



Short communication

Persistence of bactericidal antibodies 4 years after a booster dose of quadrivalent meningococcal diphtheria toxoid conjugate vaccine (MenACWY-D)

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ABSTRACT

One dose of quadrivalent meningococcal conjugate vaccine (MenACWY) was first recommended for US adolescents (ages 11–12 years) in 2005 to protect against invasive meningococcal disease (IMD). In 2010, after evidence emerged about waning protection within 5 years after MenACWY vaccination, the US Advisory Committee on Immunization Practices (ACIP) recommended a MenACWY booster at age 16 years. We used a serum bactericidal assay with human complement (hSBA) to evaluate antibody persistence after a MenACWY-D booster in a sample of 110 participants who received the booster 4 years earlier in a phase 2 study. High proportions (89.9–98.2%) of participants maintained hSBA titers ($\geq 1:4$) associated with protection against IMD; a majority (81.7–97.2%) also had hSBA titers $\geq 1:8$, a more conservative threshold. These findings support ACIP recommendations regarding MenACWY booster vaccination, which are aimed at protecting adolescents and young adults throughout the period in which they are at increased risk of IMD.

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1. Introduction

Invasive meningococcal disease (IMD), caused by *Neisseria meningitidis*, mostly manifests as meningitis and sepsis [1]. The overall fatality rate is up to 50% if untreated, 10–15% when treated, and 40% in those affected by sepsis alone [2,3]. Up to 20% of survivors suffer permanent sequelae including loss of limbs and neurologic damage [2]. Direct costs in the United States range from \$56,202 per case of meningitis to \$79,648 per case of meningococemia (in 2009 dollars) [4]. Indirect and societal costs (e.g., costs of containment of outbreaks and loss of quality of life [QoL]) add to the overall burden [5].

Six of the 12 recognized meningococcal serogroups—A, B, C, W, X, and Y—have been implicated in almost all cases of IMD [3,6]. However, the relative contributions of individual serogroups to IMD incidence vary by geography and over time. In the United States, almost all cases are attributable to 4 serogroups: B, C, W,

and Y accounted for 29%, 18%, 6%, and 23%, respectively, of cases between 2006 and 2015 [7].

Since 2005, the Advisory Committee on Immunization Practices (ACIP) of the United States Centers for Disease Control and Prevention (CDC) has recommended routine vaccination of adolescents 11 and 12 years of age with quadrivalent meningococcal conjugate vaccine (MenACWY) to help protect against IMD caused by serogroups A, C, W, and Y [8]. After accumulating evidence indicating waning of both bactericidal antibody levels [9–12] and MenACWY effectiveness [13], the ACIP updated its recommendation in 2010 to call for a routine MenACWY booster at age 16 years [14].

Following incorporation of the MenACWY booster into the immunization schedule, we assessed the safety and immunogenicity of a single booster dose of quadrivalent meningococcal polysaccharide diphtheria toxoid conjugate vaccine (MenACWY-D) in adolescents and adults who had received a dose 4–6 years earlier [15]. That study (NCT01442675; MTA77) confirmed the safety and immunogenicity of a MenACWY-D booster; vigorous bactericidal antibody responses were observed 6 days after MenACWY-D booster vaccination, indicative of immune memory. We now report the findings of a follow-up study evaluating the persistence of antibody responses approximately 4 years after receipt of the booster in study MTA77.

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2. Methods

2.1. Study design

This phase 4, open-label, multi-center study (MTA00093) conducted in the United States enrolled a convenience sample of 110 persons who had received a booster dose of MenACWY-D at least 4 years earlier in study MTA77. This antibody persistence study did not feature randomization, hypothesis testing, or study power assessment. It is registered at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02633787) (NCT02633787).

2.2. Participants

Participants who were eligible to participate in MTA00093 had received a booster dose of MenACWY-D in study MTA77, were ≥ 18 years of age, provided written informed consent, and were able to attend the sole study visit (for blood sampling) and comply with all procedures. Exclusion criteria included receipt of any meningococcal vaccine after the booster in study MTA77; receipt of immunoglobulins, blood, or blood-derived products within the preceding three months; confirmed or suspected congenital or acquired immunodeficiency; receipt of immunosuppressive therapy within six months or long-term systemic corticosteroid therapy for >2 consecutive weeks within three months; history of confirmed meningococcal infection; and receipt of any antibiotic within 72 h before blood sampling.

2.3. Endpoints and assessment methods

Endpoints for the evaluation of antibody persistence were antibody titers $\geq 1:4$ and $\geq 1:8$ for serogroups A, C, W, and Y, measured with a serum bactericidal antibody assay using human complement (hSBA), performed as previously described [16]. Briefly, 2-fold dilutions of test sera were added to microtiter plates containing meningococcal reference strains F8238 (serogroup A), C-11 (serogroup C), 2515 (serogroup W), or 3021 (serogroup Y) and human complement. Following incubation, addition of an agar overlay medium that was allowed to harden, and overnight incubation at 37 °C in an atmosphere of 5% CO₂, bacterial colonies were counted. The endpoint titer was determined by the reciprocal serum dilution yielding $\geq 50\%$ killing compared with the mean of the complement control wells. The lower limit of quantitation was a titer of 1:4. This hSBA method has been previously validated [17] and all critical assay reagents are qualified prior to use. Continuous monitoring of the performance of the assay using internal quality control sera has demonstrated the assay's consistency, within the limits of assay variability, since validation.

Functional meningococcal antibody activity was used to infer vaccine effectiveness. An hSBA titer of $\geq 1:4$ has been directly correlated to clinical protection against meningococcal disease [18], while an hSBA titer of $\geq 1:8$ is the threshold used by the United States Food and Drug Administration (FDA) to infer meningococcal vaccine effectiveness for licensure purposes [19]. The only safety data that were collected were those regarding any serious adverse events (SAEs) related to study procedures (i.e., blood sampling).

2.4. Statistical methods

No hypotheses were tested. All analyses were descriptive. Antibody persistence was reported as the proportions of participants with hSBA titers $\geq 1:4$ and $\geq 1:8$ for each serogroup and geometric mean titers (GMTs). The 95% confidence intervals (CIs) for the proportions were calculated using the Clopper-Pearson (Exact) method, while the CIs for the GMTs were calculated using the normal approximation, assuming that the log titer was normally distributed.

2.5. Populations analyzed for antibody persistence analyses

The Full Analysis Set (FAS) included participants with a valid serology result. The Per-Protocol Analysis Set (PPAS), a subset of the FAS, excluded participants not meeting all inclusion criteria or meeting ≥ 1 exclusion criterion.

2.6. Determination of sample size and power calculation

Enrollment of 105 participants who had received a booster dose in study MTA77 was planned. Antibody persistence was evaluated in a descriptive manner and statistical power was not assessed.

3. Results

3.1. Demographic characteristics and disposition of participants

A total of 110 adults who had participated in study MTA77 were enrolled. All but one of these participants had a blood sample drawn at the sole study visit and completed the trial. A single participant withdrew because a blood sample could not be drawn. Accordingly, 109 participants were included in the FAS and PPAS.

Demographic characteristics of all enrolled participants are summarized in Table 1. The mean age was 22.2 years (range: 19.4–46 years). There were slightly more females (55.5%) than males (44.5%). A majority (93.6%) were Caucasian; 95.5% were non-Hispanic or Latino.

3.2. Immunogenicity evaluations

Approximately 4 years after a booster dose of MenACWY-D, high proportions of participants maintained hSBA antibody titers $\geq 1:4$ for serogroups A (98.2%), C (89.9%), W (97.2%), and Y (98.2%) (Fig. 1A). Moreover, a vast majority had antibody titers $\geq 1:8$; at least 94.5% of participants maintained titers $\geq 1:8$ for serogroups A, W, and Y, while 81.7% of participants maintained such titers for serogroup C (Fig. 1B). The GMTs for all serogroups were ≥ 4 -fold greater than those measured immediately prior to administration of the booster (Fig. 2).

Table 1
Participant demographics.

Demographic Characteristics	N = 110
Gender: n (%)	
Male	49 (44.5)
Female	61 (55.5)
Age: (years)	
Mean	22.2
Median	21.4
Standard deviation	3.54
Range	19.4–46
Racial origin: n (%)	
Asian	0 (0.0)
Black	5 (4.5)
Caucasian	103 (93.6)
Mixed origin	1 (0.9)
American Indian or Alaska Native	0 (0.0)
Native Hawaiian or other Pacific Islander	0 (0.0)
Not reported	1 (0.9)
Ethnic origin: n (%)	
Hispanic or Latino	4 (3.6)
Not Hispanic or Latino	105 (95.5)
Not reported	1 (0.9)

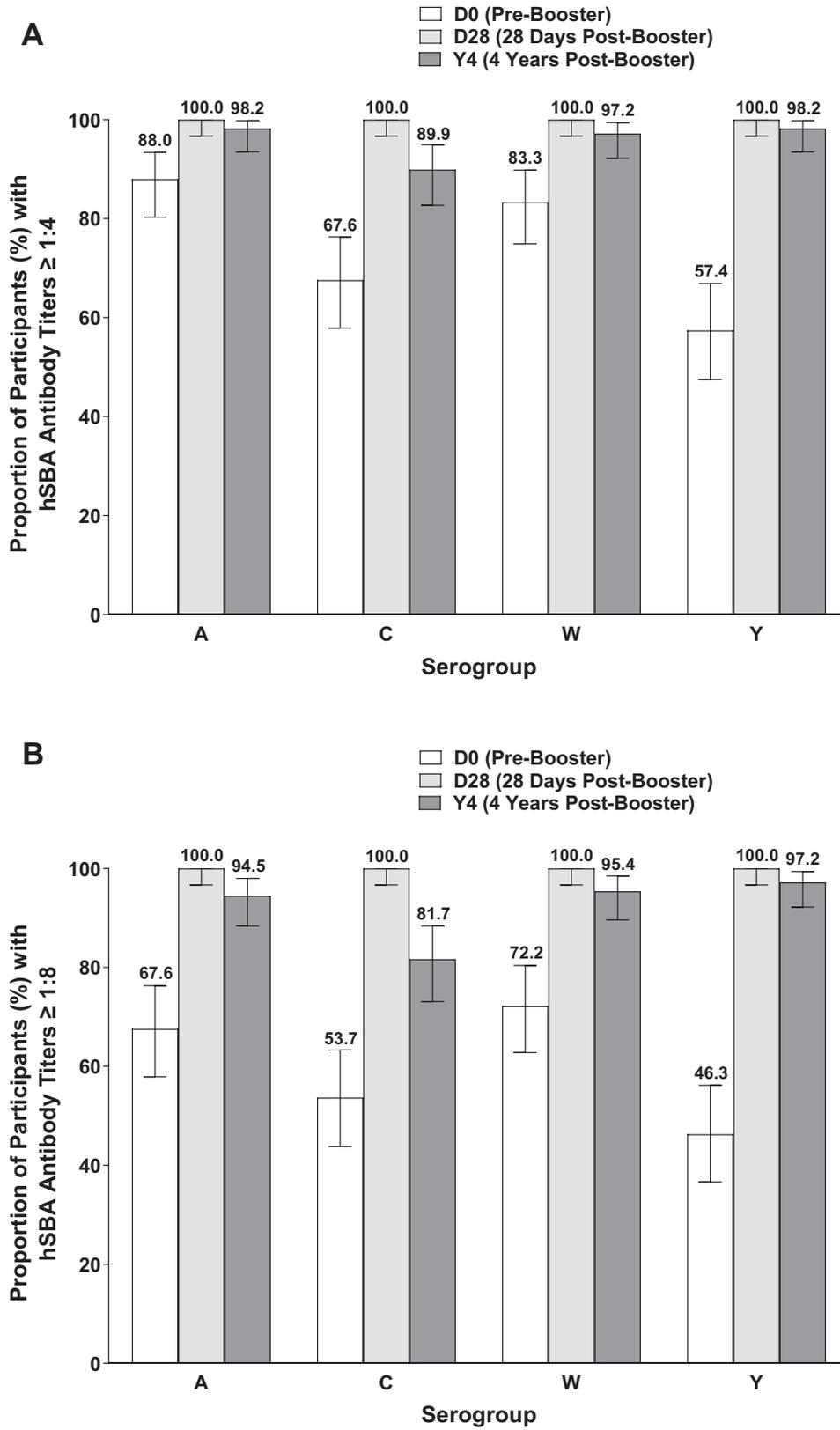


Fig. 1. Antibody persistence four years after booster dose: Proportions of participants with hSBA antibody titers $\geq 1:4$ (panel A) and $\geq 1:8$ (panel B) before and after booster vaccination. (Serology results from the pre- and ~28-days post-booster vaccination are from trial MTA77 [15], while serology results from the ~4-years post-booster vaccination are from this study [MTA00093]).

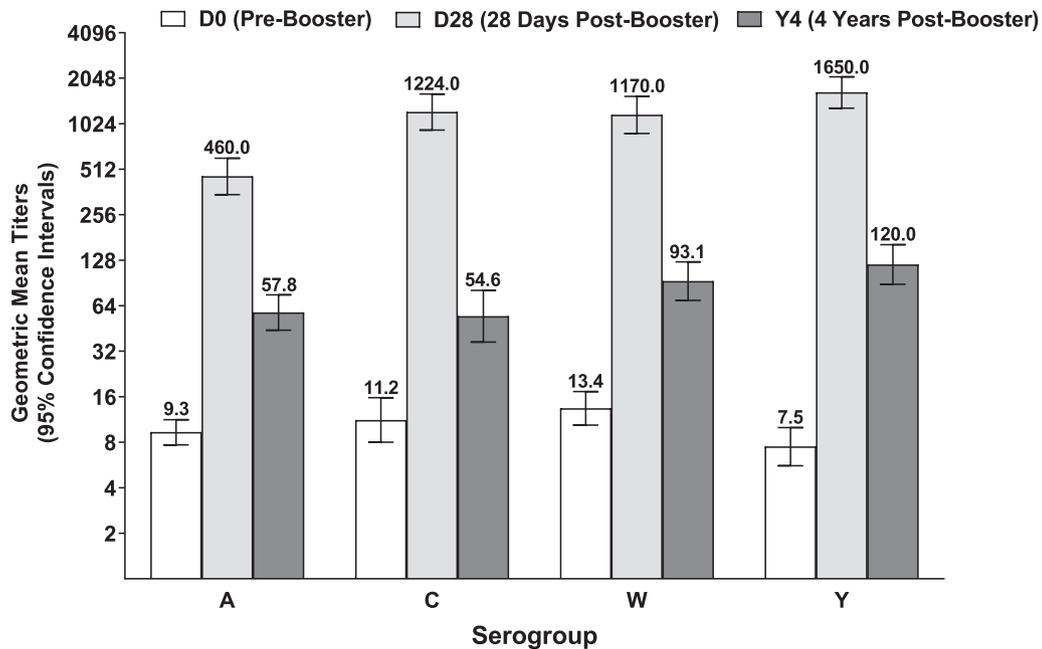


Fig. 2. Geometric mean hSBA antibody titers (Y-axis, log₂ scale) before and after booster vaccination. (Serology results from the pre- and ~28-days post-booster vaccination are from trial MTA77 [15], while serology results from the ~4-years post-booster vaccination are from this study [MTA00093]).

4. Discussion

To our knowledge, this is the only study to date to assess the persistence of bactericidal antibodies 4 years after a MenACWY booster dose since the US ACIP recommended MenACWY booster vaccination for older adolescents (ages 16–18 years) in 2010. Four to 6 years after the primary dose, a MenACWY-D booster effectively induced a vigorous anamnestic response, as evidenced by the 6-day post-booster antibody titers observed in study MTA77 [15]; however, hSBA antibody titers for all 4 vaccine serogroups declined substantially within 4 years thereafter, as observed in this extension study. Even so, most ($\geq 81.7\%$) participants still retained hSBA antibody titers at or above the threshold accepted by the US FDA as being protective (i.e., titers $\geq 1:8$). A vast majority ($\geq 89.9\%$) also maintained hSBA antibody titers considered to prevent IMD (i.e., titers $\geq 1:4$). Further, at approximately 4 years following booster vaccination, GMTs for all serogroups (range: 54.6–120) were ≥ 4 -fold higher than corresponding pre-booster GMTs (range: 7.5–13.4). Another study assessed antibody persistence in adolescents 2 years after a booster dose using a quadrivalent conjugate vaccine employing a nontoxic diphtheria toxin derivative (CRM₁₉₇) as the protein carrier (MenACWY-CRM); the booster was given 3 years after primary vaccination with MenACWY-CRM or MenACWY-D [20]. Percentages of participants retaining hSBA titers $\geq 1:8$ varied by serogroup and primary vaccine received: 77%–79% for serogroup A, 89%–95% for serogroup C, 97%–100% for serogroup W, and 93%–95% for serogroup Y. Post-booster GMTs were 2.5- to 8-fold higher than pre-booster titers. Our study, which examined antibody persistence 4 years after MenACWY-D booster vaccination, revealed 94.5% of participants with hSBA antibody titers $\geq 1:8$ against serogroup A, and 81.7% to 97.2% with hSBA antibody titers $\geq 1:8$ against the other 3 serogroups. Moreover, GMTs 4 years after the booster in our study were 4.9- to 16-fold higher than pre-booster levels. Differences between the findings of the 2 studies may be attributable in part to the different vaccines used. The serogroup-specific differences in antibody persistence observed within each study may be related to differences in natural exposure to cross-reacting polysaccharide antigens that might have occurred over time.

One limitation of this study is the use of a small convenience sample, which might have resulted in inclusion of participants who might not have been representative of the original, larger cohort. However, given the inclusion and exclusion criteria used in the extension study, it is unlikely that the participants included in MTA00093 would have differed from the original cohort in a way that would have materially impacted antibody persistence after a MenACWY-D booster dose.

Our findings support the notion that antibodies elicited following a booster dose of MenACWY-D at 16–18 years of age remain at protective levels through age 21 years in most recipients, which coincides with the age range of 16–21 years at which the second peak of IMD incidence occurs in the United States. The current study, in confirming the persistence of protective levels of antibodies following a booster for a period longer than previously documented, supports current recommendations calling for administration of a booster at age 16–18 years with the objective of maintaining vaccine-induced immunity throughout the duration of heightened vulnerability in adolescents and young adults.

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Conflicts of Interest

CAR, EB, and DPG report full-time employment at Sanofi Pasteur Inc. and ownership of Sanofi Pasteur stock or stock options. JH has no conflicts of interest to disclose.

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