UNIVERSITE TOULOUSE III- PAUL SABATIER

FACULTES DE MEDECINE

ANNEE 2021

N° 2021 TOU3 1905

THESE

POUR LE DIPLOME D'ETAT DE DOCTEUR EN MEDECINE
SPECIALITE BIOLOGIE MEDICALE

Présentée et soutenue publiquement le 15 octobre 2021 par

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née le 28 mai 1993 à Toulouse

IMMUNOGENICITE D'UNE VACCINATION ANTIRABIQUE PREEXPOSITION EN DEUX INJECTIONS INTRAMUSCULAIRES

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Remerciements

A Monsieur le **Professeur Pierre DELOBEL**
Je vous remercie d'avoir accepté de présider ce jury, et de me faire l'honneur d'évaluer ce travail. Je vous suis aussi très reconnaissante de m'avoir donné l'opportunité de faire un stage dans votre service et d'avoir pu me former à la médecine des voyages. Veuillez trouver ici le témoignage de mon profond respect.

A Monsieur le **Professeur Christophe PASQUIER**
Je vous remercie d'avoir accepté de siéger au sein de mon jury et de votre participation à ce travail. Je vous remercie également de m'avoir intégrée au sein de l'équipe de virologie durant ce stage. Je vous prie d'accepter mes considérations respectueuses.

A Monsieur le **Professeur Guillaume MARTIN-BLONDEL**
Je vous remercie d'avoir accepté d'être membre de ce jury et de l'aide précieuse apportée à cette étude. Je vous suis très reconnaissante de l'intérêt et de l'implication que vous avez portés à ce travail. Soyez assuré de mon respect et de ma profonde gratitude.

A Madame le **Docteur Véronique NANEIX-LAROCHE**
Je vous remercie de m'avoir confié ce travail et de m'avoir fait confiance. Je vous remercie également pour votre disponibilité, votre aide et pour m'avoir accueillie et formée avec vous au Centre de vaccinations internationales. Ce fut un plaisir de pouvoir apprendre et travailler avec vous.

Je remercie le Docteur Perrine PARIZE de l'Institut Pasteur et son équipe pour avoir accepté de participer à cette étude.

Je remercie l'équipe du CVI pour son accueil chaleureux, sa bonne humeur et son soutien.

Je remercie également les techniciens de virologie qui ont permis la réalisation de ce travail, pour leur gentillesse et leur aide.

A ma famille,

A mes parents, pour avoir toujours été là pour moi, je vous remercie de l'éducation que vous m'avez donnée, de votre amour et votre soutien sans faille qui m'ont permis d'arriver jusqu'ici.

A Emilie ma petite sœur, ma confidente, je te remercie pour ta douceur et surtout ta patience à mon égard. Je serai toujours là pour toi.

A Alexandre, ma moitié, mon pilier, merci de me rendre si heureuse et de partager ma vie. Je te remercie de me soutenir depuis toutes ces années.

A mes amis, d'ici ou d'ailleurs, je vous remercie de tous les instants passés avec vous, et d'être venus (parfois de loin) partager ce moment important avec moi. Votre amitié est précieuse.

Table of Contents

List of Abbreviations

BBLV: Bokeloh bat Lyssavirus

CDC: Center for Disease Control

CHU : Centre hospitalier universitaire

CNIL : Commission nationale de l'informatique et des libertés

CNRR: National Reference Centre for Rabies

D: Day

EBLV: European bat Lyssavirus

ED 50: 50 % end-point

ELISA: Enzyme Linked ImmunoSorbent Essay

ENVT : Ecole Nationale Vétérinaire de Toulouse

EU : Equivalent Unit

FITC : fluorescein isothiocyanate

HCSP : Haut conseil de santé publique

HDCV: Human diploid cell vaccine

ID: Intradermal route

Ig: Immunoglobulins

IM: Intramuscular route

IU: International units

LLEBV: Lleida bat Lyssavirus

PCECV: purified chicken embryo cell vaccine

PPE: Post-exposure prophylaxis

PrEP: Pre-exposure prophylaxis

PVRV: Purified Vero cell Rabies Vaccine

RABV: Rabies Virus, genotype 1

RFFIT: Rapid Fluorescent Focus Inhibition Test

RIG: Rabies Immunoglobulins

RVNA: rabies virus neutralizing antibodies

SAGE: Strategic Advisory Group of Experts

USD: United States Dollar

VCCOE: vaccines made from rabies virus prepared in cell culture or on embryonated eggs

WHO: World Health Organization

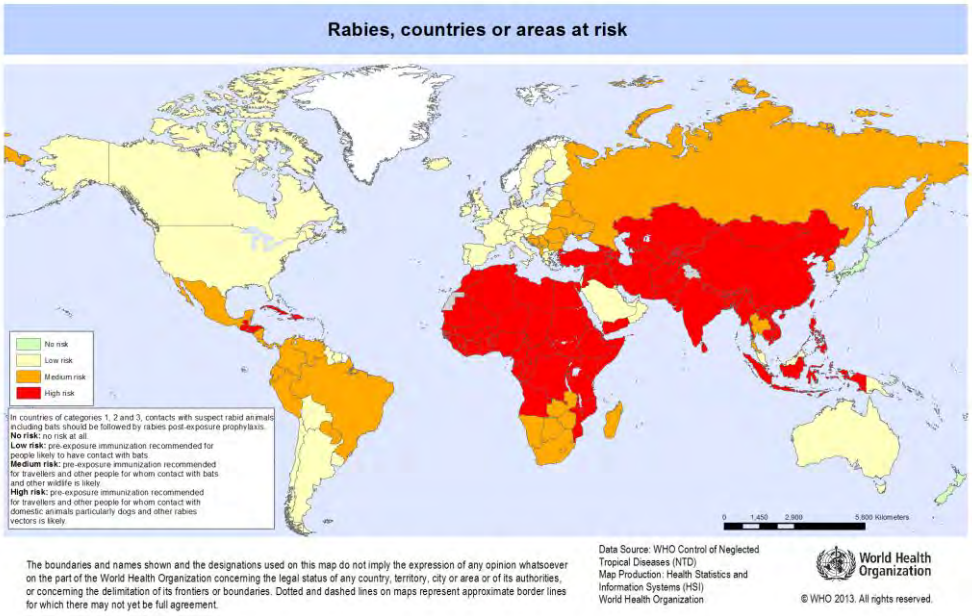
I. Introduction

Rabies is a viral zoonosis responsible for acute encephalomyelitis that systematically causes death without early medical cares. It is a notifiable inoculation disease, transmitted to humans by bite, scratching or licking by an animal infected, mainly dogs, which excretes the virus in its saliva. Rabies is widespread throughout the world and remains a scourge responsible for 59,000 deaths per year (1). However, preventive measures exist and could make it possible to eradicate human rabies. It represents a public health priority for WHO, which in its "Zero by 30" program plans to eradicate cases of human deaths due to canine rabies by 2030 (2). One of the prevention strategies is based on pre-exposure prophylaxis (PrEP), which consists of vaccinating persons at risk of exposure to rabies. Currently the vaccination scheme in force is long and restrictive because it requires three intramuscular (IM) doses of vaccine at day (D) 0, D7 and D21, not always allowing to carry out the complete scheme (3). According to the latest WHO recommendations, this vaccination regimen could be shortened into two injections IM seven days apart (1,4). Currently, few studies have evaluated the effectiveness of this shortened scheme (5–10). Our study is the first in France to test the immunogenicity of vaccination remotely on a large sample of volunteers at risk of exposure to rabies. Its objective is to determine whether a shortened vaccination regimen allows the development of sufficient and lasting post-vaccine immunity.

1. Epidemiology of rabies

Rabies is widespread throughout the world and remains an important cause of mortality in developing countries. Asia and Africa are the main centers of this endemic disease, especially in rural areas and among marginalized populations where infection is often neglected. Indeed, in these countries, animal rabies, particularly of canine origin, is not controlled therefore causing many animal and human cases (Figure 1 and 2).

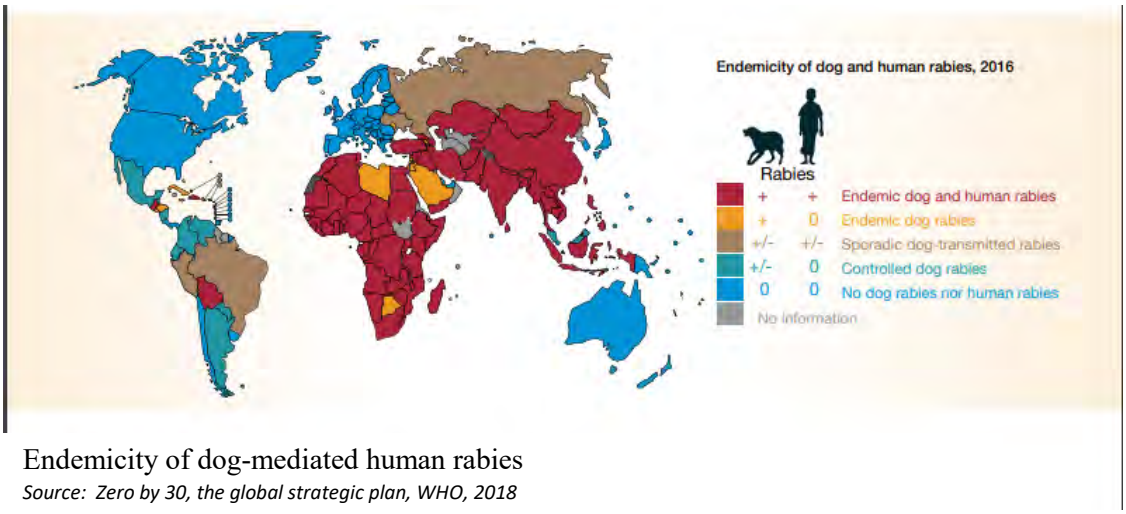
Figure 1: Countries or areas at risk of rabies infection:



Rabies affects all terrestrial mammals. Dogs represent the main reserve of the disease since they are responsible for 99% of human rabies cases in endemic regions, the remaining 1% being transmitted by wild animals mainly of two orders: (Figure 3)

- Chiroptera (blood-sucking, insectivorous and frugivore bats)
- Carnivores (fox, skunk, mongoose for example).

Figure 2: Endemicity of dog-mediated human rabies:



Endemicity of dog-mediated human rabies
Source: Zero by 30, the global strategic plan, WHO, 2018

In metropolitan France, bats represent the only reservoir of rabies. Three species of Lyssavirus are mainly found and detected in insectivorous bats:

-European bat1 Lyssavirus (EBLV-1 and 2)

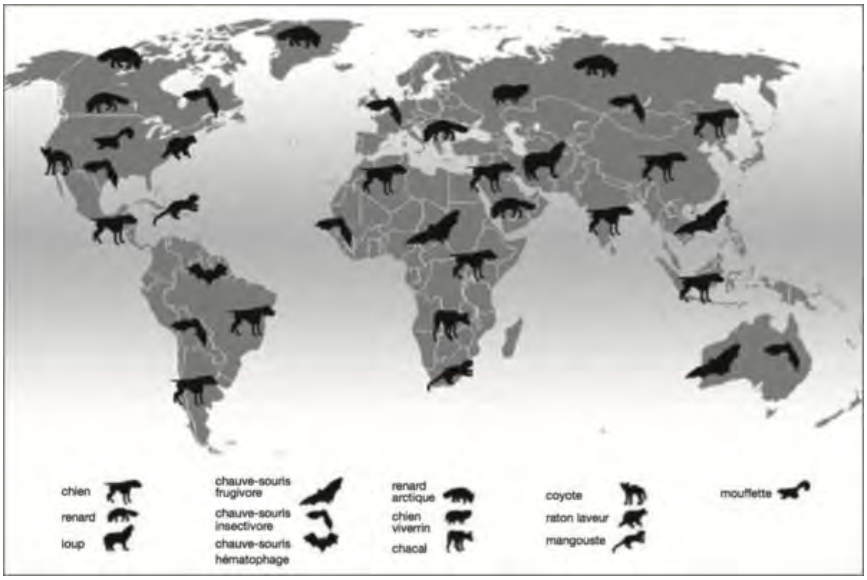
-Bokeloh bat Lyssavirus (BBLV)

-Lleida bat Lyssavirus (LLEBV)

EBLV 1 and 2 cause clinically similar disease in humans to that one caused by classical rabies virus. However, human cases due to LLEBV are very rare (3).

French Guyana is an exception due to its borders with countries where rabies is not controlled (Brazil, Surinam). The risk of rabies in French Guyana exists with respect to carnivores that may have arrived infected from a neighboring country. In addition, Guyana, like the rest of Latin America, is exposed to rabies viruses from hematophagous bats.

Figure 3: Distribution of rabies vector species in the world:

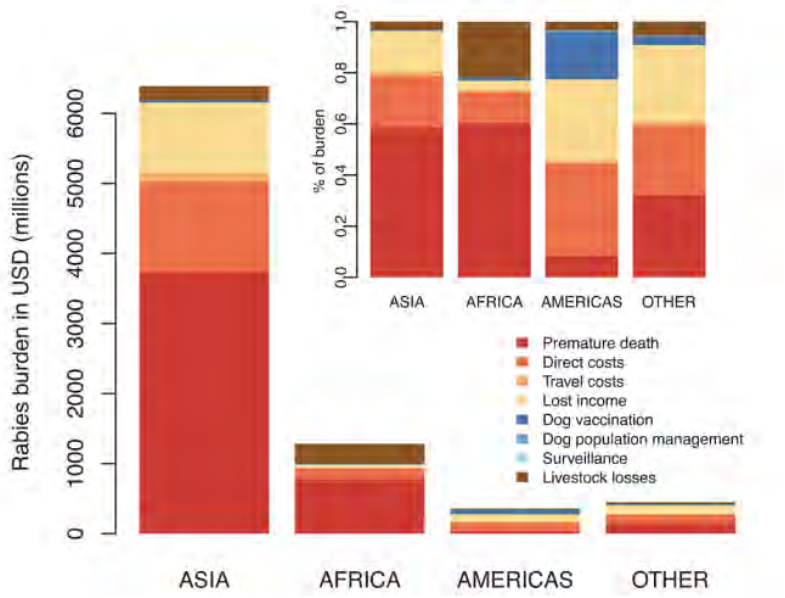


Sources: www.afas.fr

2. Rabies cost and prevention in the world

Rabies represents a global economic burden, causing an estimated loss of USD 8.6 billion/year worldwide (11). Premature deaths related to rabies account for more than half of the expenditure (55%). The other economic losses are mainly related to the direct cost of the post-exposition prophylaxis (PEP, 20%), loss of income due to the disease and loss of livestock (15%, Figure 4).

Figure 4: Division of costs associated with rabies, prevention and control across sectors by region. Inset shows proportional expenditure in different regions. (Hampson et al., 2015)



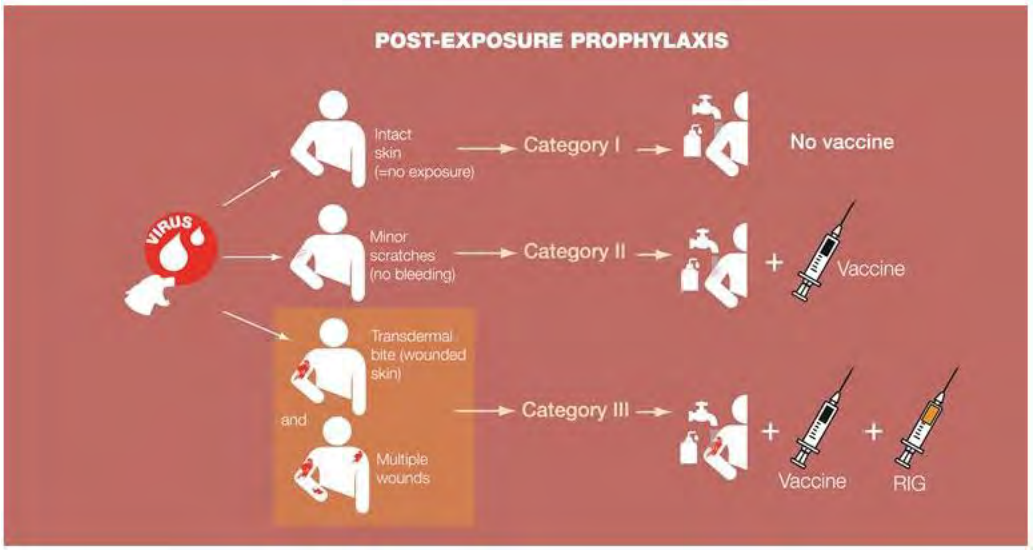
Rabies prevention has two aspects: animal rabies control and human rabies prevention. Prevention of human rabies is based primarily on recommendations to travellers to avoid high-risk situations and contacts, and on the use of active (vaccines) and passive (immunoglobulins) prophylaxis.

Indeed, the risk of being bitten by a domestic animal (dog, cat) or wild animal (monkey, bat) during a stay in a tropical country is not to be neglected. Therefore, it is recommended that travellers to risk areas avoid any direct contact with animals, including animals with apparently normal behaviour.

Preventive vaccination before or after exposure to the virus may be recommended in some specific circumstances. WHO recommends two main vaccination strategies for the prevention of human rabies:

- PEP allows for post exposure treatment of an individual bitten before symptoms appear. This prophylaxis includes careful and thorough washing of the wound (bite or lick), combined with the administration of a series of several doses of rabies vaccine and rabies immunoglobulin if necessary. This post-exposure treatment is only carried out in specialized vaccine centre. As the incubation period of the rabies virus is very long (several weeks-months), PEP can trigger a rapid and massive production of rabies antibodies preventing disease development before the individual becomes ill (Figure 5).
- PrEP is the administration of several doses of rabies vaccine before exposure to the rabies virus. WHO recommends PrEP for individuals at high risk of exposure to the rabies virus. It is recommended in particular for sub-populations living in highly endemic areas where access to timely and adequate PEP is limited, for travellers to these endemic areas (especially children), and for people at occupational risk such as veterinarians or chiropterologists. It is done by administering the vaccine at D0, D7 and D21 or 28. In the event of a bite, PrEP allows for lighter post-exposure management with only booster vaccinations, thus avoiding the need for anti-rabies immunoglobulin, which is sometimes difficult to obtain and less well tolerated than the vaccine (12,13).

Figure 5: Post-exposure prophylaxis



Source : https://www.who.int/teams/control-of-neglected-tropical-diseases/rabies/vaccinations-and-immunization

Professionals who are continuously or frequently exposed to risk in the course of their work should receive PrEP and should have regular serological monitoring, from every 6 months to every two years depending on the level of risk exposure. If vaccine-induced neutralising antibody level is considered to be lower than the protective antibody level, a 1-site intra-dermal (ID) or intra-muscular (IM) booster dose is recommended. If serological monitoring is not available for individuals at continuous or frequent occupational risk, periodic administration of a booster dose (ID or IM) may be considered based on relative risk assessment. PrEP should be considered in populations living in rabies endemic areas, where the incidence of dog bites is > 5% per year or rabies is known to occur in vampire bats. The decision to conduct a population-based PrEP intervention should be based on an assessment of the local context and rabies epidemiology, including the feasibility of controlling rabies in the animal source (1).

3. Rabies vaccine

The first injectable live attenuated rabies vaccine, developed by Louis Pasteur and Emile Roux, was first tested on a bitten person in 1885. It used inactivated homogenates of rabbit nerve tissue infected with rabies virus. Since 1984, WHO has strongly recommended that the production and use of nerve tissue vaccines be discontinued and replaced by modern cell cultured, concentrated and purified rabies vaccines or vaccines prepared in embryonated eggs (VCCOE). VCCOEs are intended for both PrEP and PEP. These rabies vaccines are highly effective, safe and well tolerated (1).

VCCOEs contain inactivated rabies viruses that have been grown in embryonated eggs (embryonated duck or chicken eggs) or cells (primary cultures of chicken embryonic cells, Vero cells or human diploid cells (PCECV, PVRV, HDCV)). The virus harvested is then concentrated, purified, inactivated and lyophilised. Some VCCOE contain human albumin or treated gelatine as a stabilising agent. Rabies vaccines for humans must meet WHO recommendations for manufacturing and clinical evaluation. All VCCOE should contain ≥2.5 international units (IU) per IM dose (volume after reconstitution of 0.5 ml or 1.0 ml, depending on the vaccine type).

The new WHO recommendations for PEP promote the administration of VCCOE vaccines by both the ID and IM routes as studies have shown that ID injection in PEP induces an antibody titer as high as the IM pathway.

Indeed, ID administration regimens offer advantages in terms of cost savings, doses and time. In this way, WHO strongly encourages vaccine manufacturers to extend their route of administration authorization to include the ID route (1,14). Available data suggest that a change in the route of administration or of vaccine product during PEP or PrEP is safe and immunogenic. Many Asian countries are now using the ID route for rabies PEP. Indeed, the main interest of the ID route is to facilitate the exposure of several antigens to the numerous antigen-presenting cells that are more present in the skin than in muscles (15–17).

The recommended site for IM injection is the deltoid region of the arm for adults and children aged ≥ 2 years and the anterolateral thigh region for children aged < 2 years. Rabies vaccine should not be administered intramuscularly in the gluteal area. Indeed, injection into the buttocks is not recommended because the adipose tissue is thick and the needle is short: the injection is very often intra-greasy and not IM, which may reduce the effectiveness of some vaccines.

Two rabies vaccines are available in France: Rabipur® and Rabique Pasteur® which can be used for PrEP and PPE:

- The inactivated vaccine produced in Vero continuous cell culture using the Wistar Pitman Moore L503 3M strain is the Rabique Pasteur® vaccine. The protective activity of the vaccine is greater than or equal to 2.5 IU per human dose. It is supplied as a powder in a vial and a solvent in a pre-filled syringe (0.5 ml) (18).

- The inactivated chicken embryo cell vaccine using the Flury LEP strain is Rabipur® vaccine. The protective activity of the vaccine is greater than or equal to 2.5 IU per human dose. It is presented as a powder in a vial and a solvent in an ampoule with or without a disposable syringe (1 ml) (19).

4. Protective antibody level after vaccination

According to the WHO, the protective antibody level accepted as an adequate immune response after vaccination is 0.5 IU/ml although there is no specific level of rabies virus neutralizing antibodies (RVNA) that is recognized as being protective against rabies in humans. Indeed, this threshold value is only based on empirical values in animals and had never been studied in rabies human cases (3,15).

Initially, this threshold value was established in order to ease the regulation of international domestic animal movements and thus to stop the quarantine of vaccinated and immunized animals.

This threshold value has been established by the Center for Disease Control (CDC) based on animal studies and fixed at a serum dilution of 1:5 in RFFIT corresponding to 0.1-0.2 IU/ml. Subsequently, the WHO arbitrarily adopted an upper threshold at 0.5 IU/ml in 1992 (20–26). In their study, *Dean et al.* showed that 95.3 % of vaccinated dogs with detectable serum antibody survived to rabies on challenge, while 64.3 % of vaccinated dogs with no detectable antibody died (27,28). Others studies have observed antibody titers in domestical animals after vaccination. *Aubert*'s work on dogs and cats showed that animals with a neutralizing antibody threshold value > 0.1 IU/ml in dogs and > 0.2 IU/ml in cats measured in RFFIT were associated with survival after rabies infection (21). *Cliquet et al*. studied the frequency of titers above the positivity threshold value in 25,000 sera after vaccination. They showed that after the first vaccination only 7.4% of dogs'sera and 1.9% of cats'sera had antibody titer lower than 0.5 IU/ml. They suggested this threshold value may be too stringent, but constitutes an extra guarantee for importing countries (20). Finally, *Nicholson et al.* studied in 1978 the immunity elicited after rabies vaccination in 77 volunteers. An antibody response was detected in all the volunteers one month after one dose of vaccine (29). They discussed that even if the protective antibody level was unknown, until then, no case of rabies in patients who had detectable antibodies at the time of the infection was reported (29,30).

5. Review of literature on interests of shorter vaccination regimens

Different shortened vaccine regimens have been tested. Main studies are listed in Table 1 (5–8,10,31–36). Most studies in the literature have investigated immunogenicity in the short term (28 days post-vaccination) or after a booster at one-year post-vaccination. Few studies have exclusively investigated the post-vaccination immunogenicity of the shortened schedule with two injections over the long term (5–10). The WHO recommendations were based on the immunogenicity results after booster vaccination. Our review of the literature shows that two doses of pre-exposure vaccination provide a high rate of seroconversion at 28 days, often effective to cover the duration of a trip. Similarly, at one year, although immunogenicity tends to decrease in shortened regimens, a booster dose will most often provide a protective antibody level greater than 0.5 IU/ml.

Thus, since a bite will require two vaccine boosters, a shortened PrEP regimen allows achieving sufficient immunity after boosters.

Moreover, the recent study by *Parize et al*, studying immunogenicity after the classical 3-dose IM vaccine regimen shows similar results to those found in the shortened regimens: 82.8% immunogenicity before booster, while *Cramer et al* found 68% immunogenicity and *Jonkers et al* found 73 % at one-year post PrEP (9,10,37).

In France, the current pre-exposure vaccination schedule, recommended by the French High Council for Public Health (HCSP), consists of three IM injections of rabies vaccine given on a D0-D7-D21 schedule with serology at one year or more proving competent immunity if it is higher than 0.5 IU/ml (3). This three-dose vaccination schedule often represents a constraint for travellers who often prefer not to be vaccinated. Indeed, vaccination requires three visits over a month, implying a sufficient time before the trip that cannot always be respected, and a significant cost making difficult to carry out the full vaccination schedule. Furthermore, the vaccine cost often discourages travellers from rabies vaccination. Similarly, access to vaccines in the most remote and in high-risk areas often limits the ability to carry out a complete 3-dose regimen. Finally, in a context of global vaccine shortage, limiting the number of doses represents a strategic economic interest. Rabies control is a public health priority for the WHO, which aims to reduce the number of human deaths due to rabies of canine origin to zero by 2030 in its "Zero by 30" program. One of the control strategies is pre-exposure prophylaxis (2).

Indeed, PrEP allows a simplified management by simple vaccine boosters in case of exposure to rabies by avoiding the use of immunoglobulins that are excessively expensive, difficult to find and not widely available, especially in remote areas (12,38). For example, the dosage of rabies immunoglobulins (RIG) to treat a bitten person being 20 IU/kg, a 60 kg person will need 4 vials of 300 IU/ml RIG at 400 euros the vial that is to say 1600 euros for the RIG treatment while a vaccine dose cost around 50 euros in France.

Recommendations for the PrEP vaccine regimen were discussed again at the WHO Strategic Advisory Group of Experts on Immunization (SAGE) in October 2017 (4). Actually, recent data indicate that PrEP regimens can be shortened in duration and require fewer doses which would facilitate access to vaccination. SAGE now recommends that the pre-exposure regimen be reduced to two doses injected at D0 and D7 IM. In addition, the WHO following these recommendations, published a position paper in this sense in 2018.

The evolution of practices tends towards a pre-exposure vaccination schedule of two doses on D0 and D7 (1,12).

Despite the WHO recommendations, French health authorities continue to follow the HCSP's guidelines with the previous 3-injection vaccination scheme pending the conclusions of the HCSP working group on a shortened vaccination scheme.

The literature review (6–10,31,32) shows that two doses of pre-exposure vaccination allow a high rate of seroconversion at 28 days. Similarly, at one year, even if immunogenicity tends to decrease in shortened regimens, a booster allows to obtain a protective antibody level. Thus, since in case of a bite, the person will have to receive vaccine boosters, a shortened PrEP regimen allows obtaining sufficient immunity after boosters.

Currently in France, we have little data on the long-term effectiveness of a short vaccination scheme. Indeed, very few vaccine studies have evaluated the immunogenicity of the short vaccination regimen, and moreover these studies have been carried out on small numbers. The RABICOURT study conducted at the Bordeaux University Hospital in 2018 studied the short-term immunogenicity of a two-injection regimen on 19 travelers. In the short term, the level of antibodies in travelers before their departure was enough to conclude that a shortened vaccination regimen was effective. However, the literature review has somewhat reserved views on about the intensity and durability of immunogenicity over the long term (5). Indeed, *Cramer et al*. showed in 2016, that immunogenicity declined faster after a short PrEP regimen versus the conventional regimen, with a low immunogenicity rate of 68% versus 80% respectively at 1 year (9).

The aim of our study is to investigate the long-term immunogenicity of pre-exposure rabies vaccination, which has been performed by injecting two doses IM of Pasteur rabies vaccine 7 days apart, on a large population and at a distance from the vaccination, in order to support the practice of a shortened vaccination schedule.

Table 1: State of literature: Different vaccination regimens

References	Population of the study	Route	Vaccination regimen	% Sufficient immunogenicity after PrEP (≥0.5 IU/ml)					
				D21	D28	D35	D56	Y1	Y2
Jonkers et al. JTM, 2017(10)	30 volunteers 18-65 aged	IM	D0		93			73	
Khawplod et al, Developments in Biologicals, 2012, Vaccine (35)	33 vet students, 18-45aged	IM	D0			97			
Khawplod et al, Developments in Biologicals, 2007, Vaccine(7)	40 vet students, 18-45 aged	ID	2 at D0			75			
Zabbé et al. Médecine et Maladies Infectieuses, 2019	19 travellers	IM	D0-D7	79					
Kamoltham et al. Journals of Pediatrics,2007 Advances in Preventive Medicine, 2011 (6)	703 school children in Thailand	ID	D0-D28		98				
Jelinek et coll. JTM, 2015 (33)	217 volunteers 18-65 aged	IM	D0-D3-D7 associated with EJ*				97		
Cramer et al. JTM, 2016 (9)	217 volunteers 18-65 aged	IM	D0-D3-D7 associated with EJ*					68	
Parize et al, Vaccines 2021(37)	355 individuals at risk of occupational exposure	IM	D0-D7-D21					82.8	
De Pijper et al. JTM, 2018 (36)	430 Dutch soldiers	ID	D0-D7-D21	99.3					
Soentjens et al. CID. 2019 (8)	249 Belgian soldiers, median age : 28 yo	ID	2 D0- 2 D7			100			
Lau et coll. JTM 2013 (34)	54 volunteers	ID	2 D0-2 D7		94.4				
Mills et al, JTM, 2011 (32)	420 australien travellers	ID	2 D0-2 D7	94.5					

II. Method

1. Conduct of the study

Students from the National Veterinary School of Toulouse (ENVT) are professionally exposed to the rabies virus. WHO and HCSP recommend rabies PrEP in people exposed in their occupational environment. During March 2019, 228 ENVT students, representing all the students of the school in their second and third years of scholarship, received a rabies PrEP primo-vaccination at the Vaccination Centre of the Toulouse University Hospital with two IM injections of Rabique Pasteur vaccine given during two consultations one week apart (D0 and D7), according to recent WHO recommendations. In March 2021, two years after vaccination, ENVT students performed a rabies ELISA serology. The serological tests were carried out in the virology laboratory of the Toulouse University Hospital where antibody levels were collected and considered as enough if they were higher than >0.5 EU/ml. If result was <0.5 EU/mL, sera were sent to the National Reference Centre for Rabies (CNRR) of the Institut Pasteur in Paris, to dose the neutralising antibody titre by RFFIT which represents the standard method. The primary endpoint was the presence of effective immunogenicity if serological titer was ≥ 0.5 IU/ml by indirect ELISA technique and/or RFFIT.

2. Indirect ELISA technique

Rabies serologies were performed on EVOLIS with PLATELIA^{TM} RABIES II KIT from Bio-Rad. It is an immuno-enzymatic technique for the detection and titration of rabies virus anti-glycoprotein antibodies in human's serum samples (Figure 6). The ELISA test was performed as described in the package insert supplied by Bio-Rad. A 96-well microplate coated with rabies glycoprotein extracted from inactivated and purified virus membrane constitutes the solid phase for the ELISA. The enzymatic conjugate is a protein A from Staphylococcus aureus coupled with peroxidase. Negative control and two positives' controls were used to valid the results. Positive controls (R4a and R4b) were calibrated against WHO standards. The R4b control is used to construct a standard curve out of the Quantification standards (S1-S6), obtained by serial dilutions of R4b.

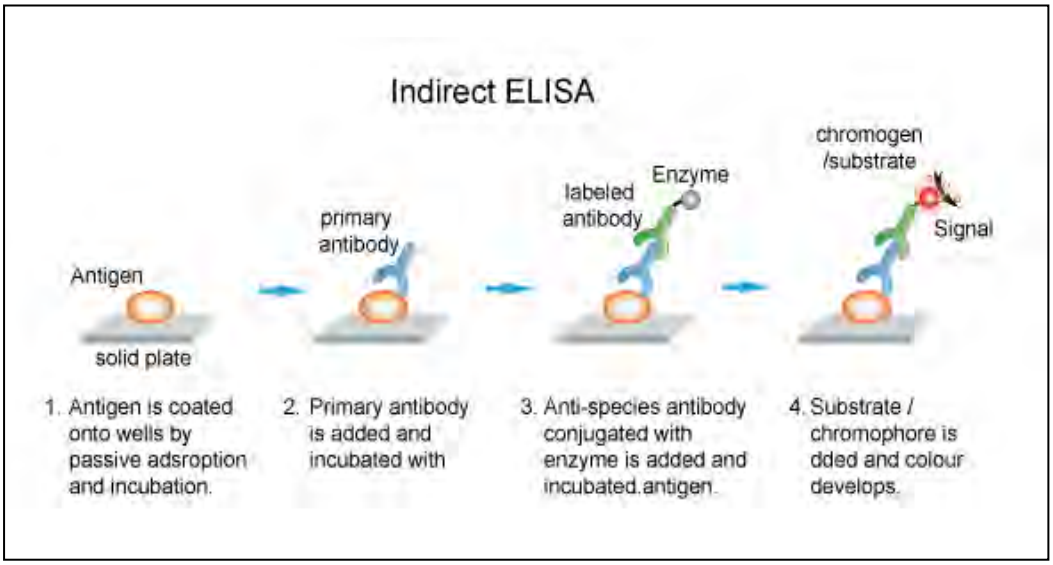
The different steps of the techniques are described briefly:

First, one-hour incubation at 37°C allows the binding of the anti-rabies antibodies present in the sample to the glycoprotein fixed in the micro wells. After incubation, unbound antibodies and other serum proteins are removed by washing.

After that, the conjugate (peroxidase labelled protein A) is added to the wells. A second incubation of 1 hour at 37°C allows the conjugate to bind to the antigen-antibody complex previously formed in the first step. Excess unbound conjugate is removed by washing. The presence of the immune complex is revealed by the addition of a solution containing a peroxidase labelled substrate and a chromogen to induce a colour reaction. After 30 min of incubation the enzymatic reaction between the peroxidase and its substrate is stopped by adding a 1N sulphuric acid solution.

Absorbance was measured at 450-620 nm with a microplate reader. The optical density read is proportional to the amount of anti-rabies antibodies present in the samples. The optical density values for the sample were compared with the positive controls. Sera titres in quantification are obtained after a direct reading on the standard curve and expressed as equivalent units per ml (EU/ml) i.e unit equivalent to the IU/ml.

Figure 6. Indirect ELISA technique Source : *https://www.creative-diagnostics.com/ELISA-guide.htm*



3. Rapid Fluorescent Focus Inhibition Test (RFFIT)

Rabies neutralising antibodies were measured by using the WHO procedure (22).

A defined amount of rabies virus is incubated with increasing dilutions of the test serum and then incubated in the presence of cells. After 24 hours of incubation and the addition of the FITC conjugate antibody, the foci of viral infection are then revealed by direct immunofluorescence and counted under a fluorescence microscope.

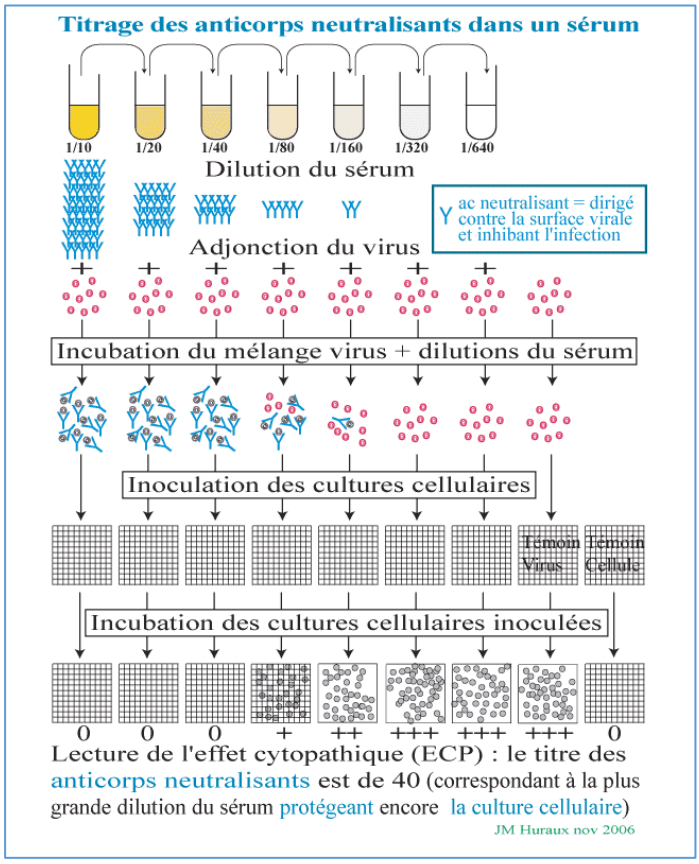
The number of foci decreases in proportion to the titre of neutralising rabies antibody present in the test sample (Figure 7). A cell control is used as a control for cell cultures. A negative serum control and a positive one with a RVNA titre known are used to valid the results.

The titre of the serum corresponds to the dilution at which 50% of the constant viral dose is neutralised by the antibodies (ED 50). This value may be determined by both titration methods: determining a 100% neutralization titre by recording the highest serum dilution at which 100% of the challenge inoculum is neutralized or may be calculated by mathematical interpolation (Reed and Muench method) (39). Titres of sera are determined by comparison of the results of the tested sera with the WHO reference serum of known titre. Finally, a titre in international units (IU) is calculated from reference sera using this formula:

$$\textit{Tested serum Titer (IU/ml)} = \frac{ED50\ titer\ of\ test\ serum}{ED50\ titre\ of\ reference\ serum\ diluted\ to\ contain\ 2.0IU/ml}\ \textbf{X}\ \textit{Titer of the reference serum (2 IU/ml)}$$

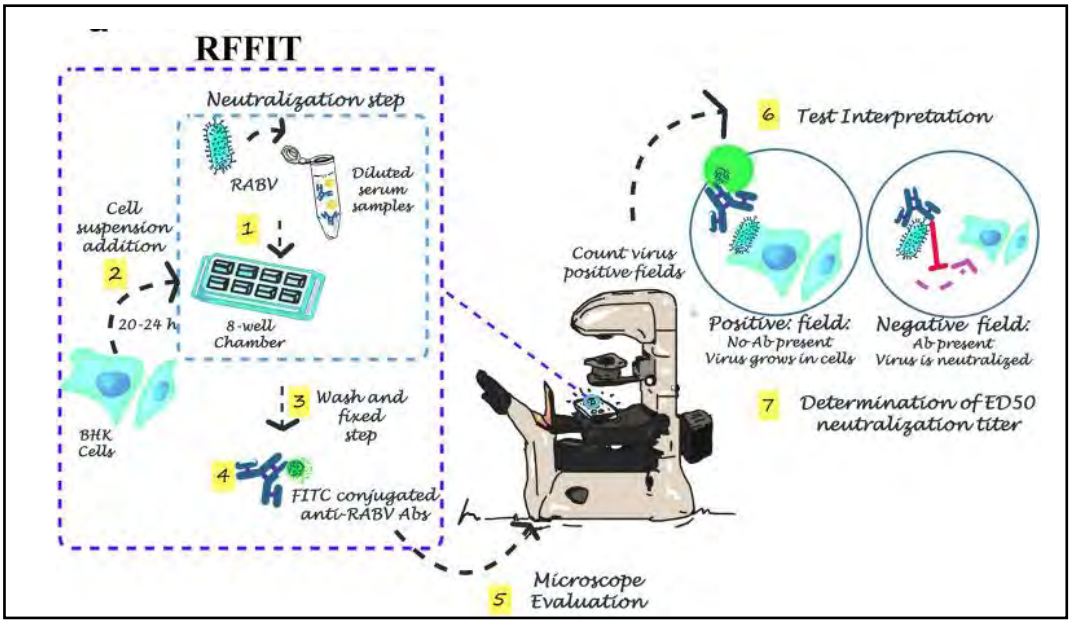
This technique is still only available in authorised reference centres, the CNRR (40,41).

Figure 7a. Principe of Antibody neutralization titration:



Source : FMPMC-PS - Virologie - Niveau DCEM1 (jussieu.fr)

Figure 7.b RFFIT technique (42)



4. Ethics

A retrospective analysis of clinical and serological data of all ENVT students vaccinated against rabies with the WHO protocol in 2019, was performed in 2021 at the Toulouse University Hospital. According to French law on ethics, patients were informed that their codified data will be used for the study and signed a consent. According to the French ethic and regulatory law (public health code) retrospective studies based on the exploitation of usual care data should not be submitted to an ethic committee but they have to be declared or covered by reference methodology of the French National Commission for Informatics and Liberties (CNIL). A collection and computer processing of personal and medical data was implemented to analyze the results of the research. Toulouse University Hospital signed a commitment of compliance to the reference methodology MR-004 of the French National Commission for Informatics and Liberties (CNIL). After evaluation and validation by the data protection officer and according to the General Data Protection Regulation (Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016), this study fulfilled all the criteria and was registered in the register of retrospective study of the Toulouse University Hospital (number's register: (RnIPH 2021-89) and covered by the MR-004 (CNIL number: 2206723 v 0).

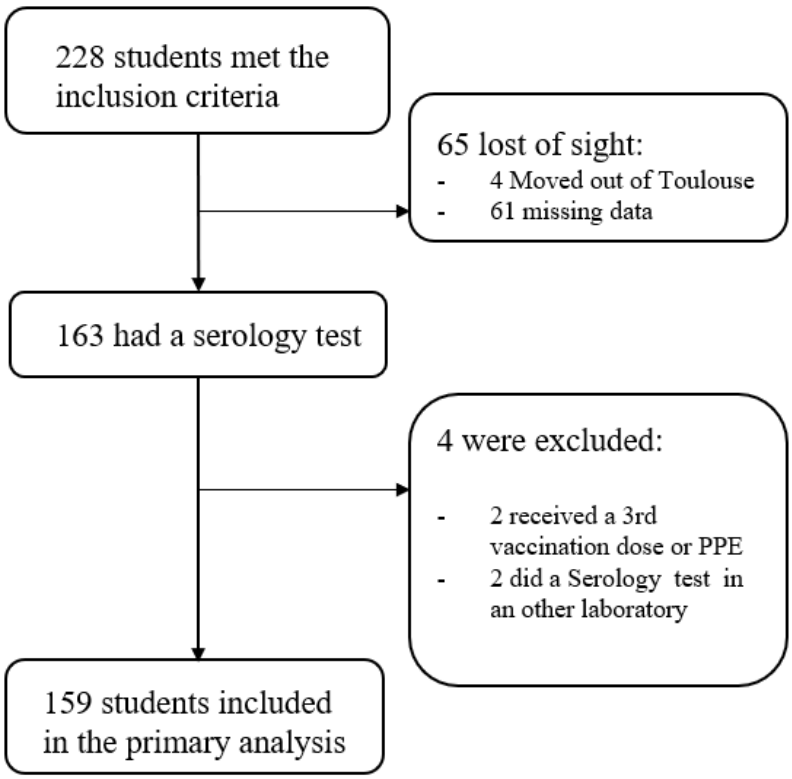
5. Statistical analysis

Baseline characteristics were summarized using median (interquartile range) and percentages for continuous and categorical variables respectively.

III. Results

Among the 228 participants vaccinated with two IM injections of rabies vaccine in 2019, 163 students had a serological test results two years after vaccination, and 65 were not included in this survey because they moved out of Toulouse or because of missing data. Out of the 163 patients, four students were excluded from the study because they had received a third dose of vaccine before the serological test or had performed serological tests in another laboratory. Finally, 159 samplings were included in the analyses (Figure 1). These 159 students had never been vaccinated against rabies before.

Figure 1. Flow-chart



1. Baseline characteristics

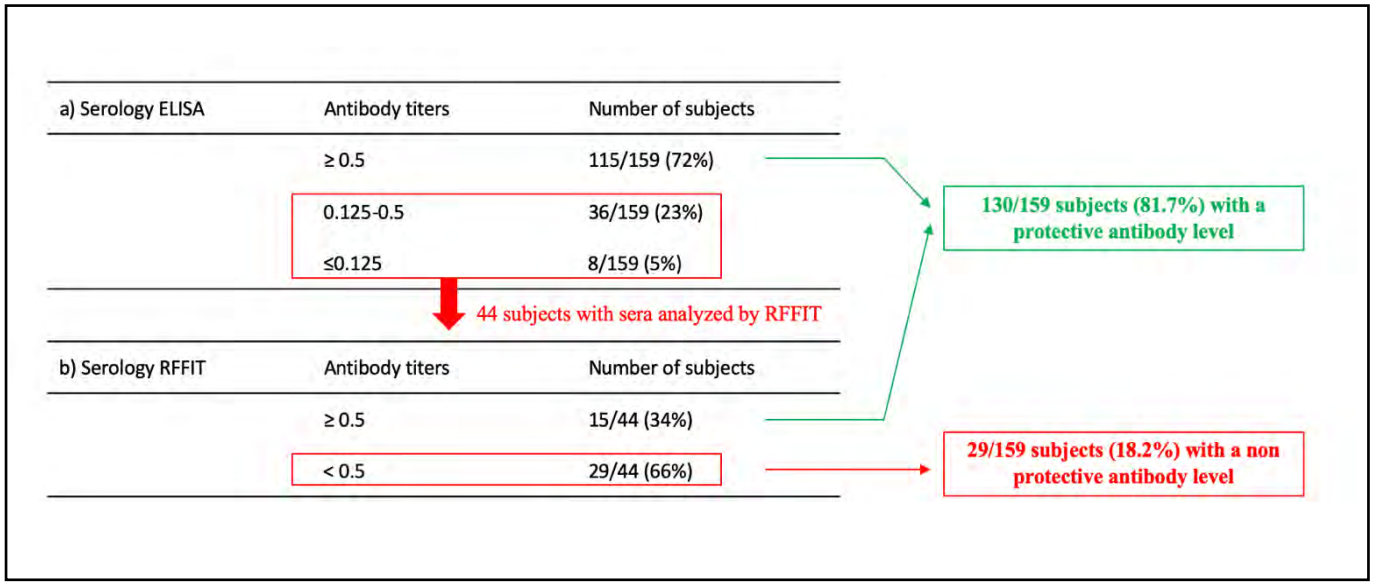
Among the 159 participants included, 132 (83%) had no past medical history. The 27 other students (17%) had a past medical history of allergies, asthma, hypothyroidism or were under treatment for cystitis. The median age of the participants was 23.5 years (IQR= 1; ET= 1.48). The age of the participants was distributed between 21 and 32 years. Women represented 82% of the participants. The vaccine lot between D0 and D7 was the same for 84 individuals (53%) and 75 (47%) received a different lot between the two doses.

2. Immunogenicity 24 months after vaccination

Results in ELISA show that 115/159 (72%) of the students sampled had positive rabies serology with a protective antibody level above the recommended threshold of 0.5 EU/ml (Figure 2a). However, 36/159 (23%) of the students had a low antibody level between 0.125 and 0.5 EU/ml and 8/159 (5%) had a level lower than or equal to 0.125 EU/ml. These 44 subjects were considered as having inadequate antibody titers, below the recommended threshold and therefore did not show satisfactory immunogenicity against rabies.

Sera from these 44 subjects with ELISA antibody titers <0.5 IU/ml were analyzed by RFFIT at the Pasteur Institute (Figure 2b). Among the 44 sera, 15/44 (34%) had a neutralizing antibody level above the threshold of 0.5 IU/ml in RFFIT, and were considered as having satisfactory immunogenicity against rabies, suggesting that ELISA underestimated neutralizing antibody level in those subjects. Among them, 14 had an intermediate ELISA antibody level (0.125- 0.5 EU/ml) and only one had a level below 0.125 EU/ml in ELISA. Finally, 130/159 subjects (81.7%) had by ELISA and/or RFFIT sera ≥ 0.5 IU/ml and were considered as having satisfactory immunogenicity against rabies.

Figure 2. Serological results 24 months after rabies vaccine



The remaining 29 students with a sub-threshold RFFIT level were advised for receiving a vaccine booster with a serological test one month afterward to ensure satisfactory immunity. At this time, only seven so far came back at the center in Toulouse to receive a booster, among whom only four of them did the ELISA test one month after the booster. All the four had an antibody titer in ELISA > 4 EU/mL. We are so far waiting for the 25 remaining subjects.

IV. Discussion

This study evaluated the immunogenicity of the pre-exposure vaccine regimen in two IM doses as recommended by WHO at D0 and D7. The preliminary results show a satisfactory level of neutralising antibody at 24 months in 81.7% of ENVT students. These results are consistent with the data of the literature, as shown in particular by *Cramer et al* who find an immunogenicity of 68%, or *Jonkers et al.* who found 73 % at 1 year with a shortened pre-exposure vaccination regimen (9,10). Moreover, the percentage of people with inadequate antibody levels is similar to those found in the 3-injection regimens. Indeed, the recent study by *Parize et al*, studying immunogenicity after the classical 3-dose vaccine regimen shows similar results to those found in the shortened regimens: 82.8% immunogenicity before booster (37). Similarly, *Banga et al* found 29% of veterinary students with inadequate antibody titers two years after vaccination (43).

The literature review (7–10) shows that two doses of pre-exposure vaccination provide a high rate of seroconversion at 28 days, often effective to cover the duration of a trip. Similarly, at one year, although immunogenicity tends to decrease in shortened regimens (8–10,35), a booster dose will most often provide a protective antibody level greater than 0.5 IU / ml. Thus, since a bite will require vaccine boosters, a shortened PrEP regimen allows achieving sufficient immunity after boosters.

About professionals who are occupationally exposed to risk, WHO recommends a regular serological monitoring. If vaccine-induced neutralising antibody levels fall to <0.5 IU/ml, a 1-site ID or IM booster dose is recommended. Although WHO recommends an antibody level of 0.5 IU/mL as being proof of an adequate immune response after vaccination, this level is based on empirical values validated by observation and has never been challenged by retrospective analysis of human rabies cases (3,15). According to the HCSP, there was no scientific validation of the protective value of rabies antibody titers in case of exposure to bat lyssavirus and recommended a higher titer (1 IU/ml) as the correct threshold because of the lack of complete cross-protection between RABV species and other lyssavirus species.

The results of sera in RFFIT showed that the percentage of immunogenicity in ELISA is probably underestimated. This may be explained by the poorer performance of the ELISA technique compared to the reference technique (RFFIT). First, the ELISA technique is a semi-quantitative technique that does not always allow to obtain a precise antibody titer.

Thus, sera with a limit antibody level (0.3- 0.4 IU / ml) could actually have a sufficient neutralizing antibody level in RFFIT. In addition, as the Rabicourt study has shown, there is no correlation between the level of antibodies in ELISA and the number of antibodies neutralizing in RFFIT. Some patients with low levels of ELISA still had a sufficient threshold in RFFIT. Nevertheless, it would be relevant to compare also the results of the positive ELISA with RFFIT in order to comfort our hypotheses. The limitations of ELISA kits may differ with the commercial's kits such as species specificity, immunoglobulin class detected and linear range (12, 33). The ELISA's specificity depends on the target antigen used in the test. Indeed, those using purified viral proteins would present less cross-reactivity and false positives than those using whole virus (45,46). Moreover, antibodies detected in ELISA are not necessarily RVNA. However, the PLATELIA TM RABIES II ELISA kit reported a sensitivity and specificity of approximately 95% in comparative testing with the RFFIT (15,47). Indeed, qualified ELISA have been shown to correlate well with the post-vaccination antibody titers against RABV glycoprotein measured in RFFIT (40,47).

Among the eight patients with negative serology in ELISA, seven were also negative in RFFIT. One case with no ELISA antibodies had an RFFIT titre higher than 0.5 IU/ml. This may be explained by the lower sensitivity of the ELISA technique compared to RFFIT. Among the non-responders, one also had a nonresponse to the hepatitis B vaccination. The other non- responders had no past medical history or known intercurrent event that could explain the absence of antibodies. However, these seven non-responders received a booster 2 years after vaccination. Among those for whom we have a serological result one month after booster, all had satisfactory immunity.

Moreover, the post-vaccine immune response involves both the humoral and cellular pathways. Rabies vaccination allows the activation of B cells and CD4+ T lymphocytes that induce an immune response mediated by the production of antibody-secreting plasmocytes and RAVN that migrate along the central nervous system. The production of RVNA will target and destroy rabies virus (45). Thus, the humoral response measured with the RFFIT technique represents only one pathway of the immune response. People with an antibody level < 0.5 IU / ml may present a cellular immunity non-negligible, not yet clearly understood, and not assessed (48).

The study found satisfactory immunogenicity in a young population without comorbidity, which represents a major selection bias limiting the generalizability of our results. In order to extend the shortened vaccination regimen to the general population, it would be necessary to study immunogenicity in older, immunocompromised or children volunteers.

Indeed, as *Kamoltham et al.* immunogenicity at one year in children who received PrEP in two doses ID at D0 and D3, was insufficient (RFFIT < 0.5 IU/ml) and lower than the values of the other groups. However, after injection of a booster, 100% of children had sufficient immunogenicity in the group that received two or three doses of PrEP (21). Several studies including older people over 50 years old showed that immunity declines more rapidly in this population compared to younger people probably due to a less efficient immune system (32,49,50). Indeed, immunosenescence is known to be a cause of poor response to vaccination (51). Similarly, studies of HIV patients or immunocompromised patients with low CD4+ T cells show a lower response after primary vaccination (48,52,53). However, factors leading to inadequate antibodies titres are unpredictable and not clearly understood, as *Parize et al* showed with immunocompromised patients under immunosuppressive therapies (54).

Although our vaccination scheme uses the IM route as recommended by the vaccine producer license, WHO now recommends the ID route. Indeed, the main interest of the ID route is to facilitate the exposure of several antigens to the numerous antigen-presenting cells more prevalent in the skin than muscle (15–17). Furthermore, the ID route may allow a gain in doses since the dosages injected are lower. Indeed, since the vaccine vial's capacity is 0.5ml and the ID vaccine regimen needs 0.2 ml, it seems necessary for vaccine producers to request an extension of the license in order to facilitate the use of the ID route and not waste vaccine. In addition, ID vaccination requires qualifications on the part of the vaccinator. The feasibility makes its implementation difficult and adapted only for centers using many vaccines. However, new devices such as the ID injectors are being developed to standardize and facilitate ID vaccination (55). Different kinds of injectors exist and have already been tested in trials especially with the poliovirus vaccine (56). For example, the "PharmaJet Tropis jet injector" has been tested in a randomized controlled trial in Cuba after one fractional dose of inactivated poliovirus vaccine (1/5 the dose size) as compared to a full dose with traditional needle and syringe intradermal technique. The use of injectors allows a reduction of sharps, needlestick injuries and associated costs and facilitates the vaccine delivery.

Moreover, one of the benefits is its potential for dose-sparing with the ID route that enables to improve accessibility for high cost vaccines and for areas where manufacturing capacities are limited (57).

Thus, it would be interesting to compare the ID and IM routes of administration in order to confirm or not the benefit of the ID delivery. It would be relevant to test the efficiency and the immune response of the rabies vaccine delivered with the ID injector since it has been demonstrated for the poliovirus vaccine (56,58). Several studies have evaluated the immunogenicity of the ID route for the rabies vaccination. Indeed, *Endy et al*. showed acceptable antibody level (50% at D365) in all subject vaccinated with a two ID injections regimen compared with IM scheme (40%) (59). Furthermore, *Soentjens P. et coll* showed a higher immune response after booster in people who received a shortened PrEP vaccine regimen with two ID injections at D0 and D7 compared to a 3-injection ID regimen (8).

V. Conclusion

Although WHO recommend the 2-injection vaccination scheme, France continues to follow the HCSP's recommendations with the 3-injection vaccination scheme pending the conclusions of the HCSP working group on a shortened vaccination scheme. Our study showed in a population of healthy young students a good post-vaccination immunogenicity at two years in 81.7% of cases. We recommend for young people occupationally exposed a short regimen accompanied by serology control with a booster in case of a drop below the threshold value.

A Toulouse le 27/09/2021

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Immunogenicity of a pre-exposure rabies vaccination in two intramuscular injections

Background: The current rabies pre-exposition prophylaxis vaccination scheme in France, requiring three injections intramuscular (IM) of vaccine at D0, D7 and D21 is long, expensive and restrictive. According to the latest WHO recommendations (2018), the pre-exposure prophylaxis could be shortened into two injections IM seven days apart. We surveyed a cohort of veterinary students occupationally exposed to rabies who received a shortened vaccination regimen in two injections IM at D0 and D7. We analyzed serological data two years later in order to assess the immunogenicity of this short regimen.

Methods: After exclusion of patients with missing data or having received a third dose of vaccine, 159 students vaccinated with 2 injections IM seven days apart in 2019 and who performed a serological test in 2021 were included in the study.

Findings: Sera from 115/159 (72%) subjects displayed a protective antibody level by ELISA two years after vaccination. Among the 44 remaining subjects for whom sera were tested by RFFIT, 15 displayed a protective antibody level (34%). Finally, 130/159 subjects (81.7%) were considered as being protected against rabies, while 29/159 (18.2%) were not and were call back to receive a third injection.

Interpretation: In this retrospective survey of young healthy subjects who received PrEP with two IM injections, 81.7% had sufficient immunogenicity 2 years after vaccination and didn't need a third dose of vaccine. We believe that PrEP with this shortened vaccination scheme is relevant and could be applied for young healthy people occupationally exposed to rabies, followed by a serological control with a booster in case of a drop below the threshold value.

Key words: Rabies, pre-exposure vaccination, shortened regimen, immunogenicity, intramuscular route

Immunogénicité d’une vaccination antirabique préexposition en deux injections intramusculaires

Contexte : La prophylaxie pré-exposition (PrEP) contre la rage en vigueur en France nécessite trois injections intramusculaires (IM) de vaccin à J0, J7 et J21 rendant ce schéma vaccinal long, coûteux et restrictif. Selon les dernières recommandations de l'OMS (2018), la prophylaxie pré-exposition pourrait être raccourcie en deux injections IM à sept jours d'intervalle. Nous avons étudié une cohorte d'étudiants vétérinaires exposés professionnellement à la rage qui ont reçu un schéma vaccinal raccourci en deux injections IM à J0 et J7. Nous avons analysé les données sérologiques deux ans plus tard afin d'évaluer l'immunogénicité de ce schéma court.

Méthodes : Après exclusion des patients ayant des données manquantes ou ayant reçu une troisième dose de vaccin, 159 étudiants vaccinés avec 2 injections IM à sept jours d'intervalle en 2019 et ayant réalisé un test sérologique en 2021 ont été inclus dans l'étude.

Résultats : Les sérums de 115/159 (72 %) sujets présentaient un taux d'anticorps protecteur en technique ELISA deux ans après la vaccination. Parmi les 44 sujets restants dont les sérums ont été testés par RFFIT, 15 présentaient un niveau d'anticorps protecteur (34%). Enfin, 130/159 sujets (81,7%) ont été considérés comme protégés contre la rage, tandis que 29/159 (18,2%) ne l'étaient pas et ont été rappelés pour recevoir une troisième injection.

Interprétation : Dans cette étude rétrospective de jeunes sujets sains qui ont reçu une PrEP en deux injections IM, 81,7% avaient une immunogénicité suffisante 2 ans après la vaccination et n'ont pas eu besoin d'une troisième dose de vaccin. Nous pensons que la PrEP avec ce schéma de vaccination raccourci est pertinente et pourrait être appliquée pour les jeunes sujets sains exposés professionnellement à la rage, suivie d'un contrôle sérologique avec un rappel en cas de baisse en dessous du seuil.

Mots clés : Rage, vaccination pré-exposition, schéma court, immunogénicité, voie intramusculaire