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Preexposure Intradermal Rabies Vaccination: A Noninferiority Trial in Healthy Adults on Shortening the Vaccination Schedule From 28 to 7 Days

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Background. The existing 4-week preexposure rabies vaccination schedule is costly and often not practicable. Shorter effective schedules would result in wider acceptance.

Methods. We conducted a noninferiority trial in 500 healthy adults comparing the safety and immunogenicity of a 2-visit (days 0 and 7) intradermal (ID) primary vaccination (2 doses of 0.1 mL ID of the human diploid cell culture rabies vaccine [HDCV] at days 0 and 7) vs a standard 3-visit schedule (single dose of 0.1 mL ID at days 0, 7, and 28). One year to 3 years after primary vaccination, a single booster dose of 0.1 mL ID of HDCV was given to evaluate the anamnestic rabies antibody response. The primary endpoint for immunogenicity was the percentage of subjects with an adequate antibody level >0.5 IU/mL 7 days after the booster injection. The safety endpoint was the proportion of participants developing adverse reactions following the primary vaccination and/or booster dose.

Results. All subjects in both study groups possessed a rabies antibody titer >0.5 IU/mL on day 7 following the booster dose. Following the booster dose, subjects exposed to the double-dose 2-visit ID schedule had a geometric mean titer of 37 IU/mL, compared with 25 IU/mL for the single-dose 3-visit schedule ($P < .001$). Local reactions at the injection site following primary vaccination were mild and transient.

Conclusions. In healthy adults, ID administration of a double dose of 0.1 mL of HDCV over 2 visits (days 0 and 7) was safe and not inferior to the single-dose 3-visit schedule.

Clinical Trials Registration. NCT01388985, EudraCT 2011-001612-62.

Keywords. rabies preexposure; prophylaxis; intradermal; accelerated–shortened schedule; rabies vaccination.

Rabies is a neglected tropical disease with a case-fatality rate of nearly 100% [1]. The global annual death toll is approximately 61 000 cases, with greater prevalence in Asia and Africa, where 40% of all animal bite exposures occur in children [2, 3].

Preexposure prophylaxis (PrEP) using rabies vaccine is an important cornerstone in rabies prevention. Because the previous 4-week PrEP schedule was often not practicable, effective, and safe, double-dose 2-visit intradermal (ID) and single-dose 2-visit intramuscular (IM) schedules have recently been recommended as a first-line regimen by the World Health Organization (WHO), with the primary aim of wider acceptance and use both in international travelers and in subjects at risk in endemic countries, especially in children [3–5].

Intradermal administration of 0.1 mL of rabies vaccine (0.1ID) has proven to be as immunogenic as the 1.0-mL IM dose (1IM) vaccination [3–13], offering substantial cost savings when vaccine recipients can be clustered [14]. In addition, ID injections induce a more rapid immune response compared with IM injections via stimulating cutaneous dendritic cells and their draining lymph nodes [15–17]. Studies have demonstrated that a single-dose 3-visit ID schedule can induce long-lasting immunogenicity and result in rapid anamnestic responses following a booster dose many years later [18–23].

Initial priming, defined as PrEP, sometimes occurring long before exposure to effective rabies risk, substantially simplifies the postexposure prophylaxis (PEP) procedures required in case of an animal bite (no need for immunoglobulin administration, and only 2 vaccine injections are needed instead of 5) [3]. 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 [6, 15, 24].

PrEP with rabies vaccine is recommended under the new WHO guideline for individuals at high risk for exposure to rabies due to

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their occupation, travel, and/or residence in an endemic setting with limited access to timely, adequate PEP [3]. Particularly for travelers (including expatriates), rabies PrEP is often not planned in a timely manner prior to departure. Moreover, the high cost of rabies PrEP results in the noninclusion in standard vaccination schemas, thereby resulting in low vaccination rates, in particular for children at risk in low-income countries [3–5].

This noncommercial noninferiority trial aimed to compare immunogenicity 7 days after a single ID booster injection following 2 different priming schedules 1–3 years earlier: a double-dose 2-visit (days 0 and 7) rabies ID vaccination schedule vs a single-dose 3-visit ID schedule (days 0, 7, and 28). The booster injection used in this trial aimed to mimic a true PEP situation by evaluating the anamnestic response.

METHODS

Study Design

This is a single-center, randomized, open-label, noninferiority clinical trial, comparing the booster response following 2 different primary vaccination schedules (PrEP):

- Control group: 3 × 0.1ID schedule (3ID); single-dose 3-visit regimen of 1 intradermal injection (a dose of 0.1 mL [0.1ID]) on days 0, 7, and 28.
- Intervention group: 2 × 2 × 0.1ID schedule (2ID); double-dose 2-visit regimen of 2 ID injections (0.1 mL in 2 separate injection sites [2 × 0.1ID]) on day 0, and 2 injections (in separate sites [2 × 0.1ID]) on day 7.

Study Endpoints

The primary objective of this study was to demonstrate noninferiority of the 2-visit (2ID) schedule compared to the 3-visit (3ID) schedule as assessed by the proportion of participants with adequate rabies antibody titers, measured by rapid fluorescent focus inhibition test (RFFIT), >0.5 IU/mL 7 days following a booster vaccine injection (0.1 mL of human diploid cell culture vaccine [HDCV] administered 1–3 years after primary vaccination). Clinical noninferiority was defined as a loss of no more than 10% of subjects who have adequate rabies antibody levels compared to the 3ID schedule. Notably, subjects showing an antibody titer >0.5 IU/mL at the day 7 postbooster injection are considered to be "lifelong boostable," meaning that additional injections would induce an adequate antibody response [3].

Secondary endpoints were (1) the respective percentage of subjects with RFFIT levels >10.0 IU/mL (corresponding to long-lasting immunity), (2) the geometric mean titer (GMT) of rabies antibody, and (3) the fold increases compared to baseline values 7 days after a booster injection.

Another secondary objective was to assess the percentage of subjects with rabies antibody levels >0.5 IU/mL, the GMT, and the fold increases compared for both study groups on day 35 after the start of primary vaccination.

To evaluate safety objectives, possible serious local and systemic adverse events were assessed after primary and booster vaccination.

Study Site and Subjects

Study participants were recruited from the Belgian Armed Forces. Inclusion criteria were aged 18–47 years, being in preparation for overseas deployment, and willingness to provide informed consent. Subjects who had previously received rabies vaccines or had positive serology, and pregnant or breastfeeding women were excluded. No other vaccinations were given simultaneously with the rabies vaccination. Moreover, subjects with known or suspected immunodeficiency, chronic disease, mefloquine prophylaxis, known allergy to any of the vaccine components, or with overseas deployment within 35 days were also excluded.

A total of 500 participants were recruited and randomized using block randomization to 1 of the 2 ID PrEP schedules. Participation in this study was entirely voluntary and free of any type of coercion or undue influence by superiors.

Ethics and Registration

The trial was conducted in compliance with the Helsinki Declaration and with Good Clinical Practice guidelines [25] and was registered at ClinicalTrials.gov (NCT01388985) and the European Clinical Trials Database (EudraCT 2011-001612-62) .

Vaccination Procedure

The HDCV Mérieux 1 mL vaccine for rabies (Sanofi), registered in Belgium, was used. The vaccine was stored between 2°C and 8°C as recommended by the manufacturer. The following lots were used: E0042, E0374, E0777, G1510, J1248, H1341, and L1204.

Preparation of the injection solution of 0.1 mL (from an ampoule of 1.0 mL) was performed using a separate Gauche 29 fixed needle for insulin injection for each participant. The vaccine was injected intradermally on the forearm. The ID papule was measured and had to be at least 4 mm.

An ID booster dose of 0.1 mL for both groups was planned at least 1 year later, though no later than 3 years following the primary vaccination (day 365–1095).

Immunogenicity

Antibody titers were measured by RFFIT on day 0 (the day of the primary vaccination), on day 35 after the start of the primary vaccination, on the day of the booster vaccine injection, and 7 days later.

Safety

Adverse events and serious adverse events (SAEs) were recorded until 7 and 28 days, respectively, following the completion of the primary vaccination and booster vaccination.

Study Information

This clinical trial was sponsored by the Institute of Tropical Medicine, Antwerp. The recruitment began in October 2011, and the study was completed in January 2016.

Statistical Analysis

For the immunogenicity component, statistical analysis involved per-protocol (PP) analysis, excluding participants who were seropositive on day 0, who did not fully comply with the protocol. The intention-to-treat analysis (ITT) evaluated additional cases mostly in those where serology results were obtained outside of the time window (Table 1). For the safety analysis, all subjects who had received at least 1 dose were included.

Baseline characteristics were summarized in terms of medians and interquartile ranges and categorical characteristics were described as frequency counts and percentages. Serology measurements are presented as percentages of subjects above different cutoff levels, and GMTs are presented with 95% confidence intervals (CIs). The comparison of antibody levels between the 2 groups was assessed by GMT ratios and their respective *P* values.

Two-sided 95% Wilson CIs for the difference in proportions between the 2 groups were used to assess immunogenicity outcomes. Noninferiority of the 2ID schedule was inferred if the 95% CI of the difference was entirely above the −10% noninferiority margin. Segmented mixed models were used to explain the changes in serology over time. Differences in safety results between the 2 groups were assessed using Fisher exact test.

RESULTS

Subject Accounting and Characteristics

Among the 911 screened subjects, a total of 500 subjects were included and randomized (55%) (Table 1). Moreover, among the 240 and 242 subjects completing the primary vaccination schedules in the 3ID and 2ID schedules, 200 (83%) and 211 (87%) received the booster injection, respectively. Of these, 185 (77%) and 183 (75%) subjects were included in the PP analyses for immunogenicity on the 3ID and 2ID schedule, respectively (Table 1). Baseline characteristics of the 498 randomized subjects who received at least 1 rabies vaccination dose are described in Table 2. Both groups were similar in all demographic aspects.

Adequate RFFIT ≥0.5 IU/mL at Day 7 After a Single Booster

Evaluating the ITT analysis, the booster dose was provided to 59% of 211 study participants vs 54% of 200 subjects in the first year following primary vaccination, in 35% vs 38% in the second year, and in 6% vs 8% in the third year, for the 2ID and 3ID schedules, respectively.

In the PP analysis (Table 3), all subjects (100%) in both groups displayed RFFIT >0.5 IU/mL on day 7 following a single 0.1ID booster dose. The difference of the 2 groups ranged between −2% and 2%.

RFFIT ≥10 IU/mL at Day 7 After a Single Booster

Regarding antibody titer >10 IU/mL following a single 0.1ID booster dose, the proportion of participants reaching this level

Table 1. Study Participants Accounting for Intention-to-Treat and Per-protocol Analysis on Day 7 After Booster Dose Injection (N = 410)

Characteristic	No. (%)	
Screening failures	410	
Not interested/unwilling	294 (71.5)	
Unable to respect timelines	60 (15)	
Exclusion criteria (eg, chronic disease, immunodeficiency, pregnancy, breastfeeding, on mefloquine)	56 (13.5)	
Randomized but withdrawal before start procedures (n = 250)	1	1
Excluded from ITT analysis day 35 (n = 249)	9 (3.6)	7 (2.8)
Lost to follow-up	5	4
Patient unavailable (deployed in mission; left military service)	1	1
Sample unavailable/inadequate	3	2
ITT analysis (n = 240)		
Excluded from ITT analysis days 365–1095	40 (16.7)	31 (12.8)
Lost to follow-up	25	26
Death	0	1
Sample unavailable/inadequate	15	3
Other	0	1
Included in ITT analysis	200 (83.3)	211 (87.2)
Excluded from PP analysis	15	28
Above age limit	1	3
Sample unavailable/inadequate	0	2
Baseline rabies serology >0.5 IU/mL	3	1
Serology result obtained outside of time window	11	22
Included in PP analysis	185 (77)	183 (75.5)

Abbreviations: 2ID, double-dose intradermal vaccination, 2 visits over 7 days; 3ID, single-dose intradermal vaccination, 3 visits over 28 days; ITT, intention-to-treat; PP, per-protocol.

Table 2. Baseline Characteristics of All Study Participants

Characteristic	3ID Schedule	2ID Schedule
No.	249	249
Age, y, median (IQR)	29 (24–35)	28 (23–34)
Age category, y		
≤20	11 (4.4)	17 (6.8)
21–30	138 (55.4)	136 (54.6)
31–40	71 (28.5)	60 (24.1)
41–50	29 (11.7)	36 (14.5)
Sex		
Male	237 (95.2)	241 (96.8)
Female	12 (4.8)	8 (3.2)
Serology category at baseline		
≤0.5, IU/mL	245 (98.4)	248 (99.6)
>0.5, IU/mL	4 (1.6)	1 (0.4)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: 2ID, double-dose intradermal vaccination, 2 visits over 7 days; 3ID, single-dose intradermal vaccination, 3 visits over 28 days; IQR, interquartile range.

in the 2ID schedule was higher than in the 3ID schedule (96% vs 83% with a difference of 13% [95% CI, 7%–19%]). However, ITT analysis results and additional batch analysis for the different lots were similar (not shown).

Other Serology Results

Furthermore, subjects in the 2ID group exhibited a GMT of 37 (95% CI, 33–42) IU/mL following the booster vaccination offered 1–3 years later, compared with a GMT of 25 (95% CI, 22–29) IU/mL for the 3ID group ($P < .001$) (Figure 1 and Table 4). In addition, GMT values on the day of booster injection in the 2ID schedule were higher (3.4 [95% CI, 2.9–3.9] IU/mL) compared with these of the 3ID schedule (2.0 [95% CI, 1.7–2.4] IU/mL) ($P < .001$).

Changes in serology over time are presented in Figure 2. The 2ID schedule exhibited a higher slope following the booster dose (46.4 [95% CI, 39.1–53.6]) compared with the 3ID schedule (35.7 [95% CI, 26.1–45.3]).

In the descriptive statistics (results not shown), an overall trend was observed in GMT levels being significantly higher following primary vaccination for the 3ID schedule and higher following the booster dose for the 2ID schedule. Furthermore, male sex ($P < .0001$), age between 20 and 30 years ($P = .0021$) and between 30 and 40 years ($P = .0023$), and a higher prebooster GMT ($P < .0001$) were associated with improved postbooster results in favor of the 2ID schedule. Moreover, postbooster GMT levels were also higher in favor of the 2ID schedule when analyzed by booster dose timing, though these were only significant when the interval between PrEP and PEP was >25 months ($P = .0002$).

Day 35 Results After Primary Vaccination

All subjects in the PP analysis set attained RFFIT results >0.5 IU/mL 35 days after starting primary vaccination. Additionally, more subjects exhibited rabies antibody titers >10 IU/mL in the 3ID group (82%) compared with the 2ID group (70%) (difference, −12% [95% CI, −19% to 4.3%]). Furthermore, ITT and additional batch analysis results for the different lots were similar (not shown).

Safety

A summary of safety data throughout the entire study period is presented in Table 5. Notably, 1 SAE (reversible diplopia and hemianopsia) occurred during the primary vaccination session 14 days after receiving the final rabies vaccine injection (3ID schedule) and some days after receiving a measles-rubella-mumps vaccine in another medical center, in violation of the protocol. Also, 2 SAEs (1 case of esophagitis and another with dyspnea, angioedema, and urticaria) occurred following a booster dose (2ID schedule).

Local irritation at the injection site (mild and transient) following primary vaccination tended to occur more frequently in the 3ID compared with the 2ID schedule (51.8% vs 43.4%; $P = .07$). In contrast, local irritation was more often observed following the booster dose in the 2ID group (38.8% vs 48.8%; $P = .03$). The number of subjects with systemic discomfort related to injections was very low and did not differ significantly between the 2 groups (3ID vs 2ID) following primary vaccination (14.5% vs 11.6%; $P = .42$) or booster injection (5.4% vs 5.8%; $P = 1$).

DISCUSSION

In this trial, noninferiority was met for the primary immunogenicity endpoint, with a 100% observed adequate antibody

Table 3. Seroprotection Rates, Per-protocol Analysis, Day 7 After Booster Vaccination

Serology	3ID Schedule	2ID Schedule	% Difference (95% CI)[a]
Per-protocol analysis	n = 185	n = 183	
Subjects with serology >0.5 IU/mL	185/185 (100 [98–100])	183/183 (100 [98–100])	0 (–2.1 to 2)
No. of subjects with serology >10 IU/mL	154/185 (83 [78–89])	176/183 (96 [93–99])	13 (7–19)

Data are presented as no./No (% [95% CI]) unless otherwise indicated.

Abbreviations: 2ID, double-dose intradermal vaccination, 2 visits over 7 days; 3ID, single-dose intradermal vaccination, 3 visits over 28 days; CI, confidence interval.

[a]Two-sided 95% Wilson CIs for the difference in proportions between the 2 groups (2ID–3ID).

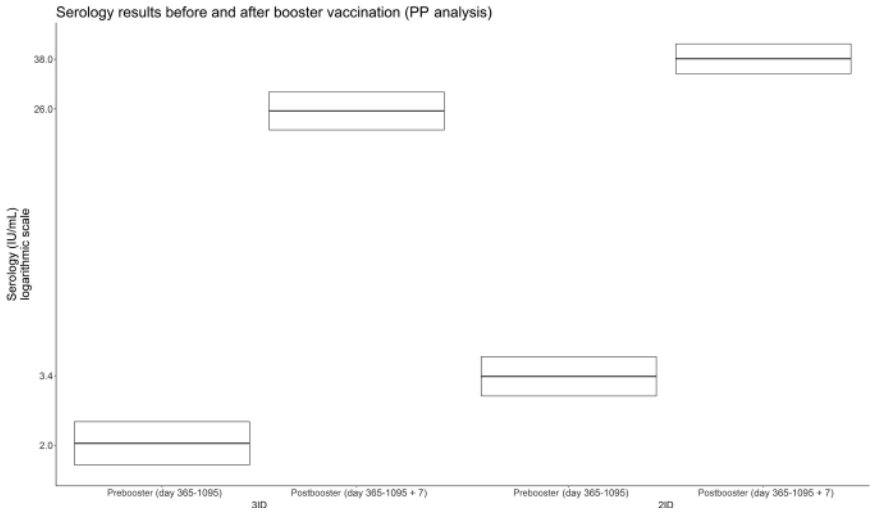

Figure 1. Serology results (geometric mean titer and 95% confidence interval) before and 7 days after booster vaccination (per-protocol analysis by dot plot). Abbreviations: 2ID, double-dose intradermal, 2 visits over 7 days; 3ID, single-dose intradermal, 3 visits over 28 days; PP, per-protocol.

response (>0.5 IU/mL) observed 7 days after booster dose injection of 0.1 mL ID administered 1–3 years following primary vaccination. Furthermore, analysis of secondary endpoints highlighted the superiority of the 2ID schedule, both in the proportion of participants with long-lasting protection >10 IU/mL (96% vs 83%) and for the obtained GMT (37 vs 25) following booster injection. In addition, a double-dose 2-visit 0.1 mL ID PrEP with HDCV in adult subjects was shown to be as safe as the single-dose 3-visit schedule.

All subjects in the PP and ITT analysis sets (100%) attained RFFIT results of >0.5 IU/mL at day 35 following primary vaccination. Notably, the clinical trial was designed to evaluate results following a booster dose between the 2 groups (and not following primary vaccination results). Therefore, the timelines for serology testing after final injection in the 2 primary vaccination schedules were different in the 3ID schedule (+7 days after last vaccination) compared with the 2ID schedule (+28 days after last vaccination), which explains significant differences in the proportion of successful vaccinations, serology outcomes, GMTs, and side effects for both groups. The higher titers and more frequent side effects following primary vaccination observed with the 3ID schedule were likely attributable to the longer period of primary vaccination in this group.

This noncommercial clinical trial has several strengths including the randomized controlled design, high statistical power (at least 85%), good follow-up rates (>80%), substantial experience in performing appropriate ID injections and conducting vaccine trials, and blinding of laboratory study staff, as well as the use of the gold standard for serology in a laboratory with proficiency in testing. Study limitations include most participants being healthy young adult males, and the follow-up after booster injection not exceeding the 3-year-interval. Moreover, different batches of HDCV vaccine were used in this trial over 4 years. Also, for budgetary reasons, the standard single-dose 1IM 3-visit schedule was not included in the comparison.

Notably, no consensus exists on how high GMT levels must be following primary and booster vaccination. We aim to underline the need for uniform definitions due to the fact that usage of different rabies vaccines may lead to different antibody responses, making comparisons between schedules, vaccines, routes of administration, and diagnostic techniques very challenging. In the present study, GMT results 7 days after booster injection were much higher compared with other trials using priming 2-visit vaccine ID schedules (total vaccine dose of 0.2ID or 0.4ID) [26–29], and were similar with 2-visit IM schemes (total vaccine dose of 2IM) [29–31].

Table 4. Geometric Mean Titers Before and After Booster Vaccination (Per-protocol Analysis)

Serology	3ID Schedule, GMT (95% CI)	2ID Schedule, GMT (95% CI)	Geometric Mean Ratio	*P* Value
Overall				
Prebooster serology, IU/mL	2.0 (1.7–2.4)	3.4 (2.9–3.9)	0.60 (.48–.75)	<.0001
Postbooster serology, IU/mL	25 (22–29)	37 (33–42)	0.68 (.57–.81)	<.0001

Abbreviations: 2ID, double-dose intradermal vaccination, 2 visits over 7 days; 3ID, single-dose intradermal vaccination, 3 visits over 28 days; CI, confidence interval; GMT, geometric mean titer.

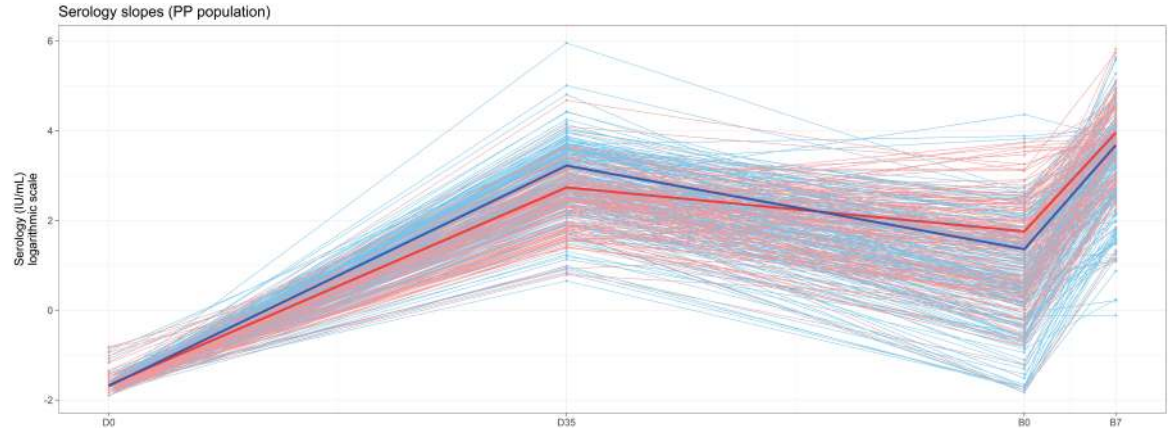

Figure 2. Segmented mixed models of respective serology slopes (per-protocol analysis). The changes in serology over time in the 2 groups were evaluated using segmented mixed models with random intercept and random slopes fitted separately in the subsets of each vaccination schedule. Time and indicator variables before and after booster were used as fixed effects. Single-dose 3-visit (3ID) model predictions on population (thick blue line) and on individual base (thin blue line). Double-dose 2-visit (2ID) model predictions on population (thick red line) and on individual base (thin red line). Abbreviations: 2ID, double-dose intradermal, 2 visits over 7 days; 3ID, single-dose intradermal, 3 visits over 28 days; B0, serology check before booster dose; B7, serology check 7 days after booster dose; D0, serology check at day 0 of start of primary vaccination; D35, serology check at day 35 after start of primary vaccination; PP, per-protocol.

In addition, "boostability" following a single booster dose is characterized by a rapid increase in anamnestic antibodies due to an earlier priming. The moment to evaluate an adequate booster response—in contrast with many other trials—was defined by our protocol as 7 days instead of 14 days after the booster dose [24, 32]. After a bite, the time to adequate "boostability" is crucial following booster vaccination, due to the fact that the incubation time of rabies is at least 5–7 days.

Data from the present study substantiate the safety and the immunogenicity of the 2ID regimen for rabies immunization in adult healthy travelers. However, whether this could be a cost-effective alternative to IM vaccination in at-risk populations in endemic regions warrants further investigation. Indeed, 2ID schedules with fewer visits would make treatment simpler and less expensive (compared to routinely used IM). Notably, the results of this 2ID PrEP schedule in healthy soldiers were discussed with members of the Strategic Group of Experts on Immunization, which recommended this schedule as a new first-line PrEP schedule both in international travelers and in subjects at risk in endemic countries [3].

Currently available licensed rabies vaccines, designed and manufactured for IM use, could be safely used via the ID route [3]. The WHO now endorses a double-dose 0.1ID to be equivalent compared to the single 1IM dose [3]. Many countries hesitate to use the ID route due to lack of regulatory authorization, even when stockpile problems exist [3]. Recent evidence has confirmed that ID use (with purified chick embryo cell vaccine [PCECV] against rabies), compared with IM for PrEP and PEP, was safe and produced adequate antibody responses [10]. Similar reluctance for ID use has been observed for influenza and yellow fever vaccination, although ID vaccination exhibited adequate efficacy, and even exhibited superiority to IM vaccination in some indications [33–35]. The Belgian Health Authority adopted both new WHO first-line PrEP regimens from 1 May 2018 [36], and many other countries will hopefully follow. This hesitancy against shortening the PrEP schedule to 2 visits or using the ID technique is, in our opinion, not justified. In contrast with all other vaccine-preventable diseases, and considering the concept of prime and boost in rabies prevention, subjects will always require additional rabies postexposure injections

Table 5. Safety Analyses for the Primary Vaccination Period for the Whole Study Period

Reaction	3ID Schedule (n = 249)	2ID Schedule (n = 249)	*P* Value
Any AE	190 (76.3 [70.6–81.2])	190 (76.3 [70.6–81.2])	1
Any possibly, probably, or definitely vaccine-related AE	173 (69.5 [63.5–74.9])	171 (68.7 [62.7–74.1])	.92
Any serious AE	1[a] (0.4 [.07–2.24])	2[b] (0.8 [.22–2.88])	1
Local irritation of injection site (redness, swelling, rash, itching)	164 (65.9 [59.8–71.5])	165 (66.3 [60.2–71.9])	1
Systemic reaction related to injections	46 (18.5 [14.1–23.8])	43 (17.3 [13.1–22.5])	.82

Data are presented as No. of subjects (% [95% confidence interval]).

Abbreviations: 2ID, double-dose intradermal vaccination, 2 visits over 7 days; 3ID, single-dose intradermal vaccination, 3 visits over 28 days; AE, adverse event.

[a]Diplopia and hemianopia.

[b]Esophagitis, dyspnea, angioedema, and urticaria.

following exposure to rabies risk to stimulate the adaptive "trained" immunity [37].

CONCLUSIONS

Rabies represents an unremitting and neglected global challenge. As such, new shortened ID schedules aim to be cost-, dose-, and time-sparing, while maintaining safety and effectiveness [3, 38]. Safe and effective PrEP for travelers or people living in endemic rabies regions may be achieved with a double-dose 2-visit 0.1ID regimen, with 100% adequate antibody response following a booster injection of 0.1ID 1–3 years after primary vaccination. Whether this schedule is safe and effective in children in low-income countries still needs to be explored. Shortened PrEP ID schedules, using simpler low-dose vaccine regimens, can be considered an illustration that less can be more [6, 8, 11, 24, 38–43].

Notes

Author contributions. A. A. and P. S. conceived the research project. P. S., P. A., and A. A. researched, designed, and executed the trial. H. V. L. organized and coordinated data management. A. T. analyzed the data and P. S., E. B., Y. V. H., A. T., H. V. L., R. R., A. A., and P. V. D. wrote the manuscript. B. B. and S. V. G. were responsible for laboratory analyses.

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