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Comparative Immunogenicity and Safety Trial of 2 Different Schedules of Single-visit Intradermal Rabies Postexposure Vaccination

Patrick Soentjens,[1,2] Katrien De Koninck,[1] Achilleas Tsoumanis,[2] Natacha Herssens,[2] Dorien Van Den Bossche,[1,2] Sanne Terryn,[3] Steven Van Gucht,[3] Pierre Van Damme,[4] Yven Van Herrewege,[2] and Emmanuel Bottieau[2]

[1]Center for Infectious Diseases, Queen Astrid Military Hospital, Brussels, [2]Department of Clinical Sciences, Institute of Tropical Medicine, Antwerp, [3]National Reference Centre for Rabies, Sciensano, Brussels, and [4]Center for the Evaluation of Vaccination, University of Antwerp, Belgium

Background. Effective and safe single-visit rabies vaccination for pre- and postexposure prophylaxis (PrEP and PEP) could substantially simplify rabies prevention and therefore increase compliance.

Methods. In a comparative trial, 303 healthy adults received a primary vaccination that consisted of 2 intradermal (ID) doses of 0.1 mL of the purified chicken embryo cell vaccine (PCEV) during a single visit. One year later, participants were randomly assigned to receive either 4 or 2 ID PEP booster doses of 0.1 mL PCEV during a single visit. The primary endpoint for immunogenicity was the percentage of participants with an adequate antibody level (>0.5 IU/mL) 7 days after the booster doses. The safety endpoint was the proportion of participants who developed adverse events (AEs) following primary and/or booster vaccination.

Results. All participants, except 1 (99.3%) in each study group, had a rabies antibody titer >0.5 IU/mL on day 7 following the booster schedules. Participants exposed to the 4-dose PEP schedule had a geometric mean titer of 20 IU/mL vs 14 IU/mL for the 2-dose PEP schedule ($P = .0228$). Local reactions at the injection site following PrEP and PEP were mild and transient and only seen in 14.9% and 49.6%–53% of the participants, respectively. No serious AEs were reported.

Conclusions. In healthy adults, a 2-dose (2 × 0.1 mL) single-visit ID PEP schedule was as immunologically adequate and safe as a 4-dose (4 × 0.1 mL) single-visit PEP schedule 7 to 28 months following a 2-dose (2 × 0.1 mL) single-visit ID PREP.

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Keywords. Rabies; postexposure prophylaxis; pre-exposure prophylaxis; intradermal; single-visit.

Rabies is a preventable neglected tropical disease with a very high case-fatality rate [1]. The annual death toll is approximately 61 000 cases, 40% of them children, with higher prevalence in Asia and Africa [2, 3]. In 2015, the World Health Organization (WHO) called for action by setting a goal of zero dog-mediated rabies deaths in humans by 2030, worldwide [4].

WHO has recently recommended rabies 2-visit pre-exposure prophylaxis (PrEP) schedules instead of 3-visit schedules, with the main aim to be cost-, dose-, and time-sparing, while still ensuring the safety and clinical effectiveness of these preventive interventions [3]. WHO recommends as first-line 2-visit PrEP: a 2-dose (0.1 mL in 2 different anatomic sites) intradermal (ID) schedule (2^2ID) (2: 2 visits, ^{2}: 2-dose on each visit) or a single-dose (1 mL) intramuscular (IM) schedule (2^1IM) (2: 2 visits, ^{2}: 1-dose on each visit), each administered on days 0 and 7 [3]. This new rabies PrEP schedule has been recently implemented in Belgium [5]. A recent metaanalysis has confirmed that all PrEP regimens given ID or IM within 2-visit or 3-visit schedules according to WHO recommendations provide an adequate rabies antibody level of >0.5 IU/mL after booster injection(s) [6].

The advantages of priming and "training" the immune system before the risk (through PrEP) [7, 8], the concept of "lifelong boostability" after priming (adequate anamnestic serological response >0.5 IU/mL 7 days after booster doses following an initial primary vaccination administered once before) [9–14], and the need for additional booster doses through postexposure prophylaxis (PEP) after the risk [3] are key in rabies prevention. The 2-visit ID or IM PrEP regimens, which are safe, sufficiently immunogenic, and convenient, are in line with these concepts [7, 15–23].

There is, however, some growing evidence that a single-visit PrEP, as well as a single-visit PEP, may constitute a valid and less expensive alternative to this recently recommended 2-visit schedule or to the widely used 3-visit schedule (ID or IM) [24–27]. If proven to be safe and effective, such single-visit PrEP and

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Correspondence: P. Soentjens, Nationalestraat 155, 2000 Antwerp, Belgium (psoentjens@itg.be, patrick.soentjens@mil.be).

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PEP schedules would be much more convenient for international travelers as well as for children at high risk in endemic low-income countries [7–28].

The study hypothesis is that a single-visit administration of 0.1 mL ID in 2 anatomic sites (hereafter, referred as 1^2ID according to our convention) as primary vaccination (PrEP) is sufficient to prime the immune system in such a way that it will result in a fast and adequate anamnestic response following a single-visit booster vaccination (mimicking an immunological response following PEP). Our primary objective in this study was to evaluate the immunogenicity of 2 PEP schedules (2 doses of 0.1 mL [1^2ID] vs 4 doses of 0.1 mL [1^4ID]) of the purified chicken embryo cell vaccine (PCEV) during a single visit planned approximately 1 year following a single-visit PrEP (1^2ID). Secondary objectives were to determine the "intermediate" immunogenicity of the PrEP schedule and to evaluate the safety of both the PrEP and PEP schedules.

METHODS

Study Design and Endpoints

This single-center, randomized, open-label, clinical trial aimed to compare the immunogenicity and safety of 2 single-visit ID rabies PEP schedules planned approximately 1 year after all participants had received a 2-dose single-visit ID primary vaccination (PrEP; 1^2ID); 0.1 mL of the PCEV vaccine was injected by ID route in each forearm for a total dose of 2 × 0.1 mL ID on day 0.

The participants were randomized to 1 of the following PEP vaccination schedules: group 1 (1^4ID), 0.1 mL of the PCEV vaccine was injected by ID route in each forearm and in each Musculus deltoid for a total dose of 4 × 0.1 mL ID on day 0 of the booster vaccination or group 2 (1^2ID), 0.1 mL of the PCEV vaccine was injected by ID route in each forearm for a total dose of 2 × 0.1 mL ID on day 0 of the booster vaccination.

The primary study endpoints were the proportion of participants with antibody titers >0.5 IU/mL, as measured by rabies fluorescent focus inhibition test (RFFIT), 7 days following 1 of these 2 ID booster regimens (1^4ID vs 1^2ID) and the difference of those proportions.

Secondary endpoints were to determine and compare [1] the percentage of participants with RFFIT levels >10.0 IU/mL in the 2 arms [2], the geometric mean titer (GMT) of rabies antibody, and [3] its fold increases at day 7 compared to day 0 of the booster vaccination. Other secondary endpoints were to determine the percentage of participants with RFFIT levels >0.5 IU/mL, the GMT, and the fold increases on day 14 (compared to day 0) of the single-visit primary vaccination, in order to evaluate the intermediate immunogenicity.

Safety endpoints included the proportion and pattern of adverse events (AEs) and serious AEs (SAEs) within 7 days and 14 days after initial and booster vaccinations, respectively.

Study Site and Participants

Study participants were recruited from the Belgian Armed Forces. Inclusion criteria were age between 18–54 years, being in preparation for overseas deployment, and willingness to provide informed consent. Participants who had previously received rabies vaccines or had positive rabies serology and pregnant or breast-feeding women were excluded, as well as participants with known or suspected immunodeficiency, chronic disease, mefloquine prophylaxis, or known allergy to 1 of the vaccine components. Participants with planned overseas deployment within the next 28 days (to rabies nonendemic regions) or within 2 years (to rabies endemic regions) were also excluded. No other vaccinations were given simultaneously with the rabies vaccination. Approximately 1 year following PrEP, participants were randomized to 1 of the 2 ID PEP schedules using block randomization.

The target sample size for the primary analysis was 300. 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 Declaration of Helsinki and national regulations [29, 30].

Vaccination Procedure

The 1.0-mL PCEV for rabies (GlaxoSmithKline Biologicals), registered in Belgium, was used. It contains no adjuvants. The rabies vaccine was stored at a temperature between +2°C and +8°C as recommended by the manufacturer. Different lots were used for primary and booster vaccinations (546011G, 555011C, 529011C, 610011A, 533011C).

Preparation of the injecting 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 dose. After ID injection (using the Mantoux technique), the papule was measured and had to be at least 4 mm.

Immunogenicity

Antibody titers were measured by RFFIT on day 0 (prior to the primary vaccination), on day 14, on the day of the booster vaccination (planned approximately 1 year after day 0), and 7 days after the booster vaccination.

Safety

AEs and SAEs were recorded until 7 and 14 days, respectively, following the completion of the primary and booster vaccination.

Study Information

The Institute of Tropical Medicine, Antwerp, sponsored this clinical trial. Clinical activities were performed at the Military Hospital Queen Astrid in Brussels. The recruitment began in October 2014, and the study was completed in March 2017.

Table 1. Study Participants Accounting on Day 7 After Booster Dose Injection

Subjects	Initial Screening n (%)
N	524
Screening failures	N = 221
Not interested, unwilling	116 (52.5)
Unable to respect timelines due to deployment	16 (7.2)
Seropositive at screening for rabies	38 (17.2)
Intake of immunomodulating medication	5 (2.3)
Known allergy to vaccine	2 (0.9)
Not deployable anymore	44 (19.9)

Subjects	Initial Recruitment n (%)
N	303
Completed primary vaccination period (including day 14 follow-up)	303 (100)
Did not complete PEP (including day 7 follow-up)	32 (10.6)
Lost to follow-up	14 (43.8)
On military mission	1 (3.1)
Participants left the service	5 (15.6)
Participants discontinued (consent of withdrawal)	12 (37.5)
Completed PEP (including day 7 follow-up)	271 (89.4)

Subjects	PEP schedule	
	4 Doses 1^4ID n/N (%)	2 Doses 1^2ID n/N (%)
N	134/271(49.4)	137/271 (50.6)
Time of PEP following primary vaccination		
<12 months	18/134 (13.4)	17/137 (12.4)
12–24 months	96/134 (71.6)	96/137 (70.1)
>24 months	20/134 (14.9)	24/137 (17.5)

Abbreviations: ID, intradermal; PEP, single-visit postexposure prophylaxis schedule of 4 doses, 4 × 0.1ID (1^4ID) or 2 doses, 2 × 0.1ID (1^2ID) during a single visit.

Statistical Analyses

For the immunogenicity component, participants who were seropositive on day 0 and participants who did not fully comply with the protocol were excluded from the statistical analysis. For the safety analysis, all participants 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 participants above different cutoff levels and 1-sided 95% Wilson confidence intervals (CIs), and GMTs are presented with 2-sided 95% CI.

Two-sided 95% Wilson CIs for the difference (Diff) in proportions between the 2 groups were used to assess immunogenicity outcomes. The comparison of antibody levels between the 2 groups was assessed by GMT ratios and their respective *t* test *P* values. 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

Participant Accounting and Characteristics

Of the 524 screened participants, 303 were included (57.8%). Reasons for exclusion are listed in Table 1. Of the 303 participants who completed the primary vaccination schedule, 271 (89.4%) were randomized, completed the booster vaccination (including the 7 day follow-up), and were included in the analyses (Table 2). Among those, 134 participants (49.4%) received the 4-dose booster and 137 participants (50.6%) received the 2-dose booster.

Day 7 Results Following Booster Doses

The planned timing of the booster vaccination approximately 1 year following primary vaccination needed to be adapted because most soldiers had to comply with unexpected security tasks related to the 2016 terrorist attacks in Belgium. As a result, the booster doses (the 1^4ID compared to the 1^2ID booster schedule) were given in different timeframes following the primary vaccination (between 7 and 28 months), that is, in 13.4% vs 12.4% in the first 12 months (pooled, 13%), in 71.6% vs 70.1% between 12 and 24 months (pooled, 71%), and in 14.9% and 17.5% (pooled, 16%) after 24 months (Table 1).

All participants (except 1 in each group, 99.3%) displayed rabies antibody titers >0.5 IU/mL on day 7 after the booster vaccination that were unrelated to the timing of the booster regimen (Table 3). The 95% CIs indicated that the success rate of RFFIT >0.5 IU/mL was at least 96.7% and that the difference in

Table 2. Baseline Characteristics of All Study Participants

Characteristic	Pooled PrEP ID n (%)	PEP 4 Doses 1^4ID n (%)	PEP 2 Doses 1^2ID n (%)
N	303	134	137
Age (years): median (interquartile range)	36 (26–47)	35 (26–46)	39 (27–47)
Age category, n (%)			
≤20	10 (3.3)	7 (5.2)	3 (2.2)
21–30	93 (30.7)	39 (29.1)	42 (30.7)
31–40	75 (24.8)	40 (29.9)	28 (20.4)
41–50	80 (26.4)	31 (23.1)	45 (32.8)
>50	45 (14.9)	17 (12.7)	19 (13.9)
Gender, n (%)			
Male	269 (88.8)	119 (88.8)	122 (89.1)
Female	34 (11.2)	15 (11.2)	15 (10.9)

Pooled after inclusion.

Abbreviations: PEP, single-visit postexposure prophylaxis schedule of either 4 intradermal doses of 0.1 mL (1^4ID) or 2 intradermal doses of 0.1 mL (1^2ID); PrEP ID, single-visit pre-exposure prophylaxis schedule of 1^2ID.

Table 3. Seroprotection Rates: Day 7 After Booster Vaccination

Subjects	Pooled n/N (%; 95% CI)[a]	4 Doses (1^4ID) PEP n/N (%; 95% CI)[a]	2 Doses (1^2ID) PEP n/N (%; 95% CI)[a]	Proportion Difference % (95% CI)[b]	*P*-Value
Number of participants with serology >0.5 IU/mL	269/271 (99.3; 97.8–99.8)	133/134 (99.3; 96.7–99.8)	136/137 (99.3; 96.8–99.8)	−0.2 (−2.1–2.2)	1
Number of participants with serology >10 IU/mL	202/271 (74.5; 70.0–78.6)	107/134 (79.9; 73.6–84.9)	95/137 (69.3; 62.5–75.4)	10.5 (0.23–20.8)	.052

Pooled PEP results.

Abbreviations: CI, confidence interval; PEP, single-visit postexposure prophylaxis schedule of either 4 intradermal doses of 0.1 mL (1^4ID) or 2 intradermal doses of 0.1 mL (1^2ID).

[a]One-sided 95% CI.

[b]Two-sided 95% CI.

success rate between the 2 booster schedules did not exceed 2%. Regarding the RFFIT results >10 IU/mL 7 days after booster doses, the proportion of participants who reached this level following the 1^4ID booster tended to be higher than in the 1^2ID group (79.9% vs 69.3%); a difference (95% CI) of 10.6 % (0.23–20.8) was demonstrated ($P = .052$; Table 3).

Of note, the 2 "slow-responsive" cases postboosting (a 51-year-old male and a 49-year-old female in the 1^4ID and 1^2ID booster group, respectively) were followed up serologically according to protocol, and both had an adequate antibody response (without additional booster doses) at a later time point (2.02 IU/mL at 3 months for the first participant and 0.67 IU/mL at 6 months for the second one).

After the 1^4ID booster, participants had a GMT (95% CI) of 20 IU/mL (16–25) compared to a GMT of 14 IU/mL (12–18) for the 1^2ID booster group ($P = .0228$; Table 4 and Figure 1). Moreover, female participants after 1^4ID had significantly higher GMT levels (95% CI) than male participants after 1^4ID boosters (42 IU/mL [28–62] vs 18 IU/mL [15–23]; $P < .001$).

In addition, RFFIT results seem to increase with interval since administration of the PrEP. After 24 months or more in a subgroup of 44 participants, GMT levels (95% CI) were 41 IU/mL (29–59) and 35 IU/mL (25–49) for 1^4ID and 1^2ID PEP schedules, respectively. All of these 44 participants were male and were significantly younger (a median age of 25.5 years compared to 42 and 39 years for the time group <12 months and 12 to 24 months, respectively).

Changes in serology over time are presented in Figure 2. The 1^4ID booster schedule showed a slightly steeper increase (95% CI) after the booster vaccination (35.39; 27.24–43.54) compared to the 1^2ID booster schedule (26.09; 19.92–32.25; Figure 2).

Day 14 Results Following Primary Vaccination

Of the 303 participants (17.5%), 53 did not develop adequate antibody responses on day 14 following 1^2ID primary vaccination. Fourteen days after completing primary vaccination, 82.5% (95% CI, 78.6–85.8) of all participants in the pooled analysis set attained rabies serology results >0.5 IU/mL; 81.3% (95% CI, 75.2–86.2) and 81.8% (95% CI, 75.7–86.2) receiving

Table 4. Geometric Mean Titers Before and After Booster Vaccination

	4 Doses 1^4ID PEP (N = 134) (GMT; 95% CI)	2 Doses 1^2ID PEP (N = 137) (GMT; 95% CI)	Geometrical Mean Ratio (95% CI)	*P* Value
GMT overall				
Prebooster serology (IU/mL)	.29 (.25–.33)	.30 (.26–.34)	0.97 (0.79–1.18)	.7542
Postbooster serology (IU/mL)	20 (16–25)	14 (12–18)	1.41 (1.05–1.89)	.0228
GMT by timing of booster injections				
Prebooster serology (IU/mL)				
<12 months	.21 (.16–.28)	.24 (.16–.37)	0.88 (0.55–1.42)	.5946
12–24 months	.27 (.23–.31)	.27 (.23–.32)	0.97 (0.78–1.21)	.8042
>24 months	.52 (.31–.87)	.46 (.31–.67)	1.14 (0.62–2.10)	.6657
Postbooster serology (IU/mL)				
<12 months	12 (7.4–21)	8.6 (4.3–17)	1.44 (0.63–3.32)	.3780
12–24 months	19 (15–25)	12 (9.7–16)	1.52 (1.07–2.17)	.0211
>24 months	41 (29–59)	35 (25–49)	1.18 (0.73–1.90)	.4848

Abbreviations: CI, confidence interval; GMT, geometric mean titer; PEP, single-visit postexposure prophylaxis schedule of either 4 intradermal doses of 0.1 mL (1^4ID) or 2 intradermal doses of 0.1 mL (1^2ID).

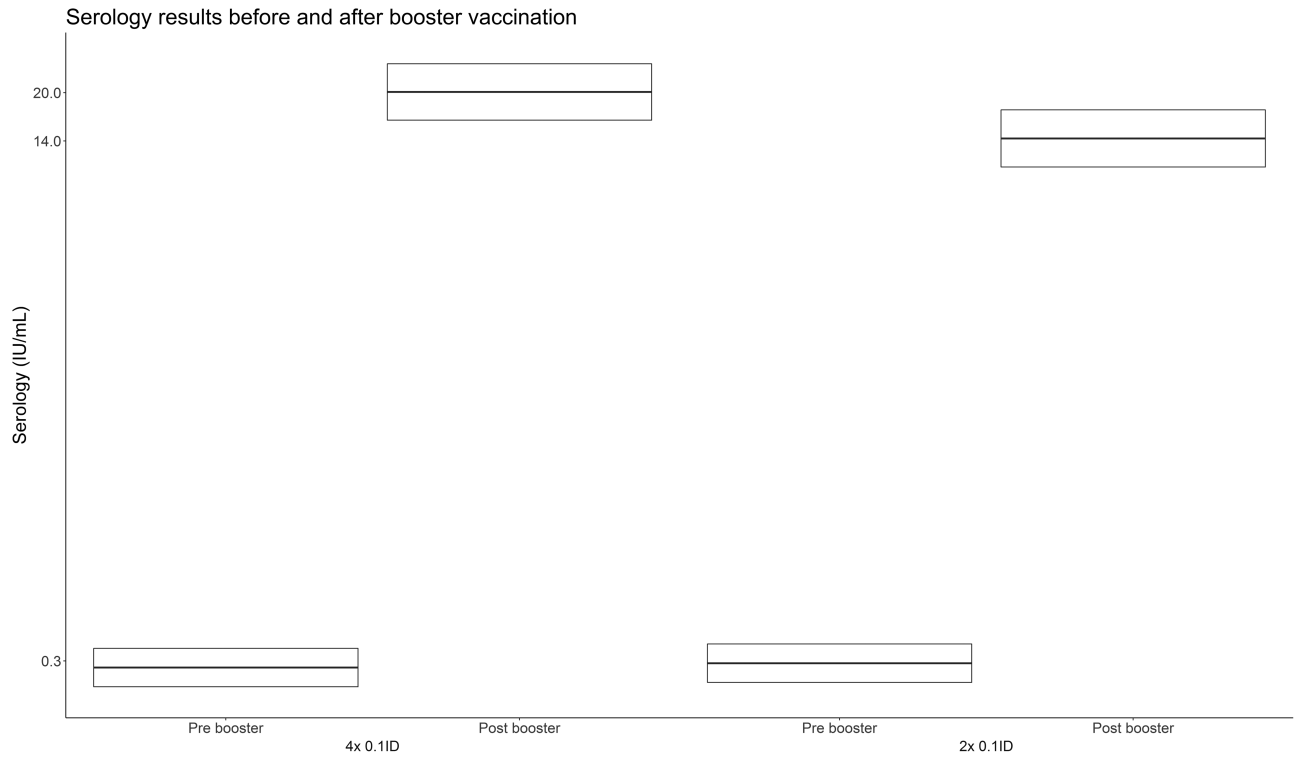

Figure 1. Serology results (IU/mL; geometric mean titer and 95% confidence interval) before and 7 days after booster vaccination. Single-visit postexposure prophylaxis schedule of either 4 intradermal (ID) doses of 0.1 mL (4 × 0.1ID or 1^4ID) or 2 ID doses of 0.1 mL (2 × 0.1ID or 1^2ID).

later after randomization a 1^4ID compared to a 1^2ID booster schedule, respectively.

Safety

A summary of the safety data for the primary vaccination period and for the booster period is provided in Table 5–6. No SAEs were reported during the study; 14.9% showed local irritation at the injection site (mild and transient) after primary vaccination. After the booster vaccination, local irritation was slightly more often observed after the 1^4ID booster regimen compared to the 1^2ID schedule 53% (95% CI, 44.6–61.2) vs 49.6% (95% CI, 41.4–57.9; $P = .63$).

DISCUSSION

In this trial, adequate antibody responses were achieved in 99.3% of healthy adults 7 days after a 1^4ID or a 1^2ID single-visit PEP following a single-visit 1^2ID PrEP administered 7 to 28 months earlier. The GMT and the proportion of antibody levels >10 IU/mL were significantly higher in the 1^4ID booster regimen compared to the 1^2ID booster regimen.

This noncommercial clinical trial has several strengths including the randomized, controlled design; good follow-up rates; blinding of laboratory study staff; use of the golden standard for serology (RFFIT) in a laboratory with proficiency in testing; and substantial expertise of nurses in performing appropriate ID injections and conducting vaccine trials. Moreover, different batches of the PCEV vaccine were used in this trial over a 3-year period, reflecting a real-life situation. Study limitations include most participants being healthy, young adult males and the follow-up with booster vaccination not exceeding a 3-year period.

The GMT results obtained 7 days postbooster (with cumulative total ID PrEP and ID PEP doses between 0.6 and 0.4 mL) were similar and/or higher compared to results form some pilot studies conducted in Thailand and evaluating ID single-visit ID PrEP with single-visit ID PEP or two-visit IM PEP (total dose, between 0.6 and 2.2 mL) [25]. They were also similar to results observed in 15 recently published cases of ID PrEP and IM PEP (total dose, between 2.2 and 2.6 mL) [27]. In contrast, GMT results of IM single-visit priming studies with additional IM PEP (total doses of 1.4–3 mL) were rather different, with lower and higher GMT results in 33 and 10 cases, respectively [25, 27]. It must, however, be noted that no consensus exists for the optimal GMT levels after booster vaccination [7]. In addition, male gender and young age can explain the high GMT levels when booster doses were given more than 24 months following the primary vaccination. Notably, as seen with other vaccines, female participants had, in general, higher antibody responses than males [31].

Although only 82.5% (N = 250) of participants after primary vaccination attained rabies seroconversion results >0.5 IU/mL at day 14, this initial priming was sufficient in almost all participants

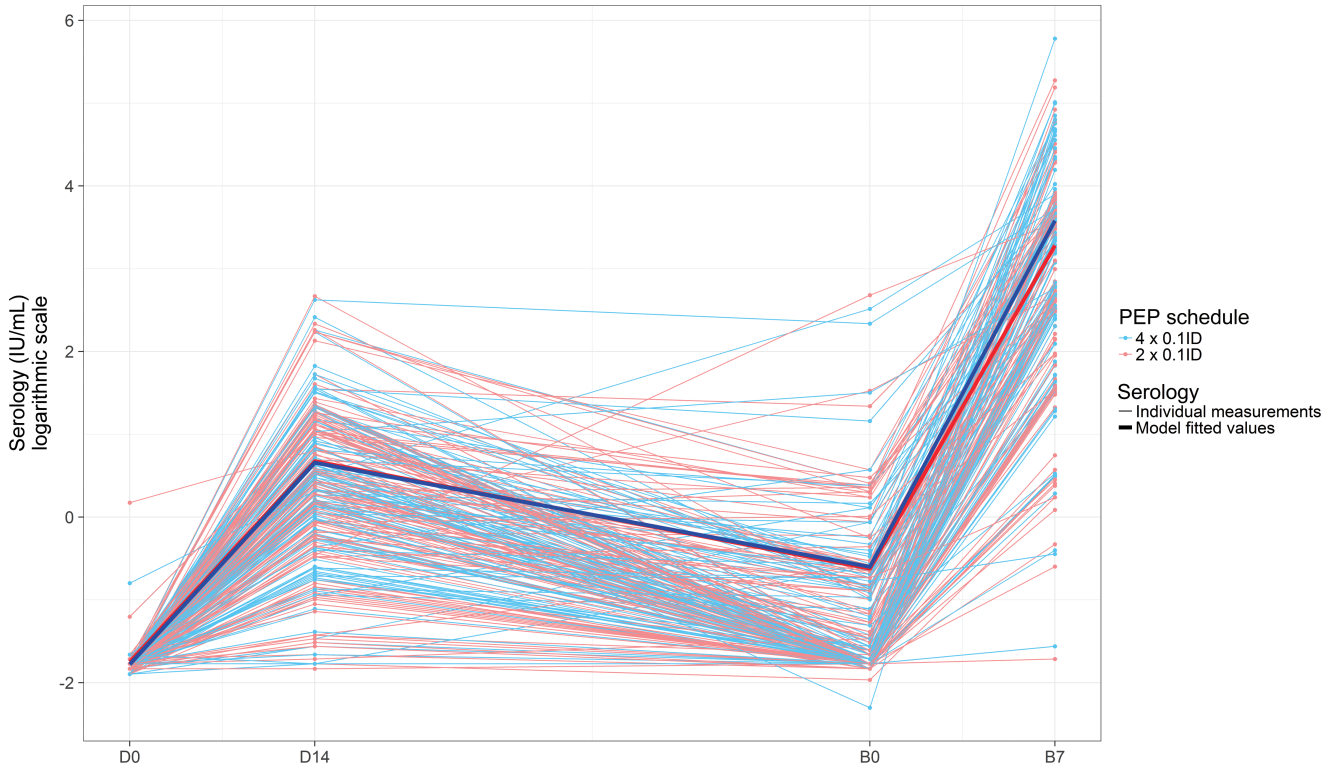

Figure 2. Segmented mixed models of respective serology slopes (per-protocol analysis). Postexposure prophylaxis model predictions on population (thick red line) and on individual basis (thin red line). The changes in serology over time in the 2 groups were evaluated using segmented mixed models with 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. 1^4ID PEP: model predictions on population (thick blue line) and on individual base (thin blue line); 12ID: PEP model predictions on population (thick red line) and on individual base (thin red line). Abbreviations: B0, serology check before booster dose; B7, serology check 7 days after booster dose; D0, serology check at day 0 of start primary vaccination; D14, serology check at day 14 after start of primary vaccination; ID, intradermal; PEP, single-visit postexposure prophylaxis schedule of either 4 intradermal doses of 0.1 mL (1^4ID) (blue lines) or 2 intradermal doses of 0.1 mL (1^2ID) (red lines).

to induce an adequate anamnestic response within 7 days after additional boosters around 1 year later. This time interval of 14 days between PrEP priming and serological testing is likely too short to evaluate the total amount of seroconverters following low-dose ID PrEP, 53 of participants did not respond adequately.

The 1^2ID single-visit ID PrEP regimen showed fewer side effects in total than 3- or 3-visit ID regimens [7]. Only minor local irritation was seen in 14.9% of the participants. In our previous trial comparing a 2-dose 2-visit PrEP 2^2ID regimen with a 1-dose 1-visit PrEP 3^1ID regimen, the proportions of participants with general discomfort were similar, while local site irritations were more frequent, directly related to the cumulation of AEs, higher total vaccine doses, and more ID injection-related immunological triggers during each visit [7]. In this trial, more local AEs were reported during the post-PEP period compared to the PrEP vaccination, which might be related to a "trigger" effect in the PEP regimen group following the earlier primary vaccination.

Table 5. Safety Analyses of All Participants for the Primary Vaccination Period

Number of Participants (%) With:	All Participants (N = 303)
Any adverse event	54 (17.8)
Any possibly, probably, or definitely drug-related adverse event	46 (15)
Any serious adverse event	0 (0.0)
Local irritation of injection site (redness, swelling, rash, itching)	45 (14.9)
General side effects related to injections	13 (4.3)

Although a single-visit 1^2ID PrEP course conferred adequate immune responses in at least 78.6% and 97.8% of the participants after PrEP and PEP, respectively, it is not recommended by WHO as the first-line regimen at this stage [4]. Still, in their new guideline WHO recommends giving last-minute travelers at least 1 ID or IM PrEP course (of the complete 2-visit regimen), instead of no injections at all due to late presentation. Moreover, in such cases, a second PrEP visit has to be scheduled after travel to complete the full PrEP regimen. In case of exposure during travel, a full PEP (4 or 5 injections of vaccine and immunoglobulins) is required. This new guideline is changing slowly toward a new paradigm of a rabies PrEP regimen, from a strict 3-visit 3^1ID or 3^1IM regimen to a more convenient 2-visit 2^2ID or 2^1IM and, but only as second choice, if there is not enough time to a single-visit 1^2ID PrEP [3]. In individuals who

Table 6. Safety Analyses for the Booster Vaccination Period

Number of Participants (%; 95% Confidence Interval) With:	4 Doses 1^4ID PEP (N = 134)	2 Doses 1^2ID PEP (N = 137)	*P* Value
Any adverse event	73 (54.5; 46.0–62.7)	70 (51.1; 42.8–59.3)	.63
Any possibly, probably, or definitely drug-related adverse event	72 (53.7; 45.3–62.0)	68 (49.6; 41.4–57.9)	.54
Any serious adverse event	0 (0)	0 (0)	…
Local irritation of injection site (redness, swelling, rash, itching)	71 (53.0; 44.6–61.2)	68 (49.6; 41.4–57.9)	.63
General side effects related to injections	6 (4.5; 2.07–9.42)	11 (8.0; 4.54–13.8)	.32

Abbreviation: PEP, single-visit postexposure prophylaxis schedule: of either 4 intradermal doses of 0.1 mL (1^4ID) 2 intradermal doses of 0.1 mL (1^2ID).

receive PrEP (2-visit regimen), additional PEP injections are always promptly needed after a risk exposure [3].

This trial, with 271 participants, adds additional evidence to the previous 74 cases in the literature (345 participants in total) that a single-visit 1^2ID PrEP can induce robust anamnestic responses 7 days after additional booster doses [25, 27]. In contrast, only 43 participants have been evaluated to date with single-visit 1^1IM PrEP [25, 27].

A 1^2ID PrEP schedule, given only once or possibly repeated without a specific time window, may be appropriate for any healthy traveler. Further research is required to assess whether it would also be immunogenic in more vulnerable travelers or groups of populations (children, the elderly, and the immunosuppressed), particularly in low-income countries [28].

Additional randomized, controlled trials are currently evaluating single-visit PrEP and boostability after PEP with PCEV vaccine. The first study in a Dutch population aims to compare a single-visit 1^1IM (N = 70) and 1^2ID (N = 70) with a 2-visit IM (2^2IM) and 3-visit IM (3^1IM) PrEP schedule and their respective B-cell and T-cell responses (EudraCT 2017-000089-31). Our research group is conducting the second trial. We are valuating the immunological added value of topical imiquimod and the use of an ID device (VAX-ID) in Belgian soldiers (N = 268) subjected to single-visit 1^2ID PrEP (EudraCT 2017-002953-12 / MedDev 80M0688).

CONCLUSIONS

In our cohort of healthy adults, a 1^2ID PEP schedule was immunologically adequate to and as safe as a 1^4ID PEP schedule following a 1^2ID PrEP regimen approximately 7 to 28 months earlier. Single-visit 2-dose pre- and PEP appear to be adequate, result in minor local side effects, and are more convenient for travelers.

Notes

Author contributions. P. S. conceived the research project, performed research, and designed the trial; P. S. and K. D. executed the trial; H. V. L. created the database (electronic Case Report Forms) and coordinated data management; A. T. analyzed the data; and P. S., E. B., Y. V. H., K. D., N. H., S. T., S. V. G., D. V. B., A. T., and P. V. wrote the paper. S. T. and S. V. G. were responsible for laboratory analyses.

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