Aventis

Menactra™

Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine

VRBPAC Briefing Document

Aventis Pasteur Inc.

Table of Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations

List of Abbreviations	
ABC	Active Bacterial Core
ACIP	Advisory Committee on Immunization Practices
AE	Adverse Event
AvP	Aventis Pasteur
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CFR	Case Fatality Rate
CI	Confidence Interval
COSTART	Coding Symbols for a Thesaurus of Adverse Reaction Terms
D	Day
DNA	Deoxyribonucleic Acid
DT	Diphtheria and Tetanus Toxoids Adsorbed USP (For Pediatric Use)
DTaP	Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed
ELISA	Enzyme Linked Immunosorbent Assay
FDA	Food and Drug Administration
GMT	Geometric Mean Titer
ICD9	International Classification of Diseases 9th Edition
IND	Investigational New Drug Application
ISS	Integrated Summary of Safety
IU	International Unit
LF	Limit of Flocculation
MD	Meningococcal Disease
MMWR	Morbidity and Mortality Weekly Report
N. meningitidis	*Neisseria meningitidis*
NDSS	Notifiable Disease Surveillance System
PCR	Polymerase Chain Reaction
PP	Per-protocol
PS	Polysaccharide

List of Abbreviations	
RCDC	Reverse Cumulative Distribution Curve
SAE	Serious Adverse Event
SBA	Serum Bactericidal Assay
SBA-BR	Serum Bactericidal Assay performed using Baby Rabbit complement
SN	Seronegative
Td	Tetanus and Diphtheria Toxoids Adsorbed for Adult Use
TetraMenD	Tetravalent (A, C, Y and W-135) Meningococcal Polysaccharide Diphtheria Toxoid Conjugate Vaccine (Menactra™)
Typhim Vi®	Typhoid Vi Polysaccharide Vaccine
URI	Upper Respiratory Infection
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization

1 Introduction

On September 22, 2004, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) will meet to review the new Biologic License Application (BLA) for Menactra™, submitted by Aventis Pasteur, Inc. Menactra™, Meningococcal (Groups A, C, Y and W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine, is a liquid, sterile solution of the group-specific polysaccharide antigens from *Neisseria meningitidis*, Group A, Group C, Group Y and Group W-135 conjugated to diphtheria toxoid protein. The vaccine contains no preservative and the 0.5 mL dose is administered intramuscularly. The proposed indication for Menactra™ is for active immunization against invasive meningococcal disease caused by serogroups A, C, Y, and W-135 in adolescents and adults aged 11 to 55.

Aventis Pasteur began research activities on meningococcal conjugate vaccines in 1994, by evaluating a bivalent vaccine. In 1997, an investigational new drug application (IND) for the quadrivalent conjugate product was opened and over the subsequent six years a full clinical development program involving children, adolescents and adults was executed. The Biologics License Application for Menactra™ was submitted to the Food and Drug Administration (FDA) in December 2003.

This briefing document provides information regarding the epidemiology of meningococcal disease, the basis for our understanding of the mechanism for immunologic protection against invasive meningococcal disease and the rationale supporting the clinical development program. Included are clinical data supporting the immunogenicity and safety of Menactra™ for the prevention of invasive meningococcal disease.

2 Meningococci and Meningococcal Disease

Meningococci

Neisseria meningitidis (meningococcus) is a Gram-negative aerobic diplococcus that is exclusively a human pathogen. Meningococci colonize the nasopharynx of 10 to 20% of healthy adults and are transmitted by respiratory secretions (1). Few carriers contract invasive disease, but predicting an individual person's risk is difficult.

The current classification system for identifying meningococci by serogroup is based on the immunochemistry of the polysaccharide capsule surrounding the bacterium (2). Of the 13 known serogroups, 5 (serogroups A, B, C, Y, and W-135) cause the majority of cases of meningococcal disease. Meningococci are further classified as serotypes and subtypes based on the outer membrane proteins (specifically PorB and PorA, respectively) that, with lipopolysaccharide (endotoxin), are the major surface antigens of the outer membrane (3).

Meningococcal disease

N. meningitidis causes both sporadic endemic and epidemic disease throughout the world. The common disease manifestations are meningococcemia (severe sepsis) and meningitis. Over

500,000 cases of meningococcal disease occur worldwide per year, resulting in approximately 135,000 deaths (4). Approximately 10% to 15% of survivors of meningococcal disease experience neurological sequelae, loss of limbs, mental retardation, hearing loss or paralysis.

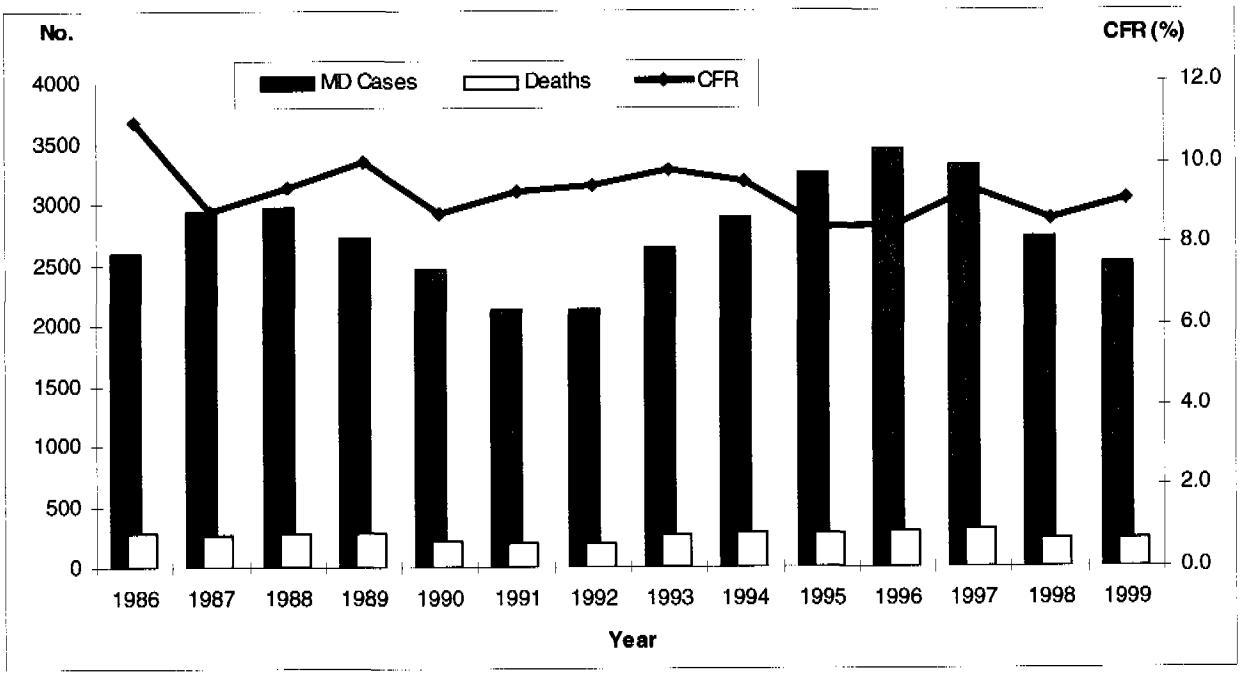
Invasive meningococcal disease may occur in exposed persons depending on the virulence of the particular isolate, host factors that affect innate mechanisms of immunity, and the presence or absence of protective antibodies. Disease onset is sudden and often occurs in otherwise healthy individuals. Meningococcemia is characterized by abrupt onset of fever and a petechial or purpuric rash, which may progress to purpura fulminans and is often associated with a rapid onset of hypotension, acute adrenal hemorrhage (the Waterhouse-Friderichsen syndrome) and multi-organ failure. Other syndromes associated with meningococcal infection are pneumonia, arthritis, otitis media, epiglottitis, and pericarditis. Meningitis is characterized by sudden onset of headache, fever and neck stiffness, sometimes with nausea, vomiting, photophobia, or altered mental status. Presentation in infants may have a slower onset; fever, poor feeding and lethargy are common symptoms.

Meningococcal disease may be difficult to diagnose because of the similarity of symptoms to those of other conditions. Diagnosis is achieved through conventional cultures of blood, cerebrospinal fluid, hemorrhagic skin lesions, or other infected sites. Techniques such as latex agglutination for the detection of meningococcal polysaccharide and polymerase chain reaction (PCR) analysis for the detection of meningococcal DNA (1) may also be used.

Pre-existing bactericidal antibody against *N. meningitidis* (humoral immunity) is probably the most important host factor in determining whether or not a person will become ill (1). Risk factors for invasive meningococcal disease include close contact with infected individuals, crowded conditions, cigarette smoke exposure, bar patronage, complement deficiencies, immune deficiencies, and asplenism. Certain groups of adolescents and young adults, particularly college freshmen living in dormitories, have been identified as having increased risk of contracting meningococcal disease. In one study, the relative risk of contracting meningococcal disease was 1.9 for all freshman students, 2.3 for all dormitory residents, and 5.1 for freshmen living in dormitories (5).

The case fatality rate (CFR) from meningococcal disease in the US has remained relatively stable, at around 8% to 10%, despite the availability of effective antibiotic treatment (Figure 1). The CFR in the US for meningococcal disease is similar to that of other developed countries.

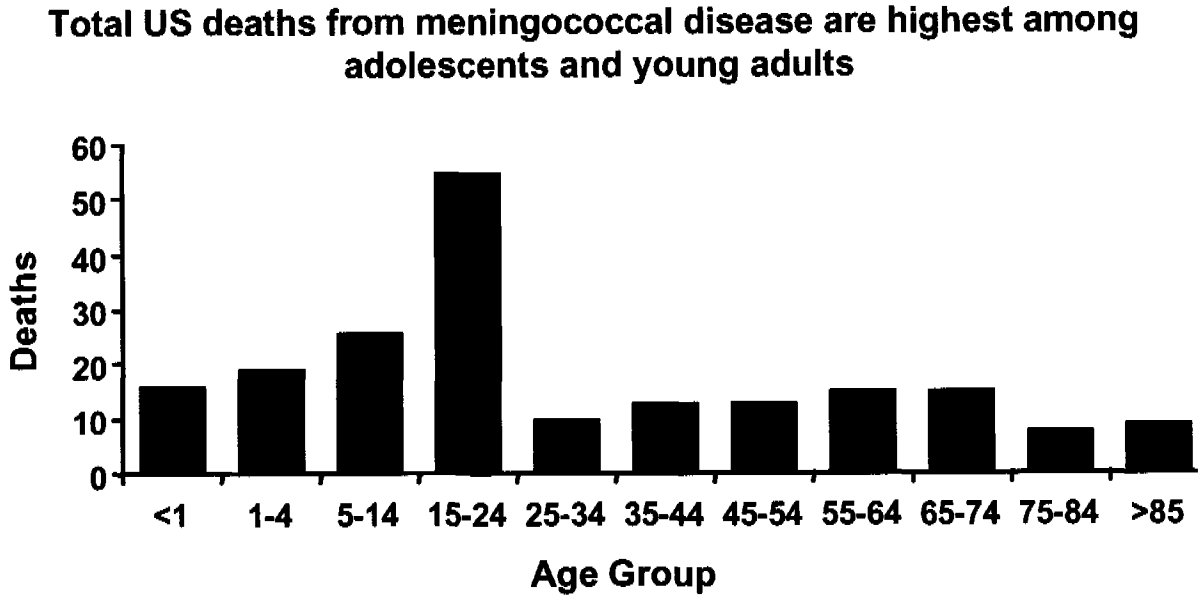
Figure 1: Deaths and Case Fatality Rates From Meningococcal Disease, US 1986-1999



Data compiled from CDC, Summary of notifiable diseases – United States. MMWR Weekly Reports 1986 to 1999
Deaths: Number of deaths based on ICD-9 code 036.0

Mortality varies by age, being lower in infants and young children and highest in adolescents and young adults. A higher proportion of fatalities occur in 15- to 24-year olds, as shown in Figure 2. This circumstance is due not only to the higher incidence of disease, but also to a higher CFR in this age group (6).

Figure 2: Distribution of Meningococcal Fatalities by Age Group, US 2001



Source: CDC. 2003. National Vital Statistics Reports. 52:30 (7).

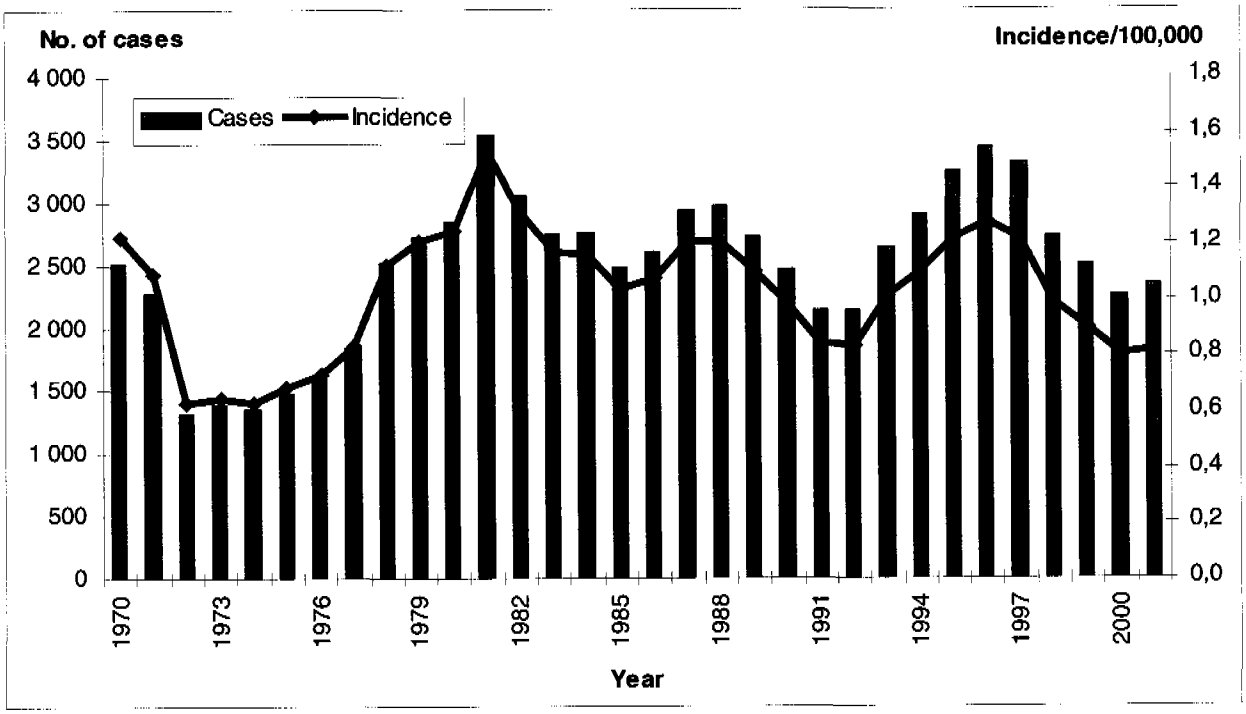
3 Epidemiology of Meningococcal Disease in the United States

The epidemiology of meningococcal disease in the US is dynamic resulting in changes in disease rates, in distribution of disease by age group and geographic location, and circulating strains.

Incidence of meningococcal disease

Based on CDC surveillance data, *N. meningitidis* causes an estimated 2,000 to 3,000 (0.8 to 1.3/100,000) cases of invasive meningococcal disease annually in the US (8). In general, both the number of cases and the incidence of meningococcal disease have shown a cyclical pattern since 1970 as illustrated in Figure 3. Peak incidence of disease occurs during the winter and early spring.

Figure 3: Meningococcal Disease. Cases and Incidence per 100,000 - US, 1970–2001



Source: Summary of notifiable diseases--United States, 2002 (9).

Rates are per 100,000 population and based on total mid-year population estimates from US Census Bureau

The rate of meningococcal disease is highest among infants less than 1 year of age, ranging from 10 to 16 per 100,000 and decreases to less than 1 per 100,000 during early childhood. A second peak incidence of disease is noted in adolescents and young adults, with a peak rate of 1.5 to 2.5 per 100,000, which spans the age range from 10 to 25 years. The incidence rate falls in adults above 25 years of age but rises in those over 65 years of age. Although the highest rate of meningococcal disease occurs in infants and young children, approximately 50% of all cases occur in adolescents and adults (9) (10). While the number of meningococcal disease outbreaks in the US has increased since 1990, only 3% of cases are associated with outbreaks (11).

Serogroup distribution

Surveillance data indicate that serogroups B, C, Y, and W-135 are the predominant strains circulating in the US. More recently, disease caused by serogroup Y has increased dramatically. As shown in Figure 4 between 1990 and 2003, disease caused by serogroups B and C have decreased from 83% to 58% overall, while serogroup Y disease has increased from 9% to 28%.

Figure 4: Changing Meningococcal Serogroup Distribution in the US

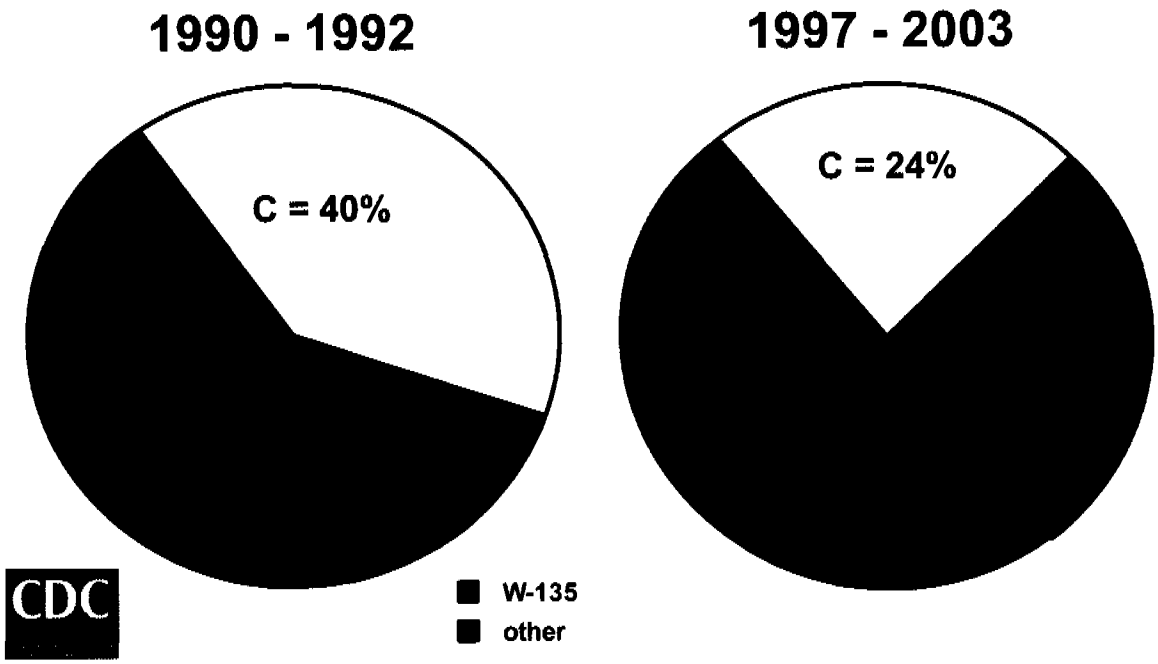


Figure 4 was based on ABCs data.

In the US, serogroup distribution differs somewhat from that of other regions of the world. Serogroups B and C predominate in developed countries and serogroup A remains the leading cause of meningococcal disease in developing countries, particularly in sub-Saharan Africa. More recently, serogroup W-135 disease has been associated with Hajj pilgrims and epidemics in sub-Saharan Africa.

Current status of vaccination for meningococcal disease in the United States

Meningococcal disease remains an important public health problem despite available treatments and vaccines. The sudden onset of the disease in healthy individuals together with a high case fatality rate and the possibility for developing permanent sequelae have been a cause of public alarm (1). Although the introduction of sulphonamides and penicillin led to a reduced rate of fatality among patients suffering from meningococcal disease, fatality rates have not been significantly reduced since the mid twentieth century (2). Presently, the greatest number of deaths from meningococcal disease occurs in adolescents and young adults (7).

The currently available quadrivalent meningococcal polysaccharide vaccine has been demonstrated to be efficacious and is recommended for use in high-risk groups and outbreak situations, but does not prime individuals for a booster dose when immunity declines. Experts and policymakers have indicated that the development of conjugate vaccines is desirable (8). Three meningococcal C-conjugate vaccines, with proven benefits over polysaccharide vaccines, are approved for use in the United Kingdom (UK) where serogroup C has been shown to be responsible for 32% of meningococcal disease. In the US, the vast majority of cases in 15- to 24-year olds (up to 80%) could be prevented with the use of the quadrivalent vaccine.

4 Basis of Protective Immunity and Vaccine Development

The central role of bactericidal antibody in protection

Evidence that complement-mediated bactericidal antibody provides protection against invasive meningococcal disease was observed in studies conducted at the Walter Reed Army Institute of Research (12) (13). Goldschneider et al. demonstrated that the age-specific incidence of meningococcal disease caused by groups A, B, and C meningococci inversely correlated with the age-specific prevalence of bactericidal antibody as illustrated in Figure 5 (14) (15). The peak incidence of meningococcal disease was highest in children less than 1 year of age who had little or no bactericidal antibody. As people age and acquire immunity, the incidence of meningococcal disease declines.

Figure 5: Age-Related Incidence of Disease and Prevalence of Serum Bactericidal Activity

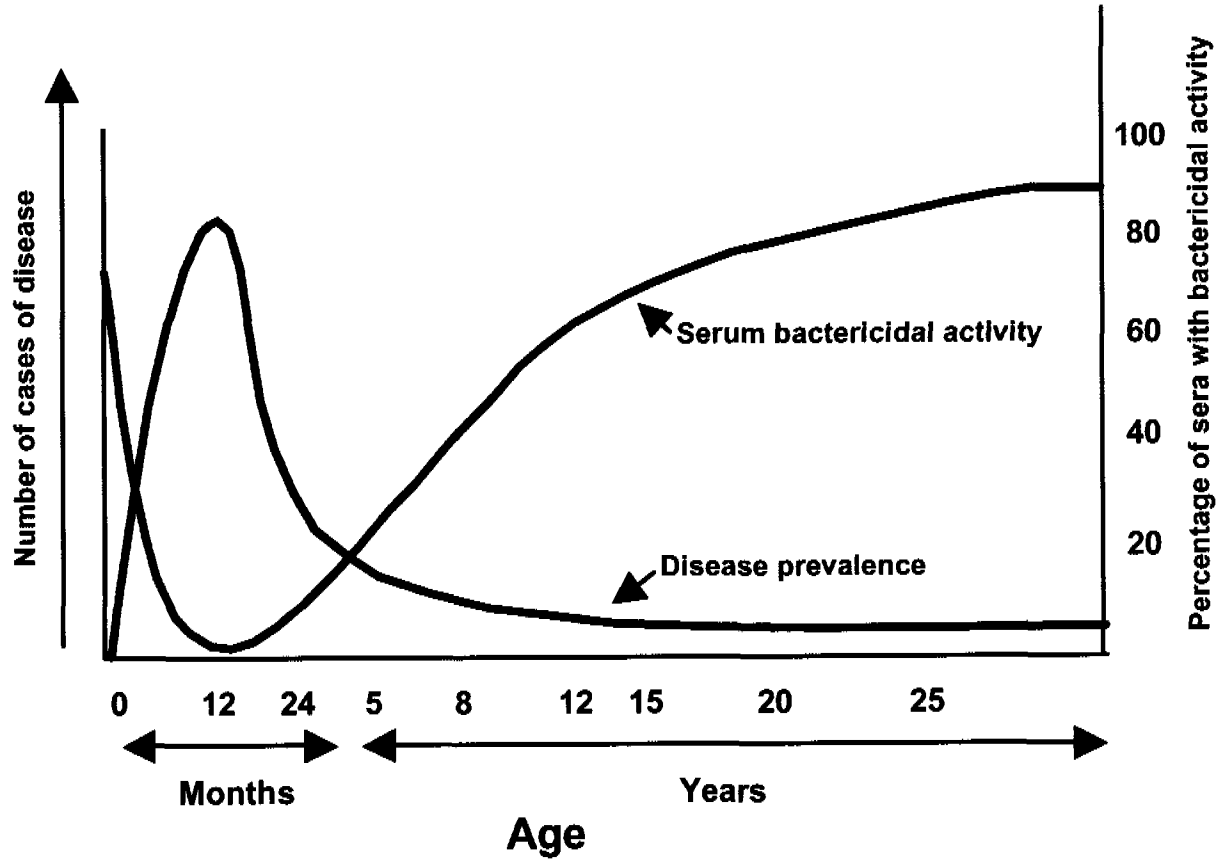


Figure from Pollard and Frasch (15) adapted from Goldschneider, Gotschlich and Artenstein (14).

Goldschneider et al. also showed that susceptibility to invasive meningococcal disease in US Army recruits correlated with the absence of bactericidal antibody against the meningococci

serogroup C isolate acquired during recruit training (12). Summarized in Table 1 are the results from this study, in which individuals with bactericidal antibody titers ≥ 1:4 at baseline had a serogroup C meningococcal disease attack rate of 0.3 per thousand versus 19.1 per thousand among those with a baseline bactericidal antibody titer < 1:4 (14). They concluded that bactericidal antibody titers ≥ 1:4 correlated strongly with protection from meningococcal disease.

Table 1: US Army Recruit Study - the Protective Effect of Bactericidal Antibody

Number of Recruits	Bactericidal Titer at Baseline	Number of Cases	Attack Rate/1000 (8 weeks)	Percent Protective Effect
12,073 (82%)	≥ 1:4	3	0.3	98.4%
2,668 (18%)	< 1:4	51	19.1	

Upon further analysis of underlying factors for protection, they also found that most of the serum bactericidal activity of recruits who did not develop invasive disease could be absorbed with the group specific capsular polysaccharide demonstrating that antibody directed against the serogroup C polysaccharide constituted the bulk of the bactericidal antibody (16).

In summary, the importance of bactericidal antibodies directed against capsular polysaccharide is evident from the following observations:

- The peak incidence of meningococcal disease is in children less than 1-year of age who have little or no bactericidal antibody and there is an age-related inverse relationship between disease prevalence and percentage of individuals with bactericidal antibody.
- Among military recruits, bactericidal antibody titers ≥ 1:4 correlated strongly with protection from serogroup C meningococcal disease.
- Serum bactericidal activity in sera of recruits who became colonized with the epidemic serogroup C strain and who did not develop invasive disease could be absorbed with the group specific capsular polysaccharide.

Efficacy of meningococcal polysaccharide vaccines

Controlled field trials to examine the efficacy of serogroup C meningococcal polysaccharide vaccines were carried out first among US Army recruits in 1968-71, and later in the Italian Army (17) as summarized in Table 2. These trials demonstrated that protective efficacy of the polysaccharide vaccines ranged between 88% to 91% (13) (18). As a result of these studies, routine immunization of all new recruits was adopted by the US military resulting in the elimination of group C epidemics in the military (19).

The efficacy of a group A polysaccharide vaccine was demonstrated in several controlled trials involving infants, children, and adults (20) (21) (22) (23) (24). The overall efficacy of the group A vaccine was 89% in adults.

Table 2: Efficacy of Meningococcal Polysaccharide Vaccines in Military Recruits

Source	Serogroup	Country	Efficacy
Makela et al.	A	Finland	89%
Artenestein et al.	C	United States	90%
Gold and Artenestein	C	United States	88%
Biselli et al.	C	Italy	91%

Source references (13) (18) (17) (25) (26).

Field efficacy studies have not been performed utilizing serogroup Y and W-135 polysaccharide vaccines; rather, the effectiveness of the groups Y and W-135 vaccines is based on their ability to induce similar levels of bactericidal antibody to those shown to be protective for serogroup A and C vaccines. The routine use of the quadrivalent vaccine in the US military has virtually eliminated the appearance of sporadic cases of invasive disease caused by groups Y and W-135 in the military.

Meningococcal polysaccharide vaccines have been used successfully throughout the world for many years to prevent invasive meningococcal disease and are used to protect against endemic disease in high-risk populations such as adolescents, military recruits, university students, and international travelers (1) (8). In addition to providing protection against invasive disease, meningococcal vaccines are highly effective in limiting the spread of disease during outbreaks.

Menomune® - A/C/Y/W-135, the quadrivalent polysaccharide meningococcal vaccine approved for use in the US, was found to be safe and immunogenic in a placebo-controlled study in 150 adults over 18 years of age in comparison to 25 placebo recipients. Seroconversion rates measured as a 4-fold rise in bactericidal titer were achieved in over 90% of subjects. Antibody persisted at titers above baseline for up to 55 months (27) (28).

Capsular polysaccharide vaccines such as Menomune® induce T-cell independent immune responses, which have several limitations, including the inability to induce immune memory (1). In recent years, protein-polysaccharide conjugate vaccines have been developed to overcome the inherent limitations of polysaccharide vaccines and have been successfully implemented in immunization programs.

Meningococcal serogroup C conjugate vaccines – United Kingdom experience

Recent experience in the UK with monovalent serogroup C conjugate vaccines has demonstrated the effectiveness of the meningococcal polysaccharide-conjugate vaccine approach in reducing both invasive disease rates and mortality rates. From 1992 to 1997, rates of serogroup C disease and associated mortality increased particularly in persons 10 to 19 years of age (29). Across all age groups, the estimated overall CFR for serogroup C disease was 12.5% in 1999, corresponding to at least 150 deaths per year. The rise in serogroup C disease provided the impetus for the UK Department of Health to focus on meningococcal disease prevention and the development of conjugate group C meningococcal vaccines.

Meningococcal C conjugate vaccines were introduced in the UK in November 1999. Those deemed to be at highest risk were targeted first for vaccination, beginning with 15- to 17-year olds followed by infants. Vaccine was offered to all other children younger than 18 years in a catch-up campaign that was rolled out over one year (29).

Since the introduction of meningococcal C conjugate vaccines in the UK, coverage has exceeded 80% in all targeted age groups. Comparing the period from 1999 to 2001, an overall reduction of 86.7% in the incidence of serogroup C invasive disease in the targeted age groups has been observed, with a concomitant reduction in deaths, from 67 to 5 (30). Maiden et al. described a 67% reduction in the prevalence of nasopharyngeal carriage of serogroup C meningococci in adolescents (from 0.45% before to 0.15% after the vaccination program) (31). Evidence for herd immunity in the unvaccinated population was described by Ramsey et al. (32). The attack rate for invasive meningococcal group C disease in the unvaccinated population was reduced by 67%. Follow-up data showed that overall vaccine effectiveness has remained above 90% after 1 year for the cohorts of children aged 3 to 4 and adolescents 11 to 16 years (33) as shown in Table 3.

Table 3: Overall Effectiveness of Meningococcal C Conjugate Vaccines in the UK

Age Group (years)	Overall Cases		Vaccine Effectiveness > 1 Year Post-Vaccination (95% CI)
	Total	Vaccinated	
3 to 4	64	5	93% (78, 98)
11 to 16	84	12	90% (77, 96)

Table 3 was based on the overall effectiveness following a single dose of meningococcal C - conjugate vaccine during follow-up case surveillance from 2000 to 2004 (33).

5 Menactra™ Clinical Development Program

5.1 Summary of the Clinical Program

The clinical program for Menactra™ began in July 1997 with the implementation of a phase 1 study (Study 603-01). In this study, Menactra™ was administered to adults in an escalating dose design that evaluated 1 µg, 4 µg, and 10 µg of conjugated polysaccharide per serogroup dose. Based on the clinical information collected from that study, the 4 µg conjugated polysaccharide dose was selected for further evaluation in adolescents and adults in the phase 2/3 program.

The phase 2 and phase 3 studies conducted in adolescents and adults included:

- Comparative studies with Menactra™ versus Menomune®, the US licensed control vaccine:
  - in adolescents, (Studies MTA02 and MTA04)
  - in adults, (Studies MTA09 and MTA14)
- Lot-consistency:
  - in adults (Study MTA14)
- Concomitant Use:
  - with Tetanus and Diphtheria Toxoids Adsorbed for Adult Use (Td) in adolescents (Study MTA12)
  - with the *Salmonella typhi* polysaccharide Vi vaccine (Typhim Vi®) in adults (Study MTA11)

Table 4 summarizes the clinical studies completed to support licensure and included in the BLA.

Table 4: Phase 2 and Phase 3 Clinical Studies in the Menactra™ Program included in the Biologics License Application

Study Number	Type of Study	Number of Injections/ Vaccination Schedule	Age of Population	Enrolled to receive Menactra™	Enrolled to receive Menomune®
MTA02	Safety & Immunogenicity Comparison of Menactra™ versus Menomune®	1 vaccination (Day 0)	11 to 18 yrs	**440**	**441**
MTA04	Safety Comparison of Menactra™ versus Menomune®	1 vaccination (Day 0)	11 to 18 yrs	**2270**	**972**
MTA09	Safety & Immunogenicity Comparison of Menactra™ versus Menomune®	1 vaccination (Day 0)	18 to 55 yrs	**1384**	**1170**
MTA14	Consistency of Immunogenicity of Menactra™ and Safety Comparison of Menactra™ versus Menomune®	1 vaccination (Day 0)	18 to 55 yrs	**1582**	**458**
MTA12	Safety & Immunogenicity of Concomitant Administration of Menactra™ with Tetanus Diphtheria Combined Vaccine	2 vaccinations Group A: Td + Menactra™ (Day 0) and Placebo (Day 28) Group B: Td + Placebo (Day 0) and Menactra™ (Day 28)	11 to 17 yrs	**1021**	--
MTA11	Safety & Immunogenicity of Concomitant Administration of Menactra™ with Typhim Vi® Vaccine	2 vaccinations Group A: Typhim Vi® + Menactra™ (Day 0) and Placebo (Day 28) Group B: Typhim Vi® + Placebo (Day 0) and Menactra™ (Day 28)	18 to 55 yrs	**945**	--
Total				**7642**	**3041**

Table 5 summarizes additional trials conducted in children, adolescents and adults, as part of the comprehensive clinical development program for Menactra™. These data are not included in the original BLA for the 11- to 55-year olds. BLA supplements for additional age indications are planned.

Table 5: Phase 2 and Phase 3 Clinical Studies in the Menactra™ Program not part of the original BLA

Study Number	Type of Study	Number of Injections/ Vaccination Schedule	Age of Population	Enrolled to receive Menactra™	Enrolled to receive Menomune®
603-02	Safety & Immunogenicity Comparison of Menactra™ versus Menomune®	1 vaccination (Day 0)	2 to 10 yrs	**696**	**702**
MTA08	Safety Comparison of Menactra™ versus Menomune®	1 vaccination (Day 0)	2 to 10 yrs	**1712**	**1519**
MTA17	Low dose polysaccharide challenge administered 2 years after Menactra™ in a subset of participants from Study 603-02	1 vaccination (Day 0)	3 to 5 yrs	--	**171**
MTA19	Menactra™ booster administered 3 years after primary dose in a subset of participants from MTA02	1 vaccination (Day 0)	13 to 21 yrs	**241**	--
Total				**2649**	**2392**

5.2 Immunogenicity - Assessment

5.2.1 Serology Methods

Regulatory Perspective

In 1999, the Vaccines and Related Biological Products Advisory Committee met to consider questions regarding the use of immunological correlates of protection to be used in support of licensure of meningococcal conjugate vaccines. The Committee agreed on the following:

- Immunological correlates to predict efficacy of meningococcal vaccines can be used for individuals for whom the current polysaccharide is licensed.
- The presence of bactericidal antibodies may be used as a measure of functional antibody and therefore presumed protective activity.
- Total antibody quantitated by Enzyme Linked Immunosorbent Assay (ELISA) techniques could not be used as a serological correlate for functional bactericidal antibody.

The original studies that established bactericidal antibody as an acceptable serological surrogate and defined a correlate of protection against meningococcal serogroup C disease (SBA titer of ≥ 1:4) used human sera as the source of complement in the Serum Bactericidal Assay (SBA) assay (14) (16). In practice, the use of human complement poses problems of consistency associated with the level of characterization, quality, and quantity of a reliable source. The approval of the currently licensed meningococcal polysaccharide vaccine Menomune® was based on antibody responses measured in the bactericidal assay with baby rabbit sera as the exogenous source of complement as recommended by both the World Health Organization (WHO) (34) (35) and the US FDA. A standardized SBA using baby rabbit complement was established through a multilaboratory study conducted by the Centers for Disease Control and Prevention (CDC), Atlanta, GA, in which Aventis Pasteur was a participant (38).

Standardization of the SBA Assay and Definition of a Correlate of Protection

In 1999 and 2000, the WHO convened a series of meetings to review laboratory assays for the analysis of human sera for meningococcal antibodies. Several recommendations emerged regarding the serum bactericidal assay including adoption of the CDC standardized SBA using baby rabbit complement as the optimal methodology (39). The Committee recommended that a correlation be determined relative to using human complement in the assay for reference. In order to determine a threshold titer for baby rabbit complement-based assays that correlates with seroprotection, three laboratories with experience performing the SBA agreed to analyze a set of data from sera that had been tested in both assays. Following this analysis, the expert panel agreed to a number of recommendations for use of the SBA in the development of serogroup C conjugate vaccines (40):

- SBA titers < 1:8 using baby rabbit complement correlate with a < 1:4 using human complement
- SBA titers ≥ 1:128 using baby rabbit complement correlate with the established bactericidal protective response of ≥ 1:4 obtained when using human complement in the assay
- SBA titers in the equivocal zone (1:8, 1:16, 1:32, and 1:64) should be reassessed in the SBA using human complement

More recently the monovalent serogroup C conjugate vaccines have been shown to be efficacious in the United Kingdom by nearly eliminating serogroup C disease as summarized above (Section 4) and in Table 3. Antibody responses were assessed using the SBA assay. The demonstrated efficacy experience in the UK with the monovalent C conjugate vaccines support a serological correlate of protection of 1:8 in the SBA using baby rabbit complement (36) (37).

The Aventis Pasteur SBA

The Aventis Pasteur SBA conforms to requirements prescribed by the WHO and CBER guidelines for measuring *N. meningitidis* bactericidal antibody and uses the CDC standardized assay (38).

The AvP assay correlated well in the CDC multilaboratory comparison study. The AvP SBA continues to utilize the same reference standard that was one of the Quality Control serum samples used in the multilaboratory study (38) (39) (40).

5.2.2 Immunogenicity Parameters

Per-Protocol Population

All analyses were performed on the per-protocol population. The per-protocol (PP) population for immunogenicity was defined as including all participants meeting the following criteria:

1. The participant received the assigned vaccine according to the randomization.
2. On the day of vaccination (Day 0), the participant was at least 11 years of age but not yet 56 years of age (i.e., met age criteria for inclusion by individual study protocol).
3. All blood draws were taken within the visit window on Day 0 and all other days specified in each protocol.

5.2.3 Immunogenicity Objectives and Statistical Hypotheses Tested

For the six clinical studies submitted in the eBLA, evaluation of immunogenicity was either a primary (MTA02 and MTA09) or co-primary objective (MTA11 and MTA12). Table 6 provides the immunogenicity hypotheses for each of these clinical studies.

Table 6: Non-inferiority Hypotheses Testing in the Comparative and Concomitant Studies for Immunogenicity

Study	Objective	Hypothesis tested
MTA02	Primary	Upper limit of the one-sided 95% confidence interval of $p_{\text{Menomune}}® - p_{\text{Menactra}}™ < 0.10$ where p represents the proportion of participants with an SBA-BR titer ≥ 4-fold rise from baseline.
MTA09	Primary	Upper limit of the one-sided 95% confidence interval of $p_{\text{Menomune}}® - p_{\text{Menactra}}™ < 0.10$ where p represents the proportion of participants with an SBA-BR titer ≥ 4-fold rise from baseline.
MTA09	Secondary	Upper limit of the two-sided 95% CI of $\tau_{Menomune}® - \tau_{Menactra}™ < \log2\ (2)$, where $\tau_{Menomune}®$ and $\tau_{Menactra}™$ are the estimated effects in the groups receiving Menomune® and Menactra™, respectively. Twenty-eight days post-vaccination, the SBA-BR GMT of each of the serogroups A, C, Y and W-135 in the Menactra™ group is non-inferior to the GMT of the same serogroup in the Menomune® group, using baseline titers as a covariate.
MTA11	Primary	Upper limit of the two-sided 95% CI of the difference $P_{\text{Vi + placebo}} - P_{\text{Vi + Menactra}}™ < 0.1$, where $P_{\text{Vi + placebo}}$ and $P_{\text{Vi + Menactra}}™$ are the proportions of participants who achieve > 1 µg/mL Typhoid Vi antibody from the group receiving Typhim Vi® + placebo and the group receiving Typhim Vi® + Menactra™, respectively.
MTA11	Primary	Upper limit of the two-sided 95% CI of $P_{\text{Menactra}}™ - P_{\text{Vi + Menactra}}™ < 0.1$, where $P_{\text{Menactra}}™$ and $P_{\text{Vi + Menactra}}™$ are the proportions of participants with at least a 4-fold rise in antibody from the group receiving Typhim Vi® + placebo followed by Menactra™ and the group receiving Typhim Vi® + Menactra™ concomitantly, respectively, for each serogroup A, C, Y, and W-135
MTA12	Primary	Upper limit of the two-sided 95% confidence interval of $P_{\text{Td + Placebo}} - P_{\text{Td + Menactra}}™ < 0.1$, where $P_{\text{Td + Placebo}}$ and $P_{\text{Td + Menactra}}™$ are the proportions of participants with acceptable antibody titers in the group receiving Td with placebo and the group receiving Menactra™ concomitantly with Td, respectively, for each of the diphtheria and tetanus titers. Twenty-eight days post-vaccination, the proportion of participants who have an acceptable booster response to Td vaccine in the group receiving Menactra™ concomitantly with Td is non-inferior to that proportion in the group receiving Td with placebo. The acceptable booster response to Td vaccine at Day 28 following vaccination is defined as at least a 4-fold rise in baseline titer, given a diphtheria pre-titer ≤ 2.56 IU/mL and a tetanus pre-titer ≤ 2.7 IU/mL or a 2-fold rise given a diphtheria pre-titer > 2.56 IU/mL and a tetanus pre-titer > 2.7 IU/mL
MTA12	Primary	Upper two-sided 95% confidence limit of $P_{\text{Menactra}}™ - P_{\text{Td+Menactra}}™ < 0.1$, where $P_{\text{Menactra}}™$ is the proportion of participants with at least a 4-fold rise in antibody titer in the group receiving Td followed by Menactra™, and $P_{\text{Td+Menactra}}™$ is the proportion of participants with at least a 4-fold rise in antibody titer in the group receiving Menactra™ concomitantly with Td

Non-inferiority was demonstrated for a particular study endpoint when the upper limit of the 95% CI for the difference (for seroprotection and 4-fold rise) or ratio (for GMTs) between Menactra™

and a comparator was below the specified clinical limits [one-sided equivalence test; alpha = 0.025 (for two sided 95% CI), alpha = 0.05 (for one sided 95% CI)].

The primary analysis was supported by other analyses including:

- **Seroconversion**: comparison of SBA seroconversion rates (defined as proportion of participants with SBA titers <1:8 on Day 0 who reached ≥ 1:32 on Day 28)
- **Geometric Mean Titer**: comparison of geometric mean SBA titers (GMTs)
- **Reverse Cumulative Distribution Curves**: distribution of pre and post SBA antibody titers by constructing reverse cumulative distribution curves (RCDCs)

Menactra™ Versus Menomune® Comparisons

To establish the efficacy of Menactra™ , the clinical trials were designed to show that the immune response to Menactra™ is non-inferior to the immune response induced by Menomune®. The pivotal immunogenicity studies were MTA09 (adults) and MTA02 (adolescents). In both studies, non-inferiority between Menactra™ conjugate vaccine and Menomune® polysaccharide vaccine was measured by the percentage of participants with a 4-fold rise in SBA titer. The 4-fold rise in antibody titer was chosen as the primary serologic endpoint for non-inferiority for the following reasons:

- 4-fold rise in bactericidal antibody titer was the primary immunogenicity criterion for the approval of Menomune®
- 4-fold rise in bactericidal antibody titer is the WHO recommended method of evaluation for unconjugated meningococcal vaccines (34) (35)
- 4-fold increase in titer from baseline in the SBA is considered a significant immunological response and therefore provides a level of assurance that the immune response to Menactra™ is non-inferior to the licensed comparator Menomune®

Concomitant Use Studies

In each of these trials, the levels of antibody against *N. meningitidis* serogroups A, C, Y, and W-135 were assessed at baseline (Day 0) prior to vaccination, and at 28 days after vaccination.

Two concomitant use studies evaluated administration of:

- Typhim Vi® vaccine in healthy adults (MTA11)
- Td in adolescents (MTA12)

For these two trials, antibody levels for Menactra™ were evaluated according to the assigned treatment group in a non-inferiority comparison.

5.3 Immunogenicity – Results

5.3.1 Comparative Studies

5.3.1.1 MTA09 (Adults)

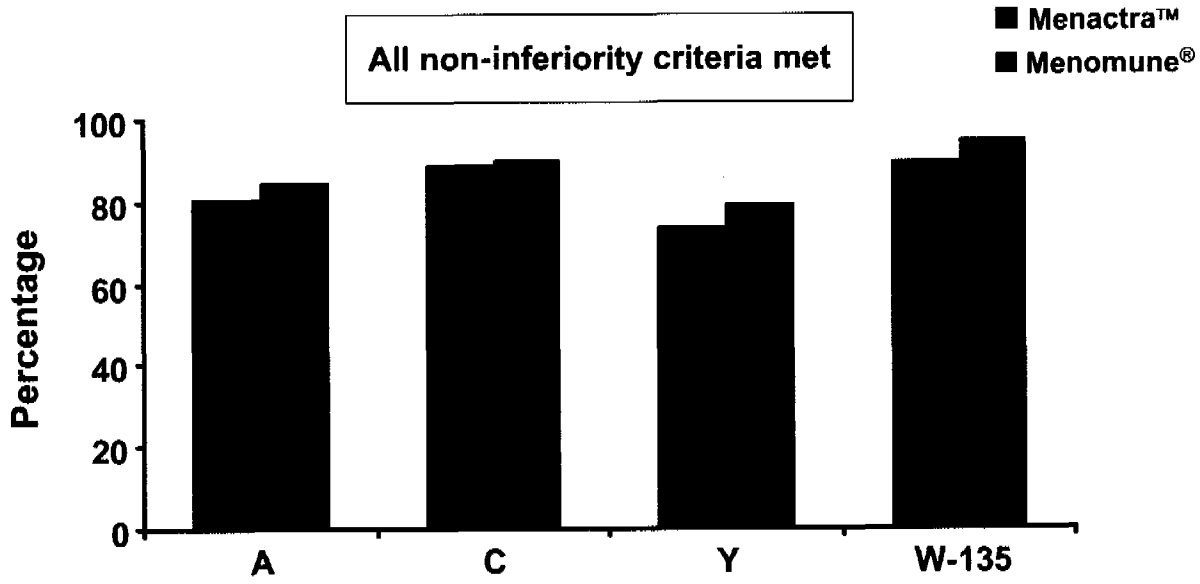
Study MTA09 is a phase 3, modified double-blind, comparative safety and immunogenicity study in healthy 18- to 55-year olds in the US. The primary objective of this study was to describe and compare the antibody response after one dose of either Menactra™ or Menomune®.

There were a total of 2554 participants enrolled in this study, where 1384 received Menactra™ and 1170 received Menomune®, based on a prescribed randomization. Participants were evenly distributed by age, sex and race between the two study groups. Sixty two percent of participants were female with the median age of all participants being 24 years. In the Menactra™ group 1280 (92.5%) participants met the criteria for inclusion in the per-protocol population compared to 1098 (93.8%) for the Menomune® group.

Four-Fold Rise in SBA Titer

Twenty-eight days after receiving Menactra™ , the majority of participants experienced a ≥ 4-fold rise in the SBA antibody titer for each of the serogroups contained in the vaccine. The percentages of Menactra™ recipients achieving a 4-fold rise in antibody titer to all four serogroups were comparable to those recipients who received Menomune® (Figure 6).

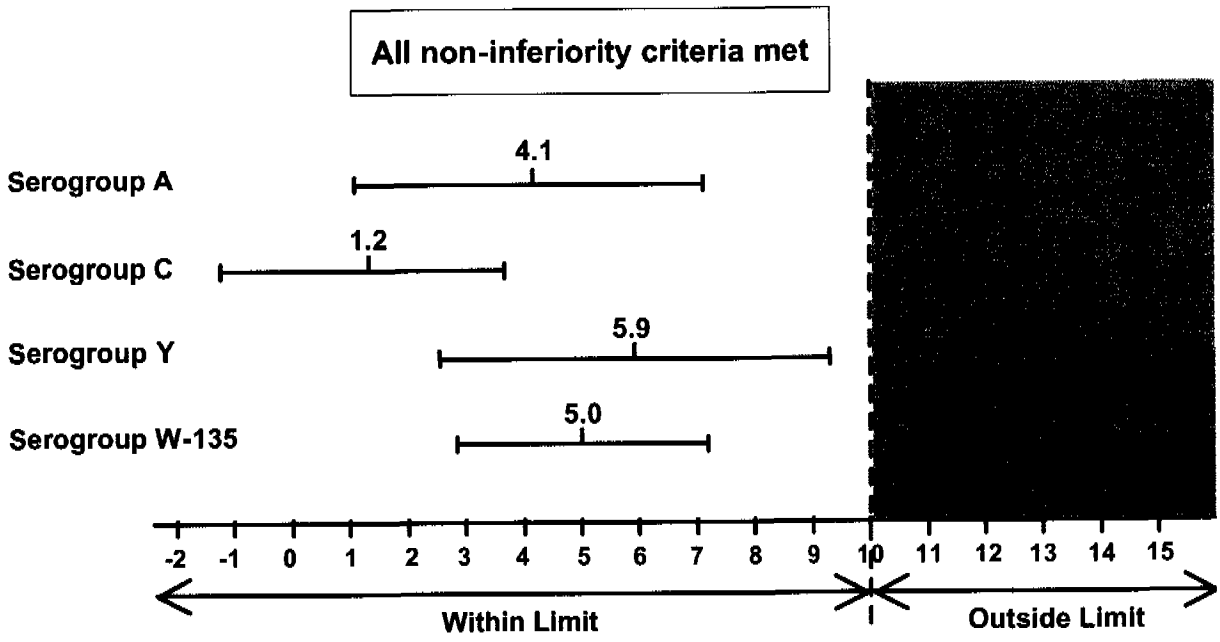
Figure 6: MTA09 4-Fold Rise in SBA Titer by Serogroup



Menactra™	1030 of 1280 80.5%	1133 of 1280 88.5%	941 of 1280 73.5%	1144 of 1280 89.4%
Menomune®	929 of 1098 84.6%	985 of 1098 89.7%	872 of 1098 79.4%	1036 of 1098 94.4%

The primary objective was met. That is, the proportion of participants with a ≥ 4-fold rise in SBA-BR titer for *N. meningitidis* serogroups A, C, Y, and W-135 in Menactra™ was non-inferior to the corresponding proportion in the Menomune® group (Figure 7).

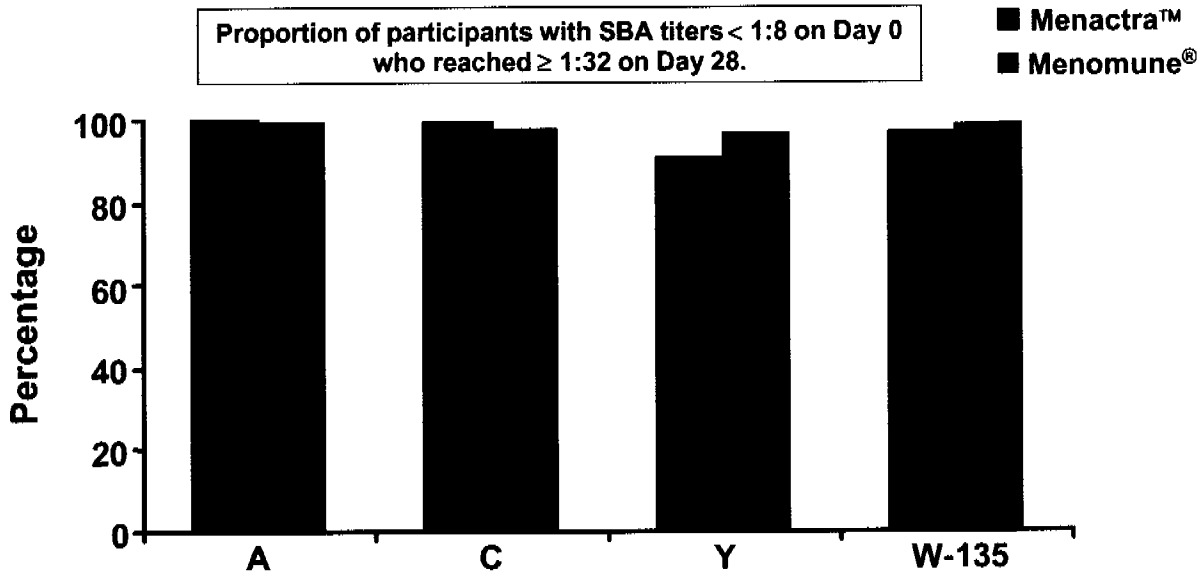
Figure 7: MTA09 Non-Inferiority Testing of the 4-Fold Rise in SBA Titer



Seroconversion

Seroconversion is defined as the proportion of participants who achieved a ≥ 4-fold rise in antibody titer when their pre-vaccination titer for any serogroup was < 1:8. A titer < 1:8 as measured by the SBA is considered to represent an undetectable level of circulating antibody. When participants were evaluated using this criterion, the seroconversion rates were greater than 90% for each of the four serogroups following vaccination with one dose of either Menactra™ or Menomune® (Figure 8).

Figure 8: MTA09 SBA Seroconversion Rates by Serogroup

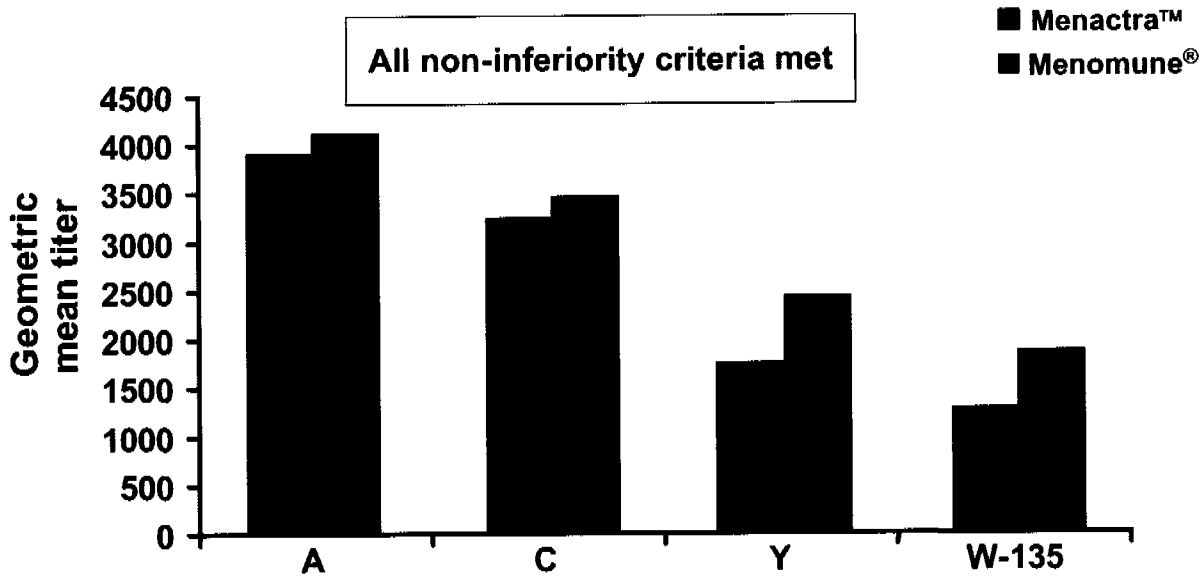


Menactra™	156 of 156 100%	343 of 345 99.4%	253 of 279 90.7%	360 of 373 96.5%
Menomune®	143 of 144 99.3%	297 of 304 97.7%	221 of 228 96.9%	325 of 328 99.1%

GMTs

The SBA geometric mean titers show that both vaccines elicit a bactericidal response significantly higher than that deemed predictive of protection. The GMTs were comparable between the Menactra™ and Menomune® groups (Figure 9).

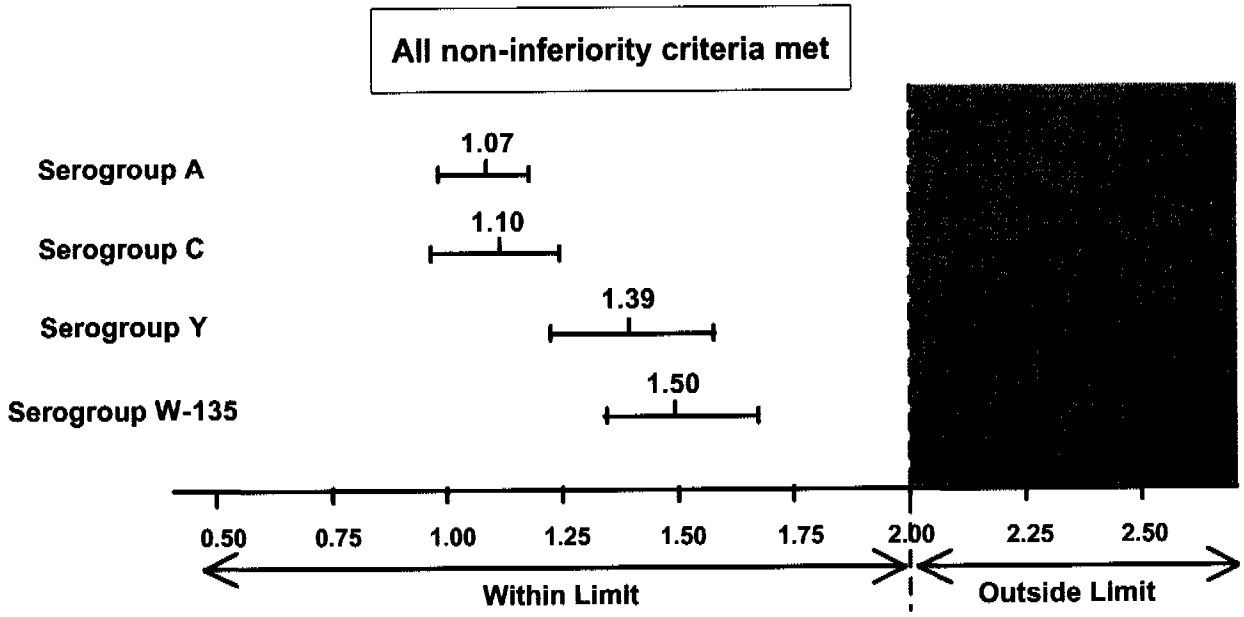
Figure 9: MTA09 SBA Geometric Mean Titers by Serogroup



Menactra™	3897	3231	1750	1271
Menomune®	4114	3469	2449	1871

The ratios of the GMTs in the Menactra™ group at Day 28 to the corresponding GMTs in the Menomune® group, adjusted for any disparities at baseline were calculated for *N. meningitidis* serogroups A, C, Y, and W-135. Based on these results, Menactra™ is non-inferior to Menomune® by the measured SBA GMT at Day 28 (Figure 10).

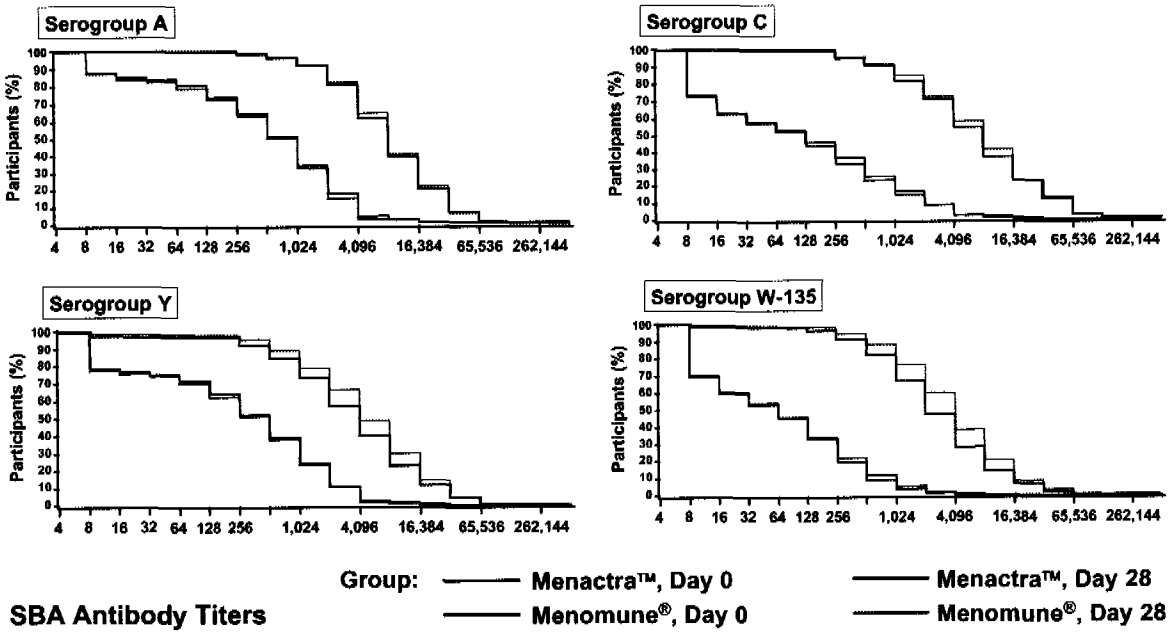
Figure 10: MTA09 Non-Inferiority Testing of the SBA GMTs



RCDCs

The post-vaccination reverse cumulative distribution curves demonstrate that, overall, more than 98% of participants achieved antibody levels that are predictive of protection for each of the four serogroups for either Menactra™ or Menomune®. The profile of the distribution of titers for each serogroup shows a significant increase following one dose of Menactra™ (Figure 11). The distribution of titers is comparable (overlapping) between Menactra™ and Menomune® groups.

Figure 11: MTA09 SBA Titer Reverse Cumulative Distribution Curves



Together, these data demonstrate that Menactra™ is highly immunogenic in the adult population studied. When these data are used to test the primary immunogenicity hypothesis, Menactra™ is non-inferior to the licensed vaccine Menomune®. In addition, the SBA GMTs are similar for each of the four serogroups for both vaccines, and the titers achieved are predictive of protection.

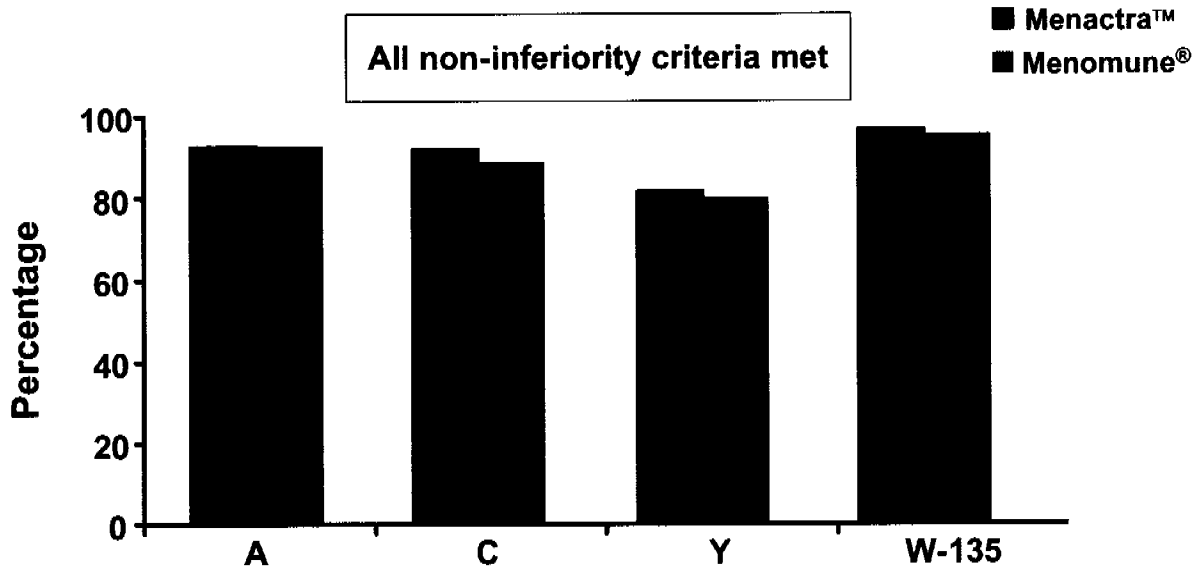
5.3.1.2 MTA02 (Adolescents)

Study MTA02 is a phase 2, comparative safety and immunogenicity study in healthy 11- to 18-year olds in the US. There were a total of 881 participants enrolled in this study. A total of 440 received Menactra™ and 441 received Menomune® and 98.9% of the subjects completed the study. Subjects were evenly distributed by age, sex and race between the two study groups. Fifty five percent of participants were male with a median age of all participants being 14 years. In the Menactra™ group 425 (96.6%) study participants met the criteria for inclusion in the per-protocol population compared with 423 (95.9%) for the Menomune® group.

Four-Fold Rise in SBA Titer

Twenty-eight days after receiving the study vaccination, Menactra™, the majority of participants experienced a ≥ 4-fold rise in the SBA antibody titer for each of the serogroups contained in the vaccine. The percentages of Menactra™ recipients achieving a 4-fold rise in antibody titer to all four serogroups were comparable to those recipients who received Menomune® (Figure 12).

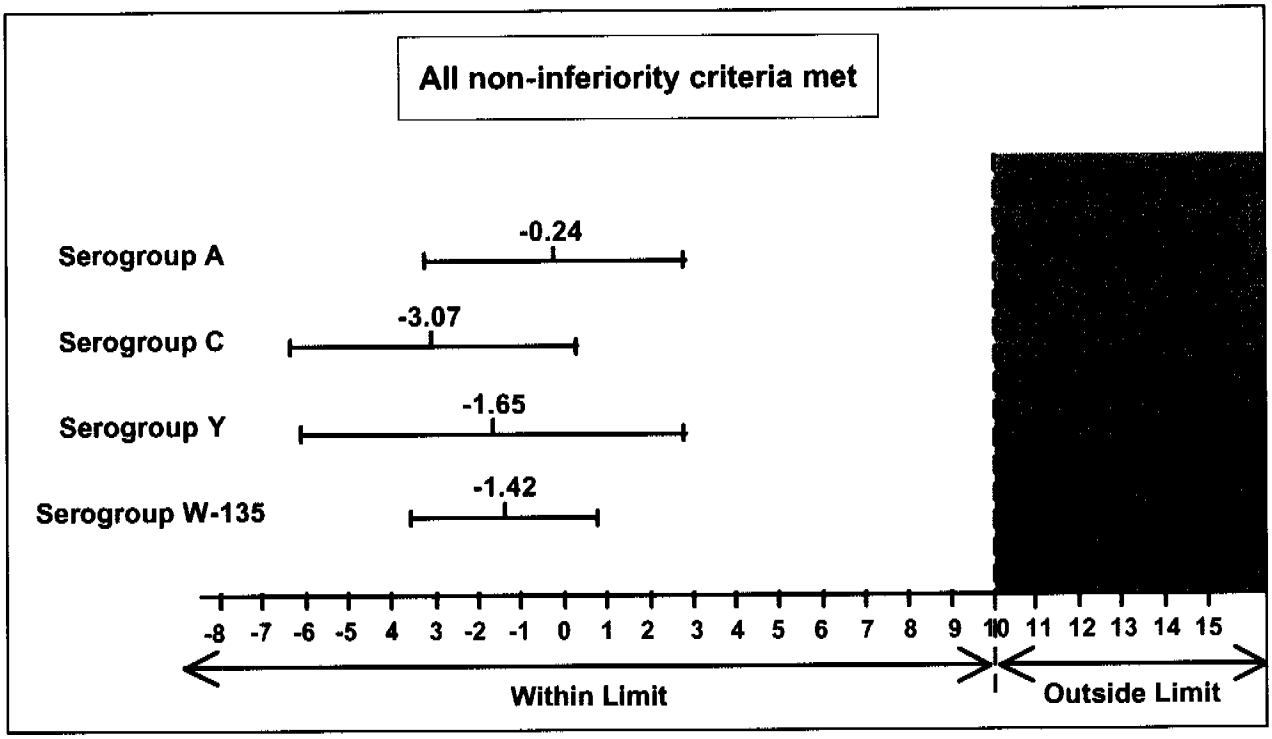
Figure 12: MTA02 4-Fold Rise in SBA Titer by Serogroup



Menactra™	392 of 423 92.7%	388 of 423 91.7%	346 of 423 81.8%	409 of 423 96.7%
Menomune®	391 of 423 92.4%	375 of 423 88.7%	339 of 423 80.1%	403 of 423 95.3%

The primary objective was successfully met. That is, Menactra™ is considered non-inferior to Menomune® by the proportion of participants with a ≥ 4-fold rise in SBA titer for *N. meningitidis* serogroups A, C, Y, and W-135 (Figure 13).

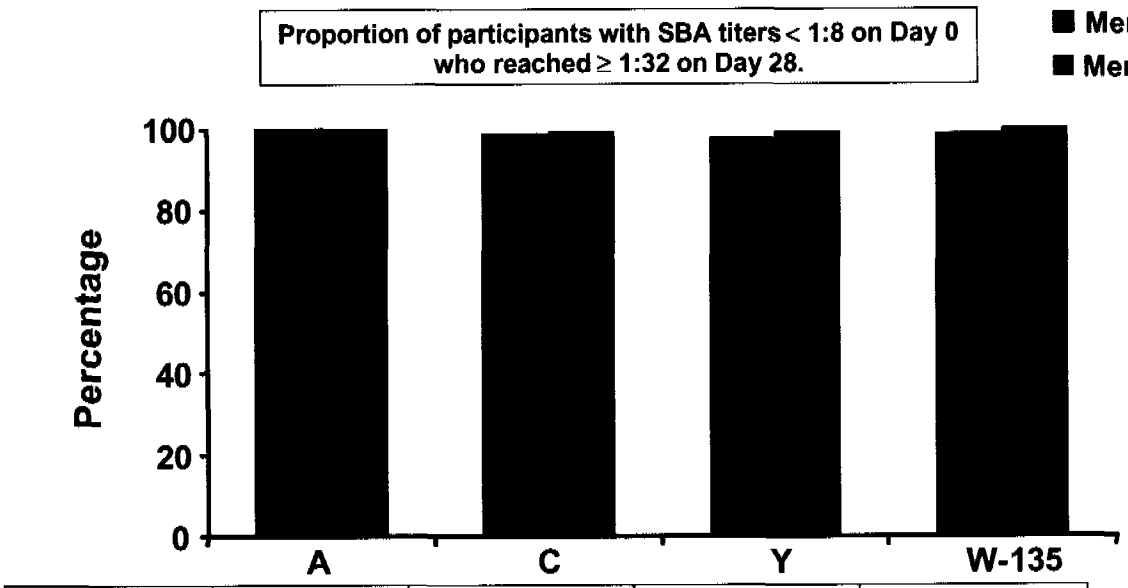
Figure 13: MTA02 Non-Inferiority Testing of the 4-Fold Rise in SBA Titer



Seroconversion

Seroconversion is defined as the proportion of participants who achieved a ≥ 4-fold rise in antibody titer when their pre-vaccination titer for any serogroup was < 1:8. A titer < 1:8 by the SBA is considered to represent an undetectable level of circulating antibody. When participants were evaluated using this criterion, the seroconversion rates were greater than 98% for all four serogroups following vaccination with one dose of either Menactra™ or Menomune® (Figure 14).

Figure 14: MTA02 SBA Seroconversion Rates by Serogroup

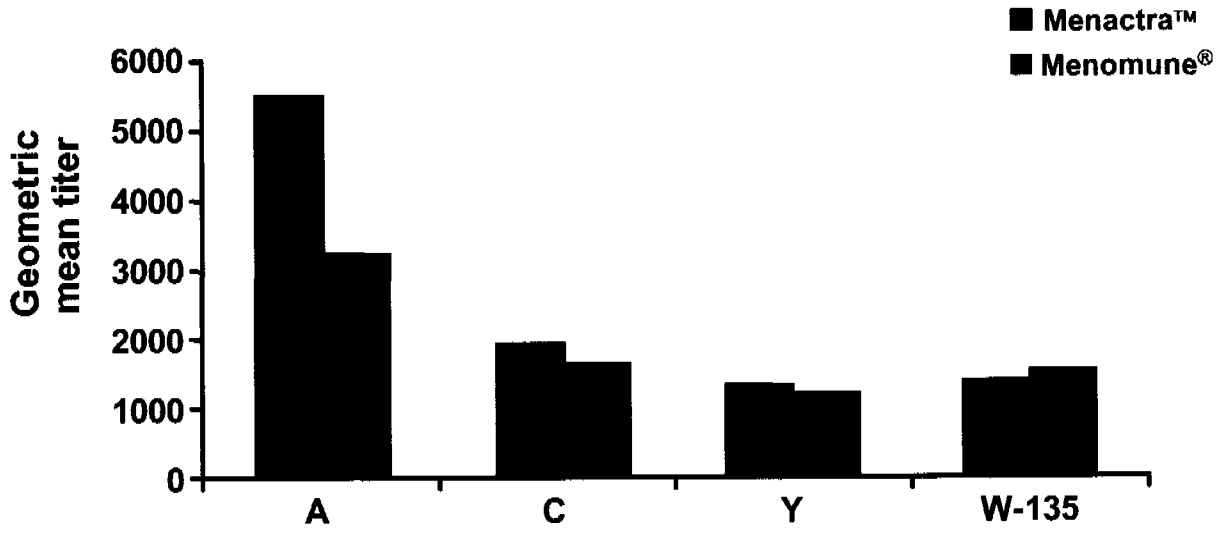


Menactra™	81 of 81 100%	153 of 155 98.7%	60 of 61 98.4%	161 of 164 98.2%
Menomune®	93 of 93 100%	151of 152 99.3%	47 of 47 100%	138 of 139 99.3%

GMTs

The post-vaccination SBA GMT levels for serogroups C, Y, and W-135, are similar in each treatment group, whereas for serogroup A, the response was higher in the Menactra™ group (Figure 15).

Figure 15: MTA02 SBA Geometric Mean Titers by Serogroup

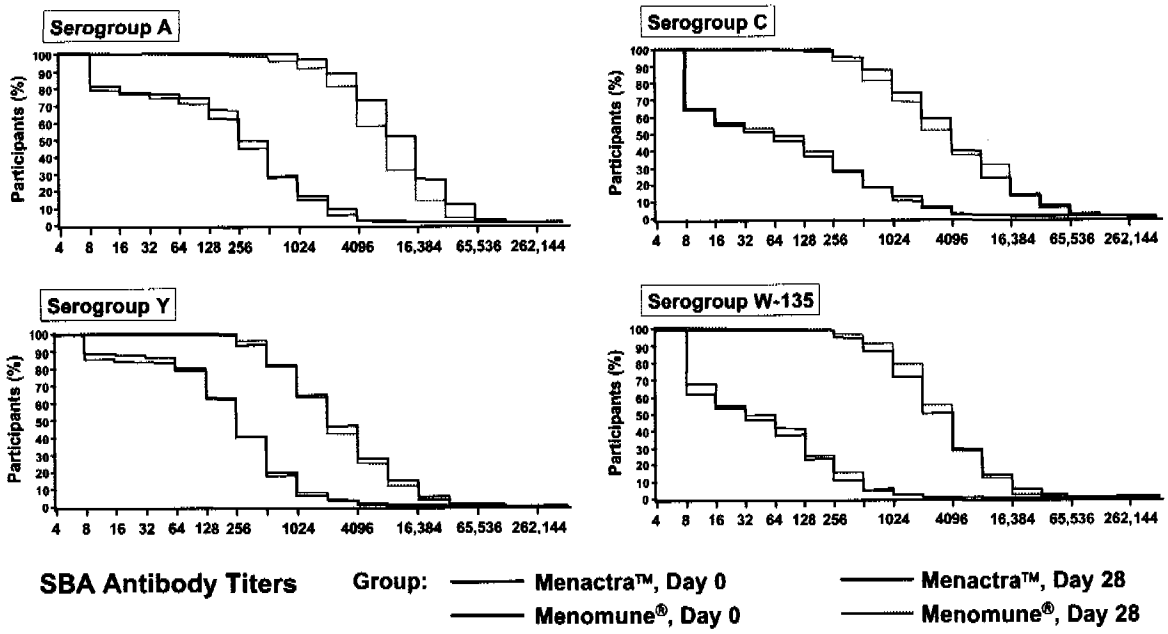


Menactra™	5483	1924	1322	1407
Menomune®	3246	1639	1228	1545

RCDCs

The post-vaccination reverse cumulative distribution curves demonstrate that, overall, more than 94% of participants achieved antibody levels that are predictive of protection for each of the four serogroups for either Menactra™ or Menomune®. The profile of the distribution of titers for each serogroup shows a significant increase following one dose of Menactra™ (Figure 16). The distribution of titers is comparable (overlapping) between Menactra™ and Menomune® groups.

Figure 16: MTA02 SBA Titer Reverse Cumulative Distribution Curves



Together, these data demonstrate that Menactra™ is highly immunogenic in the adolescent population studied. When these data are used to test the primary hypothesis, Menactra™ is non-inferior to the licensed vaccine Menomune®. In addition, the SBA GMTs are similar for each of the four serogroups for both vaccines and titers achieved are predictive of protection.

5.3.1.3 MTA19 (Three Year Follow-Up of Adolescents included in Study MTA02)

Study MTA19 is a 3 year follow up immunogenicity study in a subset of participants from Study MTA02. Study MTA19 was not included in the original BLA submission and as such has not been reviewed by CBER. Participants were followed for three years to determine the duration of the SBA response to a single dose of Menactra™. Study MTA19 design included three groups:

1) MTA02 participants vaccinated with Menactra™ 3 years earlier that were revaccinated with a booster dose of Menactra™ (N=76). Sera were collected pre, day 8 and day 28 post booster dose of Menactra™.

2) MTA02 participants vaccinated with Menomune® 3 years earlier that were revaccinated with a booster dose of Menactra™ (N=77). Sera were collected pre, day 8 and day 28 post booster dose of Menactra™ .

3) Naïve (non vaccinated) age matched participants who received a dose of Menactra™ (N=88). Sera were collected pre, day 8 and day 28 post primary dose of Menactra™ .

This subset of participants in the 3 year follow up study was representative of those in the MTA02 study based on a comparison of the SBA GMTs. Sixty percent of participants were male with a median age of all participants being 17 years. The median time since the primary dose of Menactra™ or Menomune® was 3.0 years.

Sera collected at the pre booster visit were analyzed for duration of an SBA titer 3 years after a primary vaccination. SBA GMTs for all four serogroups remained significantly higher than baseline titers 3 years after the initial immunization (Figure 17). The duration of the response to one dose of Menactra™ was greater than that seen 3 years after 1 dose of Menomune®.

Figure 17: MTA19 SBA GMTs Three Years Post-Vaccination

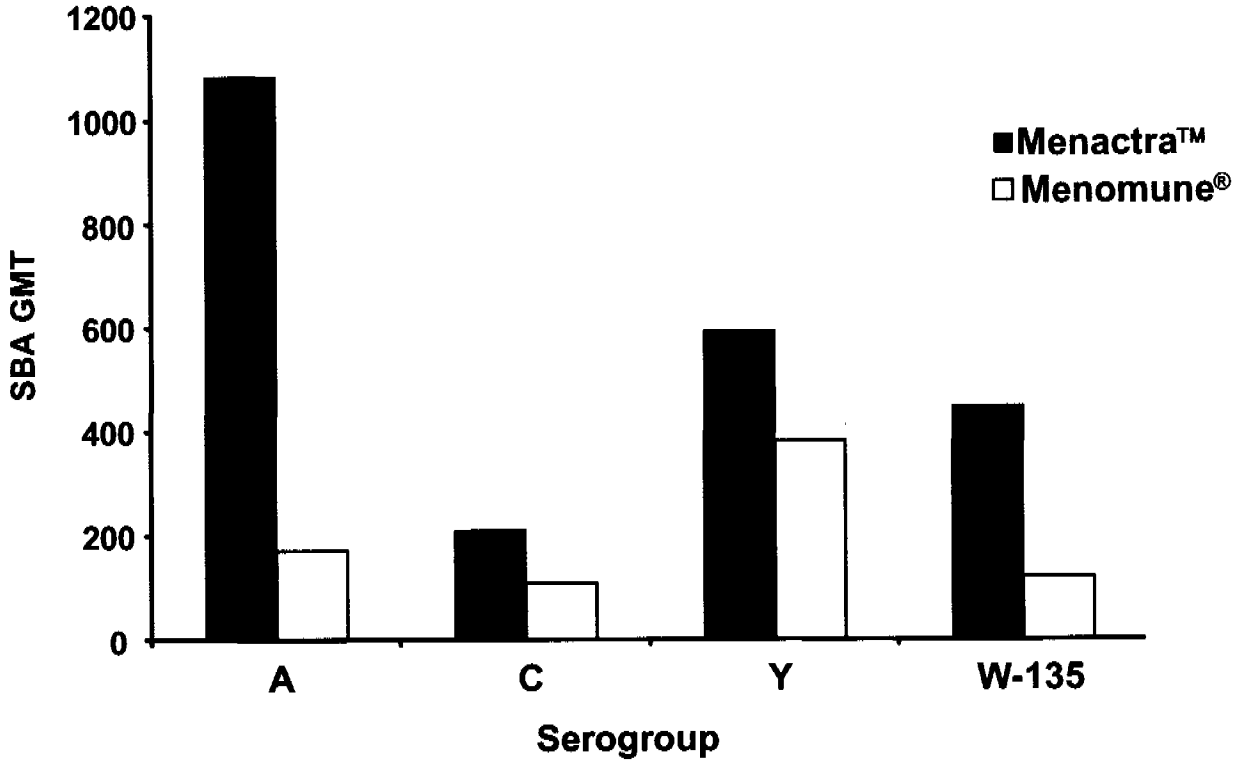
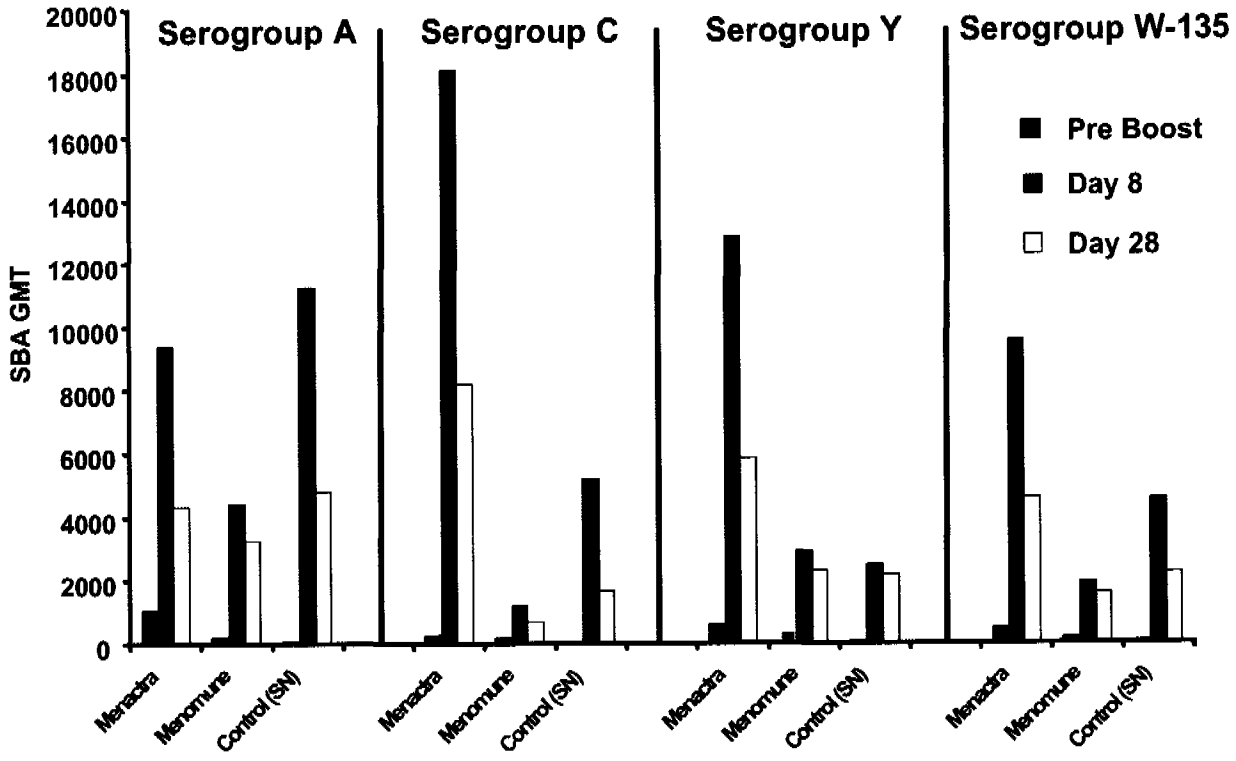


Figure 18 shows the pre booster, day 8 and day 28 post booster SBA results after one dose of Menactra™. Participants primed with Menactra™ in study MTA02 showed a booster response to all four serogroups. This response was significantly higher for serogroups C, Y and W-135 than

that seen in the aged matched vaccine naïve group. Peak responses were observed 8 days after boosting. These results are consistent with a memory response. Participants primed with Menomune® also showed increased antibody responses at day 8 and day 28, demonstrating the ability of the conjugate vaccine to overcome the immunologic hyporesponsiveness seen with successive doses of polysaccharide vaccine.

Figure 18: MTA19 SBA GMTs After a Booster Dose of Menactra™ at Three Years



In summary, the data from study MTA19 demonstrate that:

- One dose of Menactra™ induces an immune response that persists out to at least 3 years
- One dose of Menactra™ primes for memory as demonstrated by a rapid and high SBA response at day 8 for all four serogroups
- A booster dose of Menactra™ is not associated with the hyporesponsiveness observed with multiple doses of polysaccharide vaccines (41) (42)

5.3.2 Concomitant Administration

5.3.2.1 MTA11 (Menactra™ with Typhim Vi®)

Study MTA11 is a phase 2b modified double-blinded, safety and immunogenicity study of Menactra™ given alone or concomitantly with the licensed Typhim Vi® vaccine in healthy 18- to

55-year olds in the US. A total of 945 participants were enrolled in this study. Participants were randomized to either one of two treatment groups: Group A received Menactra™ and Typhim Vi® concomitantly at Visit 1 and a physiologic saline placebo 28 days later at Visit 2; Group B received Typhim Vi® and placebo at Visit 1 and Menactra™ 28 days later at Visit 2. A total of 469 study participants were enrolled in Group A and 476 in Group B. There were two primary immunogenicity objectives in this study. The first objective was to describe and compare the antibody responses after one dose of Typhim Vi® in each of the study groups 28 days post-vaccination. Antibody responses to Typhim Vi® in participants from Group A would be considered non-inferior to the antibody responses to Typhim Vi® from Group B if the difference in the proportion of recipients achieving an antibody level of > 1.0 µg/mL from Group B minus the proportion from Group A was less than 10%. A level of > 1.0 µg/mL of anti-Vi polysaccharide antibody was chosen as the primary serologic endpoint as this antibody level is considered protective.

The second of the two primary objectives was to describe and compare the % 4-fold rise in SBA antibody responses to each of the four serogroups in Menactra™ recipients 28 days post-vaccination. Participants were evenly distributed by age, sex and race between the two study groups. Sixty-eight percent of participants were female with a median age of all subjects being 31 years.

In Group A, 419 (89.3%) of study participants met the criteria for inclusion in the per-protocol population for immunogenicity and 420 (88.8%) for Group B.

Anti-Vi Polysaccharide Antibody Titers and 4-Fold Rise in SBA Titers

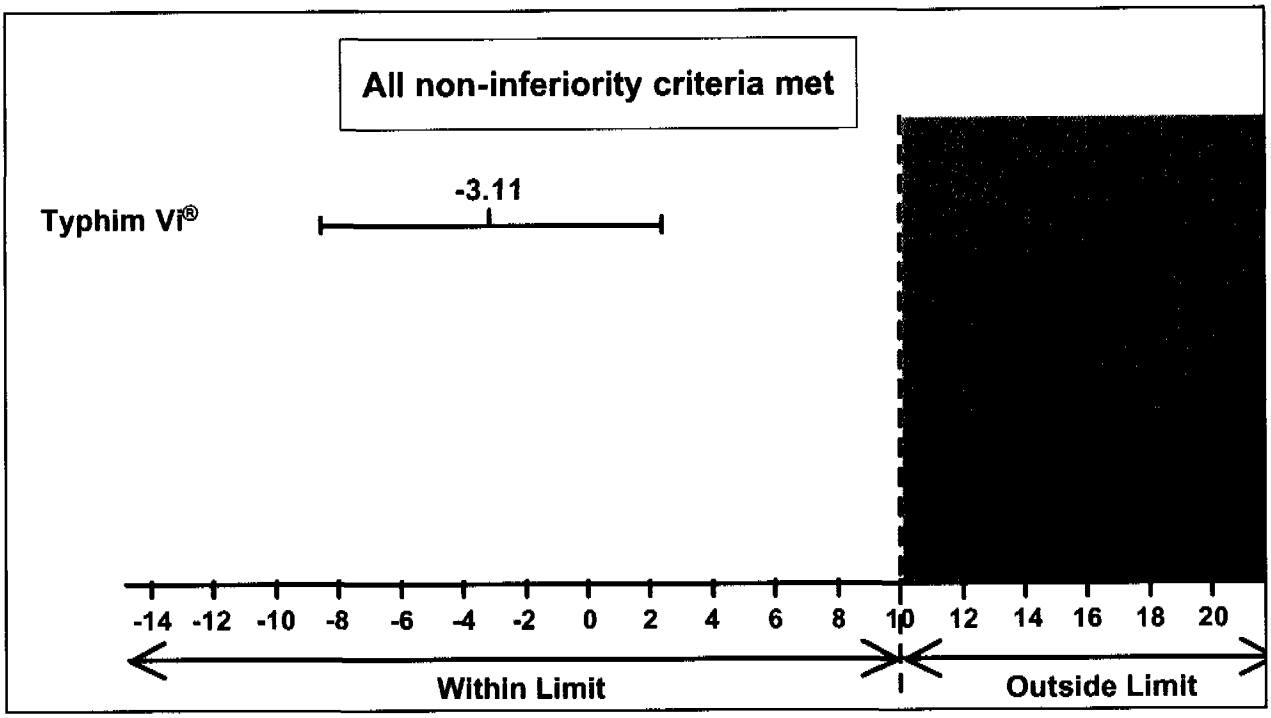
Twenty-eight days post-vaccination with Typhim Vi® vaccine 81.6% of participants from Group A and 78.5% of participants from Group B achieved antibody levels > 1.0 µg/mL (Table 7).

Table 7: MTA11 Percentage with Anti-Vi Polysaccharide Antibody Titer > 1.0 µg/mL

	Group A Typhim Vi® + Menactra™	**Group B Typhim Vi® + Placebo**
% anti-Vi PS titer > 1.0 µg/mL	(341 of 418) 81.6%	(328 of 418) 78.5%

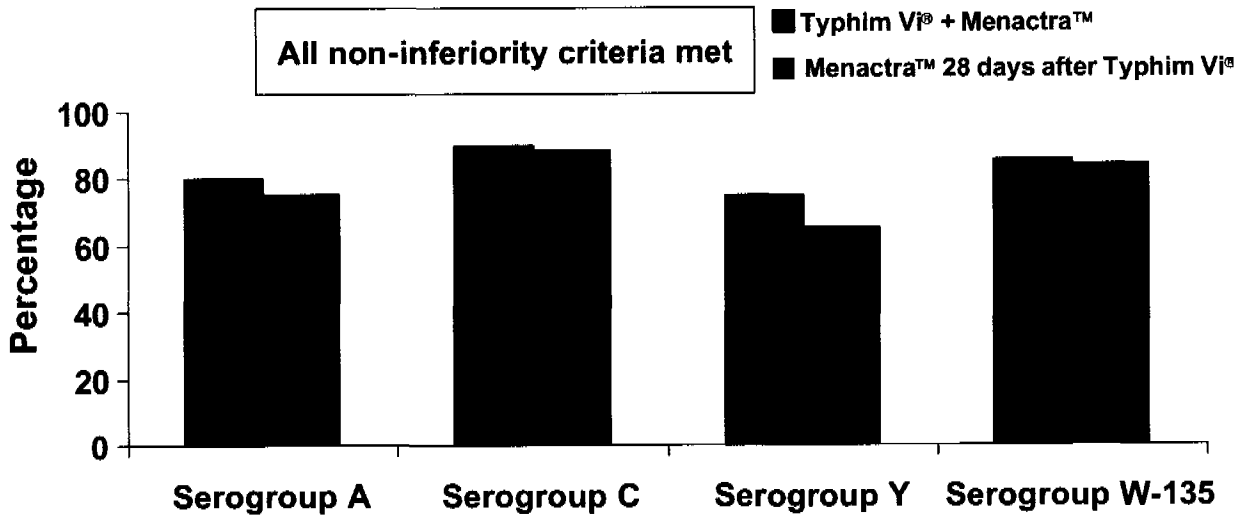
The antibody response to Typhim Vi® when administered concomitantly with Menactra™ is non-inferior to the corresponding response when Typhim Vi® is given alone, using two-sided Type I error rate $\alpha = 0.05$ and non-inferiority margin of 10% (Figure 19). These results were expected based on the seroconversion rates reported in the literature when Typhim Vi® is given alone or together with other common traveler vaccines including meningococcal polysaccharide and Hepatitis A vaccines (45).

Figure 19: MTA11 Non-Inferiority Testing of the Anti-Vi Antibody Titers > 1.0 µg/mL



The proportion of participants achieving a 4-fold rise in SBA antibody titer from Group A, when Menactra™ is given concomitantly with Typhim Vi® vaccine, was comparable to that demonstrated in Group B, when Menactra™ was administered one month after a Typhim Vi® vaccination (Figure 20).

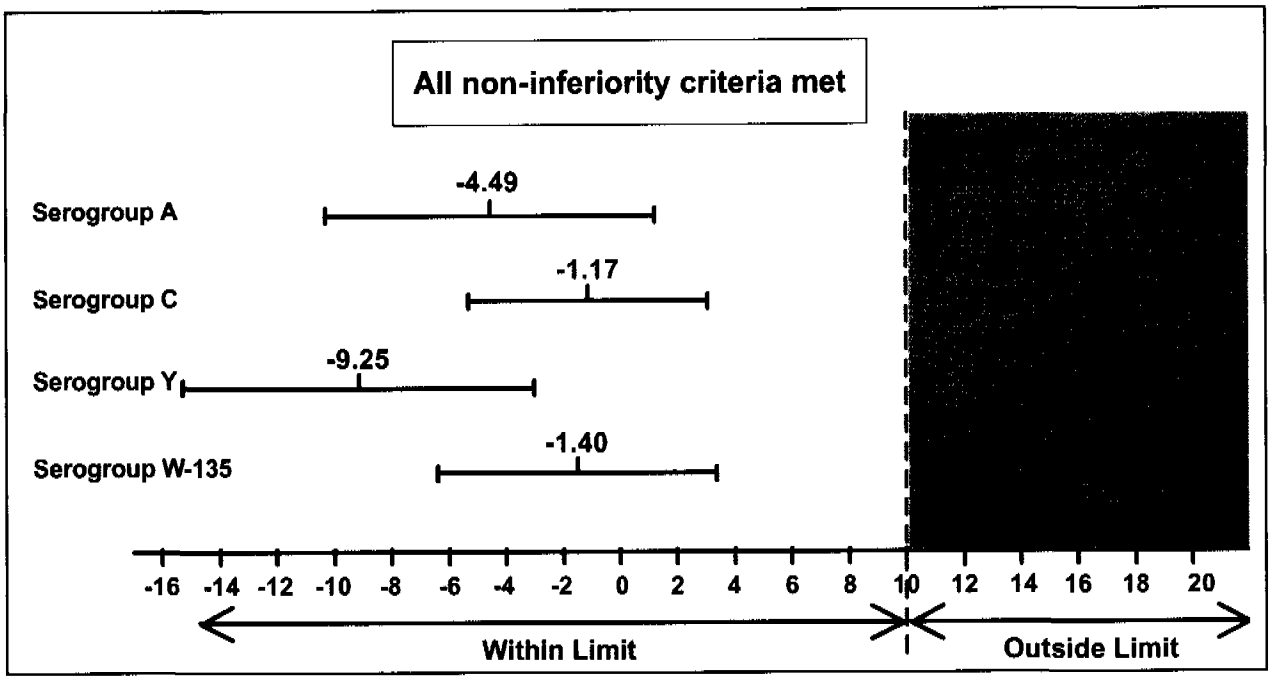
Figure 20: MTA11 4-Fold Rise in SBA Titer by Serogroup



Serogroup	Typhim Vi® + Menactra™	Menactra™ 28 days after Typhim Vi®
A	333 of 418 (79.7%)	315 of 419 (75.2%)
C	374 of 418 (89.5%)	370 of 419 (88.3%)
Y	311 of 418 (74.4%)	273 of 419 (65.2%)
W-135	356 of 418 (85.2%)	351 of 419 (83.8%)

The 4-fold rise in antibody to Menactra™ when administered concomitantly with Typhim Vi® is non-inferior to the corresponding response when Menactra™ is given alone, using two-sided Type I error rate $\alpha = 0.05$ and non-inferiority margin of 10% (Figure 21).

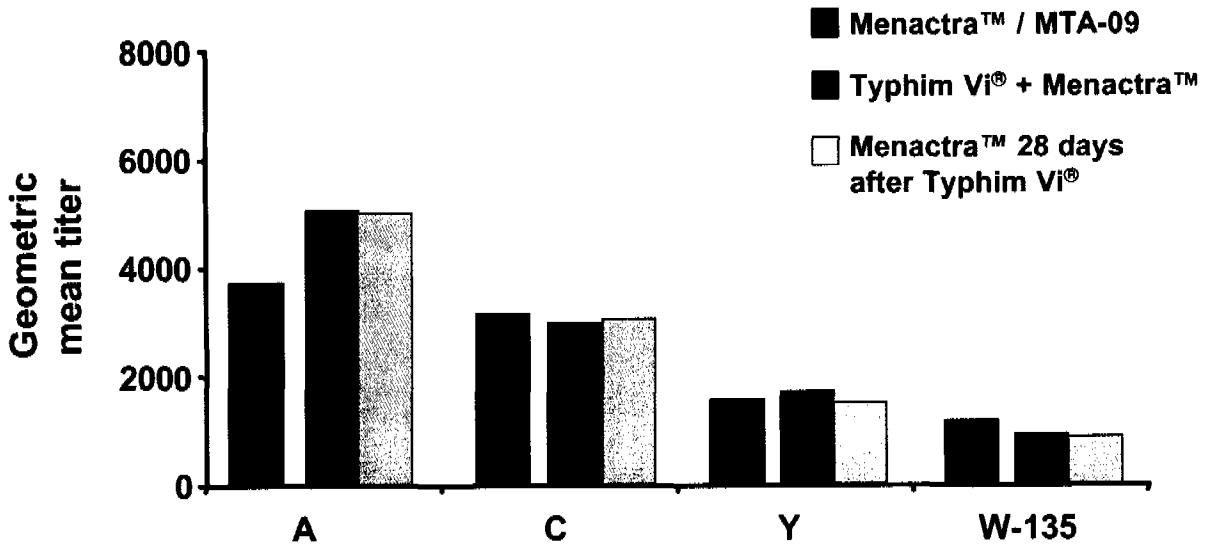
Figure 21: MTA11 Non-Inferiority Testing of the 4-Fold Rise in SBA Titer



GMTs

An observational objective was added to compare the GMT of the responses to Menactra™ in participants who were enrolled in a separate safety and immunogenicity trial in healthy adults (MTA09) to the GMT of Menactra™ recipients from both study groups in trial MTA11. The same criteria used in the secondary immunogenicity hypothesis was applied to this comparison. In each case, the GMT for each serogroup in MTA09 participants compared favorably with that of Menactra™ recipients from either Group A or B in this trial (Figure 22). In no case did the upper 97.5% confidence limit (which is equivalent to the upper two-sided 95% confidence limit) of the ratio of the GMT exceed 2 for any serogroup In addition, over 95% of participants in both study groups demonstrate antibody titers above the level of protection for all 4 serogroups

Figure 22: MTA11 SBA Geometric Mean Titers by Serogroup



MTA-09	3897	3231	1750	1271
With Typhim Vi®	5138	3061	1821	1002
After Typhim Vi®	5110	3145	1742	929

Together, these data demonstrate that Menactra™ is highly immunogenic in the adult population when given alone or concomitantly with the travel vaccine Typhim Vi®. When these data are used to test the primary hypothesis, all non-inferiority criteria are met.

5.3.2.2 MTA12 (Menactra™ with Tetanus and Diphtheria Toxoids Adsorbed for Adult Use)

Study MTA12 is a phase 2b modified double-blind, safety and immunogenicity study of Menactra™ given concomitantly with or one month after the licensed tetanus/diphtheria vaccine in healthy 11- to 17-year olds in the US. The purpose of this study was to evaluate the antibody

responses to tetanus and diphtheria toxoid when Td vaccine was administered concomitantly with Menactra™ and to evaluate the effect of Td vaccine co-administration on polysaccharide responses. The age range of 11 to 17 years was chosen to capture those individuals who would normally receive Td vaccine as part of the routine childhood immunization schedule. In addition, this age range has been identified as high risk for development of invasive meningococcal disease and these participants would most likely be candidates for vaccination with the meningococcal conjugate vaccine.

There were a total of 1019 evaluable participants enrolled in this study. Participants were randomized to one of two study groups: Group A received Td and Menactra™ at Visit 1 and the placebo consisting of physiologic saline 28 days later at Visit 2, while Group B received Td and the placebo at Visit 1 and Menactra™ at Visit 2. A total of 507 participants were enrolled in Group A and 512 were enrolled in Group B. Approximately 96% of enrolled participants completed the study. Participants were evenly distributed by age, sex and race between the two study groups. Forty-nine percent of participants were female with a median age of all subjects being 12 years.

There were several immunogenicity objectives in this trial. One objective was to describe and compare the 4-fold rise in SBA antibody response to each of the four serogroups contained in Menactra™ 28 days post vaccination. For each serogroup (A, C, Y, W-135), antibody responses to Menactra™ in participants from Group A would be considered non-inferior to antibody responses to Menactra™ in participants from Group B if the upper one-sided 97.5% confidence limit of the difference in the percentage of recipients from Group B achieving a 4-fold rise in SBA antibody titer minus the percentage from Group A was less than 10%.

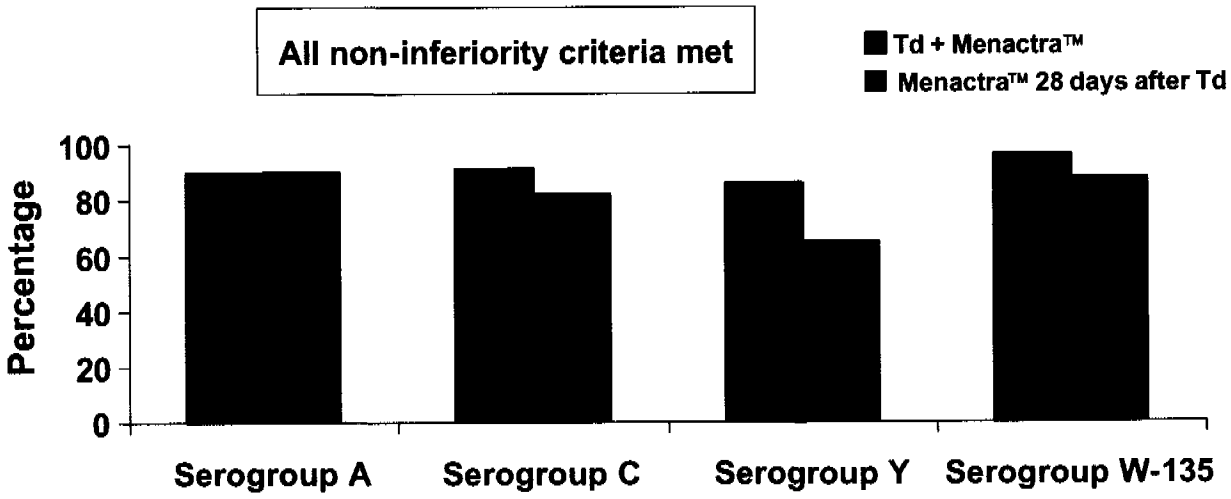
The second objective was to describe and compare the diphtheria and tetanus booster response rate (at least a 4-fold rise in baseline titer, given a diphtheria pre-titer $\leq$ 2.56 IU/mL and a tetanus pre-titer $\leq$ 2.7 IU/mL or a 2-fold rise given a diphtheria pre-titer > 2.56 IU/mL and a tetanus pre-titer > 2.7 IU/mL) when Td vaccine was administered concomitantly with Menactra™.

In Group A, 469 (92.5%) met the criteria for inclusion in the per-protocol population and 478 (93.4%) for Group B.

Four-Fold Rise in SBA Titer

The proportion of participants achieving a 4-fold rise in SBA antibody titer from Group A, when Menactra™ is administered concomitantly with Td vaccine, was comparable to the proportion in Group B, when Menactra™ is administered one month after Td vaccination (Figure 23). In addition, for serogroups C, Y, and W-135, we observed that the proportion of participants achieving a 4-fold rise in the group receiving Td concomitantly with Menactra™ was higher than in the group receiving Menactra™ alone.

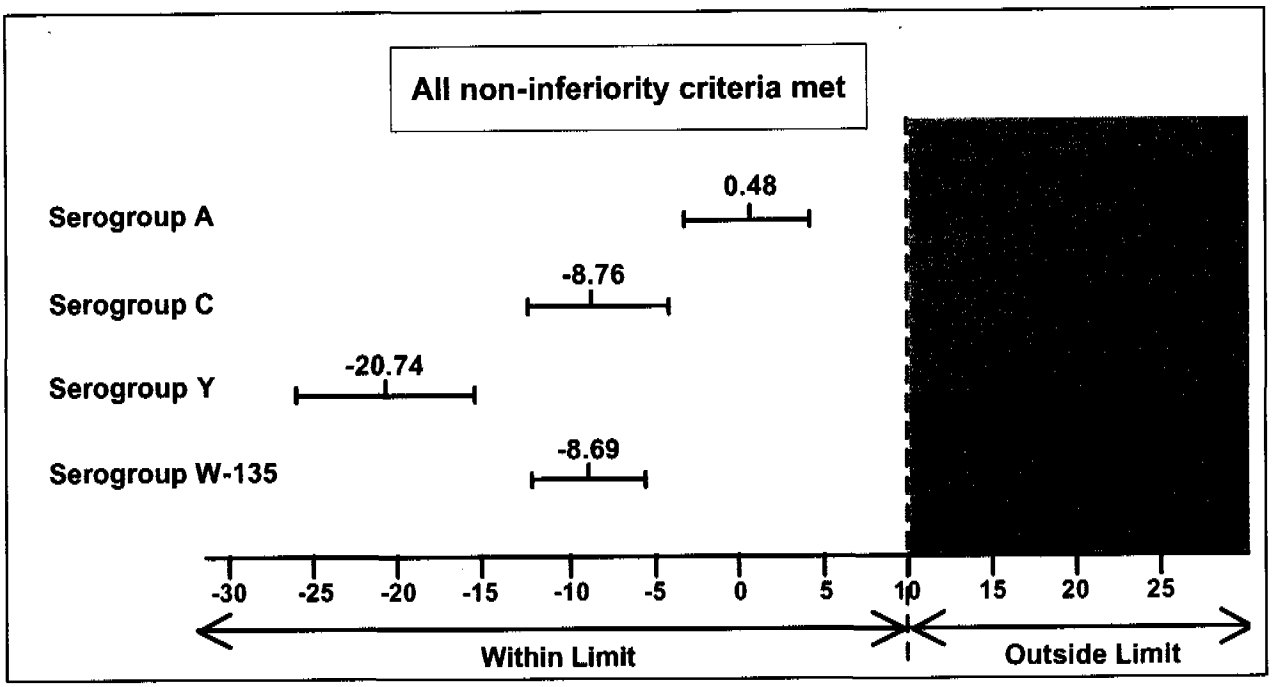
Figure 23: MTA12 4-Fold Rise in SBA Titer by Serogroup



Serogroup	Td + Menactra™	Menactra™ 28 days after Td
Serogroup A	419 of 465 (90.1%)	433 of 478 (90.6%)
Serogroup C	424 of 465 (91.2%)	394 of 478 (82.4%)
Serogroup Y	399 of 465 (85.8%)	311 of 478 (65.1%)
Serogroup W-135	448 of 465 (96.3%)	419 of 478 (87.7%)

The results of the analysis of the 4-fold rise data show that responses to each of the 4 serogroups from Group A participants are non-inferior to those observed in Group B (Figure 24).

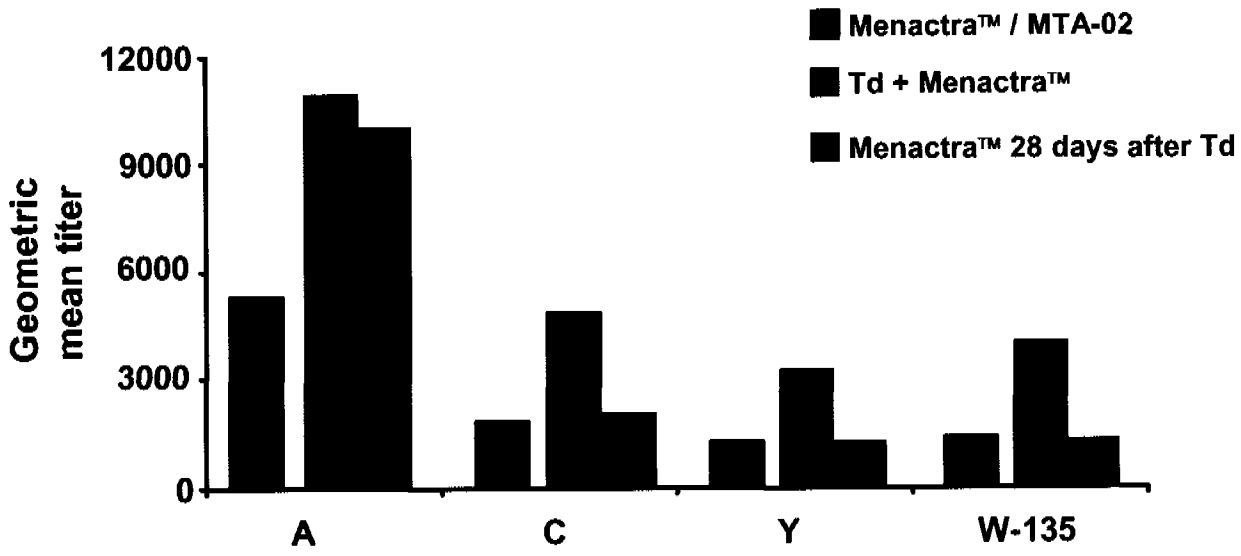
Figure 24: MTA12 Non-Inferiority Testing of the 4-Fold Rise in SBA Titers



GMTs

When comparing group A and group B, an enhancement of the SBA responses to the polysaccharide components of Menactra™ were observed when evaluating the GMT in participants who received Td and Menactra™ concomitantly. These Group A participants had a 2-3 fold higher response in GMT to serogroups C, Y, and W-135 than those participants in Group B who received Menactra™ alone (Group B, Day 28 after Menactra™ administration) (Figure 25). For the purpose of comparison, GMT antibody results from participants who received Menactra™ alone in Trial MTA02 were compared to those observed in Trial MTA12. The SBA responses to Menactra™ when administered 28 days after Td were comparable to when Menactra™ was administered alone.

Figure 25: MTA12 SBA Geometric Mean Titers by Serogroup

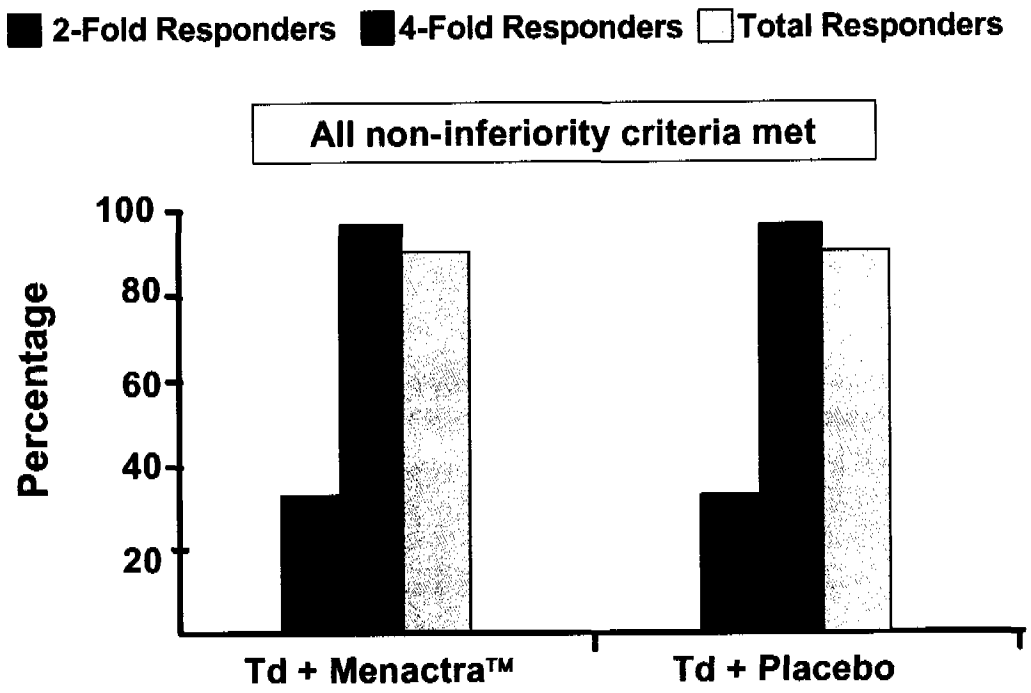


MTA-02	5483	1924	1322	1407
With Td	11,313	5059	3391	4195
After Td	10,391	2136	1331	1339

Td antibody Response and Booster Response Rates

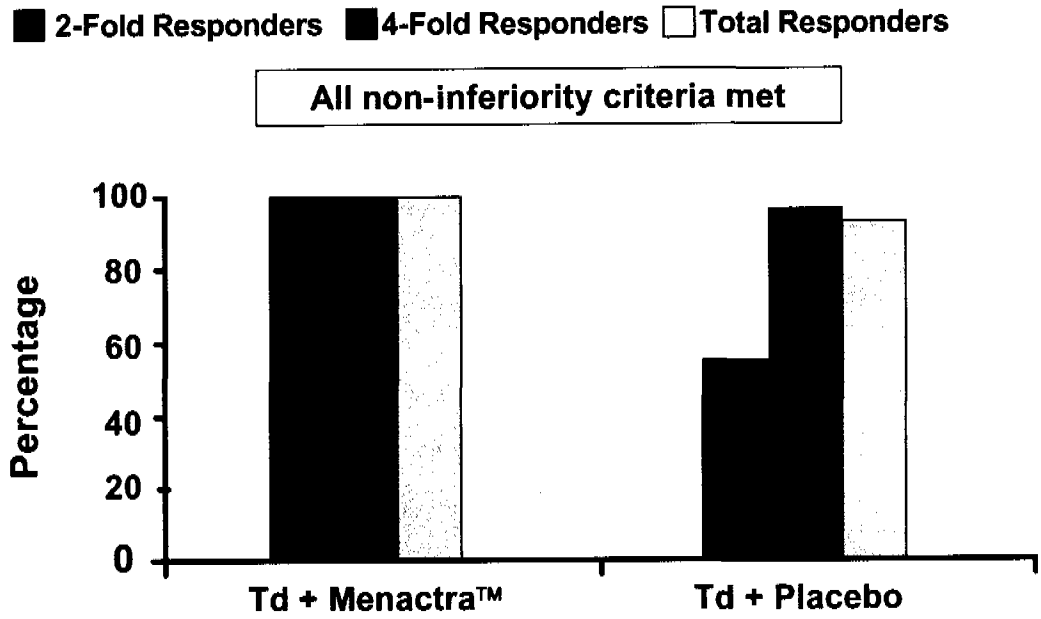
The anti-diphtheria and anti-tetanus booster response rates were similar between Group A participants administered Td and Menactra™ concomitantly and Group B participants who were administered Td alone (Figure 26 and Figure 27). At least 88% and 94% of participants in either group showed a booster response to Tetanus and Diphtheria, respectively.

Figure 26: MTA12 Percentage of Participants with Tetanus Booster Response



Tetanus Response	Td + Menactra™	Td + Placebo
2-Fold (Pre-titer > 2.7 IU/mL)	18/49 (36.7%)	17/45 (37.8%)
4-Fold (Pre-titer ≤ 2.7 IU/mL)	391/413 (94.7%)	408/426 (95.8%)
Total Responders	409/462 (88.5%)	425/471 (90.2%)

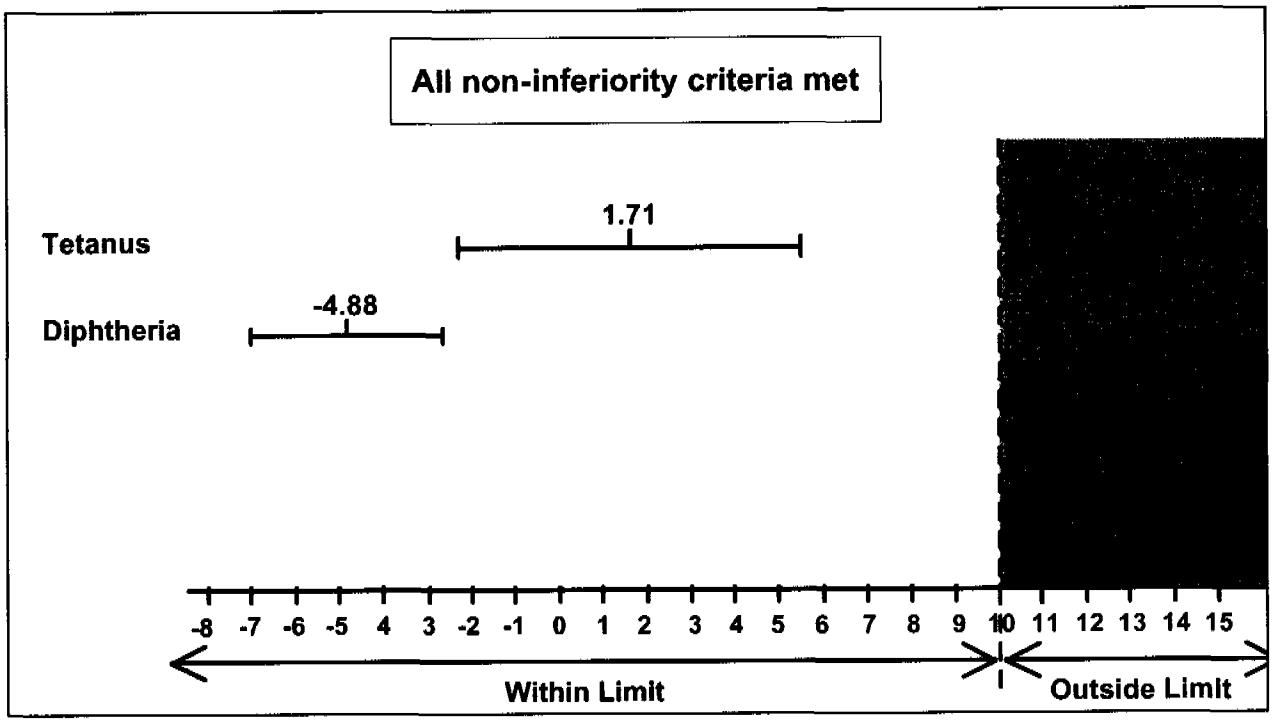
Figure 27: MTA12 Percentage of Participants with Diphtheria Booster Response



Diphtheria Response	Td + Menactra™	Td + Placebo
2-Fold (Pre-titer > 2.56 IU/mL)	8/8 (100.0%)	7/13 (53.9%)
4-Fold (Pre-titer ≤ 2.56 IU/mL)	454/456 (99.6%)	439/458 (95.9%)
Total Responders	462/464 (99.6%)	446/471 (94.7%)

The anti-diphtheria and anti-tetanus booster response rates when Td and Menactra™ were administered concomitantly were non-inferior to the rates when Td was administered alone (Figure 28).

Figure 28: MTA12 Non-Inferiority Testing of Tetanus/Diphtheria Booster Response Rates

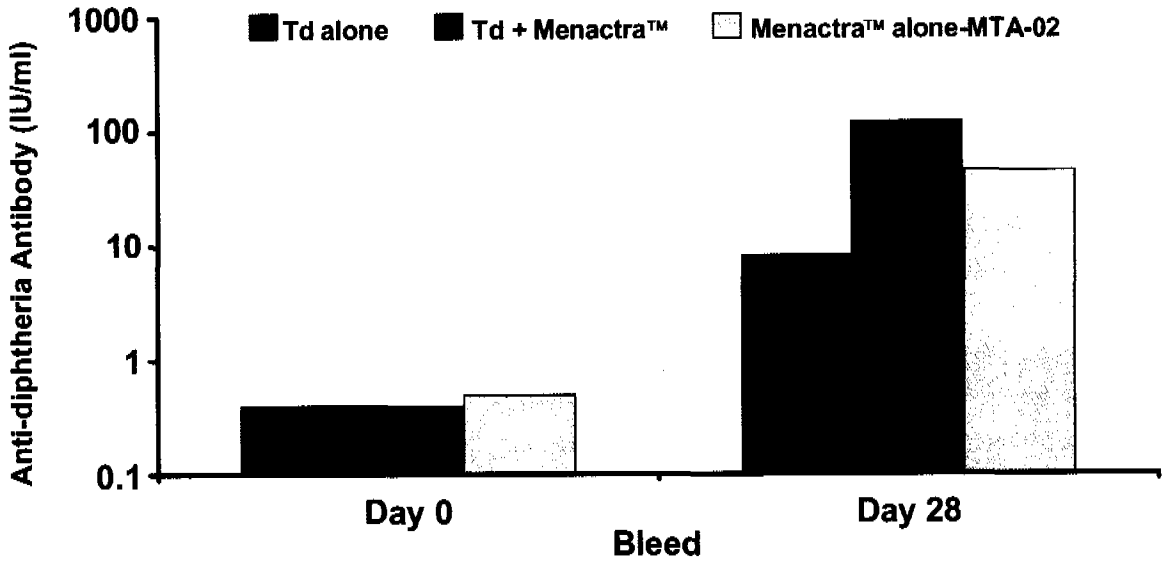


Several investigators have observed that the diphtheria toxoid carrier protein bound to polysaccharide antigens is capable of boosting diphtheria antibody responses in children and in adolescents who have been primed in childhood with diphtheria-containing vaccines (43). The magnitude of the response does not appear to be related to the level of pre-vaccination antibody titers, but appears to be related to the quantity of diphtheria toxoid contained in the vaccine.

In this study, Td adsorbed vaccine contains approximately 8 μg of diphtheria toxoid, while the study vaccine Menactra™ contains approximately 48 μg. Participants from Group A, who received one dose of Td concomitantly with Menactra™ on Day 0, achieved a diphtheria GMT of 120.9 IU/mL 28 days post first vaccination, while participants from Group B, who received one dose of Td with placebo, achieved a diphtheria GMT of 8.4 IU/mL. Group B participants demonstrated a boost in their diphtheria GMT to 16.9 IU/mL 28 days after receiving their subsequent vaccination with Menactra™ alone.

For the purposes of comparison, a random subset of participants enrolled in the comparative immunogenicity study MTA02 and who received one dose of Menactra™ had sera evaluated for diphtheria antibody. This subset achieved a GMT of 46.5 IU/mL at Day 28 post-vaccination, which is 5 times higher than the antibody level observed after administration of Td alone (Figure 29). The enhanced anti-diphtheria response is consistent with the increase in diphtheria toxoid content of Menactra™.

Figure 29: MTA12 Anti-Diphtheria Geometric Mean Titers



	Td alone	Td + Menactra™	Menactra™ alone-MTA02
Anti-diphtheria Titer (IU/ml) Day 0	0.4	0.4	0.5
Anti-diphtheria Titer (IU/ml) Day 28	8.4	120.9	46.5

Menactra™ is highly immunogenic when administered concomitantly with Td or when administered one month after a Td vaccination. Protective titers were achieved for all four serogroups and for diphtheria and tetanus. When these data are used to test the primary hypothesis, all non-inferiority criteria are met.

5.4 Immunogenicity - Conclusions

Based on the immunogenicity data from these studies, we conclude:

- Menactra™ is consistently immunogenic in adolescents and adults.

- Immune responses to the four polysaccharide conjugates included in Menactra™ (meningococcal serogroups A, C, Y, and W-135) were non-inferior to those induced by the licensed reference vaccine (Menomune®).
- Menactra™ can be administered concomitantly with Td vaccine.
- Menactra™ can be administered concomitantly with Typhim Vi® vaccine.
- Bactericidal antibody elicited by a single dose of Menactra™ persists for at least three years.
- One dose of Menactra™ primes for memory as demonstrated by a rapid and high SBA response at day 8 for all four serogroups.
- Adolescents primed with one dose of Menactra™ exhibited a booster response to a second dose of Menactra™ when administered three years after the primary dose.
- A booster dose of Menactra™ is not associated with the hyporesponsiveness observed with multiple doses of polysaccharide vaccines.

5.5 Safety - Assessment

The safety program for Menactra™ was developed to provide an expanded safety database in adolescents and adults and to compare the safety profile of Menactra™ with that of Menomune®. The clinical safety database included six phase 2 and phase 3 studies; four comparative studies (MTA02 and MTA04 in adolescents; MTA09 and MTA14 in adults) and two concomitant use studies (MTA12 – concomitant use with Td vaccine; and MTA11 – concomitant use with Typhim Vi® vaccine). A total of 7642 participants were enrolled to receive Menactra™ and 3041 were enrolled to receive Menomune®

5.5.1 Safety Parameters

The following categories of safety information were collected. Definition and severity rating scales for each type of event are detailed in Appendix 1.

- Immediate reactions (within 30 minutes)
- Solicited local reactions (Days 0-7)
- Solicited systemic reactions (Days 0-7)
- Unsolicited adverse events (AEs)
  - Days 0-28
  - Day 29- Month 6 (only for comparative studies)
- Serious adverse events (SAEs) (Duration of study)

5.5.2 Safety Objectives and Statistical Hypotheses Tested

Menactra™ versus Menomune® Comparisons

As a polysaccharide diphtheria toxoid conjugate vaccine, Menactra™ was expected to be associated with higher rates of local reactions than Menomune®, a polysaccharide vaccine. Menactra™ contains 48 micrograms of diphtheria toxoid per dose. Diphtheria toxoid is contained in a number of licensed vaccines, including DTaP, Td and DT. In these vaccines the quantity of diphtheria toxoid is expressed in limit of flocculation (LF) units. One LF unit is approximately equal to 4 micrograms of protein. Based on this conversion factor, the US-licensed DTaP vaccines contain from 30 to 100 micrograms of diphtheria toxoid and Td vaccine contains 8 micrograms. Menactra™ was expected to have a local reactogenicity profile more similar to Td vaccine.

For the four comparative studies, the safety objective was defined as a comparison between treatment groups of the safety profile for Menactra™ and Menomune® recipients. The safety endpoint was defined as the percentage of participants presenting at least one severe (graded 3 on a scale of 1 to 3) solicited systemic reaction during Days 0-7. This endpoint focused on the events most likely to affect participant's daily lives and therefore clinically relevant for comparing the safety profile of the two groups. While the program was designed to show that there is not a significantly increase risk of clinically important systemic reactions, as noted above, the local reactogenicity profile for Menactra™ was expected to be different. All statistical hypotheses tested the non-inferiority of Menactra™ when compared with Menomune® (Table 8).

Table 8: Non-inferiority Hypotheses Testing in the Comparative Studies for Safety

Study	Objective	Hypothesis tested
MTA04	Primary	Upper limit of the two-sided 95% CI of the ratio of % of participants presenting at least one severe solicited systemic reaction during Days 0-7 (Menactra™ divided by Menomune®) is less than 3.
MTA09	Primary	Upper limit of the two-sided 95% CI of the ratio of % of participants presenting at least one severe solicited systemic reaction during Days 0-7 (Menactra™ divided by Menomune®) is less than 3.
MTA02	Secondary	Upper limit of the two-sided 95% CI of the difference in % of participants presenting at least one severe solicited systemic reaction during Days 0-7 (Menactra™ minus Menomune®) is less than 10 percentage points.
MTA14	Secondary	Upper limit of the two-sided 95% CI of the difference in % of 26- to 55-year old participants presenting at least one severe solicited systemic reaction during Days 0-7 (Menactra™ [all consistency lots pooled] minus Menomune®) is less than 10 percentage points.

5.6 Safety – Results

Results for immediate reactions, solicited systemic reactions and solicited local reactions are summarized by study. Information on unsolicited adverse events and serious adverse events are summarized across all studies and presented in Sections 5.7 and 5.8, respectively.

5.6.1 Comparative Studies

5.6.1.1 MTA09 (Adults)

The primary safety objective of this study was to describe and compare the safety profile of Menactra™, with the licensed vaccine Menomune®. Ninety-four percent of enrolled subjects completed the 6-month follow-up. There were no withdrawals due to adverse events. Subjects were evenly distributed by age, sex and race between the two study groups. Sixty-two percent of subjects were females and the median age of all subjects was 24 years.

Overall Safety Profile in MTA09

Table 9 shows the summary of the safety profile of participants in study MTA09.

Table 9: MTA09 Safety Population - Overall Participant Safety Profile

Type of Adverse Events	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
Solicited Systemic Reactions (Days 0-7)	849/1371	61.9	699/1159	60.3
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
Serious Adverse Events (Day 0-Month 6)	23/1384	1.7	20/1170	1.7

Immediate Reactions

In the Menactra™ group, 0.1% of the participants reported immediate reactions: itching at the injection site; bruising at the injection site. In the Menomune® group, 0.3% of the participants reported immediate reactions: dry cough and throat tightness; swelling and erythema at the injection site (both of which were classified by the investigator as mild and nonserious); and a cough and a sore throat. All reported reactions were mild and all 5 participants recovered without sequelae.

Solicited Systemic Reactions

Overall, the frequency of solicited systemic reactions was similar in both treatment groups. In the group receiving Menactra™, 61.9% of participants reported at least one solicited systemic

reaction, compared with 60.3% in the group receiving Menomune® (Table 10). Headache, fatigue and malaise were the most common complaints, occurring in 41.4%, 34.7% and 23.6% of Menactra™ recipients and 41.8%, 32.3% and 22.3% of Menomune® recipients, respectively. The frequency of the remaining solicited systemic reactions was similar in both treatment groups. Most solicited systemic reactions were reported as mild and their median duration was 3 days in both treatment groups. Severe solicited systemic reactions were less common, occurring in 3.8% of Menactra™ recipients vs. 2.6% of Menomune® recipients, the most common severe reactions being headache and malaise, occurring in 1.2% and 1.1% of Menactra™ recipients, respectively, and in 0.9% of Menomune® recipients.

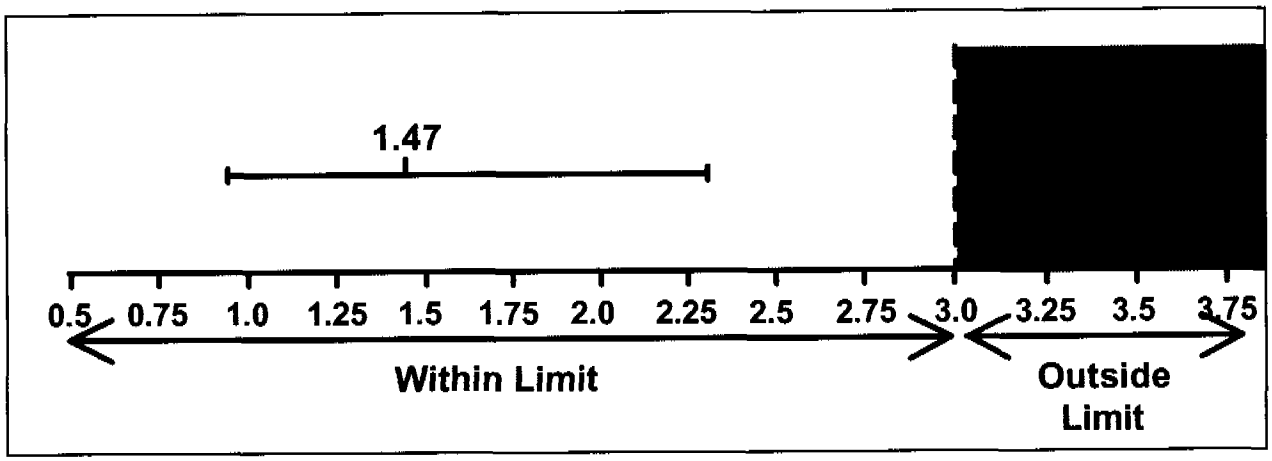
Rash was uncommon in both treatment groups and were categorized as mild, localized reactions (Table 10). No clinically consistent pattern of rash emerged. Areas affected by rash included the face, neck, torso, and extremities. The duration of rash reported ranged from 1 hour to 11 days. The median duration was 2 days for the Menactra™ group and 1 day for the Menomune® group.

Table 10: MTA09 Percentage with Solicited Systemic Reactions by Severity

Reaction	Severity	Menactra™ (N=1371) % Participants	Menomune® (N=1159) % Participants
Any Reaction	Any	61.9	60.3
	Mild	39.9	41.5
	Moderate	18.2	16.2
	Severe	3.8	2.6
Headache	Any	41.4	41.8
	Mild	30.2	31.9
	Moderate	10.1	8.9
	Severe	1.2	0.9
Fatigue	Any	34.7	32.3
	Mild	25.5	25.3
	Moderate	8.3	6.6
	Severe	0.9	0.4
Malaise	Any	23.6	22.3
	Mild	16.0	16.8
	Moderate	6.6	4.7
	Severe	1.1	0.9
Arthralgia	Any	19.8	16.0
	Mild	14.9	13.3
	Moderate	4.7	2.6
	Severe	0.3	0.1
Diarrhea	Any	16.0	14.0
	Mild	13.0	10.7
	Moderate	2.6	2.9
	Severe	0.4	0.3
Anorexia	Any	11.8	9.9
	Mild	9.1	7.9
	Moderate	2.3	1.6
	Severe	0.4	0.4
Chills	Any	9.7	5.6
	Mild	7.0	4.6
	Moderate	2.1	1.0
	Severe	0.6	0.0
Vomiting	Any	2.3	1.5
	Mild	1.8	0.9
	Moderate	0.4	0.2
	Severe	0.2	0.4
Fever	Any	1.5	0.5
	Mild	1.2	0.4
	Moderate	0.3	0.1
	Severe	0.0	0.0
Rash		1.4	0.8
Seizures		0.0	0.0

The results of pre-defined non-inferiority testing are shown in Figure 30. The ratio of the percentage of participants with any severe solicited reaction (Menactra™/Menomune®) is 1.47 and the upper limit of the 95% confidence interval is 2.28, meeting the criteria for non-inferiority. Menactra™ was found to be non-inferior to the control vaccine Menomune® for the criteria specified in the primary safety hypothesis.

Figure 30: MTA09 Non-Inferiority Hypothesis Testing for Safety



Solicited Local Reactions

In the group receiving Menactra™, 57.6% of participants reported at least one solicited local reaction, compared with 55.6% in the group receiving Menomune® (Table 11). For both treatment groups, most solicited local reactions were reported as mild and their median duration was 2 days.

Table 11: MTA09 Percentage with Solicited Local Reactions by Severity

Reaction	Severity	Menactra™ (N=1371) % Participants	Menomune® (N=1159) % Participants
Any Reaction	Any	57.6	55.6
	Mild	42.6	50.0
	Moderate	13.3	5.3
	Severe	1.7	0.2
Pain	Any	53.9	48.1
	Mild	42.4	44.8
	Moderate	11.3	3.3
	Severe	0.2	0.1
Induration	Any	17.1	11.0
	Mild	13.1	9.9
	Moderate	3.4	1.0
	Severe	0.7	0.0
Redness	Any	14.4	16.0
	Mild	10.4	14.0
	Moderate	2.9	1.9
	Severe	1.1	0.1
Swelling	Any	12.6	7.6
	Mild	9.3	6.9
	Moderate	2.3	0.7
	Severe	0.9	0.0

Overall, the safety profile of Menactra™ that emerges from this study is similar to that reported for other meningococcal conjugate vaccines. In a recent review of adverse events following a countrywide meningococcal C-conjugate vaccination campaign in the United Kingdom from 1999 through 2001, a summary of the adverse event profile was presented after approximately 18 million doses of vaccine had been administered. The most common adverse events reported included injection site reactions (pain, swelling and redness), fever, headache, fatigue, myalgia, vomiting, and diarrhea (44).

5.6.1.2 MTA14 (Lot Consistency and Comparative Safety in Adults)

Comparative safety was evaluated in 26- to 55-year old participants with the licensed vaccine Menomune®. A total of 686 participants were in the Menactra™ arm and 458 participants were enrolled in the Menomune® arm; and of these, 94.1% completed the six-month follow-up. No participants discontinued due to an adverse event.

Table 12 shows the summary of the safety profile of participants in study MTA14.

Table 12: MTA14 Safety Population - Overall Participant Safety Profile, Menomune® Comparison

Type of Adverse Events	Menactra™		Menomune®	
	n/N	%	n/N	%
Immediate Reactions (Within 30 Minutes)	0/686	0.0	0/458	0.0
Solicited Local Reactions (Days 0-7)	290/685	42.3	118/454	26.0
Solicited Systemic Reactions (Days 0-7)	366/685	53.4	224/455	49.2
Unsolicited Adverse Events (Days 0-28)	169/679	24.9	101/445	22.7
Unsolicited Significant Adverse Events (Day 29-Month 6)	46/653	7.0	31/427	7.3
Serious Adverse Events (Day 0-Month 6)	11/686	1.6	12/458	2.6

Immediate Reactions

There were no immediate reactions in either treatment group.

Solicited Systemic Reactions

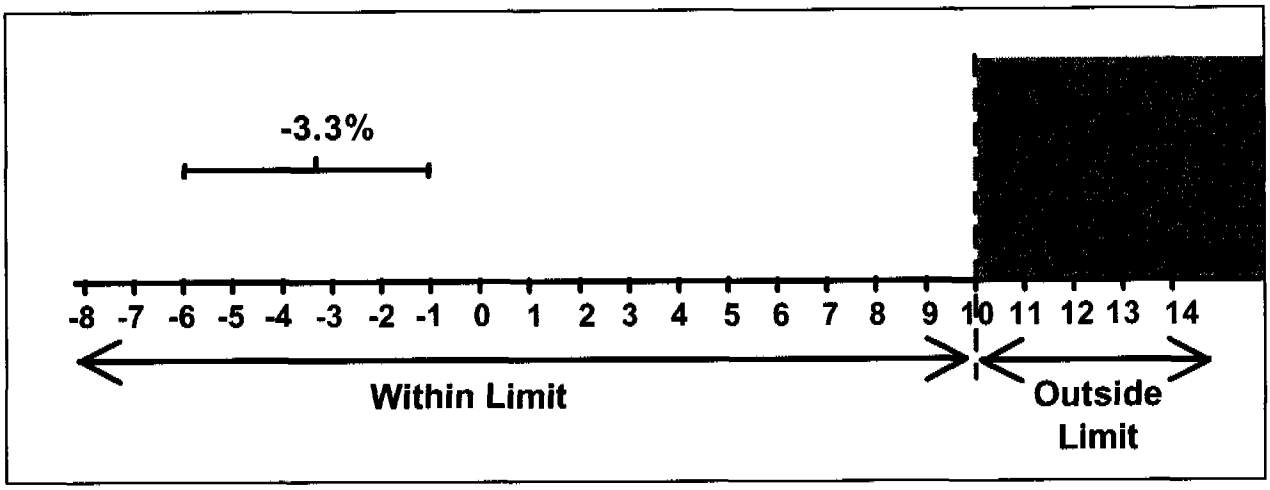
Solicited systemic reactions occurred with similar frequency in both groups, with 53.4% of Menactra™ recipients reporting at least one solicited systemic reaction and 49.2% of Menomune® recipients reporting at least one solicited systemic reaction (Table 13). Most reactions were mild in intensity and the median duration of solicited systemic reactions was 3.0 days for the 2 treatment groups.

Table 13: MTA14 Percentage with Solicited Systemic Reactions

Reaction	Severity	Menactra™ (N=685) % Participants	Menomune® (N=455) % Participants
Any Systemic Reaction	Any	53.4	49.2
	Mild	33.7	31.2
	Moderate	17.5	12.5
	Severe	2.2	5.5
Headache	Any	35.0	33.6
	Mild	25.4	24.8
	Moderate	9.2	7.7
	Severe	0.4	1.1
Fatigue	Any	28.0	25.1
	Mild	20.3	19.3
	Moderate	7.2	4.4
	Severe	0.6	1.3
Malaise	Any	19.6	17.6
	Mild	14.5	12.3
	Moderate	4.8	3.5
	Severe	0.3	1.8
Diarrhea	Any	15.3	15.4
	Mild	12.0	11.2
	Moderate	3.1	3.5
	Severe	0.3	0.7
Arthralgia	Any	15.2	12.5
	Mild	11.8	9.0
	Moderate	3.4	3.1
	Severe	0.0	0.4
Anorexia	Any	9.3	7.7
	Mild	7.4	5.9
	Moderate	1.8	1.5
	Severe	0.1	0.2
Chills	Any	6.6	3.3
	Mild	5.7	2.4
	Moderate	0.9	0.4
	Severe	0.0	0.4
Vomiting	Any	1.2	1.3
	Mild	0.9	0.7
	Moderate	0.3	0.7
	Severe	0.0	0.0
Fever	Any	0.6	0.4
	Mild	0.6	0.4
	Moderate	0.0	0.0
	Severe	0.0	0.0
Rash		1.0	2.4
Seizure		0.0	0.0

The result of the non-inferiority analysis is shown in Figure 31. The difference in the percentage of participants with any severe solicited reaction (Menactra™ - Menomune®) is –3.30% and the upper limit of the 95% confidence interval is –1%, meeting the criteria for non-inferiority. Menactra™ is therefore found to be non-inferior to the control vaccine Menomune® for the criteria specified in the primary safety hypothesis.

Figure 31: MTA14 Non-Inferiority Hypothesis Testing for Safety



Solicited Local Reactions

Of the 685 Menactra™ recipients, 42.3% reported at least one solicited local reaction, while only 26.0% of the 454 Menomune® recipients reported a reaction (Table 14). Most reactions in both vaccine groups were mild. Severe reactions were uncommon, occurring in less than one percent of participants. The median duration of solicited local reactions was 2 days for Menactra™ and 1 day for Menomune® recipients. This result was probably due to the nature of the conjugate vaccine (diphtheria carrier protein). Overall, the safety profile that emerges for Menactra™ from this study is similar to that reported for MTA09.

Table 14: MTA14 Percentage with Solicited Local Reactions

Reaction	Severity	Menactra™ (N=685) % Participants	Menomune® (N=454) % Participants
Any Reaction	Any	42.3	26.0
	Mild	35.9	24.2
	Moderate	5.5	1.8
	Severe	0.9	0.0
Pain	Any	38.5	19.8
	Mild	33.9	18.9
	Moderate	4.7	0.9
	Severe	0.0	0.0
Induration	Any	13.4	5.5
	Mild	11.4	5.1
	Moderate	1.5	0.4
	Severe	0.6	0.0
Swelling	Any	10.7	4.6
	Mild	8.9	4.2
	Moderate	1.3	0.4
	Severe	0.4	0.0
Redness	Any	10.5	9.9
	Mild	8.3	9.0
	Moderate	1.6	0.9
	Severe	0.6	0.0

5.6.1.3 MTA04 (Adolescents)

Study MTA04 is a phase 3, modified double-blind, comparative safety study of Menactra™ with Menomune® in healthy 11- to 18-year olds in the US. There were a total of 3242 participants enrolled in this study. A total of 2270 received Menactra™, and 972 received Menomune® and 99% completed the 6-month follow-up. There were no withdrawals due to adverse events.

Overall Safety Profile in MTA04

Table 15 shows the summary of the safety profile of participants in study MTA04.

Table 15: MTA04 Safety Population - Overall Participant Safety Profile

Type of Adverse Event	Menactra™		Menomune®	
	n/N	%	n/N	%
Immediate reactions (within 30 minutes)	8/2270	0.4	3/972	0.3
Solicited local reactions (Days 0-7)	1420/2264	62.7	310/970	32.0
Solicited systemic reactions (Days 0-7)	1247/2265	55.1	472/970	48.7
Unsolicited adverse events (Days 0-28)	601/2264	26.5	228/971	23.5
Unsolicited significant adverse events (Day 29-Month 6)	169/2251	7.5	69/962	7.2
Serious Adverse Events (Day 0-Month 6)	22/2270	1.0	6/972	0.6

Immediate Reactions

A total of 0.4% Menactra™ participants and 0.3% Menomune® participants had immediate reactions. In the Menactra™ group, most immediate reactions were vasovagal in nature and consisted primarily of dizziness, nausea, sweats, hypotension, bradycardia, and syncope. Two participants in the Menomune® group had similar vasovagal events. Two participants (1 from each group) reported immediate local redness and swelling. All immediate reactions were judged to be nonserious, mild to moderate in severity and resolved without sequalae within 24 hours.

Solicited Systemic Reactions

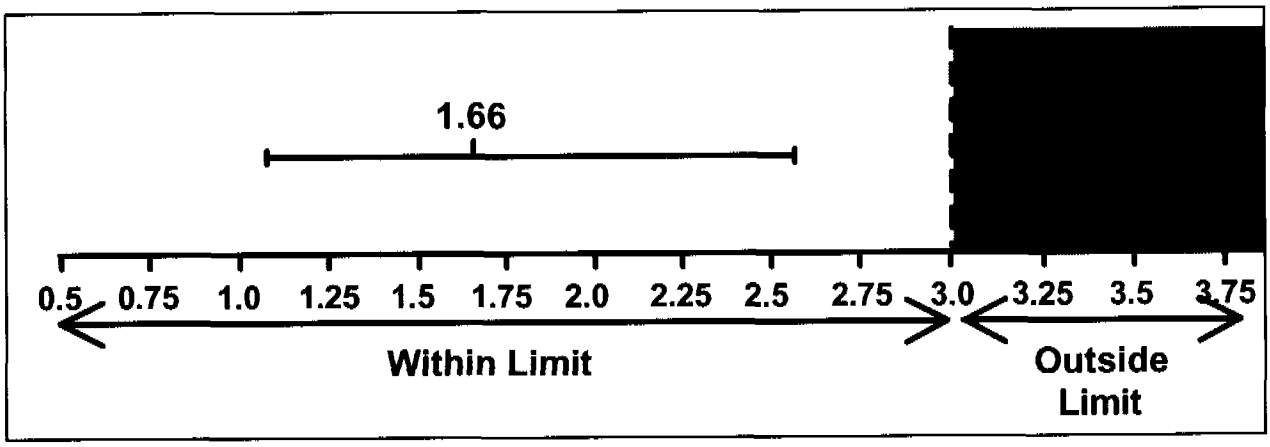
The frequency of systemic reactions was similar in both treatment groups. Fifty-five percent of Menactra™ recipients and 48.7% of Menomune® recipients reported at least 1 solicited systemic reaction (Table 16). Headache, malaise, and arthralgias tended to occur more frequently in Menactra™ recipients (35.6%, 21.9%, 17.4%) than in Menomune® recipients (29.3%, 16.8%, 10.2%) while the frequency of other solicited systemic reactions was similar in both treatment groups. Most solicited systemic reactions were reported as mild and overall, the median duration was 3 days. Severe solicited systemic reactions occurred in 4.3% of Menactra™ recipients and 2.6% of Menomune® recipients.

Table 16: MTA04 Percentage with Solicited Systemic Reactions by Severity

Reaction	Severity	Menactra™ (N=2265) % Participants	Menomune® (N=970) % Participants
Any Reaction	Any	55.1	48.7
	Mild	34.3	33.7
	Moderate	16.5	12.4
	Severe	4.3	2.6
Headache	Any	35.6	29.3
	Mild	25.0	22.4
	Moderate	9.6	6.5
	Severe	1.1	0.4
Fatigue	Any	30.0	25.1
	Mild	21.4	18.7
	Moderate	7.5	6.2
	Severe	1.1	0.2
Malaise	Any	21.9	16.8
	Mild	15.0	13.0
	Moderate	5.8	3.4
	Severe	1.1	0.4
Arthralgia	Any	17.4	10.2
	Mild	13.4	8.0
	Moderate	3.6	2.1
	Severe	0.4	0.1
Diarrhea	Any	12.0	10.2
	Mild	10.1	8.9
	Moderate	1.6	1.3
	Severe	0.3	0.0
Anorexia	Any	10.7	7.7
	Mild	8.4	6.4
	Moderate	2.0	1.1
	Severe	0.3	0.2
Chills	Any	7.0	3.5
	Mild	5.1	3.0
	Moderate	1.7	0.4
	Severe	0.2	0.1
Fever	Any	5.1	3.0
	Mild	4.5	2.6
	Moderate	0.6	0.3
	Severe	0.0	0.1
Vomiting	Any	1.9	1.4
	Mild	1.3	0.6
	Moderate	0.4	0.5
	Severe	0.3	0.3
Rash		1.6	1.4
Seizures		0.0	0.0

The result of the non-inferiority analysis is shown in Figure 32. The ratio of the percentage of participants with any severe solicited systemic reaction (Menactra™/Menomune®) is 1.66, and the upper limit of the 95% confidence interval is 2.56, meeting the criteria for non-inferiority. In this study, Menactra™ is non-inferior to the control vaccine Menomune® for the criteria specified in the primary safety hypothesis.

Figure 32: MTA04 Non-Inferiority Hypothesis Testing for Safety



Solicited Local Reactions

The frequency of local reactions was more common in the group receiving Menactra™ (62.7%) than in the group receiving Menomune® (32.0%). In both vaccine groups, most local solicited reactions were reported as mild and resolved within 2 days of vaccination (Table 17). Severe reactions were uncommon, occurring in less than 1 % of participants. This result is likely due to the nature of the conjugate vaccine (diphtheria carrier protein). The rates of local reactions for Menactra™ were very similar to the licensed Td vaccine (Section 5.6.2.2 below for MTA12 results).

Table 17: MTA04 Percentage with Solicited Local Reactions by Severity

Reaction	Severity	Menactra™ (N=2264) % Participants	Menomune® (N=970) % Participants
Any Reaction	Any	62.7	32.0
	Mild	46.9	28.9
	Moderate	14.7	3.1
	Severe	1.1	0.0
Pain	Any	59.2	28.7
	Mild	46.2	26.1
	Moderate	12.8	2.6
	Severe	0.3	0.0
Induration	Any	15.7	5.2
	Mild	12.9	4.6
	Moderate	2.5	0.5
	Severe	0.3	0.0
Redness	Any	10.9	5.7
	Mild	8.7	5.3
	Moderate	1.6	0.4
	Severe	0.6	0.0
Swelling	Any	10.8	3.6
	Mild	8.4	3.3
	Moderate	1.9	0.3
	Severe	0.5	0.0

5.6.1.4 MTA02 (Adolescents)

The safety objective of the study was to describe and compare the safety profile of the study vaccine, Menactra™, with the licensed vaccine Menomune®. Of the 881 enrolled subjects, 98.9% completed the study. There were no withdrawals due to an adverse event. Subjects were evenly distributed by age, sex and race between the two study groups. Fifty-five percent of subjects were male with a median age of all subjects being 14 years.

Overall Participant Safety Profile

Table 18 shows the summary of the safety profile of participants in study MTA02.

Table 18: MTA02 Safety Population - Overall Participant Safety Profile

Type of Adverse Events	Menactra™		Menomune®	
	n/N	%	n/N	%
Immediate reactions (within 30 minutes)	2/440	0.5	0/441	0.0
Solicited local reactions (Days 0-7)	317/438	72.4	153/441	34.7
Solicited systemic reactions (Days 0-7)	251/439	57.2	229/441	51.9
Unsolicited adverse events (Days 0-28)	165/440	37.5	169/440	38.4
Unsolicited significant adverse events (Day 29-Month 6)	26/436	6.0	18/435	4.1
All serious adverse events (Day 0-Month 6)	5/440	1.1	1/441	0.2

Immediate Reactions

In the Menactra™ group, 0.5% of subjects reported a vasovagal episode and both recovered without sequelae.

Solicited Systemic Reactions

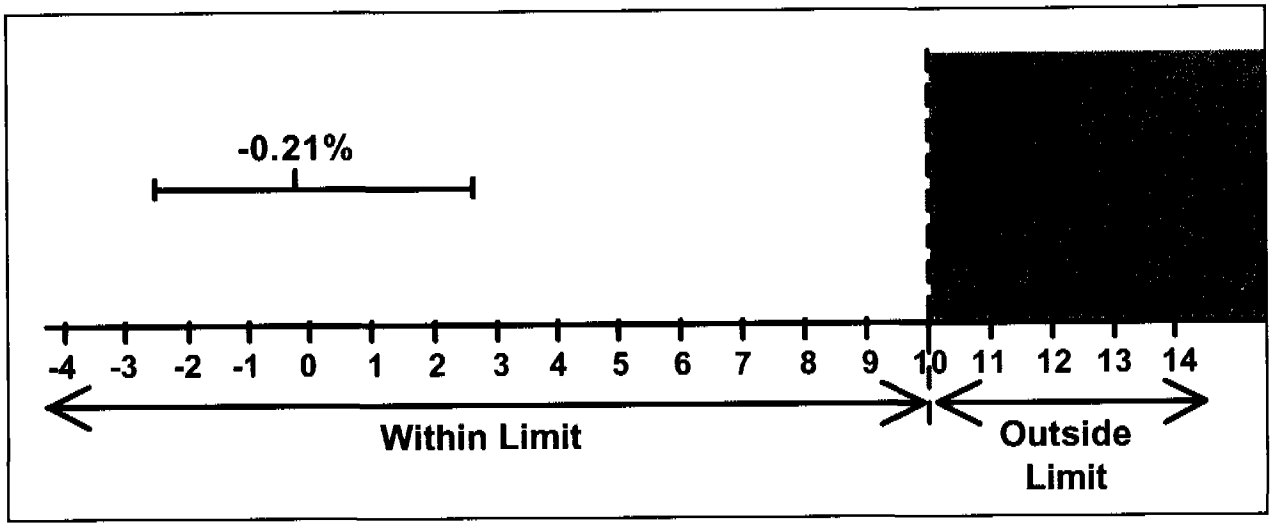
Overall, the frequency of systemic reactions was similar in both treatment groups (Table 19). A total of 57.2% of Menactra™ recipients and 51.9% of Menomune® recipients reported at least one solicited systemic reaction. Most solicited systemic reactions were mild and resolved within 3 days (median duration). Headache and fatigue were the most common complaints, occurring in 44.9% and 28.2% of Menactra™ recipients and 39.5% and 23.6% of Menomune® recipients, respectively. The frequency of the remaining systemic events was similar in both treatment groups. Severe reactions were less common occurring in 3.9% of Menactra™ recipients vs. 4.1% of Menomune® recipients, the most common severe reaction being headache occurring in 1.6% of Menactra™ and 1.8% of Menomune® recipients.

Table 19: MTA02 Percentage with Solicited Systemic Reactions by Severity

Reaction	Severity	Menactra™ (N=439) % Participants	Menomune® (N=441) % Participants
Any Reaction	Any	57.2	51.9
	Mild	33.0	34.0
	Moderate	20.3	13.8
	Severe	3.9	4.1
Headache	Any	44.9	39.5
	Mild	27.3	28.6
	Moderate	15.9	9.1
	Severe	1.6	1.8
Fatigue	Any	28.2	23.6
	Mild	19.6	17.9
	Moderate	7.5	5.0
	Severe	1.1	0.7
Anorexia	Any	12.3	12.2
	Mild	9.1	8.8
	Moderate	2.3	2.7
	Severe	0.9	0.7
Diarrhea	Any	10.9	14.1
	Mild	9.6	11.8
	Moderate	1.4	2.0
	Severe	0.0	0.2
Fever	Any	3.4	2.5
	Mild	2.7	2.3
	Moderate	0.5	0.2
	Severe	0.2	0.0
Vomiting	Any	2.3	2.0
	Mild	1.6	0.5
	Moderate	0.5	1.4
	Severe	0.2	0.2
Rash		1.6	1.6

Results of the non-inferiority analysis are shown in Figure 33. The difference in the percentage of participants with any severe solicited systemic reaction (Menactra™ - Menomune®) is –0.21%, and the upper limit the 95% confidence interval is 2.4%, meeting the criteria for non-inferiority. Menactra™ is therefore found to be non-inferior to the control vaccine Menomune® for the criteria specified in the safety hypothesis.

Figure 33: MTA02 Non-Inferiority Hypothesis Testing for Safety



Solicited Local Reactions

Local reactions were more frequently reported in Menactra™ (72.4%) recipients compared to Menomune® (34.7%) recipients (Table 20). Most solicited local reactions were reported as mild and severe reactions were uncommon occurring in less than 1% of participants. Local reactions in Menactra™ participants had a median duration of 2 days and a median duration of 1 day in Menomune® recipients. The higher rate of local events observed in the Menactra™ recipients is likely due to the nature of the conjugate vaccine (diphtheria carrier protein). Compared to Td vaccine, the rates of local reactions for Menactra™ were within expectations for a protein vaccine (Section 5.6.2.2 MTA12 results).

Table 20: MTA02 Percentage with Solicited Local Reactions

Reaction	Severity	Menactra™ (N=438) % Participants	Menomune® (N=441) % Participants
Any Reaction	Any	72.4	34.7
	Mild	52.5	30.6
	Moderate	18.7	4.1
	Severe	1.1	0.0
Pain	Any	68.9	30.2
	Mild	52.1	26.3
	Moderate	16.7	3.9
	Severe	0.2	0.0
Induration	Any	20.3	7.7
	Mild	16.7	7.3
	Moderate	3.0	0.5
	Severe	0.7	0.0
Swelling	Any	14.4	5.4
	Mild	11.2	4.8
	Moderate	2.5	0.7
	Severe	0.7	0.0
Redness	Any	12.1	6.3
	Mild	10.3	6.1
	Moderate	1.6	0.2
	Severe	0.2	0.0

5.6.2 Concomitant Administration

5.6.2.1 MTA11 (Menactra™ with Typhim Vi®)

Study MTA11 studied Menactra™ given alone or concomitantly with the licensed Typhim Vi® vaccine in healthy 18- to 55-year olds. In this study, 945 participants were randomized to either

one of two treatment groups: Group A received Menactra™ and Typhim Vi® concomitantly at Visit 1 and Menactra™ 28 days later at Visit 2, while Group B received Typhim Vi® and physiologic saline placebo concomitantly at Visit 1 and Menactra™ at Visit 2. A total of 469 and 476 participants were enrolled in Groups A and B, respectively and, overall, 92.2% completed the study.

Overall Participant Safety Profile

Table 21 shows the summary of the safety profile of participants in study MTA11.

Table 21: MTA11 Safety Population - Overall Participant Safety Profile

Type of Adverse Event	Group A Typhim Vi®+ Menactra™ then Placebo		Group B Typhim Vi® + Placebo then Menactra™	
	n/N	%	n/N	%
Immediate Reactions				
After 1st Vaccination (within 30 minutes)	3/469	0.6	2/476	0.4
After 2nd Vaccination (within 30 minutes)	0/433	0.0	0/446	0.0
Solicited Local Reactions (Days 0-7)				
After 1st Vaccination:				
Menactra™ Injection site (Group A) or the Placebo Injection site (Group B)	234/456	51.3	123/470	26.2
At the Typhim Vi® Injection site (Groups A and B)	353/456	77.4	364/470	77.4
After 2nd Vaccination: Placebo Injection site (Group A) or the Menactra™ Injection site (Group B)	68/427	15.9	207/439	47.2
Solicited Systemic Reactions (Days 0-7)				
After 1st Vaccination	276/456	60.5	280/470	59.6
After 2nd Vaccination	155/427	36.3	211/439	48.1
Unsolicited Adverse Events (during study)	160/435	36.8	174/448	38.8
Serious Adverse Events (during study)	1/469	0.2	1/476	0.2

Immediate Reactions

Three participants in Group A and 2 participants in Group B reported immediate reactions. The most common events were tingling at the injection site and vasovagal reactions.

Solicited Systemic Reactions

After Visit 1, the frequency of systemic reactions was similar in both treatment groups. A total of 60.5% of Group A participants and 59.6% of Group B participants reported at least one solicited systemic reaction. Most solicited systemic reactions were reported as mild and resolved within 3 days post-vaccination (Figure 21).

After Visit 2, 36.3% from Group A (placebo) reported at least one solicited systemic reaction while 48.1% were reported from Group B (Menactra™). As expected, the group receiving Menactra™ at Visit 2 experienced a higher frequency of solicited systemic reactions compared to placebo. These reactions occurred with a similar frequency in trial MTA09 where 61.9% reported at least one solicited systemic reaction. In both treatment groups, the most common reactions were headache and fatigue. Study participants reported slightly more systemic reactions when Typhim Vi® vaccine was included in the treatment schedule. For example, headache was reported in 40.6% in Group A at Visit 1 (Menactra™ + Typhim Vi®) and 41.7% of subjects in Group B (Typhim Vi® + placebo) compared to 32.6% of subjects when Menactra™ was given alone at Visit 2 or 28.1% of subjects when placebo was given alone at Visit 2.

Table 22: MTA11 Percentage with Solicited Systemic Reactions by Severity

Reaction	Severity	Group A Typhim Vi®+ Menactra™ (V1*; N=456) % Participants	Group A Placebo (V2*; N=427) % Participants	Group B Typhim Vi® + Placebo (V1*; N=470) % Participants	Group B Menactra™ (V2*; N=439) % Participants
Any Reaction	Any	60.5	36.3	59.6	48.1
	Mild	36.6	24.4	39.8	30.8
	Moderate	18.6	10.8	18.3	15.0
	Severe	5.3	1.2	1.5	2.3
Headache	Any	40.6	28.1	41.7	32.6
	Mild	27.9	22.0	31.5	23.7
	Moderate	11.4	5.9	9.8	8.4
	Severe	1.3	0.2	0.4	0.5
Fatigue	Any	37.7	18.0	35.3	27.1
	Mild	27.0	12.9	26.0	18.5
	Moderate	9.0	4.9	8.7	7.7
	Severe	1.8	0.2	0.6	0.9
Malaise	Any	23.3	11.9	23.0	19.8
	Mild	13.4	8.2	16.8	12.5
	Moderate	8.6	3.5	5.5	5.7
	Severe	1.3	0.2	0.6	1.6
Arthralgia	Any	18.5	5.6	17.4	11.6
	Mild	13.4	4.0	12.8	7.5
	Moderate	4.4	1.4	4.3	3.6
	Severe	0.7	0.2	0.4	0.5
Diarrhea	Any	11.9	4.2	11.5	7.3
	Mild	8.8	3.0	10.0	5.7
	Moderate	2.9	1.2	1.5	1.6
	Severe	0.2	0.0	0.0	0.0
Anorexia	Any	11.0	4.2	11.9	8.7
	Mild	8.1	3.5	10.2	7.3
	Moderate	2.2	0.7	1.5	0.9
	Severe	0.7	0.0	0.2	0.5
Chills	Any	6.6	3.3	4.3	8.0
	Mild	4.8	3.0	4.0	6.6
	Moderate	1.3	0.2	0.2	0.9
	Severe	0.4	0.0	0.0	0.5
Vomiting	Any	2.2	1.4	0.6	1.8
	Mild	1.1	1.2	0.2	1.6
	Moderate	0.7	0.2	0.4	0.0
	Severe	0.4	0.0	0.0	0.2
Fever	Any	0.9	0.0	0.4	1.2
	Mild	0.7	0.0	0.4	1.2
	Moderate	0.2	0.0	0.0	0.0
	Severe	0.0	0.0	0.0	0.0
Rash		2.4	0.2	0.2	0.5
Seizures		0.0	0.0	0.0	0.0

* V1 = Vaccination 1, V2 = Vaccination 2.

Solicited Local Reactions

For all participants in both treatment groups, the majority of local solicited reactions for both treatment groups were reported as mild and resolved within 3 days post-vaccination. The frequency of local reactions was similar for both treatment groups when comparing injection sites having received similar vaccines. At Visit 1 (Table 23), Group A received Typhim Vi® in one arm and Menactra™ in the opposite arm. Group B received Typhim Vi® in one arm and a placebo in the opposite arm. Comparing reactions in the Typhim Vi® site, 77.4% of participants reported at least one solicited local reaction in each treatment group. The most common reaction was pain at the injection site. Comparing local solicited reactions in the Menactra™ site in Group A participants who received Menactra™ at Visit 1 and Group B who received Menactra™ at Visit 2, 51.3% reported at least one reaction in Group A and 47.2% reported a reaction in Group B. Comparing local reactions at the placebo site, 15.9% of Group A participants (placebo at Visit 2, Table 24) reported at least one reaction while 26.2% of Group B participants reported at least one reaction (placebo at Visit 1).

The frequency of local solicited reactions is very similar to that from other adult trials (MTA09) where 57.6% of Menactra™ recipients reported at least one reaction. Similarly, the frequency of local reactions reported after Typhim Vi® vaccine are very similar to those reported in the literature (45) (46) (47) (48) (49) (50). The frequency of local reactions were more common at the Typhim Vi® injection site when compared to Menactra™.

Table 23: MTA11 Percentage with Solicited Local Reactions by Severity, Vaccination Visit 1

Reaction	Severity	Group A Vi®+ Menactra™ (V1*; N=456) (Menactra™ Injection site) % Participants	Group A Vi®+ Menactra™ (V1*; N=456) (Vi® Injection site) % Participants	Group B Vi®+ Placebo (V1*; N=470) (Vi® Injection site) % Participants	Group B Vi®+ Placebo (V1*; N=470) (Placebo Injection site) % Participant
Any Reaction	Any	51.3	77.4	77.4	26.2
	Mild	39.3	57.7	55.5	22.3
	Moderate	10.1	19.1	20.9	3.4
	Severe	2.0	0.7	1.1	0.4
Pain	Any	46.5	75.2	75.7	21.9
	Mild	38.6	57.2	57.0	19.1
	Moderate	7.2	17.5	18.1	2.8
	Severe	0.7	0.4	0.6	0.0
Induration	Any	17.1	20.0	21.7	5.7
	Mild	12.5	16.4	16.6	4.9
	Moderate	3.9	3.3	4.7	0.6
	Severe	0.7	0.2	0.4	0.2
Swelling	Any	13.4	14.9	16.8	3.8
	Mild	9.6	13.2	14.3	3.0
	Moderate	3.1	1.5	2.6	0.9
	Severe	0.7	0.2	0.0	0.0
Redness	Any	11.4	14.0	14.7	6.0
	Mild	7.0	11.4	10.9	4.9
	Moderate	3.5	2.6	3.8	0.9
	Severe	0.9	0.0	0.0	0.2

* V1 = Vaccination 1.

Table 24: MTA11 Percentage with Solicited Local Reactions by Severity, Vaccination Visit 2

Reaction	Severity	Group A Placebo (Visit 2, N=427) (Placebo Injection site) % Participants	Group B Menactra™ (Visit 2, N=439) (Menactra™ Injection site) % Participant
Any Reaction	Any	15.9	47.2
	Mild	15.2	32.8
	Moderate	0.5	11.6
	Severe	0.2	2.7
Pain	Any	13.6	43.7
	Mild	13.3	31.9
	Moderate	0.0	10.0
	Severe	0.2	1.8
Redness	Any	3.3	14.1
	Mild	3.0	9.8
	Moderate	0.2	3.6
	Severe	0.0	0.7
Swelling	Any	2.8	11.4
	Mild	2.8	7.1
	Moderate	0.0	3.4
	Severe	0.0	0.9
Induration	Any	2.8	15.3
	Mild	2.3	10.5
	Moderate	0.5	4.1
	Severe	0.0	0.7

5.6.2.2 MTA12 (Menactra™ with Tetanus and Diphtheria Toxoids Adsorbed for Adult Use)

MTA12 studied Menactra™ given concomitantly with or one month after the licensed tetanus/diphtheria (Td adsorbed) vaccine in healthy 11- to 17-year olds in the US. In this study, 1019 evaluable participants were randomized to one of two treatment groups: Group A received Td and Menactra™ concomitantly at Visit 1 and placebo consisting of physiologic saline 28 days later at Visit 2, while Group B received Td and placebo concomitantly at Visit 1 and Menactra™ at Visit 2. Of these, 96.8% completed the study.

Overall safety profile

Table 25 shows the summary of the safety profile of participants in study MTA12.

Table 25: MTA12 Safety Population - Overall Participant Safety Profile

Type of Adverse Event	Group A Td + Menactra™ then Placebo		Group B Td + Placebo then Menactra™	
	n/N	%	n/N	%
Immediate Reactions				
After 1st Vaccination (within 30 minutes)	5/507	1.0	2/512	0.4
After 2nd Vaccination (within 30 minutes)	0/493	0.0	1/503	0.2
Solicited Local Reactions (Days 0-7)				
After 1st Vaccination:				
Menactra™ Injection site (Group A) or	293/505	58.0	147/510	28.8
Placebo Injection site (Group B)				
Td Injection site (Groups A and B)	377/505	74.7	374/510	73.3
Solicited Local Reactions (Days 0-7)				
After 2nd Vaccination:				
Placebo Injection site (Group A) or	96/490	19.6	288/505	57.0
Menactra™ Injection site (Group B)				
Solicited Systemic Reactions (Days 0-7)				
After 1st Vaccination	296/505	58.6	276/510	54.1
After 2nd Vaccination	159/490	32.4	181/505	35.8
Unsolicited Adverse Events (during study)	245/492	49.8	255/505	50.5
Serious Adverse Events (during study)	2/507	0.4	1/512	0.2

Immediate Reactions

Five participants in Group A and 3 in Group B reported immediate reactions. In group A, 2 subjects reported a vasovagal episode and 2 reported dizziness; one subjects reported vomiting attributable to menstrual cramping. In Group B, 2 subjects reported dizziness and one had an episode of swelling at the injection site after Menactra™. All events were reported as mild to moderate in severity and resolved within 24 hours.

Solicited Systemic Reactions

The overall frequency of solicited systemic reactions after either Visit 1 or Visit 2 was similar between the two study groups. For participants receiving Menactra™ + Td, 58.6% reported at least one systemic event while 54.1% were reported in participants receiving Td + placebo at Visit 1 (Table 26). A similar frequency with Menactra™ (35.8%) or placebo alone (32.4%) was seen at Visit 2. Most events were reported as mild and of short duration (median duration of 2 days for Group A and 3 days for Group B).

Table 26: MTA12 Percentage with Solicited Systemic Reactions by Severity

Reaction	Severity	Group A Td + Menactra™ (V1*; N=505) % Participants	Group A Placebo (V2*; N=490) % Participants	Group B Td + Placebo (V1*; N=510) % Participants	Group B Menactra™ (V2*; N = 505) % Participants
Any Reaction	Any	58.6	32.4	54.1	35.8
	Mild	34.3	22.0	37.6	23.0
	Moderate	19.6	8.2	12.7	9.7
	Severe	4.8	2.2	3.7	3.2
Headache	Any	35.6	20.6	33.5	21.8
	Mild	23.0	15.1	25.5	15.6
	Moderate	10.7	5.3	6.7	5.5
	Severe	2.0	0.2	1.4	0.6
Fatigue	Any	31.9	13.9	29.4	16.8
	Mild	19.0	10.4	22.5	12.3
	Moderate	11.5	3.5	6.3	3.6
	Severe	1.4	0.0	0.6	1.0
Arthralgia	Any	25.1	8.0	20.2	12.1
	Mild	18.6	6.3	17.6	8.9
	Moderate	5.7	1.4	2.4	3.0
	Severe	0.8	0.2	0.2	0.2
Malaise	Any	23.6	10.6	21.0	12.1
	Mild	14.3	6.1	15.1	6.9
	Moderate	7.1	4.3	4.7	4.2
	Severe	2.2	0.2	1.2	1.0
Anorexia	Any	12.7	4.3	9.8	4.4
	Mild	8.5	2.7	7.8	3.0
	Moderate	3.2	1.6	1.4	1.0
	Severe	1.0	0.0	0.6	0.4
Chills	Any	11.1	3.1	9.6	3.6
	Mild	6.9	2.2	8.6	3.2
	Moderate	3.6	0.6	0.8	0.4
	Severe	0.6	0.2	0.2	0.0
Diarrhea	Any	8.9	4.7	7.3	3.8
	Mild	7.7	3.9	6.7	3.0
	Moderate	1.0	0.6	0.4	0.8
	Severe	0.2	0.2	0.2	0.0
Fever	Any	5.0	1.2	2.2	2.2
	Mild	3.8	1.0	2.0	2.0
	Moderate	1.0	0.0	0.2	0.2
	Severe	0.2	0.2	0.0	0.0
Vomiting	Any	4.6	1.2	2.4	1.4
	Mild	3.4	0.8	1.2	1.0
	Moderate	1.2	0.2	0.6	0.2
	Severe	0.0	0.2	0.6	0.2
Rash		1.8	1.4	1.6	1.4
Seizures		0.0	0.0	0.0	0.0

* V1 = vaccination 1; V2 = vaccination 2

Solicited Local Reactions

Local reactions were compared based upon the site of vaccination as well as the type of vaccine administered. At Visit 1 (Table 27), reactions reported at the Td site of vaccination occurred with similar frequencies, with 74.7% reporting at least one event in Group A while 73.3 % reported the same in Group B. Most reactions were mild or moderate in severity and the median duration was 3 days. The local reactogenicity profile for Td was similar when given either concomitantly with Menactra™ or alone.

The Menactra™ vaccination sites were compared at Visits 1 and 2 (Table 28). The frequency of participants reporting at least one event was very similar between both groups: 58.0% in Group A at Visit 1 and 57.0% in Group B at Visit 2. Most reactions were classified as mild and severe reactions were uncommon. The median duration was 2 days. The local reactogenicity profile for Menactra™ given either concomitantly with Td or 28 days after Td were similar. Additionally, local reactions at the Menactra™ injection site were less frequently than those at the Td injections site.

Table 27: MTA12 Percentage with Solicited Local Reactions by Severity, Vaccination Visit 1

Reaction	Severity	Group A Td + Menactra™ (V1* N=505) (Menactra™ Injection site) % Participants	Group A Td + Menactra™ (V1* N=505) (Td Injection site) % Participants	Group B (Td + Placebo) (V1* N = 510) (Td Injection site) % Participants	Group B (Td + Placebo) (V1* N = 510) (Placebo Injection site) % Participants
Any Reaction	Any	58.0	74.7	73.3	28.8
	Mild	44.6	49.1	49.2	26.1
	Moderate	11.3	24.2	21.2	2.5
	Severe	2.2	1.4	2.9	0.2
Pain	Any	52.9	70.9	71.0	22.7
	Mild	42.2	48.3	50.4	20.4
	Moderate	10.7	22.4	20.4	2.4
	Severe	0.0	0.2	0.2	0.0
Induration	Any	17.0	20.8	25.9	7.6
	Mild	13.5	14.9	21.8	7.1
	Moderate	2.6	5.3	2.9	0.6
	Severe	1.0	0.6	1.2	0.0
Redness	Any	12.1	14.5	17.5	4.9
	Mild	10.3	11.5	12.5	4.5
	Moderate	0.6	2.4	3.3	0.4
	Severe	1.2	0.6	1.6	0.0
Swelling	Any	11.7	16.4	20.8	4.7
	Mild	9.3	12.5	15.7	3.9
	Moderate	1.8	3.8	3.7	0.6
	Severe	0.6	0.2	1.4	0.2

*V1 = Visit 1

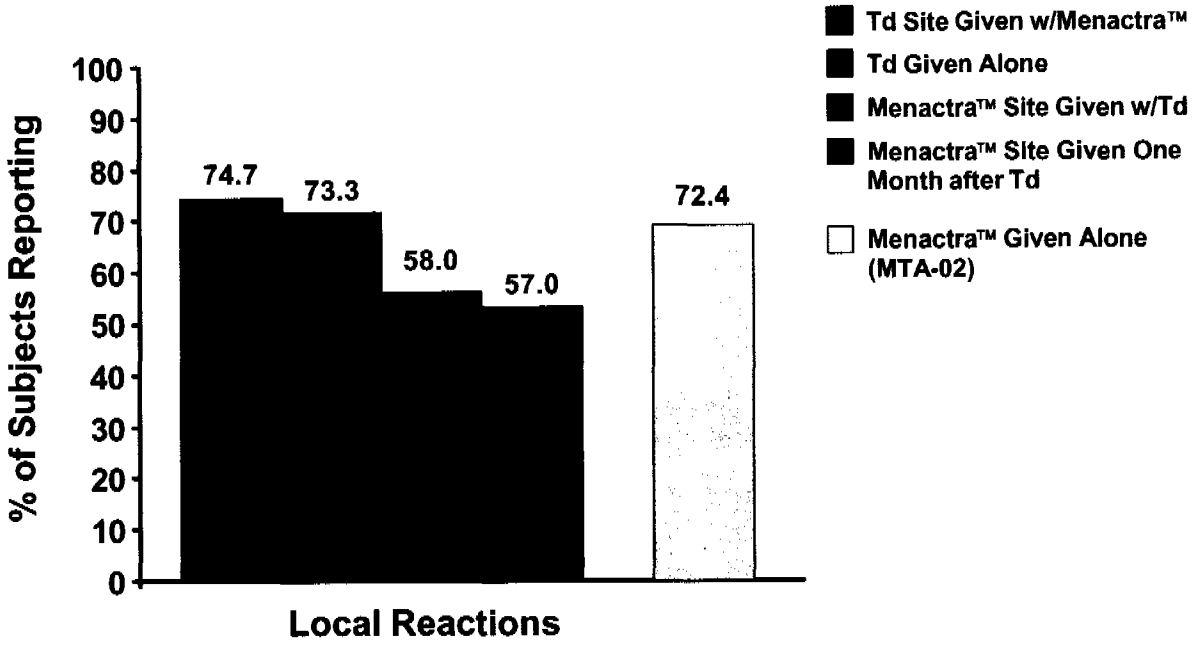
Table 28: MTA12 Percentage with Solicited Local Reactions by Severity, Vaccination Visit 2

Reaction	Severity	Group A Placebo (V2; N=490) % Participants	Group B Menactra™ (V2; N=505) % Participants
Any Reaction	Any	19.6	57.0
	Mild	18.0	40.6
	Moderate	1.6	14.3
	Severe	0.0	2.2
Pain	Any	15.5	53.5
	Mild	14.3	39.2
	Moderate	1.2	13.5
	Severe	0.0	0.8
Induration	Any	4.7	15.4
	Mild	4.3	12.1
	Moderate	0.4	2.4
	Severe	0.0	1.0
Swelling	Any	1.6	13.1
	Mild	1.4	8.7
	Moderate	0.2	3.0
	Severe	0.0	1.4
Redness	Any	4.3	11.1
	Mild	3.9	7.9
	Moderate	0.4	2.2
	Severe	0.0	1.0

*V2 = Visit 2

Figure 34 shows the overall rates of local reactions at the Td and Menactra site in MTA12 and the rate of local reactions reported by the Menactra recipients in MTA02. The rates observed for the Menactra recipients in MTA02 were similar to the rates observed for Td in MTA12. These results show that in adolescents, the local reactogenicity rate for Menactra™ is comparable to Td vaccine.

Figure 34: MTA12 Comparison of the Frequency of Local Reactions by Injection Site



5.7 Unsolicited Adverse Events

Day 0 to Day 28

Across all studies, 28.3% of Menactra™ participants and 28.6% of Menomune® participants reported at least one unsolicited AE from Day 0 to Day 28. The most frequent unsolicited AEs reported by at least 1% of participants are presented in Table 29 . The frequencies of the events reported were similar between the two vaccine groups. Most of the AEs were of mild or moderate severity. Of Menactra™ participants, 0.9% reported at least one severe unsolicited AE compared to 1.1% of Menomune® participants. Only 0.2% (7 participants) of Menactra™ participants presented at least one unsolicited AE considered by the investigator to be definitely related to study vaccine compared to 0.3% (2 participants) in Menomune® group. These events included injection site reactions, ecchymosis, dizziness, malaise, thinking abnormal, arthralgia, pruritus, and sweating.

Table 29: Safety Population - Unsolicited Adverse Events (During Day 0 to Day 28)

Body System / Adverse Event	Menactra™ (N = 7670) % Participants	Menomune® (N = 3041) % Participants
Body as a Whole		
Infection	2.9	4.1
Pain	2.0	1.9
Injury Accidental	1.9	1.9
Pain back	1.8	1.4
Allergic reaction	1.6	1.6
Headache	1.2	1.3
Pain abdominal	0.8	1.2
Respiratory System		
Pharyngitis	3.7	4.4
Rhinitis	2.9	3.4
Increased cough	1.6	1.2
Sinusitis	1.1	1.0
Urogenital System		
Dysmenorrhea	3.1	3.3
Digestive System		
Dyspepsia	0.9	1.5

Day 29 to Month 6

From Day 29 through Month 6, adverse events considered significant were recorded (see Appendix 1). A total of 5.8% of Menactra™ participants reported at least one unsolicited significant adverse event and 5.7% of Menomune® participants reported at least one unsolicited significant AE (Table 30). No difference was observed in the incidences of reported events in Menactra™ and Menomune® recipients. Most of the reported unsolicited significant AEs were of mild or moderate severity, and only 0.8% of Menactra™ participants and 1.0% of Menomune® participants reported at least one severe unsolicited significant AE. Most of the reported events were considered unrelated to study vaccine in both groups. Only 0.3% of Menactra™ and 0.1% of Menomune® participants presented at least one unsolicited significant AE considered as possibly related to study vaccine.

Table 30: Safety Population - Unsolicited Adverse Events (During Day 29 to Month 6)

Body System	Menactra™ (N = 5676) % Participants	Menomune® (N = 3041) % Participants
At Least one Unsolicited significant AE	**5.8**	**5.7**
Body as a Whole	2.2	1.5
Skin and Appendages	1.0	0.8
Respiratory System	1.0	1.0
Urogenital System	0.8	0.8
Musculoskeletal System	0.5	0.5
Digestive System	0.4	0.5
Nervous System	0.4	0.5
Hemic and Lymphatic System	0.3	0.3
Cardiovascular System	0.2	0.3
Special Senses	0.2	0.3
Metabolic and Nutritional Disorders	0.1	0.1
Endocrine System	0.0	0.1

5.8 Serious Adverse Events

There were 77 (1.0%) Menactra™ recipients and 39 (1.3%) Menomune® recipients who reported a serious adverse event. All SAEs, except one, were reported as unrelated to study vaccine. One event was reported as possibly related by the investigator and was reported to the FDA in an expedited report. The participant was a 17-year old male who reported a sports related injury about 4 weeks prior to enrollment in the study. He took over-the-counter non-steroidal anti-inflammatory medication for 4 weeks without relief. His physician subsequently prescribed Vioxx which he took prior to enrollment. Two days after receiving the study vaccine, he experienced fever, chest discomfort and difficulty in swallowing. A diagnosis of esophagitis with distal

ulcerations was made by endoscopy. He was treated and recovered without sequelae. The esophagitis likely has an alternative explanation given the history of non-steroidal anti-inflammatory use.

There were 2 deaths reported across all studies. Both of these events were reported as unrelated to vaccine by the investigator. One participant was killed in a motor vehicle accident and the other participant died after a drug overdose.

5.9 Safety - Conclusions

The safety of Menactra™ was evaluated in six clinical studies where a total of 7642 participants were vaccinated. Based on the data from these studies it is possible to draw the following conclusions:

- Menactra™ was safe and well-tolerated in adolescents and adults.
- The systemic safety profiles of Menactra™ and Menomune® are similar, and both vaccines are well tolerated. Menactra™ was demonstrated to be non-inferior to Menomune® by the proportion of participants with at least one severe solicited systemic reaction. Headache, fatigue, malaise, arthralgia, diarrhea, and anorexia were the most commonly reported solicited systemic reactions. The majority of solicited systemic reactions were mild and of short duration.
- Local reactions were more frequently reported in Menactra™ recipients than in Menomune® recipients. The rates of local reactions seen with Menactra™ are comparable to, or less than the rates seen with Td vaccine and are consistent with expectations for diphtheria containing vaccines. Most local reactions were mild and of short duration. Pain at the injection site was the most commonly reported solicited local reaction and in most cases was mild in nature and of short duration.
- The majority of unsolicited AEs in both vaccine groups were classified as unrelated to study vaccine. The types of events and their frequencies were similar in the Menactra™ and Menomune® recipients.
- The safety profile of Menactra™ was similar when it was administered concomitantly or 28 days after Td vaccine or Typhim Vi® and therefore, Menactra™ can be administered concomitantly with Td or Typhim Vi® vaccines in adolescents and adults.

6 Overall Conclusions – Benefit/Risk Assessment

The clinical data submitted to the eBLA and described in this briefing document included a total of 10,683 participants aged 11 to 55 years who were enrolled in six clinical studies performed in the US. Participants received either one dose of Menactra™ (N = 7642) or one dose of

Menomune® (N = 3041). This license application, has focused on adolescents and adults, who are included in the existing meningococcal vaccine recommendations:

- Adolescents aged from 11 to 18 years
- Adults aged from 18 to 55 years

The basis of the license application for Menactra™ is the demonstration of non-inferiority when compared to the licensed polysaccharide vaccine Menomune®.

Benefit Assessment - Immunogenicity

Menactra™ has been shown to be highly immunogenic in the populations studied, based on four-fold rise in SBA titers, seroconversion rates, and geometric mean titers. All hypothesis-driven immunogenicity comparisons confirmed the non-inferiority of the immune responses induced by Menactra™ compared with those induced by Menomune®. Follow-up of a subset of participants from MTA02 demonstrated the persistence of SBA antibodies for at least three years. Furthermore, Menactra™-primed subjects displayed rapid and substantial booster responses following a second dose of Menactra™ administered three years after receiving the primary dose. These data confirm that Menactra™ demonstrates the characteristics expected of a conjugate vaccine: priming, memory, and boosting.

Risk Assessment - Safety

Menactra™ was safe and well tolerated among adolescents and adults. Menactra™ was demonstrated to be non-inferior to Menomune® with respect to the proportion of subjects who reported severe systemic reactions. Although local reactions were more frequently reported in Menactra™ recipients than in Menomune® recipients, this was not unexpected given the nature of the vaccine. The majority of the local reactions were mild and of short duration, and the local reactogenicity profile of Menactra™ was comparable to that of Td vaccine.

Conclusions

The Menactra™ clinical development program has demonstrated Menactra™ to be safe, immunogenic, and non-inferior to Menomune® with respect to hypothesis-driven comparisons. The safety profile of Menactra™ is similar to that of Menomune® and Td vaccine, and the aggregate safety database does not appear to contain any signals suggesting a pattern of rare adverse events. The demonstrated immune responses are in accord with those expected of a conjugate vaccine and support the inference of efficacy. Based on these results, we anticipate that Menactra™ can induce immunologic memory in the targeted age groups, provide long-term primary protection, reduce carriage rates, and thereby provide herd immunity.

The balance of benefits and risks support the use of Menactra™ for active immunization for the prevention of invasive meningococcal disease due to serogroups A, C, Y and W-135.

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Appendix 1: Definition of Safety Parameters

Immediate Reactions (Within 30 minutes)

An immediate reaction was defined as any AE that occurred (onset) within the 30-minute period following any vaccination. Clinical severity and relatedness to the study vaccines of all immediate reactions were documented.

Solicited Local Reactions (Days 0-7)

Solicited local reactions included redness, swelling, induration and pain at the injection site. Data were collected on pre-printed diary cards on Day 0 through Day 7 after vaccination.

Any of the events on the diary card that began on or after Day 8 were reported and analyzed as unsolicited AEs. Solicited local reactions were collected following all study visits in which vaccination(s) was (were) performed and for all vaccine injection sites.

The clinical severity (mild, moderate, severe) of all solicited local reactions was documented.

Rules for Clinical Severity Ranking of Solicited Local Reactions

For the 'redness', 'swelling', 'induration' and 'bruising' reactions:

0 = None

1 = Mild: < 1.0 inch

2 = Moderate: 1.0 – 2.0 inches (inclusive)

3 = Severe: > 2.0 inches

The longest diameter in inches was recorded for each these reactions and used to rank them based on the above scale.

For 'pain at injection site' reaction:

0 = None

1 = Mild: symptom present, but vaccination site member movement was not affected

2 = Moderate: discomfort, interferes with or limits vaccination site member movement

3 = Severe: disabling, individual unable to move vaccination site member

Solicited Systemic Reactions (Days 0-7)

Solicited systemic reactions included: temperature, anorexia, vomiting, diarrhea, headache, rash, fatigue, chills, arthralgia, malaise, seizures. Data were collected on pre-printed diary cards on Days 0 through 7 after vaccination.

Any of the events on the diary card that began on or after Day 8 were reported and analyzed as unsolicited AEs. Solicited systemic reactions were collected following all study visits in which vaccination(s) was (were) performed.

The clinical severity (mild, moderate, severe) of all solicited systemic reactions was documented.

Rules for Clinical Severity Ranking of Solicited Systemic Reactions

Fever: the participant's highest oral temperature in °F was recorded in the diary on the evening of and for 7 days following all vaccinations. All temperatures were collected orally in °F and converted to °C using the following equation: (°F – 32)/1.8 = °C

0 = < 37.5

1 = Mild: 37.5°C – 38.4°C

2 = Moderate: 38.5°C – 39.4°C

3 = Severe: ≥ 39.5°C

Fatigue, Arthralgia, Chills and Malaise:

0 = None

1 = Mild: aware but easily tolerated

2 = Moderate: interferes with normal activities

3 = Severe: disabling, requires bed rest

Anorexia:

0 = Same as usual

1 = Mild: skips 1 meal

2 = Moderate: skips 2 meals

3 = Severe: skips ≥ 3 meals

Vomiting (per 24 hours):

0 = None

1 = Mild: 1 episode

2 = Moderate: 2 episodes

3= Severe: ≥ 3 episodes

Diarrhea (defined as 'looser than normal stools') (per 24 hours):

0 = Same as usual stools

1 = Mild: 1 – 2 diarrhea stools

2 = Moderate: 3 – 4 diarrhea stools

3 = Severe: ≥ 5 diarrhea stools

Headache:

0 = None

1 = Mild: aware but easily tolerated

2 = Moderate: discomforting enough to interfere with activities

3 = Severe: disabling requires bed rest and analgesics

Seizure: Yes/No

Rash: Yes/No

The nature of rashes was documented as:

- Generalized or localized
- Raised or not raised
- Itchy or not itchy
- Blanching or not blanching
- Pink or red or purple or brown or other

In addition, the duration of each rash was documented.

Unsolicited Adverse Events - Day 0 to Day 28

An unsolicited AE was defined as any AE not identified as a solicited event that occurred between Days 0-28. AEs were coded using the COSTART dictionary, and were classified by body system and COSTART preferred term (abbreviated format). Clinical severity and relatedness to the study vaccines of all unsolicited AEs Days 0-28 were assessed by the investigators and documented.

Rules for Clinical Severity Ranking of Unsolicited Adverse Event

The clinical intensity was ranked using the following rule:

0 = None,

1 = Mild; awareness of sign or symptom, but easily tolerated,

2 = Moderate; discomfort enough to cause interference with usual activity,

3 = Severe; incapacitating with inability to do usual activity.

Rules for Ranking Relatedness of Vaccination to Unsolicited Adverse Event

The relatedness to vaccination was evaluated by the investigator using the following definitions:

Relationship to vaccine: Definite/Certain: is applied to these AEs which have a timely relation to the study vaccine and no alternative etiology is present. It must have occurred within a reasonable temporal sequence of the vaccine administration (0 – 7 days), must not be reasonably explained by any alternative etiology, and must follow a known pattern of response.

Probable: has a timely relation to the study vaccine and a potential alternative etiology is not apparent (i.e., fever or malaise when no other symptoms suggestive of an illness are present).

Possible: has a timely relation to the study vaccine; however, a potential alternative etiology exists which may be responsible for the symptom (i.e., fever or malaise when other symptoms are present that suggest another etiology such as URI).

Unrelated/Unlikely: is applied to these AEs where evidence exists that the symptom is definitely related to an etiology other than the study vaccine (i.e., auto accident, or a symptom suggestive of another illness, which is not accepted to be a possible reaction to the vaccine).

Unsolicited Adverse Events - Day 29 to Month 6

Comparative safety was evaluated between Day 29 and 6 Months while concomitant safety was limited to Day 56 post-vaccination. In order to maximize the relevance of this follow-up, only significant AEs from the period Day 29 through Month 6 were collected.

Significant AEs were defined as any new onset of a sign, symptom, or laboratory abnormality discovered within the period Day 29-Month 6 following vaccination which prompted the participant to seek medical advice or attention either at a physician's office or Emergency Department, or required hospitalization. This definition excluded, but was not limited to, care for common medical ailments such as upper respiratory infection, urinary tract infections, sinusitis, otitis, sports related injuries or pre-existing medical conditions. Particular attention was given to newly diagnosed or new onset of febrile or afebrile seizure, idiopathic thrombocytopenia, autoimmune hemolytic anemia, bronchial asthma, insulin dependant diabetes mellitus, neutropenia and autoimmune disease not otherwise specified. Unsolicited AEs (Days 29-Month 6) were coded using the COSTART dictionary and were classified by body system and COSTART preferred term (abbreviated format). Clinical severity and relatedness to the study vaccines were assessed by the investigators and documented.

Serious Adverse Events

A serious adverse event (SAE) was defined as any AE which occurred any time during the participant's presence in the study that resulted in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization were also considered as SAE when, based upon appropriate medical judgment, induced medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

The clinical severity and relatedness to the study vaccines of all SAEs were documented.

By definition, all the events categorized as SAEs were also reported in one of the four above-mentioned safety categories (i.e., SAEs are a subset of all AEs or reactions in each time period).