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Predictive factors for the neutralizing antibody response following pre-exposure rabies immunization: validation of a new booster dose strategy

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Abstract

A prospective cohort of 312 subjects who received pre-exposure rabies immunization and who were monitored serologically with a 10-year follow-up was assessed using multivariate analysis. The aim was to propose a new booster dose strategy by identifying predictive factors for the durability of the neutralizing antibody response. Evaluation bore on several factors relating to: (1) demographic characteristics: age, gender; (2) vaccines: type of vaccine (HDCV or PVRV), injection regimen (D0–D28–D365 or D0–D7–D28–D365) and vaccine lots' antigenic potency; and (3) resulting antibody titers. Logistic regression analysis enabled the authors to establish a predictive model for immunized subjects' serological status at ten years' follow-up expressed as a *P* probability for seroreversion (antibody titer <0.5 IU/ml). Highly significant factors were the immunization regimen, the type of vaccine used and the antibody titer at D379. A *P* value <0.4 identified subjects as "good" responders who were sure to be have satisfactory antibody titers at 10 years and who required a single booster dose every 10 years. A *P* value ≥ 0.4 identified subjects as "poor" responders in whom a specific follow-up and booster dose strategy is proposed. This new immunization strategy could at least be applied to subjects with a frequent risk of exposure, as defined by institutional recommendations. This new immunization strategy should nevertheless undergo an external validation and a cost-effectiveness evaluation.

Keywords: Rabies; Pre-exposure; Immunization

1. Introduction

Pre-exposure immunization using cell-culture rabies vaccines administered by intramuscular injection should include three doses at D0, D7 and D28 (or D21) according to institutional recommendations issued by the World Health Organization (WHO) and the Advisory Committee of Immunization Practices (ACIP) of the Centers for Disease Control and Prevention [1,2]. Although not included in these recommendations, the usefulness of a booster dose administered systematically at 1 year (D365) has recently been shown [3]. This booster dose is associated with a seroconversion rate of 96.8% at 10 years, seroconversion being defined as a neutralizing antibody titer ≥ 0.5 IU/ml as measured by the Rapid Fluorescent Focus Inhibition Test (RFFIT) [1,2,4].

The predictive factors for the durability of the neutralizing antibody response to pre-exposure immunization are surely not all identified. The influence of age has been mentioned [3,5]. In a univariate analysis carried out in a prospective study over a 10-year period, we have shown the influence of the type of vaccine and the immunization route used as well as the predictive value of the results of a titer measurement at 14

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days following the 1-year booster dose on the subsequent evolution of antibody titers in immunized subjects [3]. Furthermore, discriminating factors between a "good" and a "poor" responder have never been analyzed in a systematic way, although observation has long suggested that such a dichotomy does indeed exists [3,6]. Based on all these factors, institutional recommendations advise that antibody titers be monitored every 6 months in subjects with a continuous risk of exposure and once every one (WHO) to two (ACIP) years in subjects with a frequent risk of exposure [1,2].

The aims of this multivariate analysis study based on data obtained in a cohort of immunized subjects followed prospectively for a period of 10 years [3] were: (1) to identify factors with a predictive and discriminating value relating to the durability of the neutralizing antibody response; (2) to build a predictive model based on these factors and (3) to conclude with proposals for a new immunization strategy.

2. Material and method

2.1. Subject database

The subject database documented demographic, immunization and serological data pertaining to a cohort of 312 subjects having received pre-exposure rabies immunization in 1984 and 1985 and followed prospectively until 1996 [3,7].

Demographic data were subjects' gender and age. Initially, the cohort was composed of 224 men and 88 women. Subjects' average age was 41.6 ± 13.5 years, with values ranging between 12 and 79 years. Subjects were mostly occupationally exposed personnel who were registered with the Mutualité Sociale Agricole, the French health insurance system for agricultural workers. Subjects were residents of eight districts in the Aisne Département where vulpine rabies has been enzootic since 1972. The number of subjects lost to follow-up was 8.3%, 33.3% and 43.6% at 1, 5 and 10 years, respectively, after the initiation of immunization.

Immunization data were vaccine type, vaccine lots' antigenic potency and the injection regimen used. Two types of vaccines were used: human diploid cell culture rabies vaccine (HDCV) [8–10] and purified Vero cell rabies vaccines (PVRV) [11,12]. Lots used and their antigenic potency evaluated by the NIH test [13] were as follows: for HDCV vaccine, lot W1250 (1.5 IU/dose), lot X1290 (3.9 IU/dose), lot Y0652 (2.6 IU/dose); for PVRV vaccine, vaccine lot S14001 (4.5 IU/dose), lot S1441 (2.7 IU/dose), lot S1425 (3.0 IU/dose). Both of these vaccines were administered by intramuscular injection in the deltoid area using two different regimens: either (1) immunization at D0 and D28; or (2) immunization at D0, D7 and D28 followed in both cases by a booster dose at D365. The type of vaccine and immunization regimen were randomly assigned to each of the eight districts.

The serological data pertained to the neutralizing antibody titers. These titers were evaluated using the RFFIT at D42 (14 days following the D28 vaccine dose), at D365 (on the day of the D365 booster dose), at D379 (14 days after the D365 booster dose), and each year during a 10-year period. None of the subjects had measurable neutralizing antibody titers on the day of the first injection (D0). Subjects found to have a titer <0.5 IU/ml after D379 were defined as seroreverted (seroreversion) and immediately received a booster dose. A dose was injected in all subjects at 10 years' follow-up, and antibody titers were measured 14 days later.

2.2. Statistical analysis

Dichotomous qualitative variables were gender, type of vaccine and injection regimen. A discrete quantitative variable, the antigenic potency of the vaccine lots used was converted to a dichotomous qualitative variable based on whether the vaccine titer was greater or lower than 2.9 IU/dose. This arbitrary threshold divided the lots equally into two categories. Continuous quantitative variables were the neutralizing antibody titers measured at D42, D365 and D379. All these variables were a priori potentially predictive of subjects' serological status at 10 years' follow-up. This serological status was a dichotomous, qualitative variable based on whether the antibody titer was <0.5 IU/ml (seroreversion) or ≥ 0.5 IU/ml (seroconversion).

Univariate analysis was initially performed in order to determine which among the potentially predictive variables were significantly linked to the subjects' serological status at 10 years. Qualitative data were compared using a Chi-square test. The average for quantitative variables were compared using Student's *t*-test, antibody titers being expressed as logarithms in order to observe conditions for normal distribution of variables.

Multivariate analysis was subsequently carried out by introducing potentially significant variables whose degree of significance was lower than 0.25 in a logistical regression model using univariate analysis ($p < 0.25$). Significance tests for these explanatory variables in multivariate analysis were based on the maximum likelihood for this model. The model's adequacy was confirmed using Hosmer and Lemeshow's test [14].

The probability of seroreversion (P) at 10 years' follow-up in immunized subjects was calculated based on the logistical regression analysis results. A Receiver Operating Characteristic (ROC) curve was designed

based on the sensitivity and specificity of the model computed for various successive P thresholds ranging between 0 and 1. The area under the curve was estimated using Hanley's method, in order to determine the model's discriminative power [14,15].

3. Results

One-hundred and seventy-six subjects out of 312 initially included were evaluated at 10 years' follow-up. Data were missing in seven out of these 176 subjects. Final analysis was therefore conducted using the data collected in 169 subjects. Among these, 47 subjects had seroreverted, including three subjects who had been immunized using the three-dose regimen and 44 who had received the two-dose regimen. There was no significant difference between the 176 subjects present at 10 years' follow-up and the 136 subjects lost to follow-up in terms of seroconversion or the antibody titer as measured at D42, D365 and D379.

The immunization and serological data significantly linked with the serological status at 10 years in univariate analysis were the type of vaccine and the injection regimen used, the antigenic potency of the vaccine lots and the neutralizing antibody titers at D42, D365 and D379. Demographic data were not significantly linked with the serological status at 10 years' follow-up. Although it had been introduced into the logistical regression model, age had no influence on the neutralizing antibody response, unlike what has been suggested in a previous study [5]. The results of this univariate analysis are presented in detail in Table 1.

Multivariate analysis was performed by successively introducing neutralizing antibody titers at D42, D365 and D379 in a basic model which included the vaccine type, the injection regimen, the vaccine lots' antigenic potency and subjects' age. The serological data which warranted the highest degree of likelihood to the model was the subjects' antibody titer at D379. Similarly, various antibody thresholds at D379 were successively introduced in the same basic model. Thresholds of 30, 35 and 40 IU/ml were those which provided the greatest degree of likelihood to the model. The threshold value of 30 IU/ml was used for the model which was finally chosen. Results of this analysis are presented in detail in Table 2.

Odds ratios were calculated for each variable using the logistical regression model. These odds ratios are presented in Table 3. The injection regimen used and the antibody titer at D379 had highly significant and comparable predictive values. The type of vaccine used also had a significant — although lower — predictive value. On the other hand, the antigenic potency of vaccine lots and subjects' age had no significant predictive value. The equation for the logistical regression model which allows the computation of P at 10 years and the value of variables used in this model are shown in Fig. 1. Hosmer and Lemeshow's test confirmed the adequation of the model with $\chi^2 = 103.5$ for 137 d.f. with $p = 0.98$. Fig. 2 shows the ROC curve thus calculated. The area under the curve was estimated at 0.91, which confirms the model's discriminating power. The choice of a P threshold at 0.4 conferred a positive predictive value (PPV) of 100% to the model and a negative predictive value (NPV) of 40.5%. In other words,

Table 1
Univariate analysis results according to serological status at 10 years post-immunization leading to the choice of variables used in the multivariate analysis

Variables[a] Qualitative	N	SC $n1/n2$	SN $n1/n2$	p
Type of vaccine[b] (HDCV/PVRV)	176	54/75	9/38	0.005
Injection regimen[b] (2/3 injections)	176	65/64	44/3	< 0.001
Antigenic potency of the lots[b] (< 2.9/ > 2.9 IU/dose)	176	42/87	22/25	0.08
Gender (male/female)	176	96/33	35/12	0.99
Quantitative		m/SD	m/SD	p
Age: years[c]	176	42.96/12.75	44.23/11.68	0.55
Antibody titers at D42: log (IU/ml)[b]	172	1.36/0.32	0.89/0.42	< 0.001
Antibody titers at D365: log (IU/ml)[b]	172	0.01/0.48	−4.73/0.27	< 0.001
Antibody titers at D379: log (IU/ml)[b]	169	1.73/0.42	1.14/0.36	< 0.001

[a] N, total number of sample subjects; SC, group of study subjects who had seroconverted at 10 years (titer ≥0.5 IU/ml); SN, group of study subjects who had seroreverted at 10 years (titer < 0.5 IU/ml); p, degree of statistical significance; $n1/n2$, sample of subjects for dichotomous qualitative variables; m, mean; SD, standard deviation.

[b] Variables included in the multivariate analysis since $p < 0.25$.

[c] Variables included in the multivariate analysis in spite of $p > 0.25$.

Table 2
Multivariate analysis results leading to the choice of a logistical regression model used to predict subjects' serological status at 10 years' follow-up

Model	L	OR	*p*
M[a]	−75.165		
M + antibody titer at D42 in IU/ml	−67.258	1.032	0.014
M + antibody titer at D365 in IU/ml	−67.091	0.282	0.0084
M + antibody titer at D379 in IU/ml	−56.066	0.946	< 0.001
M + antibody titer at D379 < or ≥15 IU/ml	−63.032	9.7	< 0.001
M + antibody titer at D379 < or ≥20 IU/ml	−60.137	9.4	< 0.001
M + antibody titer at D379 < or ≥25 IU/ml	−60.364	8.8	< 0.001
M + antibody titer at D379 < or ≥30 IU/ml[b]	−56.737	13.0	< 0.001
M + antibody titer at D379 < or ≥35 IU/ml	−57.029	14.3	< 0.001
M + antibody titer at D379 < or ≥40 IU/ml	−56.080	21.7	< 0.001
M + antibody titer at D379 < or ≥50 IU/ml	−64.362	9.0	0.009
M + antibody titer at D379 < or ≥60 IU/ml	−65.616	9.8	0.003

[a] M, basic model which included the type of vaccine, the injection regimen, the vaccine lots' antigenic potency and subjects' age; L, likelihood of the model; OR, odds ratio; *p*, degree of significance.
[b] Model used.

100% of subjects with a calculated *P* value <0.4 will remain seroconverted at 10 years and 40.5% of subjects with a *P* value calculated to be ≥0.4 will have seroreverted at 10 years' follow-up.

4. Discussion

To date, designing a model to predict the long-term humoral immunity conferred by pre-exposure rabies immunization is a novel approach. Firstly, the multivariate analysis used to design this tool confirms the predictive value of the injection regimen used. The immunogenicity of the three-dose regimen — in compliance with international recommendations — but with a booster dose at 1 year is confirmed in terms of ensuring a lasting humoral immunity, and especially in terms of ensuring a 96.8% seroconversion rate at 10 years' follow-up [3]. Secondly, this analysis confirms the high predictive value of the antibody titer measured at D379. This serological monitoring, which evaluates primoimmunization and the effect of the booster dose at 1 year, is highly predictive of the evolution of subjects' immunization status at 10 years. These findings serve as basis for a rational booster dose strategy. Furthermore, this analysis confirms the higher degree of immunogenicity of HDCV in comparison with PVRV. On the other hand, the antigenic potency of the vaccine lots used had no significant influence, based on the antigenic potency of the lots used in our study (1.5–4.5 IU/dose) and bearing in mind that a vaccine dose must henceforth have an antigenic potency ≥2.5 IU/dose [1]. Similarly, the age of immunized subjects had no significant influence regarding the studied range (from 12 to 79). Its seems to be in contradiction with the results of a previous study [5]. However, two extreme ranges of age were compared and post-exposure vaccination was concerned in this study.

The validity of this study is first and foremost due to the database's characteristics. These data were collected in a cohort of subjects immunized and followed prospectively for 10 years in field conditions, in a target population residing in an enzootic area. Although

Table 3
Variables' weight used in the logistical regression model

Variable	Definition	OR[a]	CI 95%	*p*
Type of vaccine	HDCV	1		
	PVRV	4.4	[1.4–13.5]	0.009
Injection regimen	3 injections	1		
	2 injections	16.4	[4.1–65.5]	< 0.001
Lots' antigenic potency	> 2.9 IU/dose	1		
	< 2,9 IU/dose	1.4	[0.5–4.0]	0.48
Antibody titer at D379	≥ 30 IU/ml	1		
	< 30 IU/ml	13	[4.8–35.6]	< 0.001
Age	Years	1.033	[0.98–1.08]	0.15

[a] OR, odds ratio; CI 95%, 95% confidence interval; *p*, degree of significance.

$$P = \frac{e^{(-7.111 + 1.484V + 2.801I + 0.366G + 0.032A + 2.567T)}}{1 + e^{(-7.111 + 1.484V + 2.801I + 0.366G + 0.032A + 2.567T)}}$$

Fig. 1. Equation for the logistical regression model used to compute the probability for seroreversion (P) of immunized subjects' at 10 years' follow-up according to the type of vaccine used (V), the type of injection regimen (I), the lots antigenic potency (G), subjects' age (A) and the antibody titer at D379 (T), $e = 2.718$; vaccine: HDCV, $V = 0$; PVRV, $V = 1$; injection regimen: three injections, $I = 0$; two injections, $I = 1$; lots' antigenic potency: >2.9, $G = 0$; <2.9, $G = 1$; age: A = years; antibody titer at D379: >30 IU/ml, $T = 0$; <30 IU/ml, $T = 1$.

subjects were not randomized, randomization effectively took place with regards to the type of vaccine and the immunization regimen used at the geographic and administrative level represented by the district. The validity of the predictive model is further warranted by the statistical method used. The quality of the predictive model used is warranted by the de facto adjustment on each factor, through the control of its adequacy and of its degree of discriminative power. Finally, this validity is confirmed by the properties of the discriminating thresholds used following analysis and while the model was designed. The threshold of 30 IU/ml used for the neutralizing antibody titer at D379 was one of the three threshold values which warranted the highest degree of likelihood to the model (Table 2). It was also the threshold associated with a PPV of 100% as shown in an earlier, univariate analysis using the recommended, three-dose regimen [3]. The threshold of 0.4 used as P value in the model's equation also provides a PPV of 100%. Such a high PPV is mandatory with regards to rabies, a disease which is associated with a mortality rate equal to that of morbidity. It warrants seroconversion, which is generally considered as a surrogate criterion of clinical efficacy [1,2,4].

The limit of this study is that it does not evaluate all the circumstances in which pre-exposure immunization is used. Its conclusions are only applicable to immunization when carried out by intramuscular, deltoid immunization using a vaccine prepared on human diploid cell culture (HDCV) or on Vero cell culture (PVRV) with the Pitman Moore strain. This model could be applied to other cell culture rabies vaccines [16,17] but specific validations would be necessary, even if these vaccines have demonstrated equivalent immunogenic potentials [18,19]. It is not applicable to other routes of vaccine administration than those studied, such as intradermal injection regimens [20,21]. The large number of subjects lost to follow-up entails a risk of statistical bias. However, the absence of significant difference in the neutralizing antibody titer measured at D42, D365 and D379, between the group of subjects subsequently lost to follow-up and that of subjects evaluated at 10 years' follow-up enable the authors to reasonably suppose that their serological status at 10 years would, on the average, have been identical [3]. Another limit of this study is the fact that RFFIT is notoriously unstandardisable and one of the available tests for neutralizing antibody titration. So it would be necessary for each laboratory and for each other type of test to calculate and validate their own titer level at D379.

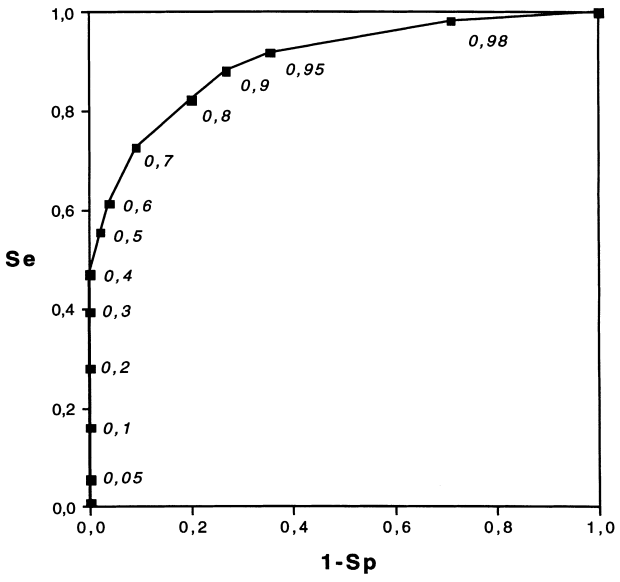

Fig. 2. ROC curve based on the logistical regression model used. The 0.4 probability threshold corresponds to a sensitivity (Se) value of 46.8%, a specificity value (Sp) of 100%, a positive predictive value of 100% and a negative predictive value of 40.5%.

The practical usefulness of this predictive model is due to its discriminating power. It allows one to distinguish between two groups of subjects, based on the computation of the P value using the equation shown in Fig. 1. The first group ($P < 0.4$) is that of "good responders", subjects who are sure to have seroconverted 10 years after the D365 booster dose. These subjects seem to need no other antibody titer measurement and who simply require a booster dose every 10 years. The second group ($P \geq 0.4$) is that of subjects considered as "poor responders", having a 40.5% probability of seroreversion before the 10-year period comes to an end. In these "poor responders", a booster dose strategy must be considered notwithstanding the results of the predictive model.

In absence of serological control after D379, the systematic injection of a vaccine dose every 5 years may also be considered. In case testing is available, a serological evaluation at 3 years (Y3) seems useful. When the three-dose regimen was used in our study cohort, all the subjects who seroreverted had done so before three years had passed. These subjects who had seroreverted at 3 years are confirmed "poor responders" and should justify the use of a booster dose every 3 years insofar as they tend to serorevert once again, in an average time span of 3 years, as shown by their follow-up in the study cohort [3]. Conversely, the subjects who were seroconverted at 3 years will remain so at 10 years and only require a booster dose every 10 years, as do "good responders".

In this recommended, three-dose regimen (D0, D7 and D28) completed with a booster dose at 1 year (D365), analysis based on the 30 IU/ml threshold at D379 may avoid having to compute the P value using the predictive model equation. In this case difference in immunogenicity of HDCV and PVRV vaccines is

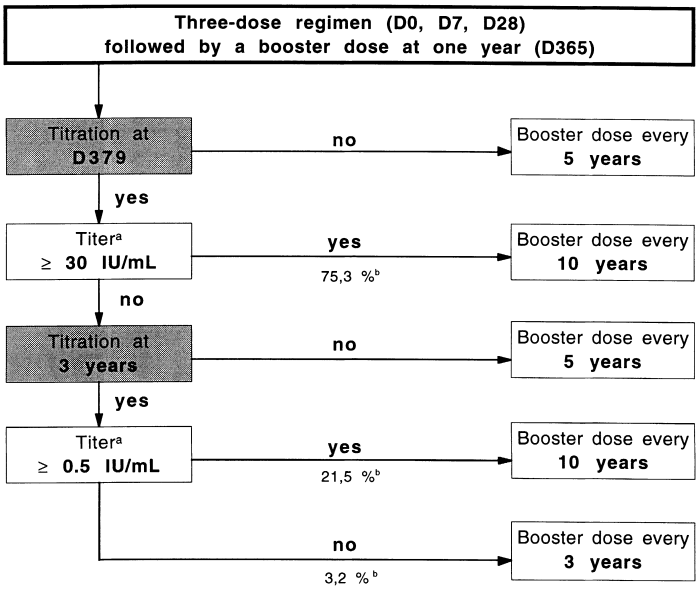

Fig. 3. Algorithm illustrating the suggested immunization strategy. a, antibody titer found using the RFFI Test; b, percentages showing the distribution of cohort subjects illustrated by the algorithm.

no longer significant [3]. The 30 IU/ml value is therefore the only significantly predictive value validated by our model. Furthermore, the proportion of subjects considered to be "good responders" using a threshold $\geq$30 IU/ml is 75.3%. Using the predictive model's equation this proportion is 76%, which is a comparable percentage.

This new strategy may be summed up in the algorithm shown in Fig. 3. It is based essentially on the evaluation of the immunological response profile to immunization. Unlike institutional recommendations, this strategy does not take into account the level of exposure to the virus. In absence of possibility of serological testing for immunization at D379 and/or Y3, this strategy proposes that a booster dose may be injected every 5 years. However, it must be borne in mind that it would leave "poor responders" vulnerable. Therefore, this strategy should not be used in place of institutional recommendations without caution and discussion. In the present instance, this strategy should not be applied to subjects with continuous risk of exposure but it would be tested in case of frequent risk of exposure (as defined by WHO or ACIP [1,2]) in the context of an external validation and cost–effectiveness evaluation.

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