For each serogroup, a higher proportion of Menomune recipients than Menactra recipients achieved ≥ four-fold increase in bactericidal antibody titer. The upper limit of the two-sided 95% confidence interval of the difference in the two proportions, however, was less than 0.1 (MTA-09 Table 3).

MTA-09 Table 3: Primary Immunogenicity Hypothesis Testing
Proportion of Participants 18-55 Years Old with a ≥ Four-fold Increase in SBA-BR Titer

Serogroup	Menomune® N=1098 $p_{Menomune®}$†	Menactra N=1280 $p_{Menactra}$‡	Difference ($p_{Menomune®} - p_{Menactra}$)	Upper Limit of the 2-sided 95% CI of the Difference§
A	0.846	0.805	0.041	0.072
C	0.897	0.885	0.012	0.037
Y	0.794	0.735	0.059	0.930
W-135	0.944	0.894	0.050	0.072

*n: number of participants with ≥ 4-fold rise in SBA-BR titer from baseline. N: total number of participants with valid serology data.
† $p_{Menomune®}$: proportion of Menomune® participants with a ≥4-fold rise in SBA-BR titer post-vaccination compared with baseline.
‡ $p_{Menactra}$: proportion of Menactra participants with a ≥ 4-fold rise in SBA-BR titer post-vaccination compared with baseline.
§ CI: Confidence interval.

GMT:
At baseline, the proportion of Menactra recipients with a SBA-BR titer ≥1:8 to serogroups A, C, Y and W-135 was 88%, 73%, 78%, and 71%, respectively. Similar distributions of pre-vaccination SBA-BR titer were observed in Menomune® recipients. Menactra recipients achieved comparable GMTs post-vaccination to serogroups A and C. Lower bactericidal antibody responses were observed for serogroups Y and W-135, although the proportion of participants who achieved seroconversion was 90.7% and 96.5%, respectively.

MTA-09 Table 4: SBA-BR Geometric Mean Antibody Titer Pre- and 28 days Post-vaccination

Serogroup	Timepoint	Menomune® N=1098 SBA-BR GMT	95% CI	Menactra N=1280 SBA-BR GMT	95% CI
A	Day 0	203.6	180.3, 229.9	223.8	200.1, 250.4
	Day 28	4114.1	3832.2, 4416.8	3896.9	3647.0, 4164.0
C	Day 0	51.7	45.4, 56.0	56.8	50.2, 64.4
	Day 28	3469.4	3148.4, 3823.1	3231.1	2954.9, 3533.2
Y	Day 0	127.2	111.8, 144.8	123.2	109.1, 139.0
	Day 28	2448.6	2237.0, 2680.2	1750.4	1597.0, 1918.5
W-135	Day 0	30.9	27.8, 34.4	33.1	29.9, 36.7
	Day 28	1871.2	1722.8, 2032.4	1271	1171.9, 1378.4

N: total number of participants with valid serology data.
†Mean fold rise: geometric mean of (SBA-BR titer at Day 28/ SBA-BR titer at Day 0)

MTA-09 Table 5 shows the SBA-BR geometric mean titer, using the baseline titer as a covariate. A greater difference in treatment effect was observed for serogroups W-135 and Y, compared with serogroup C and serogroup A. The upper limit of the two-sided 95% CI for each serogroup was less than $\log_2(2)$.

MTA-09 Table 5: Secondary Hypothesis Testing: Treatment Effect on SBA-BR GMT, Adjusted by Baseline Covariate

Serogroup	Vaccine Group	Baseline SBA-BR GMT	Estimate of Baseline GMT Effect	Difference of the Treatment Effect (Menomune®- Menactra)	Anti-Log of Treatment Effect (Menomune®- Menactra)	95% CI for Anti-Log of the Treatment Effect (Menomune®- Menactra)
A	Menomune®	203.6	-0.849	0.099	1.071	0.975, 1.177
	Menactra	223.8				
C	Menomune®	51.7	-0.771	0.134	1.097	0.968, 1.244
	Menactra	56.8				
Y	Menomune®	127.2	-0.743	0.472	1.387	1.229, 1.567
	Menactra	123.2				
W-135	Menomune®	30.9	-0.764	0.581	1.496	1.339, 1.672
	Menactra	33.1				

* Anti-Log of the treatment effect is calculated as 2 to the treatment effect (Menomune-Menactra) power.

Seroconversion rate was defined as the proportion of participants with SBA-BR antibody titer less than 1:8 pre-vaccination, who subsequently achieved a four-fold or greater increase in SBA-BR antibody titer 28 days after vaccination. All Menactra recipients with SBA-BR antibody titer less than 1:8 pre-vaccination, and 99.3% [143/144] of corresponding Menomune® recipients achieved this criterion for serogroup A. For serogroup C, seroconversion was observed in 99.4% [343/345] of Menactra recipients and 97.7% [297/304] of Menomune® recipients. For the remaining serogroups, 90.7% [253/279] and 96.5% [360/373] of Menactra participants responded with a ≥4-fold antibody rise to serogroups Y and W135, respectively, compared with 96.9% [221/228] and 99.1% [325/328] of individuals who received Menomune®.

7.1.3.4.3 Safety

Overall safety profile:

MTA-09 Table 6: Overall Participant Safety Profile

Type of AE	Menactra		Menomune®	
	n/N*	%†	n/N*	%†
Immediate reactions (within 30 minutes)	2/1384	0.1	3/1170	0.3
Solicited local reactions (Days 0-7)	790/1371	57.6	644/1159	55.6
95% Confidence Interval		55.0, 60.3		52.7, 58.5
Solicited systemic reactions (Days 0-7)	849/1371	61.9	699/1159	60.3
95% Confidence Interval		59.3, 64.5		57.4, 63.1
Unsolicited adverse events (Days 0-28)	460/1355	33.9	360/1148	31.4
Unsolicited significant adverse events (Day 29- Month 6)	51/1301	3.9	48/1099	4.4
All serious adverse events (Day 0-Month 6)	23/1384	1.7	20/1170	1.7

*n: number of participants reporting at least one event in this category.
†%: n/N expressed as a percentage.

Immediate reactions: Six reactions occurred in three Menomune® participants, and 2 reactions occurred in two Menactra participants. Both Menactra participants reported mild injection site reactions. Two Menomune® participants reported cough, with associated throat tightness and sore throat, respectively; one

Menomune® participant responded to loratadine-pseudoephedrine (Claritin-D), while the other participant did not require medical intervention. The last Menomune® participant reported mild swelling and erythema at the injection site.

Local reactions:
Except for erythema, any local reaction occurred more often in Menactra compared to Menomune® participants. The frequency of any swelling (12.6% vs. 7.6%) and any induration (17.1 vs. 11.0) was 1.6 times higher in the Menactra group than in the Menomune® group (MTA-09 Table 7). Although the reactions were mainly mild, moderate swelling (2.3% vs. 0.7%) and moderate induration (3.4% vs. 1.0%) were reported more frequently in participants receiving Menactra. Discordant frequencies of moderate injection site pain were observed overall, and when the study population was subcategorized into two age groups, 18-25 and 26-55 years old (MTA-09 Table 8).

Forty severe local reactions occurred in 23 Menactra participants, and two severe local reactions occurred in 2 Menomune® participants. Of these participants, 10 individuals receiving Menactra experienced two or more severe adverse events. Five Menactra participants with multiple reactions reported severe swelling, induration, with erythema or pain. One Menactra participant reported all solicited local reactions as severe.

Local reactions in the Menactra group that were present during Days 4-7, and represented continuations of reactions reported during Days 0-3, lasted an average of 5 days. A trend towards longer duration of local reactions was also observed in the Menomune® group.

MTA-09 Table 7: Local adverse reactions (Days 0-7)

Reaction	Severity	Menactra N=1371 n*	Menactra N=1371 %†	Menactra N=1371 95% CI	Menomune N=1159 n*	Menomune N=1159 %†	Menomune N=1159 95% CI
Redness							
	Any	198	14.4	12.6, 16.4	185	16.0	13.9, 18.2
< 1 inch	**Mild**	143	10.4	8.9, 12.2	162	14.0	12.0, 16.1
1 – 2 inches	**Moderate**	40	2.9	2.1, 4.0	22	1.9	1.2, 2.9
> 2 inches	**Severe**	15	1.1	0.6, 1.8	1	0.1	0.0, 0.5
Swelling							
	Any	173	12.6	10.9, 14.5	88	7.6	6.1, 9.3
< 1 inch	**Mild**	128	9.3	7.9, 11.0	80	6.9	5.5, 8.5
1 – 2 inches	**Moderate**	32	2.3	1.6, 3.3	8	0.7	0.3, 1.4
> 2 inches	**Severe**	13	0.9	0.5, 1.6	0	0.0	0.0, 0.3
Induration							
	Any	235	17.1	15.2, 19.2	127	11.0	9.2, 12.9
< 1 inch	**Mild**	179	13.1	11.3, 15.0	115	9.9	8.3, 11.8
1 – 2 inches	**Moderate**	47	3.4	2.5, 4.5	12	1.0	0.5, 1.8
> 2 inches	**Severe**	9	0.7	0.3, 1.2	0	0.0	0.0, 0.3
Pain							
	Any	739	53.9	51.2, 56.6	558	48.1	45.2, 51.1
	Mild	581	42.4	39.7, 45.0	519	44.8	41.9, 47.7
	Moderate	155	11.3	9.7, 13.1	38	3.3	2.3, 4.5
	Severe	3	0.2	0.1, 0.6	1	0.1	0.0, 0.5

*n: number of participants reporting at least one event in this category. Thirteen Menactra and 11 Menomune participants did not provide any information. Percentages were based on the total number of participants who did provide safety information at each time point.
†%: n/N expressed as a percentage.
Pain: 0=none, 1= (mild) sx present, but arm movement not affected, 2= (moderate) limits usual arm movement, 3= (severe) disabling

In both vaccine groups, the occurrence of any pain was higher in participants 18-25 years old than in participants 26-55 years old. Within each age category, moderate pain was reported more frequently in the Menactra group. In participants 18-28 years old, the rate of moderate pain was 4 times more frequent in the Menactra group, compared with the Menomune® group. In participants 29-55 years old, the Menactra group reported moderate pain twice as often. The frequency of mild pain was similar in the two groups, regardless of age.

MTA-09 Table 8: Injection Site Pain, Participants 18-25 & 22-55 years old, Days 0-7

Local Pain	Severity	Menactra		Menomune®	
		%	95% CI	%	95% CI
Age 18-25 years	**Any**	61.1	57.5, 64.5	51.8	47.9, 55.6
	Mild	45.8	42.3, 49.4	47.9	44.1, 51.8
	Moderate	15.2	12.9, 18.0	3.7	2.5, 5.5
	Severe	0.0	0.0, 0.0	0.2	0.0, 0.9
Age 26-55 years	**Any**	45.1	41.2, 49.1	43.6	39.4, 47.9
	Mild	38.2	34.4, 42.1	40.9	36.7, 45.2
	Moderate	6.5	4.8, 8.7	2.7	1.6, 4.5
	Severe	0.5	0.8, 1.4	0.0	0.0, 0.8

*n: number of participants reporting at least one event in this category. N= Total number of participants for whom safety information is available for this time point.
†%: n/N expressed as a percentage.
Pain: 0=none, 1= (mild) sx present, but arm movement not affected, 2= (moderate) limits usual arm movement, 3= (severe) disabling

Systemic reactions:

In both groups, mild headache and fatigue were most frequent. The occurrence of these reactions was also similar in both groups. Moderate arthralgia (4.7% vs, 2.6%) and moderate chills (2.0% vs. 0.6%) were reported twice as often by Menactra participants than Menomune® participants. Both arthralgia and chills occurred mainly in the first three days after vaccination.

Excluding rashes, 50 severe systemic reactions occurred in 35 Menactra participants, and 32 severe reactions in 22 Menomune® participants. Fifteen of 35 (43%) Menactra participants reported two or more severe systemic reactions. Of the Menactra participants with multiple reactions, all experienced severe fatigue or malaise, and some participants also experienced concurrent severe headache (40%), chills (33%), or anorexia (33%). In the Menomune® group, 8 of 23 (36%) participants reported two or more severe systemic reactions. All eight Menomune® participants reported severe fatigue or malaise, with associated vomiting (50%) or anorexia (50%). No participant in either group reported grade 3 fever.

Rash, occurring within 7 days after vaccination, was reported by 28 participants [Menactra n=19, Menomune® n=9]. Seven Menactra and three Menomune® participants, respectively, reported localized rash either at or near the injection site (MTA-09 Table 10). Lesions appeared mainly within the first two days post-vaccination (range 0-5 days). In the absence of bruising, injection site reactions were described as red or pink, macular or papular, and primarily non-itchy. For the remaining participants with localized rash, rashes described were non-specific, located more often on the extremities than on the trunk, neck or face, and lasted a median of 2 days (range: 1 hour to 11 days). One participant in each group reported hives, and responded to cetirizine (Zyrtec) and hydrocortisone, respectively. Two Menactra participants reported generalized rash, which both described the rash as raised, and itchy. In addition, one Menactra participant further described the rash as blanching, pink, started two days after vaccination and lasted one day. The second Menactra participant described the rash as red, non-blanching, with onset one day after vaccination and lasting five days. Neither of the participants required medication.

MTA-09 Table 9: Systemic adverse reactions (Days 0-7)

Reaction	Severity	Menactra N=1371 n*	%	95% CI	Menomune-A/C N=1158 n*	%	95% CI
Fever							
	Any	21	1.5	0.95, 2.33	6	0.5	0.19, 1.12
38.0°C-38.9°C	**Mild**	17	1.2	0.72, 1.98	5	0.4	0.14, 1.00
39.0°C-39.9°C	**Moderate**	4	0.3	0.08, 0.75	1	0.1	0.00, 0.48
≥ 40.0°C	**Severe**	0	0	0.00, 0.22	0	0	0.00, 0.26
Headache							
	Any	568	41.4	38.81, 44.09	484	41.8	38.90, 44.66
	Mild	414	30.2	27.77, 32.70	370	31.9	29.25, 34.69
	Moderate	138	10.1	8.52, 11.78	103	8.9	7.31, 10.67
	Severe	16	1.2	0.67, 1.89	11	0.9	0.47, 1.69
Fatigue							
	Any	476	34.7	32.20, 37.31	374	32.3	29.58, 35.05
	Mild	350	25.5	23.24, 27.92	293	25.3	22.80, 27.89
	Moderate	114	8.3	6.91, 9.90	76	6.6	5.20, 8.14
	Severe	12	0.9	0.45, 1.52	5	0.4	0.14, 1.00
Malaise							
	Any	324	23.6	21.41, 25.97	259	22.3	19.98, 24.86
	Mild	219	16	14.07, 18.02	195	16.8	14.71, 19.11
	Moderate	90	6.6	5.31, 8.01	54	4.7	3.22, 6.04
	Severe	15	1.1	0.61, 1.80	10	0.9	0.41, 1.58
Chills							
	Any	133	9.7	8.19, 11.39	65	5.6	4.35, 7.09
	Mild	96	7.0	5.71, 8.48	53	4.6	3.44, 5.94
	Moderate	29	2.1	1.42, 3.02	12	1	0.54, 1.80
	Severe	8	0.6	0.25, 1.15	0	0	0.00, 0.26
Arthralgia							
	Any	272	19.8	17.76, 22.05	185	16	13.90, 18.20
	Mild	204	14.9	13.04, 16.88	154	13.3	11.39, 15.38
	Moderate	64	4.7	3.61, 5.92	30	2.6	1.75, 3.67
	Severe	4	0.3	0.08, 0.75	1	0.1	0.00, 0.48
Anorexia							
	Any	162	11.8	10.15, 13.64	115	9.9	8.26, 11.79
Skips 1 meal	**Mild**	125	9.1	7.65, 10.77	91	7.9	6.37, 9.55
Skips 2 meals	**Moderate**	32	2.3	1.60, 3.28	19	1.6	0.99, 2.55
Skips ≥ 3 meals	**Severe**	5	0.4	0.12, 0.85	5	0.4	0.14, 1.00
Vomiting							
	Any	32	2.3	1.60, 3.28	17	1.5	0.86, 2.34
1 episode	**Mild**	24	1.8	1.12, 2.59	10	0.9	0.41, 1.58
2 episodes	**Moderate**	5	0.4	0.12, 0.85	2	0.2	0.02, 0.62
≥3 episodes	**Severe**	3	0.2	0.05, 0.64	5	0.4	0.14, 1.00
Diarrhea							
	Any	219	16	14.07, 18.02	162	14	12.03, 16.11
1-2 episodes	**Mild**	178	13	11.25, 14.88	124	10.7	8.98, 12.62
3-4 episodes	**Moderate**	36	2.6	1.85, 3.62	34	2.9	2.04, 4.08
≥ 5 episodes	**Severe**	5	0.4	0.12, 0.85	4	0.3	0.09, 0.88

cont. MTA-09 Table 9: Systemic adverse reactions (Days 0-7)							
		Menactra			Menomune®		
		N= 1371			N= 1159		
Reaction	Severity	n*	%†	95% CI	n*	%†	95% CI
Seizures (Y/N)							
Yes	**Days 0-7**	0	0	0.00, 0.22	0	0	0.00, 0.26
Rash							
Any rash	**Days 0-7**	19	1.4	0.84, 2.16	9	0.8	0.36, 1.47

*n: number of participants reporting at least one event in this category. Percentages are based on the total number of participants who did submit safety information at each time point.
†%: n/N expressed as a percentage.
Headache, chills, arthralgia, fatigue, malaise: 0= none, 1= aware, easily tolerated, 2= interferes with usual activities, 3= disabling

MTA-09 Table 10: Rash characteristics				
Rash Description	Menactra		Menomune®	
	n/N*	%†	n/N*	%†
Number of Participants with at least one Rash	19/1371	1.4	9/1159	0.8
Local	17/19	89.5	9/9	100.0
General	2/19	10.5	0/9	0.0
Raised	15/19	78.9	4/9	44.4
Smooth	4/19	21.1	5/9	55.6
Itchy	10/19	52.6	4/9	44.4
Not Itchy	9/19	47.4	5/9	55.6
Blanching	11/19	57.9	6/9	66.7
Not Blanching	8/19	42.1	3/9	33.3
Color				
Pink	4/19	21.1	5/9	55.6
Red	12/19	63.2	3/9	33.3
Purple	0/19	0.0	1/9	11.1
Brown	0/19	0.0	0/9	0.0
Other	3/19	15.8	0/9	0.0
Duration				
< 1 Hour	0/19	0.0	0/9	0.0
1 to < 24 Hours	4/19	21.1	6/9	66.7
≥ 24 Hours	14/19	73.7	3/9	33.3

*n: Number of participants reporting at least one event in this category.
†%: n/N expressed as a percentage.

Serious adverse events:
Forty-three individuals reported serious adverse events [Menactra n=23, Menomune® n=20].

- ✓ For four Menactra participants, a new chronic medical condition (depression, multiple sclerosis, diverticulosis, endocervical cancer) was reported. All illnesses were diagnosed more than 60 days after vaccination.
- ✓ Nineteen participants were hospitalized for either an acute infection (gastroenteritis, pyleonephritis, viral meningitis) or management of other acute medical conditions, e.g. motor vehicle related injury, appendicitis, dilatation and curettage, ruptured ectopic pregnancy, acute cholecystitis.
    - o One Menomune participant, a 49-year old previously healthy man, experienced a transient ischemic attack, which was characterized by upper extremity weakness, slurred speech, and facial tingling, 101 days following vaccination. No clot or vegetation was detected by transesophageal echocardiography. Carotid doppler showed no flow-limiting stenosis. The

ejection fraction was 60%, which was considered within normal limits. The participant recovered without sequelae.

- One Menomune participant, a 47-year old previously healthy man, developed Bell's palsy 53 days after vaccination. He was evaluated at an urgent care facility the same day. Laboratory studies were unremarkable, and included a radiographic study of the brain. The participant recovered, but had residual left eye and lip weakness.
- Two participants, one in each group, experienced an anaphylactic reaction. The first participant, who had prior history of a mild anaphylactic reaction following amoxillicin/clavulanic acid (Augmentin) exposure, now reported urticaria, severe pruritis, and facial swelling following ingestion of the same medication. The symptoms responded to diphenhydramine (Benedryl) and prednisone. The second participant developed bronchospasm 2 days after vaccination, which was thought by the principle investigator to be precipitated by cat exposure. The study participant responded to nebulized bronchodilator therapy and prednisone, and discharged from the emergency room the same day. She continued these medications for four days thereafter.

✓ Twenty of the 43 study participants were hospitalized for either an exacerbation of symptoms related to a pre-existing condition, e.g. chest pain in individuals with hypertension, hypercholesterolemia and /or coronary artery disease, or surgical management of prior conditions, e.g. recurrent menorrhagia, obstructive sleep apnea, patellar instability, chronic back pain. The recovery for all individuals was uneventful.

✓ No deaths occurred among participants in the study.

Primary testing of the safety hypothesis:
The upper limit of the two-sided 90% confidence interval for the proportion of participants with at least one severe solicited systemic reaction, which included all rashes, in the Menomune® and Menactra groups, respectively, was less than 3-fold. The upper limit of the two-sided 95% CI for the ratio of the two proportions was also provided by the sponsor, and is the analysis currently recommended by CBER (MTA-09 Table 11).

MTA-09 Table 11: Primary Safety Hypothesis Testing
Percentage of Participants 18-55 Years Old With At Least One Severe Solicited Systemic Reaction

Menactra N= 1391	Menomune® N=	Ratio ($p_{Menactra}$ / $p_{Menomune®}$)	Upper Limit of the 2-sided 90% CI‡ of the Ratio	Upper Limit of the 2-sided 95% CI‡ of the Ratio
3.8%	2.6%	1.465	2.12	2.31

*Number of participants with at least 1 severe systemic reaction or rash. N= Total number of participants for whom safety information is available.
†$p_{Menactra}$ and $p_{Menomune®}$: proportion of participants with at least one severe systemic reaction or rash in the Menactra and Menomune® groups, respectively.
‡CI: Confidence interval

Note: For analysis purposes, all rashes were counted as severe solicited systemic reactions. Also, for each reaction, each participant is counted no more than once.

7.1.3.5 Reviewer summary and conclusions for study MTA-09

In this study, the safety and immunogenicity of Menactra compared to Menomune was evaluated in individuals 18-55 years old. The study was designed as a one-sided equivalence trial, in which primary safety and immunogenicity hypotheses were tested. Participants were randomized in a 1: 1 ratio.

Safety:

Menactra is less reactogenic in the18-55 year old age group, compared to participants 11-18 years old, who received Menactra in study MTA-04. Moderate and severe local reactions, however, remained more frequent in the Menactra group than in the Menomune® group. Moderate pain was reported three times (11.3% vs. 3.3%) as often in participants receiving Menactra. Forty severe local reactions, which were primarily erythema or swelling greater than 2 inches, occurred in 23 Menactra participants. Two severe local reactions occurred in two Menomune® participants. A trend towards slightly longer duration of local adverse events was noted in both vaccine groups. In both groups, headache and fatigue were most frequent, and occurred in 41.4% of Menactra participants and 41.8% Menomune® participants, respectively. Both symptoms were mainly mild. Moderate chills and arthralgia occurred twice as often in Menactra group than in the Menomune® group. None of the participants experienced a seizure or fever $\geq$40.0C.

The primary safety hypothesis to demonstrate that Menactra is non-inferior to Menomune® in the proportion of participants with at least one solicited systemic reaction reported as severe during the 7-day period following vaccination was achieved. Severe systemic reactions occurred in 3.8% of Menactra participants, compared with 2.6% of participants in the Menomune® group. The upper limit of the two-sided 95% confidence interval for the ratio of the two proportions, which is the current CBER requirement for non-inferiority hypothesis testing, was 2.31, and was less than the proposed 3-fold difference.

Immunogenicity: The percentage of Menactra recipients who achieved a four-fold or greater increase in SBA-BR antibody was 88.5%, 80.5%, 73.5%, and 89.4% to serogroups C, A, Y and W135, respectively. The percentage of Menomune® recipients achieving the same criterion was 89.7%, 84.6%, 79.4% and 94.4% for the respective serogroups. While the difference in proportions of Menactra and Menomune® participants, in study MTA-09, who achieved a four-fold or greater increase in SBA-BR antibody was minimal for serogroup C (1.2%), larger differences (4-6%) in the two proportions were observed for the other three serogroups. Likewise, for serogroups A, Y and W135, the upper limit of the confidence interval for the difference in two proportions ranged from 7-9%. The upper limit of the two-sided 95% confidence interval for the difference of the two proportions was less than 0.1. The primary hypothesis for each serogroup was achieved in this study, although gradual decreases in the proportion of participants who are considered protected might pose concerns for future 1-sided equivalence trials, which include Menactra as an active control.

Menactra recipients achieved comparable GMT and fold increases post-vaccination to serogroups A and C. Lower bactericidal antibody responses were observed for serogroups Y and W-135, although the proportion of participants who achieved seroconversion was 90.7% and 96.5%, respectively. At baseline, the proportion of Menactra recipients with a SBA-BR titer $\geq$1:8 to serogroups A, C, Y and W-135 was 88%, 73%, 78%, and 71%, respectively. Similar distributions of pre-vaccination SBA-BR titer were observed in Menomune® recipients. The post-vaccination SBA-BR GMT for each serogroup, in an analysis of covariance using baseline titer as a covariate, showed no statistically significant differences.

7.1.4 Study MTA-11: Immunogenicity and Safety of Typhoid Vi® Vaccine When Administered Concomitantly with an Experimental Tetravalent (A, C, Y, and W-135) Meningococcal Diphtheria Toxoid Conjugate Vaccine in Adults in the U.S.

7.1.4.1 Objectives

- Primary objectives:
  1. To compare the post-vaccination antibody level to the typhoid Vi polysaccharide antigen (anti-Vi PS), when Typhim Vi® and Menactra are given concomitantly, to corresponding antibody levels when the two vaccines are given sequentially (Typhim Vi® first, then Menactra 28 days later).
  2. To compare the bactericidal antibody response to serogroups A, C, Y, W135, using baby rabbit complement (SBA-BR), when Menactra is co-administered with Typhim Vi®, to the corresponding antibody response when Menactra is given 28 days after Typhim Vi®.
- Secondary objectives:
  1. To compare the geometric mean antibody titer to the Vi antigen, when Typhim Vi® is co-administered with Menactra, to the corresponding titer when Typhim Vi® is given 28 days prior to Menactra.
  2. To compare the bactericidal geometric mean antibody titer to serogroups A, C, Y, W135, using baby rabbit complement (SBA-BR), when Menactra is co-administered with Typhim Vi®, to the corresponding antibody response when Menactra is given 28 days after Typhim Vi®.
- Other objectives:
  - ✓ To describe the SBA-BR titer to each serogroup, pre- and 28 days post-vaccination, in each vaccine group.
  - ✓ To describe the anti-Vi PS antibody level, pre- and 28 days post-vaccination, in each vaccine group.
  - ✓ To describe the distribution of participants with at least a 4-fold increase in anti-Vi PS antibody level, in each vaccine group.

7.1.4.2 Design

The study was a randomized, double blind, multi-center, controlled trial. Participants were randomized in a 1: 1 ratio (Menactra + Vi: Vi, then Menactra).

Study Period: July 31, 2002 to January 07, 2003

7.1.4.3 Protocol

7.1.4.3.1 Population:

The study was conducted at twelve study centers in the United States.

Inclusion criteria:

- Healthy
- Age ≥18 years and <56 years old at the time of vaccination
- Informed consent obtained

Exclusion criteria:

- Serious chronic disease (i.e. cardiac, renal, neurologic, metabolic, rheumatologic etc.)
- Known or suspected impairment immunologic function
- History of documented invasive meningococcal disease or previous meningococcal vaccination
- History of documented infection with *Salmonella typhi* or previous vaccination against *S.typhi*
- Receipt of immune globulin or other blood products within the previous 3 months, injected or oral corticosteroids within 6 weeks prior to the administration of the study vaccine

- Administration of a vaccine other than the study vaccine within 28 days of enrollment
- Antibiotic therapy within 72 hours prior to vaccination
- Known or suspected hypersensitivity to any vaccine component
- Enrolled in another clinical trial
- Any condition which, in the opinion of the investigator, would pose a health risk to the participant
- Unable to comply with scheduled visits or study procedures
- For females, a positive or equivocal urine pregnancy test result on the day of vaccination
- Breastfeeding

Reasons for deferring vaccination

- Acute medical illness, with or without fever, within the previous 72 hours. Fever was defined as an oral temp ≥38.0C.

7.1.4.3.2 Vaccine administration

Each group received two injections 28 days apart. Group A received Typhim Vi® + Menactra, then a saline placebo. Group B received Typhim Vi® + saline placebo, followed by Menactra. Participants received all injections intramuscularly. Please see Appendix 2 for the batch number of products used in this clinical trial.

The typhoid Vi polysaccharide vaccine, Typhim Vi®, is a commercially available in the United States. Each 0.5ml dose contains 25 µg of purified Vi polysaccharide, isotonic phosphate buffered saline, and 0.25% phenol, which is added as a preservative. The vaccine also contains residual polydimethylsiloxane or fatty acid ester based antifoam. The vaccine is formulated as a clear colorless liquid, and packaged in a unit dose syringe.

Buffered Sterile Normal Saline (0.9% NaCl) was utilized as the placebo control, and supplied in single dose vials.

7.1.4.3.3 Endpoints

Primary Endpoints:

- The proportion of participants who achieve an anti-Vi polysaccharide antibody ≥1µg/mL, when Typhim Vi® and Menactra are given concomitantly, compared to the corresponding proportion of participants who receive the same vaccines sequentially.
- The proportion of participants with at least a 4-fold rise in SBA-BR antibody titer to serogroups A, C, Y, and W-135, when Typhim Vi® and Menactra are given concomitantly, compared to the corresponding proportion of participants who receive the same vaccines sequentially.

Secondary endpoints:

- Anti-Vi PS geometric mean antibody titer in the group receiving Typhim Vi® and Menactra concomitantly, compared to the corresponding titer in the group given the same vaccines sequentially.
- SBA-BR geometric mean antibody titer for serogroups A, C, Y, and W135 in the group receiving Typhim Vi® and Menactra concomitantly, compared to corresponding titers in the group given the same vaccines sequentially.

7.1.4.3.4 Surveillance

Monitored parameters:

Safety: Study participants were monitored for immediate reactions 30 minutes after vaccination, and for local and systemic reactogenicity during the 7 days following vaccination. Pre-specified adverse events included localized reactions (erythema, swelling, induration, pain) and systemic symptoms (fever measured by oral temperature, headache, fatigue, chills, arthralgia, anorexia, vomiting, diarrhea, seizures, malaise and rash), which were assessed after each vaccination. These events were recorded daily on a diary card, and by telephone interview eight days after each vaccination. If rash was reported, the investigator was

prompted to record additional details on a separate case report form. Other non-serious, unexpected adverse events were obtained by telephone interview eight and twenty-eight days after each vaccination. Serious adverse events were reported and recorded for the entire duration of the study.

Efficacy (Immunogenicity):
Serum samples were obtained pre- and 28 days after each vaccination.

Anti-Meningococcal Antibody
Functional antibody activity to each serogroup was determined using a serum bactericidal assay. The lower limit of detection for this assay, using baby rabbit complement, is an antibody titer of 8. Please see Section 4.4 Laboratory Methods for additional details.

Anti-Vi Polysaccharide Antibody
Anti-Vi polysaccharide antibody was measured by a radioimmunoassay (RIA), according to a "Farr" type radioimmunologic method. Antibodies present in the blood sample bind to an Iodine 125 labeled Vi antigen, and form an immunological complex, which is then precipitated by an ammonium sulfate solution. The radioactivity measured in the precipitate is proportional to the quantity of Vi antibodies present in the sample.

7.1.4.3.5 Statistical plan

Primary Hypotheses:
Primary Hypothesis #1:
To demonstrate that 28 days following Typhim Vi® (Vi) vaccination, the proportion of participants achieving a protective level of anti-Vi polysaccharide (Vi PS) antibody in the concomitant vaccine group is non-inferior to the corresponding proportion of participants, when Typhim Vi® vaccine is given together with a saline placebo, followed by Menactra 28 days later.

This hypothesis would be supported by the data if the upper bound of the two-sided 95% CI of the difference $_pVi$ + placebo - $_pVi$ + Menactra < 0.1, where $_p$ is the proportion of participants, in the [Vi + placebo, then Menactra] and [Vi + Menactra] groups, respectively, who achieve an anti-Vi antibody level ≥1 □g/mL. Planned enrollment of 880 participants (n=440 per group), and resultant 800 evaluable participants, provided 99.9% power to achieve the primary hypothesis. Testing of the primary hypothesis was conducted at the 0.025 significance level.

Primary Hypothesis #2:
To demonstrate that 28 days post-vaccination with Menactra, the proportion of participants with at least a 4-fold rise in SBA-BR antibody titer to serogroups A, C, Y, and W-135 in the group given Typhim Vi®+ Menactra concomitantly is non-inferior to the proportion in the group receiving Typhim Vi® + placebo, followed by Menactra 28 days later.

This hypothesis would be supported by the data if the upper bound of the two-sided 95% CI of $_pMenactra$ – $_pVi$ + Menactra < 0.1, where $_p$ is the proportions of participants with at least a 4-fold rise in SBA-BR antibody to meningococcal serogroups A, C, Y, and W-135, in the [Vi + placebo, then Menactra] and [Vi + Menactra] groups, respectively. Planned enrollment of 880 participants (n=440 per group), and resultant 800 evaluable participants, provided at least 94% power to achieve the primary hypothesis for each serogroup. All tests of the primary hypothesis were conducted at the 0.025 significance level.

The primary analyses were based on data generated from the per-protocol population.

Secondary Hypotheses:
Secondary Hypothesis #1:
To demonstrate that 28 days following Typhim Vi® vaccination, the anti-Vi PS geometric mean antibody titer in the group given Typhim Vi® and Menactra concomitantly is non-inferior to the corresponding parameter in the group given Typhim Vi® and Menactra sequentially.

This hypothesis would be supported by the data if the upper bound of the two-sided 95% CI of the ratio of $GMT_{Vi + placebo}$ / $GMT_{Vi + Menactra} < 2$.

Secondary Hypothesis #2:
To demonstrate that 28 days after vaccination with Menactra, the SBA-BR geometric mean antibody titer for serogroups A, C, Y, and W135 in the group given Typhim Vi® and Menactra concomitantly is non-inferior to the same parameter in the group receiving the Typhim Vi® and Menactra sequentially.

This hypothesis would be supported by the data if the upper bound of the two-sided 95% CI of the ratio of $GMT_{Menactra}$ / $GMT_{Vi + Menactra} < 2$, where $GMT_{Menactra}$ and $GMT_{Vi + Menactra}$ are the proportion of participants with at least a 4-fold rise in SBA-BR antibody to meningococcal serogroups A, C, Y, and W-135, in the [Vi + placebo, then Menactra] and [Vi + Menactra] groups, respectively. The statistical methods include an analysis of covariance with the baseline outcome as a covariate. The post-vaccination SBA-BR GMTs are calculated as a $\log_2$ titer.

Analyses of the secondary points were performed on both per-protocol and intent-to-treat populations.

Per-protocol population for immunogenicity:
The per-protocol population included all eligible participants who received the assigned vaccine at visit 1 (1st vaccination) & visit 2 (2nd vaccination), who complied with scheduled visits for blood specimens, and for whom a sufficient quantity of paired sera was available for analysis.

Intent-to-treat population for immunogenicity:
The intent-to-treat population consisted of all enrolled participants who received one dose of vaccine underwent at least one blood draw. Analyses were performed according to the vaccine received.

For analysis purposes, if the SBA-BR antibody titer to any serogroup was reported below the limit of detection, the antibody titer assigned was a value equal to the limit of detection. ITT analyses for all primary and secondary endpoints were considered exploratory. These results were not included in the license application, but anticipated to be submitted as an appendix to the final study report.

Intent-to-treat population for safety:
The intent-to-treat population consisted of all participants who received one dose of vaccine and for whom safety information was available. Analyses were performed according to the vaccine received.

Since the nature and severity of a rash were difficult to categorize for the vaccine recipient, all rashes occurring during the first 7 days after vaccination were designated by the sponsor as a severe solicited systemic reaction, in an effort to prompt the investigator to describe additional rash characteristics.

7.1.4.4 Results

7.1.4.4.1 Population

A total of 945 (Group A (concomitant) n= 469, Group B (sequential) n= 476) adults were enrolled, and 871 (Group A n= 432, Group B n= 439) individuals completed the study.

Safety population:
The intent-to-treat population for safety included all enrolled participants (n= 945). Seventy-four participants (Group A n=37, Group B n= 37) did not complete the study due to voluntary withdrawal, non-compliance with study visits, or lost-to-follow-up.

Immunogenicity population:
The per-protocol population included 839 participants (Group A n=419, Group B n=420) of the 945 vaccinated participants. One hundred twenty-seven (Group A n=64, Group B n=63) of the 233 participants (Groups A n=113, Group B n= 119) with at least one protocol violation were considered evaluable for the per-protocol analysis, since the violation related to reasons such as an absent diary card or incomplete eligibility worksheet. Two participants, who were randomly assigned to group A, both received vaccines

according to the group B schedule. Three participants (1 group A, 2 group B) received vaccines inconsistent with the treatment assignment at one of the two visits.

Demographic characteristics: The distribution of participants, based on age, gender, race and ethnicity, was similar among the two vaccine groups. The overall study population enrolled was predominately Caucasian (73.2%), but also included African American (10.6%), Hispanic (11.4%), Asian populations (3.1%) and individuals with mixed racial background (1.7%).

7.1.4.4.2 Immunogenicity

Antibody response to Vi Polysaccharide (Vi PS):
A negative value for the difference in the proportion of participants who achieved an anti-Vi PS antibody level ≥1.0 ug/ml indicated that, 28 days after Typhim Vi® vaccination, a higher proportion in the concomitant vaccine group achieved this endpoint, than when Typhim Vi was given alone (MTA-11 Table 1). The upper limit of the 95% CI for the difference in the two proportions was less than 0.1, which is equivalent to less than a 10% difference between the two groups.

MTA-11 Table 1: Primary Hypothesis #1
Number and Percentage of Participants 18-55 Years Old With Anti-Vi PS Antibody Level ≥ 1.0 ug/ml, 28 days after Typhim Vi® vaccination

	Vi + Placebo, Then Menactra N=418		Vi + Menactra Then Placebo N=418		Difference ($p_{Vi+Placebo} - p_{Vi+Menactra}$)	Upper Limit of the 2-sided 95% CI for the Difference§
	n*	$p_{Vi+Placebo}$†	n*	$p_{Vi+Menactra}$‡		
Vi PS antibody ≥1.0 µg/mL	331	0.792	342	0.818	-0.026	0.027

* n: number of participants with anti-Vi PS antibody titer ≥ 1.0 µg/mL. N: total number of participants with valid serology results on Day 28.
† $p_{Vi+Placebo}$: proportion of participants with anti-Vi PS antibody titer ≥ 1.0 µg/mL in the group given Typhim Vi® + saline placebo, then Menactra 28 days later.
‡ $p_{Vi+Menactra}$: proportion of participants with anti-Vi PS antibody titer ≥ 1.0 µg/mL in the group given Typhim Vi® and Menactra concomitantly.
§ CI: Confidence interval.

Proportions with four-fold or greater increases in SBA-BR titer:
The proportion of participants who achieved a ≥four-fold in SBA-BR antibody titer for each serogroup, 28 days after Menactra vaccination, was higher following concomitant vaccine administration than when Menactra was given 28 days after Typhim Vi® (MTA-11 Table 2). The difference in the two proportions was largest for serogroup Y (-0.093), which resulted from a lower proportion of participants in the sequential vaccine group achieving this endpoint (0.652) than in the concomitant vaccine group (0.744). Higher baseline SBA-BR antibody titers for serogroup Y were observed in the sequential vaccine group relative to corresponding titers reported for the concomitant vaccine group (MTA-11 Table 6). Nevertheless, the upper limit of the two-sided 95% CI, for the difference in the two proportions, was less than 0.1 for each serogroup.

MTA-11 Table 2: Primary Hypothesis #2
Proportion of Participants 18-55 Years Old With a ≥ 4-Fold Increase in SBA-BR Antibody Titers, 28 Days After Menactra Vaccination, Compared to Baseline

Serogroup	Vi + Placebo, Then Menactra N=419 $p_{Vi+Placebo}$†	Vi + Menactra Then Placebo N=418 $p_{Vi+Menactra}$‡	Difference ($p_{Vi+Placebo} - p_{Vi+Menactra}$)	Upper Limit of the 2-sided 95% CI for the Difference§
A	0.752	0.797	-0.045	0.012
C	0.883	0.895	-0.012	0.031
Y	0.652	0.744	-0.093	-0.031
W-135	0.838	0.852	-0.014	0.035

* n: number of participants with a ≥ 4-fold increase in SBA-BR titer compared with baseline. N: total number of participants with valid serology results on Day 28.
† $p_{Vi+Placebo}$: proportion of participants with anti-Vi PS antibody titer ≥ 1.0 µg/mL in the group given Typhim Vi® + saline placebo, then Menactra 28 days later.
‡ $p_{Vi+Menactra}$: proportion of participants with anti-Vi PS antibody titer ≥ 1.0 µg/mL in the group given Typhim Vi® and Menactra concomitantly.
§ CI: Confidence interval.

Additional measures of antibody response to Vi Polysaccharide:

Vi PS GMT:

Twenty-eight days after Vi vaccination, the Vi PS GMT was similar in the group given Typhim Vi® and Menactra concomitantly, compared to Typhim Vi® administered with a saline placebo (MTA-11 Table 5). The upper limit of the 2-sided 95% CI for the GMT ratio was less than two fold.

MTA-11 Table 5: Secondary Hypothesis #1
Comparison of Vi PS GMT, Measured 28 Days Following Typhim Vi® Vaccination

	Vi + Placebo, Then Menactra N=418		Vi + Menactra Then Placebo N=418		Ratio of $GMT_{Vi+Placebo}$ / $GMT_{Vi+Menactra}$	Upper Limit of the 2-sided 95% CI for the GMT Ratio§
	GMT	95% CI	GMT	95% CI		
Vi PS GMT	2.07	1.86, 2.32	2.4	2.15, 2.69	0.86	1.0

§ CI: Confidence interval.

Additional meningococcal SBA-BR antibody titer data:

At baseline, the proportion of sequential vaccine group recipients with a SBA-BR titer ≥1:8 to serogroups A, C, Y and W-135 was 87% [365/419], 69% [289/419], 79% [329/419], and 54% [227/419], respectively. The respective proportions in the concomitant vaccine group were 79% [330/418], 64% [267/418], 71% [298/418], and 50% [208/418] (Table not shown).

The SBA-BR geometric mean antibody titer, prior to vaccination, for serogroups A and Y differed between the two groups. In the group receiving sequential vaccination, the baseline SBA-BR GMT for serogroup A was twice the GMT reported for the concomitant vaccine group, and 1.5 times higher for serogroup Y. Twenty days after Menactra vaccination, for each serogroup, the SBA-BR GMT was similar in both groups, and the confidence intervals were largely overlapping (MTA-11 Table 6).

MTA-11 Table 6: SBA-BR GMT 28 days after Menactra vaccination				
	Vi + placebo, then Menactra N=420		Vi + Menactra then placebo N=419	
	GMT	95% CI	GMT	95% CI
Serogroup A				
SBA-BR GMT Day 0	336.9	274.2, 414.0	174.2	137.1, 221.5
SBA-BR GMT (28d post-)	5109.8	4523.3, 5772.4	5137.9	4490.4, 5878.9
Serogroup C				
SBA-BR GMT Day 0	47.6	38.2, 59.4	34.8	28.2, 42.9
SBA-BR GMT (28d post-)	3145.4	2635.1, 3754.6	3061.4	2525.2, 3711.4
Serogroup Y				
SBA-BR GMT Day 0	159.0	127.5, 198.2	97.7	78.1, 122.2
SBA-BR GMT (28d post-)	1742.2	1455.4, 2085.5	1821.0	1534.4, 2161.2
Serogroup W135				
SBA-BR GMT Day 0	20.0	16.6, 24.1	18.7	15.4, 22.6
SBA-BR GMT (28d post-)	929.0	750.3, 1150.3	1002.2	823.1, 1220.3

N: total number of participants with valid serology results on Day 28.

Comparison of Log_2 SBA-BR Titer, using baseline titer as a covariate

MTA-09 Table 7 shows the log_2 SBA-BR geometric mean titer, using the baseline titer as a covariate. The upper limit of the two-sided 95% CI for each serogroup was less than log_2 (2).

MTA-11 Table 7: Secondary Hypothesis #2
Comparison of Log_2 SBA-BR Titer, Measured 28 Days Following Menactra Vaccination, Using Baseline Titer as a Covariate

Serogroup	Vi + Placebo, Then Menactra	Vi + Menactra Then Placebo	Difference (Log_2 $SBA_{Menactra}$ - Log_2 $SBA_{Vi+Menactra}$)	Upper Limit of the 2-sided 95% CI for the Difference§
	Log_2 $SBA_{Menactra}$†	Log_2 $SBA_{Vi+Menactra}$‡		
A	4.336	4.465	-0.129	0.13
C	6.210	6.292	-0.082	0.28
Y	3.704	3.969	-0.265	0.07
W-135	5.563	5.710	-0.147	0.25

† Log_2 $SBA_{Menactra}$: proportion of participants, with at least a 4-fold rise in SBA-BR antibody to meningococcal serogroups A, C, Y, and W135, in the group given Typhim Vi® vaccine together with a saline placebo, and then Menactra 28 days later.

‡ Log_2 $SBA_{Vi+Menactra}$: proportion of participants, with at least a 4-fold rise in SBA-BR antibody to meningococcal serogroups A, C, Y, and W135, in the group given Typhim Vi® concomitantly with Menactra.

§ CI: Confidence interval. If the upper 95% CI of the difference is less than log2 (2) = 1, the inferiority assumption is rejected.

7.1.4.4.3 Safety

MTA-11 Table 8: Overall Participant Safety Profile					
Type of AE	Time Interval*	Group A Vi + Menactra, Then Placebo†		Group B Vi + Placebo†, Then Menactra	
		n/N‡	%§	n/N‡	%§
Immediate reactions	Day 0:				
After 1st vaccination	within 30 minutes	3/469	0.6	2/476	0.4
After 2nd vaccination		0/433	0.0	0/446	0.0
Solicited local reactions					
After 1st vaccination					
· Placebo (Group B), Menactra (Group A)	Days 0-7	234/456	51.3	123/470	26.2
· Typhim Vi injection site		353/456	77.4	364/470	77.4
After 2nd vaccination					
· Menactra (Group B), Placebo (Group A)		68/427	15.9	207/439	47.2
Solicited systemic reactions					
After 1st vaccination	Days 0-7	276/456	60.5	280/470	59.6
After 2nd vaccination		155/427	36.3	211/439	48.1
Unsolicited adverse events	Days 0-56	160/435	36.8	174/448	38.8
Serious adverse events	Day 0-56	1/469	0.2	1/476	0.2

*Vaccination occurs on Day 0.
† 0.9% NaCl was administered as the placebo.
‡n: Number of participants reporting at least one event in this category.
§%: n/N expressed as a percentage.

Immediate reactions: 5 participants reported eight reactions after the first vaccination. Two concomitant vaccine group participants experienced a generalized reaction (one participant experienced nausea, fever, diaphoresis, and tinnitus, and the other participant reported syncope). A third concomitant vaccine group participant experienced local paresthesia at the Vi injection site. Two participants in Group B, who received a saline placebo, and reported local pruritis and generalized paresthesia, respectively. In both groups, no immediate reactions were reported after the second vaccination.

Local reactions

Concomitant vaccination with Menactra and Typhim Vi®

After concomitant vaccine administration, the occurrence of any local reaction at the Menactra injection site was reported by 51.3% (234/456) of participants, and, at the Vi injection site, by 77.4% (343/456) of the same participants. Pain was most common, which was reported at the Menactra site by 46.5% of participants, and at the Vi site by 75.2% of participants. The 95% CI for both mild and moderate pain were not overlapping (MTA-11 Table 9). Moderate swelling was reported twice (3.1% vs. 1.5%) as often at the Menactra site than the Vi injection site.

MTA-11 Table 9: Local Adverse Reactions After Concomitant Vaccine Administration (Days 0-7): Menactra and Vi injection sites

		Group A Vi + Menactra, Then Placebo N=456					
		(Menactra Injection site)			(Typhim Vi Injection site)		
Reaction	Severity	n*	%†	95% CI	n*	%†	95% CI
Redness							
	Any	52	11.4	8.6, 14.7	64	14.0	11.0,17.6
< 1 inch	**Mild**	32	7.0	4.8, 9.8	52	11.4	8.6,14.7
1 – 2 inches	**Moderate**	16	3.5	2.0, 5.6	12	2.6	1.4,4.6
> 2 inches	**Severe**	4	0.9	0.2, 2.2	0	0.0	0.0,0.8

Swelling							
	Any	61	13.4	10.4, 16.8	68	14.9	11.8,18.5
< 1 inch	**Mild**	44	9.6	7.1, 12.7	60	13.2	10.2,16.6
1 – 2 inches	**Moderate**	14	3.1	1.7, 5.1	7	1.5	0.6,3.1
> 2 inches	**Severe**	3	0.7	0.1, 1.9	1	0.2	0.0,1.2
Induration							
	Any	78	17.1	13.8, 20.9	91	20.0	16.4,23.9
< 1 inch	**Mild**	57	12.5	9.6, 15.9	75	16.4	13.2,20.2
1 – 2 inches	**Moderate**	18	3.9	2.4, 6.2	15	3.3	1.9,5.4
> 2 inches	**Severe**	3	0.7	0.1, 1.9	1	0.2	0.0,1.2
Pain							
	Any	212	46.5	41.8, 51.2	343	75.2	71.0,79.1
	Mild	176	38.6	34.1, 43.2	261	57.2	52.6,61.8
	Moderate	33	7.2	5.0, 10.0	80	17.5	14.2,21.4
	Severe	3	0.7	0.1, 1.9	2	0.4	0.1,1.6

*n: Number of participants reporting at least one event in this category. Thirteen participants did not provide any data. Percentages are based on the total number of participants who did submit safety information at each time point.
†%: n/N expressed as a percentage.
Pain: 0=none, 1= (mild) sx present, but arm movement not affected, 2= (moderate) limits usual arm movement, 3= (severe) disabling

Menactra injection site, after concomitant and sequential vaccination:

No statistical differences in local adverse event rates reported at the Menactra injection site was observed when Menactra was given concomitantly or 28 days following Typhim Vi®. Reduced reporting for pain, overall, was observed in both groups, compared to MTA-09 Menactra participants (53.9%). The overall rate of severe local reactions was 2.0% (9/456) and 2.7% (12/439) in the concomitant and sequential vaccine groups, respectively.

MTA-11 Table 10: Menactra Local Adverse Reactions (Days 0-7)

		Group A N=456			Group B N=439		
		Vi + Menactra, Then Placebo			Vi + Placebo, Then Menactra		
		(Menactra Injection site)			(Menactra Injection site)		
Reaction	**Severity**	**n***	**%†**	**95% CI**	**n***	**%†**	**95% CI**
Redness							
	Any	52	11.4	8.6, 14.7	62	14.1	11.0, 17.7
< 1 inch	**Mild**	32	7.0	4.8, 9.8	43	9.8	7.2, 13.0
1 – 2 inches	**Moderate**	16	3.5	2.0, 5.6	16	3.6	2.1, 5.9
> 2 inches	**Severe**	4	0.9	0.2, 2.2	3	0.7	0.1, 2.0
Swelling							
	Any	61	13.4	10.4, 16.8	50	11.4	8.6, 14.7
< 1 inch	**Mild**	44	9.6	7.1, 12.7	31	7.1	4.8, 9.9
1 – 2 inches	**Moderate**	14	3.1	1.7, 5.1	15	3.4	1.9, 5.6
> 2 inches	**Severe**	3	0.7	0.1, 1.9	4	0.9	0.2, 2.3
Induration							
	Any	78	17.1	13.8, 20.9	67	15.3	12.0, 19.0
< 1 inch	**Mild**	57	12.5	9.6, 15.9	46	10.5	7.8, 13.7
1 – 2 inches	**Moderate**	18	3.9	2.4, 6.2	18	4.1	2.4, 6.4
> 2 inches	**Severe**	3	0.7	0.1, 1.9	3	0.7	0.1, 2.0

Cont. MTA-11 Table 10: Menactra Local adverse reactions (Days 0-7)							
		Group A N=456			Group B N=439		
		Vi + Menactra, Then Placebo			Vi + Placebo, Then Menactra		
		(Menactra Injection site)			(Menactra Injection site)		
Reaction	**Severity**	**n***	**%†**	**95% CI**	**n***	**%†**	**95% CI**
Pain							
	Any	212	46.5	41.8, 51.2	192	43.7	39.0, 48.5
	Mild	176	38.6	34.1, 43.2	140	31.9	27.6, 36.5
	Moderate	33	7.2	5.0, 10.0	44	10.0	7.4, 13.2
	Severe	3	0.7	0.1, 1.9	8	1.8	0.8, 3.6

*n: Number of participants reporting at least one event in this category. Thirteen participants in Group A and 37 participants in Group B did not provide any data. Percentages are based on the total number of participants who did submit safety information at each time point.

†%: n/N expressed as a percentage.

Pain: 0=none, 1= (mild) sx present, but arm movement not affected, 2= (moderate) limits usual arm movement, 3= (severe) disabling

Systemic reactions:

The overall frequency of systemic adverse events was higher when Menactra and Typhim Vi® were given concomitantly (60.5%), then when Menactra was given 28 days after Typhim Vi® (48.1%). Headache and fatigue increased 8% (32.6% vs. 40.6%) and 10% (27.1% vs. 37.7%), respectively, after concomitant vaccination. Mild arthralgia was also more frequent, and increased from 7.5% (33/439) to 13.4% (61/455). The rate of severe systemic reactions was 5.3% in the concomitant vaccine group, and 2.3% in the sequential vaccine group. Severe headache, fatigue and malaise in the concomitant group, and fatigue and malaise in the sequential vaccine group, accounted for the main solicited reactions.

MTA-11 Table 11: Systemic Adverse Reactions after Menactra vaccination (Days 0-7)							
		Group A			Group B		
		Vi + Menactra, Then Placebo			Vi + Placebo, Then Menactra		
Reaction	**Severity**	**n*/N**	**%†**	**95% CI**	**n*/N**	**%†**	**95% CI**
Fever							
	Any	4/448	0.9	0.2, 2.3	5/434	1.2	0.4, 2.7
38.0°C-38.9°C	**Mild**	3/448	0.7	0.1, 1.9	5/434	1.2	0.4, 2.7
39.0°C-39.9°C	**Moderate**	1/448	0.2	0.0, 1.2	0/434	0.0	0.0, 0.8
≥ 40.0°C	**Severe**	0/448	0.0	0.0, 0.8	0/434	0.0	0.0, 0.8
Headache							
	Any	185/456	40.6	36.0, 45.2	143/439	32.6	28.2, 37.2
	Mild	127/456	27.9	23.8, 32.2	104/439	23.7	19.8, 28.0
	Moderate	52/456	11.4	8.6, 14.7	37/439	8.4	6.0, 11.4
	Severe	6/456	1.3	0.5, 2.8	2/439	0.5	0.1, 1.6
Fatigue							
	Any	172/456	37.7	33.3, 42.3	119/439	27.1	23.0, 31.5
	Mild	123/456	27.0	23.0, 31.3	81/439	18.5	14.9, 22.4
	Moderate	41/456	9.0	6.5, 12.0	34/439	7.7	5.4, 10.7
	Severe	8/456	1.8	0.8, 3.4	4/439	0.9	0.2, 2.3

Cont. MTA-11 Table 11: Systemic Adverse Reactions after Menactra vaccination (Days 0-7)							
		Group A Vi + Menactra, Then Placebo			Group B Vi + Placebo, Then Menactra		
Reaction	Severity	n*/N	%†	95% CI	n*/N	%†	95% CI
Malaise							
	Any	106/455	23.3	19.5, 27.5	87/439	19.8	16.2, 23.9
	Mild	61/455	13.4	10.4, 16.9	55/439	12.5	9.6, 16.0
	Moderate	39/455	8.6	6.2, 11.5	25/439	5.7	3.7, 8.3
	Severe	6/455	1.3	0.5, 2.8	7/439	1.6	0.6, 3.3
Arthralgia							
	Any	84/455	18.5	15.0, 22.3	51/439	11.6	8.8, 15.0
	Mild	61/455	13.4	10.4, 16.9	33/439	7.5	5.2, 10.4
	Moderate	20/455	4.4	2.7, 6.7	16/439	3.6	2.1, 5.9
	Severe	3/455	0.7	0.1, 1.9	2/439	0.5	0.1, 1.6
Chills							
	Any	30/455	6.6	4.5, 9.3	14/427	3.3	1.8, 5.4
	Mild	22/455	4.8	3.1, 7.2	13/427	3.0	1.6, 5.1
	Moderate	6/455	1.3	0.5, 2.8	1/427	0.2	0.0, 1.3
	Severe	2/455	0.4	0.1, 1.6	0/427	0.0	0.0, 0.9
Anorexia							
	Any	50/456	11.0	8.2, 14.2	38/439	8.7	6.2, 11.7
Skips 1 meal	**Mild**	37/456	8.1	5.8, 11.0	32/439	7.3	5.0, 10.1
Skips 2 meals	**Moderate**	10/456	2.2	1.1, 4.0	4/439	0.9	0.2, 2.3
Skips ≥ 3 meals	**Severe**	3/456	0.7	0.1, 1.9	2/439	0.5	0.1, 1.6
Vomiting							
	Any	10/456	2.2	1.1, 4.0	8/439	1.8	0.8, 3.6
1 episode	**Mild**	5/456	1.1	0.4, 2.5	7/439	1.6	0.6, 3.3
2 episodes	**Moderate**	3/456	0.7	0.1, 1.9	0/439	0.0	0.0, 0.8
≥3 episodes	**Severe**	2/456	0.4	0.1, 1.6	1/439	0.2	0.0, 1.3
Diarrhea							
	Any	54/455	11.9	9.0, 15.2	32/439	7.3	5.0, 10.1
1-2 episodes	**Mild**	40/455	8.8	6.4, 11.8	25/439	5.7	3.7, 8.3
3-4 episodes	**Moderate**	13/455	2.9	1.5, 4.8	7/439	1.6	0.6, 3.3
> 5 episodes	**Severe**	1/455	0.2	0.0, 1.2	0/439	0.0	0.0, 0.8
Seizures (Y/N)							
Yes	**Days 0-7**	0/455	0.0	0.0, 0.8	0/439	0.0	0.0, 0.8
Rash							
Any rash	**Days 0-7**	11/455	2.4	1.2, 4.3	2/439	0.5	0.1, 1.6

*n: Number of participants reporting at least one event in this category. N: number of participants who submitted diary card information. Percentages are based on the total number of participants who did submit safety information at each time point.
†%: n/N expressed as a percentage.
Headache, chills, arthralgia, fatigue, malaise: 0= none, 1= aware, easily tolerated, 2= interferes with usual activities, 3= disabling

Serious adverse events:

One serious adverse event was reported for a participant (Group A) following Menactra vaccination. This participant experienced closed head injury after falling from a six-foot platform, and recovered without sequelae. No deaths occurred among participants in the study.

7.1.4.5 Reviewer summary and conclusions for study MTA-11

In this study, the immunogenicity and safety of Menactra and Typhim Vi® when given concomitantly, compared to a group receiving Typhim Vi® 28 days prior to Menactra, was evaluated in individuals 18-55 years old.

Safety:
Local reactions occurred less often following Menactra vaccination than after Typhim Vi® when the vaccines were given concomitantly or as a sequential regimen. Pain was most common after either Menactra or Typhim Vi® vaccination. Following concomitant vaccine administration, pain at the Menactra site occurred in 46.5% of participants, with 38.6% reported as mild, and 7.2% as moderate. For the same participants, 75.2% reported local pain after Typhim Vi® vaccination, 57.2% experienced mild pain, and 17.5% reported moderate pain. Local adverse event rates at the Menactra injection site, when Menactra was given 28 days after TyphimVi®, did not differ, compared to the rates after concomitant vaccine administration. In fact, reduced reporting occurred for localized pain, in both groups, compared to MTA-09 Menactra study participants, who received Menactra alone. The severe local reaction rate, at the Menactra injection site, was 2.0% and 2.7% after concomitant and sequential vaccine regimens, respectively. As expected, the overall frequency of systemic adverse events was increased when the Menactra and Typhim Vi® were given concomitantly, compared to Menactra alone (Group B, visit 2). The occurrence of any systemic reaction was reported by 58.6% and 35.8% of participants in the two groups, respectively. Headache and fatigue were most common, and following simultaneous vaccine administration, increased 8% (32.6% vs. 40.6%) and 10% (27.1% vs. 37.7%), respectively, overall. Mild arthralgia was also more frequent, and increased from 7.5% to 13.4%. The safety profile of Typhim Vi® did not vary when the vaccine was concomitantly administered with Menactra.

Immunogenicity:
The primary hypotheses were to demonstrate equivalent immune responses to Vi polysaccharide (Vi PS) and to four meningococcal serogroups when Menactra was administered concomitantly with Typhim Vi®, or when Typhim Vi® was administered first, and Menactra given 28 days later. For Typhim Vi® vaccine, the outcome measured was the proportion of participants achieving Vi PS antibody $\geq$1.0 ug/ml, and, for Menactra, the proportion achieving a $\geq$four-fold increase in SBA-BR titer for each serogroup. Both hypotheses, which were based on the upper limit of the 2-sided 95% CI for the difference in two proportions, were achieved. When Typhim Vi® vaccine was given first, however, followed by Menactra 28 days later, the proportion of participants who achieved a $\geq$4-fold increase in SBA-BR antibody was 65.2% for serogroup Y, which was 9.3% lower compared the corresponding proportion following concomitant vaccine administration. Differences in the observed proportions could be attributed to the baseline titer, which was higher in the sequential vaccine group. SBA-BR GMT for all meningococcal serogroup, 28 days after Menactra vaccination, was similar in both groups. No difference in vaccine effect was observed between the two groups, when baseline disparities in SBA-BR titer were taken into account.

A comparison of Vi PS geometric mean antibody titer elicited in the two groups, 28 days following Typhim Vi® vaccination was also included. The ratio of the geometric mean antibody titer was less than two fold. Typhim Vi® vaccine and Menactra, when administered concomitantly or as a sequential regimen, does not appear to result lowered antibody responses to either Vi PS or to the meningococcal components.

7.1.5 Study MTA-12: Immunogenicity and Safety of Tetanus/diphtheria (Td) Vaccine When Administered Concomitantly with an Experimental Tetravalent (A, C, Y, and W-135) Meningococcal Diphtheria Toxoid Conjugate Vaccine (TetraMenD) in Adolescents in the U.S.

7.1.5.1 Objectives

- Primary objectives:
  1. To compare the tetanus and diphtheria toxoid booster response, when Td and Menactra are given concomitantly, to corresponding antibody levels when the two vaccines are given sequentially (Td first, then Menactra 28 days later).
  2. To compare the bactericidal antibody response to serogroups A, C, Y, W135, using baby rabbit complement (SBA-BR), when Menactra is co-administered with Td, to the corresponding antibody response when Menactra is given 28 days after Td vaccination.
- Secondary objectives:
  1. To compare the proportion of participants with antibody levels ≥1.0 IU/mL to tetanus and diphtheria toxoids, when Td is co-administered with Menactra, to the corresponding titer when Td is given 28 days prior to Menactra.
  2. To compare the geometric mean antibody concentrations to tetanus and diphtheria toxoids, when Td is co-administered with Menactra, to the corresponding titer when Td is given 28 days prior to Menactra.
  3. To compare the bactericidal antibody titer to serogroups A, C, Y, W135, using baby rabbit complement (SBA-BR), when Menactra is co-administered with Td, to the corresponding antibody response when Menactra is given 28 days after Td vaccination.
- Other objectives:
  - ✓ To describe the safety profile for participants in each vaccine group
  - ✓ To compare the post-vaccination SBA-BR geometric mean titer for serogroups A, C, Y and W135, in both vaccine groups of the proposed study, to the corresponding antibody response in Menactra participants in study MTA-02.

7.1.5.2 Design

The study was a randomized, double blind, multi-center, controlled trial. Participants were randomized in a 1: 1 ratio (Menactra + Td: Td, then Menactra).

Study Period: January 28, 2002 to January 06, 2003.

7.1.5.3 Protocol

7.1.5.3.1 Population:

The study was conducted at eight study centers in the United States.

Inclusion criteria:
- Healthy
- Age ≥11 years and <18 years old at the time of vaccination
- Informed assent or parent consent obtained

Exclusion criteria:
- Serious chronic disease (i.e. cardiac, renal, neurologic, metabolic, rheumatologic etc.)
- Known or suspected impairment immunologic function
- History of documented invasive meningococcal disease or previous meningococcal vaccination
- Received a Td containing vaccine in the last 5 years

- Receipt of immune globulin or other blood products within the previous 3 months, injected or oral corticosteroids within 6 weeks prior to the administration of the study vaccine
- Administration of a vaccine other than the study vaccine within 28 days of enrollment
- Antibiotic therapy within 72 hours prior to vaccination
- Known or suspected hypersensitivity to any vaccine component
- Enrolled in another clinical trial
- Any condition which, in the opinion of the investigator, would pose a health risk to the participant
- Unable to comply with scheduled visits or study procedures
- For females, a positive or equivocal urine pregnancy test result on the day of vaccination
- Breastfeeding

Reasons for deferring vaccination

- Acute medical illness, with or without fever, within the previous 72 hours. Fever was defined as an oral temp ≥38.0C.

7.1.5.3.2 Vaccine administration

Each group received two injections 28 days apart. Group A received Td + Menactra, then a saline placebo. Group B received Td + saline placebo, followed by Menactra. Participants received all injections intramuscularly. Please see Appendix 2 for the batch number of products used in this clinical trial.

Tetanus and Diphtheria Toxoids Adsorbed for Adult Use® is a commercially available in the United States. Each 0.5mL dose contains 5Lf of tetanus toxoid, 2Lf of diphtheria toxoid and not more than 0.28mg of aluminum by assay. Tetanus and diphtheria toxoids induce at least 2 units and 0.5 units of antitoxin per mL, respectively, in the guinea pig potency test. The vaccine is formulated as liquid, and after shaking, appears as a turbid, whitish gray suspension. Td vaccine was supplied in single dose vials.

Buffered Sterile Normal Saline (0.9% NaCl) was utilized as the placebo control, and supplied in single dose vials.

7.1.5.3.3 Endpoints

Primary Endpoints:

- The proportion of participants who have a booster response to tetanus and diphtheria antigens
- The proportion of participants with at least a 4-fold increase in SBA-BR antibody titer to each serogroup

Secondary endpoints:

- The proportion of participants with anti-diphtheria and anti-tetanus antibody levels ≥ 1.0 IU/ml
- Anti-diphtheria and anti-tetanus geometric mean antibody concentrations among these recipients
- SBA-BR geometric mean antibody titer to each meningococcal serogroup

7.1.5.3.4 Surveillance

Monitored parameters:

Safety: Study participants were monitored for immediate reactions 30 minutes after vaccination, and for local and systemic reactogenicity during the 7 days following vaccination. Pre-specified adverse events included localized reactions (erythema, swelling, induration, pain) and systemic symptoms (fever measured by oral temperature, headache, fatigue, chills, arthralgia, anorexia, vomiting, diarrhea, seizures, malaise and rash), which were assessed after each vaccination. These events were recorded daily on a diary card, and also collected by study personnel through telephone interview eight days after each vaccination. If rash was reported, the investigator was prompted to record additional details on a separate case report form. Other non-serious, unexpected adverse events were obtained by telephone interview eight and twenty-eight days

after each vaccination. Serious adverse events were reported and recorded for the entire duration of the study.

Efficacy (Immunogenicity):
Serum samples were obtained pre- and 28 days after each vaccination.

Anti-Meningococcal Antibody
Functional antibody activity to each serogroup was determined using a serum bactericidal assay. The lower limit of detection for this assay, using baby rabbit complement, is an antibody titer of 8. Please see Section 4.4 Laboratory Methods for additional details.

Anti-diphtheria Antibody
Anti-diphtheria antibody response, reported in International Units/mL (IU/mL), was measured by the ability of the test sera to [redacted]
The assay is calibrated using a WHO reference serum and to determine the limits of detection. The minimum detectable antitoxin level of the reference serum, and the starting dilution of the test sera, is [redacted] IU/mL.

Anti-tetanus Antibody
Anti-tetanus IgG antibody levels were measured by an [redacted] Enzyme Linked Immunosorbent Assay (ELISA). The antibody concentration was calculated by comparison to an international human reference (WHO Lot TE-3) with assigned unitage by a [redacted] method. Results are reported as International Units per milliliter (IU/mL). The minimum level of quantitation for this assay is [redacted] IU/mL.

7.1.5.3.5 Statistical plan

Primary Hypotheses:
Primary Hypothesis #1:
To demonstrate that 28 days following concomitant vaccination with Td and Menactra, the proportion of participants who have a booster response to tetanus and diphtheria antigens is non-inferior to the same parameter in the group given Td together with a saline placebo, followed by Menactra 28 days later. The definition of a post-vaccination booster response to tetanus and diphtheria antigens is based on the baseline pre-vaccination level. For participants with a baseline anti-diphtheria antibody level ≤ 2.56 IU/mL and/or an anti-tetanus antibody level ≤ 2.7 IU/mL, a booster response is at least a 4-fold increase in baseline level to each respective antigen. For participants with a baseline anti-diphtheria antibody level >2.56 IU/mL and/or an anti-tetanus antibody level >2.7 IU/mL, at least a 2-fold increase in antibody level to each respective antigen is needed.

This hypothesis would be supported if the upper bound of the two-sided 95% CI of $p_{\text{Td + placebo}} - p_{\text{Td + Menactra}} < 0.1$, where p is the proportion of participants with acceptable increases in antibody level to diphtheria and tetanus, as stated in the preceding paragraph, in the group given a sequential and concomitant dosing regimen of Td and Menactra, respectively. Planned enrollment of 1024 participants (n= 512 per group), with resultant 920 evaluable study subjects provided 99.6% and 99.9% power to achieve the primary hypothesis for tetanus and diphtheria, respectively. Testing of the primary hypothesis was conducted at the one-sided 0.025 significance level.

Primary Hypothesis #2:
To demonstrate that 28 days post Menactra vaccination, the proportion of participants with at least a 4-fold increase in SBA-BR antibody titer to serogroups A, C, Y, and W-135 in the Td + Menactra group is non-inferior to the same parameter in the group given Td together with a saline placebo, followed by Menactra 28 days later.

This hypothesis would be supported by the data if the upper limit of the two-sided 95% confidence limit $p_{\text{Menactra}} - p_{\text{Td+Menactra}} < 0.1$, where p is the proportions of participants with at least a 4-fold rise in SBA-BR antibody to meningococcal serogroups A, C, Y, and W-135, in the Td + placebo and Td + Menactra groups, respectively. Planned enrollment of 1024 participants (n= 512 per group), with resultant 920 evaluable study subjects provided 88.7% power, overall, to achieve the primary hypothesis for each serogroup. Testing of the primary hypothesis was conducted at the one-sided 0.025 significance level.
The primary analyses were based on data generated from the per-protocol population.

Secondary Hypotheses:
Secondary Hypothesis #1:
To demonstrate that 28 days following concomitant vaccination with Td vaccine and Menactra, the proportion of participants with anti-diphtheria and anti-tetanus antibody levels $\geq$ 1.0 IU/ml is non-inferior to the same parameter in the group given Td together with a saline placebo, followed by Menactra 28 days later.

This hypothesis would supported by the data if the upper bound of the two-sided 95% CI of $p_{\text{Td + placebo}} - p_{\text{Td + Menactra}} < 0.1$ for both antigens, where p is the proportion of participants with antibody titer $\geq$ 1.0 IU/ml to diphtheria and tetanus in the groups given [Td + placebo, then Menactra] and [Td + Menactra], respectively.

Secondary Hypothesis #2:
To demonstrate that 28 days following concomitant vaccination with Td vaccine and Menactra, the anti-diphtheria and anti-tetanus geometric mean antibody concentrations among these recipients is non-inferior to the same parameter in the group given Td together with a saline placebo, followed by Menactra 28 days later.

This hypothesis would be supported by the data if the upper bound of the two-sided 95% CI of the ratio $\text{GMT}_{\text{Td + Placebo}} / \text{GMT}_{\text{Td + Menactra}} < 2$.

Secondary Hypothesis #3:
To demonstrate that 28 days after vaccination with Menactra, the SBA-BR geometric mean antibody titer for serogroups A, C, Y, and W135 in the group given Td and Menactra concomitantly is non-inferior to the same parameter in the group receiving the Td and Menactra sequentially.

This hypothesis would be supported by the data if the upper bound of the two-sided 95% CI of the ratio $\text{GMT}_{\text{Menactra}} / \text{GMT}_{\text{Td + Menactra}} < 2$, where $\text{GMT}_{\text{Menactra}}$ and $\text{GMT}_{\text{Td + Menactra}}$ are the SBA-BR geometric mean antibody concentrations of serogroups A, C, Y and W-135 in the group receiving Menactra after Td 28 days later and in the group receiving Td and Menactra concomitantly.

Analyses of the secondary points were performed on both per-protocol and intent-to-treat populations.

Per-protocol population for immunogenicity:
The per-protocol population included all eligible participants who received the assigned vaccine at visits 1 & 2, who complied with scheduled visits for blood specimens, and for whom a sufficient quantity of paired sera was available for analysis.

Intent-to-treat population for immunogenicity:
The intent-to-treat population consisted of all enrolled participants who received one dose of vaccine underwent at least one blood draw. Analyses were performed according to the vaccine received.

For analysis purposes, if the SBA-BR antibody titer to any serogroup was reported below the limit of detection, the antibody titer assigned was a value equal to the limit of detection. ITT analyses for all primary and secondary endpoints were considered exploratory. These results were not included in the license application, but anticipated to be submitted as an appendix to the final study report.

Intent-to-treat population for safety:
The intent-to-treat population consisted of all participants who received one dose of vaccine and for whom safety information was available. Analyses were performed according to the vaccine received.

Since the nature and severity of a rash were difficult to categorize for the vaccine recipient, all rashes occurring during the first 7 days after vaccination were designated by the sponsor as a severe solicited systemic reaction, in an effort to prompt the investigator to describe additional rash characteristics.

7.1.5.4 Results

7.1.5.4.1 Population

A total of 1021 (Group A (concomitant) n=509, Group B (sequential) n= 512) adults were enrolled, and 990 (Group A n=492, Group B n= 498) individuals completed the study.

A single study site was found to be in breech of Good Clinical Practices as it relates to product accountability and documentation, which included verification of the treatment group. As a result, the 59 subjects enrolled at this site were excluded by the sponsor from the safety and immunogenicity analyses, as well as in the enrolled population described in the preceding paragraph.

Safety population:
The intent-to-treat population for safety included all enrolled participants (n= 1021). Thirty-four participants (Group A n=17, Group B n= 14) did not complete the study, due to voluntary withdrawal, non-compliance with study procedures, or lost-to-follow-up.

Immunogenicity population:
The per protocol population for immunogenicity included 469 Group A and 478 Group B participants. Seven (Group A n=2, Group B n=5) of 71 participants with at least one protocol violation were considered evaluable for the per-protocol analysis, based on the type of violation (e.g. absent diary card, absent urine pregnancy test in premenarcheal adolescent women). One participant (Group A) was not listed as having a protocol violation, but was excluded from the per-protocol analysis because paired sera could not be correctly verified.

Demographic characteristics: The distribution of participants, based on age, gender, race and ethnicity, was similar among the two vaccine groups. The study population enrolled was predominately Caucasian (89.8%), but also included African American (4.8%), Hispanic (2.6%), Asian populations (0.5%) and individuals with mixed racial background (2.3%).

7.1.5.4.2 Immunogenicity

Diphtheria and Tetanus booster response:
The percentage of participants with high baseline antibody level to diphtheria (>1.28 IU/ml) was 12.03% [57/474] and 11.97% [56/468] in Groups B and A, respectively. The percentage of participants with high baseline antibody level to tetanus (>5.3 IU/ml) was 4.87% [23/472] and 4.93% [23/467] in Groups B and A, respectively.

MTA-12 Table 1: Primary Hypothesis #1
Number and Proportion of Participants with Booster Responses to Diphtheria and Tetanus Toxoids Post-vaccination

	Td + Placebo, Then Menactra		Td + Menactra Then Placebo		Difference ($p_{Td + placebo}$ - $p_{Td + Menactra}$)	Upper Limit of the 2-sided 95% CI for the Difference§
	n/N*	$p_{Td + Placebo}$†	n/N*	$p_{Td + Menactra}$‡		
Diphtheria: % responders	446/471	0.947	462/464	0.996	-0.049	-0.028
2-fold: Baseline >2.56 IU/ml	7/13	0.539	8/8	1.0		
4- fold: Baseline ≤2.56 IU/ml	439/458	0.959	454/456	0.996		
Tetanus: % responders	425/471	0.902	409/462	0.885	0.017	0.057
2- fold: Baseline >5.3 IU/ml	17/45	0.378	18/49	0.367		
4-fold: Baseline ≤5.3 IU/ml	408/426	0.958	391/413	0.947		

* n: number of participants with a booster response on 28 days post-vaccination. N: total number of participants with valid serology results on Day 28.

† $p_{Td + Placebo}$: proportion of participants with a booster response in the group given Td vaccine together with a saline placebo, and then Menactra 28 days later.

‡ $p_{Td + Menactra}$: proportion of participants with a booster response in the group given Td concomitantly with Menactra.

§ CI: Confidence interval.

Proportions with four-fold or greater increases in SBA-BR titer:

When Td was given 28 days prior to Menactra, the proportion of participants achieving a ≥four-fold increase in SBA-BR antibody titer to serogroups C, Y and W135 was lower, compared to the group given the two vaccines concomitantly. The difference in the two proportions was -8.8%, -20.7% and -8.7%, respectively.

MTA-12 Table 2: Primary Hypothesis #2
Proportion of Participants 11-17 Years Old with ≥ 4-fold Increase in SBA-BR Antibody Titer on Day 28, compared to Baseline

Serogroup	Td+Placebo, Then Menactra	Td + Menactra Then Placebo	Difference ($p_{Td + placebo}$ - $p_{Td + Menactra}$)	Upper Limit of the 2-sided 95% CI for the Difference§
	N=465	N=478		
	$p_{Menactra}$†	$p_{Td + Menactra}$‡		
A	0.906	0.901	0.005	0.043
C	0.824	0.912	-0.088	-0.045
Y	0.651	0.858	-0.207	-0.154
W-135	0.877	0.963	-0.087	-0.053

* n: number of participants with a booster response on 28 days post-vaccination. N: total number of participants with valid serology results on Day 28.

† $p_{Td + Placebo}$: proportion of participants with a booster response in the group given Td vaccine together with a saline placebo, and then Menactra 28 days later.

‡ $p_{Td + Menactra}$: proportion of participants with a booster response in the group given Td concomitantly with Menactra.

§ CI: Confidence interval.

Other measures of antibody response to diphtheria and tetanus toxoid:

Proportions with diphtheria and tetanus antibody levels >1.0IU/ml or greater:

Diphtheria: Prior to vaccination, the proportion of participants with antibody level to diphtheria ≥1.0IU/ml was 25.3% in the group receiving a sequential vaccine regimen, and 28.0% in the group receiving the vaccines concomitantly. Twenty-days following Td vaccination, the proportions increased to 99.4% and 100.0%, respectively. The upper limit of the 2-sided 95% CI for the difference in two proportions was 0.001 (MTA-12 Table 3).

Tetanus: Prior to vaccination, the proportion of participants with antibody level to tetanus ≥1.0IU/ml was 41.3% in the group receiving a sequential vaccine regimen, and 38.8% in the group receiving the vaccines concomitantly. Twenty-days following Td vaccination, the proportions increased to 98.5% and 99.1%, respectively. The upper limit of the 2-sided 95% CI for the difference in two proportions was 0.008.

MTA-12 Table 3: Secondary Hypothesis #1: Proportion of Participants 11-17 Years Old with Diphtheria and Tetanus Antibody Levels ≥1.0 IU/ml Post-vaccination

	Td + Placebo, Then Menactra $p_{Td + Placebo}$†	Td + Menactra Then Placebo $p_{Td + Menactra}$‡	Difference ($p_{Td + placebo}$ - $p_{Td + Menactra}$)	Upper Limit of the 2-sided 95% CI for the Difference§
Diphtheria	0.994	1.0	-0.006	0.001
Tetanus	0.985	0.991	-0.006	0.008

* n: number of participants with a booster response on 28 days post-vaccination. N: total number of participants with valid serology results on Day 28.

† $p_{Td + Placebo}$: proportion of participants with a booster response in the group given Td vaccine together with a saline placebo, and then Menactra 28 days later.

‡ $p_{Td + Menactra}$: proportion of participants with a booster response in the group given Td concomitantly with Menactra.

§ CI: Confidence interval.

Diphtheria and Tetanus GMT:

The diphtheria GMT prior to vaccination was 0.4 IU/ml in each group. Twenty-eight days following Td vaccination, the GMT increased to 8.4 IU/ml in the group given a sequential vaccine regimen, and 120.9 IU/ml in the group given the vaccines concomitantly (MTA-12 Table 4).

MTA-12 Table 4: Secondary Hypothesis #2 Comparison of Diphtheria and Tetanus GMT (IU/ml) Post-vaccination

	Td+ Placebo, Then Menactra			Td + Menactra Then Placebo			Ratio of $GMT_{Td + Placebo}$ / $GMT_{Td + Menactra}$	Upper Limit of the 2-sided 95% CI§ for the GMT Ratio
	N	GMT	95% CI	N	GMT	95% CI		
Diphtheria	473	8.4	7.6, 9.2	465	120.9	104.6, 139.8	0.07	0.08
Tetanus	477	13.6	12.7, 14.4	464	11.5	10.8, 12.2	1.18	1.29

§ CI: Confidence interval.

Additional meningococcal SBA-BR antibody titer data:

Baseline SBA-BR GMT:

At baseline, the proportion of sequential vaccine group recipients with a SBA-BR titer ≥1:8 to serogroups A, C, Y and W-135 was 89% [425/478], 68% [325/478], 81% [385/478], and 55% [265/478], respectively. Similar distributions of pre-vaccination SBA-BR titer were observed in the concomitant vaccine group.

SBA-BR GMT 28 days after Menactra vaccination:

The bactericidal geometric mean titer, 28 days after Menactra vaccination, also showed a difference in antibody response for serogroups C, Y and W135. The effect of vaccine regimen on antibody response was not easily interpretable without direct comparison of each study group to a group of adolescents receiving Menactra alone. In the absence of this control group in study MTA-12, definite conclusions could not be drawn about whether increased meningococcal antibody response alone occurred when the two vaccines were given together, or if suppressed antibody responses also occurred in the group given Td prior to Menactra (MTA-12 Table 5).

MTA-12 Table 5: Comparison of SBA-BR GMT to Meningococcal Serogroups A, C, Y, W135 Post-vaccination		
Serogroup	Td+ Placebo, Then Menactra	Td + Menactra Then Placebo
	N=466	N=478
	GMT	GMT
A	10391.4	11312.8
C	2136.0	5059.3
Y	1331.3	3390.9
W-135	1339.1	4194.7

§ CI: Confidence interval.

Seroconversion

The seroconversion rate was defined as the proportion of participants with SBA-BR antibody titer less than 1:8 pre-vaccination, who subsequently achieved a four-fold or greater increase in SBA-BR antibody titer 28 days after vaccination. Vaccine recipients in both groups, with SBA-BR antibody titer less than 1:8 pre-vaccination, achieved this criterion for serogroup A. For serogroup C, seroconversion was observed in 96.7% [148/153] of participants given a sequential vaccine regimen and 99.3% [149/150] of participants in the concomitant vaccine group. For the remaining serogroups, of those participants who received a sequential vaccine regimen, 92.5% [86/93] and 96.7% [206/213] responded with a ≥4-fold antibody rise to serogroups Y and W135, respectively, compared with 97.0% [97/100] and 99.5% [203/204] of individuals who received the vaccines concomitantly.

7.1.5.4.3 Safety

MTA-12 Table 6: Overall Participant Safety Profile					
Type of AE	Time Interval*	Group A Td + Menactra, Then Placebo†		Group B Td + Placebo†, Then Menactra	
		n/N‡	%§	n/N‡	%§
Immediate reactions	Day 0:				
After 1st vaccination	within 30 minutes	5/507	1.0	2/512	0.4
After 2nd vaccination		0/493	0.0	1/503	0.2
Solicited local reactions					
After 1st vaccination					
· Menactra (Group A), Placebo (Group B)	Days 0-7	293/505	58.0	147/510	28.8
· Td injection site		377/505	74.7	374/510	73.3
After 2nd vaccination					
· Placebo (Group A), Menactra (Group B)		46/490	19.6	288/505 §§	57.0
Solicited systemic reactions					
After 1st vaccination	Days 0-7	296/505	58.6	276/510	54.1
After 2nd vaccination		159/490	32.4	181/505§§	35.8
Unsolicited adverse events	Days 0-56	245/492	49.8	255/505	50.5
Serious adverse events	Day 0-56	2/507	0.4	1/512	0.2

*Vaccination occurs on Day 0.
† 0.9% NaCl was administered as the placebo.
‡n: Number of participants reporting at least one event in this category.
§%: n/N expressed as a percentage.
§§503 subjects received the correct Group B vaccination schedule. Two Group A subjects received the Group B vaccination at Visit 2. They were analyzed according to the vaccine received at each time point.

Immediate reactions:
Eleven reactions were reported by eight participants, which, except for one reaction, occurred in all participants after the first vaccination. Two participants in the concomitant vaccine group reported syncope. Another two concomitant group participants experienced dizziness, with associated lightheadness, and, arthralgia/dyspepsia, respectively. Dizziness also occurred in two participants receiving Td. After the second vaccination (Menactra), one Group B participant reported injection site edema.

Local reactions

Concomitant vaccination with Menactra and Td

After the first vaccination, the occurrence of any local reaction at the Menactra injection site was reported by 58.0% of participants, and, at the Td injection site, by 74.7% of the same participants. Mild and moderate pain was most common at both injection sites (MTA-12 Table 7).

MTA-12 Table 7: Local adverse reactions After Concomitant Vaccine Administration (Days 0-7): Td and Menactra Injection sites

		Group A Td + Menactra, Then Placebo N=505					
		(Menactra Injection site)			(Td Injection site)		
Reaction	Severity	n*	%†	95% CI	n*	%†	95% CI
Redness							
	Any	61	12.1	9.4, 15.2	73	14.5	11.5, 17.8
< 1 inch	**Mild**	52	10.3	7.8, 13.3	58	11.5	8.8, 14.6
1 – 2 inches	**Moderate**	3	0.6	0.1, 1.7	12	2.4	1.2, 4.1
> 2 inches	**Severe**	6	1.2	0.4, 2.6	3	0.6	0.1, 1.7
Swelling							
	Any	59	11.7	9.0, 14.8	83	16.4	13.3, 20.0
< 1 inch	**Mild**	47	9.3	6.9, 12.2	63	12.5	9.7, 15.7
1 – 2 inches	**Moderate**	9	1.8	0.8, 3.4	19	3.8	2.3, 5.8
> 2 inches	**Severe**	3	0.6	0.1, 1.7	1	0.2	0.0, 1.1
Induration							
	Any	86	17.0	13.9, 20.6	105	20.8	17.3, 24.6
< 1 inch	**Mild**	68	13.5	10.6, 16.8	75	14.9	11.9, 18.3
1 – 2 inches	**Moderate**	13	2.6	1.4, 4.4	27	5.3	3.6, 7.7
> 2 inches	**Severe**	5	1.0	0.3, 2.3	3	0.6	0.1, 1.7
Pain							
	Any	267	52.9	48.4, 57.3	358	70.9	66.7, 74.8
	Mild	213	42.2	37.8, 46.6	244	48.3	43.9, 52.8
	Moderate	54	10.7	8.1, 13.7	113	22.4	18.8, 26.3
	Severe	0	0.0	0.0, 0.7	1	0.2	0.0, 1.1

*n: Number of participants reporting at least one event in this category.
†%: n/N expressed as a percentage.
Pain: 0=none, 1= (mild) sx present, but arm movement not affected, 2= (moderate) limits usual arm movement, 3= (severe) disabling

Menactra injection site, after concomitant and sequential vaccination:

Local adverse event rates at the Menactra injection site were not significantly different following either vaccine regimen. Reduced reporting for pain, overall, was observed in both groups, compared to MTA-04 Menactra participants. The overall rate of severe local reactions was 2.2% in both vaccine groups.

MTA-12 Table 8: Menactra local adverse reactions (Days 0-7)							
		Group A (N= 505) Td + Menactra, Then Placebo			Group B (N= 505) Td + Placebo, Then Menactra		
		Menactra Injection site			Menactra Injection site		
Reaction	Severity	n*	%†	95% CI	n*	%†	95% CI
Redness							
	Any	61	12.1	9.4, 15.2	56	11.1	8.5, 14.2
< 1 inch	**Mild**	52	10.3	7.8, 13.3	40	7.9	5.7, 10.6
1 – 2 inches	**Moderate**	3	0.6	0.1, 1.7	11	2.2	1.1, 3.9
> 2 inches	**Severe**	6	1.2	0.4, 2.6	5	1.0	0.3, 2.3
Swelling							
	Any	59	11.7	9.0, 14.8	66	13.1	10.3, 16.3
< 1 inch	**Mild**	47	9.3	6.9, 12.2	44	8.7	6.4, 11.5
1 – 2 inches	**Moderate**	9	1.8	0.8, 3.4	15	3.0	1.7, 4.9
> 2 inches	**Severe**	3	0.6	0.1, 1.7	7	1.4	0.6, 2.8
Induration							
	Any	86	17.0	13.9, 20.6	78	15.4	12.4, 18.9
< 1 inch	**Mild**	68	13.5	10.6, 16.8	61	12.1	9.4, 15.2
1 – 2 inches	**Moderate**	13	2.6	1.4, 4.4	12	2.4	1.2, 4.1
> 2 inches	**Severe**	5	1.0	0.3, 2.3	5	1.0	0.3, 2.3
Pain							
	Any	267	52.9	48.4, 57.3	270	53.5	49.0, 57.9
	Mild	213	42.2	37.8, 46.6	198	39.2	34.9, 43.6
	Moderate	54	10.7	8.1, 13.7	68	13.5	10.6, 16.8
	Severe	0	0.0	0.0, 0.7	4	0.8	0.2, 2.0

*n: Number of participants reporting at least one event in this category.
†%: n/N expressed as a percentage.
Pain: 0=none, 1= (mild) sx present, but arm movement not affected, 2= (moderate) limits usual arm movement, 3= (severe) disabling

Systemic reactions:

The overall frequency of systemic adverse events was higher when the Menactra and Td were given concomitantly, then when Menactra was given 28 days after Td. Any systemic reaction was reported by 58.6% and 35.8% of participants in the concomitant and sequential vaccine groups, respectively (MTA-12 Table 9). Arthralgia occurred in 25.1% of participants given the vaccines concomitantly, and in 12.1% of sequential vaccine group participants. Except for arthralgia, the systemic adverse event rates in the concomitant vaccine group also did not exceed rates reported for study MTA-04 Menactra participants.

MTA-12 Table 9: Systemic adverse reactions After Menactra Vaccination (Days 0-7)							
		Group A Td + Menactra, Then Placebo			Group B Td + Placebo, Then Menactra		
Reaction	Severity	n*/N	%†	95% CI	n*/N	%†	95% CI
Fever							
	Any	25/503	5.0	3.2, 7.2	11/505	2.2	1.1, 3.9
38.0°C-38.9°C	**Mild**	19/503	3.8	2.3, 5.8	10/505	2.0	1.0, 3.6
39.0°C-39.9°C	**Moderate**	5/503	1.0	0.3, 2.3	1/505	0.2	0.0, 1.1
≥ 40.0°C	**Severe**	1/503	0.2	0.0, 1.1	0/505	0.0	0.0, 0.7

Cont. MTA-12 Table 9: Systemic adverse reactions After Menactra Vaccination (Days 0-7)

Reaction	Severity	Group A: Td + Menactra, Then Placebo			Group B: Td + Placebo, Then Menactra		
		n*/N	%†	95% CI	n*/N	%†	95% CI
Headache							
	Any	180/505	35.6	31.5, 40.0	110/505	21.8	18.3, 25.6
	Mild	116/505	23.0	19.4, 26.9	79/505	15.6	12.6, 19.1
	Moderate	54/505	10.7	8.1, 13.7	28/505	5.5	3.7, 7.9
	Severe	10/505	2.0	1.0, 3.6	3/505	0.6	0.1, 1.7
Fatigue							
	Any	161/505	31.9	27.8, 36.1	85/505	16.8	13.7, 20.4
	Mild	96/505	19.0	15.7, 22.7	62/505	12.3	9.5, 15.5
	Moderate	58/505	11.5	8.8, 14.6	18/505	3.6	2.1, 5.6
	Severe	7/505	1.4	0.6, 2.8	5/505	1.0	0.3, 2.3
Malaise							
	Any	119/505	23.6	19.9, 27.5	61/505	12.1	9.4, 15.2
	Mild	72/505	14.3	11.3, 17.6	35/505	6.9	4.9, 9.5
	Moderate	36/505	7.1	5.0, 9.7	21/505	4.2	2.6, 6.3
	Severe	11/505	2.2	1.1, 3.9	5/505	1.0	0.3, 2.3
Arthralgia							
	Any	127/505	25.1	21.4, 29.2	61/505	12.1	9.4, 15.2
	Mild	94/505	18.6	15.3, 22.3	45/505	8.9	6.6, 11.7
	Moderate	29/505	5.7	3.9, 8.1	15/505	3.0	1.7, 4.9
	Severe	4/505	0.8	0.2, 2.0	1/505	0.2	0.0, 1.1
Chills							
	Any	56/505	11.1	8.5, 14.2	18/505	3.6	2.1, 5.6
	Mild	35/505	6.9	4.9, 9.5	16/505	3.2	1.8, 5.1
	Moderate	18/505	3.6	2.1, 5.6	2/505	0.4	0.0, 1.4
	Severe	3/505	0.6	0.1, 1.7	0/505	0.0	0.0, 0.7
Anorexia							
	Any	64/505	12.7	9.9, 15.9	22/505	4.4	2.7, 6.5
Skips 1 meal	**Mild**	43/505	8.5	6.2, 11.3	15/505	3.0	1.7, 4.9
Skips 2 meals	**Moderate**	16/505	3.2	1.8, 5.1	5/505	1.0	0.3, 2.3
Skips ≥ 3 meals	**Severe**	5/505	1.0	0.3, 2.3	2/505	0.4	0.0, 1.4
Vomiting							
	Any	23/505	4.6	2.9, 6.8	7/505	1.4	0.6, 2.8
1 episode	**Mild**	17/505	3.4	2.0, 5.3	5/505	1.0	0.3, 2.3
2 episodes	**Moderate**	6/505	1.2	0.4, 2.6	1/505	0.2	0.0, 1.1
≥3 episodes	**Severe**	0/505	0.0	0.0, 0.7	1/505	0.2	0.0, 1.1
Diarrhea							
	Any	45/505	8.9	6.6, 11.7	19/505	3.8	2.3, 5.8
1-2 episodes	**Mild**	39/505	7.7	5.5, 10.4	15/505	3.0	1.7, 4.9
3-4 episodes	**Moderate**	5/505	1.0	0.3, 2.3	4/505	0.8	0.2, 2.0
≥ 5 episodes	**Severe**	1/505	0.2	0.0, 1.1	0/505	0.0	0.0, 0.7
Seizures (Y/N)							
Yes	**Days 0-7**	0/505	0.0	0.0, 0.7	0/505	0.0	0.0, 0.7
Rash							
Any rash	**Days 0-7**	9/505	1.8	0.8, 3.4	7/505	1.4	0.6, 2.8

*n: Number of participants reporting at least one event in this category.
†%: n/N expressed as a percentage.
Headache, chills, arthralgia, fatigue, malaise: 0= none, 1= aware, easily tolerated, 2= interferes with usual activities, 3= disabling

Serious adverse events:
Four adverse events were reported in two participants, after receiving Td and Menactra concomitantly. One participant was hospitalized for pneumonia and dehydration 29 days after vaccination. The other participant experienced a sports-related head injury with associated nausea. Both individuals recovered without sequelae. No deaths occurred among participants in the study.

7.1.5.5 Reviewer summary and conclusions for study MTA-12

In this study, the immunogenicity and safety of Menactra and Td when given concomitantly, compared to a group receiving Td 28 days prior to Menactra, was evaluated in individuals 11-17 years old.

Safety:
Local adverse event rates at the Menactra injection site, when Menactra was given 28 days after Td, were not significantly different, compared to the rates after concomitant vaccine administration. Similar Menactra adverse event profiles, whether Td was given with or 28 days prior to Menactra, suggested that the frequency of adverse reactions were related more to the amount of diphtheria contained in Menactra, than the level of pre-existing diphtheria antibody. Menactra was less reactogenic than Td vaccine. As expected, the overall frequency of systemic adverse events was increased when the Menactra and Td were given concomitantly, than when Menactra was given 28 days after Td. The occurrence of any systemic reaction was reported by 58.6% and 35.8% of participants in the concomitant and sequential vaccine groups, respectively. Headache and fatigue were most common. Arthralgia occurred in 25.1% of participants given the vaccines concomitantly, and in 12.1% of sequential vaccine group participants. Except for arthralgia, the systemic adverse event rates in the concomitant vaccine group also did not exceed rates reported for study MTA-04 Menactra participants. The safety profile of Td was not altered when concomitantly administered with Menactra.

Immunogenicity:
The primary hypotheses were to demonstrate non-inferior immune responses to diphtheria, tetanus and meningococcal components when Menactra was given concomitantly with Td, or when Td was administered first, and Menactra given 28 days later. Both hypotheses were achieved. The upper limit of the two-sided 95% CI of $p_{\text{Td + placebo}} - p_{\text{Td + Menactra}}$ was less than 10%, where p was the proportion of participants with acceptable increases in antibody level to diphtheria and tetanus, in the group given a sequential and concomitant vaccine regimen, respectively. The upper limit of the confidence interval was –4.0% and 2.6%, for the diphtheria and tetanus components, respectively. For the meningococcal serogroups, the upper limit of the two-sided 95% CI for the difference in two proportions was also less than 10%.

Prior Td immunization, however, also resulted in a notably lower proportion of participants achieving a ≥four-fold increase in SBA-BR antibody titer to serogroups C, Y and W135. The difference in the proportions achieving a ≥four-fold increase in SBA-BR antibody to serogroups C, Y and W135 was -8.8%, -20.7% and -8.7%, respectively. In the absence of a control group receiving Menactra alone in study MTA-12, it was difficult to determine if an increased meningococcal antibody response alone occurred when the two vaccines were given together, or, whether suppressed antibody responses in the group given Td prior to Menactra also occurred. Reduced immune responses to Menactra could be due to initial expansion of diphtheria toxoid-specific B-cells, with subsequent intramolecular antigenic competition between meningococcal polysaccharide and diphtheria toxoid epitopes. This phenomenon has been observed with another meningococcal vaccine, which was conjugated to a tetanus toxoid carrier protein.[15] In the absence of a group receiving Menactra alone, post-vaccination bactericidal GMT for each serogroup were compared to adolescents receiving Menactra in study MTA-02, acknowledging that cross-study comparisons might or might not be meaningful. Bactericidal GMT, 28 days after Menactra vaccination, in the sequential vaccine group appeared similar for serogroups C, Y and W135 and higher for serogroup A, compared to MTA-02 participants. The distribution of baseline titer in the two studies differed, and the age of the study

population varied slightly. Participants enrolled in MTA-12 were 11-17 years old, and 11-18 years old in MTA-02. For all serogroups, a higher proportion of MTA-12 participants had baseline titers at the upper range of reported values.

Conclusions for MTA-12:

- Menactra, when co-administered with Td vaccine, showed increased immunologic response to the diphtheria component and comparable antibody responses to tetanus toxoid. Concomitant vaccine administration of Menactra and Td did not result in decreased antibody response to the meningococcal components, compared to a group receiving the two vaccines sequentially.

- Lower proportions of participants achieving a ≥4-fold increase in SBA-BR antibody to serogroups C (82.4%), Y% (65.1%) and W135 (87.7%) were observed in the group given Td 28 days prior to Menactra. The post-vaccination SBA-BR geometric mean antibody titers were difficult to interpret in the absence of direct comparisons to a group receiving Menactra alone. The seroconversion rates in the group receiving a sequential vaccine regimen were not lowered.