‘All you wanted to know about Rabies and more…’

P. Soentjens

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

WHO Wkly Epidemiol Rec 2010
Gautret PlosNTDS2013
Gautret JTravelMed 2012; Vaccine 2012; Curr Opin Infect Dis 2012

Background

- **Questionnaire (n = 7681)**

  Estimated risk - for an animal bite in travelers: 1,11% per month

  - of being licked: 3,12% per month

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

Watcharapong Piyaphanee[1]*, Chatporn Kittitrakul[1], Saranath Lawpoolsri[2], Philippe Gautret[3], Wataru Kashino[1], Waraluk Tangkanakul[4], Prangthip Charoenpong[5], Thitiya Ponam[5], Suda Sibunruang[6], Weerapong Phumratanaprapin[1], Terapong Tantawichien[7]

September 2012

- 11,6% PrEP vaccinated (three shots)

- 15,3% PrEP incompletly vaccinated (only two shots)

Background

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

Watcharapong Piyaphanee[1]*
Wataru Kashino[1], Waraluk Ta
Weerapong Phumratanaprap

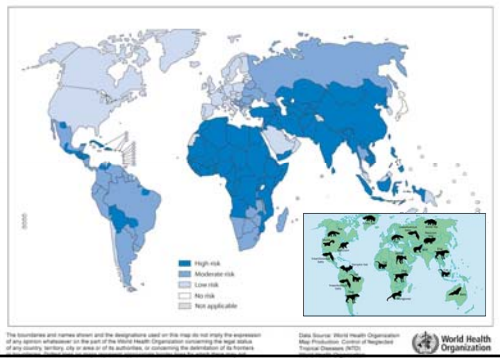
Table 5. Animal exposure during this trip (n = 7,681).

	no. exposed	%
Prevalence of Exposure (bitten-licked)	219	2.85
Number of travelers being bitten	66	0.86
Number of travelers being licked	185	2.41
Bitten or scratched by (n = 36)		
Dog	16	44.4
Monkey	14	38.9
Cat	3	8.3
Other	3	8.3
Among travelers who are bitten (n = 35)		
Clean the wound	26	74.3
Go to the hospital and get rabies vaccine	13	37.1
Do nothing	3	8.6

Country	Average stay (month)	Incidence of exposure*	95% CI
Thailand (n = 7681)	0.62	4.08	3.6–4.5
Cambodia (n = 633)	0.40	5.92	4.1–7.8
[illegible]	[illegible]	[illegible]	[illegible]
Lao PDR (n = 476)	0.49	4.29	2.5–6.1
Malaysia (n = 535)	0.33	0.95	0.0–2.0
Singapore (n = 276)	0.25	1.43	0.0–2.8
Indonesia (n = 183)	0.63	1.73	0.0–3.6
Myanmar (n = 110)	0.47	7.79	2.8–12.8
Philippines (n = 83)	0.54	2.85	0.0–6.9

Background

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



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers.

Data Source: World Health Organization
Map Production: Control of Neglected Tropical Diseases (NTD)

World Health Organization

Background

- **Rabies in travelers: 60 cases**

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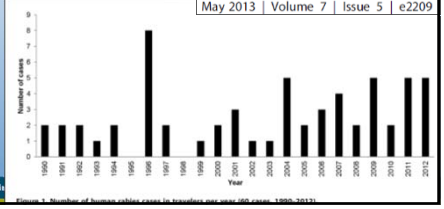
PLOS | NEGLECTED TROPICAL DISEASES

Imported Human Rabies Cases Worldwide, 1990–2012

Philippe Carrara[1], Phillipe Parola[1,2], Phillipe Brouqui[1,2], Philippe Gautret[1,2]*

1 Assistance Publique Hôpitaux de Marseille, CHU Nord, Pôle Infectieux, Institut Hospitalo-Universitaire Méditerranée Infection, Marseille, France, 2 Aix Marseille Université, Unité de Recherche en Maladies Infectieuses et Tropicales Emergentes (URMITE), UM63, CNRS 7278, IRD 198, Inserm 1095, Faculté de Médecine, Marseille, France

May 2013 | Volume 7 | Issue 5 | e2209



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Background

- **Rabies in travelers: 60 cases**

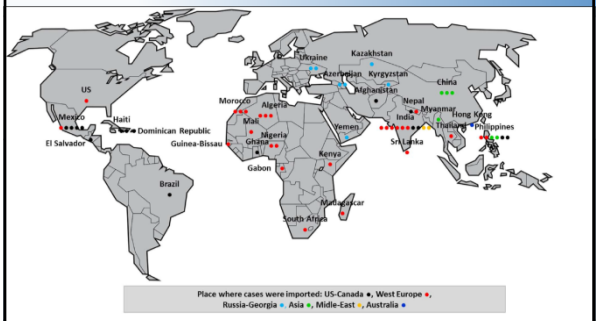
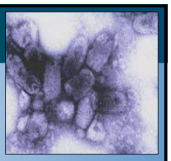
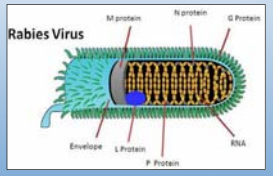


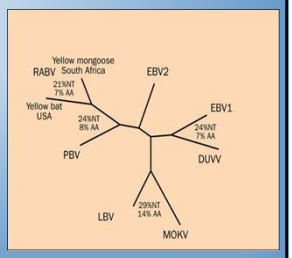
Figure 2. Country of exposure and place where the case was imported for 60 human rabies cases in travelers (1990–2012). Country

Rabies disease

- **Virus**
- Rhabdoviridae
- Genus: **Lyssavirus**







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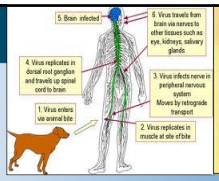
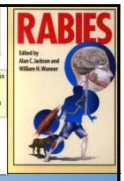
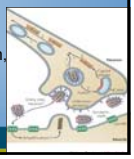
Rabies disease





- **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



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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**

Hemachudha et al. Lancet Neurology 2013

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Incubation period

- **Rabies in travelers: 60 cases**

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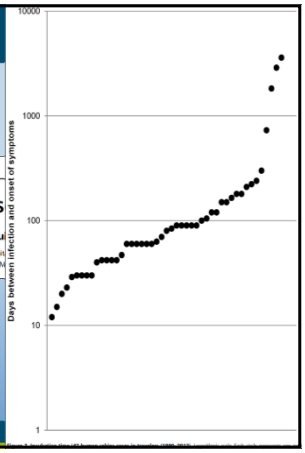
Imported Human Rabies Cas

Philippe Carrara[1], Phillipe Parola[1,2], Phillipe Brouqu

1 Assistance Publique Hôpitaux de Marseille, CHU Nord, Pôle Infectieux, Institut Hospit
Unité de Recherche en Maladies Infectieuses et Tropicales Emergentes (URMITE), UM



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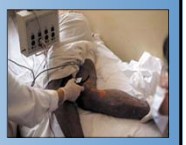
Rabies: Prodromal Features

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

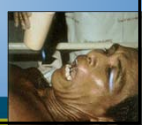
- Hypersalivation, excessive perspiration, gooseflesh, pupillary dilatation, priapism
- Periods of hyperexcitability are typically followed by periods of complete lucidity

Rabies: Encephalitic or Furious Rabies

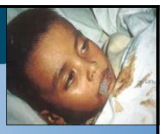
Early brainstem involvement (hallmark)

Classic symptoms

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



Rabies: Encephalitic or Furious Rabies



Combination of hypersalivation and hydrophobia

- "Foaming at the mouth"

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)

Rabies: Paralytic Rabies

Muscle weakness predominates and classic symptoms of rabies are absent

- Early and prominent **muscle weakness**
- Often starts in bitten extremity
- Spreads to produce quadriparesis 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

	Furious	Paralytic
General features in patients infected with dog RABV variants		
Prevalence[1]	2/3 (67%)	1/3 (33%)
Average survival without intensive care support	5-7 days (n=80)	11 days (n=35)
Location of bite and relation to unsuccessful immunisation[1-4]	Anywhere; not related	Anywhere; not related
Prodromal symptoms[1-4]	Non-specific with local neuropathic pain in a third of patients	Non-specific with local neuropathic pain in a third of patients
Rabies characteristics[1-4,6]	Present, but might not be seen at all stages	None or minimal, phobic spasms in only half, inspiratory spasms might not be obvious due to weakness of neck muscles and diaphragm; percussion myoedema at deltoids and chest wall (in the absence of hyponatraemia, renal failure, hypothyroidism, and severe cachexia)
Sensory deficits[1-4]	At bitten segment due to ganglionitis; loss of pinprick sensation followed by loss of joint position sense	At bitten segment due to ganglionitis; loss of pinprick sensation followed by loss of joint position sense
Flaccid weakness with areflesia[1-4]	Appears only when comatose	Ascending pure motor weakness, predominantly involving proximal and facial musculature as initial manifestation, while consciousness is fully preserved
Electrophysiological features[13]	Subclinical anterior horn cell dysfunction; sensory neuronopathy in patients with local neuropathic symptoms	Evidence of peripheral demyelination or axonopathy; sensory neuronopathy in patients with local neuropathic symptoms
MRI findings in patients infected with dog RABV variants[5]		
Prodromal phase	Enhancing hyperisignal T2 changes along the brachial plexus and associated spinal nerve roots at levels corresponding with the bitten extremity; non-enhancing ill-defined mild hyperisignal T2 changes of the spinal cord, temporal lobe cortices, hippocampal gyri, and cerebral white matter	Enhancing hyperisignal T2 changes along the brachial plexus and associated spinal nerve roots at levels corresponding with the bitten extremity; non-enhancing ill-defined mild hyperisignal T2 changes of the spinal cord, temporal lobe cortices, hippocampal gyri, and cerebral white matter
Acute neurological (non-comatose) phase	Progression of abnormal hyperisignal T2 changes	Progression of abnormal hyperisignal T2 changes
Comatose phase	Moderate gadolinium enhancement, especially in limbic structures, thalamus, substantia nigra, tectal plates, brainstem, deep grey matter, cranial nerve nuclei, spinal cord, and cranial and spinal nerve roots	Moderate gadolinium enhancement, especially in limbic structures, thalamus, substantia nigra, tectal plates, brainstem, deep grey matter, cranial nerve nuclei, spinal cord, and cranial and spinal nerve roots

Hemachudha et al. Lancet Neurology 2013

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

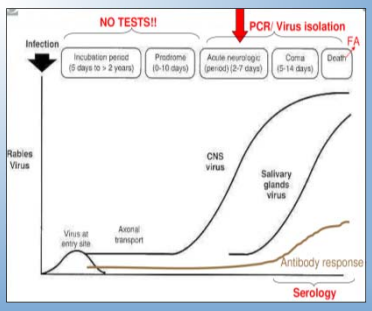
Rabies: Differential diagnosis

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

Rabies: Diagnosis

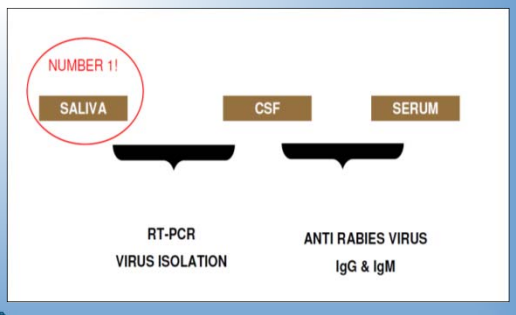
- **High clinical suspicion even in the absence of an animal bite history or hydrophobia**
- **Once suspected, essential to confirm diagnosis with rabies specific tests**
- Saliva - PCR
- CSF – PCR, Antibodies
- Brain – DFA, PCR, Histology
- Skin – DFA, PCR
- Serum (in very late disease) - Antibodies

Rabies: Diagnosis



Rupprecht CDC

Rabies: Diagnosis



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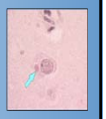
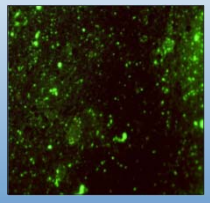
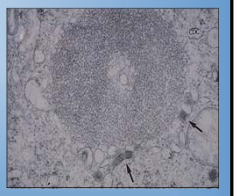
Rabies: Post mortem testing

Fluorescent antibody test
Gold standard.

Microscopy
- Bullet sign (EM)
- Negri bodies







Rabies: Use of skin biopsies

A Reliable Diagnosis of Human Rabies Based on Analysis of Skin Biopsy Specimens

Laurent Dacheux,[1] Jean-Marc Reynes,[1a] Philippe Buchy,[2] Ong Sivuth,[3] Bernard M. Diop,[3] Dominique Rousset,[1] Christian Rathat,[4] Nathalie Jolly,[2] Jean-Baptiste Dufourcq,[2] Chhor Nareth,[2] Sylvie Diop,[3] Catherine Iehlé,[1] Randrianasolo Rajerison,[3] Christine Sadorge,[2] and Hervé Bourhy[1]

Clinical Infectious Diseases 2008; 47:1410–7

Rabies: Use of skin biopsies

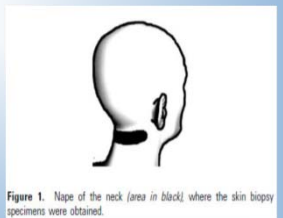


Figure 1. Nape of the neck *(area in black)*, where the skin biopsy specimens were obtained.

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**

OPEN ACCESS Freely available online

Imported Human

Philippe Carrara[1], Phillipe Parola

1 Assistance Publique Hôpitaux de Marseille, CHU Nord, Unité de Recherche en Maladies Infectieuses et Tropic

Table 2. Clinical and microbiological features of 60 travel-associated human rabies cases (1990–2012).

Category	Subcategory	N (%)
History of animal bite at presentation	Yes	21 (35.0)
	No	25 (41.7)
Number of health care providers consulted before diagnosis of rabies was made	1	13 (21.7)
	2	13 (21.7)
	3	8 (13.3)
	4	8 (13.3)
	≥5	2 (3.3)
	Not documented	16 (26.7)
Clinical form[1]	Furious	45 (75.0)
	Paralytic	6 (13.0)
	Not documented	9 (10.0)
Biological confirmation of rabies	Ante-mortem	28 (46.7)
	Post-mortem	20 (33.3)
	Not documented	12 (20.0)
Methods allowing biological confirmation of rabies[2]	RTPCR, salivary gland or saliva	16 (26.7)
	RTPCR, skin	10 (16.7)
	RTPCR, blood	3 (5.0)
	RTPCR, cerebrospinal fluid	2 (3.3)
	RTPCR, conjunctival swab	1 (1.7)
	RTPCR, throat swab	1 (1.7)
	FAT, brain	13 (21.7)
	FAT, skin	9 (15.0)
	Serology, serum and/or cerebrospinal fluid	7 (11.7)
	Virus isolation in mouse brain cells, saliva	3 (5.0)
	Not documented	14 (23.3)

Furious form : classic febrile encephalitic form where signs of irritation of the central nervous system predominate, including agitation, confusion, hydrophobia and aerophobia; paralytic form : paralysis involving the peripheral nerves, usually accompanied by fever.
[2]The sum of percentages is over 100% because rabies was confirmed by more than one method in a number of patients.; RTPCR = reverse transcriptase polymerase chain reaction; FAT = fluorescent antibody test.

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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

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Rabies: Human recovery and Survival

Case	History	Outcome
1970 Ohio, USA	Child bitten on thumb by big brown bat; Receive vaccine the next day but developed encephalitis with coma 20 days later	Recovery after 6 months
1972 Argentina	Middle-aged woman bitten by dog; receive vaccine 10 days later but developed encephalitis 21 days after the bite	Slow resolution over 1 year Hemiparesis,dysarthria
1977 New York	Young male laboratory worker, inhaled aerosol. Had pre-exposure vaccination but developed encephalitis 20 days later	Gradual improvement but personality disorder and dementia
1992 Mexico	Child bitten by dog; Received vaccine next day but developed encephalitis 19 days later	Blind, deaf, quadriplegia died 34 months later
2000 India	Child with face and hand bites by dog; no wound care only vaccine same day; developed encephalitis 16 days later	3 months of coma slow; spasticity, tremors and involuntary movements

Warrell and Warrell, 2004 Lancet 363: 959-969

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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**

Category of rabies exposure	
Risk category	Type of exposure
I	Touching/feeding animal Licking of intact
2	Nibbling of uncovered skin Superficial scratch without bleeding Licking of broken skin
3	Bites/scratches which penetrate Licking of mucous membranes

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: amoxicilline-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

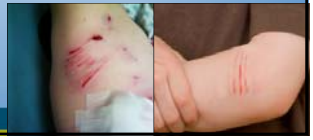
> Wound cleaning plus a course of vaccine.

Rabies: PEP or PET

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

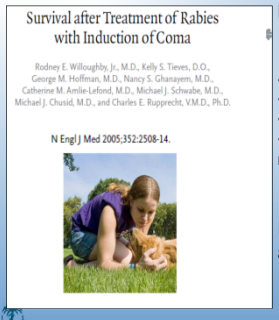
Give as soon as possible after injury, but do not withhold if presentation to health facility is delayed.

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 ampoulles 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?


Survival after Treatment of Rabies with Induction of Coma

Rodney E. Willoughby, Jr., M.D., Kelly S. Tieves, D.O., George M. Hoffman, M.D., Nancy S. Ghanayem, M.D., Catherine M. Amlie-Lefond, M.D., Michael J. Schwabe, M.D., Michael J. Chusid, M.D., and Charles E. Rupprecht, V.M.D., Ph.D.

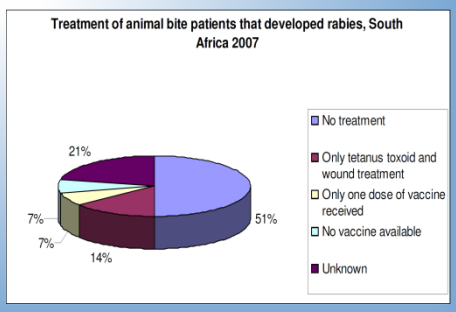
N Engl J Med 2005;352:2508-14.

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



Rabies: PET or PEP

- **Rabies in travelers: 60 cases**

OPEN ACCESS Freely available online PLOS | NEGLECTED TROPICAL DISEASES

Imported Human Rabies Cases Worldwide, 1990–2012

Philippe Carrara[1], Phillipe Parola[1,2], Phillipe Brouqui[1,2], Philippe Gautret[1,2]*

1 Assistance Publique Hôpitaux de Marseille, CHU Nord, Pôle Infectieux, Institut Hospitalo-Universitaire Méditerranée Infection, Marseille, France, **2** Aix Marseille Université, Unité de Recherche en Maladies Infectieuses et Tropicales Emergentes (URMITE), UM63, CNRS 7278, IRD 198, Inserm 1095, Faculté de Médecine, Marseille, France

Table 3. Treatment in 60 travel-associated human rabies cases (1990–2012).

Category	Subcategory	N (%)
Rabies post-exposure prophylaxis in country of exposure	None	43 (71.7)
	Rabies vaccine[a]	5 (8.3%)
	Not documented	12 (20.0)
Rabies treatment attempt in country of diagnosis[2]	None	29 (48.3)
	Rabies vaccine only	2 (3.3)
	Rabies vaccine+rabies immune globulin	5 (8.3)
	Rabies immune globulin only	1 (1.7)
	Rabies immune globulin+Milwaukee protocol	1 (1.7)
	Milwaukee protocol[b]	6 (10.0)
	Not documented	16 (26.7)

[a] Incomplete course in 2 cases.
[b] Treatment was initiated after the onset of symptoms in all cases.
Induction of coma with pentobarbital, midazolam and ketamine and use of antivirals amantadine and ribavirin.

Rabies PEP in travelers

Rabies Immunization of Travelers in a Canine Rabies Endemic Area

Suda Sibunruang, MD,* Saowaluck Tepsumethanon, RN,* Natthasri Raksakhet, PN,* and Terapong Tantawichien, MD*†

*Queen Saovabha Memorial Institute (WHO Collaborating Centre for Research on Rabies Pathogenesis and Prevention), The Thai Red Cross Society, Bangkok, Thailand; †Division of Infectious Diseases, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Table 1 Mammal-associated injuries and rabies postexposure management of travelers[2–9]

Place of travel clinics	France, Australia, New Zealand	New Zealand	United Kingdom	Israel	Switzerland	Nepal
Number of travelers	261	54	139	13	90	56
Male :female	ND	1.1 : 1	1.04 : 1	1.6 : 1	0.8 : 1	1 : 1.5
Mean age (year) (range)	ND	30.4	35 (2–84)	26	36 (median) (2–74)	ND
Age < 15 years	ND	9 (16.7%)	Age < 10 years (7, 5.0%)	ND	ND	2 (3.6%)
Main regions of injury	SEA and North Africa	South Asia and SEA	Asia	Asia	Asia	Asia
Common countries	Thailand (52, 19.9%)	Thailand (19, 35.2%)	Thailand (31, 22.3%) Turkey (31, 22.3%)	ND	ND	Nepal (56, 100%)
Responsible dog	139 (53.3%)	36 (66.7%)	69 (49.6%)	6 (46.2%)	50 (55.0%)	52 (57.1%)
Sites of wounds	Severe facial and hand injuries (20, 7.7%)	Thigh and lower limbs (26, 48.1%)	Lower limbs (67, 48.2%)	Upper limbs (8, 61.5%)	ND	Head or face (1, 1.8%)
WHO CAT III	197 (75.4%)	46 (85.2%)	ND	7 (53.8%)	ND	ND
Receiving PrEP	14 (5.4%)	14 (26%)	14 (10.1%)	1 (7.7%)	9 (10.0%)	13 (23.2%)
Initiation PEP abroad	133 (50.9%)	54 (100%)	86 (61.9%)	4 (30.8%)	54 (60.0%)	—
Indicated for RIG	170 (65.1%)	ND	76 (56.1%)	ND	81 (90.0%)	ND
Received RIG abroad	19 (7.3%)	7 (12.9%)	3 (3.8%)	ND	7 (7.8%)	—
Received RIG in home country	22 (8.4%)	3 (5.6%)	11 (7.9%)	ND	28 (31.1%)	ND

[a] Out of number of travelers, which received vaccine.
Percentages as compared with the total travelers in each study.
ND = not documented; SEA = Southeast Asia, PrEP = preexposure prophylaxis, PEP = postexposure prophylaxis, RIG = rabies immunoglobulin.

Rabies PEP in travelers

Rabies Immunization of Travelers in a Canine Rabies Endemic Area

Suda Sibunruang, MD,* Saowaluck Tepsumethanon, RN,* Natthasri Raksakhet, PN,* and Terapong Tantawichien, MD*†

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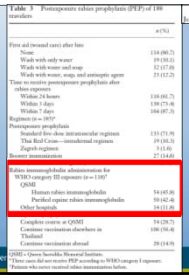


100 % recieved immunoglobulines

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

PrEP in travelers

Risk factors for potentially rabid animal bite

Meta-analyis 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

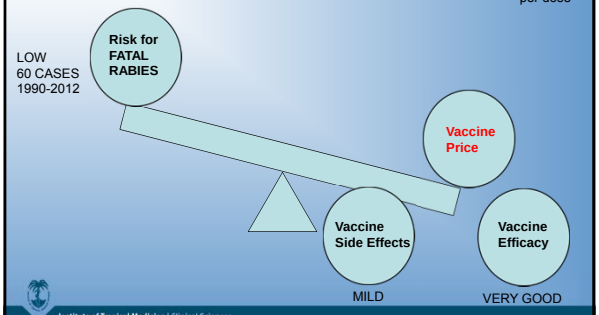
- Travel to India and Philippines
- Male
- Adult
- Migrant and VFR

PrEP

Vaccination decision:

Expensive
200 USD
per dose

LOW
60 CASES
1990-2012



PrEP

Vaccination decision:

LOW
60 CASES
1990-2012

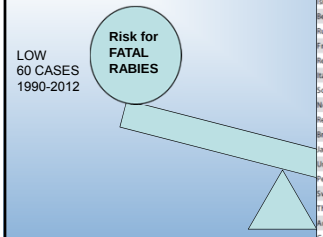


Table 4. Mean prices of cell-cultured rabies vaccine (1 dose)

Country	Mean price for one intramuscular dose (US
India[2]	16
Sri Lanka[2]	20
Spain[3]	22
Israel	32
Belgium	33
Russia	35
France	38
Republic of Ireland	45
Italy	46
South Africa	48
Norway	49
Republic of Korea	55
Brazil	63
Japan	65
United Kingdom	70
People's Republic of China[4]	70
Switzerland	73
The Netherlands	75
Australia	82
Germany	84
New Zealand	101
Finland	110
Denmark	114
Sweden	124
Canada	181
United States of America	200

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

Van Gucht S et al. Acta Clinica Belgica 2013

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.deltoideus)

Although you are urgently advised to start vaccination within 24 hours after the bite, you can still start inoculations later (vaccination and immunoglobulins) because the incubation period is usually quite long, **after consultation *with the doctors of the Agency of Contagious and Transmittable Diseases WIV/IPV – National Centre for the medical treatment of rabies*** *(formerly Pasteur Institute), Engelandstraat 642, 1180 Brussels (02/373.31.56 or 02/373.32.61 (general telephone number: 02/373.31.11) – http://www.wiv-isp.be/odobz-domti/en/index.html.*

Belgian Guidelines: PEP

- Post-exposure rabies vaccination
  Rabies PEP centres over the world

- Survey ISTM
- Survey CDC

The Global Availability of Rabies Immune Globulin and Rabies Vaccine in Clinics Providing Direct Care to Travelers†

Emily S. Jentes, PhD,* Jesse D. Blanton, MPH,† Katherine J. Johnson, MPH,*
Brett W. Petersen, MD,‡ Mark J. Lamias, BS,‡§ Kis Robertson, DVM,‡ Richard Franka, DVM,‖
Deborah Briggs, PhD,‖ Peter Costa, MPH,‖ Irene Lai, MD,¶ Doug Quarry, MD,¶
Charles E. Rupprecht, VMD,† Nina Marano, DVM,* and Gary W. Brunette, MD*

Conclusion. The availability of RV and RIG varied by geographic region. All travelers should be informed that RIG and RV might not be readily available at their destination and that travel health and medical evacuation insurance should be considered prior to departure. Travelers should be educated to avoid animal exposures; to clean all animal bites, licks, and scratches thoroughly with soap and water; and to seek medical care immediately, even if overseas.

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Journal of Travel Medicine 2013; Volume 20 (Issue 3): 148–158

PrEP: cost in Belgium

- Pre-exposure rabies vaccination

Schedule

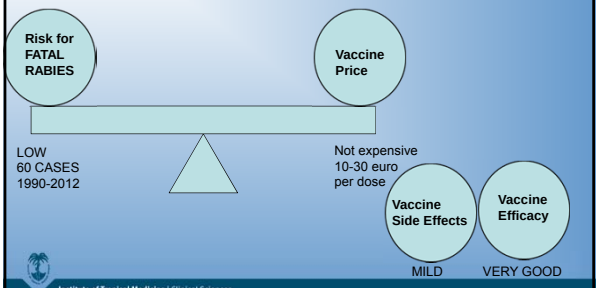
Day 0 – 7 – (21) 28 intramuscular (or intradermal)

Rabipur ® HDCV Mérieux ®	Pharmacy Travel clinic	Officina	Public price	Patients
Price (each)	28,66 euro	31,08 euro	39,07 euro	10,24 euro
Price (for three vaccines IM)	86		**117**	**31**
Price (for three intradermal vaccines 0,1ml) - cohorted	9		**12**	**3**

Belgian Guidelines

Vaccination decision

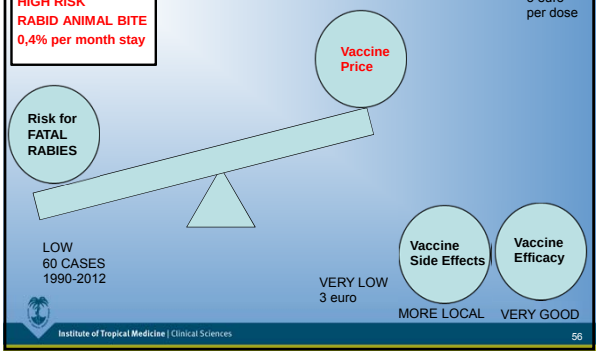
Not expensive
10-30 euro
per dose



Belgian Guidelines

HIGH RISK
RABID ANIMAL BITE
0,4% per month stay

Cheap
3 euro
per dose



PrEP in BE travelers

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.'*

Shifting towards ...

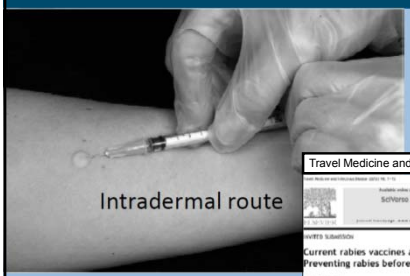
- **'From Good Protection towards Boostability'**

Antibody response (RFFIT)	Surrogate marker
< 0,5 IU/ml	Not boostable
> 0,5	Boostable Good response expected after booster
= > 0,5 - < 3,0 IU/ml	Boostable
= > 3,0 - < = 10,0 IU/ml	'Good Protection'
> 10,0 IU/ml	Long-term protection

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



Travel Medicine and Infectious Disease 2012

Current rabies vaccines and prophylaxis schedules: Preventing rabies before and after exposure

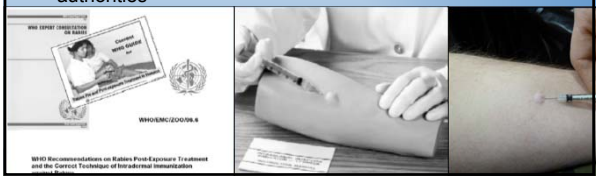
M.J. Warrell*

Intradermal Rabies Vaccination: The Evolution and Future of Pre- and Post-exposure Prophylaxis

M. J. Warrell

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

Intradermal Schedules for Rabies

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 ampoulles of 0,1 ml for direct intradermal injection with special intradermal needles
- Serology testing is recommend
  - for immunosuppression (WHO)
  - in all cases (Canada, Australia)

Who used ID already in travelers?

Table 2. Intradermal vaccine immunization studies conducted in the travel clinic setting

Country	Primary course	Prebooster test >0.5 IU/ml	Booster	Postbooster test >0.5 IU/ml
Australia n = 29	HDCV 0.1 ml ID D0, D7, D28	18–24 months after primary course: 20/29[a]	HDCV 1.0 ml IM 18–24 months after primary course n = 29	Day 5 after booster: 27/29[a] Day 28–42 after booster: 29/29[a]
Australia n = 164	HDCV 0.1 ml ID D0, D7, D28	23 days after primary course: 141/144[a]	HDCV 0.1 ml ID 12 months after primary course n = 20	Day 23 after booster: 20/20[a]
The Netherlands n = 25	PCECV D0, D7, D21	2 weeks after primary course: 25/25[b] 550 days after primary course: 8/10[b]	PCECV 0.1 ml ID 16–20 months after primary course n = 10	Day 7 after booster: 10/10[b] Day 14 after booster: 10/10[b]
New Zealand n = 263	HDCV/PCEV D0, D7, D28	2 weeks after primary course: overall 95.1%[b]	HDCV/PCEV 0.1 ml ID 12 months after primary course n = 10	2 weeks after booster: overall 95.1%[b]
Australia n = 420 n = 317	HDCV D0–2, D7–12, D21–28 HDCV D0, D7, D21–28	2–3 weeks after second visit: overall 94.5%[b] Postprimary course: overall 98.3%[b] 22 days after primary course: overall 99.4%[b]	– –	– –

RFFIT > 0,5 IU/ml > 95%

Intradermal Schedules for Rabies

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

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 31/6/2013
- D 0-7-28-365 + serology D 372
- Serology done before 31/6/2013

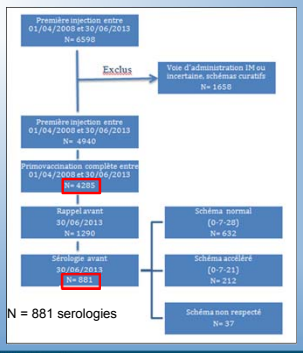
Methods:

- Study Procedure

Randomized Clinical trial	Classic Schedule
Vaccine	HDCV or Rabipur
Dose	0,1 ml ID
Primary Schedule	D0 1x 0,1 ml D7 1x 0,1 ml D28 1x 0,1 ml
Booster	D365 1 x 0,1 ml ID
Total dose	0,4 ml ID
RFFIT after booster	D+7

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)

RFFIT	N	%
<0.5	0	0
0.5-2.9	30	3,4
3-10	117	13,3
>10	734	83,3
Total	881	100

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)

	RFFIT < 3 UI/MI		RFFIT >= 3 UI/MI	
	n	%	n	%
Schedule normal	16	2,5	616	97,5
Schedule fast (d0,7,21)	12	5,7	200	94,3
Schedule not correct	2	5,4	35	94,6
Total	30	3,4	851	96,6

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

CDC protocol

- Study Procedure

Randomized Clinical trial	Intramuscular Schedule Group I	Intradermal Schedule Group II
N	65	65
Vaccine	PCEC	PCEC
Dose	1 ml IM	1 ml ID
Primary Schedule	D0 1x 1 ml D7 1x 1 ml D28 1x 1 ml	D0 1x 0,1 ml D7 1x 0,1 ml D28 1x 0,1 ml
RFFIT	D35	D35
Booster	D365 1 x 1 ml IM	D365 1 x 0,1 ml ID
Total dose	4 ml IM	0,4 ml ID
RFFIT after booster	D+14	D+14

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

Matthias Altmann, PharmD, MPH, Philippe Parola, MD, PhD, Jean Delmont, MD, Philippe Brouqui, MD, PhD, and Philippe Gautret, MD, PhD
Service des Maladies Infectieuses et Tropicales, Hôpital Nord, Marseille,

Journal of Travel Medicine 2009; Volume 16 (Issue 2): 107–111

- 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 L. Lau, MBBS, MPH&TM,†‡ Emily J. Fearnley, PhD,† and Philip Weinstein, MBBS, PhD†§

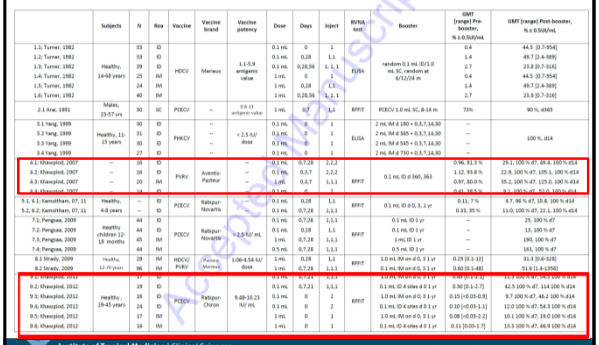
Results. A total of 420 travelers aged between 10 and 65 years were vaccinated using the modified ID course. The overall seroconversion rate was 94.5%, with 397 travelers developing antibody levels of >0.5 IU/mL when tested at approximately 21 days post-vaccination.

Elisa >< RFFIT
Not randomised

Journal of Travel Medicine 2011; Volume 18 (Issue 5): 327–332

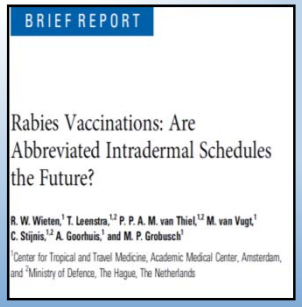
Abbreviated Intradermal Schedules

Table 1. Vaccination schedules and booster details as described in nine studies



Wieten et al. Clin Infect Dis 2012

Abbreviated Intradermal Schedules



BRIEF REPORT

Rabies Vaccinations: Are Abbreviated Intradermal Schedules the Future?

R. W. Wieten,[1] T. Leenstra,[1,2] P. P. A. M. van Thiel,[1,2] M. van Vugt,[1] C. Stijnis,[1,2] A. Goorhuis,[1] and M. P. Grobusch[1]

[1]Center for Tropical and Travel Medicine, Academic Medical Center, Amsterdam, and [2]Ministry of Defence, The Hague, The Netherlands

- Low intial 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

Wieten et al. Clin Infect Dis 2012

Abbreviated Intradermal Schedules

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

Abbreviated Intradermal Schedules

Low-Cost Intradermal Rabies Vaccination Is Indeed Very Promising

To the Editor—We read with great interest the recent article by Wieten 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

fluorescent focus inhibition test (RFFIT) or the fluorescent antibody virus neutralization test. In particular, an RFFIT titer of > 0.5 IU/mL after booster vaccination is considered to be the best surrogate marker to determine protection from rabies infection after an animal bite in endemic zones [6]. Thus, we suggest that studies using only the enzyme-linked immunosorbent assay (ELISA), although reliable as an alternative, should be excluded in future analyses assessing or comparing the boostability of preexposure and postexposure rabies vaccination schedules. For instance, a recent case

P. Soentjens,[1] A. Aerssens,[1] S. Van Gucht,[2] R. Ravinetto,[1] and A. Van Gompel[1]
[1]Vaccine Department, Military Hospital Queen Astrid, Brussels, [2]Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, and [3]WHO Rabies, Scientific Institute of Public Health, Brussels, Belgium

Abbreviated Schedules: Schedule 28 and 7

Prospective study: 2011-2016:
Initial Neutralising Antibody Response on Day 35
after Two Different Schedules of Intradermal Pre-exposure Rabies Vaccination:
Preliminary Pooled Data

P. Soentjens, P. Andries, B. Damanet, A. Wauters, K. De Koninck, W. Heuninckx, E. Dooms, S. Van Gucht, M. De Crop, R. Ravinetto, A. Van Gompel, A. Aerssens

Presented CISTM2013 Maastricht

Objective:

- **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

Not specified by protocol to publish data on day 35: Authorization of Scientific Study Committee to publish pooled data

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

Randomized Clinical trial	Classic Schedule Group I	Accelerated Schedule Group II
N	240	240
Vaccine	HDCV	HDCV
Dose	0,1 ml ID	0,1 ml ID
Primary Schedule	D0 1x 0,1 ml D7 1x 0,1 ml D28 1x 0,1 ml	D0 2x 0,1 ml D7 2x 0,1 ml
RFFIT	D35	D35
Booster	D365 - D1097 1 x 0,1 ml ID	D365 - D1097 1 x 0,1 ml ID
Total dose	0,4 ml ID	0,5 ml ID
RFFIT after booster	D+7	D+7

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

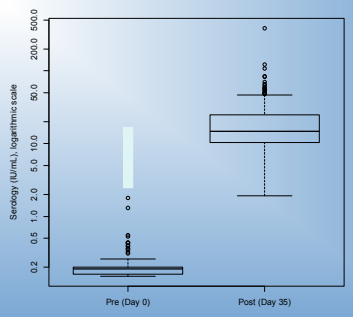
Demographics	N = 499
Age distribution	Median: 28 years Range: 18-53 years
Age categories	< 20 years: 28 (6%) 21-30 years: 275 (55%) 31-40 years: 131 (26%) > 40 years: 65 (13%)
Gender	Male: 479 (96%) Female: 20 (4%)

Results: Antibody Response on day 35

Antibody response (RFFIT) day 35	N = 464 (93%)
< 0,5 IU/ml	0 (0%)
= > 0,5 - < 3,0 IU/ml	7 (1,5%)
= > 3,0 - < = 10,0 IUml	100 (21,6%)
> 10,0 IU/ml	357 (76,9%)

RFFIT rapid fluorescent focus inhibition test

Results: Antibody Response on day 35



Results: Side effects

Drug-related Adverse effects	N = 499
Injection site related	204 (41%)
General	9 (1%)
Reversible diplopia 'Drug-relation possible'	1 (0,2%)

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)**

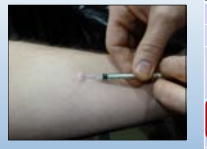
Abbreviated Schedules:

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

P. Soentjens, P. Andries, B. Damanet, A. Wauters, K. De Koninck, W. Heuninckx, E. Dooms, S. Van Gucht, M. De Crop, R. Ravinetto, A. Van Gompel, A. Aerssens

Amendment protocol October 2013

- Study Procedure



Simulated PEP booster

Randomized Clinical trial	Classic Schedule Group I	Accelerated Schedule Group II
Vaccine	HDCV	HDCV
Dose	0,1 ml ID	0,1 ml ID
Primary Schedule	D0 1x 0,1 ml D7 1x 0,1 ml D28 1x 0,1 ml	D0 2x 0,1 ml D7 2x 0,1 ml
RFFIT Final PrEP	D35	D35
Booster	D365 - D1097 1 x 0,1 ml ID	D365 - D1097 1 x 0,1 ml ID
Total dose	0,4 ml ID	0,5 ml ID
RFFIT after 0,1 ml ID PEP	D+7	D+7

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

Abbreviated Schedules:

Prospective study II: 2014-2018: Evaluation of a faster Intradermal Pre-exposure Rabies Vaccination Schedule

P. Soentjens, P. Andries, B. Damanet, K. De Koninck, W. Heuninckx, E. Dooms, S. Van Gucht, M. De Crop, R. Ravinetto, A. Van Gompel

Institute of Tropical Medicine | Clinical Sciences

To be registered

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

Institute of Tropical Medicine | Clinical Sciences

To be published

Novartis protocol October 2013

- Study Procedure

Randomized Clinical trial	Classic Schedule Group I	Accelerated Schedule Group II
N	330	330
Vaccine	Rabipur	Rabipur
Dose	1 ml IM	1 ml IM
Primary Schedule	D0 1x 1 ml D7 1x 1 ml D28 1x 1 ml	D0 1x 1 ml D3 1x 1 ml D7 1x 1 ml
RFFIT Final PrEP	D35	D14

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

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

Long lasting immunity

Persistance of Antibodies	JTM 2007 Malerczyk	Vaccine 2006 Suwansrinon	Vaccine 2008 Brown	Vaccine 2011 Fayaz
N	15	118	89	26
IM or ID	IM/ID PrEP	IM/ID PrEP	ID PrEP	IM PEP
RFFIT > 0,5 IU/ml	22%		**100 %**	**100 %**
RFFIT > 0,5 IU/ml After booster	**100%** (1 x 1ml IM)	**100%** (d0 0,1 ml ID, d3 0,1 ml ID)		**100 %** (+ 1 booster IM) (65%)
Time interval After PrEP/PEP	15 years	21 years	10 years	32 years

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

Aknowledgements

Collaborators	
Institute of Tropical Medicine Antwerp	Alfons Van Gompel, MD Raffaela Ravinetto, Pha PhD Maaike De Crop Harry Van Loen Joris Menten
Military Hospital Queen Astrid Brussels, Belgian Defense	Annelies Aerssens, MD An Wauters, MD Eric Dooms, MD Petra Andries Benjamin Damanet Katrien De Koninck Walter Heuninckx, Pha
Institute of Public Health Brussels	Steven Van Gucht, Vet PhD Raymond Vanhoof, MD PhD Jean Vanderpas, MD Bernard Brochier, MD

Courtesy slides:
Dr Jantjie Taljaard: Human Rabies 28 Sept 2009
Dr Gautret: Pretravel vaccination against rabies CISTM2013

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