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# Immunogenicity and safety of the quadrivalent meningococcal ACWY-tetanus toxoid conjugate vaccine (MenACWY-TT) in splenectomized or hyposplenic children and adolescents: Results of a phase III, open, non-randomized study

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ABSTRACT

*Background:* Individuals with functional or anatomic asplenia are at high risk for meningococcal disease. We evaluated the immunogenicity and safety of 1 and 2 doses of the quadrivalent meningococcal serogroups A, C, W, Y tetanus toxoid-conjugate vaccine (MenACWY-TT) in this high-risk population.

*Methods:* This phase III, open-label, controlled, non-randomized study (NCT01641042) enrolled 1–17-year-olds with impaired splenic activity (high-risk group) and age-matched healthy controls (control group). We measured immune responses to MenACWY-TT by serum bactericidal activity assays using rabbit (rSBA) and human (hSBA) complement and in terms of antibodies against polysaccharides of the 4 vaccine serogroups. We evaluated vaccine response rates (VRRs) as 4-fold increases from pre-vaccination levels or titers ≥1:32 (rSBA)/≥1:8 (hSBA). We recorded solicited and unsolicited adverse events (AEs) during 4 and 31 days post-vaccination, and serious AEs (SAEs) and new onset of chronic illnesses (NOCIs) throughout the study.

*Results:* The according-to-protocol cohort for immunogenicity included 40 participants per group. In both groups, the first MenACWY-TT dose induced rSBA VRRs of 92.5–100% and hSBA VRRs of 55.6–77.1% across vaccine serogroups. Following the second MenACWY-TT dose, all participants had high responses, with rSBA and hSBA VRRs of 73.0–100% across vaccine serogroups. rSBA and hSBA geometric mean titers for each serogroup increased in both groups (with different magnitudes, but ≥13.1-fold) compared with baseline levels. Polysaccharide antibody concentrations ≥2.0 μg/ml were detected in ≥84.4% of participants and were similar between groups. Incidences of solicited and unsolicited AEs were comparable between groups. We recorded SAEs in 4/43 participants in the high-risk group and 1/43 participants in the control group (none vaccine-related). No NOCIs were reported.

*Abbreviations:* ACIP, Advisory Committee on Immunization Practices; AE, adverse event; ATP, according-to-protocol; CI, confidence interval; GMC, geometric mean concentration; GMT, geometric mean titer; Hib, Haemophilus influenzae type b; HIV, human immunodeficiency virus; hSBA, serum bactericidal activity assay using human complement; MenACWY-TT, quadrivalent serogroups A, C, W and Y conjugate vaccine using tetanus toxoid as carrier protein; IU, international units; PS, polysaccharides; rSBA, serum bactericidal activity assay using rabbit complement; SAE, serious adverse event; TVC, total vaccinated cohort; US, United States; VRR, vaccine response rate.

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*Conclusion:* In this descriptive study, MenACWY-TT induced similar functional and humoral immune responses and had a clinically acceptable safety profile in children and adolescents with impaired splenic activity and in healthy controls.


## 1. Introduction

The most common clinical presentations of *Neisseria meningitidis* infection are meningitis and septicemia [1,2]. Symptoms of invasive meningococcal disease, including fever, loss of appetite, irritability, lethargy, nausea, vomiting, diarrhea, photophobia and convulsions, usually occur 1–4 days post-infection [2,3]. Individuals with medical conditions such as complement deficiencies and splenic dysfunction/asplenia have impaired immune function and lack protective bactericidal activity, and are therefore more vulnerable to infections with encapsulated bacteria [1,4–6]. These conditions induce an up to 10,000-fold higher risk of invasive meningococcal disease and higher mortality rates (40–70%) compared with healthy populations [1,4,7].

Immunizing these vulnerable patients against *N. meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) is an important strategy to prevent encapsulated bacterial infections. Many countries recommend vaccination against meningococcal disease in individuals with specific risk factors, including complement deficiencies, functional or anatomic asplenia, human immunodeficiency virus (HIV), community outbreak of meningococcal disease, travelling to high-risk countries, students living in residential housing, or microbiologists exposed to *N. meningitidis* [1,8].

In the absence of a functional spleen, immune responses to polysaccharide (PS) vaccines are impaired while those to conjugate vaccines are less impacted [9,10]. Studies have shown that monovalent meningococcal serogroup C (MenC) [11,12], pneumococcal [9] and Hib [13] conjugate vaccines are immunogenic in asplenic individuals. Pneumococcal conjugate vaccines are also effective in children with sickle cell disease [14,15]. A possible explanation is that coupling of PSs to carrier proteins induces T-cell dependent antibody responses, which may allow secondary lymphoid tissues to compensate for the absence of a functional spleen [9,11,16].

The United States (US) Food and Drug Administration has approved 2 meningococcal quadrivalent conjugate vaccines against serogroups A, C, W and Y: MenACWY-CRM$_{197}$ (*Menveo*, GSK) for individuals aged 2 months–55 years and MenACWY-DT (*Menactra*, Sanofi Pasteur) for individuals aged 9 months–55 years [8,17]. In addition to routine vaccination of adolescents, the US Advisory Committee on Immunization Practices (ACIP) recommends immunization of infants and toddlers at increased risk for meningococcal disease with either MenACWY-CRM$_{197}$ or Hib-MenCY-TT (*MenHibrix*, GSK) at 2, 4, 6, and 12 months of age or with MenACWY-DT at 9 and 12 months of age, while individuals aged 2–55 years should receive 2 doses (8–12 weeks apart) of MenACWY-CRM$_{197}$ or MenACWY-DT [2,8,17].

MenACWY-TT (*Nimenrix*, Pfizer) uses tetanus toxoid (TT) as a carrier protein [18–20] and is approved for use as a single dose in individuals as of 12 months of age in >65 countries [18,20]. Here, we evaluated the immunogenicity, safety and reactogenicity of 1 or 2 MenACWY-TT doses administered to 1–17-year-old children and adolescents at increased risk for meningococcal disease compared with age-matched healthy individuals.

## 2. Methods

### 2.1. Study design and participants

We conducted this phase III, open-label, controlled study between September 2012 and March 2015, in 14 centers in the US (12 Kaiser Permanente Vaccine Study Centers and 2 Duke University Hospital centers) and 2 centers in the Czech Republic.

We enrolled 1–17-year-old participants in a high-risk and a control group. The high-risk group included individuals with anatomic asplenia, some degree of functional asplenia (e.g. sickle-cell anemia, histiocytosis X, celiac disease), complement deficiencies, or if investigators could assess a reduced splenic function by means of an appropriate technique (scintiscan, pitted erythrocyte counting or Howell-Jolly body detection). Individuals with sickle-cell disease were enrolled without assessing splenic function because sickle-cell disease is invariably associated with severe splenic dysfunction [21]. Children aged <2 years with functional or anatomic asplenia were not enrolled. The control group included healthy individuals who were age-matched to high-risk participants according to 1–5, 6–10 and 11–17 years age strata.

In line with the ACIP recommendations for at-risk individuals, participants from both groups received 2 MenACWY-TT doses administered 2 months apart [8,22]. One 0.5 mL dose of MenACWY-TT contains 5 μg of each of the capsular PSs (MenA, MenC, MenW and MenY) conjugated to TT (~44 μg). We administered the vaccine intramuscularly in the non-dominant deltoid or thigh (dominant deltoid for 1 participant).

All parents/legally acceptable representatives signed an informed consent form prior to enrolment; participants aged ≥7 years signed an informed assent. The study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki [23] and was approved by Institutional Review Boards.

This study is registered at www.clinicaltrials.gov (NCT01641042). A protocol summary is available at http://www.gsk-clinicalstudyregister.com (ID: 115524).

### 2.2. Study objectives

The primary objective was to assess the immunogenicity of MenACWY-TT administered to high-risk participants as a 2-dose schedule compared with age-matched control participants, in terms of serum bactericidal activity vaccine response rates (VRRs) for MenA, MenC, MenW and MenY, using rabbit (rSBA) or human (hSBA) complement assays. The secondary objectives compared the immunogenicity, safety and reactogenicity of MenACWY-TT in both groups.

### 2.3. Immunogenicity

We collected blood samples at pre-vaccination and at 1 month after each dose. We measured serum bactericidal activity by rSBA (Public Health England, United Kingdom) and hSBA (Neomed-Labs inc, Canada) assays [24–26]. We used an rSBA titer of 1:8 and an hSBA titer of 1:4 as serological correlates of protection,

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