Statistical Analysis Report – Final Analysis:

Towards an optimal accelerated Tick-Borne Encephalitis (TBE) vaccination schedule for the last-minute traveler

FASTBEPROTECT

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1. Introduction

1.1. General Introduction

This study is an exploratory single-center prospective randomized open-label study. The purpose of this study is to evaluate different TBE vaccination schedules for a last-minute traveler.

Table 1 Vaccination groups

Group 1 (Classic accelerated schedule)	Day 0: 1 dose 0.5ml IM Day 14: 1 dose 0.5 ml IM Month 12: 1 dose 0.5ml IM
Group 2	Day 0: 2 doses 0.5ml IM Month 12: 1 dose 0.5ml IM
Group 3	Day 0: 2 doses 0.1ml ID Month 12: 2 doses 0.1ml ID
Group 4	Day 0: 2 doses 0.1ml ID Day 7: 2 doses 0,1 ml ID Month 12: 2 doses 0.1ml ID
Group 5	Day 0: 2 doses 0.1ml ID Day 14: 2 doses 0.1 ml ID Month 12: 2 doses 0.1ml ID

The primary vaccination period covers D0 - D14. A booster shot was given 1 year after the first vaccination. Serology was determined at screening (prior to the first vaccination) and on day 7, 14, 21, 28, month 3 and month 6 after the first vaccination. Serology was determined again at month 12 (prior to completion of the primary vaccination schedule) and on day 21 after this vaccination.

An interim analysis was already performed once all subjects completed the day 28 visit. Data until day 28 were extracted on 22 June 2020. The interim analysis consists of the analysis of the primary objective and the results were described in the statistical analysis report finalized on the 22nd of June 2020. For completeness the results for the primary objective are also included in this report. The final analysis consists of the analysis of the secondary objective and safety objectives. Data was extracted on December 17, 2021.

1.2. Summary of Statistical Methods and deviations

Statistical analyses were performed according to the Statistical Analysis Plan (SAP), which was approved on 17 January 2020. For the final analysis there is one deviation from the SAP. In the SAP it is stated that out-of-window visits as specified in the protocol are a major protocol violation and patients with at least one out-of-window visit should be excluded from the PP population. However, due to the COVID19 pandemic all patients had at least one out-of-window visit. It was therefore decided to exclude individual out-of-window visits for the individuals in

the PP population. Thus, the denominator in the analyses will change according to the number of subjects without out-of-window visits, but the subjects will not be excluded entirely from the PP analyses.

As a sensitivity ITT analysis, intermediate missing serology results were imputed based on a linear regression model with previous serology results, gender, and age as independent variables. We randomly imputed 10 datasets, performed the analysis on each imputed data set, and obtained final effect estimates by combining results using Rubin's rules. The results from the imputed ITT secondary analysis are used to verify the robustness of the results.

For the interim/primary analysis there was one deviation from the SAP. In the SAP, it is stated that multiple imputation will be used to impute intermediate missing serology results. Only three participants had a missing intermediate serology result an all other serology results (before and after missing result) were <10. Therefore, it was decided to impute the missing values as <10.

Additional exploratory tables and analyses were requested, which were not specified in the SAP. These methods are further described in section 7.5.

All analyses were carried out in SAS/STAT® 12.3.

2. Patient accounting

Ninety-six (96) patients were screened, and 77 patients were enrolled. Nineteen (19) patients were excluded at enrolment. All 77 patients completed the primary vaccination. Sixty-seven (67) patients completed the booster vaccination, 4 were lost to follow-up and 6 withdrew consent.

Table 2 Patient accounting

	VACCINATION SCHEDULE					
	Pooled	Group 1	Group 2	Group 3	Group 4	Group 5
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Completed primary vaccination	77	15	16	15	15	16
Did not complete booster vaccination	10 (13)		1 (6.3)	2 (13)	4 (27)	3 (19)
Lost to follow-up	4		1	1	1	1
Withdrawn by participant	6			1	3	2
Completed booster vaccination	67 (87)	15 (100)	15 (94)	13 (87)	11 (73)	13 (81)

3. Analysis population

A total of 77 participants were enrolled in the study. All enrolled participants were seronegative at screening, and all are included in ITT analysis of the primary and secondary endpoint.

Interim analysis (primary endpoint): Of the 77 enrolled participants, 1 missed a vaccination and was excluded from the PP analysis. For four participants the D28 visit was out of window and the corresponding serology result was excluded from the PP analysis of the primary endpoint.

Final analysis (secondary endpoints): Of the 77 enrolled participants, 17 were excluded from the PP population for the reasons described below in table 3. The PP consists of 60 patients in total.

All enrolled patients received at least one dose of their vaccination regimen and there were no violations to the randomized regimen. The ITT population is therefore identical to the safety population (all patients treated approach).

Table 3 Analysis population

	VACCINATION SCHEDULE				
	Group 1	Group 2	Group 3	Group 4	Group 5
	N = 15	N = 16	N = 15	N = 15	N = 16
	n (%)	n (%)	n (%)	n (%)	n (%)
Included in ITT analysis	15 (100)	16 (100)	15 (100)	15 (100)	16 (100)
Excluded from PP analysis	0 (0.0)	1 (6.3)	4 (27)	6 (40)	6 (38)
Booster shot not in arm	0	0	1	0	1
Lost to follow-up	0	1	1	1	1
Missed at least one vaccination, missing serology result, and booster shot not in arm	0	0	0	0	1
Missing serology result	0	0	0	2	1
Missing serology result, and booster shot not in arm	0	0	1	0	0
Withdrawn by participant	0	0	1	3	2
Included in PP analysis	15 (100)	15 (94)	11 (73)	9 (60)	10 (63)

3.1. ITT population per scheduled follow-up visit

Table 4 ITT population per scheduled follow-up visit

Time point	Nr of patients per visit	Reason
Day 7	76 patients (98.7%)	1 missing lab visit
Day 14	74 patients (96.1%)	3 missing lab visits
Day 21	76 patients (98.7%)	1 missing lab visit
Day 28	75 patients (97.4%)	2 missing lab visits
Month 3	77 patients (100%)	
Month 6	76 patients (98.7%)	1 missing serology result (scheduled visit)
Month 12	67 patients (97.4%)	4 lost to follow-up & 6

		withdrew consent
Month 12+ 21 days	67 patients (97.4%)	4 lost to follow-up & 6 withdrew consent

There were 6 subjects with in total 8 missing intermediate serology values. There were 10 additional subjects with missing serology values at visit M12 and M12 + 21 days due to drop-out. Only missing intermediate serology values were imputed.

3.2. PP population per scheduled follow-up visit

Table 5 ITT population per scheduled follow-up visit

Time point	Nr of patients	Reason
Day 7	60 patients (100%)	
Day 14	60 patients (100%)	
Day 21	60 patients (100%)	
Day 28	57 patients (95%)	3 out-of-window visits
Month 3	54 patients (90%)	6 out-of-window visits
Month 6	5 patients (8.33%)	55 out-of-window visits
Month 12	4 patients (6.67%)	56 out-of-window visits
Month 12+ 21 days	55 patients (91.67%)	5 out-of-window visits

4. Description of study population

Participants in each treatment group are described with respect to baseline characteristics. No major imbalances were detected.

Table 6 Baseline characteristics per group

	VACCINATION SCHEDULE				
	Group1	Group 2	Group 3	Group 4	Group 5
	n (%)	n (%)	n (%)	n (%)	n (%)
N	15	16	15	15	16
Age (yr): median (IQR)	19.0 (18.0 - 20.0)	19.0 (18.0 - 19.5)	19.0 (19.0 - 20.0)	19.0 (18.0 - 21.0)	19.5 (18.0 - 21.5)
Gender: n(%)					
Female	2 (13.3%)	4 (25.0%)	2 (13.3%)	3 (20.0%)	2 (12.5%)
Male	13 (86.7%)	12 (75.0%)	13 (86.7%)	12 (80.0%)	14 (87.5%)

5. Analysis of the primary objective

Primary objective: To estimate the time to seroconversion of the different schedules of accelerated TBE vaccination based on reactogenicity data up to 28 days after the first dose.

5.1. Intention-to-Treat analysis

The Kaplan-Meier curve of time to seropositivity is shown in Figure 1. The quartiles are estimated in Table 7.

Figure 1: Time to seropositivity - ITT analysis

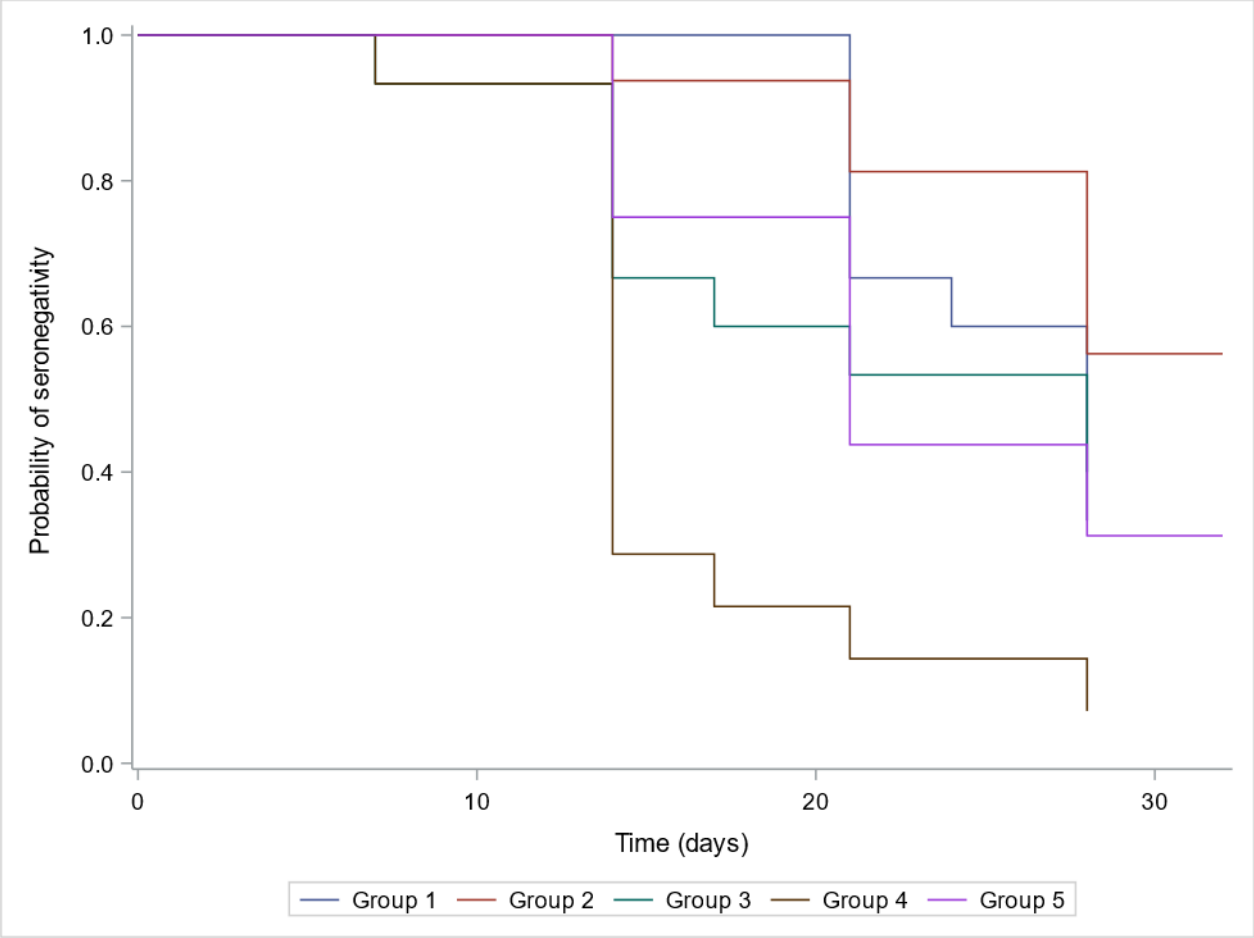

Table 7: Time to seropositivity - ITT analysis

quartile	Group1 (95% CI)	Group 2 (95% CI)	Group 3 (95% CI)	Group 4 (95% CI)	Group 5 (95% CI)
25	21 (21,28)	28 (14, .)	14 (7,21)	14 (7,14)	18 (14,21)
50	28 (21, .)	. (28, .)	28 (14, .)	14 (14,17)	21 (14, .)
75	. (28, .)	. (., .)	. (28, .)	17 (14, .)	. (21, .)

5.2. Per protocol analysis

Figure 2: Time to seropositivity - PP analysis

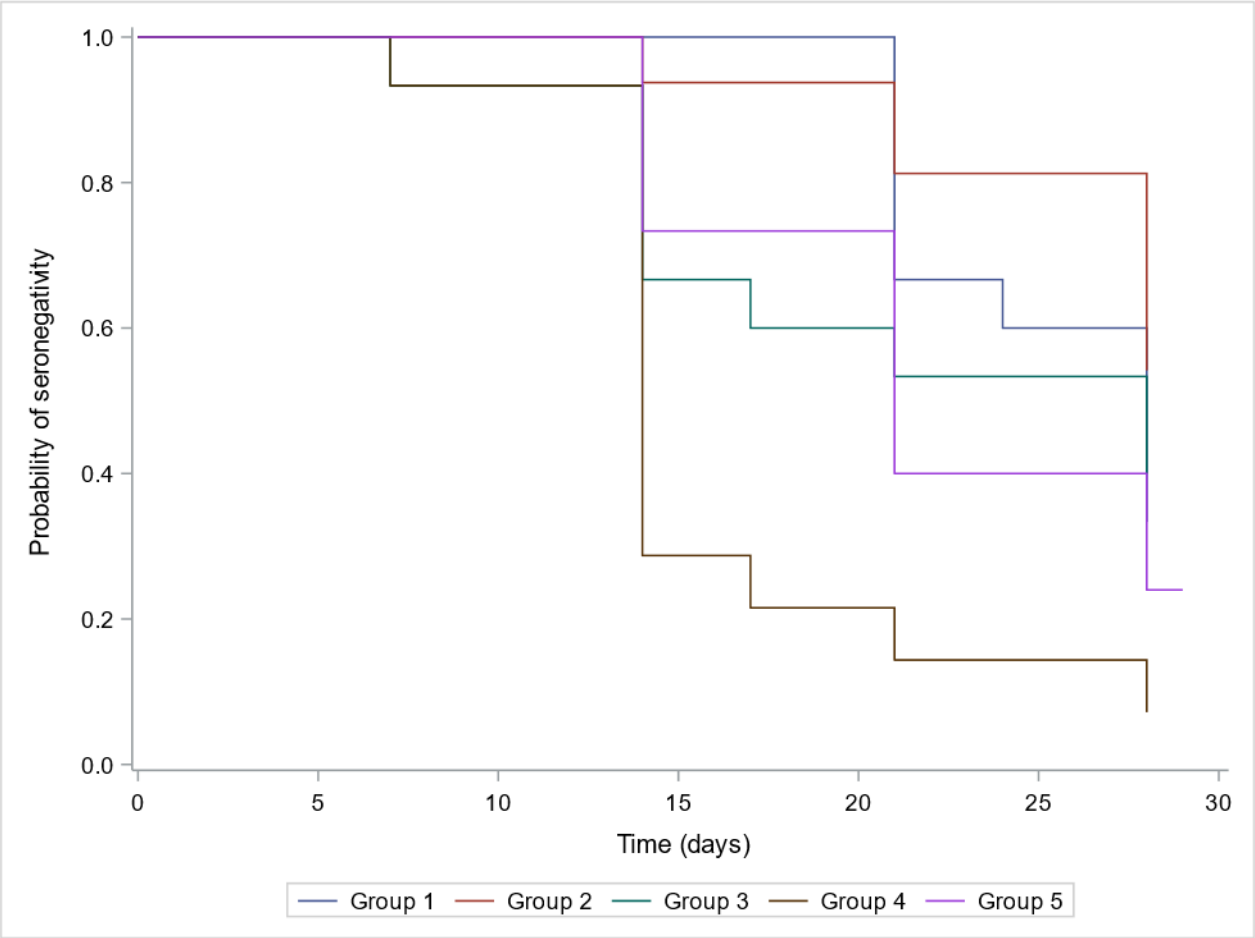

Table 8: Time to seropositivity - PP analysis

quartile	Group1 (95% CI)	Group 2 (95% CI)	Group 3 (95% CI)	Group 4 (95% CI)	Group 5 (95% CI)
25	21 (21,28)	28 (14, .)	14 (7,21)	14 (7,14)	14 (14,21)
50	28 (21, .)	. (28, .)	28 (14, .)	14 (14,17)	21 (14,28)
75	. (28, .)	. (., .)	. (28, .)	17 (14, .)	28 (21, .)

6. Analysis of secondary objectives

Secondary objectives: To estimate the proportion of subjects with neutralizing antibodies (≥ 10) at day 7, day 14, day 21, day 28, month 3, month 6, 1 year and 1 year + 21 days after the start of the primary vaccination with 95% Wilson confidence interval for the five vaccination regimens.

6.1. Intention-to-Treat analysis

Table 9 Proportion of ITT subjects with neutralizing antibodies (≥ 10) per vaccination regimen at scheduled follow-up visits with 95% Wilson confidence intervals.

	VACCINATION SCHEDULE				
Visit	Group1	Group 2	Group 3	Group 4	Group 5
	% seropositive	% seropositive	% seropositive	% seropositive	% seropositive
	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
Day 7	0/15	0/16	1/14	1/15	0/16
	0.0 (0.0, 20.4)	0.0 (0.0, 19.4)	7.1 (1.3, 31.5)	6.7 (1.2, 29.8)	0.0 (0.0, 19.4)
Day 14	0/15	1/15	6/15	11/14	4/15
	0.0 (0.0, 20.4)	6.7 (1.2, 29.8)	40.0 (19.8, 64.3)	78.6 (52.4, 92.4)	26.7 (10.9, 52.0)
Day 21	6/15	3/16	4/15	11/14	9/16
	40.0 (19.8, 64.3)	18.8 (6.6, 43.0)	26.7 (10.9, 52.0)	71.4 (45.4, 88.3)	56.3 (33.2, 76.9)
Day 28	8/15	4/16	7/15	9/13	9/16
	53.3 (30.1, 75.2)	25.0 (10.2, 49.5)	46.7 (24.8, 69.9)	69.2 (42.4, 87.3)	56.3 (33.2, 76.9)
Month 3	0/15	1/16	1/15	1/15	0/16
	0.0 (0.0, 20.4)	6.3 (1.1, 28.3)	6.7 (1.2, 29.8)	6.7 (1.2, 29.8)	0.0 (0.0, 19.4)
Month 6	0/15	1/16	2/15	2/15	1/15
	0.0 (0.0, 20.4)	6.3 (1.1, 28.3)	13.3 (3.7, 37.9)	13.3 (3.7, 37.9)	6.7 (1.2, 29.8)
Month 12	0/15	1/15	1/13	5/11	4/13
	0.0 (0.0, 20.4)	6.7 (1.2, 29.8)	7.7 (1.4, 33.3)	45.5 (21.3, 72.0)	30.8 (12.7, 57.6)
Month 12 + 21 days	15/15	14/15	13/13	10/11	13/13
	100.0 (79.6,100.0)	93.3 (70.2, 98.8)	100.0 (77.2,100.0)	90.9 (62.3, 98.4)	100.0 (77.2,100.0)

6.1.1. ITT - Multiple imputation

Table 10 Proportion of ITT subjects with neutralizing antibodies (≥ 10) per vaccination regimen at scheduled follow-up visits with 95% Wilson confidence intervals after imputation

	VACCINATION SCHEDULE				
Visit	Group1	Group 2	Group 3	Group 4	Group 5
	% seropositive	% seropositive	% seropositive	% seropositive	% seropositive
	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
Day 7	0.0 (0.0, 20.4)	0.0 (0.0, 19.4)	6.7 (1.2, 29.8)	6.7 (1.2, 29.8)	0.0 (0.0, 19.4)
Day 14	0.0 (0.0, 20.4)	10.0 (2.4, 33.0)	40.0 (19.8, 64.3)	74.7 (49.4, 89.9)	29.4 (12.9, 53.8)
Day 21	40.0 (19.8, 64.3)	18.8 (6.6, 43.0)	26.7 (10.9, 52.0)	67.3 (42.3, 85.3)	56.3 (33.2, 76.9)
Day 28	53.3 (30.1, 75.2)	25.0 (10.2, 49.5)	46.7 (24.8, 69.9)	64.0 (39.3, 83.0)	56.3 (33.2, 76.9)
Month 3	0.0 (0.0, 20.4)	6.3 (1.1, 28.3)	6.7 (1.2, 29.8)	6.7 (1.2, 29.8)	0.0 (0.0, 19.4)
Month 6	0.0 (0.0, 20.4)	6.3 (1.1, 28.3)	13.3 (3.7, 37.9)	13.3 (3.7, 37.9)	6.3 (1.1, 28.3)
Month 12	0.0 (0.0, 20.4)	6.7 (1.2, 29.8)	7.7 (1.4, 33.3)	45.5 (21.3, 72.0)	30.8 (12.7, 57.6)
Month 12 + 21 days	100.0 (79.6,100.0)	93.3 (70.2, 98.8)	100.0 (77.2,100.0)	90.9 (62.3, 98.4)	100.0 (77.2,100.0)

Differences (I.e., where missing intermediate results were imputed) are highlighted in yellow.

6.2. Per protocol analysis

Table 11 Proportion of PP subjects with neutralizing antibodies (≥ 10) per vaccination regimen at scheduled follow-up visits with 95% Wilson confidence intervals.

	VACCINATION SCHEDULE				
Visit	Group1	Group 2	Group 3	Group 4	Group 5
	% seropositive	% seropositive	% seropositive	% seropositive	% seropositive
	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
Day 7	0/15	0/15	1/11	1/ 9	0/10
	0.0 (0.0, 20.4)	0.0 (0.0, 20.4)	9.1 (1.6, 37.7)	11.1 (2.0, 43.5)	0.0 (0.0, 27.8)
Day 14	0/15	1/15	5/11	6/ 9	2/10
	0.0 (0.0, 20.4)	6.7 (1.2, 29.8)	45.5 (21.3, 72.0)	66.7 (35.4, 87.9)	20.0 (5.7, 51.0)
Day 21	6/15	3/15	3/11	6/ 9	7/10
	40.0 (19.8, 64.3)	20.0 (7.0, 45.2)	27.3 (9.7, 56.6)	66.7 (35.4, 87.9)	70.0 (39.7, 89.2)
Day 28	8/14	4/14	5/10	7/ 9	7/10
	57.1 (32.6, 78.6)	28.6 (11.7, 54.6)	50.0 (23.7, 76.3)	77.8 (45.3, 93.7)	70.0 (39.7, 89.2)
Month 3	0/14	1/13	1/ 9	1/ 9	0/ 9
	0.0 (0.0, 21.5)	7.7 (1.4, 33.3)	11.1 (2.0, 43.5)	11.1 (2.0, 43.5)	0.0 (0.0, 29.9)
Month 6	0/ 1	0/ 1	1/ 2		0/ 1
	0.0 (0.0, 79.3)	0.0 (0.0, 79.3)	50.0 (9.5, 90.5)		0.0 (0.0, 79.3)
Month 12	0/ 1	0/ 1	0/ 1		0/ 1
	0.0 (0.0, 79.3)	0.0 (0.0, 79.3)	0.0 (0.0, 79.3)		0.0 (0.0, 79.3)
Month 12 + 21 days	14/14	12/12	10/10	8/ 9	10/10
	100.0 (78.5,100.0)	100.0 (75.8,100.0)	100.0 (72.2,100.0)	88.9 (56.5, 98.0)	100.0 (72.2,100.0)

7. Analysis of safety endpoints

Safety occurrence:

- Occurrence of solicited local and general symptoms within 7 days after each vaccination.
- Occurrence of (vaccine-related) AEs for 7 days after each vaccination.
- Occurrence of (vaccine-related) SAEs for 14 days after each vaccination.

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MEDDRA) and are reported based on MEDDRA preferred terms and body systems. The relationship between AEs and treatment is determined by the investigator and categorized as "drug-related" if possibly, probably, or definitely related to treatment in the study database.

General reactions /symptoms to the injection are AEs that were determined as general AEs by the investigator. Local AEs are AEs that were determined as local by the investigator. Local reactions/symptoms are defined as local reactions to the injection. Local AEs (Armpit pain, Axillary mass, Leg infection, Lumbago, Torticollis, Urinary infection) were either not related to the injection or already captured by the local reactions.

All AEs and local and general reactions were analysed based on counts of subjects with a specific category and not on counts of individual adverse events.

Safety analyses were performed on the following data

- Pooling all safety endpoints in the primary vaccination period (vaccinations at D0-D14)
- Safety endpoints of the booster vaccination
- Safety endpoints at D0, D7, D14 vaccination separately

7.1. Safety summary

An overview of the occurrence of AEs (any, any drug-related, general, local) for 7 days after each vaccination is displayed in Table 12. The was no occurrence of SAEs for 14 days after each vaccination.

Table 12 overview of the occurrence of AEs

	VACCINATION SCHEDULE				
	Group1	Group 2	Group 3	Group 4	Group 5
	n (%; 95% CI)	n (%; 95% CI)	n (%; 95% CI)	n (%; 95% CI)	n (%; 95% CI)
Any adverse event	4 (26.7; 10.9-52.0)	2 (12.5; 3.50-36.0)	3 (20.0; 7.05-45.2)	2 (13.3; 3.74-37.9)	4 (25.0; 10.2-49.5)
Any drug-related adverse event	4 (26.7; 10.9-52.0)		1 (6.7; 1.19-29.8)	2 (13.3; 3.74-37.9)	2 (12.5; 3.50-36.0)
Any general adverse event	3 (20.0; 7.05-45.2)	1 (6.3; 1.11-28.3)	2 (13.3; 3.74-37.9)		4 (25.0; 10.2-49.5)
Any local adverse event	1 (6.7; 1.19-29.8)	1 (6.3; 1.11-28.3)	1 (6.7; 1.19-29.8)	2 (13.3; 3.74-37.9)	

7.2. Adverse events

7.2.1. Any AE

AE safety endpoint: the total number and proportion of participants with any AE by preferred term and body system up to 7 days after vaccination with 95% Wilson confidence interval.

a. Primary vaccination period

Table 13 Occurrence of AEs in the primary vaccination period per group

	VACCINATION SCHEDULE				
	Group 1	Group 2	Group 3	Group 4	Group 5
	N = 15	N = 16	N = 15	N = 15	N = 16
	n (%)	n (%)	n (%)	n (%)	n (%)
	95% CI	95% CI	95% CI	95% CI	95% CI
Any AE	4 (26.7%)	2 (12.5%)	3 (20.0%)	2 (13.3%)	3 (18.8%)
	(10.9 - 52.0)	(3.5 - 36.0)	(7.0 - 45.2)	(3.7 - 37.9)	(6.6 - 43.0)
General disorders and administration site conditions	2 (13.3%)	0 (0.0%)	2 (13.3%)	0 (0.0%)	2 (12.5%)
	(3.7 - 37.9)	(0.0 - 19.4)	(3.7 - 37.9)	(0.0 - 20.4)	(3.5 - 36.0)
Asthenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)
	(0.0 - 20.4)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(1.1 - 28.3)
Axillary pain	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Fatigue	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Influenza like illness	0 (0.0%)	0 (0.0%)	2 (13.3%)	0 (0.0%)	1 (6.3%)
	(0.0 - 20.4)	(0.0 - 19.4)	(3.7 - 37.9)	(0.0 - 20.4)	(1.1 - 28.3)
Infections and infestations	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(1.1 - 28.3)

Mumps	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)
	(0.0 - 20.4)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(1.1 - 28.3)
Urinary tract infection	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Musculoskeletal and connective tissue disorders	1 (6.7%)	1 (6.3%)	1 (6.7%)	2 (13.3%)	0 (0.0%)
	(1.2 - 29.8)	(1.1 - 28.3)	(1.2 - 29.8)	(3.7 - 37.9)	(0.0 - 19.4)
Axillary mass	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (13.3%)	0 (0.0%)
	(0.0 - 20.4)	(0.0 - 19.4)	(0.0 - 20.4)	(3.7 - 37.9)	(0.0 - 19.4)
Back pain	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(0.0 - 20.4)	(1.1 - 28.3)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Muscle rigidity	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Torticollis	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)
	(0.0 - 20.4)	(0.0 - 19.4)	(1.2 - 29.8)	(0.0 - 20.4)	(0.0 - 19.4)
Nervous system disorders	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(0.0 - 20.4)	(1.1 - 28.3)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Headache	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(0.0 - 20.4)	(1.1 - 28.3)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Skin and subcutaneous tissue disorders	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Dermatitis allergic	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)

b. Booster period

Table 14 Occurrence of AEs in the booster period per group

	VACCINATION SCHEDULE				
	Group 1	Group 2	Group 3	Group 4	Group 5
	N = 15	N = 15	N = 13	N = 11	N = 13
	n (%)	n (%)	n (%)	n (%)	n (%)
	95% CI	95% CI	95% CI	95% CI	95% CI
Any AE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 22.8)	(0.0 - 25.9)	(1.4 - 33.3)
General disorders and administration site conditions	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 22.8)	(0.0 - 25.9)	(1.4 - 33.3)
Chills	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 22.8)	(0.0 - 25.9)	(1.4 - 33.3)
Immune system disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 22.8)	(0.0 - 25.9)	(1.4 - 33.3)
Hypersensitivity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 22.8)	(0.0 - 25.9)	(1.4 - 33.3)
Nervous system disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 22.8)	(0.0 - 25.9)	(1.4 - 33.3)
Dizziness	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 22.8)	(0.0 - 25.9)	(1.4 - 33.3)
Skin and subcutaneous tissue disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 22.8)	(0.0 - 25.9)	(1.4 - 33.3)
Hyperhidrosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 22.8)	(0.0 - 25.9)	(1.4 - 33.3)

c. Day 0

Table 15 Occurrence of AEs after vaccination on Day 0 per group

	VACCINATION SCHEDULE				
	Group 1	Group 2	Group 3	Group 4	Group 5
	N = 15	N = 16	N = 15	N = 15	N = 16
	n (%)	n (%)	n (%)	n (%)	n (%)
	95% CI	95% CI	95% CI	95% CI	95% CI
Any AE	3 (20.0%)	2 (12.5%)	3 (20.0%)	0 (0.0%)	1 (6.3%)
	(7.0 - 45.2)	(3.5 - 36.0)	(7.0 - 45.2)	(0.0 - 20.4)	(1.1 - 28.3)
General disorders and administration site conditions	0 (0.0%)	0 (0.0%)	2 (13.3%)	0 (0.0%)	1 (6.3%)
	(0.0 - 20.4)	(0.0 - 19.4)	(3.7 - 37.9)	(0.0 - 20.4)	(1.1 - 28.3)
Influenza like illness	0 (0.0%)	0 (0.0%)	2 (13.3%)	0 (0.0%)	1 (6.3%)
	(0.0 - 20.4)	(0.0 - 19.4)	(3.7 - 37.9)	(0.0 - 20.4)	(1.1 - 28.3)
Infections and infestations	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Urinary tract infection	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Musculoskeletal and connective tissue disorders	1 (6.7%)	1 (6.3%)	1 (6.7%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(1.1 - 28.3)	(1.2 - 29.8)	(0.0 - 20.4)	(0.0 - 19.4)
Back pain	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(0.0 - 20.4)	(1.1 - 28.3)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Muscle rigidity	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Torticollis	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	0 (0.0%)
	(0.0 - 20.4)	(0.0 - 19.4)	(1.2 - 29.8)	(0.0 - 20.4)	(0.0 - 19.4)
Nervous system disorders	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(0.0 - 20.4)	(1.1 - 28.3)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Headache	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

	(0.0 - 20.4)	(1.1 - 28.3)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Skin and subcutaneous tissue disorders	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Dermatitis allergic	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)

d. Day 7

Table 16 Occurrence of AEs after vaccination on Day 7 per group

	VACCINATION SCHEDULE
	Group 4
	N = 15
	n (%)
	95% CI
Any AE	2 (13.3%)
	(3.7 - 37.9)
Musculoskeletal and connective tissue disorders	2 (13.3%)
	(3.7 - 37.9)
Axillary mass	2 (13.3%)
	(3.7 - 37.9)

e. Day 14

Table 17 Occurrence of AEs after vaccination on Day 14 per group

	VACCINATION SCHEDULE	
	Group 1	Group 5
	N = 15	N = 15
	n (%)	n (%)
	95% CI	95% CI
Any AE	2 (13.3%)	2 (13.3%)
	(3.7 - 37.9)	(3.7 - 37.9)
General disorders and administration site conditions	2 (13.3%)	1 (6.7%)
	(3.7 - 37.9)	(1.2 - 29.8)
Asthenia	0 (0.0%)	1 (6.7%)
	(0.0 - 20.4)	(1.2 - 29.8)
Axillary pain	1 (6.7%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 20.4)
Fatigue	1 (6.7%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 20.4)
Infections and infestations	0 (0.0%)	1 (6.7%)
	(0.0 - 20.4)	(1.2 - 29.8)
Mumps	0 (0.0%)	1 (6.7%)
	(0.0 - 20.4)	(1.2 - 29.8)

7.2.2. Any vaccine-related AE

Vaccine-related AE endpoint: the total number and proportion of participants with any vaccine-related AE by preferred term and body system up to 7 days after vaccination with 95% Wilson confidence interval.

a. Primary vaccination period

Table 18 Occurrence of vaccine-related AEs in the primary vaccination period per group

	VACCINATION SCHEDULE				
	Group 1	Group 2	Group 3	Group 4	Group 5
	N = 15	N = 16	N = 15	N = 15	N = 16
	n (%)	n (%)	n (%)	n (%)	n (%)
	95% CI	95% CI	95% CI	95% CI	95% CI
Any AE	4 (26.7%)	0 (0.0%)	1 (6.7%)	2 (13.3%)	1 (6.3%)
	(10.9 - 52.0)	(0.0 - 19.4)	(1.2 - 29.8)	(3.7 - 37.9)	(1.1 - 28.3)
General disorders and administration site conditions	2 (13.3%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (6.3%)
	(3.7 - 37.9)	(0.0 - 19.4)	(1.2 - 29.8)	(0.0 - 20.4)	(1.1 - 28.3)
Axillary pain	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Fatigue	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Influenza like illness	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (6.3%)
	(0.0 - 20.4)	(0.0 - 19.4)	(1.2 - 29.8)	(0.0 - 20.4)	(1.1 - 28.3)
Musculoskeletal and connective tissue disorders	1 (6.7%)	0 (0.0%)	0 (0.0%)	2 (13.3%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(3.7 - 37.9)	(0.0 - 19.4)
Axillary mass	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (13.3%)	0 (0.0%)
	(0.0 - 20.4)	(0.0 - 19.4)	(0.0 - 20.4)	(3.7 - 37.9)	(0.0 - 19.4)
Muscle rigidity	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Skin and subcutaneous tissue disorders	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Dermatitis allergic	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)

b. Booster period

Table 19 Occurrence of vaccine-related AEs in the booster period per group

	VACCINATION SCHEDULE				
	Group 1	Group 2	Group 3	Group 4	Group 5
	N = 15	N = 15	N = 13	N = 11	N = 13
	n (%)	n (%)	n (%)	n (%)	n (%)
	95% CI	95% CI	95% CI	95% CI	95% CI
Any AE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 22.8)	(0.0 - 25.9)	(1.4 - 33.3)
General disorders and administration site conditions	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 22.8)	(0.0 - 25.9)	(1.4 - 33.3)
Chills	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 22.8)	(0.0 - 25.9)	(1.4 - 33.3)
Immune system disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 22.8)	(0.0 - 25.9)	(1.4 - 33.3)
Hypersensitivity	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 22.8)	(0.0 - 25.9)	(1.4 - 33.3)
Nervous system disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 22.8)	(0.0 - 25.9)	(1.4 - 33.3)
Dizziness	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 22.8)	(0.0 - 25.9)	(1.4 - 33.3)
Skin and subcutaneous tissue disorders	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 22.8)	(0.0 - 25.9)	(1.4 - 33.3)
Hyperhidrosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.7%)
	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 22.8)	(0.0 - 25.9)	(1.4 - 33.3)

c. Day 0

Table 20 Occurrence of vaccine-related AEs after vaccination on Day 0 per group

	VACCINATION SCHEDULE				
	Group 1	Group 2	Group 3	Group 4	Group 5
	N = 15	N = 16	N = 15	N = 15	N = 16
	n (%)	n (%)	n (%)	n (%)	n (%)
	95% CI	95% CI	95% CI	95% CI	95% CI
Any AE	2 (13.3%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (6.3%)
	(3.7 - 37.9)	(0.0 - 19.4)	(1.2 - 29.8)	(0.0 - 20.4)	(1.1 - 28.3)
General disorders and administration site conditions	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (6.3%)
	(0.0 - 20.4)	(0.0 - 19.4)	(1.2 - 29.8)	(0.0 - 20.4)	(1.1 - 28.3)
Influenza like illness	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	1 (6.3%)
	(0.0 - 20.4)	(0.0 - 19.4)	(1.2 - 29.8)	(0.0 - 20.4)	(1.1 - 28.3)
Musculoskeletal and connective tissue disorders	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Muscle rigidity	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Skin and subcutaneous tissue disorders	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Dermatitis allergic	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)

d. Day 7

Table 21 Occurrence of vaccine-related AEs after vaccination on Day 7 per group

	VACCINATION SCHEDULE
	Group 4
	N = 15
	n (%)
	95% CI
Any AE	2 (13.3%)
	(3.7 - 37.9)
Musculoskeletal and connective tissue disorders	2 (13.3%)
	(3.7 - 37.9)
Axillary mass	2 (13.3%)
	(3.7 - 37.9)

e. Day 14

Table 22 Occurrence of vaccine-related AEs after vaccination on Day 14 per group

	VACCINATION SCHEDULE	
	Group 1	Group 5
	N = 15	N = 15
	n (%)	n (%)
	95% CI	95% CI
Any AE	2 (13.3%)	0 (0.0%)
	(3.7 - 37.9)	(0.0 - 20.4)
General disorders and administration site conditions	2 (13.3%)	0 (0.0%)
	(3.7 - 37.9)	(0.0 - 20.4)
Axillary pain	1 (6.7%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 20.4)
Fatigue	1 (6.7%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 20.4)

7.3. General symptoms (AEs)

General symptom safety endpoint: The total number and proportion of participants with any general symptoms (in total and by symptom) up to 7 days after vaccination calculated with 95% Wilson confidence interval.

7.3.1. Primary vaccination period

Table 23 Occurrence of general symptoms during the primary vaccination period per group

	VACCINATION SCHEDULE				
	Group 1	Group 2	Group 3	Group 4	Group 5
	N = 15	N = 16	N = 15	N = 15	N = 16
	n (%)	n (%)	n (%)	n (%)	n (%)
	95% CI	95% CI	95% CI	95% CI	95% CI
Asthenia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)
	(0.0 - 20.4)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(1.1 - 28.3)
Dermatitis allergic	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Fatigue	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Headache	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(0.0 - 20.4)	(1.1 - 28.3)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Influenza like illness	0 (0.0%)	0 (0.0%)	2 (13.3%)	0 (0.0%)	1 (6.3%)
	(0.0 - 20.4)	(0.0 - 19.4)	(3.7 - 37.9)	(0.0 - 20.4)	(1.1 - 28.3)
Mumps	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (6.3%)
	(0.0 - 20.4)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(1.1 - 28.3)
Muscle rigidity	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
_Any general symptom	3 (20.0%)	1 (6.3%)	2 (13.3%)	0 (0.0%)	3 (18.8%)
	(7.0 - 45.2)	(1.1 - 28.3)	(3.7 - 37.9)	(0.0 - 20.4)	(6.6 - 43.0)

7.3.2. Booster period

Table 24 Occurrence of general symptoms during the booster period per group

	VACCINATION SCHEDULE				
	Group 1	Group 2	Group 3	Group 4	Group 5
	N = 15	N = 15	N = 13	N = 11	N = 13
	n (%)	n (%)	n (%)	n (%)	n (%)
	95% CI	95% CI	95% CI	95% CI	95% CI
Chills	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	1 (7.7 %)
	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 22.8)	(0.0 - 25.9)	(1.4 - 33.3)
Dizziness	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	1 (7.7 %)
	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 22.8)	(0.0 - 25.9)	(1.4 - 33.3)
Hyperhidrosis	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	1 (7.7 %)
	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 22.8)	(0.0 - 25.9)	(1.4 - 33.3)
Hypersensitivity	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	1 (7.7 %)
	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 22.8)	(0.0 - 25.9)	(1.4 - 33.3)
_Any general symptom	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	1 (7.7 %)
	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 22.8)	(0.0 - 25.9)	(1.4 - 33.3)

7.3.3. Day 0

Table 25 Occurrence of general symptoms after vaccination on Day 0 per group

	VACCINATION SCHEDULE				
	Group 1	Group 2	Group 3	Group 4	Group 5
	N = 15	N = 16	N = 15	N = 15	N = 16
	n (%)	n (%)	n (%)	n (%)	n (%)
	95% CI	95% CI	95% CI	95% CI	95% CI
Dermatitis allergic	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Headache	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(0.0 - 20.4)	(1.1 - 28.3)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Influenza like illness	0 (0.0%)	0 (0.0%)	2 (13.3%)	0 (0.0%)	1 (6.3%)
	(0.0 - 20.4)	(0.0 - 19.4)	(3.7 - 37.9)	(0.0 - 20.4)	(1.1 - 28.3)
Muscle rigidity	1 (6.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 19.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
_Any general symptom	2 (13.3%)	1 (6.3%)	2 (13.3%)	0 (0.0%)	1 (6.3%)
	(3.7 - 37.9)	(1.1 - 28.3)	(3.7 - 37.9)	(0.0 - 20.4)	(1.1 - 28.3)

7.3.4. Day 7

None were observed

7.3.5. Day 14

Table 26 Occurrence of general symptoms after vaccination on Day 14 per group

	VACCINATION SCHEDULE	
	Group 1	Group 5
	N = 15	N = 15
	n (%)	n (%)
	95% CI	95% CI
Asthenia	0 (0.0%)	1 (6.7%)
	(0.0 - 20.4)	(1.2 - 29.8)
Fatigue	1 (6.7%)	0 (0.0%)
	(1.2 - 29.8)	(0.0 - 20.4)
Mumps	0 (0.0%)	1 (6.7%)
	(0.0 - 20.4)	(1.2 - 29.8)
_Any general symptom	1 (6.7%)	2 (13.3%)
	(1.2 - 29.8)	(3.7 - 37.9)

7.4. Local Reactions

Local reactions safety endpoint: The total number and proportion of participants with any local symptoms (in total and by symptom) up to 7 days after vaccination calculated with 95% Wilson confidence interval.

7.4.1. Primary vaccination period

Table 27 Occurrence of local reactions during the primary vaccination period per group

	VACCINATION SCHEDULE				
	Group 1	Group 2	Group 3	Group 4	Group 5
	N = 15	N = 16	N = 15	N = 15	N = 16
	n (%)	n (%)	n (%)	n (%)	n (%)
	95% CI	95% CI	95% CI	95% CI	95% CI
Bruising	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(0.0 - 20.4)	(1.1 - 28.3)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Itching	0 (0.0%)	0 (0.0%)	3 (20.0%)	11 (73.3%)	11 (68.8%)
	(0.0 - 20.4)	(0.0 - 19.4)	(7.0 - 45.2)	(48.0 - 89.1)	(44.4 - 85.8)
Pain	2 (13.3%)	6 (37.5%)	0 (0.0%)	1 (6.7%)	0 (0.0%)
	(3.7 - 37.9)	(18.5 - 61.4)	(0.0 - 20.4)	(1.2 - 29.8)	(0.0 - 19.4)
Redness	0 (0.0%)	0 (0.0%)	15 (100%)	15 (100%)	16 (100%)
	(0.0 - 20.4)	(0.0 - 19.4)	(79.6 - 100)	(79.6 - 100)	(80.6 - 100)
Swelling	0 (0.0%)	0 (0.0%)	1 (6.7%)	4 (26.7%)	4 (25.0%)
	(0.0 - 20.4)	(0.0 - 19.4)	(1.2 - 29.8)	(10.9 - 52.0)	(10.2 - 49.5)
_Any local symptom	2 (13.3%)	6 (37.5%)	15 (100%)	15 (100%)	16 (100%)
	(3.7 - 37.9)	(18.5 - 61.4)	(79.6 - 100)	(79.6 - 100)	(80.6 - 100)

7.4.2. Booster period

Table 28 Occurrence of local reactions during the booster period per group

	VACCINATION SCHEDULE				
	Group 1	Group 2	Group 3	Group 4	Group 5
	N = 15	N = 15	N = 13	N = 11	N = 13
	n (%)	n (%)	n (%)	n (%)	n (%)
	95% CI	95% CI	95% CI	95% CI	95% CI
Itching	0 (0.0 %)	0 (0.0 %)	3 (23.1 %)	2 (18.2 %)	4 (30.8 %)
	(0.0 - 20.4)	(0.0 - 20.4)	(8.2 - 50.3)	(5.1 - 47.7)	(12.7 - 57.6)
Pain	0 (0.0 %)	0 (0.0 %)	1 (7.7 %)	1 (9.1 %)	2 (15.4 %)
	(0.0 - 20.4)	(0.0 - 20.4)	(1.4 - 33.3)	(1.6 - 37.7)	(4.3 - 42.2)
Redness	0 (0.0 %)	0 (0.0 %)	10 (76.9 %)	8 (72.7 %)	12 (92.3 %)
	(0.0 - 20.4)	(0.0 - 20.4)	(49.7 - 91.8)	(43.4 - 90.3)	(66.7 - 98.6)
Swelling	0 (0.0 %)	0 (0.0 %)	4 (30.8 %)	6 (54.5 %)	7 (53.8 %)
	(0.0 - 20.4)	(0.0 - 20.4)	(12.7 - 57.6)	(28.0 - 78.7)	(29.1 - 76.8)
_Any local symptom	0 (0.0 %)	0 (0.0 %)	10 (76.9 %)	8 (72.7 %)	13 (100 %)
	(0.0 - 20.4)	(0.0 - 20.4)	(49.7 - 91.8)	(43.4 - 90.3)	(77.2 - 100)

7.4.3. Day 0

Table 29 Occurrence of local reactions after vaccination on Day 0 per group

	VACCINATION SCHEDULE				
	Group 1	Group 2	Group 3	Group 4	Group 5
	N = 15	N = 16	N = 15	N = 15	N = 16
	n (%)	n (%)	n (%)	n (%)	n (%)
	95% CI	95% CI	95% CI	95% CI	95% CI
Bruising	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(0.0 - 20.4)	(1.1 - 28.3)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Itching	0 (0.0%)	0 (0.0%)	3 (20.0%)	7 (46.7%)	6 (37.5%)
	(0.0 - 20.4)	(0.0 - 19.4)	(7.0 - 45.2)	(24.8 - 69.9)	(18.5 - 61.4)
Pain	2 (13.3%)	6 (37.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	(3.7 - 37.9)	(18.5 - 61.4)	(0.0 - 20.4)	(0.0 - 20.4)	(0.0 - 19.4)
Redness	0 (0.0%)	0 (0.0%)	15 (100%)	14 (93.3%)	16 (100%)
	(0.0 - 20.4)	(0.0 - 19.4)	(79.6 - 100)	(70.2 - 98.8)	(80.6 - 100)
Swelling	0 (0.0%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	2 (12.5%)
	(0.0 - 20.4)	(0.0 - 19.4)	(1.2 - 29.8)	(0.0 - 20.4)	(3.5 - 36.0)
_Any local symptom	2 (13.3%)	6 (37.5%)	15 (100%)	14 (93.3%)	16 (100%)
	(3.7 - 37.9)	(18.5 - 61.4)	(79.6 - 100)	(70.2 - 98.8)	(80.6 - 100)

7.4.4. Day 7

Table 30 Occurrence of local reactions after vaccination on Day 7 per group

	VACCINATION SCHEDULE
	Group 4
	N = 15
	n (%)
	95% CI
Itching	8 (53.3%)
	(30.1 - 75.2)
Pain	1 (6.7%)
	(1.2 - 29.8)
Redness	12 (80.0%)
	(54.8 - 93.0)
Swelling	4 (26.7%)
	(10.9 - 52.0)
_Any local symptom	12 (80.0%)
	(54.8 - 93.0)

7.4.5. Day 14

Table 31 Occurrence of local reactions after vaccination on Day 14 per group

	VACCINATION SCHEDULE	
	Group 1	Group 5
	N = 15	N = 15
	n (%)	n (%)
	95% CI	95% CI
Itching	0 (0.0%)	7 (46.7%)
	(0.0 - 20.4)	(24.8 - 69.9)
Redness	0 (0.0%)	12 (80.0%)
	(0.0 - 20.4)	(54.8 - 93.0)
Swelling	0 (0.0%)	3 (20.0%)
	(0.0 - 20.4)	(7.0 - 45.2)
_Any local symptom	0 (0.0%)	12 (80.0%)
	(0.0 - 20.4)	(54.8 - 93.0)

7.5. Exploratory analyses

7.5.1. Description of characteristics of patients that did not respond to the booster

There were two patients, in Group 2 and Group 4 respectively, that did not respond to the booster. They displayed no seropositivity at month 12 + 21 days as is shown in Table 9 Proportion of ITT subjects with neutralizing antibodies (≥ 10) per vaccination regimen at scheduled follow-up visits with 95% Wilson confidence intervals. An overview was made for baseline characteristics and antibody titres at other visits.

Table 32 Baseline characteristics for the patients that did not respond to the booster

PersonId	AGE	SEX	Group
39	33	Male	Group 4
96	33	Female	Group 2

Table 33 Antibody titres at each visit for the patients that did not respond to the booster

PersonId	sero10736	sero10739	sero10740	sero10741	sero10742	sero10743	sero10744	sero10745	sero10847
39	5	5	5	5	5	5	5	5	5
96	5	5	5	5	5	5	5	5	5

7.5.2. Yellow fever vaccination

Yellow fever vaccination might potentially influence the outcome of TBE vaccination. In an exploratory analysis it was investigated whether their antibody responses differed from the antibody responses of those unvaccinated for yellow fever. Both antibody titres and proportion of subjects with neutralizing antibodies (≥ 10) were compared, pooled over the arms.

For the antibody titres, the geometric means per vaccination group (no/yes) and their ratio were calculated with 95% confidence intervals (CIs). The geometric mean titre (GMT) is the exponentiation of the mean of the natural logarithm of the antibody titres and is a natural parameter of interest for data that follow a lognormal distribution. The 95% CI of the ratio takes into account whether the coefficients of variation (CVs) were equal (pooled method) or unequal (Satterthwaite method) in both groups, and assumes lognormality of the data. Only for the last visit there was not enough evidence to state that the CVs for the two groups were different, hence a pooled variance estimator was used. The p-value was obtained by means of a t-test for lognormal data (PROC TTEST Procedure with dist. = lognormal).

Due to the exploratory character of this analysis, the results are indicative and not inferential. Caution should be taken with the interpretation of the confidence intervals and p-values due to the small sample size (definitely in the vaccine group, but also overall) en the assumption of lognormality of the data.

Figure 3 Descriptive comparison of log antibody titres for yellow fever vaccination (no/yes) per visit

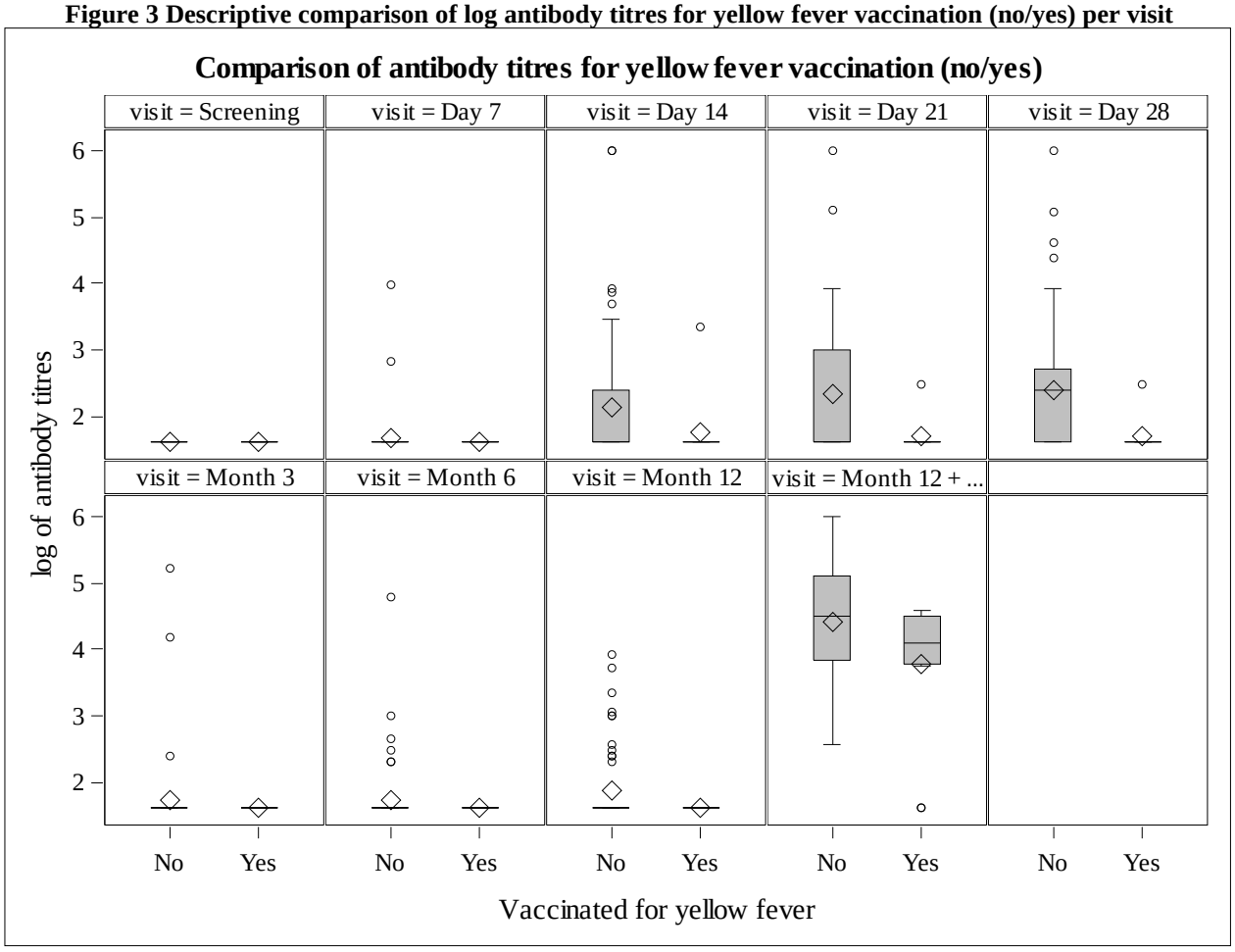

Table 34 Comparison of the geometric means, their ratio, and percentages of seropositivity for yellow fever vaccination (no/yes) per visit

Yellow fever vaccination: Geometric mean ab titres, ratio, and percentages						
	Geometric mean (95% CI)		Ratio geometric means (95% CI and p-value)		n seropositive % seropositive (95% Wilson CI)	
visit	No yellow fever vaccination	Yellow fever vaccination	Ratio (95% CI)	p-value	No yellow fever vaccination	Yellow fever vaccination
Day 0	5.00 (5.00- 5.00)	5.00 (5.00- 5.00)	1.00 (1.00- 1.00)	.	0/65 0.0 (0.0 - 5.6)	0/12 0.0 (0.0 - 24.2)
Day 7	5.29 (4.87- 5.74)	5.00 (5.00- 5.00)	1.06 (0.97- 1.15)	0.1797	2/64 3.1 (0.9 - 10.7)	0/12 0.0 (0.0 - 24.2)
Day 14	8.43 (6.61- 10.7)	5.85 (4.13- 8.29)	1.44 (0.96- 2.17)	0.0774	21/63 33.3 (22.9 - 45.6)	1/11 9.1 (1.6 - 37.7)
Day 21	10.4 (8.22- 13.2)	5.41 (4.53- 6.46)	1.92 (1.44- 2.55)	<.0001	31/65 47.7 (36.0 - 59.6)	1/11 9.1 (1.6 - 37.7)
Day 28	10.9 (8.62- 13.8)	5.41 (4.53- 6.46)	2.02 (1.52- 2.68)	<.0001	36/64 56.3 (44.1 - 67.7)	1/11 9.1 (1.6 - 37.7)
Month 3	5.57 (4.85- 6.38)	5.00 (5.00- 5.00)	1.11 (0.97- 1.28)	0.1224	3/65 4.6 (1.6 - 12.7)	0/12 0.0 (0.0 - 24.2)
Month 6	5.64 (5.03- 6.33)	5.00 (5.00- 5.00)	1.13 (1.01- 1.27)	0.0404	6/65 9.2 (4.3 - 18.7)	0/11 0.0 (0.0 - 25.9)
Month 12	6.50 (5.56- 7.61)	5.00 (5.00- 5.00)	1.30 (1.11- 1.52)	0.0015	11/55 20.0 (11.6 - 32.4)	0/12 0.0 (0.0 - 24.2)
Month 12 + 21 days	82.2 (66.2- 102)	43.7 (22.2- 85.9)	1.88 (1.09- 3.23)	0.0229	55/55 100.0 (93.5 - 100.0)	10/12 83.3 (55.2 - 95.3)

Figure 4 Geometric mean titres for yellow fever vaccination (no/yes) per visit with 95% CI

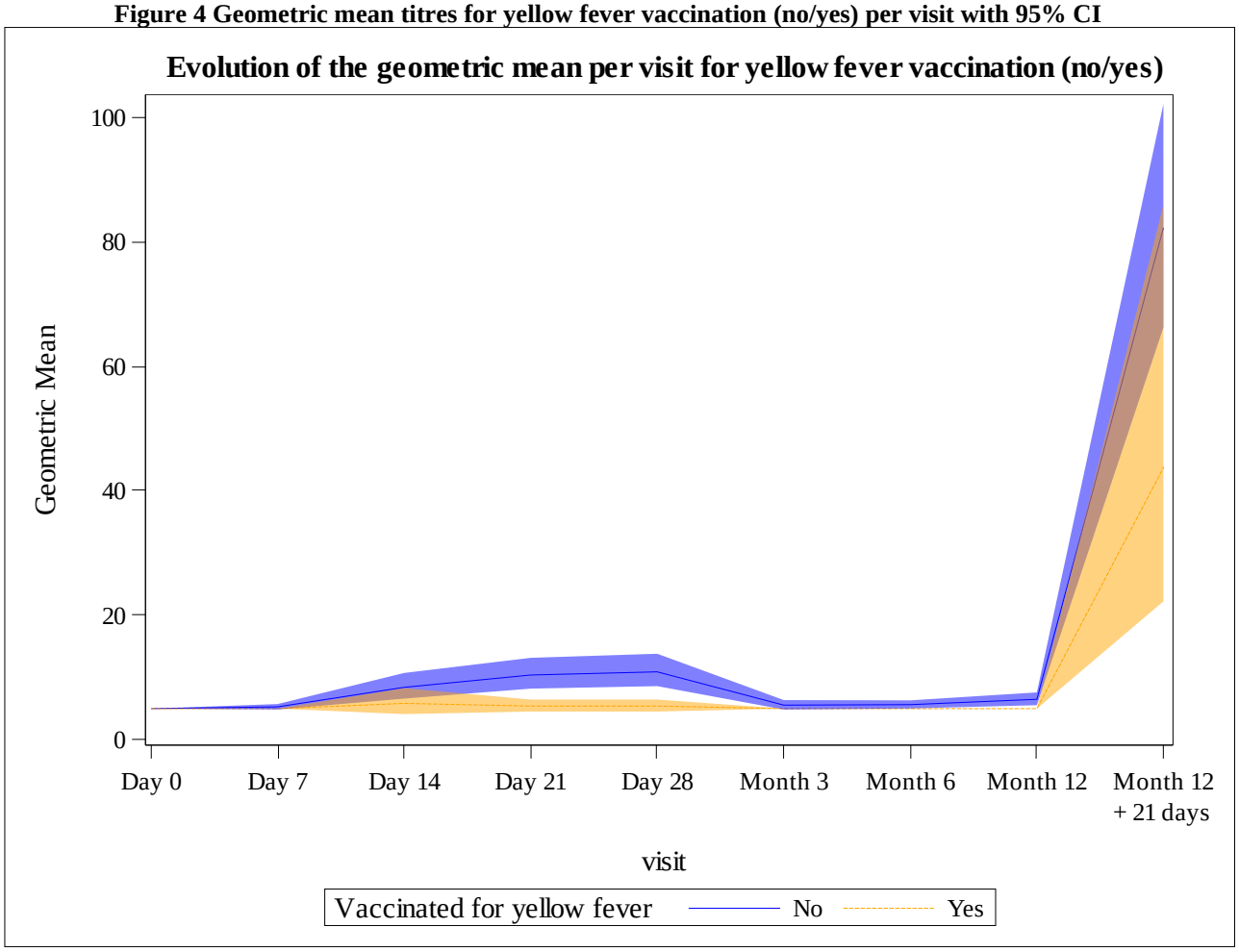

Figure 5 Geometric mean titres for yellow fever vaccination (no/yes) over time with 95% CI

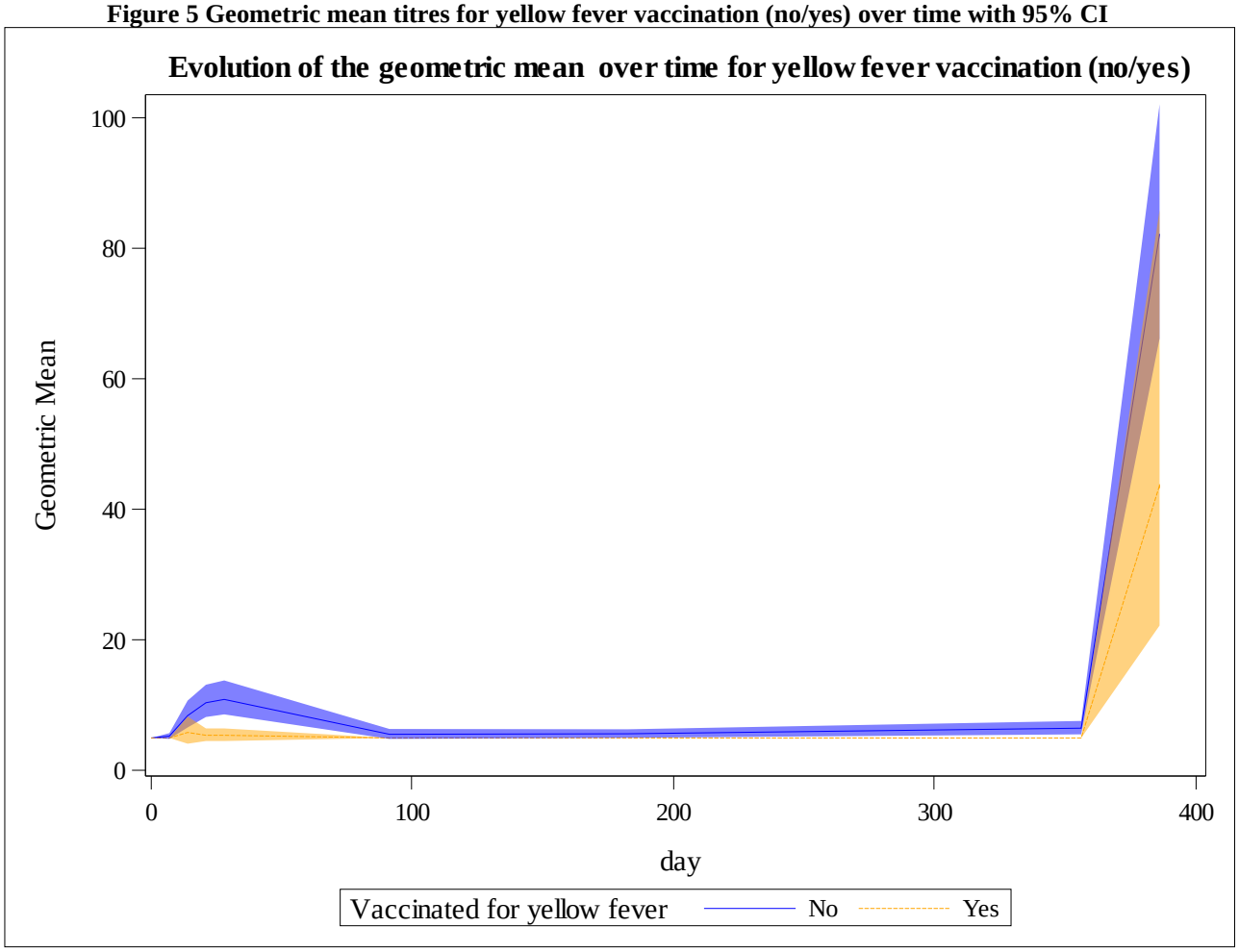

Figure 6 Ratio of geometric mean titres for yellow fever vaccination (no/yes) per visit with 95% CI

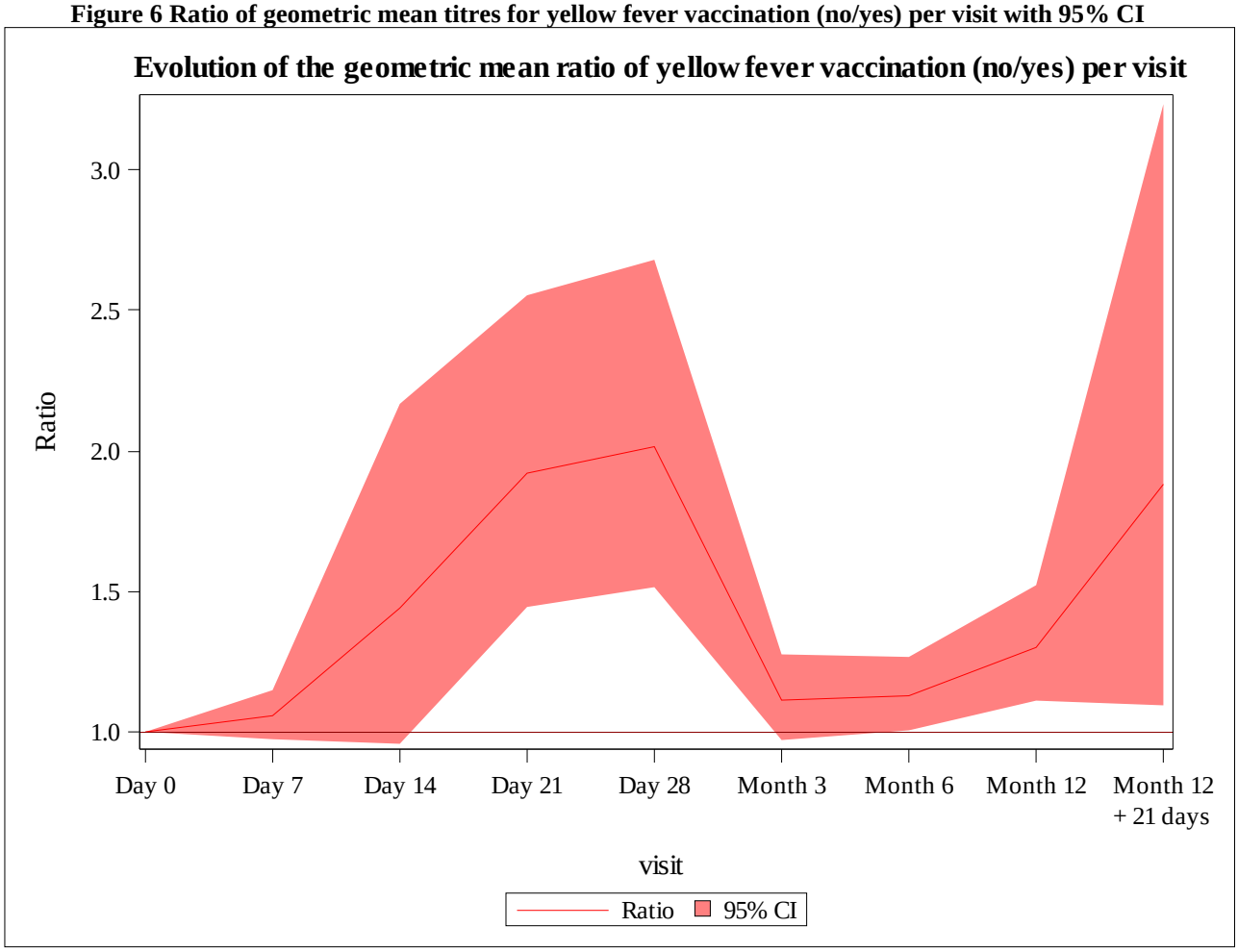

Figure 7 Ratio of geometric mean titres for yellow fever vaccination (no/yes) over time with 95% CI