Efficacy and Safety of a Booster Dose of the MenACWY-TT Vaccine Administered 10 Years After Primary Vaccination With MenACWY-TT or MenACWY-PS

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BACKGROUND

- Invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* is associated with substantial morbidity and mortality.[1]
  - The incidence of IMD is highest in infants and young children, with a second peak seen in late adolescence.[2]
- Quadrivalent conjugate vaccines targeting meningococcal serogroups A, C, W, and Y (MenACWY) are currently available to protect against IMD.[1]
- MenACWY-TT (Nimenrix®, Pfizer Ltd, Sandwich, UK), a quadrivalent meningococcal conjugate vaccine using tetanus toxoid as a carrier, is licensed in Europe and other regions across the globe for individuals ≥6 weeks of age.
  - MenACWY-TT elicits robust immune responses and is well tolerated when administered to children aged ≥1 year, adolescents, and adults.[3] However, the importance of a booster dose for sustained protection against IMD and the persistence of immune responses after vaccination is less well understood.
- Thus, this extension study assessed long-term protection in subjects who previously completed a phase 3, multicenter study where they received primary vaccination with either MenACWY-TT or a licensed quadrivalent meningococcal polysaccharide vaccine (MenACWY-PS) at 11–17 years of age.[4]

OBJECTIVES

- To evaluate the immunogenicity and safety of a MenACWY-TT booster dose administered 10 years after primary vaccination
- To evaluate long-term antibody persistence 10 years after primary vaccination at 11–17 years of age with MenACWY-TT or MenACWY-PS

METHODS

Study Design

- The primary study (NCT00464815) was a phase 3, open-label, multicenter study conducted in 3 countries (India, Philippines, Taiwan) that randomized subjects 11–17 years of age to receive a single dose of either MenACWY-TT or MenACWY-PS.[4]
- This phase 3b, open-label extension study (EudraCT number 2013-001512-29) enrolled subjects in the Philippines who completed vaccination with MenACWY-TT or MenACWY-PS in the primary study.

Study Populations

- All subjects from the participating site in the Philippines who were vaccinated with 1 dose of either vaccine in the primary study were invited to participate in this study.
- Key inclusion criteria at study entry
  - Written informed consent obtained before study
  - Completion of vaccination in the primary study
  - Healthy, as established by medical history and physical examination before study entry
  - Men and women using adequate contraception ≥1 month before, during, and 2 months after study completion

METHODS (continued)

- Key exclusion criteria at study entry
  - Use of any investigational or nonregistered product other than study vaccine(s)
  - Chronic administration (>14 days total) of immunosuppressants or immune-modifying drugs
  - Administration of immunoglobulins or blood products
  - Previous vaccination with any meningococcal vaccine besides the vaccination received in the primary study
  - Any confirmed or suspected immunosuppressive or immunodeficient condition
  - Pregnant, lactating, or planning to discontinue contraceptive precautions

Immunogenicity Assessments

- Immune responses to serogroups A, C, W, and Y were measured using serum bactericidal assays using rabbit complement (rSBA).[5]
- Primary immunogenicity endpoint
  - Percentages of subjects with postbooster responses for serogroups A, C, W, and Y, which were defined as follows:
    - rSBA titers ≥1:32 at 1 month after booster dose administration for subjects initially seronegative (prevaccination titer <1:8)
    - Increase in rSBA titers ≥4-fold at 1 month after booster dose administration for subjects initially seropositive (prevaccination titer ≥1:8)
- Secondary immunogenicity endpoints
  - Percentages of subjects with rSBA titers ≥1:8 and geometric mean titers (GMTs) 10 years after primary and 1 month after booster vaccination.

Safety Assessments

- Reactogenicity events, adverse events (AEs), serious AEs (SAEs), new onset of chronic illnesses (NOCIs), and cases of Guillain Barré Syndrome (GBS) of a MenACWY-TT booster dose were evaluated.
  - Reactogenicity events were those occurring ≤4 days after administration of the booster dose and included solicited local events (pain, redness, swelling at the injection site) and solicited general events (fatigue, fever, gastrointestinal symptoms, headache).
  - Unsolicited AEs, SAEs, and NOCIs and cases of GBS were collected ≤31 days after booster dose administration.
- Safety through 10 years after primary vaccination was evaluated and included SAEs associated with primary vaccination and any event associated with lack of vaccine efficacy.

Statistical Analyses

Safety

- Safety analyses were descriptive in nature.

Immunogenicity

- The percentages of subjects with an rSBA response (rSBA titers ≥1:8) were calculated for each serogroup with exact 2-sided 95% CIs using the Clopper and Pearson method.
- For GMTs, 95% CIs were calculated as back transformations of CIs based on the Student t distributions for the mean logarithm of titers.

RESULTS

Subject Demographics

- A total of 229 subjects were enrolled and 227 completed the study (169/170 and 58/59 subjects in the MenACWY-TT and MenACWY-PS groups, respectively).
- Demographic and baseline characteristics for the MenACWY-TT and MenACWY-PS groups are shown in **Table 1**.

Table 1. Study Population Demographics

Demographic	Antibody Persistence Stage		Booster Stage	
	MenACWY-TT	MenACWY-PS	MenACWY-TT	MenACWY-PS
Enrolled, N	170	59	170	59
Completed phase,* n (%)	170 (100.0)	59 (100.0)	169 (99.4)	58 (98.3)
Men, n	90	36	90	36
Age at enrollment, median (range), y	24.0 (21–27)	24.0 (21–28)	24.0 (21–27)	24 (21–28)
Ethnicity, n (%)				
Not American Hispanic or Latino	169 (99.4)	59 (100.0)	169 (99.4)	59 (100.0)
American Hispanic or Latino	1 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)
Race, n (%)				
Asian – Southeast Asian heritage	170 (100.0)	59 (100.0)	170 (100.0)	59 (100.0)

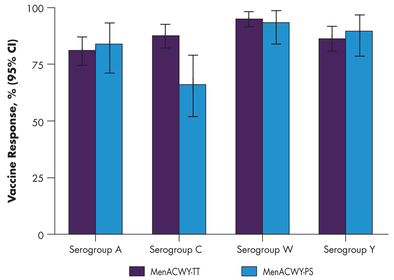
MenACWY-PS=quadrivalent meningococcal polysaccharide vaccine; MenACWY-TT= quadrivalent meningococcal tetanus toxoid conjugate vaccine; N=number of subjects in each vaccine group; n=number of subjects in a given category. *In the persistence stage, completed through 10 years after primary vaccination; in the booster stage, completed through 1 month after booster administration.

Immunogenicity

Booster Dose

- Robust immune responses were observed 1 month after the MenACWY-TT booster dose, administered 10 years after primary vaccination, in both the MenACWY-TT and MenACWY-PS groups (**Figure 1**).

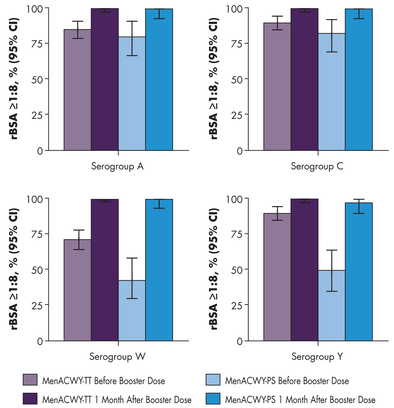
Figure 1. Percentage of Subjects With Vaccine Response for Serogroups A, C, W, and Y at 1 Month After MenACWY-TT Booster Dose



MenACWY-PS=quadrivalent meningococcal polysaccharide vaccine; MenACWY-TT=quadrivalent meningococcal tetanus toxoid conjugate vaccine.

- After a MenACWY-TT booster dose, rSBA titers ≥1:8 were achieved in most subjects in both the MenACWY-TT and MenACWY-PS groups (**Figure 2**).

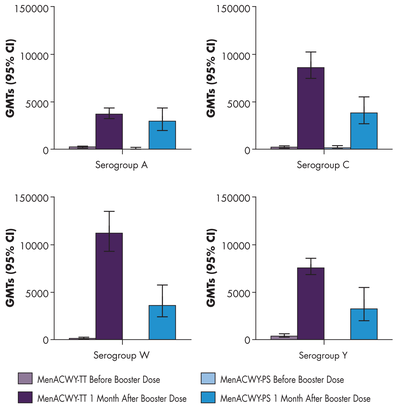
Figure 2. Percentage of Subjects With rSBA Titers ≥1:8 Before and After MenACWY-TT Booster Dose



MenACWY-PS=quadrivalent meningococcal polysaccharide vaccine; MenACWY-TT=quadrivalent meningococcal tetanus toxoid conjugate vaccine; rSBA=serum bactericidal assay using baby rabbit complement.

- In both groups, rSBA GMTs increased after MenACWY-TT booster dose administration (**Figure 3**).

Figure 3. GMTs for Serogroups A, C, W, and Y Before and After MenACWY-TT Booster Dose



GMT=geometric mean titer; MenACWY-PS=quadrivalent meningococcal polysaccharide vaccine; MenACWY-TT=quadrivalent meningococcal tetanus toxoid conjugate vaccine.

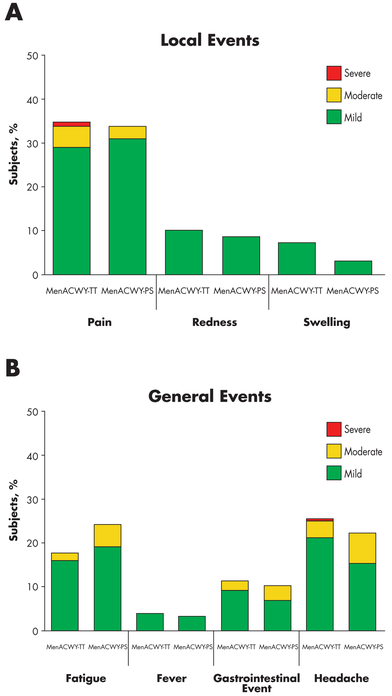
Long-Term Persistence

- **Figure 2** shows rSBA titers ≥1:8 against the 4 serogroups at 10 years after primary vaccination with MenACWY-TT and MenACWY-PS.
- The rSBA GMTs against all serogroups at 10 years after primary vaccination with MenACWY-TT and MenACWY-PS are shown in **Figure 3**.

Safety

- The rate and severity of solicited events in the MenACWY-TT and MenACWY-PS groups after the MenACWY-TT booster dose are shown in **Figure 4**.
- No new safety signals were observed after the MenACWY-TT booster dose.
- No SAEs, NOCIs, or cases of GBS were reported throughout the study.

Figure 4. Percentage of Subjects Reporting Solicited Local and General Reactogenicity Events After MenACWY-TT Booster Dose



MenACWY-PS=quadrivalent meningococcal polysaccharide vaccine; MenACWY-TT=quadrivalent meningococcal tetanus toxoid conjugate vaccine; mild=an event easily tolerated by subject; moderate=an event sufficiently discomforting to interfere with everyday activities; severe=an event that prevents normal everyday activities.

CONCLUSIONS

- **A MenACWY-TT booster dose administered 10 years after primary vaccination with MenACWY-TT or MenACWY-PS in subjects 10–17 years of age elicited robust immune responses with no new safety signals observed.**
- **Similar immune responses to the MenACWY-TT booster dose were observed in subjects vaccinated previously with either MenACWY-TT or MenACWY-PS.**
  - These results suggest that primary vaccination with either a meningococcal polysaccharide or conjugate vaccine does not influence immune responses to a booster meningococcal conjugate vaccine dose administered 10 years later.
- **Functional antibody titers persisted up to 10 years after primary vaccination with MenACWY-TT in adolescents, providing important insights into the long-term protection afforded by primary vaccination and the requirement for booster dosing.**

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