PhD defense: **Dr Patrick Soentjens**

Simplifying rabies vaccination schedules

Friday, June 26, 2020, 16:00 – 19:00
ITG Campus Rochus, Aula Janssen
Sint Rochusstraat 43, 2000 Antwerpen

Keynote lecture

Declaration of Public Health Emergencies of International Concern:
Whether, When, and Why (not)?

Prof Dr Robert Steffen

University of Zurich and
University of Texas School of Public Health, Houston

Program

> Keynote : 16:00
> PhD defence : 17:00

Supervisors

Prof. dr. Emmanuel Bottieau
Institute of Tropical Medicine, Antwerp

Prof. dr. Pierre Van Damme
University of Antwerp
Faculty of Medicine and Health Sciences

Different intradermal and intramuscular regimens

INTRADERMAL REGIMEN

1^1ID	1-visit	0.1 mL	one site	
1^2ID	1-visit	0.1 mL	two sites	
1^4ID	1-visit	0.1 mL	four sites	
2^2ID	2-visit	0.1 mL	two sites	
3^1ID	3-visit	0.1 mL	one site	

INTRAMUSCULAR REGIMEN

1^1IM	1-visit	1.0 mL	one site	
2^1IM	2-visit	1.0 mL	one site	
3^1IM	3-visit	1.0 mL	one site	
5^1IM	5-visit	1.0 mL	one site	
5^1IM + HRIG	5-visit + 1-visit	1.0 mL + x mL	one site	+ in the wound
6^1IM	6-visit	1.0 mL	one site	

Patrick Soentjens

Simplifying rabies vaccination schedules

University of Antwerp
Faculty of Medicine
and Health Sciences

Thesis submitted for the degree
of Doctor in Medical Sciences
at the University of Antwerp

Antwerp, 2020
Supervisors: Prof. dr. Emmanuel Bottieau
Prof. dr. Pierre Van Damme

University of Antwerp
Faculty of Medicine
and Health Sciences

Simplifying rabies vaccination schedules

Vereenvoudigde rabies vaccinatieschema's

Thesis submitted in fulfilment of the requirements for
the degree of Doctor in Medical Sciences
at the University of Antwerp to be defended by

Proefschrift voorgelegd tot het behalen van de graad
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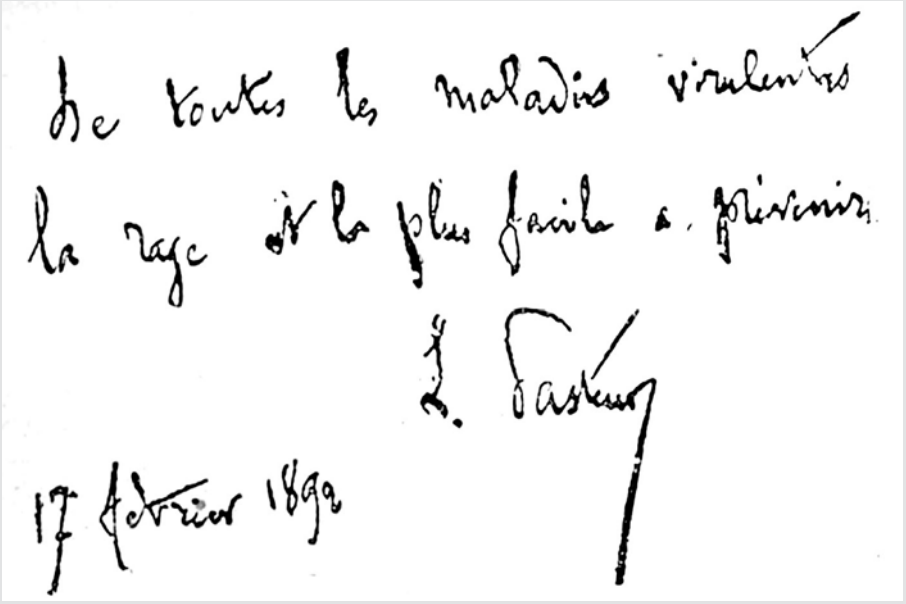
Universiteit Antwerpen te verdedigen door

Patrick Soentjens

Antwerpen, 2020
Supervisors: Prof. dr. Emmanuel Bottieau
Prof. dr. Pierre Van Damme



Louis Pasteur

Composition of the Doctoral Committee

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Colofon

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Faculteit Geneeskunde, Universiteit Antwerpen, Antwerpen 2020
Academic Thesis Universiteit Antwerpen – with summary in Dutch

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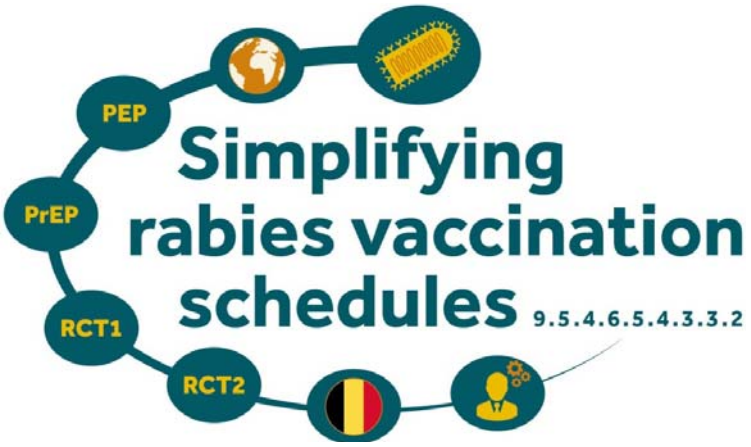
PEP
PrEP
RCT1
RCT2
Simplifying
rabies vaccination
schedules
9.5.4.6.5.4.3.3.2

Table of contents

List of Abbreviations

1^1ID	1-visit intradermal regimen, 0.1 mL, one-site
1^2ID	1-visit intradermal regimen, 0.1 mL, two-sites
1^3ID	1-visit intradermal regimen, 0.1 mL, one-site
1^4ID	1-visit intradermal regimen, 0.1 mL, four-sites
2^2ID	2-visit intradermal regimen, 0.1 mL, two-sites
3^1ID	3-visit intradermal regimen, 0.1 mL, one-site
1^1IM	1-visit intramuscular regimen, 1.0 mL, one-site
2^1IM	2-visit intramuscular regimen, 1.0 mL, one-site
3^1IM	3-visit intramuscular regimen, 1.0 mL, one-site
5^1IM	5-visit intramuscular regimen, 1.0 mL, one-site
6^1IM	6-visit intramuscular regimen, 1.0 mL, one-site

APC	Antigen presenting cells
EUDRACT	European Union Drug Regulating Authorities Clinical Trials Database
FAO	Food and Agriculture Organization
GARC	Global Alliance for Rabies Control
GAVI	Global Alliance for Vaccines and Immunization
GMT	Geometric mean titer
HRIG	Human Rabies Immunoglobulins
HDCV	Human diploid cell vaccine
ID	Intradermal
IM	Intramuscular
ITM	Institute of Tropical Medicine, Antwerp
LIC	Low-income countries
LMTs	Last-minute Travellers
NAb	Neutralizing antibodies
NITAG	
NK	Natural killer cells
OIE	World Organization for Animal Health
PEP	Post-exposure Prophylaxis
PI	Principal Investigator
PrEP	Pre-exposure Prophylaxis
PCECV	Purified chick embryo cell vaccine
PVRV	Purified Vero cell rabies vaccine
QAMH	Queen Astrid Military Hospital, Brussels
RCT	Randomized Clinical Trial
RFFIT	Rapid Fluorescent Focus Inhibition Test
RVNA	Rabies Virus Neutralizing Antibodies
SAGE	Strategic Group of Experts on Immunization
SHC	Superior Health Council
VFR	Visiting Friends and Relatives
WMA	World Medical Association
WVA	World Veterinary Association
WHO	World Health Organization

Chapter 1

Introduction

Rabies virus and fatal disease in humans

Rabies is one of the neglected tropical viral diseases prioritized by World Health Organization (WHO) and it is the infectious disease with the highest case-fatality rate (1). The human death toll is highest in Asia and Africa, with invariably fatal encephalitis in an estimated 60.000 people yearly (1-3) (Figure 1.1). The WHO Rabies modelling consortium predicts that more than 1 million deaths will occur in the 67 rabies endemic countries considered from 2020 to 2035, under status quo (4).

Dogs are responsible for up to 99% of human rabies cases, although other carnivores and bats can also transmit the disease (1, 2). Rural populations and children are disproportionately affected (5).

In Belgium, rabies only occurs in bats and - exceptionally - in (illegally) imported mammals. Since 1922, only imported cases have been detected in humans (6). Since July 2001, Belgium has been officially declared free from classical rabies in terrestrial animals (7).

The viruses causing rabies are lyssaviruses that are classified in three phylogroups containing in total 12 different species, of which the rabies virus species (phylogroup I) is the most prominent in dog-related human disease (6). Most other virus species has been isolated from bats. Rabies is spread through the bite or scratch of an infected animal. The incubation period can range between 1 to 12 weeks, but also to several years (1, 8). The virus infects almost exclusively the nerves of the host and then travels to the brain, where it causes classic furious or paralytic rabies and kills the host, usually owing to respiratory insufficiency (9). The genome of the lyssaviruses consists of a single-stranded, non-segmented, negative RNA molecule (1). The glycoproteine or G protein, a transmembrane pro-

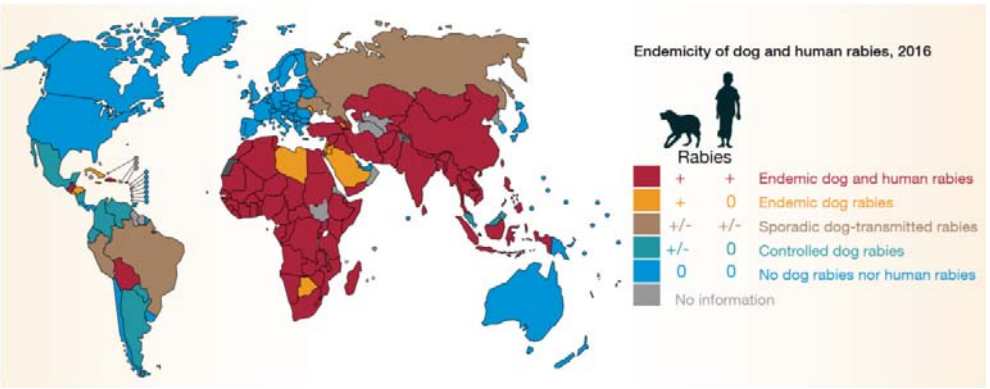

Figure 1.1. *Endemicity of dog mediated human rabies, 2018 (source WHO).*

tein and the only surface protein on the virus, plays a major role in rabies pathogenesis and for the induction of virus-neutralizing and protective antibodies (2).

The 'One Health' approach in endemic countries

In 2015, the WHO called for action by setting a global elimination target of zero human deaths due to dog-mediated rabies by 2030: "Zero by 30". In response to the goal 2030, WHO and partners (Food and Agriculture Organization (FAO), Global Alliance for Rabies Control (GARC), World Organization for Animal Health (OIE), World Veterinary Association (WVA) and World Medical Association (WMA)) have formed the United Against Rabies collaboration to provide global leadership to catalyse and empower countries to prevent human rabies deaths (5).

Areas of priority actions in Asia and Africa are: improving the laboratory-based surveillance, the pathogen detection and characterization; the access to human rabies prophylaxis; to veterinary vaccines; the implementation of canine vaccination; and the oral vaccination of free-ranging community dogs (10). Investment in the following areas will assure success of the plan: increased awareness at all levels of society; dog vaccination campaigns and population management and provision of human biologicals for post- and pre-exposure prophylaxis (5). The Global Strategic Plan to End Human Deaths from Dog-Mediated Rabies by 2030 aims to ensure equitable access to rabies post-exposure prophylaxis (PEP) vaccines by 2030, but will probably not meet its targets (3). The Global Alliance for Vaccines and Immunization (GAVI) plan puts a focus on immunizing children who are not currently receiving adequate vaccine coverage (4). Almost half of undervaccinated children live in just 16 countries, where lack of access, conflict, and displacement are important barriers to vaccination (4). However, none of the objectives of GAVI can be achieved without adequate funding (4).

Post-exposure prophylaxis in travellers

Travel to many endemic countries is associated with a very low risk of rabies (< 1/1.000.000) (11). Only 60 cases of human rabies in international travellers were reported over a period of 22 years (12). In contrast, the need to start prompt post-exposure prophylaxis for an animal injury in travellers is very high (> 1/1000 and < 1/100) (11).

Incidentally, within the last three years 6 fatal cases were reported in Europeans after travel to Sri Lanka, Morocco (two cases), The Philippines,

Cambodia and Tanzania respectively, of which four were related to exposure to dogs and two to cats (13, news reports). The last travellers case received timely PEP without HRIG overseas in November 2019 without effect.

The World Health Organization (WHO) strictly recommends to immediately (within days) initiate rabies postexposure prophylaxis (PEP) with or without human rabies immunoglobulins (HRIG), after an individual risk assessment (Table 1.1, available preventive tools) (1, 2, 14). HRIG administration serves to neutralize the virus locally, prevent its spread and span the period of the 7 to 10 days necessary to develop adequate antibodies response after rabies vaccination (1). Notably, HRIG are expensive and their availability is low in endemic countries, frequently resulting in stressful situations following an animal-related injury abroad. Even when HRIG are available, a lack of medical awareness of their importance in post-exposure prophylaxis means that its use is often not considered (8).

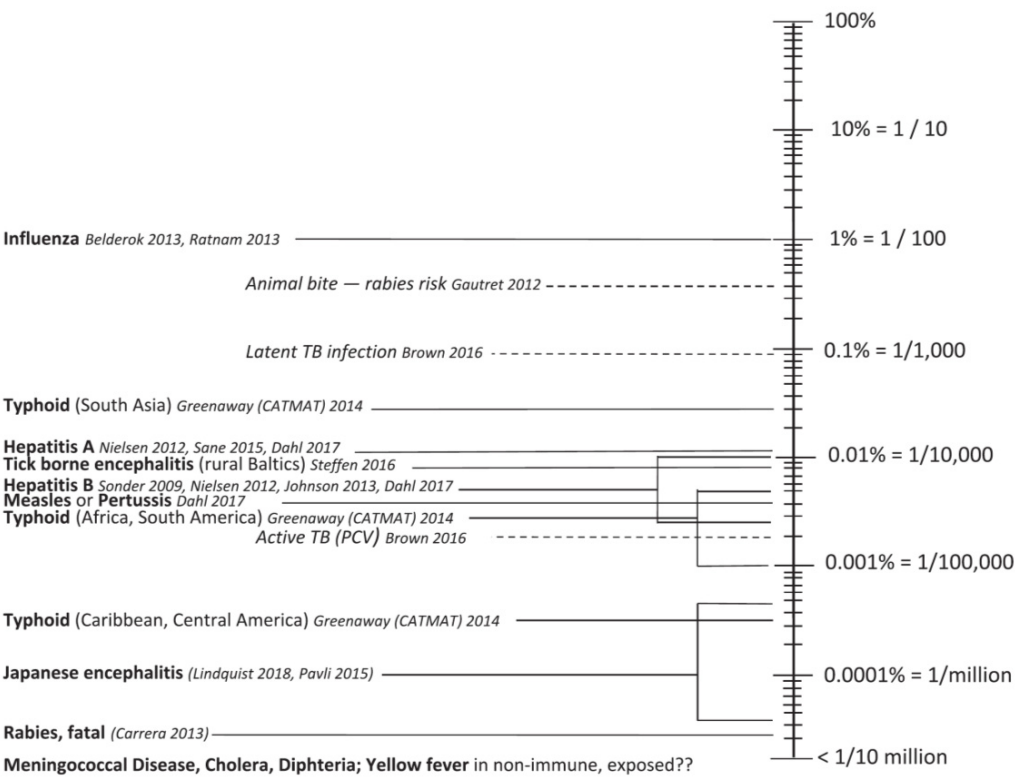

Figure 1.2. *Vaccine preventable disease travel health risks: estimated incidence per month in lower income countries among no-immunes (12).*

Human rabies immunoglobulins (HRIG) are only needed in non-rabies-vaccinated individuals and mainly indicated for category III lesions encountered by an at-risk animal (e.g. dog, monkey, cat, fox) in an endemic region (e.g. Asia or Africa) (1, 2). Category III lesions are defined as single or multiple transdermal bites or scratches of animals, licks on broken skin, or contamination of mucous membrane with saliva from licks. Of note, a category III exposure also corresponds to any direct contact with bats (with or without a skin lesion) (1, 2). Passive immunization with (HRIG) (20 IU/kg of Berirab® vials of 2.0 mL or 5.0 mL) is in general performed by injection in and around the wound and the remaining volume in the adjacent limb (1-2). In addition, HRIG should be administered as soon as possible and preferably within 2 days after a potential rabies risk, and not anymore 7 days after the start of rabies vaccination (1).

Additional active immunization with five injections of 1.0 mL rabies vaccine are administered at day 0, 3, 7, 14 and 28 (5^1IM PEP schedule: 1 intramuscular injection (IM) during five different visits)(5^1IM) (1). In Belgium, antibody titers by rapid fluorescent focus inhibition test (RFFIT) should be always measured in a subject receiving PEP with HRIG, preferably 10 days after the last vaccine dose (usually at day 38 post-initial injection). The test is offered for free by the national reference laboratory (14). A correlate of protection is defined as a titer of the neutralizing antibody test (RFFIT) of > 0.5 IU/mL 14 to 28 days following the last rabies vaccine injection (1, 2, 14). However in Belgium, an adequate antibody response is stricter with a titer of > 5.0 IU/mL in case of bat-related exposure and > 3.0 IU/mL in case of exposure to other animals (14).

Pre-exposure prophylaxis in travellers

Pre-exposure prophylaxis (PrEP) using rabies vaccine is key in rabies prevention and is not often administered. Since 1985 different robust and safe inactivated rabies vaccines are on the market: such as the purified chick embryo cell vaccine (PCECV), human diploid cell vaccine (HDCV) and purified vero cell vaccine (PVRV) (15).

Initial priming with vaccines, defined as PrEP, sometimes occurring long before exposure to effective rabies risk, substantially simplifies the post-exposure prophylaxis (PEP) procedures required in case of an animal bite (no need for immunoglobulin administration, and only 2 vaccine injections (2^1IM) are needed instead of 5 (5^1IM)) (1,2). Other important advantages

of the PrEP priming strategy include higher and more rapid anamnestic responses, and a higher affinity to specific antibodies against rabies virus following a PEP booster vaccination (16-18).

PrEP with rabies vaccine is recommended under the new WHO guideline for individuals at high risk for exposure to rabies due to their occupation, travel, and/or residence in an endemic setting with limited access to timely, adequate PEP (2). Particularly for travellers (including expatriates), rabies PrEP is often not planned in a timely manner prior to departure. Moreover, rabies PrEP schedules are not included in standard child vaccination schemas in high endemic setting (4).

In the literature, pre-exposure intradermal (ID) vaccination for rabies has proven to be as effective for pre-exposure prophylaxis as intramuscular (IM) vaccination (13, 19-21). These schedules consisted of injections on day 0, 7, 28 and 365 (4-visit) (till 2012) and on day 0, 7 and 28 (3-visit) (till 2018) with a dose of 0.1 mL and 1.0 mL by ID and IM route respectively. Intradermal administration of these vaccines offers an equally safe alternative, yet requires less vaccine antigen content. Intradermal administration of low-

Table 1.1. *Overview of available prevention tools against rabies in Belgium.*

Available tools in prevention													
Rabies awareness **Avoidance of risk**													
Rabies PrEP before risk Rabis vaccines: PCECV (purified chick embryo cell vaccine - HDCV (human diploid cell vaccine) - PVRV (purified Vero cell vaccine)													
Washing with water and soap 15' **Desinfection**													
Rabies PEP following PrEP													
Rabies PEP without PrEP **RFFIT testing > 3.0 IU/mL**													
Vaccine schedules	**PrEP**	**Volume**	**Day 0**	**Day 7**	**Day 28**	**PEP**	**Volume**	**Day 0**	**Day 3**	**Day 7**	**Day 21**	**Day 28**	**Tot Vol**
Classical PrEP IM regimen (3 visits) with PEP IM (2 visits)	**3^{1}IM**	3 x 1.0 mL				**2^{1}IM**	2 x 1.0 mL						5.0 mL
PEP IM: schedule without HRIG (3 visits - 4 injections) (category II lesion)						**3^{211}IM**	4 x 1.0 mL						4.0 mL
Standard PEP IM (5 visits) with HRIG (category III lesion)						**5^{1}IM** + **HRIG**	5 x 1.0 mL						5.0 mL + 2 to 8 mL +RFFIT

RFFIT Rabies Fluorescent Focus Inhibition Test

Intradermal injection *Intramuscular injection* *Rabies immunoglobulines*

Risk category II is defined as superficial lesions from scratches or grazes, without bleeding and category III as a single or multiple bites or scratches that penetrate the dermis.

dose vaccines indeed enhances immunogenicity by rapid trafficking of antigen to antigen presenting cells (APC) in the papillary dermis. Activated APC drain to lymph nodes where subsequent T-cell and B-cell activation and initiation of an adaptive immune response occurs (22, 23). Moreover periodic PrEP booster injections (every 5 years), although mentioned in the package insert, are not recommended anymore since 2002 by the WHO (1, 2).

Primary pre-exposure vaccination with rabies vaccine will enhance the innate and naive immune response after antigen challenge which results in low levels of antigen-specific IgG levels after one week (21).

The primed and thus the "trained" immune system can secondly evoke very enhanced responses to additional booster PEP doses after re-challenge with PEP booster doses (24-26). Such responses are provoked by the stimulation history during primary vaccination (= priming) with the formation of rabies antigen specific memory B cells and T follicular helper cells (24). After re-challenge, high levels rabies-specific IgG antibodies are produced within a few days by rapid plasma cell differentiation and secondary germinal centre responses (24, 25).

Intradermal PrEP regimens, although exceptionally used, have been successfully introduced for pre-exposure prophylaxis in countries such as Thailand, Canada, Australia and the Netherlands. Nevertheless, with a schedule of 3 injections in 28 days, time is often lacking to give vaccination before travel: a 2-visit schedule over 7 days or a 1-visit schedule is less time consuming and improves compliance and were evaluated in some observational studies over the years (16, 18, 27-31).

A recent systematic review of the anamnestic responses following booster PEP doses (boostability) after previous IM and ID rabies PrEP vaccination sessions (3-visit and 2-visit), highlighted a 100% vaccinal efficacy (neutralizing antibodies (NAb) > 0.5 IU/mL) following booster PEP doses (32). We can conclude that various combinations of PrEP and PEP regimens are highly immunogenic. In addition, the accelerated IM and ID PrEP regimens (2-visit) showed very promising geometric mean titer (GMT) levels following booster PEP doses (59.87 IU/mL versus 17.64 IU/mL respectively) (32). However, the methodology of the studies was very different (in populations (very young children in some groups), in vaccine brand, in injected total vaccine volumes (between 0.75 - 3 mL and 0.3 - 0.4 mL for the IM group and ID group respectively), in neutralizing antibody testing and in timing for serology testing after booster doses). This makes some compari-

sons difficult. In addition, the 4 included studies that evaluated boostability following a 2-visit IM or ID PrEP regimen were published over a large time span, between 1993 and 2009 (33-37).

The travel market of last minute holidays and trips to remote areas has expanded enormously. Until now, most travellers in Belgian Travel clinics are still vaccinated via the intramuscular route. Frequently, there is not enough time before departure or practical problems arise to complete the classical PrEP schedule of 28 days; thus an effective and shorter schedule would be very practical with the primary aim of wider acceptance and use in international travellers, especially in children.

For all these reasons, shortened, simple, acceptable, immunogenic and economical ID regimens which are compliant with the WHO requirements on vaccination, would be preferable over the classical vaccination schedule of 28 days.

Research objectives

In this thesis we focus on intradermal vaccination schedules in healthy Belgian soldiers. We want to evaluate shortened low-dose intradermal rabies vaccine schedules by decreasing the amount of visits and dosages for PrEP.

Also we want to study if single-visit booster PEP vaccinations (single shot, double shot or four shots) gives good amnestic responses in an initially primed cohort.

We defined different research questions and objectives:

To assess the use of human rabies immunoglobulins in a single centre in Antwerp, Belgium (Chapter 2).
To evaluate retrospectively the coverage of rabies PrEP in expatriate children in a single centre in Antwerp, Belgium (Chapter 2).
To evaluate retrospectively the immune responses following different ID PrEP regimens and their flexibility after a booster dose in a single centre in Brussels, Belgium (Chapter 3).
Is an accelerated two-dose two-visit 7-day intradermal PrEP regimen (2^2ID) non-inferior to the classical one-dose three-visit 28-day regimen (3^1ID) in producing a post-booster protective antibody response (Chapter 4)?
Is a two-dose single-visit intradermal PEP (1^2ID) comparable to a four-dose single-visit intradermal PEP regimen (1^4ID) after a two-dose single-visit PrEP regimen (1^2ID) in producing a post-booster protective antibody response (Chapter 5)?
To describe the implementation of new guidelines for PrEP and PEP in Belgium (Chapter 6).

References

1. WHO Background Paper: proposed revision of the policy on rabies vaccines and rabies immunoglobulins: prepared by the SAGE Working Group on Rabies vaccines and immunoglobulins and the WHO Secretariat. Sep 2017. http://www.who.int/immunization/sage/meetings/2017/october/1_Background_paper_WG_RABIES_final.pdf. Accessed 7 Nov 2019.
2. WHO Expert Consultation on Rabies: third report: WHO Technical Report Series N°1012. Apr 2018. http://apps.who.int/iris/bitstream/handle/10665/272364/9789241210218-eng.pdf?ua=1. Accessed 7 Nov 2019.
3. Zero by 2030: the Global Strategic Plan. https://apps.who.int/iris/bitstream/handle/10665/272756/9789241513838-eng.pdf?ua=1. Accessed 7 Nov 2019.
4. WHO Rabies Modelling Consortium. The potential effect of improved provision of rabies post-exposure prophylaxis in Gavi-eligible countries: a modelling study. Lancet Infect Dis. 2019;19(1):102-111.
5. Abela-Ridder B. Preface on rabies special issue. Vaccine. 2019;37 Suppl 1:A2.
6. Vanhoof R, Costy F. Rabies prophylaxis. Acta Clin Belg. 1996;51(5):328-39.
7. Besch A. Two more countries rabies-free in Europe: the Grand Duchy of Luxembourg and Belgium. In: WHO rabies bulletin Europe 2001. http://www.who-rabies-bulletin.org/q2_2001/frame2_01.html. Accessed 7 Nov 2019.
8. Fooks AR, Banyard AC, Horton DL, Johnson N, McElhinney LM, Jackson AC. Current status of rabies and prospects for elimination. Lancet. 2014;384(9951):1389-99.
9. Hemachudha T, Ugolini G, Wacharapluesadee S, Sungkarat W, Shuangshoti S, Laothamatas J. Human rabies: neuropathogenesis, diagnosis, and management. Lancet Neurol. 2013:12:498-513.
10. Rupprecht CE, Kuzmin IV, Yale G, Nagarajan T, Meslin FX. Priorities in applied research to ensure programmatic success in the global elimination of canine rabies. Vaccine. 2019;37 Suppl 1:A77-A84.
11. Carrara P, Parola P, Brouqui P, Gautret P. Imported human rabies cases worldwide 1990-2012. PLoS Negl Trop Dis. 2013;7(5):e2209.
12. Steffen R. Travel vaccine preventable diseases-updated logarithmic scale with monthly incidence rates. J Travel Med. 2018;25(1).
13. WHO rabies bulletin: news. https://www.who-rabies-bulletin.org/news/three-imported-human-rabies-cases-reported-europe-within-last-three-months. Accessed 12 Dec 2019.
14. Soentjens P, Burm C, Declerq S, Croughs M, Maniewski U, Theunissen C, Huits R, Florence E, Brosius I, Kenyon C, Van Griensven J, Van Ierssel S, Van den Broucke S, Clerinx J, Lynen L, Balliauw K, Van Gucht S, Van Esbroeck M, Vlieghe E, Bottieau E, Van Herrewege Y. The use of human rabies immunoglobulins in Belgium: a single-centre retrospective study. Acta Clin Belg. 2019:1-7.
15. Warrell MJ. Current rabies vaccines and prophylaxis schedules: preventing rabies before and after exposure. Travel Med Infect Dis. 2012;10(1):1-15.

16. Khawplod P, Wilde H, Benjavongkulchai M, Sriaroon C, Chomchey P. Immunogenicity study of abbreviated rabies preexposure vaccination schedules. J Travel Med. 2007;14:173-6.
17. Tantawichien T, Benjavongkulchai M, Limsuwan K, Khawplod P, Kaewchompoo W, Chomchey P, Sitprija V. Antibody response after a four-site intradermal booster vaccination with cell-culture rabies vaccine. Clin Infect Dis. 1999;28(5):1100-3.
18. Jonker EFF, Visser LG. Single visit rabies pre-exposure priming induces a robust anamnestic antibody response after simulated post-exposure vaccination: results of a dose-finding study. J Travel Med. 2017;24(5):1-8.
19. Plotkin SA. Rabies vaccine prepared in human cell cultures: progress and perspectives. Rev Infect Dis. 1980;2(3):433-48. Review.
20. Kessels JA, Recuenco S, Navarro-Vela AM, Deray R, Vigilato M, Ertl H, Durrheim D, Rees H, Nel LH, Abela-Ridder B, Briggs D. Pre-exposure rabies prophylaxis: a systematic review. Bull World Health Organ 2017; 95(3):210-219C.
21. Recuenco S, Warnock E, Osinubi MOV, Rupprecht CE. A single center, open label study of intradermal administration of an inactivated purified chick embryo cell culture rabies virus vaccine in adults. Vaccine. 2017; 35(34):4315-4320.
22. Kurosaki T, Kometani K, Ise W. Memory B cells. Nat Rev Immunol. 2015;15(3):149-59.
23. Inoue T, Moran I, Shinnakasu R, Phan TG, Kurosaki T. Generation of memory B cells and their reactivation. Immunol Rev. 2018;283(1):138-149.
24. Blok BA, Arts RJ, van Crevel R, Benn CS, Netea MG. Trained innate immunity as underlying mechanism for the long-term, nonspecific effects of vaccines. J Leukoc Biol. 2015;98(3):347-56.
25. Steinman RM, Pope M. Exploiting dendritic cells to improve vaccine efficacy. J Clin Invest. 2002;109:1519-26.
26. Dubois B, Bridon JM, Fayette J, et al. Dendritic cells directly modulate B cell growth and differentiation. J Leukoc Biol. 1999;66:224-30.
27. Mills D, Lau C, Fearnley E, Weinstein P. The immunogenicity of a modified intradermal pre-exposure rabies vaccination schedule - A case series of 420 travellers. J Travel Med. 2012;18:327-32.
28. Lau CL, Hohl N. Immunogenicity of a modified intradermal pre-exposure rabies vaccination schedule using a purified chick embryo cell vaccine: an observational study. Travel Med Infect Dis. 2013;11(6):427-3.
29. De Pijper CA, Boersma J, Terryn S, Van Gucht S, Goorhuis A, Grobusch MP, Stijnis C. Rabies antibody response after two intradermal pre-exposure prophylaxis immunizations: An observational cohort study. Travel Med Infect Dis. 2018;22:36-39.
30. Khawplod P, Jaijaroensup W, Sawangvaree A, Prakongsri S, Wilde H. One clinic visit for pre-exposure rabies vaccination (a preliminary one year study). Vaccine. 2012;30:2918-20.
31. Wieten RW, Leenstra T, van Thiel PPA, van Vugt M, Stijnis C, Goorhuis A, Grobusch MP. Rabies Vaccinations: are abbreviated intradermal schedules the future? Clin Infec Dis. 2012:1-6.
32. Langedijk AC, De Pijper CA, Spijker R, Holman R, Grobusch MP, Stijnis C. Rabies Antibody Response After Booster Immunization: A Systematic Review and Meta-analysis. Clin Infect Dis. 2018;67(12):1932-1947.

33. Vien NC, Feroldi E, Lang J. Long-term anti-rabies antibody persistence following intramuscular or low-dose intradermal vaccination of young Vietnamese children. Trans R Soc Trop Med Hyg. 2008:102(3):294-6.

34. Strady C, Andreoletti L, Baumard S, Servettaz A, Jaussaud R, Strady A. Immunogenicity and booster efficacy of pre-exposure rabies vaccination. Trans R Soc Trop Med Hyg. 2009;103(11):1159-64.

35. Kamoltham T, Thinyounyong W, Khawplod P, Phraisuwan P, Phongchamnaphai P, Anders G, Malerczyk C. Immunogenicity of Simulated PCECV Postexposure Booster Doses 1, 3, and 5 Years after 2-Dose and 3-Dose Primary Rabies Vaccination in Schoolchildren. Adv Prev Med. 2011:403201.

36. Pengsaa K, Limkittikul K, Sabchareon A, Ariyasriwatana C, Chanthavanich P, Attanath P, Malerczyk C. A three-year clinical study on immunogenicity, safety, and booster response of purified chick embryo cell rabies vaccine administered intramuscularly or intradermally to 12- to 18-month-old Thai children, concomitantly with Japanese encephalitis vaccine. Pediatr Infect Dis J. 2009:28:335-7.

37. Wongsaroj P, Udomchaisakul P, Tepsumethanon S, Khawplod P, Tantawichien T. Rabies neutralizing antibody after 2 intradermal doses on days 0 and 21 for pre-exposure prophylaxis. Vaccine. 2013;31(13):1748-51.