The last-minute traveller: an update on accelerated schedules.

P. Soentjens

Introduction

Background

Solutions in vaccinology in the last-minute traveller

- **Differentiate risk and impact of diseases**
- **Combining antigens in prefilled vaccines**
- **Off-label vaccine dosing: accelerated - intradermal**

Rabies studies in BE Defense

Conclusion

Background

Advising the last-minute traveller is challenging

'one day - one week to several weeks before travel'

Table 1 Considerations for risk assessment in the prioritisation of vaccination in travellers.

Travel-related considerations
Country(ies) of destination
Purpose of travel
Duration and type of travel
Mandatory or recommended requirement
Host-related considerations
Personal immune status
State of health
Age and specific contraindications for vaccination
Lifestyle and attitudes to risk of infection
Disease-related considerations
Associated morbidity/mortality
Available treatment options, including antibiotic resistance
Vaccine-related considerations
Efficacy
Tolerability
Schedule
Compliance/convenience
Cost

Zuckerman Travel Med Infect Dis 2003.

Background

Advising the last-minute traveller is challenging

'one day - one week to several weeks before travel'

> General health counselling

> Malaria advice

> Required vaccinations

> Pre-existing medical conditions?

> Extended stay?

> Multiple continents?

Rosselot Yellow Book CDC 2016

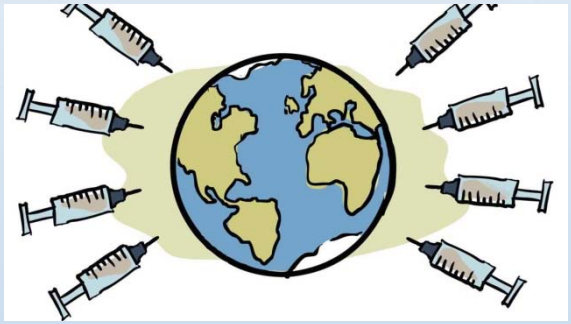
Background

Required vaccinations in the last-minute traveller

> routine primary vaccinations

> travel vaccinations in the past?

Related to the itenary and time spent in high risk areas



Hampson et

Background

Single visit: primary and booster vaccinations

• **Yellow fever**	(>)10 years?
• **Tetanos-Diphteria-Pertussis-Polio**	10 years
• **Measles-Rubella-Mumps**	2 injections
• **Hepatitis A**	2 injections
• **Typhoid fever**	3 years
• **Meningitis ACWY**	5 years
• **Influenza**	1 year

Background

More than one visit: primary vaccinations and boosters

- **Hepatitis B or AB** (d0 > m1 > m4-6) (d0 > m1 > m2 > m12)
- **Tick Borne Enceph.** (d0 > m1-3 > m9-12 > y3 > y5)
- **Japanese Enceph.** (d0 > d28 > y1-2)
- **Rabies** (d0 > d7 > d21-28)

Background

Single visit consultation:

Start vaccination also when there is no enough time?

- MMR together with Yellow Fever?
- Hepatitis B - Rabies - TBE - JE?

Maximum 4 vaccine shots

- Tetanos - Diptheria - Pertussis - Polio - Measles - Rubella - Mumps - Hepatitis A - Meningitis - Typhoid fever - Influenza - Yellow fever
- Hepatitis B - Japanese Encephalitis - Rabies - Tick borne encephalitis

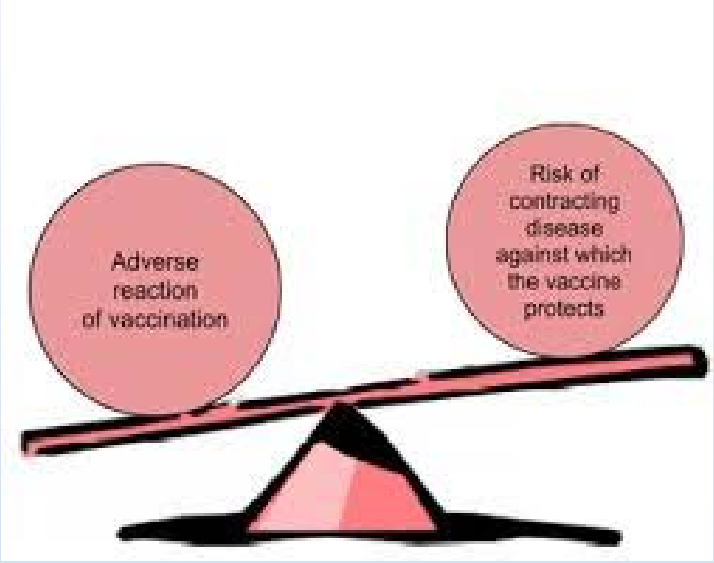
Plotkin - Vaccines, 5th Edition

World Health Organization
Organisation mondiale de la Santé
Weekly epidemiological record
Relevé épidémiologique hebdomadaire

Administration of multiple injectable vaccines in a single visit

Solutions in vaccinology

Balancing adverse reactions of vaccinations versus preventing infection:



Differentiate risk and impact of diseases

Travellers risk: incidences: ‘Steffen tree’

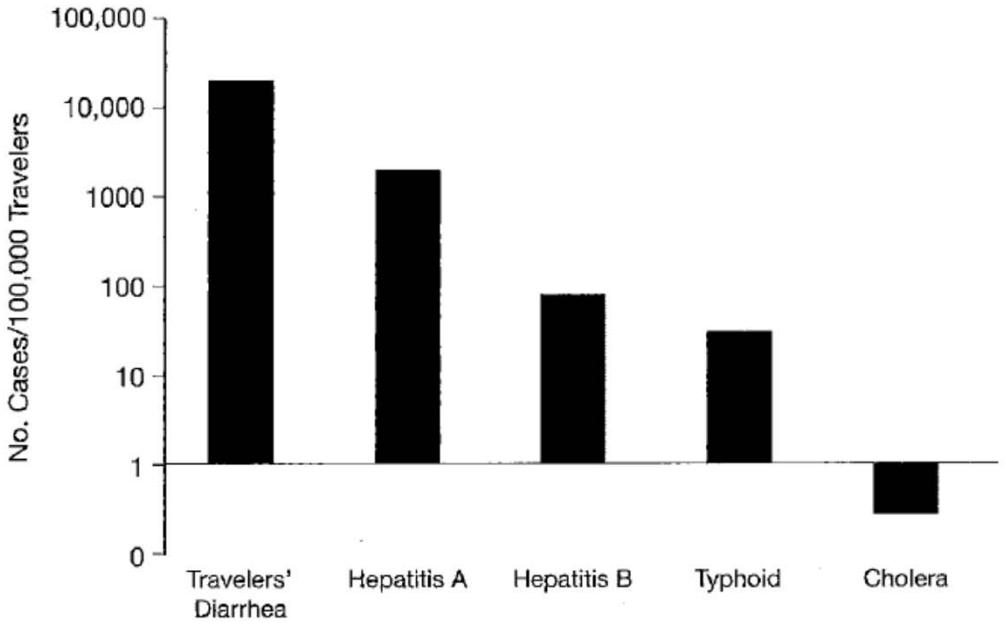


Figure 1 Vaccine-preventable illnesses per 100,000 international travelers. (Adapted from *J Wilderness Med.*[8])

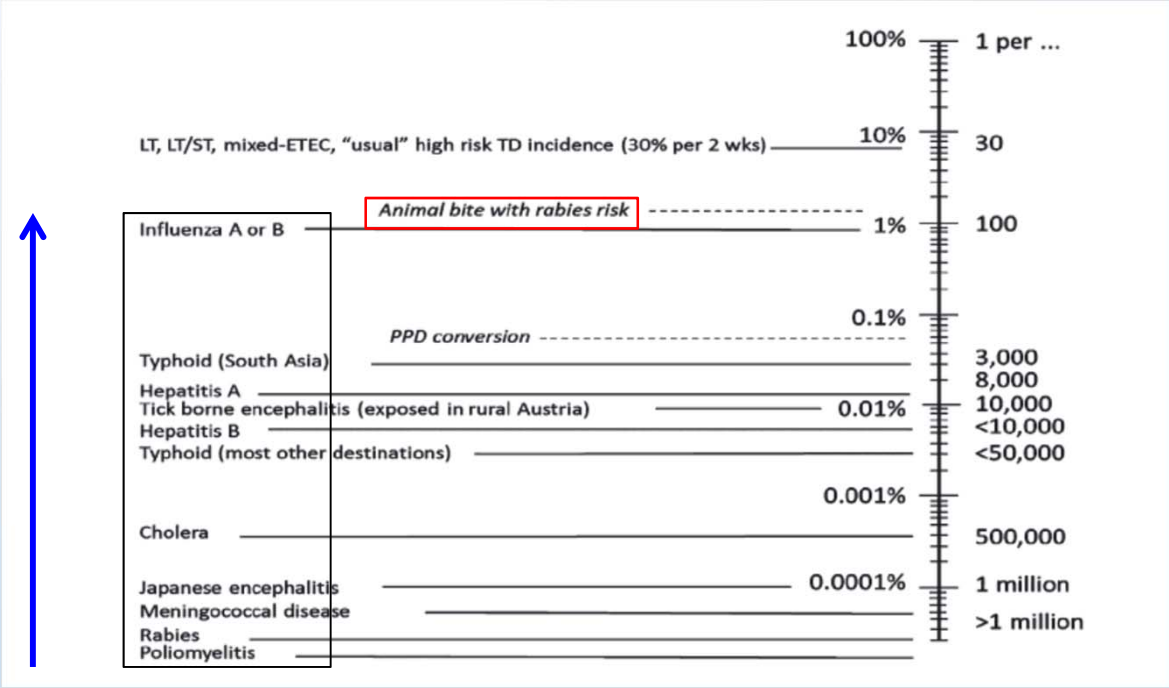
Keystone J: Am J Med 2005.

Solutions in Vaccinology

Differentiate risk and impact of diseases

Travellers risk: incidences: ‘Steffen tree’

VACCINATION ESSENTIAL



Steffen: J Travel Med 2015

Solutions in Vaccinology

Differentiate risk and impact of diseases

Travel Medicine and Infectious Disease (2014) 12, 330–340

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevierhealth.com/journals/tmid

Prevention of infectious diseases during military deployments: A review of the French armed forces strategy

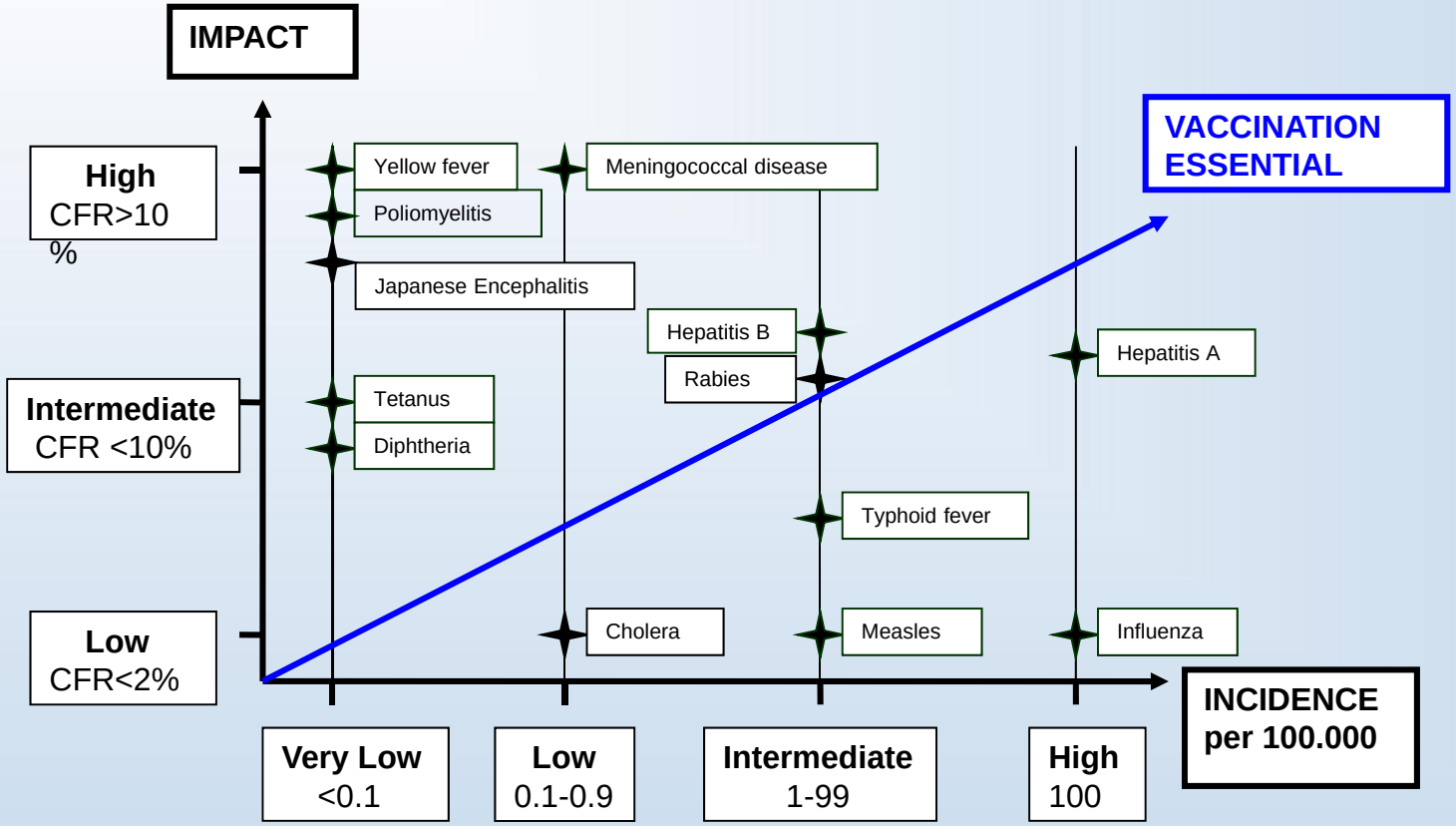
R. Michel [a,d,*], J.P. Demoncheaux [b], M.A. Créach [a], C. Rapp [c,d], F. Simon [d,e], R. Haus-Cheymol [f], R. Migliani [d,f]

Table 1 Main infectious risks for French troops deployed overseas and abroad.

Risk	Main infections or situation at risk	Incidence	Severity	Contagiousness	Available control measures
Vector borne infection	Malaria	+++	High	No	HE, PVC, chemoprophylaxis
	Arboviruses	++	Medium	Low	HE, PVC
	Cutaneous leishmaniasis	++	Low	No	HE, PVC
	Visceral leishmaniasis	+/−	Medium	No	HE, PVC
	Trypanosomiasis	+/−	Medium	No	HE, PVC
Air-borne infection	Tuberculosis	+	Medium	Medium	–
	Influenza	+++	Medium	High	HE, hygiene, vaccine
	Respiratory viral infection	+++	Low	Medium	HE, hygiene
	Measles	+	Medium	High	Hygiene, vaccines
	Rubella, mumps, pertussis	+	Low	Medium	Hygiene, vaccine
	Meningococcal infections	+/−	Low	Medium	Hygiene, vaccine
	Q fever	+	low	Medium	–
	Histoplasmosis		Low	No	–
	Anthrax and pneumonic plague	T	High	Medium	–
Water and foodborne diseases	Typhoid fever	+/−	Medium	Low	Hygiene, vaccine
	Hepatitis A,E	+	Medium	Low	He, hygiene, vaccine (HVA)
	Foodborne outbreak	++	Low	Medium	HE, hygiene
	Traveller's diarrhea	++	Low	Low	HE, hygiene
	Intestinal parasites	++	Low	Low	HE, hygiene
	Toxoplasmosis	+/−	Low	No	HE
Sexually Transmitted Infections	Sexual exposure to HIV	+++	Medium	No	HE, condom
	HIV	+	Medium	Low	HE, condom, PEP
	Gonococcal-, chlamydial-, herpes infection	++	+/-	Low	HE, condom
	Human papillomavirus	++	Low	Low	HE, condom, Vaccine (Females)
	Hepatitis B	+/−	Low	Low	HE, condom, vaccine
Water infection (contact)	Schistosomiasis	+	Medium	No	HE
	Leptospirosis	+/−	Medium	No	HE, vaccine (Positional exposure)
Animal-transmitted infection	Leptospirosis	+/−	Low	No	HE, vaccine (Positional exposure)
	Animal bites	++	High	No	HE, vaccine (Positional exposure)
	Viral haemorrhagic fevers	T	High	Medium	HE
Warfare infections	Infection of war wounds	+	High	No	Surgery antibiotic prophylaxis and adapted treatment
	Blood exposure to HIV or hepatitis C	+	Medium	No	HE, hygiene, gloves, PEP

HE: Health Education; PVC: Pest and Vector Control; PEP: Post-Exposure Prophylaxis.
+++: >100 cases/year; ++: 11–100 cases/year; +: 1–10 cases/year; +/−: rare cases; T: theoretical risk.

Differentiate risk and impact of diseases



CFR Case Fatality rate

Steffen. J Travel Med 2005

Solutions in Vaccinology

Differentiate cumulative risk versus single trip

Vaccine 30 (2012) 2600–2604

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Aggregate travel vs. single trip assessment: Arguments for cumulative risk analysis

K. Leder[a,b,*], L.H. Chen[c,d], M.E. Wilson[e]

Table 1
Short, medium and long term disease risk estimates per 100,000 trips for possible travel itineraries.[a]

Vaccine	2-Week trip	2 trips/year × 2 years	4 trips/year × 10 years	Comment
Hepatitis A	3 to 14 [34]	12 to 56	120 to 560	Estimate is for non-immune travellers
Hepatitis B	4.5 to 40–210 [35,36]	18 to 840	180 to 8400	(Presumed, duration of stay not calculated) Lower estimate is based on Dutch short-term travellers, whereas the upper range is for expatriates
JE	0.0015 to 10–40 [37,38]	0.006 to 160	0.06 to 1600	Lower estimate is based on reported cases in European travellers
Meningococcal disease	0.02 to 100 [39]	0.08 to 400	0.8 to 4000	Lower estimate is based on tourists and business travellers, whereas higher estimate is based on pilgrims to Mecca
Animal-related injury leading to possible rabies exposure	8 to 100 [40] see comment	32 to 400	320 to 4000	Lower estimate is based on tourists only. Exposure risk estimated at <1/1000 to 23/1000 per month in tourist travellers, and 5.7/1000 to 43.6/1000 per year in expatriates [16,40] Recent estimate of overall risk in travellers of 0.4% (0.01–2.3%) per month [41]
Typhoid fever	9 to 12 [42,43]	36 to 48	360 to 480	(Presumed, duration of stay not calculated) Estimate is for travellers to India
YF	5 to 50 [44]	20 to 200	200 to 2000	Estimate is for West Africa

[a] In this table, we have assumed that there is a linear association between risk and travel length, which may not be the case for all diseases.

Solutions in Vaccinology

Combining antigens in prefilled vaccines

- Tetanos-Diphteria-Pertussis-Polio
- Hepatitis A-Typhoid fever
- …

Future? One shot combination vaccines?

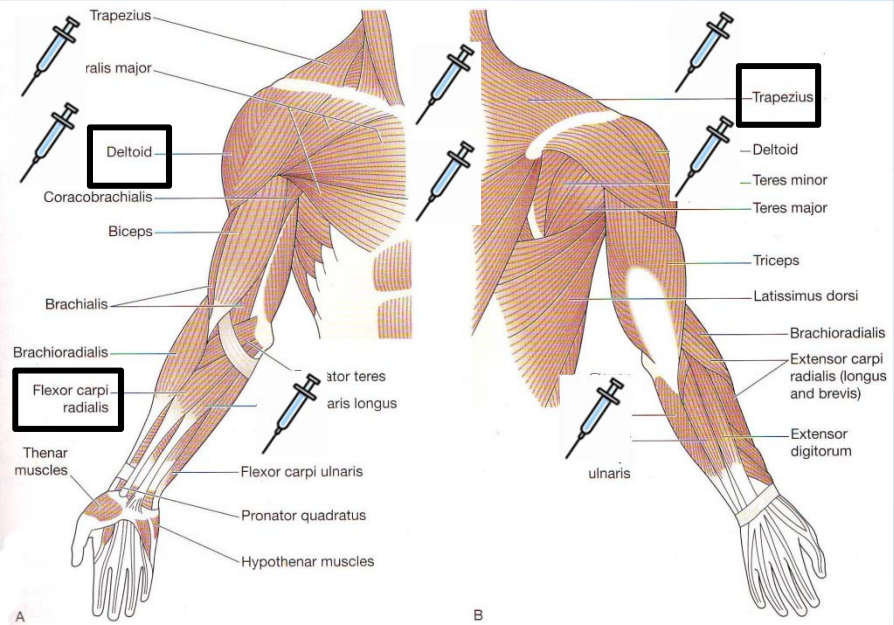
- Yellow fever-HepatitisA(B)-Typhoid fever-Tetanos-Diphteria-Polio
- Yellow-fever-HepatitisA(B)-Typhoid fever-Tetanos-Diphteria-Polio-Meningitis-Rabies
- HepA(B)-Typhoid fever-Tetanos-Diphteria-Polio-Rabies-Japanese encephalitis

Single visit consultation: More shots at once

Maximum 4 IM/SC vaccination shots: 2 x 2 M deltoideus

Additional 2 ID vaccination shots: 2 fore-arms

Additional 2 ID upper-arms or other regions (M. Trapezius)



The main muscles of the shoulder and upper limb. A: anterior view. B: posterior view.

Solutions in Vaccinology

Off-label vaccine dosing: intradermal injection (ID)

- Large clinical trials - studies: **Influenza ID** - **Rabies ID**

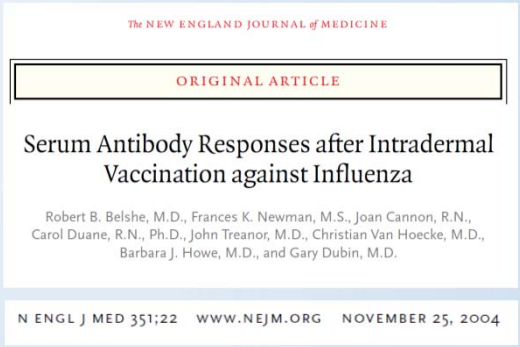

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dose Sparing with Intradermal Injection of Influenza Vaccine

Richard T. Kenney, M.D., Sarah A. Frech, D.V.M., Larry R. Muenz, Ph.D., Christina P. Villar, M.P.H., and Gregory M. Glenn, M.D.

N ENGL J MED 351;22 WWW.NEJM.ORG NOVEMBER 25, 2004

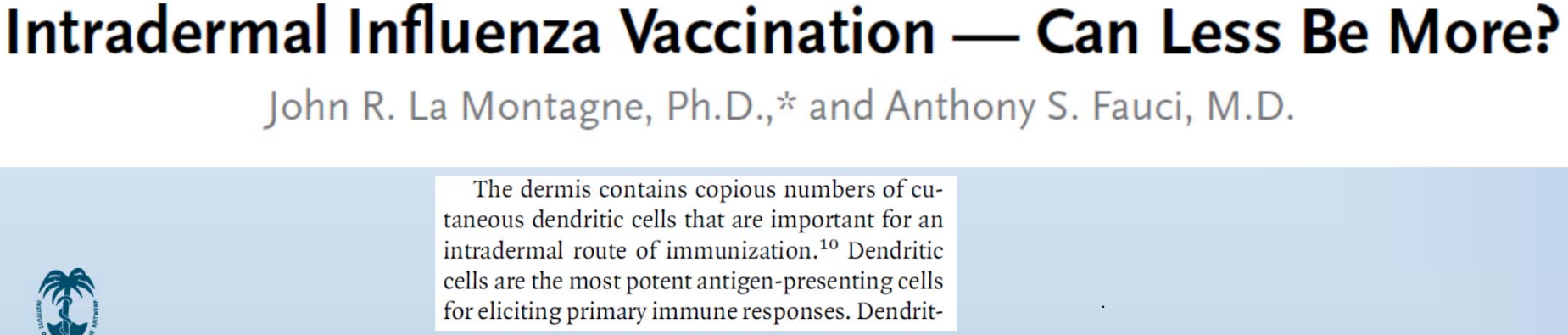

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Serum Antibody Responses after Intradermal Vaccination against Influenza

Robert B. Belshe, M.D., Frances K. Newman, M.S., Joan Cannon, R.N., Carol Duane, R.N., Ph.D., John Treanor, M.D., Christian Van Hoecke, M.D., Barbara J. Howe, M.D., and Gary Dubin, M.D.

N ENGL J MED 351;22 WWW.NEJM.ORG NOVEMBER 25, 2004


Intradermal Influenza Vaccination — Can Less Be More?

John R. La Montagne, Ph.D.,* and Anthony S. Fauci, M.D.

The dermis contains copious numbers of cutaneous dendritic cells that are important for an intradermal route of immunization.[10] Dendritic cells are the most potent antigen-presenting cells for eliciting primary immune responses. Dendrit-

Off-label vaccine dosing: intradermal injection (ID)

- Large clinical trials - studies: **Influenza ID - Rabies ID**

Rabies 21-28 day ID schedules Three visits	**3x 0,1ml ID** d0-d7-d21-d28	**N**	**Antibody response RFFIT = golden standard**	
Mills et al. JTM 2012	HDCV	420	94,5% ELISA day 28	Case series
Lau et al. TM&ID 2013	PCECV	54	94,5% ELISA day 28	Case series
Soentjens unpublished 2008-2015 Abstract CISTM 2015	HDCV-PCECV	498	82% RFFIT	Delay in serology testing Mean = 405 days

Off-label vaccine dosing: intradermal injection (ID)

- Large clinical trials - studies: **Influenza ID - Rabies ID**

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

CID 2013:56 (1 February)

CONCLUSIONS

Strong initial immune responses appear to induce strong booster responses, provided that sufficient time is taken between PreP and booster vaccinations. However, low initial responses also elicit booster responses above the WHO threshold. In addition, ID administration leads to higher booster responses than IM administration if equal doses are used. Booster responses following multiple dose ID PreP on 1 or 2 days are effective. Finally, boosters are more effective if 4 ID (0.1 mL) vaccinations are used compared with the routine (2 × 1.0 mL IM) schedule. Further studies investigating various

Interesting pathway

PrEP
2 x 0,1 ml ID One visit

PEP
4 x 0,1 ml ID One visit

Off-label vaccine dosing: intradermal injection (ID)

- Small pilot studies: **Yellow fever ID** - Hepatitis B ID - Meningitis ID

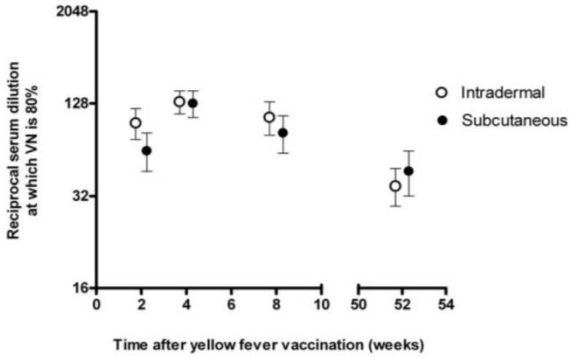
OPEN ACCESS Freely available online

PLoS one

Intradermally Administered Yellow Fever Vaccine at Reduced Dose Induces a Protective Immune Response: A Randomized Controlled Non-Inferiority Trial

Anna H. Roukens[1], Ann C. Vossen[2¤], Peter J. Bredenbeek[3], Jaap T. van Dissel[1], Leo G. Visser[1]*

1 Department of Infectious Diseases, Leiden University Medical Center, Leiden, The Netherlands, 2 Department of Virology, Erasmus University Rotterdam, Rotterdam, The Netherlands, 3 Department of Research Virology, Leiden University Medical Center, Leiden, The Netherlands



Vaccine 27 (2009) 2408–2409

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Short communication

Reduced intradermal test dose of yellow fever vaccine induces protective immunity in individuals with egg allergy

Anna H. Roukens[a,*], Ann C. Vossen[b], Jaap T. van Dissel[a], Leo G. Visser[a]

[a] Dept. of Infectious Diseases, Leiden University Medical Center, The Netherlands
[b] Dept. of Medical Microbiology, Leiden University Medical Center, The Netherlands

Figure 2. Protective virus neutralization after intradermal or subcutaneous vaccination against yellow fever. Comparison of reciprocal serum dilutions at which 80% of yellow fever virus is neutralized in constant virus – varying serum dilution test after intradermal and subcutaneous YF

	17D YF	Neutralizing Ab > 80%	Side effects			
			Local Erythema	Local Muscle pain	Systemic mylagia	Fever
N= 77	0,5 ml SC	100 %	25 (32%)	15 (19%)	27 (22%)	8 (10%)
N= 78	0,1 ml ID	100 %	63 (82%)	6 (8%)	12 (16%)	4 (5%)

Off-label vaccine dosing: intradermal injection (ID)

- Small pilot studies: Yellow fever ID - **Hepatitis B ID** - Meningitis ID

Vaccine 28 (2010) 4288–4293

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Intradermal hepatitis B vaccination in non-responders after topical application of imiquimod (Aldara®)

Anna H. Roukens[a,*], Ann C. Vossen[b], Greet J. Boland[c], Willem Verduyn[d], Jaap T. van Dissel[a], Leo G. Visser[a]

Non-responders Hep B vaccine IM Engerix 20 µg 1 ml after 2 series of three injections 2x (d0-1m-6m) IM	Fendrix B 20 µg 0,5 ml (d0-1m-6m)	HepsAB > 10 IU/ml 1 month after third ID injection
N= 21	5µg 0,125 ml ID	70 % response

Off-label vaccine dosing: intradermal injection (ID)

- Small pilot studies: Yellow fever ID - Hepatitis B ID - **Meningitis ID**

Nimenrix/Menveo		AB
N= 7	ID	100 % response

.

Jonker, Visser t al.
CISTM 2015.

Off-label vaccine dosing: accelerated schedules

Faster vaccine schedules: Hepatitis A-B IM

(d0 > m1 > m4-6) → **IM d0 - d7 - d21 - d365**

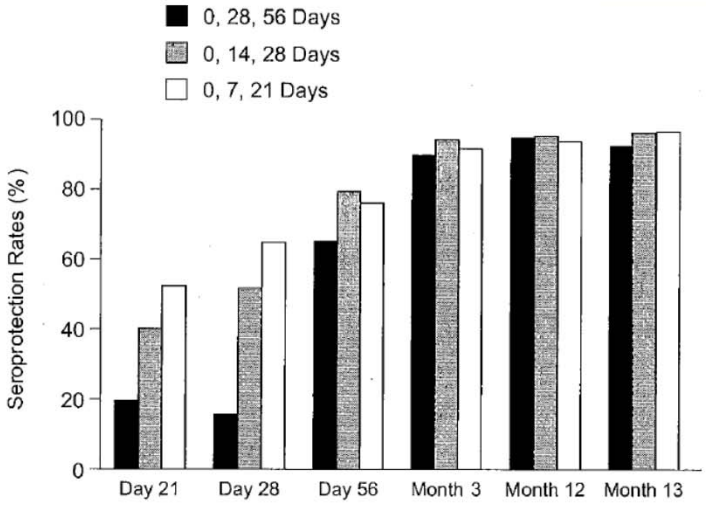


Figure 2 Seroprotection associated with an accelerated regimen of recombinant hepatitis B vaccine. (Reprinted with permission from *J Travel Med.*[38])

38. Bock HL, Loscher T, Scheiermann N, et al. Accelerated schedule for hepatitis B immunization. *J Travel Med.* 1995;2:213–217.

Off-label vaccine dosing: accelerated schedules

Faster vaccine schedules: Hepatitis A-B IM

(d0 > m1 > m4-6) → **IM d0 - d7 - d21 - d365**

N= 479
Control
N= 239
N= 240

ELSEVIER

Vaccine 20 (2002) 1157–1162

Vaccine

www.elsevier.com/locate/vaccine

A new accelerated vaccination schedule for rapid protection against hepatitis A and B

H.D. Nothdurft [a,*], M. Dietrich [b], J.N. Zuckerman [c], J. Knobloch [d], P. Kern [e], J. Vollmar [f], R. Sänger [f]

Hepatitis B: Accelerated Schedule

Vaccine schedule	Month 1	Month 2	Month 3
Twinrix 0,1,6 mo	34%	84%	
Twinrix 0,7,21 d	82%	85%	95%
Engerix 0,7,21 d	84%	85%	91%

Nothdurft et al.

Off-label vaccine dosing: accelerated schedules

Faster vaccine schedules: Hepatitis A-B IM

(d0 > m1 > m4-6) → **IM d0 - d7 - d14 - check Hep BsAb**

BE Defense	N	Antibodies Hep BsAB after 2-3 m
Engerix D0-7-14	38	94%
Twinrix D0-7-14	85	96%

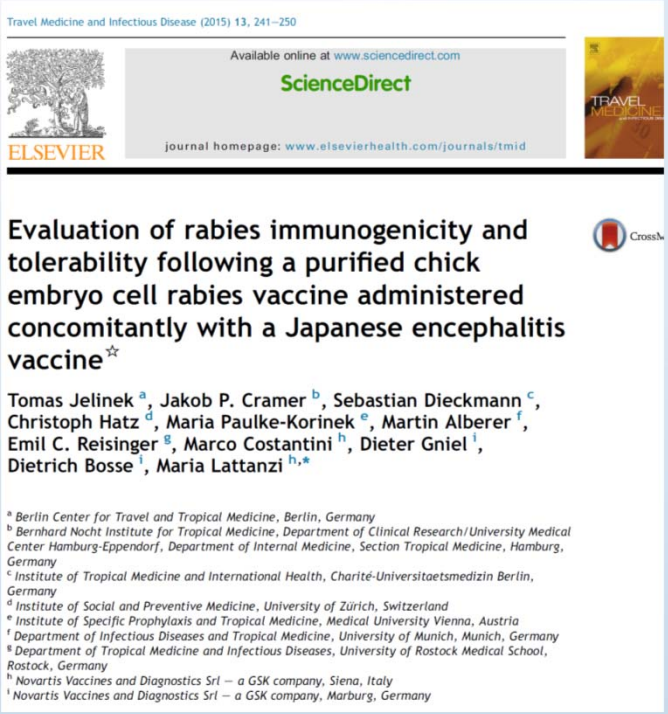
Soentjens Unpublished data

Off-label vaccine dosing: accelerated schedules

Faster vaccine schedules: Rabies IM

(IM/ID d0 > d7 > d21-28) → **Rabipur IM**

IM d0 - 3 - 7



Travel Medicine and Infectious Disease (2015) 13, 241–250

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevierhealth.com/journals/tmid

ELSEVIER

Evaluation of rabies immunogenicity and tolerability following a purified chick embryo cell rabies vaccine administered concomitantly with a Japanese encephalitis vaccine☆

Tomas Jelinek [a], Jakob P. Cramer [b], Sebastian Dieckmann [c], Christoph Hatz [d], Maria Paulke-Korinek [e], Martin Alberer [f], Emil C. Reisinger [g], Marco Costantini [h], Dieter Gniel [i], Dietrich Bosse [i], Maria Lattanzi [h,*]

[a] Berlin Center for Travel and Tropical Medicine, Berlin, Germany
[b] Bernhard Nocht Institute for Tropical Medicine, Department of Clinical Research/University Medical Center Hamburg-Eppendorf, Department of Internal Medicine, Section Tropical Medicine, Hamburg, Germany
[c] Institute of Tropical Medicine and International Health, Charité-Universitaetsmedizin Berlin, Germany
[d] Institute of Social and Preventive Medicine, University of Zürich, Switzerland
[e] Institute of Specific Prophylaxis and Tropical Medicine, Medical University Vienna, Austria
[f] Department of Infectious Diseases and Tropical Medicine, University of Munich, Munich, Germany
[g] Department of Tropical Medicine and Infectious Diseases, University of Rostock Medical School, Rostock, Germany
[h] Novartis Vaccines and Diagnostics Srl – a GSK company, Siena, Italy
[i] Novartis Vaccines and Diagnostics Srl – a GSK company, Marburg, Germany

Off-label vaccine dosing: accelerated schedules

Faster vaccine schedules: Rabies IM
(IM/ID d0 > d7 > d21-28) → **Rabipur IM**
IM d0 - 3 - 7

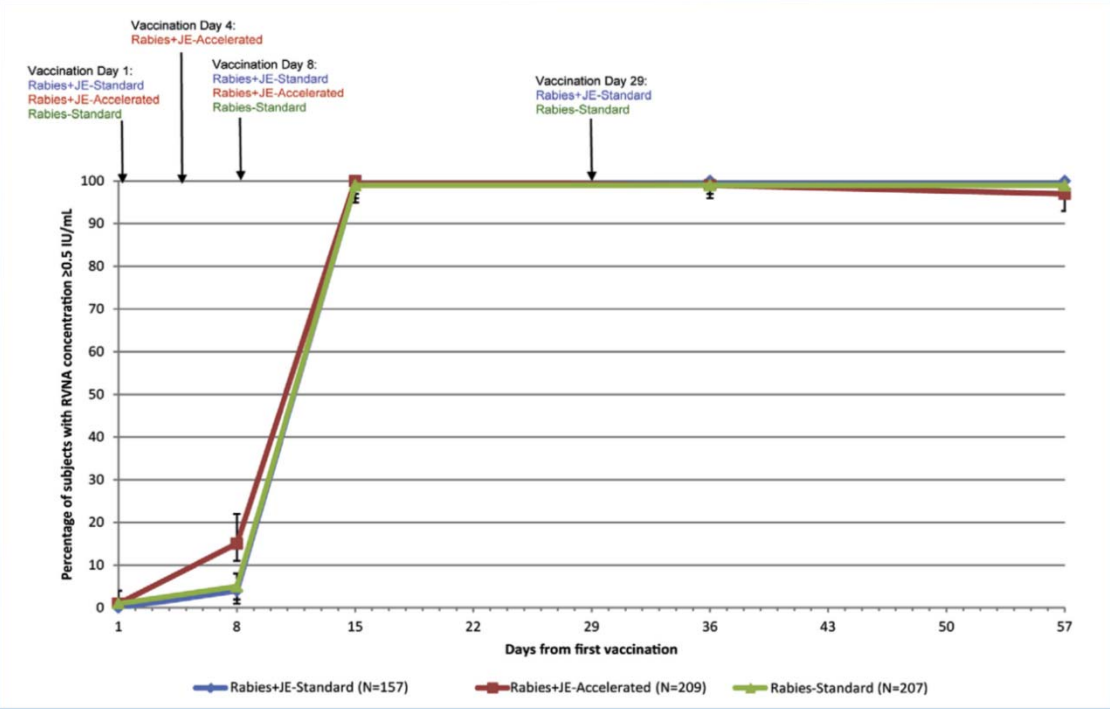
Randomized Clinical trial	Classic Schedule Rabies and JE (+ JE Ixiaro 28 day)	Classic Schedule Rabies only	Accelerated Schedule (+ JE Ixiaro 7 day)
N	167	221	217
Rabies Vaccine	1 ml PCECV	1 ml PCECV	1 ml PCECV
Dose	1 ml IM	1 ml IM	1 ml IM
Primary Schedule	D0 1x 1 ml D7 1x 1 ml D28 1x 1 ml	D0 1x 1 ml D7 1x 1 ml D28 1x 1 ml	D0 1x 1 ml D3 1x 1 ml D7 1x 1 ml
RFFIT	D35	D35	D35

Off-label vaccine dosing: accelerated schedules

Faster vaccine schedules: Rabies IM

(IM/ID d0 > d7 > d21-28) → **Rabipur IM**

IM d0 - 3 - 7

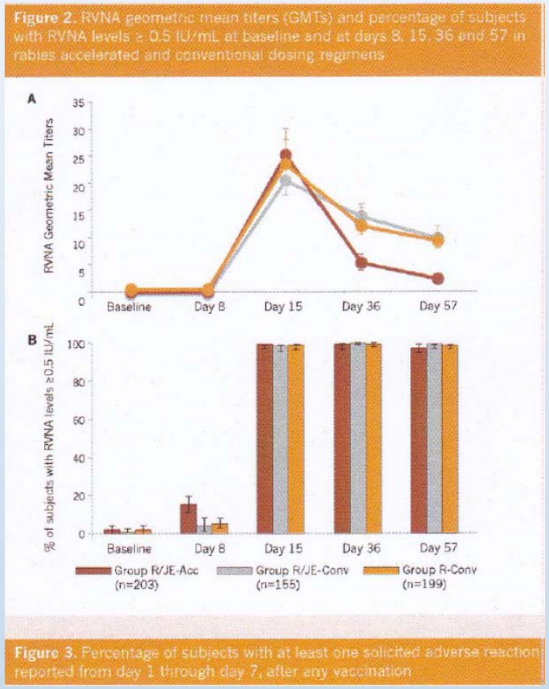


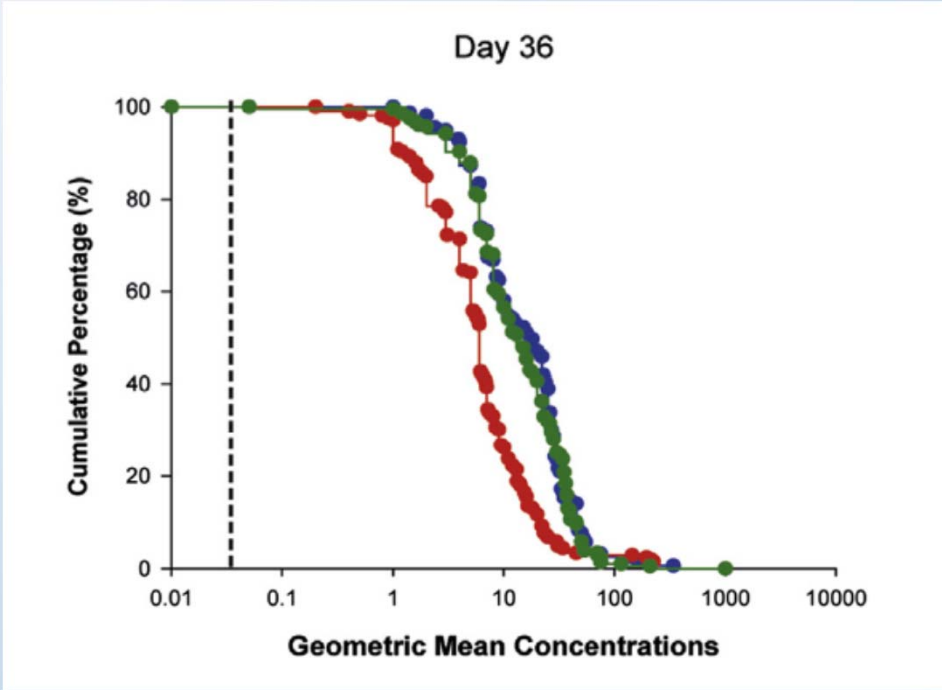
Off-label vaccine dosing: accelerated schedules

Faster vaccine schedules: Rabies IM

(IM/ID d0 > d7 > d21-28) → **Rabipur IM**

IM d0 - 3 - 7





Off-label vaccine dosing: accelerated schedules

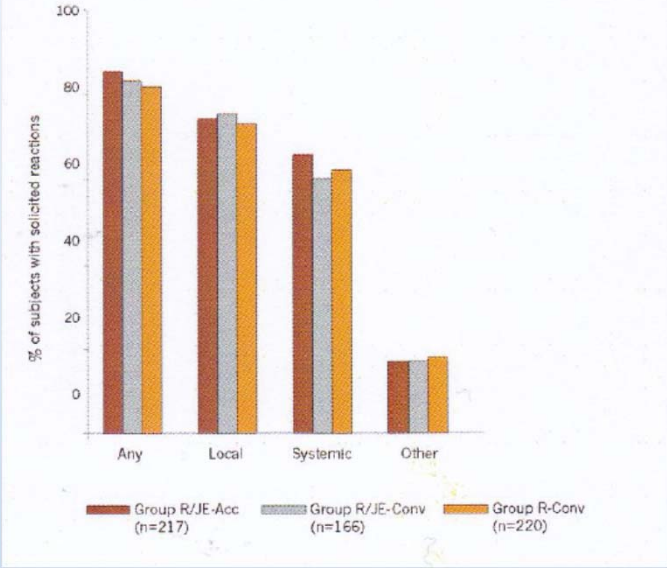
Faster vaccine schedules: Rabies IM

(IM/ID d0 > d7 > d21-28) →

Rabipur IM

IM d0 - 3 - 7

Figure 3. Percentage of subjects with at least one solicited adverse reaction reported from day 1 through day 7, after any vaccination



- Any local solicited reactions were reported by 73% to 75% of subjects across groups, systemic reactions were observed in 60% to 66% of subjects across groups (Figure 3).
- The most common local reaction after any vaccination was pain (51% to 57% across groups); the most common systemic reactions after any vaccination were fatigue (33% to 43% across groups) and headache (37% to 41% across groups). Severe reactions occurred in ≤ 3% (local) and ≤ 4% (systemic) of subjects across rabies groups.

Off-label vaccine dosing: accelerated schedules

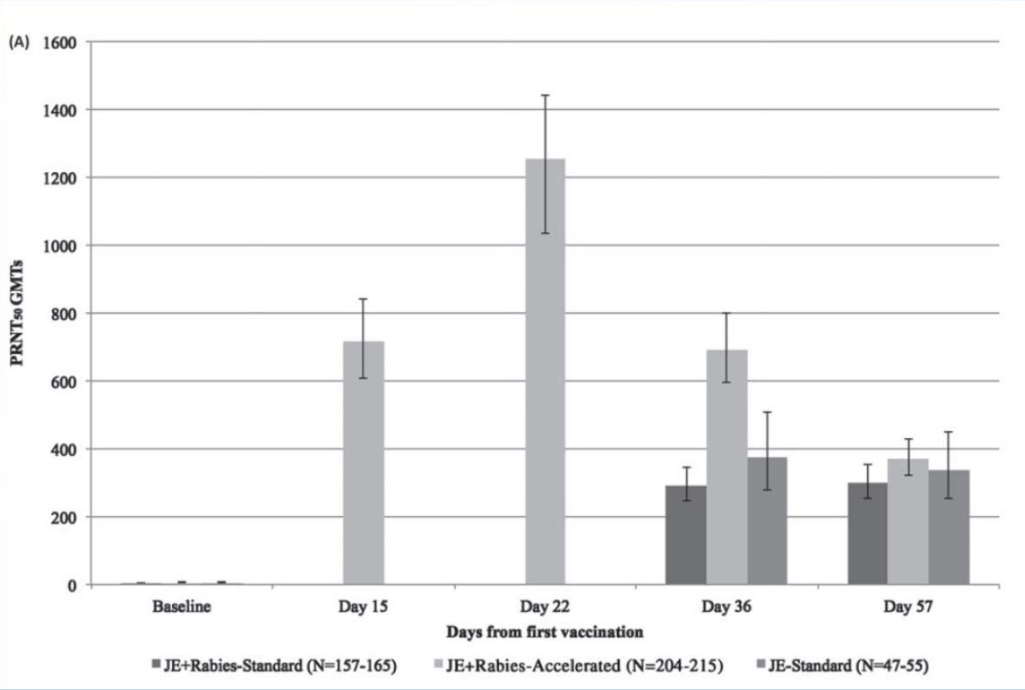
Faster vaccine schedules: Rabies IM
(IM/ID d0 > d7 > d21-28) → **Rabipur IM**
IM d0 - 3 - 7

Randomized Clinical trial	Classic Schedule (+ JE Ixiaro 28 day)	Classic Schedule	Accelerated Schedule (+ JE Ixiaro 7 day)
N	167	221	217
Rabies Vaccine	1 ml PCECV d0,7,28 IM	1 ml PCECV IM	1 ml PCECV d0,3,7 IM
RFFIT day 35		203/204 99%	203/206 99%
GMC day 35	11 (N= 157)	9,9 (N= 204)	?
Side effects	Systemic 60-66% Local 73-75%		

Off-label vaccine dosing: accelerated schedules

Faster vaccine schedules: Japanese encephalitis Ixiaro IM

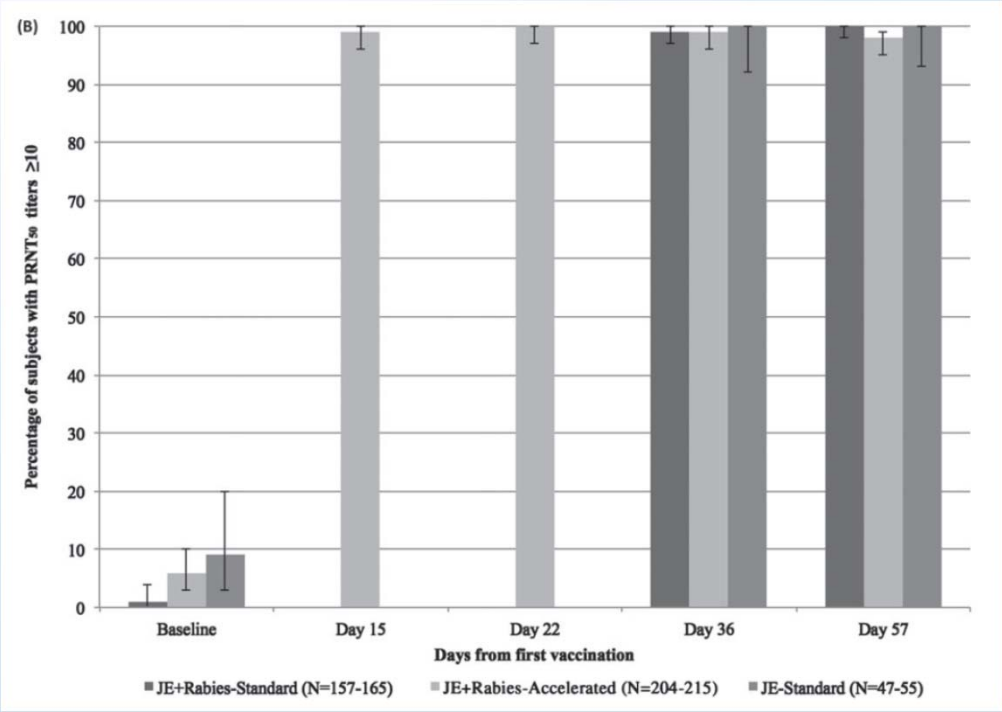
Ixiaro (d0 > d28 > y1-2) → **IM d0 - d7**



Off-label vaccine dosing: accelerated schedules

Faster vaccine schedules: Japanese encephalitis Ixiaro IM

Ixiaro (d0 > d28 > y1-2) → **IM d0 - d7**



Off-label vaccine dosing: accelerated schedules

Faster vaccine schedules: Japanese encephalitis

- **Ixiaro** **d0 - d7**

Available only in Asia

- **CDJ Vax®**

Live-attenuated **d0 - d365**
China Booster after one year

- **IMOJEV MD®**

Chimeric - Live attenuated **d0**
Sanofi Pasteur
No booster
55 dollar (Cambodja) - 47 dollar (Thailand) (personal communications)

Off-label vaccine dosing: accelerated schedules

Faster vaccine schedules: Tick Borne Encephalitis

(d0 > m1-3 > m9-12 > y3 > y5) → **d0 > d7 > d21**

d0 > d14 > d365

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Available online at www.sciencedirect.com

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Vaccine 25 (2007) 1470–1475

Vaccine

www.elsevier.com/locate/vaccine

Tick-borne encephalitis (TBE) vaccination: Applying the most suitable vaccination schedule

I. Schöndorf [a,*], J. Beran [b], D. Cizkova [b], V. Lesna [b], A. Banzhoff [a], O. Zent [a]

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Received 18 August 2006; accepted 18 October 2006
Available online 10 November 2006

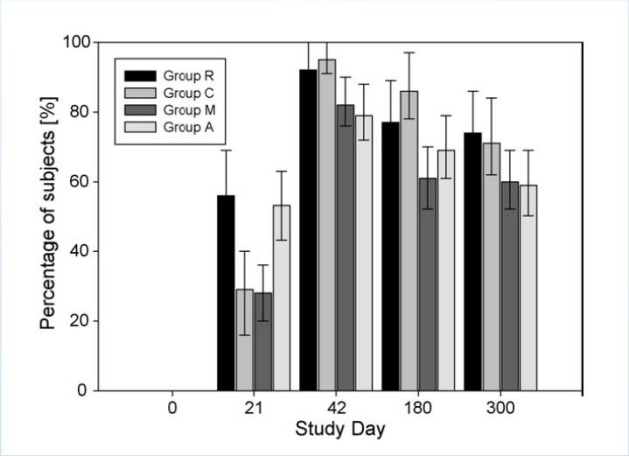
Off-label vaccine dosing: accelerated schedules

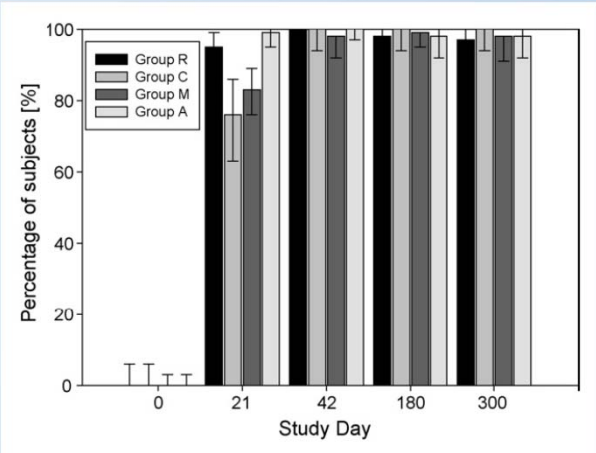
Faster vaccine schedules: Tick Borne Encephalitis

(d0 > m1-3 > m9-12 > y3 > y5) → **d0 > d7 > d21**

d0 > d14 > d365

Encepur Vaccine	Schedule	N AB Day 21	N AB Day 42
Group R N= 66	D0-7-21	95%	100%
Group C N= 66	D0-28-300	76%	100%
Group M N= 133	D0-21-300	83%	98,5%
Group A N= 133	D0-14-300	99%	100%





Rabies intradermal vaccinations in BE Defense

Simplifying Rabies PrEP schedules in BE troops

	Different Intradermal Rabies Pre-exposure Schedules	
N = 9205	started rabies vaccination since 2008	
N = 881	**4ID retrospectif**	
N = 489	**3ID retrospectif**	
N = 250	**3ID prospectif**	
N = 250	**2ID prospectif**	
N = 330	**1ID prospectif**	

Simplifying PrEP

Rabies pre-exposure prophylaxis (PrEP)

365 day intradermal schedule (4ID) in BE troops

N= 881

Neutralizing antibodies	Day +7 (372)
RFFIT > 0,5 IU/ml (WHO)	**881 (100%)**
RFFIT > 3,0 IU/ml	851 (96,6%)

RFFIT Rapid Fluorescent Focus Inhibition Test

Delay in serology testing

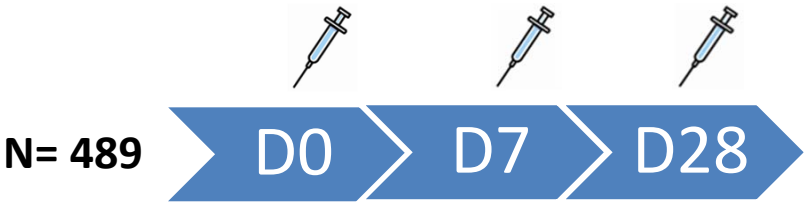
mean = **145** days (SD 6,3 / range 7 – 1603)

P Geeraerts, P Soentjens. ICID, Cape Town, April 2014.

Simplifying PrEP

Rabies pre-exposure prophylaxis (PrEP)

28 day intradermal schedule (3ID) in BE troops



Neutralizing antibodies	Day +7 (372)
RFFIT > 0,5 IU/ml (WHO)	**400 (82%)**
RFFIT > 3,0 IU/ml	171 (35%)
RFFIT < 0,5 IU/ml	**89 (18%)**

RFFIT Rapid Fluorescent Focus Inhibition Test

Delay in serology testing

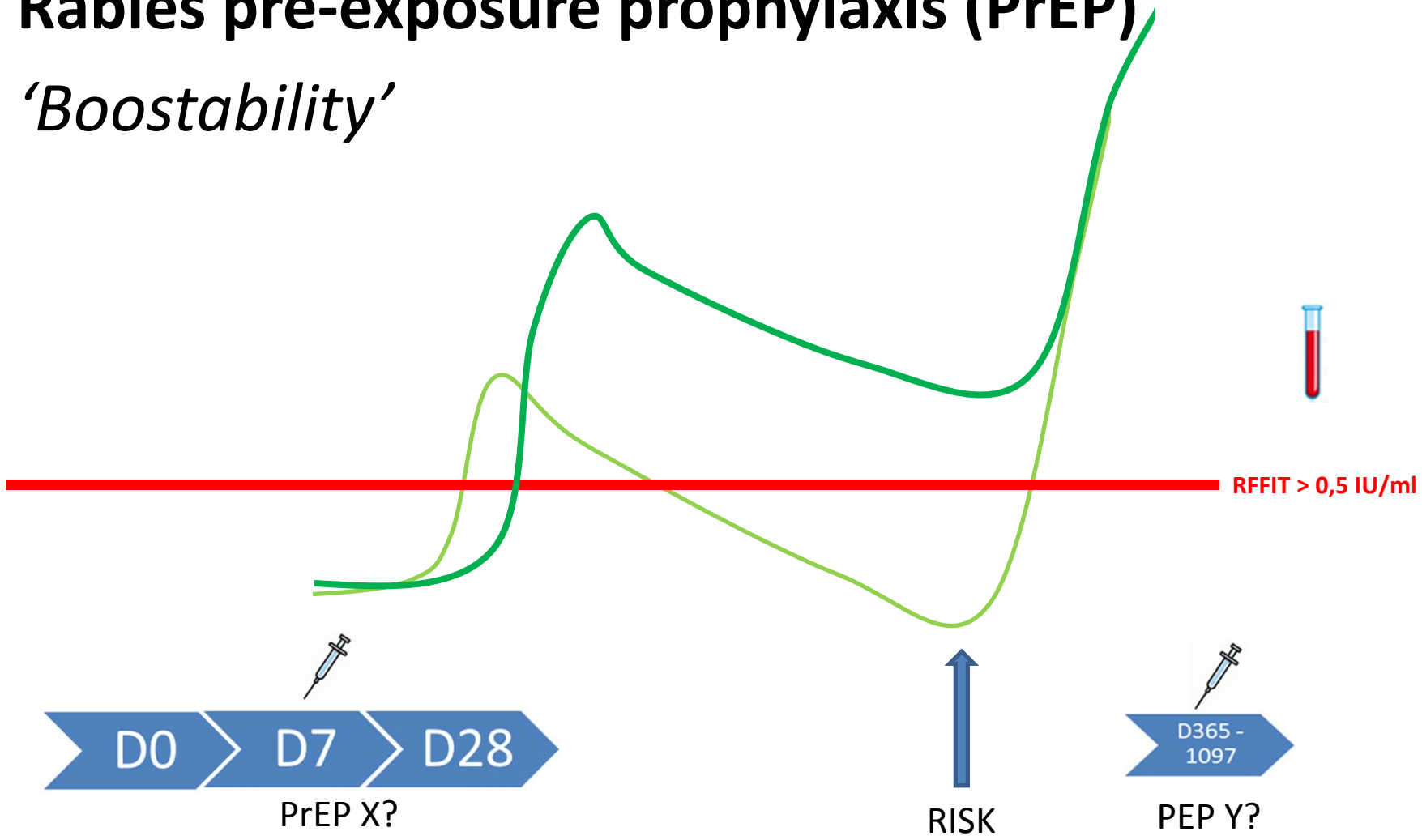
Mean = **405** days

Soentjens et al. CISTM, Quebec, May 2015.

Simplifying PrEP

Rabies pre-exposure prophylaxis (PrEP)

'Boostability'



Simplifying PrEP

Rabies pre-exposure prophylaxis (PrEP)

28 day intradermal schedule (3ID) in BE troops

+ 1 booster

N= 43/89 D0 D7 D28 **booster**

Neutralizing antibodies	Day +7
RFFIT > 0,5 IU/ml (WHO)	43 (100%)

RFFIT Rapid Fluorescent Focus Inhibition Test

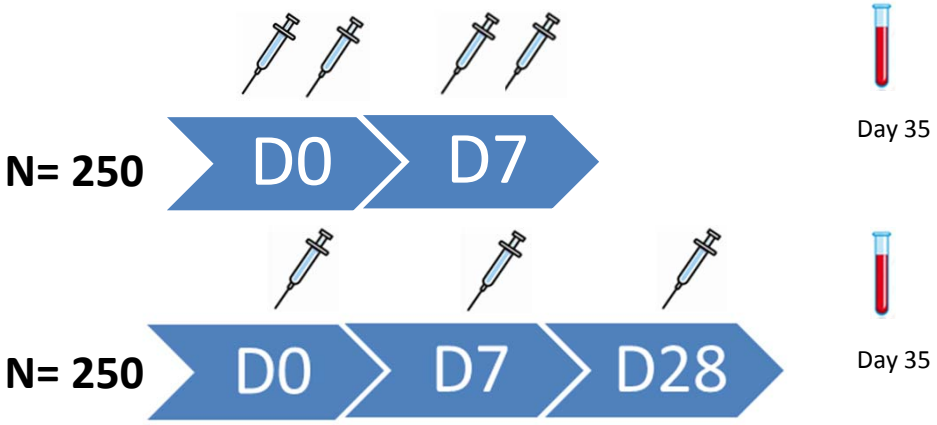
Soentjens et al. CISTM, Quebec, May 2015.

Simplifying PrEP

Rabies pre-exposure prophylaxis (PrEP)

7 day intradermal schedule (2ID)

Non-inferiority trial (EUDRACT 2011-001612-62)

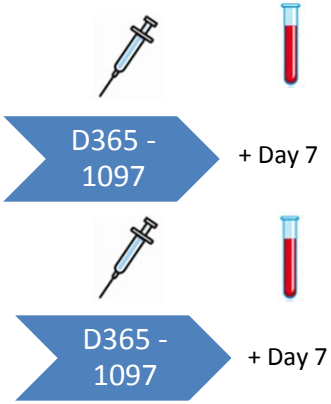


Day 35

Day 35

Neutralizing antibodies	Day 35
RFFIT > 0,5 IU/ml WHO	**241/241 (100%)**
RFFIT > 3,0 IU/ml	238 (99%)

Neutralizing antibodies	Day 35
RFFIT > 0,5 IU/ml WHO	**241/241 (100%)**
RFFIT > 3,0 IU/ml	236 (98%)



Pre-exposure prophylaxis

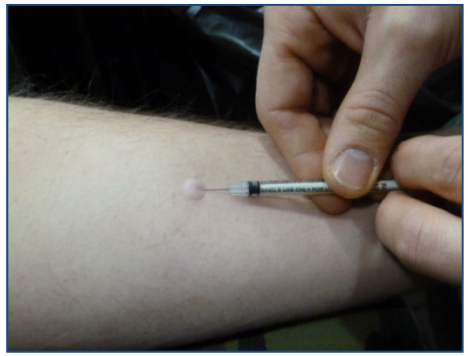
'Simulated' 1 injection post-exposure prophylaxis

Soentjens et al. NECTM, Bergen, June 2014.

Simplifying PrEP

ID4C

- Primary objective 2ID



Randomized Clinical trial	Classic Schedule	Accelerated Schedule
Vaccine	1 ml HDCV	1 ml 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	D365-D1097 D(365-1097) +7	D365-D1097 D(365-1097) +7

407/482 (84%) subjects completed the study protocol by April 2015

End of study foreseen in Nov 2015

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

Comparing accelerated Rabies Schedules
7 day ID versus 7 day IM

Off-label vaccine dosing: accelerated schedules

Randomized Clinical trial	Accelerated Schedule HDCV ID Non-commercial	Accelerated Schedule Rabipur IM PCECV Commercial
N	250	217
Median age	28 years	36,8 years
Gender	96,8% male	41% male
Rabies Vaccine	2 x 0,1 ml HDCV d d0 d0 - d7 ID	1 ml PCECV d0 - d3 - d7 IM
RFFIT day 35	241/241 100%	203/206 99%
GMC day 35	15,4	? (< 9,9)
Side effects Local	48%	73-75%
Side effects Systemic	9%	60-66%

Rabies risks in soldiers:
‘Be prepared before risk’

Pre-exposure prophylaxis (PrEP)	Intramuscular route (IM)	Intradermal route (ID)
Example	German troops	Belgian troops
Schedule	Day 0, 7, (21) 28, every 5 years	Day 0, 7, (21) 28
One dose	**1,0 ml**	**0,1 ml**
Total dose	**3,0 ml**	**0,3 ml cohorted**
Technique	**IM**	**ID (teaching)**
Short Immune response	**Very good > 95% (ID > IM)**	
Long-term immune response	**Good - Boostable Very responsive in days after 1 booster injection**	
Shorter schedules	1 commercial RCT	multiple reports - 2 RCTs
Side effects	Systemic reactions	Local irritation
Immunological control	Not done	Preferably
Administration (HDCV – PCVC)	Registered	Off-label

Warrel et al. Travel Med and Infectious Diseases 2012

‘Pittfals of ID schedules’

Pittfalls	Intradermal route (ID)
Vaccine	**HDCV (Sanofi Mérieux)** **PCECV (Rabipur – Rabivert)** PVCV VeroRab
	Cold Chain Safety
	Antigen potency (> 2,5 IU/ml) Batch variability (2,5 - 13,8 - …)
ID Technique Method	Trained personnel
	Injection site: Forearm
	Volume: 0,12 ml
RFFIT test	Lab accreditation report evaluation
	Transport method
Host	> 70 years Toddlers and infants Immunodeficiency

Objective Rabies OneDay

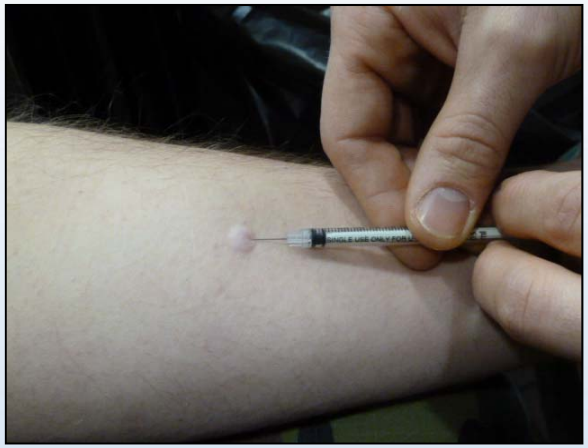
RABIES ONEDAY STUDY:

- **Non-commercial study**
  registered at EUDRACT 2014-00183612,
  sponsored by the ITM in Antwerp; ethical approval.

- Clinical trial with a low initial priming dose and comparing two different PEP vaccination schedules after one year

Methods

- Study Procedure



Randomized Clinical trial	Schedule PEP low dose	Schedule PEP
Vaccine	1 ml PCEV (Rabipur® Novartis)	
Dose	0,1 ml ID	
Primary Schedule	D0 2x 0,1 ml	
RFFIT	D14	
PEP booster	D365 2 x 0,1 ml ID	D365 4 x 0,1 ml ID
Total dose	0,4 ml ID	0,6 ml ID
RFFIT after booster	D372	D372

PCEV Purified Chicken Embryo cell vaccine; ID intradermal; D day; RFFIT: Rapid Fluorescent Focus Inhibition Test

Rabies ONEDAY

Rabies pre-exposure prophylaxis (PrEP)

1 day intradermal schedule (1ID)

Clinical trial Rabipur® (PCEV) (EUDRACT 2014-00183612)

Results: Demographics

- In total 238 of 330 subjects were included
  till end of March 2015
- Approximately +- 35% informed subjects not willing to participate

Demographics	N = 238	
Age distribution	**Median:** **Range:**	**28 years** **20-54 years**
Gender	**Male:** **Female:**	**92,5 %** **7,5 %**

Simplifying PrEP

Rabies pre-exposure prophylaxis (PrEP)
1 day intradermal schedule (1ID)

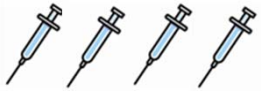
Clinical trial (EUDRACT 2014-0018361)

N= 330 D0

Day 14

Neutralizing antibodies	Day 14
RFFIT > 0,5 IU/ml WHO	**169/208 (81,25%)**
RFFIT > 3,0 IU/ml	34/208 (16%)

D365 + Day 7



D365 + Day 7

Pre-exposure prophylaxis

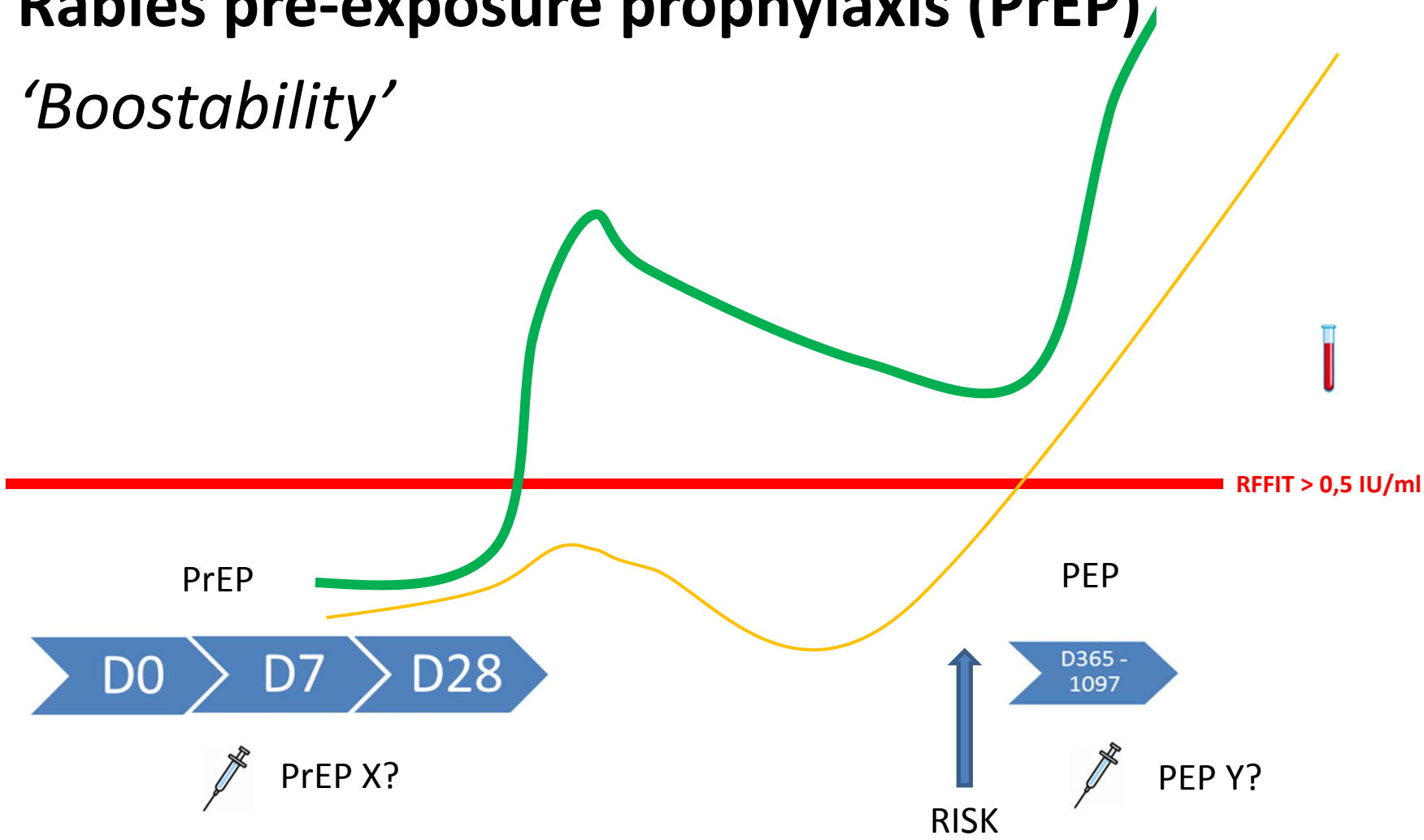
'Simulated' post-exposure prophylaxis

Soentjens et al. CISTM, Quebec, May 2015.

Simplifying PrEP

Rabies pre-exposure prophylaxis (PrEP)

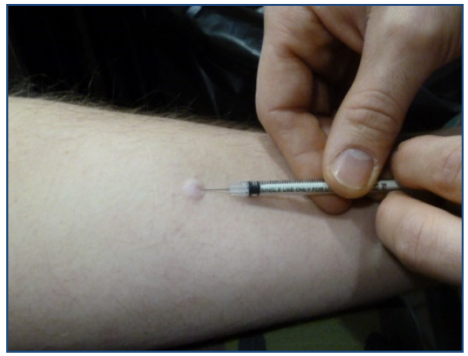
'Boostability'



Simplifying PrEP: Rabies ONEDAY

ID4C

- Primary objective 1ID



Randomized Clinical trial	Schedule PEP low dose	Schedule PEP
Vaccine	1 ml PCEV (Rabipur Novartis)	
Dose	0,1 ml ID	
Primary Schedule	D0 2x 0,1 ml D7 2x 0,1 ml	
RFFIT	D14	
PEP booster	D365 2 x 0,1 ml ID	D365 4 x 0,1 ml ID
Total dose	0,4 ml ID	0,6 ml ID
RFFIT after booster	D372	D372

End of study is foreseen end of Jun 2016

ID intradermal; D day; RFFIT: Rapid Fluorescent Focus Inhibition Test

Simplifying PrEP

Rabies PrEP in BE troops

N	Rabies Pre-exposure Schedule	RFFIT >0,5IU/ml	RFFIT after PEP
N = 9205	Started rabies vaccination since 2008		
N = 881	**4ID retrospectif** 	**100%**	
N = 489	**3ID retrospectif** 	**82%**	**100%**
N = 250	**3ID prospectif** 	**100%**	**?** end 2015
N = 250	**2ID prospectif** 	**100%**	**?** end 2015
N = 330	**1ID prospectif** 	**81%**	**?** mid 2016

Conclusion: Rabies Oneday Study

RABIES ONEDAY: promising results

169 (81,25%) of subjects had a sufficient initial antibody response on day 14 (> 0,5 IU/ml)

28 (13,5%) of subjects had a low initial but insufficient response on day 14 (> 0,2 IU/ml)

We expect fast increasing antibodies after booster injections (2015-2016)

Conclusion

Advising the last-minute traveller is challenging

Table 1 Considerations for risk assessment in the prioritisation of vaccination in travellers.

Travel-related considerations
Country(ies) of destination
Purpose of travel
Duration and type of travel
Mandatory or recommended requirement
Host-related considerations
Personal immune status
State of health
Age and specific contraindications for vaccination
Lifestyle and attitudes to risk of infection
Disease-related considerations
Associated morbidity/mortality
Available treatment options, including antibiotic resistance
Vaccine-related considerations
Efficacy
Tolerability
Schedule
Compliance/convenience
Cost

Zuckerman Travel Med Infect Dis 2003.

Conclusion

Advising the last-minute traveller is challenging

N	Accelerated Schedules
Rabies	IM d0 - d3 - d7 or ID d0 2x - d7 2x
JE	IM d0 - d7
Hep B	IM d0 - d7 - d21 (d14?)
TBE	IM d0 - d7 - d21 or IM d0 - d14
One single visit low dose ID injection	Influenza - Yellow fever – Rabies Meningitis? - HepatitisB?

Zuckerman Travel Med Infect Dis 2003.

Aknowledgements

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