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Immunogenicity and booster efficacy of pre-exposure rabies vaccination

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Summary A multivariate analysis was used to identify factors influencing the immunogenicity of rabies vaccine and to assess the efficacy of booster injections in a cohort of 407 people monitored prospectively for 10 years after primary vaccination. Rabies vaccine (HDCV or PVRV) was injected by intramuscular route either on days 0 and 28 or on days 0, 7 and 28. All the participants received a booster injection on day 365. At the end of follow-up (year 10), 163 subjects had titers >0.5 IU/ml (group A) and 59 subjects had titers <0.5 IU/ml (group B: poor responders). The number of injections had a significant influence ($P < 0.001$) on the magnitude of the serological response to rabies vaccine, but the type of vaccine and the potency of the batches did not ($P = 0.07$ and $P = 0.06$, respectively). The difference between GMTs on day 365 and day 379 was significantly lower in group B than in group A (13 and 50.70 IU/ml, respectively; $P < 0.001$). In conclusion, our study confirms that the rabies pre-exposure vaccination protocol of three intramuscular injections significantly decreases the proportion of poor responders at 10 years. Moreover, our findings indicate that a routine booster injection at 1 year could significantly increase the levels and duration of antibody titers.

1. Introduction

Pre-exposure rabies vaccination (PrEV) is recommended by WHO for people at high risk of exposure to the virus, such as those working in rabies diagnostic or research laboratories, veterinarians, animal handlers, animal rehabilitators and wildlife officers.[1] The Asian Rabies Expert Bureau believes systematic PrEV will result in a rapid decrease in human deaths from rabies.[2] Systematic PrEV of children, who are the most frequent victims of rabies, may prevent premature deaths in areas with a high incidence of canine rabies and where rabies control in dogs has not been achieved or is not effective.

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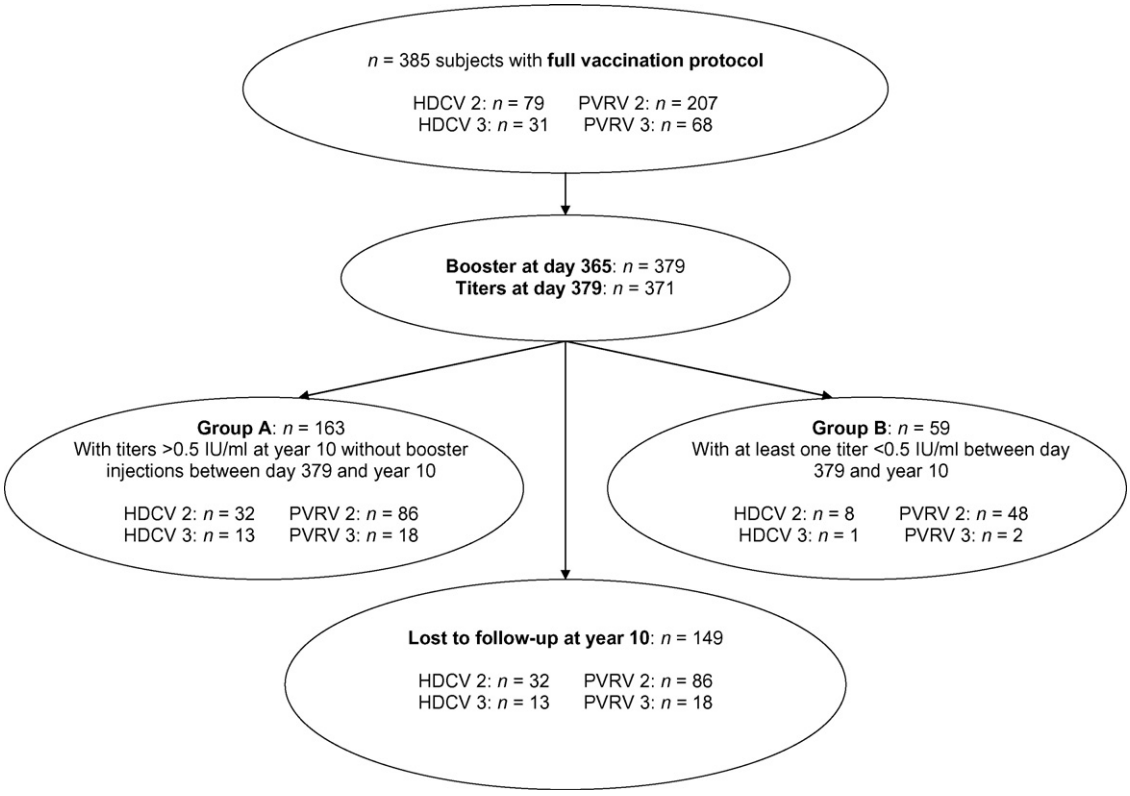

Figure 1 Flowchart of enrolled subjects. HDCV 3: the three-injection protocol with HDCV vaccine; HDCV 2: the two-injection protocol with HDCV vaccine; PVRV 3: the three-injection protocol with PVRV vaccine; PVRV 2: the two-injection protocol with PVRV vaccine.

WHO recommends injections of PrEV, on day 0, day 7 and day 28 (or day 21).[1] The intramuscular route is recommended, but the intradermal route can be used if limited vaccine is available.[1] Periodic booster injections are only recommended for people who are at continual risk of exposure to rabies virus (workers in rabies diagnostic or research laboratories). In this case, the utility of booster injections is based on the results of regular monitoring of neutralizing antibody titers using the rapid fluorescent focus inhibition (RFFI) test. A booster is recommended when the titer falls below 0.5 IU/ml.

PrEV against this invariably fatal disease is designed to protect against occult exposure to rabies virus (laboratory staff, subjects with regular contact with bats, etc.), and also to protect travelers and inhabitants in enzootic zones, where reliable post-exposure treatment against infection by a rabid animal may be difficult to obtain in a timely manner.[3] Serum therapy is not necessary in these circumstances and can be replaced by two vaccine injections 3 days apart.[1] No maximum time limits (between the primary vaccination and the exposure) have been defined for this booster policy.

The efficacy of a rabies vaccine can be estimated only on the basis of its immunogenicity, as clinical studies are not feasible. Many studies have shown that immunogenicity is linked to the type of vaccine and to the mode of administration.[1] By contrast, there are very few data on the variability of immune responses to rabies vaccination. The objective of the present study, based on a cohort of French vaccinees monitored prospectively for 10 years, was to identify factors influencing immunogenicity and, more specifically, to evaluate the efficacy of booster injections.

2. Materials and methods

2.1. Study population

A cohort of 407 subjects (288 men and 119 women) who received PrEV in 1984 and 1985 was followed for 10 years. This cohort consisted of two subgroups enrolled in two studies of intramuscular PrEV. One was published previously and included 312 subjects,[4] and the other included 95 subjects who were immunized using a full-dose vaccination strategy (CHU Reims, 1985, unpublished data). The mean age of enrolled subjects was 42.1 years (range 12—79 years) and all were at risk of exposure through their employment. They lived in eight areas of a French department (Aisne), where fox rabies had been endemic since 1972.

2.2. Protocol of primary vaccination

The two types of vaccine (HDCV prepared on human diploid cells or PVRV prepared on purified Vero cells) and the two injection protocols (vaccine injected into a deltoid muscle on day 0 and day 28 or on day 0, day 7 and day 28) were allocated randomly among the eight areas. The potency of the vaccine batches ranged from 1.06 to 4.54 IU/dose. Since