Supplementary Table 1. Summary of demographic characteristics (total vaccinated cohort)

Characteristics	Parameter or category	5/10 N=15	5/10AS N=15	10/30 N=14	10/30AS N=14	Placebo N=30
Age	Mean (range)	31.1 (19 – 39)	31.9 (21 – 40)	30.9 (19 – 40)	30.6 (21 – 39)	30.1 (18 – 40)
Gender	Female, n (%)	11 (73.3)	5 (33.3)	6 (42.9)	7 (50.0)	15 (50.0)
Race	Caucasian, n (%)	15 (100)	14 (93.3)	13 (92.9)	14 (100)	27 (90.0)
	Arabic/North African, n (%)	0	1 (6.7)	1 (7.1)	0	2 (6.7)
	Asian, n (%)	0	0	0	0	1 (3.3)

5/10 = 5 µg CPS5-TT, 5 µg CPS8-TT, 10 µg AT, 10 µg ClfA
5/10AS = 5 µg CPS5-TT, 5 µg CPS8-TT, 10 µg AT, 10 µg ClfA adjuvanted with $AS03_B$
10/30 = 10 µg CPS5-TT, 10 µg CPS8-TT, 30 µg AT, 30 µg ClfA
10/30AS = 10 µg CPS5-TT, 10 µg CPS8-TT, 30 µg AT, 30 µg ClfA adjuvanted with $AS03_B$
N, number of patients within study group; n (%), number (percentage) of patients within the category

Supplementary Table 2. Percentage of subjects with unsolicited adverse events reported within 30 days after each vaccine dose (total vaccinated cohort)

	5/10	5/10AS	10/30	10/30AS	Placebo
	n (%)	n (%)	n (%)	n (%)	n (%)
Doses 1 and 2 (any grading)	10 (66.7)	14 (93.3)	9 (64.3)	13 (92.9)	25 (83.3)
Grade 3	**4 (26.7)**	0 (0.0)	**1 (7.1)**	**2 (14.3)**	**6 (20.0)**
Abdominal pain	**1 (6.7)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	**1 (7.1)**	0 (0.0)
Fatigue	**1 (6.7)**	0 (0.0)	0 (0.0)	0 (0.0)	**1 (3.3)**
Hangover	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (3.3)**
Nasopharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (3.3)**
Pharyngitis	**1 (6.7)**	0 (0.0)	0 (0.0)	0 (0.0)	**1 (3.3)**
Rhinotracheitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (3.3)**
Tracheitis	0 (0.0)	0 (0.0)	0 (0.0)	**1 (7.1)**	0 (0.0)
Muscle spasms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (3.3)**
Headache	**1 (6.7)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intercostal neuralgia	0 (0.0)	0 (0.0)	**1 (7.1)**	0 (0.0)	0 (0.0)
dose 3 (any grading)	6 (66.7)	6 (66.7)	2 (40.0)	6 (50.0)	9 (42.9)
Grade 3	**2 (22.2)**	**2 (22.2)**	**2 (40.0)**	**2 (16.7)**	**2 (9.5)**
Abdominal pain	**1 (11.1)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ear infection	0 (0.0)	**1 (11.1)**	0 (0.0)	**1 (8.3)**	0 (0.0)
Gastroenteritis	0 (0.0)	**1 (11.1)**	0 (0.0)	0 (0.0)	0 (0.0)
Pharyngitis	**1 (11.1)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhinotracheitis	**1 (11.1)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ligament sprain	**1 (11.1)**	0 (0.0)	0 (0.0)	0 (0.0)	**1 (4.8)**
Wound	0 (0.0)	0 (0.0)	**1 (20.0)**	0 (0.0)	0 (0.0)
Coccydynia	0 (0.0)	0 (0.0)	0 (0.0)	**1 (8.3)**	0 (0.0)
Cholelithiasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (4.8)**
Haematoma	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)

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10/30 = 10µg CPS5-TT, 10µg CPS8-TT, 30µg AT, 30µg ClfA
10/30AS = 10µg CPS5-TT, 10µg CPS8-TT, 30µg AT, 30µg ClfA adjuvanted with $AS03_B$
n/%, number/percentage of subjects reporting the symptom at least once

Supplementary Table 3. Change of carriage status from baseline (according-to-protocol cohort for immunogenicity)

			Non carrier at baseline N = 46	Intermediate carrier at baseline N = 9	Carrier at baseline N = 17
Group	**Timing**	**Carriage post vaccination**	**n**	**n**	**n**
5/10	PI(D30)	Non Carrier	8	-	1
		Carrier	0	-	2
	PII(D60)	Non Carrier	7	-	1
		Carrier	0	-	2
	PII(D180)	Non Carrier	5	-	1
		Carrier	1	-	2
	PIII(D210)	Non Carrier	5	-	0
		Carrier	1	-	3
	PIII(D540)	Non Carrier	5	-	1
		Carrier	1	-	2
5/10AS	PI(D30)	Non Carrier	7	0	1
		Carrier	0	1	3
	PII(D60)	Non Carrier	7	0	0
		Carrier	0	1	4
	PII(D180)	Non Carrier	5	0	2
		Carrier	0	1	1
	PIII(D210)	Non Carrier	5	1	1
		Carrier	0	0	2
	PIII(D540)	Non Carrier	5	0	0
		Carrier	0	1	3
10/30	PI(D30)	Non Carrier	8	1	0
		Carrier	0	0	3
	PII(D60)	Non Carrier	7	1	0
		Carrier	1	0	3
	PII(D180)	Non Carrier	4	-	-
		Carrier	0	-	-
	PIII(D210)	Non Carrier	4	-	-
		Carrier	0	-	-
	PIII(D540)	Non Carrier	4	-	-
		Carrier	0	-	-
10/30AS	PI(D30)	Non Carrier	9	2	0
		Carrier	1	0	1
	PII(D60)	Non Carrier	7	2	0
		Carrier	3	0	1
	PII(D180)	Non Carrier	7	1	0
		Carrier	2	1	1
	PIII(D210)	Non Carrier	8	2	0

		Carrier	1	0	1
	PIII(D540)	Non Carrier	6	2	0
		Carrier	2	0	1
SALINE	PI(D30)	Non Carrier	13	3	1
		Carrier	0	2	5
	PII(D60)	Non Carrier	12	4	1
		Carrier	1	1	5
	PII(D180)	Non Carrier	12	4	1
		Carrier	1	0	3
	PIII(D210)	Non Carrier	12	3	2
		Carrier	1	1	2
	PIII(D540)	Non Carrier	10	4	1
		Carrier	2	0	1

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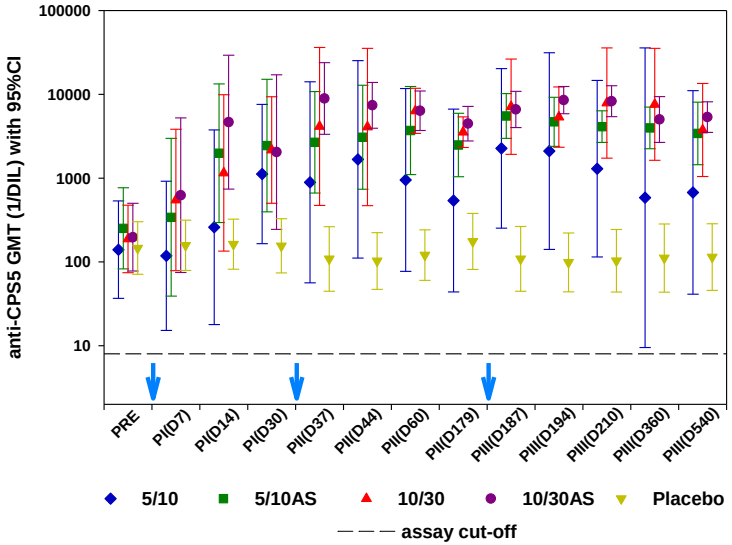
10/30 = 10 µg CPS5-TT, 10 µg CPS8-TT, 30 µg AT, 30 µg ClfA
10/30AS = 10 µg CPS5-TT, 10 µg CPS8-TT, 30 µg AT, 30 µg ClfA adjuvanted with $AS03_B$
N, number of subjects in the specified carriage status at baseline with at least one post vaccination result available; n, number of subjects in the specified carriage status at post vaccination time point; PI(D30), 30 days post-dose 1; PII(D60), 30 days post-dose 2; PII(D180), pre-dose 3; PIII(D210), 30 days post-dose 3; PIII(D360), 1 year post-dose 1 or 6 months post-dose 3; PIII(D540), 1.5 year post-dose 1 or 1 year post-dose 3

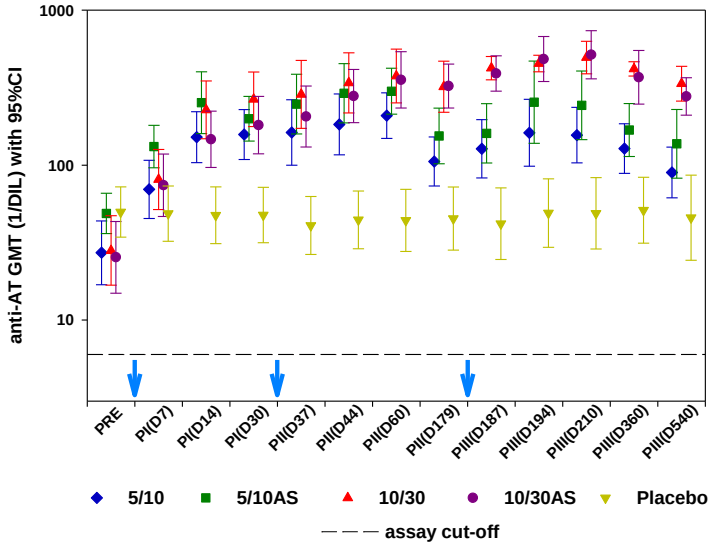
Non carrier at baseline = swab samples negative for *S. aureus* at screening and at Day 0
Intermediate carrier at baseline = *S. aureus* detected only at one baseline time point (either screening or Day 0)
Carrier at baseline = *S. aureus* detected in at least one swab sample at screening and at Day 0, whatever the swab sample type
Non-carrier at post vaccination time point = swab samples negative for *S.aureus* at the considered time point
Carrier at post vaccination time point = *S. aureus* detected in at least one swab sample at the considered time point

Supplementary figure 1. Geometric mean titers for functional assays: OPA for CPS5 (panel A), inhibition assay for α-toxin (panel B), inhibition assay for ClfA (initial test, panel C and new test, panel D) (according-to-protocol cohort for immunogenicity)

A



B



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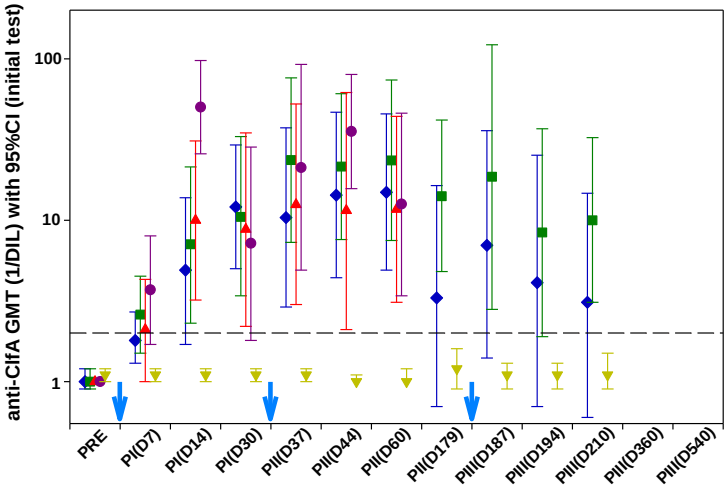
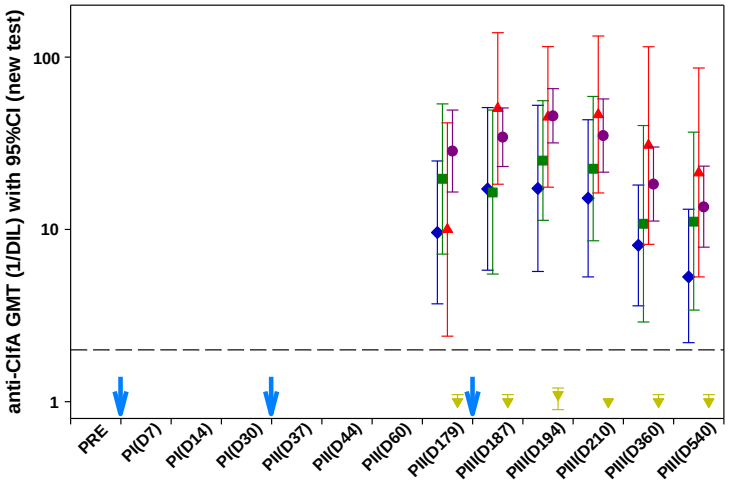


D



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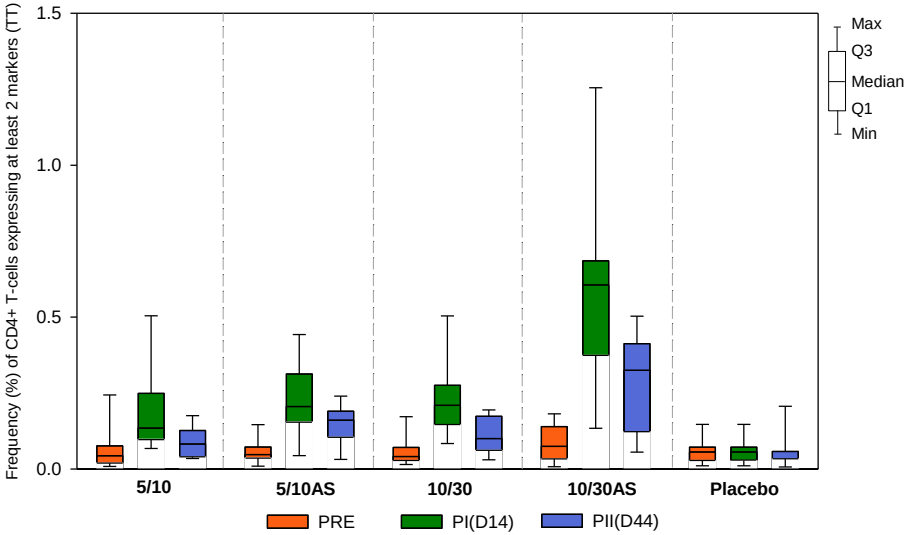
GMT, geometric mean titer; 95% CI, 95% confidence interval; CPS5, capsular polysaccharides type 5; TT, , tetanus toxoid; AT, α-toxin; ClfA, clumping factor A; PRE, pre-dose 1; PI(D7), 7 days post-dose 1; PI(D14), 14 days post-dose 1; PI(D30), 30 days post-dose 1; PII(D37), 7 days post-dose 2; PII(D44), 14 days post-dose 2; PII(D60), 30 days post-dose 2; PII(D179), pre-dose 3; PIII(D187), 7 days post-dose 3; PIII(D194), 14 days post-dose 3; PIII(D210), 30 days post-dose 3; PIII(D360), 1 year post-dose 1 or 6 months post-dose 3; PIII(D540), 1.5 year post-dose 1 or 1 year post-dose 3.

The cut-off values for these assays (dashed line) were: 8 1/DIL for OPA (CPS5), 6 1/DIL for the inhibition assay (α-toxin) and 2 1/DIL for the inhibition assay (ClfA); Blue arrows indicate days of vaccine or placebo administration.

Supplementary figure 2. Frequency (%) of *S. aureus* tetanus toxoid-specific CD4$^+$ T-cells expressing at least 2 markers amongst IL-2, IFN-γ, IL-13, IL-17, TNF-α and CD40L prior and after each vaccination (according-to-protocol cohort for immunogenicity).



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10/30AS = 10 µg CPS5-TT, 10 µg CPS8-TT, 30 µg AT, 30 µg ClfA adjuvanted with $AS03_B$
TT, tetanus toxoid, PRE, pre-dose 1; PI(D14), 14 days post-dose 1; PII(D44), 14 days post-dose 2; Min/Max, Minimum/Maximum; Q1,Q3, First and third quartiles