COMPARATIVE CLINICAL TRIAL OF THE SAFETY, IMMUNOGENICITY AND PROTECTIVE EFFICACY OF ONE DOSE OF A TETRAVALENT (A, C, Y AND W-135) MENINGOCOCCAL POLYSACCHARIDE DIPHTHERIA TOXOID CONJUGATE VACCINE VERSUS A LICENSED TETRAVALENT MENINGOCOCCAL POLYSACCHARIDE DIPHTHERIA TOXOID CONJUGATE VACCINE (MENACTRA) IN SUB-SAHARAN AFRICA WITHIN THE MENINGITIS BELT.

FINAL REPORT

COMPILED BY

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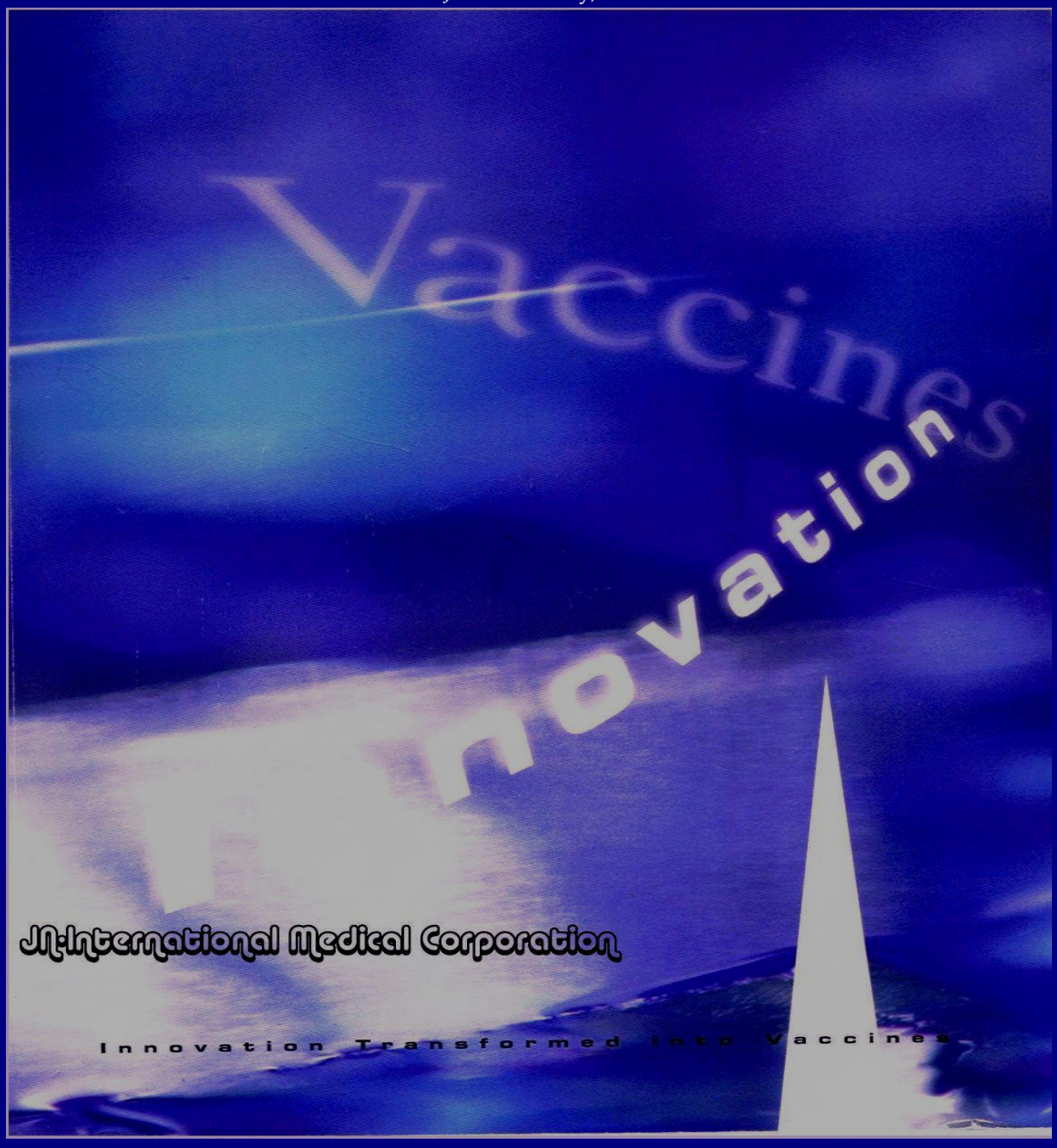

CONFIDENTIAL DOCUMENT

COMPARATIVE CLINICAL TRIAL OF THE SAFETY, IMMUNOGENICITY AND PROTECTIVE EFFICACY OF ONE DOSE OF A TETRAVALENT (A, C, Y AND W-135) MENINGOCOCCAL POLYSACCHARIDE DIPHTHERIA TOXOID CONJUGATE VACCINE VERSUS A LICENSED TETRAVALENT MENINGOCOCCAL POLYSACCHARIDE DIPHTHERIA TOXOID CONJUGATE VACCINE (MENACTRA) IN SUB-SAHARAN AFRICA WITHIN THE MENINGITIS BELT.

PREFACE

Over the past decade, we have witnessed important changes in the epidemiology of Meningococcal disease, with a higher incidence of infection and a shift from Serogroups A & C to A, C, Y and W-135. Apart from epidemics, at least 1.2 million cases of bacterial meningitis are estimated to occur every year; 135,000 of them are fatal. Approximately 500,000 of these cases and 50,000 of the deaths are due to Meningococcus. Meningococcal disease is one of the most significant contributors to morbidity and mortality in children and young people in the world. In sub-Saharan Africa epidemics flaring for 2 to 3 consecutive years with epidemic cycles every 8 to 12 years were observed in the past, and the intervals between major epidemics have become shorter more irregular and unpredictable. Meningococcal meningitis is the only form of bacterial meningitis, which causes epidemics. Dry weather from December to June, overcrowded living conditions in villages and high prevalence of upper respiratory tract infections which make the individual susceptible to infection are all contributors to the survival, spread, high incidence and epidemics of meningococcal infection in 18 countries of sub-Saharan Africa, called the meningitis belt. There is an urgent need of a more promising and affordable vaccine for usage in mass immunization in these under developed countries as a preventive measure to tackle this problem.

Our Clinical Trial Report details evaluation of the immunogenicity, protective efficacy and safety of one dose of NmVac A, C, Y, W-135 DT conjugate vaccine compared to Aventis Pasteur's Menactra A, C, Y, W-135 DT conjugate vaccine in 101 naïve healthy volunteers, 13 to 30 years of age, in city of Bouake in Ivory Coast. The immune response to meningococcal capsular polysaccharides conjugated to carrier protein, the diphtheria toxoid, is by T-helper cell activation the benefits of which are an enhanced immune response, affinity antibody maturation, immunologic memory hence the response can be boosted and elicits herd immunity. These are lacking in the plain polysaccharide vaccine. The report clearly acknowledges the development of an effective and safe vaccine against meningococcal infection which being affordable can be used in mass immunization and campaigns in the underdeveloped countries of sub-Saharan Africa with the highest burden of this disease in the world. This would serve as a preventive and control measure against the increasing incidence and changing epidemiology of the disease. The risk to benefit ratio would apply to the general population and aid in improving public health. Prevention is always better than cure!!

Jeeri R. Reddy

Jeeri R. Reddy, M.S., Ph.D.
Director Research and Development

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3.0 PRODUCT INFORMATION

3.1 PRODUCT NAME

3.1.1 Generic Name : Meningococcal(Serogroups A,C,Y,W-135)Polysaccharide Diphtheria Toxoid Conjugate Vaccine.

3.1.2 Proposed Trade Name: NmVac A, C, Y, W-135 DT conjugate vaccine.

3.2 PRODUCT APPROVAL DETAILS

3.2.1 USA IBC Approval Number: **Date:**

3.2.2 USA IEC Approval Number: **Date:**

3.2.3 IRB Approval Number: **Date:**

3.3 SPONSOR: JN-International Medical Corporation, Omaha, Nebraska, USA.

3.4 PHARMACOLOGIC CATEGORY: Vaccine

3.5 PRODUCT COMPOSITION: NmVac A, C, Y, W-135 DT conjugate vaccine is a sterile, clear to slightly turbid liquid, composed of Neisseria Meningitidis serogroups A, C, Y and W-135, purified capsular polysaccharides antigens, each of them conjugated to diphtheria toxoid protein. Each 0.5 ml dose of the vaccine is formulated in sodium phosphate buffered isotonic sodium chloride solution to contain 4 µg each of meningococcal A, C, Y and W-135 polysaccharides conjugated to approximately 48 µg of diphtheria toxoid protein as a carrier. It also contains Lactose as a stabilizer.

3.6 HOW SUPPLIED: 1 ml Vial.

3.7 STORAGE: 2°C to 8°C.Away from sunlight. Do not freeze.

3.8 SHELF LIFE: 24 months stored at 2°C to 8°C.

3.9 DOSING REGIMEN: Single Dose of 0.5 ml.

3.10 PROPOSED INDICATION: Active immunization of adolescents and adults 11-55 years age

3.11 CONTRAINDICATION: (1) Individuals who are Latex sensitive, as the stopper of the vial contains dry natural rubber latex, which may cause allergic reactions in them. (2) Individuals with any bleeding disorder such as hemophilia or thrombocytopenia or patient on anti-coagulant therapy, should be used with caution, because of the risk of haemorrhage and hematoma formation. (3) Individuals with history of Gullian Barre syndrome.

3.12 DRUG INTERACTION: 1) Concomitant use with other vaccines refer to the principal investigator.
2) Immunosuppressive therapy may reduce the immune response to the vaccine.

3.13 USE IN PREGNANCY AND LACTATION: Can be vaccinated, with caution.

3.14 DRUG SUPPLIES AND LABELS: Yes, as per the stipulated guidelines.

3.15 DRUG ACCOUNTABILITY: Yes.

4.0 INTRODUCTION AND BACKGROUND

4.1 EPIDEMIOLOGY OF MENINGOCOCCAL DISEASE

Invasive Meningococcal Disease is caused by a bacterium Neisseria Meningitidis, the common manifestations of which are meningococcemia and meningitis, others being pneumonia and occult bacteremia. Worldwide, at any given time, 25% of the population are carriers of this bacterium in the nasopharynx. Transmission occurs from person to person through droplets of nasopharyngeal secretions. This is an acute, contagious and potentially life threatening disease characterized by sudden onset of fever, headache, stiff neck which can progress rapidly to coma and death. Even with early and appropriate treatment patients can die within 24 to 48 hours.

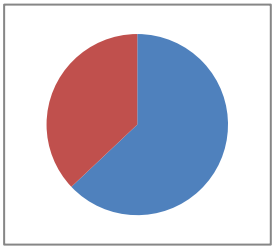
Meningococcal disease occurs globally. The disease is endemic in temperate climates causing a steady number of sporadic cases or small clusters with a seasonal increase in winter and spring. A different pattern, with epidemics flaring for 2 to 3 consecutive years, which are widespread and unpredictable has been observed in sub-Saharan African countries. This area has experienced epidemic cycles every 8 to 12 years in the past, and the intervals between major epidemics have become shorter and more irregular since the beginning of the 1980s. Meningococcal meningitis is the only form of bacterial meningitis, which causes epidemics. Epidemics occur in the dry season. While the highest disease rates are found in young children, during epidemics older children, teenagers and young adults are also affected.

Important changes in the epidemiology of Meningococcal disease, with a higher incidence of infection and a shift of Serogroups A and C to Serogroups A, C, Y and W-135 have occurred over the past decade. In the late 1990s, the incidence of infections caused by group C Meningococci alone accounted for about 40% of infections. Apart from epidemics, about 1.2 million cases of bacterial meningitis occur every year, 135,000 of which are fatal. Meningococcus accounts for about 500,000 of these cases and 50,000 of the deaths. Meningococcal disease is one of the most significant contributors to morbidity and mortality in children and young people. Indeed, in individuals younger than 20 years of age, it is the foremost infectious cause of death. The overall mortality rate is 7% to 19% and for meningococcemia is 18% to 53%. Despite susceptibility of the meningococcus to many antibiotics, there is a morbidity of 10% to 20% in the form of permanent sequelae such as digit and limb loss due to ischaemia, neurosensory hearing loss, cognitive defects and seizure disorder.

Figure:1 Population Mortality due to Bacterial Meningitis per year (excluding epidemics)

Neisseria Meningitidis: 37% (50,000)

Other Bacterial Pathogens: 63% (85,000)



Hence, Neisseria Meningitidis is the major contributor of mortality due to bacterial meningitis.

4.2 IMMUNE CORRELATE

4.2.1 ENZYME-LINKED IMMUNOSORBENT ASSAY

Enzyme-linked immunosorbent assay (ELISA, EIA) is a highly versatile and sensitive technique that is used for quantitative as well as qualitative determination of almost any antigen or antibody. Reagents are stable, non-radioactive and, in most cases, commercially available. Owing to the simplicity and versatility of the method, ELISA represents probably one of the most used methods for studying antibody responses and antibody levels. Since Engvall and Perlmanºs first paper describing the ELISA, almost all laboratories working in serology or immunology have designed their own assays with different protocols for coating with antigens, incubation conditions, detecting systems, and ways of reporting of the results. In most cases, there is no need for strict inter-laboratory standardization of ELISAs and each laboratory will develop a system that suits their needs. However, for some ELISAs, e.g., used in diagnostic laboratories and in vaccine trials, standardization is important.

Noncompetitive ELISAs used to detect anti meningococcal antibodies involve: 1) coating of a microtiter plate with the antigen to be studied; 2) blocking of unbound sites on the plate with an immunologically neutral protein; 3) addition of test sera and specific binding of antibodies to the solid-phase antigen on the plate; 4) addition of a detector antibody that recognizes the class or subclass of serum antibody; 5) generation of a color change on the ELISA plate linked to the amount of bound detector antibody; 6) calculation of concentration of specific antibodies in test sample.

4.2.2 SERUM BACTERICIDAL ANTIBODY

Although some investigators have described the immunogenicity of meningococcal vaccines in terms of the presence of polysaccharide binding antibody measured by radio-immuno assay, radio-antigen binding assay, enzyme linked immunosorbent assay or hemagglutination, only bactericidal titres measured by serum bactericidal assay (SBA) are shown to be associated with protection from meningococcal disease. The prevalence of meningococcal disease is inversely proportional to the polysaccharide specific bactericidal titre in the serum.

Principle of Assay N. Meningitidis target strains are lysed in the presence of meningococcal specific antibody and complement (antibody mediated complement dependent killing). Serial dilutions of human sera are incubated with appropriate target strains and complement. Meningococcal specific antibody binds to the target cell surface via meningococcal specific protein or carbohydrate moieties. The serum bactericidal titer for each unknown serum is expressed as the reciprocal serum dilution yielding 50% killing as compared to the number of target cells present before incubation with serum and complement.

4.3 RATIONALE (SIGNIFICANCE) FOR SELECTED FORMULATION

NmVac A, C, Y, W135 DT conjugate vaccine is composed of N.Meningitidis serogroups A, C, Y & W135 purified capsular polysaccharides antigens each of which are conjugated to diphtheria toxoid as a carrier protein. With a shift from Sero-groups A & C to Sero-groups A, C, Y & W-135 in several countries in Central Africa causing wide spread epidemics, a vaccine covering these four serogroups has attained considerable significance to control the spread of the meningococcal disease.

Plain polysaccharides(or other macromolecules with a repeating structure) are able to induce an immune response, by directly activating B lymphocytes. Hence the immune response in infants and at later ages of life is poor, of short duration, the affinity does not mature and has no immunologic memory, therefore the response cannot be boosted and no herd immunity is possible.

It was recognized early this century that small molecules, called haptens, can be made immunogenic after conjugation to carrier proteins. This principle was applied successfully to improve the immunogenicity of polysaccharides. The carrier proteins ensure the involvement of T-helper lymphocytes in the activation of the hapten or polysaccharide specific antibody producing B lymphocytes.

The immune response to polysaccharides conjugated to carrier protein the diphtheria toxoid, is by T cell activation the benefits of which are an enhanced immune response, affinity antibody maturation, immunologic memory hence the response can be boosted and elicits herd immunity. These are lacking in the tetravalent plain polysaccharide vaccine and it is also expensive for usage in mass immunization and therefore, it has not been used in the general population for its eradication worldwide.

JNI has developed a tetravalent polysaccharide A, C, Y & W-135 DT conjugate vaccine which is immunologically efficient even in infants and children and is cost-effective for usage in mass immunization.

5.0 PRODUCT COMPOSITION, MANUFACTURE AND CONTROLS

5.1 PRODUCT COMPOSITION

NmVac A, C, Y, W-135 DT conjugate vaccine is a sterile, clear to slightly turbid liquid, composed of Neisseria Meningitidis serogroups A, C, Y and W135 purified capsular polysaccharide antigens each of them conjugated to diphtheria toxoid protein. Each 0.5 ml dose of the vaccine is formulated in sodium phosphate buffered isotonic sodium chloride solution to contain 4 µg each of meningococcal Serogroups A, C, Y & W135 capsular polysaccharides conjugated to approximately 48 µg of diphtheria toxoid protein as a carrier. It contains Lactose as a stabilizer.

5.2 PRODUCT MANUFACTURE

Institute Pasture, Cote d' Ivory for
JN-International Medical Corporation, Omaha, Nebraska, USA.

5.3 VACCINE STABILITY STUDIES

5.4 CONTROL VACCINE

Menactra of Aventis Pasteur (Meningococcal Serogroups A, C, Y & W135 Polysaccharides Diphtheria Toxoid Conjugate Vaccine).

Each 0.5 ml dose of the vaccine contains:

- 4 µg each of meningococcal serogroups A, C, Y & W 135 capsular polysaccharides.
- 48 µg of diphtheria toxoid protein total (each polysaccharide is conjugated to diphtheria toxoid)
- 0.6 mg of sodium phosphate.
- 4.4 mg of sodium chloride.

The vaccine contains neither an adjuvant nor a preservative.

5.5 VACCINE LOTS DETAILS

(1) NmVAC : (Test Vaccine) Lot Number: A00017A, Expiry: 01 July 2007.
Manufactured by: Institute Pasture, Cote d' Ivory

(2) MENACTRA: (Reference Vaccine) Lot Number: U2003AA, Expiry: 01 September 2007,
Lot Number: U1997AA, Expiry: 13 July 2007.

Manufactured by: Aventis Pasteur.

6.0 ANIMAL PHARMACOLOGY AND TOXICOLOGY STUDIES

Animal studies conducted at Spring Valley Laboratories, Woodbine, Maryland, USA, under the guidance from JN International, Inc, USA involving 24 Balb/c mice and 24 Neonatal mice have demonstrated that NmVac A, C, Y & W-135 DT conjugate is safe and non-toxic. In-vitro bactericidal assays conducted at Institute Pasture, Cote d' Ivory has demonstrated that NmVac A, C, Y & W-135 DT conjugate elicited good immune response providing sero-conversion rates as measured by bactericidal antibody assays: Sensitivity: Group A: 81%, Group C: 87%, Group Y: 90% and Group W-135: 82%; Specificity: Group A: 86%, Group C: 82%, Group Y: 91% and Group W-135: 93%.

7.0 CLINICAL STUDIES

7.1 OVERVIEW OF CLINICAL STUDIES

STUDY	DESCRIPTION	STUDY POPULATION	NUMBER OF PARTICIPANTS ENROLLED		
			TOTAL (N)	NmVAC	MENACTRA
Bouake in Ivory Coast	Safety and Immunogenicity	13- 30 Years Male & Female	101	49	52

112 volunteers were screened, out of which 101 volunteers were found to be eligible for entering the clinical study. The enrolled and coded participants were administered the coded vaccine (NmVac or Menactra) by double blind, random sampling and hence entered into 2 groups for the comparative, double blind, randomized controlled study. The participants were assessed at follow-up visits. All the volunteers in each group completed the trial.

7.2 OBJECTIVES

MAIN OBJECTIVE

To evaluate the Safety, Immunogenicity and Protective Efficacy of a new vaccine NmVac A, C, Y and W-135 DT conjugate against Meningococcal infection.

SPECIFIC OBJECTIVES

- To evaluate the Safety, Immunogenicity and Protective Efficacy of a new vaccine NmVac A, C, Y and W-135 DT conjugate against Meningococcal infection in naive healthy human volunteers, both females and males, between 13-30 years age.

- To study the correlation between the antibody titers and protective efficacy of NmVac A, C, Y and W-135 DT conjugate vaccine compared to Aventis Pasture Menactra A, C, Y and W-135 DT conjugate vaccine.
- To study the levels of antibody titres after a single injection with NmVac A,C,Y,W-135 DT conjugate vaccine and the correlation to Menactra comparison to a single injection by Menactra.

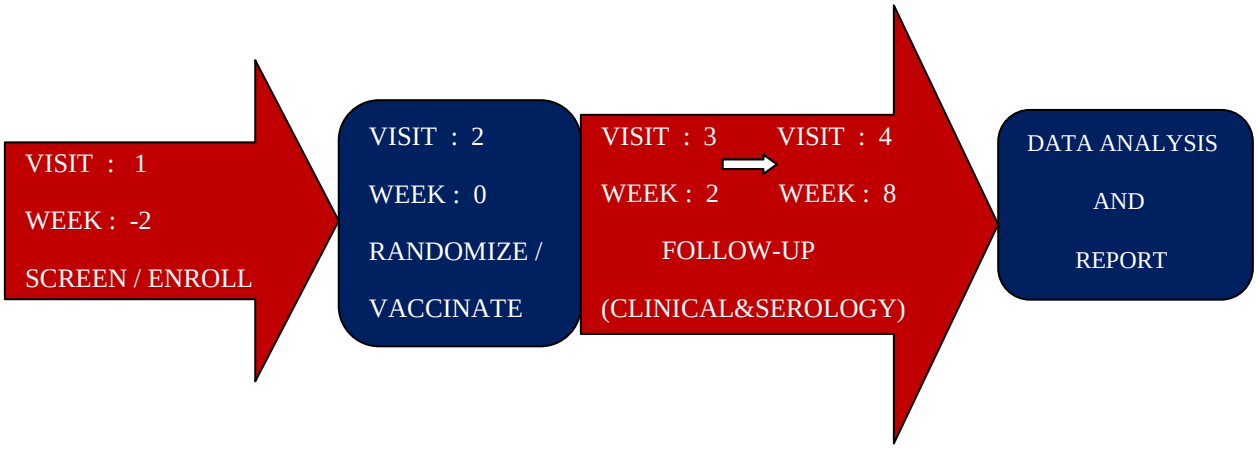
7.3 STUDY DESIGN

The study was a double blinded randomized controlled single arm experiment in Africa to evaluate the safety, protective efficacy and immunogenicity of quadrivalent meningococcal meningitis vaccine (NmVac A,C,Y & W-135 DT conjugate vaccine) in healthy subjects using an established product in the market Menactra A, C, Y and W-135 DT conjugate as a control.

STUDY PERIOD

November 2006 to November 2007.

TRIAL DESIGN AND ACTIVITY CHART



ACTIVITY IN BRIEF

VISIT 1	VISIT 2	VISIT 3 & 4	Data Analysis & Report
* Screening	* Enroll	* Physical Exam	* Decoding
* Informed Consent	* Physical Exam	* Vitals	- Volunteer
* Demographic Data	*Vitals	* Adverse Events	- Vaccine
* Medical History	*Vaccination	* Lab Investigation	* Safety
* Physical Exam	* Immediate Reaction	-Hematology	* Adverse Events
* Vitals	* Adverse Events	-LFT	* Serologic Titres
* Lab Investigation	* Medication Compliance	-Serology	-Immunogenicity
-Hematology	* Intercurrent Illness &	* Medication Compliance	-Seroconversion
-LFT	Concomitant Medication	*Intercurrent Illness &	-Protective Efficacy
-Serology: baseline	* Patient Instruction	Concomitant Medication	* Comparison between
* Patient Instruction		* Patient Instruction	test and reference
		* Study Termination	vaccine.

7.4 PROTOCOL

7.4.1 STUDY POPULATION

A total of 101 volunteers between the ages of 13-30 years of both genders fulfilling the eligibility criteria and willing to sign the informed consent were included in the study. The demographic profile of the volunteers represents the population profile of that age group.

ELIGIBILITY CRITERIA FOR PARTICIPATING IN THE TRIAL

INCLUSION CRITERIA

**a. Screening – ***Healthy volunteers who did not suffer from Meningococcal meningitis during the preceding two years of the study and who did not have meningitis vaccination in the past.

***** Healthy Volunteers: For the purpose of this study, a healthy volunteer is defined as healthy male or female, age 13 and above, with no history compatible with acute or chronic meningococcal infection as proven in the clinical examination.

b. Age -Volunteers aged between *13 and 30 years.

* In the case of children under the age of 18 years, parental consent shall be obtained prior to recruitment in the study.

c. Gender – Both Male and Female are eligible.

EXCLUSION CRITERIA

a. General exclusion criteria:

- Age less than 13 years.
- Pregnancy or lactation.
- Clinically significant laboratory abnormalities including positive test for meningococcal infection.
- People with cirrhosis of liver or acute Hepatitis.
- Not able to understand all of the requirements of the study or unable to give informed consent and/or comply with all aspects of the evaluation.
- People who participated in the trials in the last 6 months.

b. In addition to the general exclusion criteria, these following individuals will be excluded due to:

- Use of immunosuppressive drugs such as systemic (but not topical or inhalant) steroids and cytotoxic agents.
- History of severe allergy.
- Serious pre-existing or concurrent chronic medical or psychiatric illnesses.
- Past history of significant head trauma, alcohol or substance abuse or other medical illnesses that might produce neurological deficit (such as cerebro-vascular disease).
- Use of systemic antibiotics in the previous month.
- Chronic medication use will be evaluated in a case-by-case basis.

Patients will be excluded from this protocol if they are judged by the Principal Investigator as having a significant impairment in their capacity for judgment and reasoning that compromise their ability to make decisions in their best interest.

ELIMINATION CRITERIA FOR THE VOLUNTEERS PARTICIPATED IN THE STUDY

- Development of severe adverse reaction following the injection.
- Development of high fever $>100^0$ F (higher than 38^0 C) persistently beyond two days.
- Abnormal liver function tests detected during the course of trial or other findings detrimental to the continuation of the subject in the trial as determined by the Principal investigator.
- Development of purpuric cutaneous rash with temperature during the period of trials.
- Any volunteer not attending the test center at specified visits at least till the end of eight weeks study after the injection by the drug.
- Breach of abstinence.
- Taking medicines not allowed in the protocol during treatment.

7.4.2 VACCINE ADMINISTRATION

The Participants were coded, randomized and given a single dose of the coded vaccine. Both vaccines were administered intramuscularly in the deltoid region of the arm by the research nurse.

7.4.3 ENDPOINTS

PRIMARY EFFICACY ENDPOINTS

- The primary efficacy end point is taken as complete absence of symptoms or signs indicative of Meningococcal meningitis in the volunteers injected with NmVac A, C, Y, W-135 DT conjugate as confirmed by immunological assays showing the antibody titers comparable to Menactra.

SECONDARY EFFICACY ENDPOINTS

- The serological and immunological assays should confirm the levels of antibody titers for each serogroup A, C, Y, W-135 comparable to those titers from the volunteers injected Menactra..
- The serum/blood samples collected from the volunteers injected with NmVac A, C, Y, W-135 DT conjugate do not exhibit any growth of Meningococcus in the cultures or in Gram staining.

7.4.4 EVALUATION OF RESPONSE

A clinically significant response (CSR) should include the following:

- There should be no symptoms or signs indicative of Meningococcal meningitis in the volunteers injected with NmVac A, C, Y and W-135 DT conjugate vaccine as confirmed by immunological assays showing the antibody titres comparable to those vaccinated by Menactra A,C,Y and W-135.
- The serological and immunological assays should confirm the levels of antibody titers for each serogroup A, C, Y and W-135 comparable to those titers from the volunteers injected with Menactra A, C, Y and W-135.

The serum / blood samples collected from the volunteers injected with NmVac A, C, Y and W-135 conjugate vaccine do not exhibit any growth of Meningococcus in the cultures or in Gram staining.

7.4.5 SURVEILLANCE

MONITIRED PARAMETERS

SAFETY

Safety was monitored throughout the study by:

- Incidence of adverse events**.**
- Grading of adverse events.
- Recording attribution of causality.
- Expected side effects and vaccine limiting toxicities.
- Pre and post treatment differences in laboratory evaluation, physical examination, temperature, BP, HR and RR.

The Study Participants were monitored for immediate reactions 15 minutes post-vaccination and the local and systemic reactions were noted in the case report form before discharge. Further the participants were contacted by the medical officer at 24 hours,48 hours and 72 hours for pre-specified adverse events which included local reactions (pain, erythema , swelling and induration) and systemic reactions (fever, rash, headache, photophobia, weakness, myalgia, arthralgia, nausea, vomiting, abdominal pain, diarrhea) Adverse events were also monitored at the subsequent Visits at week 2 and week 8.

ADVERSE EVENTS

A treatment emergent adverse event defined as an unfavorable or abnormal finding that was either not present at base line or, if present at baseline, increased in severity as the study progressed.

GRADE	DESCRIPTION
Mild	The Adverse Event does not significantly interfere with the subjects normal functioning. The patient may be aware of the sign or symptom but tolerates it reasonably well
Moderate	The AE result in a noticeable detriment to the patient's functioning but is not deleterious to his/her health. It is discomforting and stressing
Severe	The AE is incapacitating and causes definite harm to subject's health.

ADVERSE EVENTS SEVERITY GRADE CLASSIFICATION

SERIOUS ADVERSE EVENTS

Any AE that

- Results in death
- Is life threatening
- Requires hospitalization or prolongation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

No serious adverse events occurred to any participant of both vaccine groups during the study period.

RELATIONSHIP TO STUDY DRUG

AE is related to study drug	Comment
Definitely Not	No relationship. Adequate information exists to show unrelatedness of the AE etiology to the study drug
Probably not	Relationship is not likely. AE may be attributed to the study drug but the phenomena observed are much more likely to be sequelae of some other identifiable factor
Possibly	Relationship may or may not exist. AE follows a known an expected response pattern to the study drug but could easily have been produced by a number of other factors.
Probably	Relationship is likely. AE follows a reasonable temporal sequence from the administration of the study drug, demonstrates a known or expected response pattern, and disappears or fades away after the injection of the drug, but there is still a fair chance of some other factor being responsible for the reaction or overlapping in time with the study drug post-administration period.

Definitely	Unquestionable relationship. AE follows a reasonable temporal sequence from the administration of the study drug, demonstrates a known or expected response pattern, and disappears or fades away after the injection of the drug, and no other agent or condition could reasonably have explained the reaction developed.

EFFICACY / IMMUNOGENICITY

Blood samples were obtained 2 weeks pre-vaccination, 2 weeks and 8 weeks post-vaccination. Antibody response was determined using Serum Bactericidal Antibody assay. All the samples were reported at Pasteur Institute, Ivory Coast.
Serum Bactericidal Antibody titres of 128 and above were taken to be protective and of positive seroconversion

Primary Efficacy Criteria

Percent of participants completely protected from Meningococcal infection or incidence rate.

Secondary Efficacy Criteria

Quantity of antibody titres and percent of seropositive and seronegative participants.

7.4.6 STATISTICAL PLAN

PRIMARY HYPOTHESIS

To demonstrate that 8 weeks after vaccination NmVac is non-inferior to Menactra, by proportion of participants with Serum Bactericidal Antibody Titre ≥ 128 for Neisseria Meningitidis Serogroups A, C, Y and W-135.

This hypothesis would be supported if the upper limit of the one-sided 95% confidence interval of the difference of the proportion of subjects achieving seroconversion for the two vaccine groups is less than 0.10. To be in accord with the current preferences of the United States Center for Biologics Evaluation and Research (CBER) for testing non-inferiority immunogenicity hypotheses, the upper limit of the two-sided 95% confidence interval is also evaluated. All tests of the primary hypothesis are conducted at 5% level of significance using single tailed probability on ITT population. Planned enrollment of 101 participants with evaluable number in each group was NmVac: 49 and Menactra: 52. The primary analysis was based on data generated from the per-protocol population.

Per-protocol population

The per-protocol population included all eligible participants who received one dose of the vaccine according to the treatment assignment, who complied with scheduled visits for blood specimens and for whom a sufficient quantity of sera was available for analysis.

Intent-to-treat population for immunogenicity

The Intent-to-treat population for immunogenicity included all eligible participants who received one dose of the vaccine and had post baseline efficacy data for analysis.

SECONDARY HYPOTHESIS

To demonstrate that the frequency of adverse events in NmVac recipients is non-inferior to the frequency of adverse events in the Menactra recipients.

This hypothesis would be supported if the upper bound of the one-sided 95% confidence interval of the difference of the proportion of subjects with adverse events for the two vaccine groups is less than 0.10. To be in accord with the current preferences of the United States Center for Biologics Evaluation and Research (CBER) for testing non-inferiority immunogenicity hypotheses, the upper limit of the two-sided 95% confidence interval is also evaluated. All tests of the primary hypothesis are conducted at 5% level of significance using single tailed probability on ITT population.

Intent-to-treat population for Safety

The Intent-to-treat population for safety included all eligible participants who received one dose of the vaccine and had safety data for analysis.

7.5 RESULTS

7.5.1 POPULATION

A total of 101 participants were enrolled (NmVac N= 49, Menactra N= 52) and all the participants completed the study.

Immunogenicity Population

The 101 per protocol participants enrolled (NmVac N= 49 , Menactra N= 52), received the vaccine and were available at the subsequent visits for blood samples for serum bactericidal antibody titre estimation. There were 6 participants (NmVac=2, Menactra= 4), who had protective baseline serum bactericidal antibody titres for the W- 135 capsular polysaccharide antigen. These were excluded for the immunogenicity analysis, hence the population for NmVac N=47 and Menactra N=48, for the W-135 capsular polysaccharide antigen

Safety Population

The 101 per protocol participants enrolled (NmVac N= 49 , Menactra N= 52), received the vaccine, were available at the subsequent visits for clinical assessment, recording adverse events and had blood samples withdrawn for laboratory values for safety analysis.

Demographic Characters

The distribution of the participants based on age, gender, race and ethnicity was similar among the two vaccine groups.
The study population enrolled was entirely Ivoriens,who are residents of city of Bouake in Ivory Coast.

7.5.2 IMMUNOGENICITY / EFFICACY

TABLE: 2 Number and Percentage of Participants, 13-30 Years old, achieving a Serum Bactericidal Antibody Titre ≥ 128 , with 95% C.I, at 2 Weeks.						
Serogroup	**NmVAC**			**MENACTRA**		
	N = 49			**N = 52**		
	n	**%**	**95% C.I**	**n**	**%**	**95% C.I**
A	7	14.29	4.49, 24.09	5	9.61	1.60, 17.62
C	6	12.24	3.06, 21.42	1	1.92	0.00, 5.65
Y	5	10.20	1.73, 18.67	3	5.77	0.00, 12.11
W- 135	6	12.77	3.23, 22.31	5	10.42	1.78, 19.06

C.I = Confidence Interval

Seroconversion Rate:

Defined as the proportion of participants with Serum Bactericidal antibody (SBA) Titres < 128 pre-vaccination (baseline), who subsequently achieved SBA Titres ≥ 128 post-vaccination.

TABLE: 1 Baseline Mean Serum Bactericidal Antibody(SBA) Titres of the Partcipants, 13-30 Years old, with 95% C.I, at -2 Week.				
Serogroup	**NmVAC**		**MENACTRA**	
	N = 49		**N = 52**	
	Mean	**95% C.I**	**Mean**	**95% C.I**
A	5.36	3.43, 7.29	4.35	5.23, 3.49
C	4.68	3.12, 6.24	4.92	3.82, 6.03
Y	8.88	4.73, 13.03	7.45	4.62, 10.28
W-135	10.31	5.55, 15.07	10.45	5.82, 15.08

N = Total number of participants with valid serology data. (For W 135, NmVac N= 47, Menactra N= 48)

n = Number of participants with Serum Bactericidal Antibody (SBA) Titre ≥ 128.
% = Percentage of participants with Serum Bactericidal Antibody (SBA) Titre ≥ 128.
C.I = Confidence Interval

TABLE : 5 Overall Safety Profile of the Participants by the Adverse Events (AE)

TABLE: 3 Number and Percentage of Participants, 13-30 Years old, achieving a Serum Bactericidal Antibody Titre ≥ 128 , with 95% C.I, at 8 Weeks.

Serogroup	NmVac			MENACTRA		
	N = 49			N = 52		
	n	%	95% C.I	n	%	95% C.I
A	48	97.96	93.99, 100.00	52	100.00	98.04, 100.00
C	47	95.92	90.38, 100.00	51	98.08	94.35, 100.00
Y	46	93.88	87.17, 100.00	51	98.08	94.35, 100.00
W- 135	44	93.62	86.62, 100.00	48	100.00	98.04, 100.00

N = Total number of participants with valid serology data. (For W 135, NmVac N= 47, Menactra N= 48)
n = Number of participants with Serum Bactericidal Antibody (SBA) Titre ≥ 128.

TABLE: 4 PRIMARY HYPOTHESIS TESTING
Proportion of participants, 13-30 Years old, with Serum Bactericidal Antibody (SBA) Titre ≥ 128, at 8 Weeks.

Serogroup	NmVAC	MENACTRA	Difference in proportion	Upper Limit of 1-sided 95% C.I of the difference in proportion	Upper Limit of 2-sided 95% C.I of the difference in proportion
	N = 49	N =52			
	ρ NmVac	ρ Menactra	(ρ Menactra - ρ NmVac)		
A	0.9795	1.0000	0.0205	0.0932	0.1069
C	0.9591	0.9807	0.0216	0.1038	0.1192
Y	0.9387	0.9807	0.0420	0.1306	0.1472
W- 135	0.9361	1.0000	0.0639	0.1547	0.1716

% = Percentage of participants with Serum Bactericidal Antibody (SBA) Titre ≥ 128.
C.I = Confidence Interval
N = Total number of participants with valid serology data. (For W 135, NmVac N= 47, Menactra N= 48)
ρ NmVac = Proportion of NmVac Participants with a SBA Titre ≥ 128.
ρ Menactra = Proportion of Menactra Participants with a SBA Titre ≥ 128.
C.I = Confidence Interval

Type of Adverse Event	NmVAC			MENACTRA		
	N= 49			N= 52		
	n	%	95% C.I	n	%	95% C.I
Immediate Reactions (within 15 mins)	0	0.00	0.00, 2.80	0	0.00	0.00, 2.60
Solicited Local Reactions (Days 0-7)	1	2.04	0.00, 6.00	2	3.85	0.00, 9.08
Solicited Systemic Reactions (Days 0-7)	0	0.00	0.00, 2.80	2	3.85	0.00, 9.08
Unsolicited Serious Adverse Events. (Days 0-56)	0	0.00	0.00, 2.80	0	0.00	0.00, 2.60
All Serious Adverse Events (Days 0-56)	0	0.00	0.00, 2.80	0	0.00	0.00, 2.60

The upper limit of the one-sided 95% confidence interval of the difference of the proportion of participants achieving seroconversion for the two vaccine groups is less than 0.10 for serogroup A. To be in accord with the current preferences of the United States Center for Biologics Evaluation and Research (CBER) for testing non-inferiority immunogenicity hypotheses, the upper limit of the two-sided 95% confidence interval is also evaluated and is less than 0.10.

For the other Serogroups C, Y, and W-135, the upper limit of the one-sided 95% confidence interval of the difference of the proportion of subjects achieving seroconversion for the two vaccine groups is slightly above 0.1. The upper limit of the two-sided 95% confidence interval is also evaluated and is less also slightly above 0.1

7.5.3 SAFETY

N = Total number of participants
n = Number of participants reporting the Adverse Events
% = Percentage of participants with Adverse Events
C.I = Confidence Interval

Immediate Reactions:

No immediate reactions occurred in any vaccine recipient of both groups.

Local Adverse Reactions:

The percentage of participants reporting **any local reaction** was NmVac = 2.04 %, and Menactra = 5.77 %.
Among these reactions, **pain** (0 % vs. 3.85 %) was reported with less frequency in the NmVac recipients compared to the Menactra recipients. S**welling/induration** (2.04 % vs. 1.92 %), was reported with similar frequency in the NmVac and the Menactra recipients.
Redness > 3 cm was not reported in any participant of both the vaccine groups.

The NmVac recipients reported **swelling/induration** in 2.04 %. All were of mild severity (0.5 cm, Grade 1).

No recipient reported **pain** tolerable or of greater severity, and **redness** 3 cm or greater.
The Menactra recipients reported **pain** in 3.85 %. Among these 1.92 % were of mild severity and 1.92 % of moderate severity.
Swelling/induration in 1.92 %, all were of mild severity (0.5 cm, Grade 1). No participant reported **redness** 3 cm or greater.
All these reactions occurred within the first three days of vaccination.

TABLE: 6 Local Adverse Reactions in the Participants.

Reaction	Severity	NmVac N= 49			Menactra N= 52		
		n	%	95%C.I	n	%	95% C.I
PAIN							
Any		0	0.00	0.00, 2.80	2	3.85	0.00, 9.08
Tolerable	**Mild Grade 1**	0	0.00	0.00, 2.80	1	1.92	0.00, 5.65
Intolerable	**Moderate Grade 2**	0	0.00	0.00, 2.80	1	1.92	0.00, 5.65
Limit Movement	**Severe Grade 3**	0	0.00	0.00, 2.80	0	0.00	0.00, 2.60
REDNESS							
Any		0	0.00	0.00, 2.80	0	0.00	0.00, 2.60
3-5 cm	**Mild Grade 1**	0	0.00	0.00, 2.80	0	0.00	0.00, 2.60
5-7 cm	**Moderate Grade 2**	0	0.00	0.00, 2.80	0	0.00	0.00, 2.60
>7 cm	**Severe Grade 3**	0	0.00	0.00, 2.80	0	0.00	0.00, 2.60
SWELLING/ INDURATION							
Any		1	2.04	0.00, 6.00	1	1.92	0.00, 5.65
0.5 cm	**Mild Grade 1**	1	2.04	0.00, 6.00	1	1.92	0.00, 5.65
0.6-1.5 cm	**Moderate Grade 2**	0	0.00	0.00, 2.80	0	0.00	0.00, 2.60
>1.5 cm	**Severe Grade 3**	0	0.00	0.00, 2.80	0	0.00	0.00, 2.60

N = Total number of participants
n = Number of participants reporting the Adverse Events
% = Percentage of participants with Adverse Events
C.I = Confidence Interval

TABLE: 7 Systemic Adverse Reactions in the Participants.							
Reaction	**Severity**	**NmVac**			**Menactra**		
		N= 49			**N= 52**		
		n	**%**	**95%C.I**	**n**	**%**	**95% C.I**
FEVER							
Any		0	0.00	0.00, 2.80	0	0.00	0.00, 2.60
38.5°C	**Mild**	0	0.00	0.00, 2.80	0	0.00	0.00, 2.60
38.6- 39°C	**Moderate**	0	0.00	0.00, 2.80	0	0.00	0.00, 2.60
>39°C	**Severe**	0	0.00	0.00, 2.80	0	0.00	0.00, 2.60
HEADACHE							
Any		0	0.00	0.00, 2.80	2	3.85	0.00, 9.08
Tolerable	**Mild**	0	0.00	0.00, 2.80	2	3.85	0.00, 9.08
Intolerable	**Moderate**	0	0.00	0.00, 2.80	0	0.00	0.00, 2.60
Disabling	**Severe**	0	0.00	0.00, 2.80	0	0.00	0.00, 2.60
PHOTOPHOBIA							
Any		0	0.00	0.00, 2.80	0	0.00	0.00, 2.60
RASH							
Any		0	0.00	0.00, 2.80	0	0.00	0.00, 2.60
ASTHENIA							
Any		0	0.00	0.00, 2.80	0	0.00	0.00, 2.60
MYALGIA							
Any		0	0.00	0.00, 2.80	0	0.00	0.00, 2.60
ARTHRALGIA							
Any		0	0.00	0.00, 2.80	0	0.00	0.00, 2.60
NAUSEA							
Any		0	0.00	0.00, 2.80	1	1.92	0.00, 5.65
VOMITTING							
Any		0	0.00	0.00, 2.80	0	0.00	0.00, 2.60
ABDOMINAL PAIN							
Any		0	0.00	0.00, 2.80	0	0.00	0.00, 2.60
DIARRHOEA							
Any		0	0.00	0.00, 2.80	0	0.00	0.00, 2.60

N = Total number of participants
n = Number of participants reporting the Adverse Events
% = Percentage of participants with Adverse Events
C.I = Confidence Interval

Systemic Adverse Reactions:

The NmVac recipients did not report **any systemic reaction.**
The percentage of Menactra recipients reporting **any systemic reaction** was 5.77 %.
The most common systemic reaction the Menactra recipients reported was **headache.** The Menactra recipients reported **headache** in 3.85 %, all these were of mild severity, Grade 1. **Nausea** was reported in 1.92 % of the recipients.
All these reactions occurred within the first three days of vaccination.

Serious Adverse Events:

No Serious Adverse Events occurred in any vaccine recipient of both groups.

SUMMARY AND CONCLUSIONS

The clinical study was conducted to evaluate the immunogenicity, protective efficacy and safety of a new vaccine NmVac A, C, Y and W-135 DT conjugate against Meningococcal infection, in volunteers 13-30 years of age, both male and female, in the city of Bouake in Ivory Coast, compared to Aventis Pasture Menactra A, C, Y and W-135 DT conjugate vaccine, presently in the market.

The primary objective was to evaluate the immunogenic response to NmVac A, C, Y and W-135 DT conjugate vaccine, compared to Aventis Pasture Menactra A, C, Y and W-135 DT conjugate vaccine. This was done by estimating the Serum Bactericidal Antibody Titres at 2 and 8 weeks post-vaccination.Titres above 128 were taken to be positive for seroconversion and protective efficacy.
The primary hypothesis to show that NmVac A, C, Y and W-135 DT conjugate vaccine, is non inferior to Aventis Pasture Menactra A, C, Y and W-135 DT conjugate vaccine was achieved for serogroup A. The upper limit of the one-sided 95% confidence interval of the difference of the proportion of subjects achieving seroconversion for the two vaccine groups is less than 0.10. The upper limit of the two-sided 95% confidence interval is also evaluated and found to be less than 0.1 in accordance with the current preferences of the United States Center for Biologics Evaluation and Research (CBER) for testing non-inferiority immunogenicity hypotheses. For the other Serogroups C, Y, and W-135, the upper limit of the one-sided 95% confidence interval of the difference of the proportion of subjects achieving seroconversion for the two vaccine groups is slightly above 0.1.

The secondary objective was to evaluate the safety of the NmVac A, C, Y and W-135 DT conjugate vaccine, compared to Menactra A, C, Y and W-135 DT conjugate vaccine in the population of City of Bouake. This was done by monitoring for immediate reactions 15 minutes post-vaccination and the local and systemic reactions were noted in the case report form before discharge. Further the participants were contacted by the medical officer at 24 hours,48 hours and 72 hours for pre-specified adverse events which included local reactions (pain, erythema , swelling and induration) and systemic reactions (fever, rash, headache, photophobia, weakness, myalgia, arthralgia, nausea, vomiting, abdominal pain, diarrhea) Adverse events were also monitored at the subsequent Visits at week 2 and week 8.
There were no immediate reactions or serious adverse events in participants of both vaccine groups.
The overall local reactions were fewer in the NmVac A, C, Y and W-135 DT conjugate vaccine recipients, compared to Menactra A, C, Y and W-135 DT conjugate vaccine recipients. The most common local reaction was pain at the vaccine administration site, followed by swelling/induration.
No systemic reactions were reported in the NmVac A, C, Y and W-135 DT conjugate vaccine recipients, whereas in the Menactra A, C, Y and W-135 DT conjugate vaccine recipients the most common systemic adverse reaction was headache (3.85 %), followed by nausea (1.92 %).

In conclusion, NmVac A, C, Y and W-135 DT conjugate vaccine is non inferior to Menactra A, C, Y and W-135 DT conjugate vaccine with regards to safety of the vaccine, the study demonstrates a better safety profile for the new vaccine. The immunogenicity of the vaccine is non inferior to Menactra partially at 8 weeks.