Pre-exposure intradermal rabies vaccination: a non-inferiority trial in healthy adults on shortening the vaccination schedule from 28 to 7 days

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Brief summary:

In healthy adults, intradermal (ID) administration of a double dose of 0.1 ml of human diploid cell culture rabies vaccine over two visits (day 0 and day 7) was safe and not inferior to the single-dose three-visit ID schedule.

ABSTRACT

BACKGROUND

The existing four-week pre-exposure rabies vaccination schedule is costly and often not practicable. Shorter effective schedules would result in wider acceptance.

METHODS

We conducted a non-inferiority trial in 500 healthy adults comparing the safety and immunogenicity of a two-visit (day 0 and day 7) intradermal (ID) primary vaccination (two doses of 0.1 ml ID of the human diploid cell culture rabies vaccine (HDCV) at day 0 and 7) versus a standard three-visit schedule (single dose of 0.1 mL ID at day 0, 7, and 28).

One to three 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 seven 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 two-visit ID schedule had a geometric mean titer of 37 IU/ml versus 25 IU/ml for the single-dose three-visit schedule ($p<0.001$).

Local reactions at the injection site following primary vaccination were mild and transient.

CONCLUSION

In healthy adults, ID administration of a double dose of 0.1 ml of HDCV over two-visits (day 0 and day 7) was safe and not inferior to the single-dose three-visit schedule.

Keywords: Rabies pre-exposure; prophylaxis; Intradermal; Accelerated - Shortened schedule; Rabies vaccination

INTRODUCTION

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).

Pre-exposure prophylaxis (PrEP) using rabies vaccine is an important cornerstone in rabies prevention. Since the previous four-week PrEP schedule was often not practicable, effective and safe, double-dose two-visit intradermal (ID) and single-dose two-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).

ID 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 to IM injections via stimulating cutaneous dendritic cells and their draining lymph nodes (15-17). Studies have demonstrated that a single-dose three-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 post-exposure prophylaxis (PEP) procedures required in case of an animal bite (no need for immunoglobulin administration, and only two vaccine injections are needed instead of five) (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 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 non-inclusion in standard vaccination schemas, thereby resulting in low vaccination rates, and in particular for children at risk in low-income countries (LIC) (3-5).

This non-commercial non-inferiority trial aimed to compare immunogenicity 7 days after a single ID booster injection following two different priming schedules one to three years earlier: a double-dose two-visit (day 0 and 7) rabies ID vaccination schedule versus a single-dose three-visit schedule (day 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, non-inferiority clinical trial, comparing the booster response following two different primary vaccination schedules (PrEP):

- Control group: 3x 0.1ID schedule (3ID); single-dose three-visits; 1 intradermal injection (a dose of 0.1 mL (0.1ID)) on days 0, 7, and day 28.

- Intervention group: 2x 2x0.1ID schedule (2ID); double-dose two-visit; 2 intradermal injections (of 0.1 mL in 2 separate injection sites (2x 0.1ID)) on day 0, and 2 injections (in separate sites (2x 0.1ID)) on day 7.

STUDY ENDPOINTS

The primary objective of this study was to demonstrate non-inferiority of the two-visit (2ID) schedule compared to the three-visit (3ID) schedule as assessed by the proportion of participants with adequate rabies antibody titers, measured by rapid fluorescent focus inhibition test (RFFIT), above 0.5 IU/mL 7 days following a booster vaccine injection (0.1 mL of human diploid cell culture vaccine (HDCV) administered 1 to 3 years after primary vaccination). Clinical non-inferiority was defined as a loss of no more than 10% of subjects that have adequate rabies antibody levels compared to the 3ID schedule. Notably, subjects showing an antibody titer >0.5 IU/mL at day 7 post-booster 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 above 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 above 0.5 IU/mL, the GMT, and the fold increases compared for both study groups on day 35 after the start of primary vaccination.

In order 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 age between 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 breast-feeding 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 one 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 one of the two 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 the good clinical practice guidelines (25) and was registered as EudraCT 2011-001612-62 and in clinicaltrials.gov NCT01388985.

VACCINATION PROCEDURE

The HDCV rabies Mérieux® 1 ml vaccine for rabies (Sanofi), registered in Belgium, was used. The vaccine was stored between +2 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 (AE's) and serious adverse events (SAE's) 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 (ITM). 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 time window (see Table 1). For the safety analysis, all subjects who had received at least one 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 cut-off levels, and GMT are presented with 95% confidence intervals. The comparison of antibody levels between the two groups was assessed by GMT ratios and their respective p-values.

Two-sided 95% Wilson confidence intervals for the difference (Diff) in proportions between the two groups were used to assess immunogenicity outcomes. Non-inferiority of the 2ID schedule was inferred if the 95% confidence interval of the difference was entirely above the

- 10% non-inferiority margin. Segmented mixed models were used to explain the changes in serology over time. Differences in safety results between the two groups were assessed using Fisher's 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 one 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 versus 54% of 200 subjects in the first year following primary vaccination, in 35% versus 38% in the second year and in 6% versus 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 two groups ranged between -2 and 2 percent.

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 in the 2ID schedule was higher than in the 3ID schedule (96% versus 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 (95% CI) of 37 IU/mL (33 - 42) following the booster vaccination offered one to three years later, compared to a GMT of 25 IU/mL (22 - 29) for the 3ID group ($p<0.001$) (Figure 1, Table 4). In addition, GMT values (95% CI) on the day of booster injection in the 2ID schedule were higher (3.4 IU/mL, 2.9 - 3.9) compared to these of the 3ID schedule (2.0 IU/mL, 1.7 - 2.4) ($p<0.001$).

Changes in serology over time are presented in Figure 2. The 2ID schedule exhibited a higher slope following the booster dose (46.4; 39.1 - 53.6) compared to the 3ID schedule (35.7; 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 gender ($p<.0001$), age

between 20 and 30 years (p= 0.0021) and between 30 and 40 years (p= 0.0023), and a higher pre-booster GMT (p<.0001) were associated with improved post-booster results in favor of the 2ID schedule. Moreover, post-booster 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 greater than 25 months (p= 0.0002).

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 to the 2ID group (70%) (Diff (95% CI): -12%, -19 – 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, one serious AE (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 to the protocol. Also, two serious AEs (one case of oesophagitis 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 to the 2ID schedule (51.8% vs 43.4%, p=0.07). In contrast local irritation was more often observed following the booster dose in the 2ID group (38.8% vs 48.8%, p=0.03). The number of subjects with systemic discomfort related to injections was very low and did not differ significantly between the two groups (3ID versus 2ID) following primary vaccination (14.5% vs 11.6%, p=0.42) or booster injection (5.4% vs 5.8%, p=1).

DISCUSSION

In this trial, non-inferiority was met for the primary immunogenicity endpoint, with a 100% observed adequate antibody response (>0.5 IU/mL) observed 7 days after booster dose injection of 0.1 mL ID administered 1 to 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% versus 83%) and for the obtained GMT (37 versus 25) following booster injection. In addition, a double-dose two-visit 0.1 mL ID PrEP with HDCV in adult subjects was shown to be, as safe as the single-dose three-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 two groups (and not following primary vaccination results). Therefore, the timelines for serology testing after final injection in the two primary vaccination schedules were different in the 3ID schedule (+7 days after last vaccination) compared to 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 in with the 3ID schedule were likely attributable to the longer period of primary vaccination in this group.

This non-commercial 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 intradermal injections and conducting vaccine trials, and blinding of laboratory study staff, as well as the use of the golden 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 three-year-interval. Moreover, different batches of HDCV vaccine were used in this trial over four 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 to other trials using priming two-visit vaccine ID schedules (total vaccine dose of 0.2ID or 0.4ID) (26-29), and were similar with two-visit IM schemes (total vaccine dose of 2IM) (29-31).

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 to 7 days.

Data from the present study substantiates 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 (SAGE), 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 PCECV), when compared to 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 May 1st 2018 (36), and many other countries will hopefully follow. This hesitancy against shortening the PrEP schedule to two 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 post-exposure injections following exposure to rabies risk to stimulate the adaptive ‘trained’ immunity (37).

CONCLUSION

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 two-visit 0.1ID regimen, with 100% adequate antibody response following a booster injection of 0.1ID 1 to 3 years after primary vaccination.

Whether this schedule is safe and effective in children in LIC 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).

Author contributions

AA and PS conceived the research project, PS, PA and AA researched, designed and executed the trial, HVL organized and coordinated data management, AT analyzed the data and PS, EB, YVH, AT, HVL, RR, AA, and PVD wrote the paper. BB and SVG were responsible for laboratory analyses.

Conflicts

PvD reports grants from Vaccine manufacturers, grants from Bill & Melinda Gates Foundation, outside the submitted work. All other authors have no conflicts.

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Figure Legends:

Figure 1: Serology results (IU/mL; GMT and 95% CI) before and 7 days after booster vaccination (PP-analysis by dotplot).

GMT: geometric mean titers; PP: Per-Protocol; 3ID: single-dose three-visit over 28 days; 2ID: double-dose two-visit over 7 days; CI: confidence interval.

Figure 2: Segmented mixed-models of respective serology slopes (PP-analysis).

GMT: geometric mean titers; PP: Per-Protocol; 3ID: single-dose three-visit over 28 days (blue lines); 2ID: double-dose two-visit over 7 days (red lines). D0: serology check at day 0 of start primary vaccination; D35: serology check at day 35 after start of primary vaccination; B0: serology check before booster dose; B7: serology check 7 days after booster dose. 3ID model predictions on population (tick blue line) and on individual base (thin blue line). 2ID model predictions on population (tick red line) and on individual base (thin red line).

The changes in serology over time in the two 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.

Table 1: Study participants accounting for intention-to-treat (ITT) and per-protocol (PP) analysis on day 7 after booster dose injection

N	**410**	
Screening failures	410	
- Not interested - unwilling	294 (71.5%)	
- Unable to respect timelines	60 (15%)	
- Exclusion criteria (chronic disease, immunodeficiency, pregnancy, breastfeeding, on mefloquine,…)	56 (13.5%)	
N	**250**	**250**
- Randomized but withdrawal before start procedures	1	1
N	**249**	**249**
Excluded from ITT analysis d35	9 (3.6 %)	7 (2.8 %)
- Lost to follow-up	5	4
- Patient unavailable (deployed in mission; left military services)	1	1
- Sample unavailable/Inadequate	3	2
N	**240**	**242**
Excluded from ITT analysis d365-1095	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 %)**

ITT: Intention-to-Treat; PP: Per-Protocol; 3ID: single-dose three-visit over 28 days; 2ID: double-dose two-visit over 7 days.

Table 2: Baseline Characteristics of all study participants

	3ID schedule	2ID schedule
N	249	249
Age (yr): median (IQR)	29 (24 - 35)	28 (23 - 34)
Age category:		
≤ 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)
Gender: 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)

yr: year; IQR: interquartile range; 3ID: single-dose three-visit over 28 days; 2ID: double-dose two-visit over 7 days.

Table 3: Seroprotection Rates (PP) - day 7 after booster vaccination

	3ID schedule: n/N (%, 95% CI)	2ID schedule: n/N (%, 95% CI)	% Difference (2ID - 3ID) (95% CI)
PP Analysis: N	185	183	
Number of Subjects with serology > 0.5 IU/mL	185/185 (100%; 98 - 100)	183/183 (100%; 98 - 100)	**0 (-2.1 - 2)**
Number of Subjects with serology > 10 IU/mL	154/185 (83%; 78 - 89)	176/183 (96%; 93 - 99)	**13 (7 - 19)**

PP: Per-Protocol; 3ID: single-dose three-visit over 28 days; 2ID: double-dose two-visit over 7 days ; CI: confidence interval.

Two-sided 95% Wilson confidence intervals for the difference (Diff) in proportions between the two groups (2ID - 3ID).

Table 4: Geometric Mean Titers (GMT) (PP) - before and after booster vaccination (Per Protocol)

	3ID schedule (GMT; 95% CI)	2ID schedule (GMT; 95% CI)	Geometrical mean ratio	p-value
Overall:				
Pre-booster serology (IU/mL)	2.0 (1.7-2.4)	3.4 (2.9-3.9)	0.60 (0.48-0.75)	<.0001
Post-booster serology (IU/mL)	25 (22-29)	37 (33-42)	0.68 (0.57-0.81)	<.0001

GMT: geometric mean titers; PP: Per-Protocol; 3ID: single-dose three-visit over 28-days; 2ID: double-dose two-visit over 7 days; CI: confidence interval.

Table 5: Safety Analyses for the Primary Vaccination Period for the whole study period.

Number of subjects (%; 95% CI) with:	3ID schedule (N=249)	2ID schedule (N=249)	P-value
- any adverse event	190 (76.3;70.6 - 81.2)	190 (76.3;70.6 - 81.2)	1
- any possibly, probably or definitely vaccine-related adverse event	173 (69.5;63.5 -74.9)	171 (68.7;62.7 -74.1)	0.92
- any serious adverse event	1† (0.4; 0.07 - 2.24)	2* (0.8;0.22 - 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 reactiont related to injections	46 (18.5;14.1 - 23.8)	43 (17.3;13.1-22.5)	0.82

3ID: single-dose three-visit over 28 days; 2ID: double-dose two-visit over 7 days; † Diplopia and Hemianopia, * Oesophagitis, dyspnea, angioedema and urticaria.

Figure 1

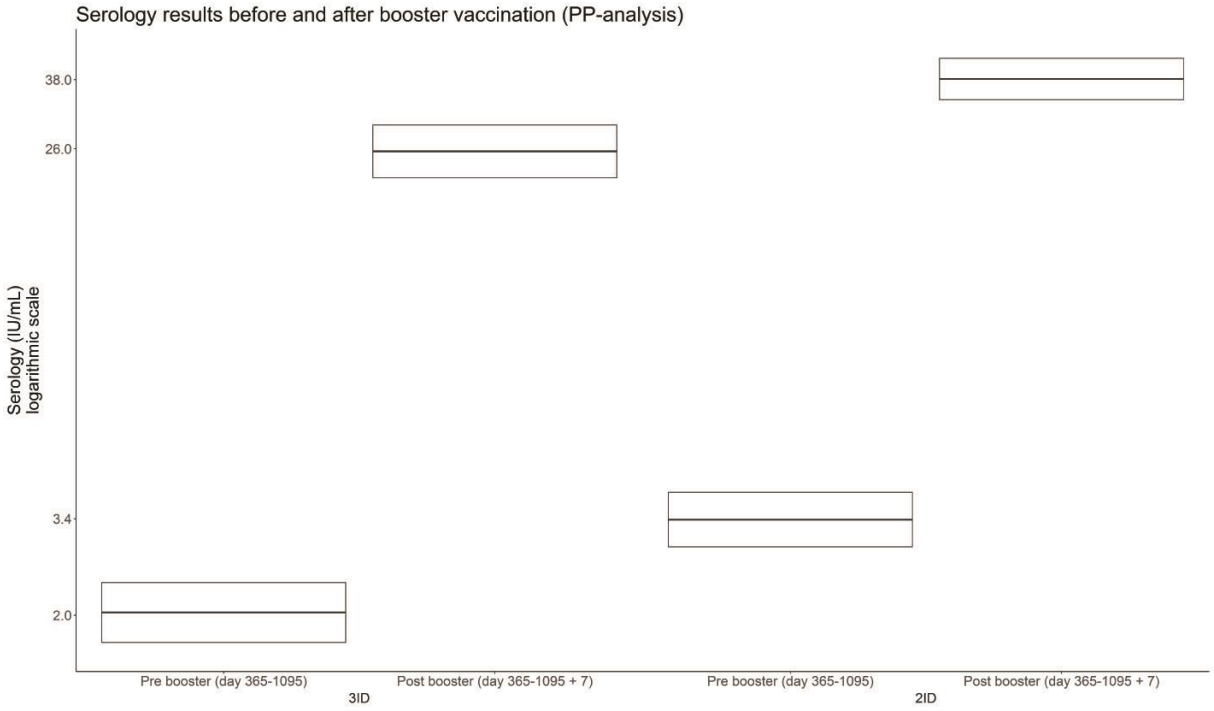

Figure 2