippines puppy bite

Birgitte Kallestad, 24 year old, was on holiday with friends when they found the puppy on a street. She fell ill soon after returning to Norway, and died on Monday at the hospital where she worked.

Family statement of Brigitte the 15th of May at www.promed.org

“Our dear Birgitte loved animals. Our fear is that such fate may happen to others who have a warm heart like her. We want rabies vaccine to be included in the program for travellers to locations where the disease is present, and that people become more aware of the danger. If we manage to achieve this, the death of our sunbeam can save others. Warm greetings from the family.”

Background
Rabies risk during travel: low risk – animal bite: high risk

Start PEP immediately

Increase awareness
Avoid contact with street dogs, monkeys and other mammals

Background
Rabies risk: have a back-up plan

Travel insurance

Backround
Rabies risk: start Rabies PEP procedure in time

Washing - Soap - Desinfection
Respective PEP schedule and HRIG
Background

Adequate Rabies Concept BOOST

Background

Belgian Rabies PEP data 2017 with use of HRIG in BE

N = 75

- 44 of the cases (58%) were female.
- Mean age was 33 years (interquartile range 24 - 51; range: 4 - 85).
- Mean time delay between exposure and the administered HRIG was 8.7 days:
  - 9.6 days (IQR 2.5 - 9) for abroad travel
  - 6 days (IQR 1 - 4) for inland bat-related risks.
- Mean time delay between exposure and the first administered dose of rabies vaccine was 7.7 days:
  - 8.3 days (IQR 0 - 8.5) for abroad travel
  - 6 days (IQR 1 - 4) for inland bat-related risks.

Background

Immunoscence following Rabies PEP: research gaps

Belgian Rabies PEP data 2017 ITM

N = 63 (of 75)

One single patient had no response (RFFIT < 0.5 IU/mL) after a full 5’IM PEP schedule with HRIG

The timing of the vaccinations and the serology test were in accordance

Age = 80 years

Serology testing (RFFIT) is crucial in Rabies PEP when decreasing PrEP and PEP doses

Background

Rabies PEP schedules in Belgium (2019)

RFFIT: rabies rapid fluorescent focus inhibition test is key in rabies prevention procedures

Concept BOOST

Rabies pre- and postexposure prophylaxis (PEP without PrEP)

‘Adequate immune response = lifelong antibodies RFFIT > 0.5 IU/mL’
Rabies PEP 2019

New BE guideline 2019: sparing HRIG
HRIG only in wound - same dosage (20 IU/kg) or less
injent minimal 2 mL

<table>
<thead>
<tr>
<th>ANATOMICAL LOCATION</th>
<th>MINIM. ml</th>
<th>MAXIM. ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finger/toe</td>
<td>2 ml</td>
<td>2 ml</td>
</tr>
<tr>
<td>Hand/foot</td>
<td>2 ml</td>
<td>4 ml</td>
</tr>
<tr>
<td>Knee/ankle/nerve/elbow</td>
<td>2 ml</td>
<td>6 ml</td>
</tr>
<tr>
<td>Forearm/foot/toe</td>
<td>4 ml</td>
<td>10 ml</td>
</tr>
<tr>
<td>Upper arm/upper leg/torso</td>
<td>4 ml</td>
<td>10 ml*</td>
</tr>
<tr>
<td>Face/eye/ear</td>
<td>2 ml</td>
<td>10 ml*</td>
</tr>
<tr>
<td>Mucous membrane</td>
<td>NONE</td>
<td>NONE</td>
</tr>
</tbody>
</table>

Rabies risk: promote pre-exposure vaccination
Revised WHO recommendations for rabies pre-exposure prophylaxis in travellers: avoid bumpy roads, select the highway!

Rabies PrEP

Background

Rabies PreP: prospective studies
Rabies PreP: retrospective studies
Discussion
Conclusion

Rabies PreP

New WHO publication since the 17th of April 2018:
- Technical Report

WHO Expert Consultation on Rabies

Guidelines on PreP and PEP

Rabies pre- and postexposure prophylaxis (PEP without PreP)

'Adequate immune response = lifelong antibodies RFFIT > 0.5 IU/mL'

No PreP schedule
Risk cat III PEP schedule

Rabies: ‘The bumpy road approach’

PrEP + PEP
2ID mL
Intradermal

PreP 2 0.4 mL
PEP 1 0.4 mL
Total visits 3 0.8 mL

Tackling the high rabies human case fatality rate
To use newer practical regimens
- 1 deceased 10 y France
- 1 deceased 58 y UK
- 1 deceased 24 y Norway
Background

- WHO publication of the 17th of Apr 2018:
  - Promote intradermal (ID) schedules
    - ID as effective as IM injection
    - Technical guidance: ID technique is not difficult
    - Use always single-dose injections on two sites during each visit
  - But ID schedules are off-label...

Rabies PrEP

- WHO guidelines: 2-visit regimen for rabies PrEP: 2ID or 2IM

- Background = WHO guidelines > 2-visit regimen for rabies PrEP: 2ID or 2IM

Rabies PrEP

- WHO guidelines: BE guideline from 1st May 2018: two-visit regimens
  
  New Rabies PrEP regimens that are recommended in first line for individuals of all ages are:
  
  - 2-site ID vaccine administration on day 0 and 7
    - 2ID double dose 2x 0.1 ml on day 0 and day 7
  
  - 1-site IM vaccine administration on day 0 and 7
    - 2IM single dose 1x ampoule (1ml) on day 0 and day 7

Rabies PrEP guideline in BE (from 1st of May 2018)

- Preferred rabies PrEP schedule: two-visit schedules
- Use a one visit rabies PrEP schedule in last-minute travelers

- ID0.1 ID (double dose)
- IM1.0 IM

Who is using this PrEP regimens? Off-label

Guideline to use off-label

- 2ID Belgium, The Netherlands, Canada, Japan, ...
- 2IM Belgium, Denmark, The Netherlands, Canada, ...
- 2ID or 2IM Belgium

Guideline to use off-label, optional by practitioner

- 2ID Ireland?, Australia?, New Zealand?
- 2IM Germany

Guidelines on 2IM + booster

- Adapted 3IM: 2IM + 1IM Switzerland

Unchanged guidelines on 3IM + booster

- Adapted 3IM + booster 1IM UK, USA, Germany, France, Italy, Spain, ...
Rabies Antibody Response following Booster Immunization: A Systematic Review and Meta-Analysis

Annelies C. Lengenfelder, MD, CoraMade, A. de Pijper, MD; Rima, Spillane, MD, Rebecca, Holman, PhD, Marita, F. Guesdon, PhD, and Cora Made, MD

22 studies included in meta-analysis

Rabies 2-visit IM: prime and boost

<table>
<thead>
<tr>
<th>N</th>
<th>Age</th>
<th>Rabies PreP IM</th>
<th>PEP IM (day 0-3)</th>
<th>GMT Mean IU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>2009</td>
<td>2M 12-17</td>
<td>1M 2009</td>
<td>100%</td>
</tr>
<tr>
<td>N 274</td>
<td>35% F</td>
<td>1M 2009</td>
<td>1M 2009</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>2-4 m</td>
<td>50% F</td>
<td>1M 2009</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>N 86</td>
<td>1M 2009</td>
<td>1M 2009</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>N 360 subjects 2IM</td>
<td></td>
<td>1M 2009</td>
<td>100%</td>
</tr>
</tbody>
</table>

PrEP rabies 2-visit ID: prime and boost

<table>
<thead>
<tr>
<th>N</th>
<th>Age</th>
<th>Rabies PreP ID</th>
<th>PEP ID (day 0-3)</th>
<th>GMT Mean IU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>2007</td>
<td>3x 0.1 mL</td>
<td>1M 2007</td>
<td>100%</td>
</tr>
<tr>
<td>N 84</td>
<td>5-8 years</td>
<td>4x 0.1 mL</td>
<td>1M 2007</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>F: 46%</td>
<td>4x 0.1 mL</td>
<td>1M 2007</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>N 86</td>
<td>4x 0.1 mL</td>
<td>1M 2007</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>18-24 years</td>
<td>4x 0.1 mL</td>
<td>1M 2007</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>N 36</td>
<td>4x 0.1 mL</td>
<td>1M 2007</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>N 164 subjects 2ID</td>
<td></td>
<td>1M 2007</td>
<td>100%</td>
</tr>
</tbody>
</table>

Other rabies 2-visit ID: prime without boost

<table>
<thead>
<tr>
<th>N</th>
<th>Age</th>
<th>Rabies PreP ID</th>
<th>GMT Mean IU/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>2011</td>
<td>200 mL 18-40</td>
<td></td>
</tr>
<tr>
<td>N 420</td>
<td>years</td>
<td>1:10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N 54</td>
<td>1:10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N 18-40</td>
<td>1:10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N 364</td>
<td>1:10</td>
<td></td>
</tr>
</tbody>
</table>

IM versus single-dose ID regimens

PrEP IM 3x 1.0 mL << ID 3x 0.1 ID d0 - d7 - d28 (single dose)
**IM versus single-dose ID regimens**

- PEP IM (1 mL) versus 1ID (0.1 mL) (single dose!)

**Recommendation of Belgian Superior Health Council**:
Preventive vaccination is recommended for the following people:

- Those who spend long periods in at-risk areas or in remote areas where no medical assistance is available promptly.
- Those who often travel to endemic regions or will do so frequently in the future.
- Travellers who undertake long cycle rides or joggers in endemic regions.
- Children who go and live with their parents in endemic regions.
- Those with an increased risk due to their profession or activities, such as vets, foresters, veterinary students or bat protection volunteers.
- Military personnel who go to endemic regions on missions.
- Laboratory staff or experts who come into contact with the virus for professional reasons (e.g. laboratory activities).

**Rabies PrEP and PEP schedules (Belgium 2019)**

- Standard PEP IM (5 visits) with MARIG
  - PEP IM (3 visits) without MARIG
  - 11IM

**Rabies vaccination schedules in Belgian soldiers**:
*"It started as a small project!"

**Rationale to use simplified intradermal (ID) regimens**

- Shortage of immunoglobulins
  - Advise pre-exposure vaccination in high risk or long-term travelers
- Shortage of vaccine
  - Promote volume-sparing intradermal vaccination
- High cost of primary vaccination
  - Promote low cost intradermal vaccination
- Lack of preparation time
  - Evaluate shorter schedules of intradermal pre-exposure vaccination
Rationale for simplified ID regimens

- Intradermal Rabies PrEP in BE troops
  - ID injection by stimulating dendritic cells in the skin and lymph nodes
  - Reduced dose - volume
    - 1/10th of 1 ml IM dose: 1 x 0.1 ml ID
    - 1/5th of 1 ml IM dose: 2 x 0.1 ml ID
  - Shortening priming schedules
  - More than N = 10,000 subjects are vaccinated

Technical problems with ID use

- Reference centers for ID use for technical reasons???
- ID technique = easy to learn
  - always double-dose ID regimens
  - use syringes for diabetic use
  - prepare 0.10 – 0.13 mL for each injection site
  - inject always in both (fore)arms
  - check the size of the papule (> 6 mm is fine, if not sure – revaccinate)
  - add a stamp in the vaccination card (necessary due the different regimens used worldwide)

Prospective RCTs on ID Rabies PrEP and PEP schedules in BE Armed Forces

- ImiQ: application of topical Imiquimod at time of injection during 6 hours
- Intramuscular injection and rabies immunoglobulines
Prospective RCTs on ID Rabies PrEP and PEP schedules in BE Armed Forces

RCT3: 1²ID: Evaluating the VAX-ID™ device

Rabies
Background
Rabies PrEP
Rabies PrEP: prospective studies
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Retrospective studies on ID Rabies PrEP (and PEP) schedules in Belgian Armed Forces
Discussion: schedule needs to be 100% effective

Use a regimen that is 100% preventable

Among all the infectious diseases, rabies is the easiest to prevent.

Discussion

To use a regimen that is 100% preventable

Discussion: future studies
Future studies on 1ID - 2ID - 1IM - 2IM

- Subject
  - Older age (> 50 years)
  - Vulnerable population like immunosuppressed
  - Children
- Booster studies after primary vaccination with some larger time delay
- Immunological studies: B-cell and T-cell function
- Use of enhancers, like adjuvants
- Use of devices or patches

Discussion: long-lasting immunity

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>15</td>
<td>118</td>
<td>89</td>
<td>26</td>
</tr>
<tr>
<td>IM or ID</td>
<td>IM/ID</td>
<td>IM/ID</td>
<td>IM/ID</td>
<td>IM/ID</td>
</tr>
<tr>
<td>RFFIT</td>
<td>22%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>RFFIT &gt; 0.5 IU/ml</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>After booster</td>
<td>1 x 1 mL IM</td>
<td>0.1 mL ID</td>
<td>0.1 mL ID</td>
<td>1 booster IM (60%)</td>
</tr>
<tr>
<td>Time interval</td>
<td>15 years</td>
<td>21 years</td>
<td>10 years</td>
<td>32 years</td>
</tr>
</tbody>
</table>

Discussion: increase in use

13 BE clinics: 2-visit ID and IM regimen (mostly 2IM)

2 BE centers: 2-visit ID rabies regimen

Discussion: costs
### Limited vaccine volume

Vaccine stock of every travel clinic = limited
(related to pharmaceutical production = limited worldwide)

<table>
<thead>
<tr>
<th>Travel clinic stock</th>
<th>Subjects reached by IM</th>
<th>Subjects reached by ID</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=1000 vaccines 1 ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-visit</td>
<td>333</td>
<td>&gt;3000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Single-dose visit</td>
</tr>
<tr>
<td>2-visit</td>
<td>500</td>
<td>&gt;2000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Double-dose visit</td>
</tr>
<tr>
<td>1-visit</td>
<td>1000</td>
<td>(or 3000)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Double-dose visit</td>
</tr>
</tbody>
</table>

### Discussion

**What are the barriers?**
- **ID:** off-label - difficult technique - painful - research on single-visit regimens
- **Vaccine:** more stock - cost - more potent (single-visit) - no cold chain - more production - small incubator
- **Devices:** needle-free – others
- **Surveillance**

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**Off-label intradermal schedules for Rabies**

- Used since 1960
- Recommended by WHO since 1984
- Packaging containing 1/10 (0.1 ml), approved by the US FDA in 1984 but withdrawn
- Still recommended by WHO in 2013
- Not recommended anymore by the UK and the US authorities
- Since 2018 recommended by WHO only as double-dose during each visit
Conclusion

- Have a plan for rabies: rabies low-risk – rabies PEP procedures high risk
- Off-label use is a regulatory barrier in some countries.

- The studies on two-visit rabies PrEP regimens = highway
  - Double-dose single-visit 1²ID and double-dose two-visit 2²ID are schedules, that are easy in use, safe, and at low cost.
  - Single-visit 1²ID PrEP schedule provides an adequate immune response 7 days after booster doses.

- Investment once in a lifetime!

Many thanks

Collaborators

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