Introduction

- Background
- Rabies Disease
- PrEP in travelers
- BE Guidelines on rabies PrEP and PEP
- Shifting from ‘Protection towards Boostability’
- Intradermal Schedules
- Abbreviated Schedules
- Long lasting immunity
- Conclusion

Background

- Rabies causes fatal encephalitis
  - a threat to over 3 billion of people
  - an estimated 55,000 human deaths every year
  - review of 60 cases in international travelers between 1990-2012
  - estimated risk for an animal bite in travelers: calculated 0.4 % (0.01 - 2.3) per month
Background

Questionnaire (n = 7681)

- Estimated risk - for an animal bite in travelers: 1.11% per month
- of being licked: 3.12% per month

Risk of Potentially Rabid Animal Exposure among Foreign Travelers in Southeast Asia

Steffen September 2012

WHO 2012 - http://www.who.int/ith

Background

Distribution of risk levels for humans contracting rabies, worldwide, 2009
Background

- Rabies in travelers: 60 cases

Rabies disease

- Virus
- Rhabdoviridae
- Genus: Lyssavirus
Rabies disease

- Pathogenesis

1. Virus inoculated (bite)
2. Viral replication in muscle
3. Virus binds to nicotinic acetylcholine receptors at neuromuscular junction
4. Virus travels within axons in peripheral nerves via retrograde fast axonal transport (80-400 mm/d)
5. Replication in motor neurons in spinal cord and local dorsal root ganglia and rapid ascent to brain
6. Infection of brain neurons with neuronal dysfunction
7. Centrifugal spread along nerves to salivary glands, skin, other organs

Rabies: Clinical manifestations

Highest case fatality rate of any infectious disease
- Incubation period (5 days > 2 years)
- 3 Phases of disease:
  - Prodromal features
  - Acute neurologic phase
    A. Encephalitic rabies (66%)
    B. Paralytic rabies (33%)
  - Coma/Death

Incubation period

- Rabies in travelers:
  60 cases
Rabies: Prodromal Features

**Nonspecific**
- Fever
- Headache
- Malaise - Nausea - Vomiting
- Anxiety or agitation

**More specific**
- **Paresthesias** (tingling and numbness), pain or pruritis near the site of exposure (50-80%)
- Bite wound has usually healed by this point.

Rabies: Encephalitic or Furious Rabies

**Symptoms common to many other viral encephalitides**
- Fever, confusion, hallucinations, combativeness, muscle spasms, hyperactivity and seizures

**Autonomic dysfunction is common**
- Hypersalivation, excessive perspiration, gooseflesh, pupillary dilatation, priapism
- Periods of hyperexcitability are typically followed by periods of complete lucidity

Rabies: Encephalitic or Furious Rabies

**Early brainstem involvement (hallmark)**

Classic symptoms
- **Hydrophobia**
- **Aerophobia**
  - Involuntary painful contraction of the diaphragm and accessory respiratory, laryngeal and pharyngeal muscles in response to swallowing fluids or a draft of air
  - Probably exaggerated defense reflexes that protect the airway
Combination of hypersalivation and hydrophobia

Brainstem dysfunction progresses rapidly
• Coma followed within days by death if unsupported
• With prolonged life support complications may include:
  • Disturbance of water balance (SIADH or DI)
  • Non cardiogenic pulmonary oedema
  • Cardiac arrhythmias (myocarditis - neural dysfunction)

Muscle weakness predominates and classic symptoms of rabies are absent
• Early and prominent muscle weakness
• Often starts in bitten extremity
• Spreads to produce quadriplegia and facial weakness
• Sphincter involvement common
• Sensory involvement is mild
• Often misdiagnosed as Guillain-Barré syndrome
• May survive longer but dies from multiple organ failure

Rabies is NOT likely in patients
• Without a fever
• With an illness lasting more than 14 days (other than Guillain-Barré-like syndrome)
• With an incubation period following an animal bite of < 10 days or > 1 year
• Who completed a full course of rabies postexposure prophylaxis including immunoglobulins
Rabies: Neurologic Diagnosis

**Non specific in early phases**
- **FBC** – usually normal
- **CSF** – mild lymphocytosis and raised protein
- **CT brain** – usually normal
- **MRI brain** – variable and non specific signal abnormalities in brainstem
- **EEG** – non specific encephalopathy

Most important tests
- To identify another treatable cause

Rabies: Laboratory tests

**Non specific in early phases**
- **FBC** – usually normal
- **CSF** – mild lymphocytosis and raised protein
- **CT brain** – usually normal
- **MRI brain** – variable and non specific signal abnormalities in brainstem
- **EEG** – non specific encephalopathy
- **Most important tests**
- **To identify another treatable cause**

Rabies: Differential diagnosis

- Other viral encephalitides: HSV, enteroviruses, arthropod borne viruses
- Post viral encephalitis: measles, mumps, influenza, varicella-zoster
- Drug reactions
- Vasculitis
- Psychiatric conditions – rabies hysteria
Rabies: Diagnosis

• High clinical suspicion even in the absence of an animal bite history or hydrophobia
• Once suspected, essential to confirm diagnosis with rabies specific tests
  • Saliva - PCR
  • CSF – PCR, Antibodies
  • Brain – DFA, PCR, Histology
  • Skin – DFA, PCR
  • Serum (in very late disease) - Antibodies
Rabies: Post mortem testing

- Fluorescent antibody test
  - Gold standard
- Microscopy
  - Bullet sign (EM)
  - Negri bodies

Rabies: Use of skin biopsies

- Relies on demonstration of virus in the cutaneous nerves at the base of hair follicles, samples from the neck should include at least 10 hair follicles.
Rabies: diagnosis

- Rabies in travelers: 60 cases

<table>
<thead>
<tr>
<th>Case</th>
<th>History</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>C10 Ohio, USA</td>
<td>Child bitten on thumb by feral brown bat, received vaccine the next day but developed encephalitis with coma 21 days later</td>
<td>Recovery after 6 months</td>
</tr>
<tr>
<td>C72 Argentina</td>
<td>Middle-aged woman bitten by dog, received vaccine 10 days later but developed encephalitis 21 days later</td>
<td>Slow resolution over 1 year, optimis, incontinence</td>
</tr>
<tr>
<td>C77 New York</td>
<td>Young male laboratory worker, infected aerosol. Had pre-exposure vaccine but developed encephalitis 21 days later</td>
<td>Gradual improvement but personality disorder and dementia</td>
</tr>
<tr>
<td>C72 Mexico</td>
<td>Child bitten by dog, received vaccine next day but developed encephalitis 19 days later</td>
<td>Died 34 months later</td>
</tr>
<tr>
<td>C80 India</td>
<td>Child with fever and headache bitten by dog not vaccinated but only vaccine given 19 days later, developed encephalitis 16 days later</td>
<td>3 months of coma, slow speech, tremors and extrapyramidal movements</td>
</tr>
</tbody>
</table>

Warrell and Warrell, 2004 Lancet 363: 999-999

Rabies: Prognosis

Almost uniformly fatal disease
but…. almost always preventable with appropriate post exposure treatment (PET/PEP) during the Incubation Period

- 7 well documented cases of survival after symptomatic rabies infection
- 5 received rabies vaccine before disease onset
- Failure of PEP

Rabies: Human recovery and Survival
Rabies: Management

- Animal assessment
- Exposure Risk category
- Wound care
- Anti rabies treatment

Rabies: Management

- Animal assessment
  The following aspects must be considered:
  1. Vaccination status
  2. Behavioural changes
  3. Possible exposure
  4. Rabies endemicity
  5. Provocation
  6. Stray (unsupervised animals)

Rabies: Management

- Exposure Risk

<table>
<thead>
<tr>
<th>Category of rabies exposure</th>
<th>Risk category</th>
<th>Type of exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>Touching/feeding animal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Licking of intact</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Nibbling of uncovered skin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Superficial scratch without bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Licking of broken skin</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Bites/scratches which penetrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Licking of mucous membranes</td>
</tr>
</tbody>
</table>
Rabies: Initial Wound Care

- Copiously flush for 5 to 10 minutes with water and soap
- Bleeding should be encouraged
- Wound suturing should preferably be avoided or delayed.
- Applying an iodine-based disinfectant or 70% alcohol to the wound
- Antibiotic prophylaxis: amoxicillin-clavulanate
- Tetanus toxoid booster 0.5 ml intramuscular

Rabies: PEP or PET

Category 1 exposure:
Touching or feeding animal or licks of intact skin
> Vaccine not indicated.

Category 2 exposure:
- Nibbling of uncovered skin
- Superficial scratch but no bleeding
- Licks of broken skin
> Wound cleaning plus a course of vaccine.

Category 3 exposure:
- Bites
- Scratches that penetrate skin and draw blood
- Licks of mucous membranes

> Wound cleaning, a course of vaccine plus rabies immunoglobulin.
**Rabies: PEP or PET**

**Vaccine:**
- Zagreb Regimen: a course of 4 doses: days 0 (2x), 7 and 21 IM.
- Essen Regimen: 5 doses: days 0, 3, 7, 14, 28 IM.
- Thai Red Cross Regimen: one week ID

Give as soon as possible after injury, but do not withhold if presentation to health facility is delayed.

**Rabies: PEP or PET**

**Passive immunisation with hyperimmune rabies immunoglobulin (HRIG):**
- Administer as much as possible into the wound (50%), and the remainder intramuscularly into the deltoid (never into M. gluteus).
- Dose: 20 IU/kg (average of 6 ampoules for an adult)
- Give as soon as possible post-exposure but can be given up to 7 days after the first vaccine.

**Rabies: Experimental treatments?**

MILWAUKEE PROTOCOL??
- Intense anti-excitatory strategy:
  - Prolonged general anesthesia
  - Antiviral drugs
  - Supportive intensive care
  - No immune prophylaxis until the native immune response matured

FUTURE: monoclonal antibodies?!
Rabies: PEP or PET in South Africa

Treatment of animal bite patients who developed rabies, South Africa 2007

- No treatment
- Only intra-tissue and wound treatment
- Only one dose of vaccine received
- No vaccine available
- Unknown

Rabies: PET or PEP

- Rabies in travelers: 60 cases

Imported Human Rabies Cases Worldwide, 1990–2012

Rabies PEP in travelers

Rabies Immunization of Travelers in a Canine Rabies Endemic Area

Table 1. Human rabies cases and rabies prophylaxis management of travelers

Table 2. Human rabies cases and rabies prophylaxis management of travelers

Table 3. Human rabies cases and rabies prophylaxis management of travelers

Table 4. Human rabies cases and rabies prophylaxis management of travelers
Rabies PEP in travelers
Rabies Immunization of Travelers in a Canine Rabies Endemic Area
Nida Sihunrungr, MD,* Saowaluck Tepsoomphon, RNC, Nonthavi Raksakh, PN,* and Teragong Tanawat, MD* Queen Saovabha Memorial Institute (WHO Collaborating Centre for Research on Rabies Pathogenesis and Prevention), The Red Cross Society, Bangkok, Thailand; Division of Infectious Diseases, Department of Medicine, Faculty of Medicine, Mahidol University, Bangkok, Thailand

100 % recievied immunoglobulines

PrEP in travelers

Indicators:

- The incidence of rabies
- The availability, quality and cost of rabies vaccine and rabies immune globulin (RIG)
- The planned activities of the traveler
- The duration of stay
- The possibility of unrecognized or unreported exposures

Risk factors for potentially rabid animal bite
Meta-analysis among 1.270.000 travelers

- Travel to South-East Asia, India and Africa
- Young age (<15 years)
- Traveling for tourism
- Duration of stay and planned activities

Gautret Vaccine 2012; Curr Opin Infect Dis 2012
PrEP in travelers
Risk factors for rabies
Imported cases, worldwide, 1990-2012
- Travel to India and Philippines
- Male
- Adult
- Migrant and VFR

PrEP
Vaccination decision:

LOW 60 CASES 1990-2012

Risk for FATAL RABIES

Vaccine Price
Expensive
200 USD per dose

Vaccine Side Effects
MILD

Vaccine Efficacy
VERY GOOD

PrEP
Vaccination decision:

LOW 60 CASES 1990-2012

Risk for FATAL RABIES

Vaccine Price
Expensive
200 USD per dose

Vaccine Side Effects
MILD

Vaccine Efficacy
VERY GOOD
Belgian Guidelines: PrEP

• Pre-exposure rabies vaccination
  Schedule
  Day 0 – 7 – (21) 28 intramuscular
  D 365 not recommended anymore
  Serology not recommended
  From 31-05-2013 on:
  no booster after 1 year or later is advised
  anymore for at least 20-30 years
  after the basic series of 3 shots (1-7-21/28)
  in persons with normal immunity

Belgian Guidelines: PrEP

• Pre-exposure rabies vaccination:
  Who needs to be vaccinated?
  Indications:

  Travelers: high incidence - remote rural areas –
  lack of biologicals in the area - long-term travel -
  frequent travel - children - activities: like jogging,
  hunting, cycling

  Professional: veterinary personnel - laboratory
  personnel - cattle dealers - speleologists

Belgian Guidelines: PrEP

• Pre-exposure rabies vaccination:
  Antibody Response

  Travelers: RFFIT > 0,5 IU/ml

  Professional:
  Veterinary personnel: RFFIT > 5.0 IU/ml
  Bat exposure: RFFIT > 5.0 IU/ml

Belgian Guidelines: PEP

- Post-exposure rabies vaccination
  - If PrEP > PEP = Vaccine d0 and d3
  - No PrEP
  > PEP = Vaccine (in 24 hours) (d0 (2x), d7 and d21) and HRIG (in 48 hours) (in lesion and M.deltoides)

Although you are usually advised to start vaccination within 24 hours after the bite, you can still start vaccination later (vaccination and immunoglobulins) because the incubation period is usually quite long. After consultation with the doctor of the Agency of Communicable and Transmissible Diseases, RUAP - National Centre for the Medical Treatment of Rabies (formerly Pasteur Institute), Engelandlaan 64, 1100 Brussels 02.513.37.56 or 02.513.37.57, please telephone number: 02.214.39.11 - http://www.cot-ap.be/clinical/doctors/index.html

Belgian Guidelines: PEP

- Post-exposure rabies vaccination
  Rabies PEP centres over the world
  - Survey ISTM
  - Survey CDC

Survey ISTM
Survey CDC

The Global Availability of Rabies Immune Globulin and Rabies Vaccine in Clinics Providing Direct Care to Travelers 1
Emily S. Stoeter, MD, Jessica R. Hansen, MPH, Katherine J. Johnson, MPH, Peter D. Holmes, MD, Jane L. Santos, RN, Nancy J. Rappleye, PhD, Richard Foye, MD, Deborah Hogan, PhD, Brian Gross, MD, Helen Q. Quan, MB, BCh, George L. Rappleye, MD, Nina Hansen, MPH, and Dana E. Foye, MD 2

PrEP: cost in Belgium

- Pre-exposure rabies vaccination
  Schedule
  Day 0 – 7 – (21) 28 intramuscular (or intradermal)

<table>
<thead>
<tr>
<th>Rabipur® HDCV Mérieux®</th>
<th>Pharmacy</th>
<th>Travel clinic</th>
<th>Officina</th>
<th>Public price</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Price (each)</td>
<td>28.66 euro</td>
<td>31.08 euro</td>
<td>36.07 euro</td>
<td>10.24 euro</td>
<td></td>
</tr>
<tr>
<td>Price (for three vaccines IM)</td>
<td>86</td>
<td><strong>117</strong></td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Price (for three intradermal vaccines 0.1ml) - cohorted</td>
<td>9</td>
<td>12</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Belgian Guidelines**

Vaccination decision

- **Risk for FATAL RABIES**
  - LOW: 60 cases 1990-2012

- **Vaccine Price**
  - Not expensive: 10-30 euro per dose

- **Vaccine Side Effects**
  - MILD

- **Vaccine Efficacy**
  - VERY GOOD

---

**Belgian Guidelines**

Risk factors and PrEP cost

Many BE travelers would benefit from preventive vaccinations against rabies once in their lifetime.

Boostability: ‘able to react very fast and with a high response of antibodies RFFIT, after booster vaccination in a person were initially the immune memory for rabies was primed by PrEP.’

**PrEP in BE travelers**

- **Risk for FATAL RABIES**
  - HIGH RISK: Rabid Animal Bite 0.4% per month stay

- **Vaccine Price**
  - Cheap: 3 euro per dose

- **Vaccine Side Effects**
  - MORE LOCAL

- **Vaccine Efficacy**
  - VERY GOOD

- **LOW 60 CASES 1990-2012**

- **VERY LOW 3 euro**
Shifting towards ...

• ‘From Good Protection towards Boostability’

<table>
<thead>
<tr>
<th>Antibody response (RFFIT)</th>
<th>Surrogate marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.5 IU/ml</td>
<td>Not boostable</td>
</tr>
<tr>
<td>≥ 0.5</td>
<td>Boostable</td>
</tr>
<tr>
<td>≥ 0.5 - &lt; 3.0 IU/ml</td>
<td>Good response expected after booster</td>
</tr>
<tr>
<td>≥ 3.0 - &lt; 10.0 IU/ml</td>
<td>'Good Protection'</td>
</tr>
<tr>
<td>≥ 10.0 IU/ml</td>
<td>Long-term protection</td>
</tr>
</tbody>
</table>

Shifting towards...

• Problems to control the virus in dog populations
  - logistical shortage = crucial barrier to tackle this NTD worldwide
• Worldwide shortage of Immunoglobulins
  - Advise pre-exposure vaccination in high risk travelers
• Worldwide shortage of Vaccine
  - Promote low-cost volume-sparing intradermal vaccination
• Lack of Preparation Time
  - Evaluate shorter schedules of intradermal pre-exposure vaccination

Intradermal Schedules for Rabies
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

Intradermal Schedules for Rabies

- Routine in general in Asia
- In Travel Medicine
  - Many studies:
    - Canada
    - Australia
    - New Zealand
  - Routine
    - The Netherlands

Limitations of the ID route

- A new syringe and needle must be used for each patient
- Opened vial needs to be kept in the fridge at 8°C
- Local adverse events occur more frequently
- Technically more demanding
- Malaria prophylaxis with chloroquine inhibits the antibody response
Intradermal Schedules for Rabies

- ID route is safe
- ID route is economical
- Pharmaceutical industries should make available ampoules of 0.1 ml for direct intradermal injection with special intradermal needles
- Serology testing is recommended
  - for immunosuppression (WHO)
  - in all cases (Canada, Australia)

Who used ID already in travelers?

<table>
<thead>
<tr>
<th>Table 3. Intradermal vaccine maintenance studies conducted in the trend of ID settings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Neutralising Antibody Response on Day 372 after the Classical Intradermal Pre-exposure Rabies Vaccination</td>
</tr>
</tbody>
</table>

Retrospective study: 2008-2013: Initial Neutralising Antibody Response on Day 372 after the Classical Intradermal Pre-exposure Rabies Vaccination

P. Geeraerts, A. Collée, P. Soentjens

To be published
Retrospective study on intradermal schedules in BE Armed Forces

• Rabies pre-exposure schedule
  HDCV Mérieux® and Rabipur®

Inclusion criteria:
- Intradermal rabies schedule
- From 01/04/2008 till 31/06/2013
- D 0-7-28-365 + serology D 372
- Serology done before 31/6/2013

Methods:

• Study Procedure

Randomized Clinical trial

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>HDCV or Rabipur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>0.1 ml ID</td>
</tr>
<tr>
<td>Primary Schedule</td>
<td></td>
</tr>
<tr>
<td>D0</td>
<td>1 x 0.1 ml</td>
</tr>
<tr>
<td>D7</td>
<td>1 x 0.1 ml</td>
</tr>
<tr>
<td>D28</td>
<td>1 x 0.1 ml</td>
</tr>
<tr>
<td>Booster</td>
<td>D365 1 x 0.1 ml ID</td>
</tr>
<tr>
<td>Total dose</td>
<td>0.4 ml ID</td>
</tr>
<tr>
<td>RFFIT after booster</td>
<td>D+7</td>
</tr>
</tbody>
</table>

HDCV: human diploid cell vaccine; ID: intradermal; D: day; RFFIT: Rapid Fluorescent Focus Inhibition Test

Intradermal schedules (d0,7,28,365)

N = 881 serologies
### Results ID (d0, 7, 28, 365)

<table>
<thead>
<tr>
<th>RFFIT</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.5-2.9</td>
<td>30</td>
<td>3.4</td>
</tr>
<tr>
<td>3-10</td>
<td>117</td>
<td>13.3</td>
</tr>
<tr>
<td>&gt;10</td>
<td>734</td>
<td>83.3</td>
</tr>
<tr>
<td>Total</td>
<td>881</td>
<td>100</td>
</tr>
</tbody>
</table>

Cohort of BE soldiers after 4 injections (d0, d7, d28, d365)

- Boostable (*> 0.5 IU/ml*) = 100%
- Good protection (*> 3.0 IU/ml*) = 96.6%

### Results ID (d0, 7, 28, 365)

<table>
<thead>
<tr>
<th>Schedule</th>
<th>RFFIT &lt; 3 IU/mL</th>
<th>RFFIT &gt;= 3 IU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>n %</td>
<td>n %</td>
<td></td>
</tr>
<tr>
<td>Schedule normal</td>
<td>16 2.5</td>
<td>616 97.5</td>
</tr>
<tr>
<td>Schedule fast  (d0, 7, 21)</td>
<td>12 5.7</td>
<td>200 94.3</td>
</tr>
<tr>
<td>Schedule not correct</td>
<td>2 5.4</td>
<td>35 94.6</td>
</tr>
<tr>
<td>Total</td>
<td>30 3.4</td>
<td>851 96.6</td>
</tr>
</tbody>
</table>

Cohort of BE soldiers after 4 injections (d0, d7, d365)

Good protection 96.6% (97.5 versus 94.3)

### Intradermal Schedules: CDC

**Prospective study:**

Neutralising Antibody Response on Day 35 and Day 375 after Two Different Schedules of Intradermal Pre-exposure Rabies Vaccination:

**IM versus ID**

PI: Dr Sergio Ruenco, CDC Atlanta

To be published
CDC protocol

• Study Procedure

<table>
<thead>
<tr>
<th>Randomized Clinical Trial</th>
<th>Intramuscular Schedule</th>
<th>Intradermal Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>Vaccine</td>
<td>PCEC</td>
<td>PCEC</td>
</tr>
<tr>
<td>Dose</td>
<td>1 ml IM</td>
<td>1 ml ID</td>
</tr>
<tr>
<td>Primary Schedule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>D0 1x 1 ml</td>
<td>D0 1x 0,1 ml</td>
</tr>
<tr>
<td></td>
<td>D7 1x 1 ml</td>
<td>D7 1x 0,1 ml</td>
</tr>
<tr>
<td></td>
<td>D28 1x 1 ml</td>
<td>D28 1x 0,1 ml</td>
</tr>
<tr>
<td>RFFIT Booster</td>
<td>D35</td>
<td>D35</td>
</tr>
<tr>
<td></td>
<td>D365</td>
<td>D365</td>
</tr>
<tr>
<td>Booster</td>
<td>1 x 1 ml IM</td>
<td>1 x 0,1 ml ID</td>
</tr>
<tr>
<td>Total dose</td>
<td>4 ml IM</td>
<td>0,4 ml ID</td>
</tr>
<tr>
<td>RFFIT after booster</td>
<td>D+14</td>
<td>D+14</td>
</tr>
</tbody>
</table>

IM intramuscular; ID Intradermal; D day; RFFIT: Rapid Fluorescent Focus Inhibition Test

Abbreviated Intradermal Schedules

Knowledge, Attitudes, and Practices of French Travelers from Marseille Regarding Rabies Risk and Prevention

Marie-Jeanne Alouane, PharmD, MPH, Philippe Parodi, MD, PhD, Jean Delorme, MD, Philippe Bouquain, MD, PhD, and Philippe Gautier, MD, PhD

Serve As Maladies Infectieuses Tropicales, Hôpital Necker, Marseille, Journal of Travel Medicine 2011; Volume 18 (Issue 5): 327–332

• 57% of individuals, traveling to rabies-endemic countries, presented to the clinic less than 21 days before departure

Abbreviated Intradermal Schedules

The Immunogenicity of a Modified Intradermal Pre-exposure Rabies Vaccination Schedule—A Case Series of 420 Travelers

Deborah J. Mills, MBBS,* Colleen I. Lau, MBBS, MPH&A Tim,† Emily J. Fernley, PhD,‡ and Philip Weinstein, MBBS, PhD§

†Jewish Hospital of St. Louis.
‡Postgraduate Institute of Medical Education and Research.
§New York University School of Medicine.

Table: A total of 420 travelers aged between 10 and 85 years were vaccinated using the modified ID course. The overall
vaccination rate was 94.5%, with 937 travelers developing antibody levels of ≥0.5 IU/mL when tested at approximately 21 days
after vaccination.
• Low initial response: still boostable
• With ID boosters: higher RFFIT response
• 4 ID booster probably better than 2 IM booster vaccination
• Recommended schedules:
  - PrEP: one day: 2 ID
  - PEP ID: 1 week: 4-4-4

• Advantages
  - Fewer clinical visits
  - Lower doses = lower cost
  - Volume-sparing

Abbreviated Intradermal Schedules

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Low-Cost Intradermal Rabies Vaccination Is Indeed Very Promising

To our Enron—We read with great interest the recent article by Weten et al in Clinical Infectious Diseases [1] and, being involved in ongoing research strictly related to this topic, we wish to bring our contribution to their reflections.

First, we fully agree that a lower-dose, abbreviated intradermal pre- and postexposure vaccination schedule may constitute a valid, shorter, and cheaper alternative to the current intramuscular schedules. Non-commercial study registered at clinicaltrial.gov NCT 013889885 and at EUDRACT 2011-001612-62, sponsored by the ITM in Antwerp; ethical approval.

• Non-commercial study registered at clinicaltrial.gov NCT 013889885 and at EUDRACT 2011-001612-62, sponsored by the ITM in Antwerp; ethical approval.

• Non-inferiority study between two different vaccination schedules (classical 28 day versus accelerated 7 day) Non-inferiority defined as a difference in proportion of no more than 10% of subjects with protective rabies serology (≥ 0.5 IU/mL).
Objective:

- Primary objective of RCT: 'boostability' after booster vaccination

To investigate the serological response (RFFIT), the Rapid Fluorescent Focus Inhibition Test, after booster vaccination (between day 365 and 1097):

- a serology value of more than 0.5 IU/ml on day 7 after booster vaccination is considered to be protective

Objective:

- Secondary objective of RCT:

To investigate the serological response, by RFFIT, after primary vaccination on day 35, between 2 different intradermal rabies vaccination schedules

A titer ≥ 0.5 IU/ml on day 35 (after primary vaccination) is considered to be protective

Methods:

- Study population:
  Belgian soldiers in need for rabies Pre-exposure Vaccination:
  - pre-deployment (Africa or Afghanistan)
  - age between 18 and 47 years

- Exclusion criteria:
  - previous rabies vaccination (anamnesis / medical file / positive RFFIT day 0)
  - chloroquine or mefloquine intake
  - deployment within 35 days

- Written informed consent
- Enrollment: started in October 2011 stopped in January 2013
Methods:

• Study Procedure

<table>
<thead>
<tr>
<th>Randomized Clinical trial</th>
<th>Classic Schedule Group I</th>
<th>Accelerated Schedule Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>240</td>
<td>240</td>
</tr>
<tr>
<td>Vaccine</td>
<td>HDCV</td>
<td>HDCV</td>
</tr>
<tr>
<td>Dose</td>
<td>0.1 ml ID</td>
<td>0.1 ml ID</td>
</tr>
<tr>
<td>Primary Schedule</td>
<td>D0 1x 0.1 ml</td>
<td>D0 2x 0.1 ml</td>
</tr>
<tr>
<td></td>
<td>D7 1x 0.1 ml</td>
<td>D7 2x 0.1 ml</td>
</tr>
<tr>
<td>RFFIT</td>
<td>D35</td>
<td>D35</td>
</tr>
<tr>
<td>Booster</td>
<td>D365 - D1097 1x 0.1 ml ID</td>
<td>D365 - D1097 1x 0.1 ml ID</td>
</tr>
<tr>
<td>Total dose</td>
<td>0.4 ml ID</td>
<td>0.5 ml ID</td>
</tr>
<tr>
<td>RFFIT after booster</td>
<td>D+7</td>
<td>D+7</td>
</tr>
</tbody>
</table>

HDCV: human diploid cell vaccine; ID: intradermal; D: day; RFFIT: Rapid Fluorescent Focus Inhibition Test

Methods:

• Statistics

The primary hypothesis will be assessed by calculating the two-sided 95% confidence interval (CI) for the difference in proportions of subjects in each group boostable at 1 to 3 year (“boostability rate”)

• Sample size calculation (N = 480)
  - High boostability rates of 90%
  - 90% power
  - Low drop-out/lost to follow-up rate of maximum 10%
  > a total of 240 subjects in each vaccination group

Results: Demographics: pooled data

• In total 499 subjects included end January 2013
• Approximately ± 50% informed subjects not willing to participate

<table>
<thead>
<tr>
<th>Demographics</th>
<th>N = 499</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age distribution</td>
<td>Median: 28 years</td>
</tr>
<tr>
<td>Age categories</td>
<td>&lt; 20 years: 28 (6%)</td>
</tr>
<tr>
<td>Gender</td>
<td>Male: 479 (96%)</td>
</tr>
<tr>
<td></td>
<td>Female: 20 (4%)</td>
</tr>
</tbody>
</table>
Results: Antibody Response on day 35

Antibody response (RFFIT) day 35

<table>
<thead>
<tr>
<th>Antibody response (IU/ml)</th>
<th>N = 464</th>
<th>(93%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 0.5 IU/ml</td>
<td>0</td>
<td>(0%)</td>
</tr>
<tr>
<td>= &gt; 0.5 - &lt; 3.0 IU/ml</td>
<td>7</td>
<td>(1.5%)</td>
</tr>
<tr>
<td>= &gt; 3.0 - &lt; = 10.0 IU/ml</td>
<td>100</td>
<td>(21.6%)</td>
</tr>
<tr>
<td>&gt; 10.0 IU/ml</td>
<td>357</td>
<td>(76.9%)</td>
</tr>
</tbody>
</table>

RFFIT: rapid fluorescent focus inhibition test

Results: Antibody Response on day 35

Pre (Day 0) Post (Day 35)

Serology (IU/mL), logarithmic scale

Results: Side effects

<table>
<thead>
<tr>
<th>Drug-related Adverse effects</th>
<th>N = 499</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site related</td>
<td>204</td>
<td>(41%)</td>
</tr>
<tr>
<td>General</td>
<td>9</td>
<td>(1%)</td>
</tr>
<tr>
<td>Reversible diplopia</td>
<td>1</td>
<td>(0.2%)</td>
</tr>
<tr>
<td>'Drug relation possible'</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusion: pooled data day 35:

- 464 (100%) of subjects had a sufficient initial antibody response on day 35
- 76.9% of subjects had a long-term initial response (> 10 IU/ml)

Abbreviated Schedules:

Prospective study: 2011-2016:
Neutralising Antibody Response on Day 35
after Two Different Schedules of Intradermal Pre-exposure Rabies Vaccination:
Final Unpooled Data: 2014


Amendment protocol October 2013

- Study Procedure


### Abbreviated Schedules: Novartis

Prospective study: Neutralising Antibody Response on Day 14 or 35 after Two Different Schedules of Intradermal Pre-exposure Rabies Vaccination: Final Data: next week Ontario

PI sponsored driven RCT
Travel clinics: Zurich, Hamburg, Wien

### Novartis protocol October 2013

**Study Procedure**

<table>
<thead>
<tr>
<th>Randomized Clinical trial</th>
<th>Classic Schedule Group I</th>
<th>Accelerated Schedule Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>330</td>
<td>330</td>
</tr>
<tr>
<td>Vaccine</td>
<td>Rabipur</td>
<td>Rabipur</td>
</tr>
<tr>
<td>Dose</td>
<td>1 ml IM</td>
<td>1 ml IM</td>
</tr>
<tr>
<td>Primary Schedule</td>
<td>D0 1x 1 ml</td>
<td>D0 1x 1 ml</td>
</tr>
<tr>
<td></td>
<td>D7 1x 1 ml</td>
<td>D3 1x 1 ml</td>
</tr>
<tr>
<td></td>
<td>D28 1x 1 ml</td>
<td>D7 1x 1 ml</td>
</tr>
<tr>
<td>RFFIT</td>
<td>D15</td>
<td>D14</td>
</tr>
</tbody>
</table>

Also evaluating:
- kinetics of RFFIT (8 controls over 365 days)
- a faster schedule for Ixiaro (28 days versus 7 days)
Long lasting immunity

<table>
<thead>
<tr>
<th></th>
<th></th>
<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>RFFIT &gt; 0.5 IU/ml</td>
<td>22%</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>RFFIT &gt; 0.5 IU/ml After booster</td>
<td>100% (1 x 1ml IM)</td>
<td>100% (d0 0.1 ml ID, d3 0.1 ml ID)</td>
<td>100% (+ 1 booster IM) (65%)</td>
<td></td>
</tr>
<tr>
<td>Time interval After PrEP/PEP</td>
<td>15 years</td>
<td>21 years</td>
<td>10 years</td>
<td>32 years</td>
</tr>
</tbody>
</table>

Long lasting immunity

- Immunologic memory is long lasting after the full primary series with modern tissue culture vaccines
- Travelers who will be making repeated trips to rabies endemic countries could consider once in a life priming against rabies

Conclusion: shifting towards...

- More travelers should be vaccinated against rabies due to worldwide shortage in immunoglobulines
- Intradermal vaccination at low cost is safe, immunogenic, and volume-sparing
- Abbreviated schedules provide adequate antibody response
- Rabies immunity is long-lasting
Acknowledgements

<table>
<thead>
<tr>
<th>Collaborators</th>
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<tbody>
<tr>
<td>Institute of Tropical Medicine Antwerp</td>
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<td>Raymond Van Gucht, Vet PhD</td>
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<tr>
<td>Bernard Brochier, MD</td>
</tr>
<tr>
<td>Courtesy slides: Dr Jantjie Taljaard: Human Rabies 28 Sept 2009</td>
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<tr>
<td>Dr Gautret: Pretravel vaccination against rabies CISTM2013</td>
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</tbody>
</table>

'Among all the infectious diseases, rabies is the most easy to prevent'