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A phase 3, randomized, controlled, open-label study to evaluate the persistence up to 5 years of 1 or 2 doses of meningococcal conjugate vaccine MenACWY-TT given with or without 13-valent pneumococcal conjugate vaccine in 12–14-month-old children

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ABSTRACT

Background: Immunogenicity and safety up to 5 years after administration of 1 or 2 doses of quadrivalent meningococcal serogroup A, C, W, and Y tetanus toxoid conjugate vaccine (MenACWY-TT) given alone or with 13-valent pneumococcal conjugate vaccine (PCV13) in children was investigated.

Methods: This phase 3 study randomized healthy 12–24-month-olds to MenACWY-TT at Month 0 (ACWY1d), MenACWY-TT at Months 0 and 2 (ACWY2d), MenACWY-TT and PCV13 at Month 0 (Co-Ad), or PCV13 at Month 0 and MenACWY-TT at Month 2 (PCV13/ACWY). Immune responses 1, 3, and 5 years after primary vaccination were evaluated with serum bactericidal activity using rabbit complement (rSBA) titers $\geq$ 1:8 and geometric mean titers (GMTs). Evaluation of serious adverse events up to 5 years after primary vaccination are reported.

Results: Of the 802 children randomized in the study, 619 completed the study through Year 5. Immune responses after vaccination declined over time but were higher 5 years after vaccination compared with levels before vaccination. At Year 5, the percentages of children with rSBA titers $\geq$ 1:8 across all serogroups were 20.5 %–58.6 %, 28.4 %–65.8 %, 23.9 %–52.8 %, and 19.4 %–55.8 % in the ACWY1d, ACWY2d, Co-Ad, and PCV13/ACWY groups, respectively. Comparable antibody persistence at Year 5 was observed for participants receiving 1 or 2 doses of MenACWY-TT, although GMTs were elevated in those who received 2 versus 1 dose. The percentage of children with protective antibody titers at Year 5 was similar in participants who received PCV13 and MenACWY-TT compared with that observed for participants who only received 1 or 2 MenACWY-TT doses. No new safety concerns were identified during the study period.

Conclusion: Antibody responses persisted in the majority of children up to 5 years after primary vaccination with MenACWY-TT administered in a 1- or 2-dose regimen with or without PCV13, with no new safety concerns identified.

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Abbreviations: ACWY1d, meningococcal serogroups A, C, W, and Y conjugated to the tetanus carrier protein at Month 0 cohort; ACWY2d, meningococcal serogroups A, C, W, and Y conjugated to the tetanus carrier protein at Months 0 and 2 cohort; AE, adverse event; ATP, according to protocol; Co-Ad, meningococcal serogroups A, C, W, and Y conjugated to the tetanus carrier protein and 13-valent pneumococcal conjugate vaccine at Month 0 cohort; GMT, geometric mean titer; hSBA, serum bactericidal activity using rabbit complement; ICH, invasive meningococcal disease; MenACWY, meningococcal serogroups A, C, W, and Y; MenACWY-TT, quadrivalent meningococcal tetanus toxoid conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; rSBA, ser um bactericidal activity using rabbit complement; SAE, serious adverse event.

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1. Introduction

Neisseria meningitidis infection causes invasive meningococcal disease (IMD), which is associated with considerable morbidity and mortality [1]. Because of the immaturity of their immune systems, infants and young children are at high risk of IMD [2]. In Europe in 2018, the age-specific rates of IMD in infants younger than 1 year and in children 1–4 years of age were 8.34 and 2.38 per 100,000, respectively, compared with the rate of 0.62 per 100,000 in the overall population [3]. Meningococcal disease incidences in the United States in 2019 were 0.82 and 0.19 per 100,000 in infants and children 1–4 years of age, respectively, and 0.11 per 100,000 in the overall population [4]. In South Africa, the incidence of IMD in the overall population was 0.2 cases per 100,000 in 2016, with children 5 years and younger at highest risk [5–7]. Between 1928 and 2018, the mean incidence of meningitis in Africa was 216 per 100,000 [7]. Cases of meningococcal meningitis showed periodicity, although the dynamics depended varied by African country [6]. Of note, the incidence of IMD in South Africa is likely to be higher because of limitations in surveillance. Additionally, the high prevalence of HIV infection in the country increases the risk of IMD.

Severe sequelae among childhood survivors of IMD include hearing loss, seizure, amputation, and skin scarring, which are more common in children younger than 5 years (21 %) than in adults (15 %) [8]. Infants and young children also often present with nonspecific signs of IMD, such as irritability and lethargy [2,8], making timely diagnosis challenging. Therefore, prevention of IMD is critical in this vulnerable population.

Vaccines are available to prevent disease caused by meningococcal serogroups A, B, C, W, and Y, which accounted for 96 % of cases in children 1–4 years of age in Europe in 2018 and 83 % of cases in children 1–4 years of age in the United States in 2019 [3,4,9]. Several quadrivalent conjugate vaccines targeting IMD caused by meningococcal serogroups A, C, W, and Y (MenACWY) are approved for the immunization of toddlers, including the MenACWY-TT vaccine (Nimenrix®, Pfizer ltd, Sandwich, UK), which contains each meningococcal serogroup conjugated to the tetanus carrier protein [1,10,11]. From 6 months of age, a single primary MenACWY-TT dose is recommended [11]. A booster dose may be given in those 12 months and older who received primary immunization with a conjugated or plain polysaccharide meningococcal vaccine [11].

A single dose of MenACWY-TT in toddlers provides sufficient protection against meningococcal disease; however, data are needed on the effect after administration of 2 vaccine doses at 12 months of age and on the persistence of antibody responses after primary vaccination. The European Medicines Agency requested the conduct of a study to evaluate the immediate and longer-term antibody titers elicited by 1 or 2 doses of MenACWY-TT administered in children 12–23 months of age. The short-term (ie, 1 month after vaccination) immune responses and safety data after 1 or 2 MenACWY-TT doses in toddlers from this phase 3 study have been reported previously [12]. Because the timing of vaccination coincided with the toddler pneumococcal conjugate vaccine (PCV) booster dose recommended in some countries, coadministration of MenACWY-TT with a 13-valent PCV (PCV13) dose was also assessed. Vaccination with 1 or 2 MenACWY-TT doses elicited robust short-term immune responses to all serogroups with a favorable safety and tolerability profile. Coadministration of PCV13 and MenACWY-TT did not affect the immunogenicity or safety of either vaccine. As part of this phase 3 study, long-term antibody persistence and safety results up to 5 years after MenACWY-TT vaccination are reported herein.

2. Methods

2.1. Study design and participants

This phase 3, open-label, randomized, controlled, multicenter study with a parallel design was conducted in Australia, Canada, the Czech Republic, Panama, South Africa, and Turkey (ClinicalTrials.gov Identifier NCT01939158; EudraCT number 2013–001083-28) and has been previously described [12]. Eligible participants were healthy 12–14-month-old children at the time of the first vaccination in the parent study, with vaccination records showing the completion of the full primary vaccination schedule with PCV13 and diphtheria, tetanus, and pertussis – containing vaccine according to local recommendations $\geq$ 5 months before the study entry. Children in care (ie, those under the control of an agency, organization, institution or entity by the courts, the government, or a government body) were excluded.

Participants were randomized in a 1:1:1:1 ratio to 1 of 4 study groups: MenACWY-TT at Month 0 (ACWY1d group), MenACWY-TT at Months 0 and 2 (ACWY2d group), MenACWY-TT and PCV13 at Month 0 (Co-Ad group), or PCV13 at Month 0 and MenACWY-TT at Month 2 (PCV13/ACWY group) [12].

Each 0.5-mL dose of MenACWY-TT contained 5 μg of each meningococcal serogroup A, C, W, and Y polysaccharide conjugated to tetanus toxoid carrier protein (TT; 44 μg total of TT). Each 0.5-mL dose of PCV13 contained 2.2 μg of each pneumococcal polysaccharide serotype 1, 3, 4, 5, 6A, 7F, 9 V, 14, 18C, 19A, 19F, and 23F and 4.4 μg of serotype 6B conjugated to cross-reactive material 197 (CRM_{197}) carrier protein and adsorbed on 0.125-mg aluminum phosphate.

Vaccines were administered intramuscularly. MenACWY-TT (lot number AMECA011B1, AMECA016C1, AMECA018B) administered at Months 0 and 2 was injected in the left anterolateral thigh or deltoid, and PCV13 (lot number DEXTA477AZ, DEXTA472AZ, DEXTA472AY) administered at Month 0 was injected in the right anterolateral thigh or deltoid.

The study was conducted in accordance with all applicable regulatory requirements, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice, all applicable participant privacy requirements, the guiding principles of the Declaration of Helsinki, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects. The study was designed and conducted in accordance with the ICH Harmonised Tripartite Guideline for clinical investigation of medicinal products in the pediatric population and all other applicable ethical guidelines. The protocol, informed consent forms, amendments, and other study documents were reviewed and approved by the Institutional Review Board/Independent Ethics Committee at each participating site. Written informed consent from the participant's legally acceptable representative(s)/parent(s) was obtained before performance of any study-specific activity.

2.2. Objectives

The primary objective was to evaluate the long-term persistence of the immune response induced by 1 or 2 doses of MenACWY-TT with respect to serum bactericidal activity using rabbit complement (rSBA)-MenA, rSBA-MenC, rSBA-MenW, and rSBA-MenY titers at 1, 3, and 5 years after the last vaccination in the ACWY1d and ACWY2d groups. Secondary objectives included evaluation of the long-term persistence of the immune response induced by 1 or 2 doses of MenACWY-TT with respect to serum bactericidal activity using human complement (hSBA)-MenA, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers in a subset of

participants at 1, 3, and 5 years after the last vaccination in the ACWY1d and ACWY2d groups. The long-term persistence of the immune response induced by 1 dose of MenACWY-TT with respect to rSBA-MenA, rSBA-MenC, rSBA-MenW, and rSBA-MenY titers at 1, 3, and 5 years after the last vaccination in the Co-Ad and PCV13/ACWY groups was also evaluated as a secondary objective. Other secondary objectives included an evaluation of the occurrence of serious adverse events (SAEs) related to study vaccine administration and any events related to lack of vaccine efficacy (ie, meningococcal disease) up to 5 years after the last vaccination.

2.3. Assessments

In the current assessment, blood sampling for antibody determination (approximately 5 mL) occurred at 1, 3, and 5 years after vaccination. Antibody determinations were performed by independent laboratories. Results of the short-term immune responses are reported elsewhere [12]. Immune responses to MenACWY-TT were assessed using hSBA and rSBA for serogroups A, C, W, and Y.

The SBA assay used in this study is a surrogate method for evaluation of meningococcal vaccine efficacy, in which serially diluted serum samples are incubated with the meningococcal strain of interest, and SBA titers are defined as the highest dilution at which ≥ 50 % killing occurs [13]. In 1969, Goldschneider et al. demonstrated the correlation between hSBA titers and protection from MenC among military recruits [14,15], establishing an hSBA titer ≥ 1:4 as the correlate of protection. Since then, a correlate of protection of hSBA titer ≥ 1:4 has been validated as well for serogroup B and has been used to support vaccine licensure across all meningococcal serogroups [14]. The rSBA assay was subsequently recommended by the World Health Organization (WHO) for evaluation of serogroups A and C due to issues in obtaining exogenous human complement sources for hSBA assays [14]. Importantly, rSBA and hSBA results do not directly correlate with one another [13].

Throughout the study, SAEs related to study vaccine administration were recorded; those occurring at Years 1, 3, and 5 are reported here. Occurrences of meningococcal and pneumococcal disease are reported from study enrollment until the end of the study as SAEs.

2.4. Statistical analyses

The target enrollment number for the study was 800 participants (200 in each study group). The power to meet the coprimary confirmatory objectives of the short-term responses (described elsewhere [12]) was ≥ 99 %.

Immunogenicity was analyzed in the according-to-protocol (ATP) cohort for persistence at Years 1, 3, and 5. This included all participants who met eligibility criteria, received the complete primary vaccination with MenACWY-TT according to randomization, had assay results available for ≥ 1 antigen tested at the year considered, complied with the protocol procedures and intervals, did not receive a product or present with a medical condition leading to elimination from analysis, and were not excluded from the ATP cohort for immunogenicity (after dose 1 for the ACWY1d and Co-Ad groups; after dose 2 for the ACWY2d and PCV13/ACWY groups) and from the previous ATP cohorts for persistence (for Years 3 and 5 only), unless the reason for exclusion was either noncompliance with the protocol-defined serum sampling windows or lack of availability of immunogenicity results at the previous time point. Participants who did not complete a study visit (eg, Year 3 or Year 5) could return and complete other study visits.

Comparative analyses were descriptive and aimed to characterize the difference in immunogenicity between groups. The following were calculated for the 4 study groups: the percentage of participants with rSBA-MenA, rSBA-MenC, rSBA-MenW, and rSBA-MenY titers ≥ 1:8 and ≥ 1:128; the percentage of participants with hSBA-MenA, hSBA-MenC, hSBA-MenW, and hSBA-MenY titers ≥ 1:4 and ≥ 1:8; and rSBA and hSBA geometric mean titers (GMTs) with 95 % CIs. GMT calculations were performed by taking the antilog of the mean of the log titer transformations. For MenA, MenC, MenW, and MenY, noninferiority was demonstrated for each serogroup separately if the lower limit of the two-sided standardized asymptotic 95 % CI for the group differed between the Co-Ad group and the Pooled group (Co-Ad group minus Pooled group) in the percentage of patients with titers ≥ 1:8 ≥ − 10 %.

Safety was analyzed in all vaccinated participants. At Year 1, all SAEs considered related to vaccination, study procedures, or a concomitant drug or vaccine and any events related to lack of vaccine efficacy were described. At Years 3 and 5, all SAEs considered related to vaccination or study procedures and any events related to lack of vaccine efficacy were described.

3. Results

3.1. Demographics

Of the 802 children randomized in the study who were vaccinated, 619 completed the study through Year 5 (Fig. 1). The percentage of children was similar among the 4 vaccine groups. From Month 0 to Year 5, 184 (22.9 %) children were withdrawn, with similar numbers of children withdrawn from each vaccine group. The most common reasons for withdrawal before Year 5 were consent withdrawal (that was not due to an AE) and loss to follow-up. No participants were withdrawn because of an SAE, and 1 child was withdrawn because of a diagnosis of a nonserious AE of autism spectrum disorder that was not considered by the investigator to be related to the study vaccine.

At Year 5, the demographic characteristics (eg, age, sex, geographic ancestry) of the ATP cohort were generally similar among the vaccine groups (Table 1). The mean age at the Year 5 visit was 73.4 months (SD, 1.7 months), and 54.3 % of participants were male.

3.2. Immunogenicity

3.2.1. Immunogenicity of 1 or 2 doses of MenACWY-TT

Before vaccination, the percentages of children achieving rSBA titers ≥ 1:8 and ≥ 1:128 across all 4 serogroups were low in the ACWY1d (≥1:8 [95 % CI]: 2.3 % [0.6, 5.7] to 9.7 % [5.8, 15.1]; ≥1:128 [95 % CI]: 1.1 % [0.1, 4.1] to 9.1 % [5.3, 14.4]) and ACWY2d (≥1:8 and ≥ 1:128 [95 % CI]: 0.7 % [0, 3.6] to 5.2 % [2.3, 10.0]) groups. However, in both vaccine groups, the percentages of children with rSBA titers above the cutoff values increased 1 month after vaccination (ACWYd1 [95 % CI]: ≥1:8, 92.8 % [88.0, 96.1] to 97.8 % [94.4, 99.4] and ≥ 1:128:, 85.5 % [79.4, 90.3] to 95.0 % [90.7, 97.7]; ACWYd2: ≥1:8:, 98.0 %–100.0 % and ≥ 1:128:, 94.7 % [89.8, 97.7] to 99.3 % [96.3, 100]). The percentages of children in the ACWY1d and ACWY2d groups with rSBA titers above the cutoff values remained greater than the baseline value up to 5 years after vaccination (Fig. 2; **Table S1**). At 5 years after vaccination, the percentages (95 % CI) of children with rSBA titers ≥ 1:8 across all serogroups were 20.5 % (13.9, 28.3) to 58.6 % (49.8, 67.1) in the ACWY1d group and 28.4 % (20.5, 37.6) to 65.8 % (56.5, 74.3) in the ACWY2d group. The corresponding percentages of children with rSBA titers ≥ 1:128 (95 % CI) across all 4 serogroups were 6.1 % (2.7, 11.6) to 43.6 % (35.0, 52.5) and 10.3 % (5.5, 17.4) to 53.0 % (43.5, 62.3), respectively.

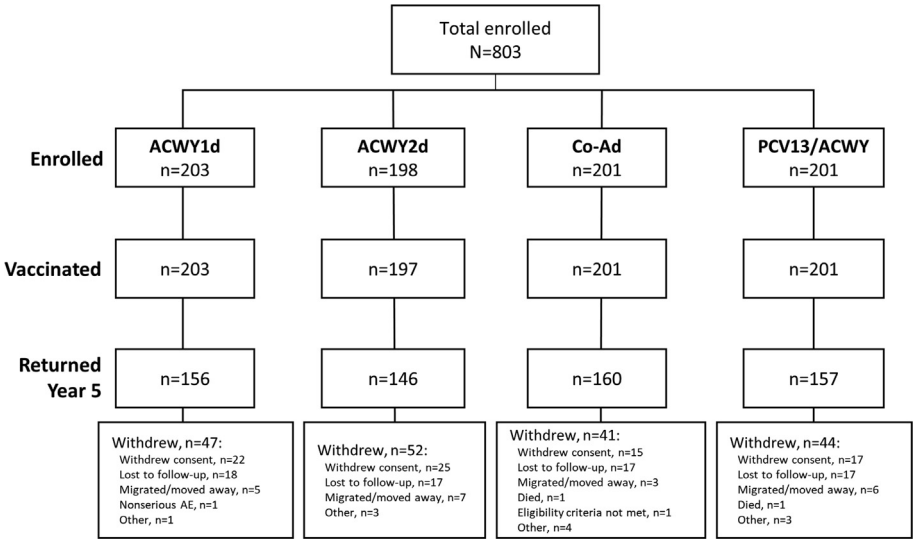

Fig. 1. Participant flow chart. ACWY1d = participants who received 1 dose of MenACWY-TT at Month 0; ACWY2d = participants who received 2 doses of MenACWY-TT at Months 0 and 2 (1 dose each); Co-Ad = participants who received 1 dose of MenACWY-TT and 1 dose of PCV13 at Month 0; MenACWY-TT: quadrivalent meningococcal tetanus toxoid conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV13/ACWY = participants who received 1 dose of PCV13 at month 0 and 1 dose of MenACWY-TT at Month 2.

Table 1
Participant demographics.

Characteristic	Vaccine group				Total (N = 521)
	ACWY1d (n = 133)	ACWY2d (n = 117)	Co-Ad (n = 142)	PCV13/ACWY (n = 129)	
Age at first vaccination, mean (SD), mo	13.2 (1.0)	13.0 (1.0)	13.2 (1.0)	13.1 (1.0)	13.1 (1.0)
Age at Year 5, mean (SD), mo	72.5 (1.4)	74.4 (1.4)	72.5 (1.3)	74.6 (1.3)	73.4 (1.7)
Months since last vaccination, mean (SD)	59.3 (1.2)	59.2 (1.2)	59.3 (1.1)	59.2 (1.1)	59.3 (1.1)
Male, n (%)	72 (54.1)	65 (55.6)	73 (51.4)	73 (56.6)	283 (54.3)
Geographic ancestry, n (%)					
White	93 (69.9)	88 (75.2)	96 (67.6)	92 (71.3)	369 (70.8)
African heritage/African American	23 (17.3)	13 (11.1)	25 (17.6)	21 (16.3)	82 (15.7)
Asian	0 (0.0)	2 (1.7)	2 (1.4)	2 (1.6)	6 (1.2)
Other	17 (12.8)	14 (12.0)	17 (12.0)	14 (10.9)	62 (11.9)
Number of PCV13 doses, n (%)					
2	16 (12.0)	17 (14.5)	24 (16.9)	19 (14.7)	76 (14.6)
3	117 (88.0)	100 (85.5)	118 (83.1)	110 (85.3)	445 (85.4)

ACWY1d = participants who received 1 dose of MenACWY-TT at Month 0; ACWY2d = participants who received 2 doses of MenACWY-TT at Months 0 and 2 (1 dose each); Co-Ad = participants who received 1 dose of MenACWY-TT and 1 dose of PCV13 at Month 0; MenACWY-TT: quadrivalent meningococcal tetanus toxoid conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV13/ACWY = participants who received 1 dose of PCV13 at Month 0 and 1 dose of MenACWY-TT at Month 2.

The percentages of children with hSBA titers ≥ 1:4 and ≥ 1:8 across all serogroups in the ACWY1d (≥1:4 and ≥ 1:8 [95 % CI]: 1.4 % [0, 7.4] to 7.7 % [2.9, 16.0]) and ACWY2d (≥1:4 and ≥ 1:8 [95 % CI]: 0.0 % [0, 5.4] to 9.7 % [3.6, 19.9]) groups were low before vaccination and increased 1 month after vaccination in both the ACWYd1 (≥1:4 and ≥ 1:8 [95 % CI]: 62.5 % [50.3, 73.6] to 98.7 % [93.1, 100]) and ACWYd2 (≥1:4 and ≥ 1:8 [95 % CI]: 95.3 % [86.9, 99.0] to 100 % [94.8, 100]) groups. The percentages of children with hSBA titers ≥ 1:4 and ≥ 1:8 across all serogroups remained greater than baseline up to 5 years following the last vaccine dose (Fig. 3; **Table S2**). The percentages (95 % CI) of children achieving hSBA titers ≥ 1:8 at Year 5 in the ACWY1d and ACWY2d groups were 27.9 % (17.1, 40.8) and 17.9 % (8.9, 30.4), respectively, for serogroup A; 60.7 % (47.3, 72.9) and 67.8 % (54.4, 79.4), respectively, for serogroup C; 58.9 % (45.0, 71.9) and 63.6 % (47.8, 77.6), respectively, for serogroup W; and 61.5 % (48.6, 73.3) and 54.2 % (39.2, 68.6), respectively, for serogroup Y. Similar titer levels were recorded for the 1:4 cutoff in both the ACWY1d and ACWY2d groups.

Compared with prevaccination GMT levels (rSBA GMTs [95 % CI]: 4.3 [4.0, 4.6] to 6.0 [5.0, 7.3] for ACWY1d, 4.2 [3.8, 4.5] to 5.2 [4.3, 6.1] for ACWY2d; hSBA GMTs: 2.2 [2.0, 2.4] to 2.5 [2.0, 3.1] for ACWY1d, 2.0 [not evaluable, not evaluable] to 2.6 [2.1, 3.2] for ACWY2d), GMTs for each vaccine group overall were higher 5 years after vaccination (rSBA GMTs: 6.6 [5.3, 8.2] to 46.8 [30.7, 71.5] for ACWY1d, 8.5 [6.4, 11.2] to 69.9 [44.7, 109.3] for ACWY2d; hSBA GMTs: 4.4 [3.1, 6.2] to 24.3 [14.3, 41.1] for ACWY1d, 3.1 [2.4, 4.0] to 29.4 [16.3, 52.9] for ACWY2d) (**Tables S1 and S2**). Generally, the GMTs of the ACWY2d group were elevated compared with the ACWY1d group.

3.2.2. Immunogenicity of coadministration of MenACWY-TT and PCV13

Before vaccination, the percentages of children achieving rSBA titers ≥ 1:8 and ≥ 1:128 across all 4 serogroups were low in the Co-Ad (≥1:8 [95 % CI]: 1.2 % [0.1, 4.2]5.9 % [2.9, 10.6]; ≥1:128 [95 % CI]: 0.6 % [0, 3.2] to 5.3 % [2.5, 9.9]) and PCV13/ACWY (≥1:8: 0.0 % [0, 2.1] to 7.0 % [3.7, 11.9]; ≥1:128: 0.0 % [0, 2.1] to 5.8 % [2.8, 10.5]) groups. In both groups, the percentages of children with rSBA titers above the cutoff values increased 1 month after vaccination (Co-Ad: ≥1:8, 89.8 % [84.4, 93.9] to 96.0 % [92.0, 98.4] and ≥ 1:128, 88.1 % [92.3, 92.5] to 93.8 % [89.2, 96.9]; PCV13/ACWY: ≥1:8, 95.3 % [90.9, 97.9] to 97.0 % [93.2,

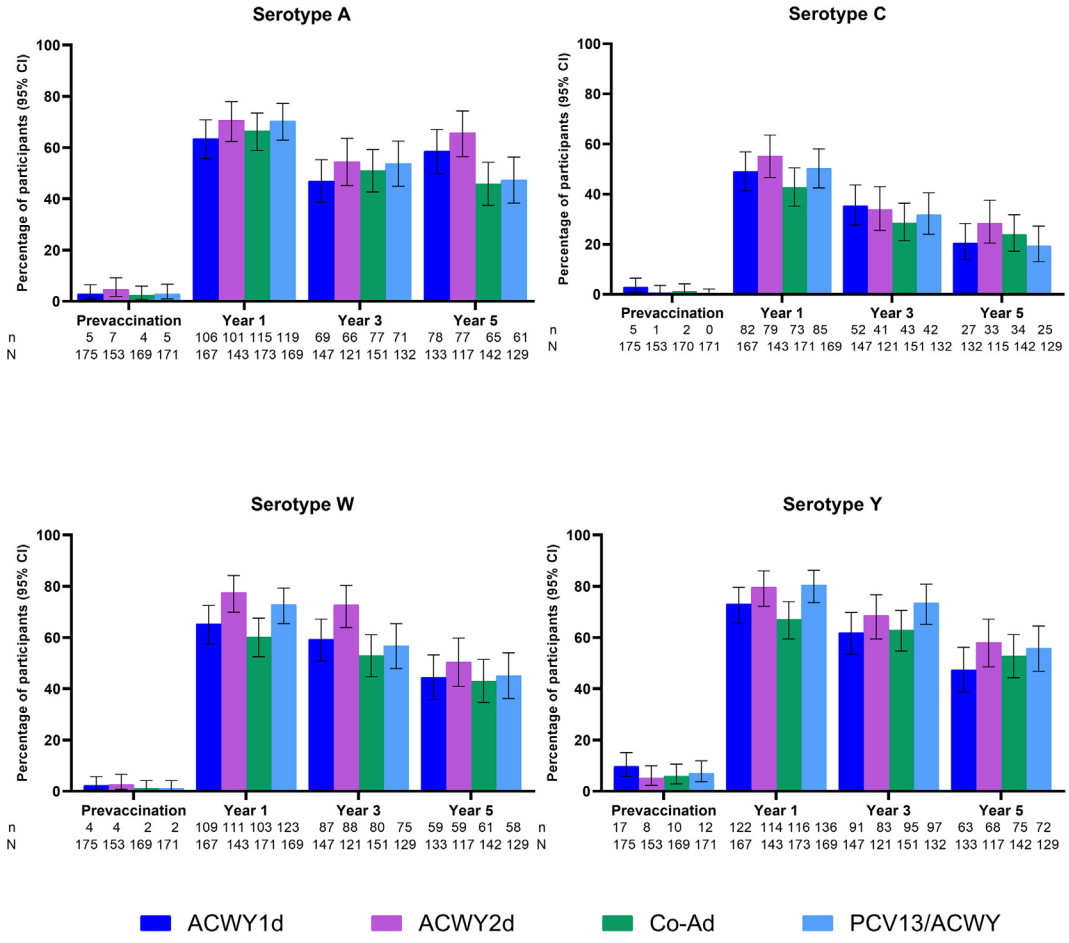

Fig. 2. Participants with rSBA titers ≥ 1:8 for persistence at Years 1, 3, and 5. ACWY1d = participants who received 1 dose of MenACWY-TT at Month 0; ACWY2d = participants who received 2 doses of MenACWY-TT at Months 0 and 2 (1 dose each); Co-Ad = participants who received 1 dose of MenACWY-TT and 1 dose of PCV13 at Month 0; MenACWY-TT = quadrivalent meningococcal tetanus toxoid conjugate vaccine; N = number or patients with available data; n = number with titer within specified range; PCV13 = 13-valent pneumococcal conjugate vaccine; PCV13/ACWY = participants who received 1 dose of PCV13 at Month 0 and 1 dose of MenACWY-TT at Month 2; rSBA = serum bactericidal activity using rabbit complement.

99.0] and ≥ 1:128, 85.8 % [79.6, 90.7] to 97.0 % [93.2, 99.0]). Similar to the ACWY1d and ACWY2d groups, the percentages of children in the Co-Ad and PCV13/ACWY groups with rSBA titers above the cut-off values remained greater than the baseline value up to 5 years after vaccination (Fig. 2; **Table S1**). The percentages (95 % CI) of children with rSBA titers ≥ 1:8 across all serogroups at Year 5 ranged from 23.9 % (17.2, 31.8) to 52.8 % (44.3, 61.2) in the Co-Ad group and 19.4 % (13.0, 27.3) to 55.8 % (46.8, 64.5) in the PCV13/ACWY group. For rSBA titers ≥ 1:128, the percentages (95 % CI) of children across all serogroups ranged from 12.0 % (7.1, 18.5) to 42.3 % (34.0, 50.8) in the Co-Ad group and 7.8 % (3.8, 13.8) to 48.1 % (39.2, 57.0) in the PCV13/ACWY group.

Similar to the ACWY1d and ACWY2d groups, immune responses in the Co-Ad and PCV13/ACWY groups declined over time but remained higher 5 years after vaccination compared with before vaccination (**Table S1**). Across all serogroups, GMTs (95 % CI) for both the Co–Ad (7.9[6.2, 10.0] to 43.3 [28.3, 66.2]) and PCV13/ACWY (7.0 [5.5, 8.8] to 53.9 [34.5, 84.2]) groups were higher 5 years after vaccination compared with before vaccination (Co-Ad: 4.1 [3.9, 4.4] to 5.1 [4.4, 6.0]; PCV13/ACWY: 4.0 [not evaluable, not evaluable] to 5.2 [4.5, 6.1]).

3.3. Safety

From the time of the first vaccination to Year 5, there were 15, 18, 19, and 18 SAEs reported by 12, 11, 13, and 16 participants in the ACWY1d, ACWY2d, Co-Ad, and PCV13/ACWY groups, respectively. In all vaccine groups, the most commonly reported SAEs were in the system organ class of infections and infestations (ACWY1d: 3.0 %; ACWY2d: 4.6 %; Co-Ad: 5.0 %; PCV13/ACWY: 5.0 %). Four related SAEs were previously reported in the primary study: 3 SAEs by 2 participants in the ACWY2d group (leukopenia and neutropenia, pneumonia) and 1 SAE by 1 participant in the Co-Ad group (pneumonia), and all of these events were reported as recovered or resolved [12].

No new safety signals were observed from Year 1 to Year 5. Three participants reported 4 SAEs, which included 1 (0.6 %) report of pneumonia pneumococcal in the ACWY1d group, 1 (0.6 %) report of meningitis aseptic in the PCV13/ACWY group, and 1 (0.6 %) participant in the Co-Ad group reported SAEs of pneumonia and diabetes mellitus. No SAEs were assessed by the investigator as related to the study vaccine, but the event of pneumonia (verbatim term of bronchopneumonia) reported in the Co-Ad group was assessed by the investigator as related to lack of efficacy of PCV13.

From Year 1 to Year 5, no participants were withdrawn from the study for safety-related reasons and no deaths were reported. Two deaths were outlined in the original publication, neither of which was considered related to vaccination (asphyxiation in the Co-Ad group occurring 121 days after vaccination and food aspiration in the PCV13/ACWY group occurring 26 days after vaccination) [12].

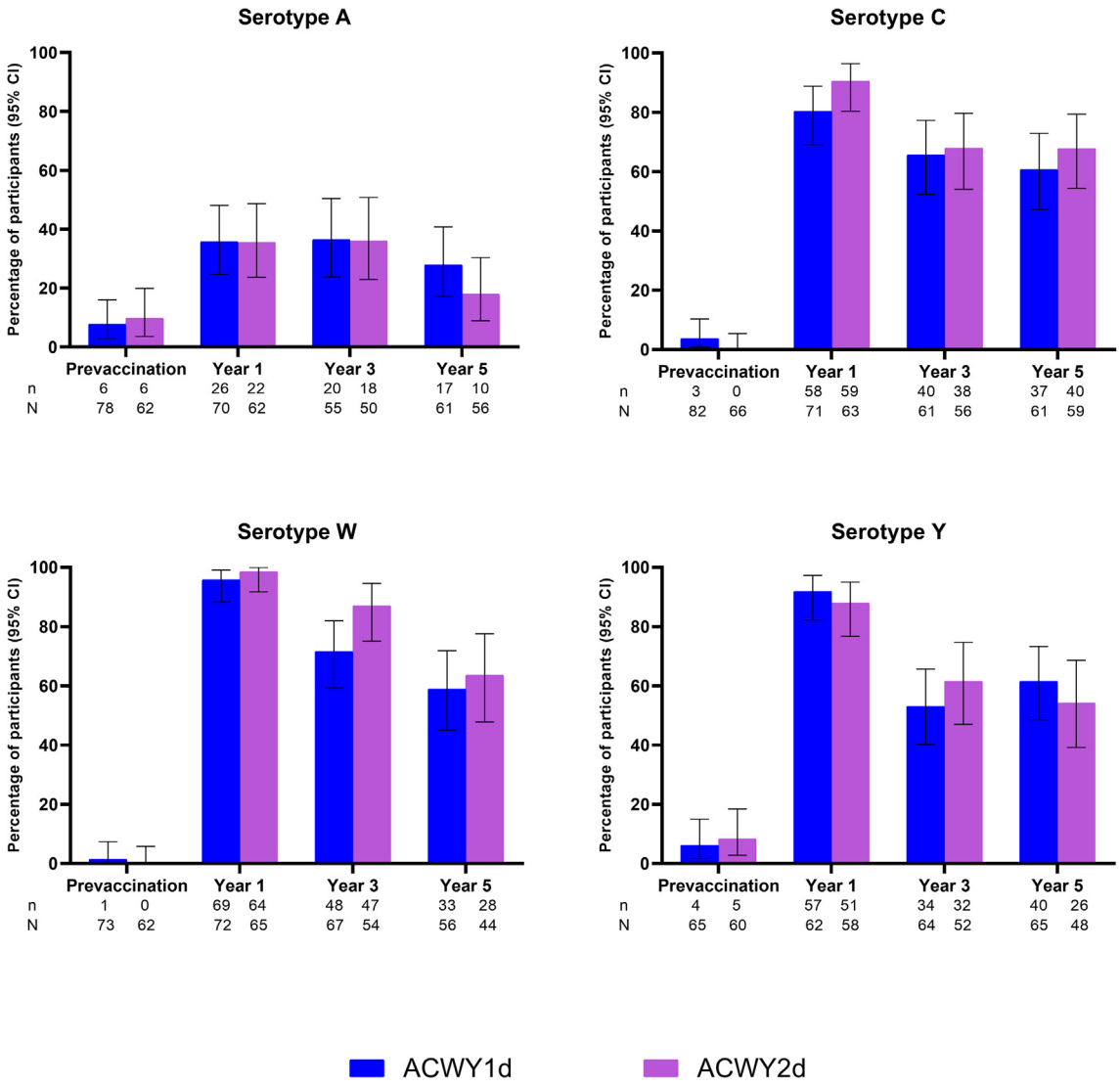

Fig. 3. Participants with hSBA titers ≥ 1:8 for persistence at Years 1, 3, and 5. ACWY1d = participants who received 1 dose of MenACWY-TT at Month 0; ACWY2d = participants who received 2 doses of MenACWY-TT at Months 0 and 2 (1 dose each); hSBA = serum bactericidal activity using human complement; MenACWY-TT = quadrivalent meningococcal tetanus toxoid conjugate vaccine; N = number or patients with available data; n = number with titer within specified range.

4. Discussion

Vaccination of young children against meningococcal disease is critical because of the high risk of IMD and related long-term sequelae and diagnostic challenges in this age group [2–4,8]. Accordingly, primary vaccination of toddlers against meningococcal disease is included in the national immunization programs of several countries [16–18]. Together with other factors, such as contemporary epidemiologic surveillance and real-world effectiveness data, clarification on the persistence of antibody responses after primary immunization with meningococcal vaccines is critical to inform policies and recommendations regarding the need for and timing of booster dosing. Therefore, we describe the long-term antibody persistence and safety results up to 5 years after MenACWY-TT vaccination of toddlers.

In the current analysis, immune responses after vaccination declined over time but were higher 5 years after vaccination compared with levels before vaccination. In our study, the proportion of participants with rSBA titers ≥ 1:8 was generally lowest for serogroup C, whereas the proportion of participants with hSBA titers ≥ 1:8 was generally lowest for serogroup A. Comparable antibody persistence at Year 5 was observed for participants receiving 1 or 2 doses of MenACWY-TT. No new safety concerns were identified since the previous publication [12].

These long-term antibody persistence results add to the existing evidence for the duration of immunologic responses up to 5 years after primary MenACWY-TT vaccination of toddlers [19–22]. In those studies, antibody responses after primary MenACWY-TT vaccination persisted for 2–3 years and subsequently decreased up to 5 years after vaccination, particularly for serogroup W [23]. The persistence of antibody responses after primary MenACWY-TT dosing has also been reported across age groups up to 10 years after primary MenACWY-TT vaccination, with 1 study that included participants who were toddlers at the time of primary vaccination [24–26]. In that study, antibody responses for serogroups A and C persisted 10 years after primary vaccination in the majority of participants, but not for serogroups W and Y [26]. Together with our results from the current study, these findings suggest that immune responses may last up to at least 5 years after primary vaccination of toddlers with MenACWY-TT.

A strength of this study was the comparison of the long-term antibody responses and safety between 1- and 2-dose MenACWY-TT schedules in young children, as well as assessment of these endpoints after coadministration of MenACWY-TT with PCV13. Limitations of the study include withdrawal of nearly-one-quarter of participants during the 5-year study period. In addition, because all analyses were descriptive, formal between-group comparisons were not possible.

In conclusion, MenACWY-TT administered in a 1- or 2-dose regimen with or without PCV13 resulted in antibody responses persisting in the majority of children up to 5 years after primary vaccination at 12–14 months of age. No new safety concerns were identified. This study contributes additional evidence that a single dose of MenACWY-TT induces robust immunogenicity and durability of protection. Together with the existing clinical trial and real-world use of MenACWY-TT in toddlers and across age groups, these long-term antibody persistence results provide important insights regarding long-term protection from primary vaccination and regarding the potential need for a booster dose in late childhood and adolescence.

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Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Contributions

All authors had full access to the data and had final responsibility to submit for publication, and attest that they meet the ICMJE criteria for authorship.

CLC collected data, carried out the study, contributed with materials/analyses, and was involved in analyses and interpretation of the data.

PP, CW, RN, and JLP collected data, contributed with materials/-analyses, and was involved in analyses and interpretation of the data.

MC collected data and was involved in analyses and interpretation of the data.

Data sharing statement

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.11.048.

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