Vaccine 37 (2019) 6171–6179

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

MenACWY-CRM conjugate vaccine booster dose given 4–6 years after priming: Results from a phase IIIb, multicenter, open label study in adolescents and adults

Mary Tipton [a], Wendy Daly [b], Shelly Senders [c], Stanley L. Block [d], Maria Lattanzi [e], Thembile Mzolo [f], Silvia Barbi [f], Michele Pellegrini [e,*], Pavitra Keshavan [e]

[a] CopperView Medical Center, South Jordan, UT, United States
[b] Brownsboro Park Pediatrics, Louisville, KY, United States
[c] Senders Pediatrics, Cleveland, OH, United States
[d] Kentucky Pediatric/Adult Research, Bardstown, KY, United States
[e] GSK, Siena, Italy
[f] GSK, Amsterdam, the Netherlands

ARTICLE INFO

Article history:
Received 31 January 2019
Received in revised form 25 August 2019
Accepted 26 August 2019
Available online 5 September 2019

Keywords:
Quadrivalent meningococcal conjugate vaccine
Booster response
Safety
Adolescents
Adults
Early immune response

ABSTRACT

Background: Vaccination strategies against bacterial meningitis vary across countries. In the United States, a single dose of quadrivalent meningococcal conjugate vaccine (MenACWY) is recommended at 11–12 years of age, with a booster dose approximately 5 years later. We assessed immune responses to a booster dose of MenACWY-CRM vaccine after priming with MenACWY-CRM or MenACWY-D vaccines in adolescents and adults.

Methods: In this phase IIIb, multicenter, open-label study, healthy 15–55-year-olds, who received MenACWY-CRM (N = 301) or MenACWY-D (N = 300) 4–6 years earlier or were meningococcal vaccine-naïve (N = 100), received one MenACWY-CRM vaccine dose. Immunogenicity was evaluated pre-vaccination, 3 or 5 days post-vaccination (sampling subgroups), and 28 days post-vaccination by serum bactericidal activity assay using human complement (hSBA). After vaccination, participants were monitored for 7 days for reactogenicity, 29 days for unsolicited adverse events (AEs), and 181 days for serious AEs and medically-attended AEs.

Results: Sufficiency of the immune response to a MenACWY-CRM booster dose was demonstrated; the lower limit of the 1-sided 97.5% confidence interval for percentages of participants with hSBA seroresponse at 28 days post-vaccination was >75% for each serogroup in those primed with either the MenACWY-CRM or MenACWY-D vaccine. Seroresponse was observed in ≥93.24% of primed participants and ≥35.87% of naïve participants 28 days post-vaccination. At 5 days post-booster, among primed participants, hSBA titers ≥1:8 were achieved in ≥47.14% of participants for MenA and in ≥85.52% of participants for MenC, MenW and MenY, and 3.25- to 8.59-fold increases in hSBA geometric mean titers against each vaccine serogroup were observed. No safety concerns were raised throughout the 6-month follow-up period.

Conclusions: A booster dose of the MenACWY-CRM vaccine induced a robust and rapid anamnestic response in adolescents and adults, irrespectively of either MenACWY-CRM or MenACWY-D vaccine administered 4–6 years earlier, with an acceptable clinical safety profile.

ClinicalTrials.gov registration: NCT02986854.

An Audio Summary linked to this article that can be found on Figshare https://figshare.com/articles/MenACWY-CRM_conjugate_vaccine_booster_dose_given_4_6_years_after_priming_Results_from_a_phase_IIIb_multicenter_open_label_study_in_adolescents_and_adults_mp4/11823048

Abbreviations: ACIP, Advisory Committee on Immunization Practices; CI, confidence interval; AE, adverse event; GMR, geometric mean ratio; GMT, geometric mean titer; hSBA, serum bactericidal assays using human complement; IMD, invasive meningococcal disease; LAR, legally acceptable representative; LL, lower limit; MenACWY-CRM, quadrivalent conjugate vaccine using a non-toxic mutant of diphtheria toxin as carrier protein; MenACWY-D, quadrivalent conjugate vaccine using diphtheria toxoid as carrier protein; SAE, serious adverse event; US, United States.

* Corresponding author at: GSK, Via Fiorentina 1, 53100 Siena, SI, Italy.
E-mail addresses: tipton@rx-research.com (M. Tipton), ssenders@senderspediatrics.com (S. Senders), maria.x.lattanzi@gsk.com (M. Lattanzi), thembile.x.mzolo@gsk.com (T. Mzolo), silvia.x.barbi@gsk.com (S. Barbi), michele.x.pellegrini@gsk.com (M. Pellegrini), pavitra.x.keshavan@gsk.com (P. Keshavan).

https://doi.org/10.1016/j.vaccine.2019.08.065
0264-410X/

1. Introduction

Neisseria meningitidis is responsible for invasive meningococcal disease (IMD), which remains a global public health problem [1,2]. Despite the availability of effective treatments, IMD has a significant morbidity and mortality due to its fulminant nature, with a case fatality rate ranging from 10% to 15% in treated individuals [1,3]. Moreover, IMD is associated with a high risk of long-term disabling sequelae, including hearing loss, neurological impairment, seizures, and intellectual disabilities [3,4].

The incidence of IMD varies by geographical region and time of the year [5,6]. In the United States (US), the average annual incidence of meningococcal disease was 0.26 cases per 100,000 population between 2006 and 2015 [7]. The incidence of IMD is highest in infants during the first year of life, with a second peak in adolescents and young adults in whom transmission is facilitated by close living conditions and socio-behavioral factors [8,9]. The majority of IMD cases worldwide are caused by serogroups MenA, MenB, MenC, MenY, MenW, and MenX [4,6,10]. In the US, the most prevalent meningococcal serogroups are MenB, MenY, and MenC [11].

There are two quadrivalent meningococcal conjugate vaccines (MenACWY) currently available in the US for active immunization in various age groups: one using diphtheria toxoid (MenACWY-D; *Menactra*, Sanofi Pasteur) and the other a non-toxic mutant of diphtheria toxin (MenACWY-CRM; *Menveo*, GSK) as carrier protein. MenACWY-CRM is approved in the US for active immunization of individuals from 2 months to 55 years of age [12], and has been shown to be immunogenic with an acceptable safety profile in all indicated age groups [13–16]. The US Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with a quadrivalent meningococcal conjugate vaccine for adolescents at 11–12 years of age with a booster dose administered approximately 5 years later [17].

Considering the current ACIP recommendation, this study aimed to evaluate the response to a booster dose of the MenACWY-CRM vaccine given 4–6 years after primary vaccination with a licensed quadrivalent meningococcal conjugate vaccine in adolescents and adults. Fig. 1 summarizes the research, clinical relevance, and impact of this study at the population level.

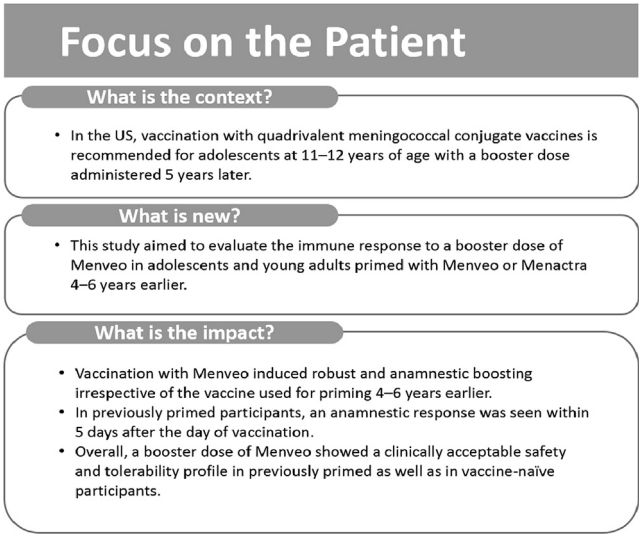

Fig. 1. Summary of the background, research, clinical relevance, and impact of this study.

2. Material and methods

2.1. Study design

This phase IIIb, open-label study was conducted at 37 centers in the US and Puerto Rico, between December 2016 and December 2017. Study participants were healthy 15–55-year-old adolescents and adults who had received a single dose of either the MenACWY-CRM vaccine (MenACWY-CRM-primed group) or the MenACWY-D vaccine (MenACWY-D-primed group) 4–6 years earlier at an age of at least 11 years. Healthy adolescents and adults who had not been previously vaccinated with any meningococcal vaccine were also enrolled (Naïve group). All participants received a single dose of the MenACWY-CRM vaccine on study Day 1. The MenACWY-CRM vaccine and its administration route are described in **Supplementary Text 1** according to the prescribing information in the US [12]. Within each group, participants were randomized (1:1) to get blood draws on Days 1, 4, and 29, or Days 1, 6 and 29 (Fig. 2).

The study was conducted in compliance with the Declaration of Helsinki and followed International Committee on Harmonization Guidelines for Good Clinical Practice. Written informed consent was provided by the participants or their legally acceptable representatives (LARs) before enrollment. This study is registered at www.clinicaltrials.gov (NCT02986854). A protocol summary is available at http://www.gsk-clinicalstudyregister.com (study 205352).

2.2. Participants

Eligible participants were healthy 15–55-year-old adolescents and adults from whom written informed consent or assent was obtained prior to enrollment, and who, in the investigator's judgement, would comply with the study procedures. If participants were younger than 18 years at the time of enrollment, their parent(s)/LAR(s) gave written informed consent. Females of childbearing potential had to use an effective birth control method up to at least 30 days after vaccination and were encouraged to remain in the study for safety follow-up in case of pregnancy. The complete list of inclusion and exclusion criteria is given in **Supplementary Text 2**.

2.3. Study objectives

The primary objective was to demonstrate sufficiency of the immune response against each vaccine serogroup following a booster dose of the MenACWY-CRM vaccine in participants primed with either the MenACWY-CRM or the MenACWY-D vaccine.

Secondary immunogenicity objectives were to compare the immune response against each vaccine serogroup induced by a dose of the MenACWY-CRM vaccine in the MenACWY-CRM-primed group, the MenACWY-D-primed group, the pooled primed group (pooled MenACWY-CRM-primed and MenACWY-D-primed participants), and the Naïve group up to 28 days post-vaccination. Additional secondary objectives were to assess the bactericidal antibody titers against each vaccine serogroup approximately 4–6 years after the primary vaccination in the MenACWY-CRM-primed and the MenACWY-D-primed groups. The reactogenicity and safety of the MenACWY-CRM vaccine were also assessed.

2.4. Immunogenicity assessments

Immune responses to the 4 meningococcal vaccine serogroups were measured in each study group on blood samples collected on Day 1 (pre-vaccination), 4 or 6, and 29 by serum bactericidal

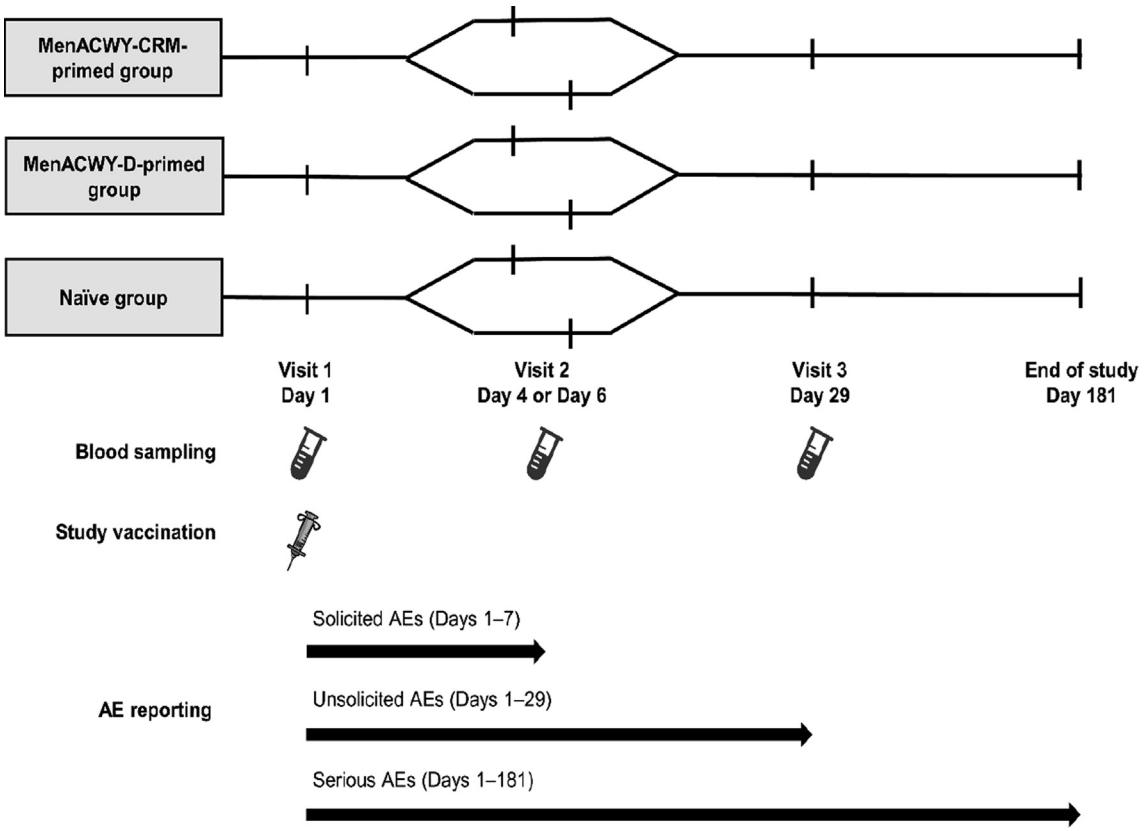

Fig. 2. Study design. MenACWY-CRM-primed, participants previously vaccinated with the MenACWY-CRM vaccine; MenACWY-D-primed, participants previously vaccinated with the MenACWY-D vaccine; Naïve, participants who were not previously vaccinated with any meningococcal vaccine; AE, adverse event.

assay using human complement (hSBA), as previously described [18].

Immune responses were evaluated by percentages of participants who had a seroresponse, percentages of participants with hSBA titers ≥1:8 and ≥1:16, and by hSBA geometric mean titers (GMTs) against MenA, MenC, MenW, and MenY. Seroresponse was defined as a post-vaccination hSBA titer ≥1:16 for participants with a pre-vaccination hSBA titer <1:4, or an increase of ≥4 times of the pre-vaccination hSBA titer for participants with a pre-vaccination hSBA titer ≥1:4.

2.5. Safety assessment

Safety of the MenACWY-CRM vaccine was assessed in the pooled primed group and in the Naïve group.

Solicited local adverse events (AEs; injection site pain, erythema, and induration), systemic AEs (fatigue, headache, myalgia, arthralgia, loss of appetite, nausea, chills, and fever [body temperature ≥38.0 °C]), and other indicators of reactogenicity (e.g., use of analgesics/antipyretics) were recorded within 7 days after vaccination, and unsolicited AEs within 29 days after vaccination. The intensity of each symptom was graded on a 3-level scale. Grade 3 redness and swelling at the injection site were recorded if their diameter was >100 mm; grade 3 fever was defined as body temperature ≥40.0 °C. All other symptoms were of grade 3 if they prevented normal activity.

Medically-attended AEs (i.e. symptoms or illnesses requiring hospitalization, emergency room visit, or visit to a health care provider), AEs leading to withdrawal from the study, and serious AEs (SAEs) were recorded during the entire study period up to Day 181.

2.6. Statistical methods

Immunogenicity analyses were conducted on the per protocol analysis set, including all evaluable participants who were randomized to the different blood draw schedules, received the study vaccine, had assay results available for at least one serogroup, and complied with all protocol-specified procedures. Safety analyses were conducted on the safety set, including all enrolled participants who received the study vaccine and had available safety data.

Immune response sufficiency (primary objective) was tested sequentially, first in the MenACWY-CRM-primed group and, if met, in the MenACWY-D-primed group. The immune response was considered as sufficient if the lower limit (LL) of the 1-sided 97.5% confidence interval (CI) for the percentage of participants with hSBA seroresponse against each vaccine serogroup was >75% at Day 29 following booster vaccination. Statistical analyses are further described in **Supplementary Text 3.**

3. Results

3.1. Study population and demographics

A total of 704 participants (301 in the MenACWY-CRM-primed group, 301 in the MenACWY-D-primed group, and 102 in the Naïve group) were enrolled in the study (Fig. 3). Of these, 1 participant in the MenACWY-D-primed group and 2 in the Naïve group did not receive the MenACWY-CRM vaccine. A total of 683 participants completed the study (298 in the MenACWY-CRM-primed group, 288 in the MenACWY-D-primed group, and 97 in the Naïve group).

Demographic and other baseline characteristics were balanced between both primed groups (Table 1). The mean age of the participants (±standard deviation) was 17.1 ± 3.7 years in the MenACWY-CRM-primed group and 17.8 ± 4.5 years in the MenACWY-D-primed group. The Naïve group enrolled mostly adults (mean age: 38.8 ± 10.5 years), with more female (67%) than male (33%) participants. Across all groups, most participants (78–83%) were Caucasian.

3.2. Immunogenicity of a booster or first dose of the MenACWY-CRM vaccine

We demonstrated sufficiency of the immune response induced by a booster dose of the MenACWY-CRM vaccine administered 4–6 years after primary vaccination with either the MenACWY-CRM or the MenACWY-D vaccine. Both co-primary immunogenicity objectives were met as the LL of the 1-sided 97.5% CI for percentages of participants with hSBA seroresponse for each vaccine serogroup at Day 29 was >75% in participants primed with either vaccine (Table 2). At Day 29, percentages of participants with hSBA seroresponse for MenA, MenC, MenW, and MenY ranged from 95.49% to 96.86% in the MenACWY-CRM-primed group and from 93.24% to 96.45% in the MenACWY-D-primed group (Table 2). Percentages of participants with hSBA seroresponse in the Naïve group are listed in **Supplementary Table 1**. At Day 29, the differences between the pooled primed group and the Naïve group in terms of hSBA seroresponse rate ranged between 30.91% (MenA) and 58.69% (MenW) across serogroups, with all LLs of 95% CIs >0 (**Supplementary Table 1**).

In all study groups, percentages of participants with hSBA titers ≥1:8 were similar or only slightly higher at Day 4 compared to Day 1 for each vaccine serogroup (Table 3). By Day 6, these percentages increased in all groups and at Day 29, ≥98.62% of participants in each primed group and ≥70.97% of participants in the Naïve group had hSBA titers ≥1:8 against each vaccine serogroup (Table 3). Differences between the pooled primed group and the Naïve group in terms of percentages of participants with hSBA titers ≥1:8 for each serogroup at Day 29 ranged between 12.73% (MenC) to 27.81% (MenA), with all LLs of 95% CIs >0 (**Supplementary Table 2**). Similar results were observed for percentages of participants with hSBA titers ≥1:16 against each vaccine serogroup, which were ≥97.52% in each primed group and ≥64.52% in the Naïve group on Day 29 (**Supplementary Table 3**).

Table 1
Demographic characteristics of the study participants (Enrolled Set).

Characteristics	MenACWY-CRM-primed N = 301	MenACWY-D-primed N = 301	Naïve N = 102
Age, years ± SD	17.1 ± 3.7	17.8 ± 4.5	38.8 ± 10.5
Gender, n (%)			
Female	144 (48)	156 (52)	68 (67)
Race, n (%)			
White-Caucasian	251 (83)	234 (78)	81 (79)
Black or African American	24 (8)	23 (8)	12 (12)
Asian	4 (1)	14 (5)	3 (3)
American Indian or Alaska Native	2 (1)	6 (2)	1 (1)
Native Hawaiian or other Pacific Islander	3 (1)	1 (<1)	0 (0)
Other	17 (6)	23 (8)	5 (5)
Ethnicity, n (%)			
Hispanic or Latino	40 (13)	75 (25)	11 (11)
Not Hispanic or Latino	258 (86)	223 (74)	91 (89)
Not reported	3 (1)	3 (1)	0 (0)

MenACWY-CRM-primed, participants previously vaccinated with the MenACWY-CRM vaccine; MenACWY-D-primed, participants previously vaccinated with the MenACWY-D vaccine; Naïve, participants who were not previously vaccinated with any meningococcal vaccine; SD, standard deviation; N, number of participants; n (%), number (percentage) of participants within the category.

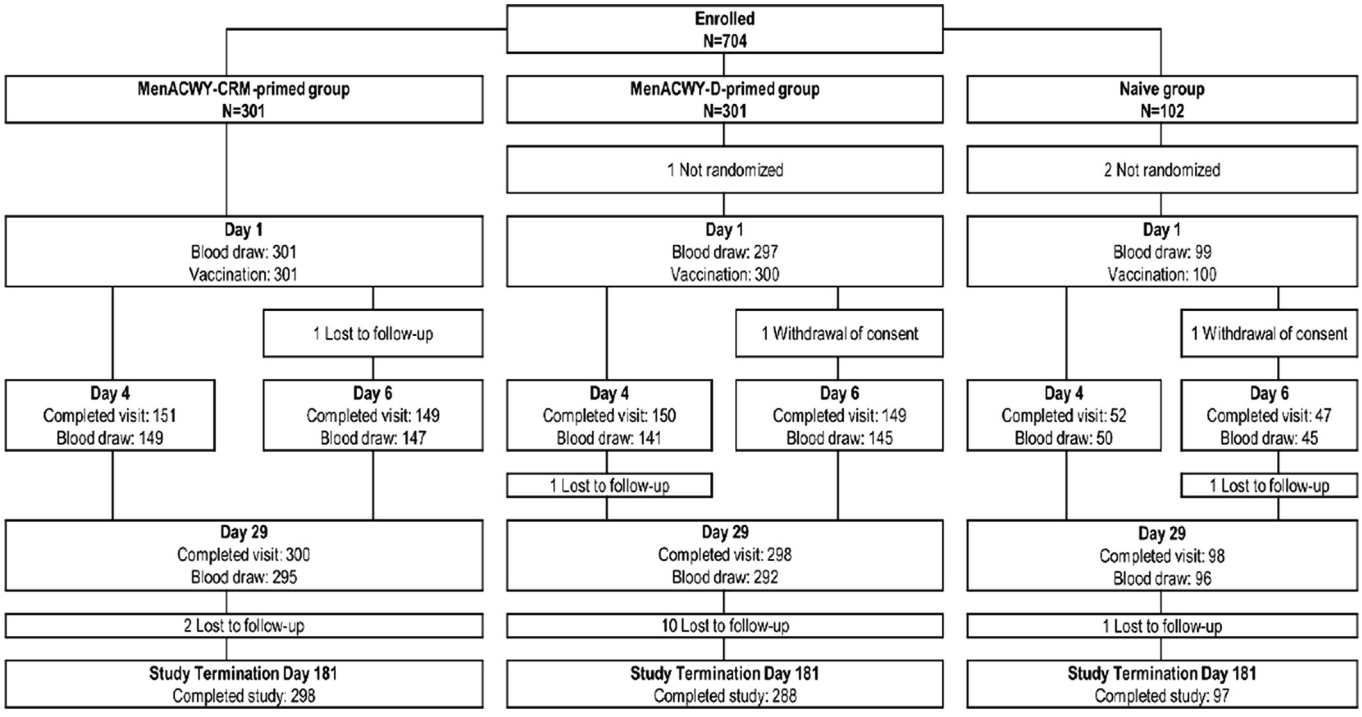

Fig. 3. Flow of participants. MenACWY-CRM-primed, participants previously vaccinated with the MenACWY-CRM vaccine; MenACWY-D-primed, participants previously vaccinated with the MenACWY-D vaccine; Naïve, participants who were not previously vaccinated with any meningococcal vaccine; N, number of participants. The numbers of participants who provided "Blood draw" refer to the numbers of participants who had their blood draw within the pre-specified window.

Table 2
Percentages of participants with seroresponse* against MenA, MenC, MenW and MenY 28 days after a booster dose of MenACWY-CRM vaccine (Per Protocol Set, Day 29).

	MenACWY-CRM-primed		MenACWY-D-primed	
Serogroup	N	% of participants with seroresponse (2-sided 95% CI)	N	% of participants with seroresponse (2-sided 95% CI)
MenA	289	96.54 (**93.73**–98.33)	282	96.45 (**93.58**–98.29)
MenC	288	95.49 (**92.40**–97.57)	280	96.07 (**93.08**–98.02)
MenW	289	95.85 (**92.86**–97.84)	281	93.24 (**89.64**–95.88)
MenY	287	96.86 (**94.13**–98.56)	280	94.29 (**90.89**–96.70)

MenACWY-CRM-primed, participants previously vaccinated with the MenACWY-CRM vaccine; MenACWY-D-primed, participants previously vaccinated with the MenACWY-D vaccine; hSBA, human serum bactericidal assay; N, number of participants; CI, confidence interval. *Seroresponse was defined as a post-vaccination hSBA titer≥1:16 for participants with a pre-vaccination hSBA titer <1:4, or an increase of ≥4 times of the pre-vaccination hSBA titer for participants with a pre-vaccination hSBA titer ≥1:4. The immune response was considered as sufficient if the lower limit of the one sided 97.5% CI (equivalent to 2 sided 95% CI) for percentage of participants with hSBA seroresponse against serogroups A, C, W and Y was >75%. **Bold:** sufficiency criterion met.

Compared to Day 1, hSBA GMTs at Day 4 remained similar for MenA and had slightly increased for MenC, MenW, and MenY in all groups (Table 3). By Day 6, hSBA GMTs against all vaccine serogroups had increased in both primed groups, with geometric mean ratios (GMRs; Day 6/Day 1) ranging between 3.25 and 8.59, and had also slightly increased in the Naïve group, with GMRs (Day 6/Day 1) ranging between 1.09 and 1.48 (**Supplementary Table 4**). By Day 29, hSBA GMTs against all vaccine serogroups had further increased in all study groups. hSBA GMT ratios (pooled primed group over Naïve group) increased from Day 4 over Day 6 to Day 29, with all LLs of the 95% CIs >1 except for Men A at Day 4 (**Supplementary Table 5**).

Percentages of participants with hSBA titers ≥1:8 before administration of the MenACWY-CRM vaccine dose in this study against all serogroups are detailed in Table 3. Group differences in terms of percentages of participants with hSBA titers ≥1:8 against MenA at Day 1 were 8.16% for MenACWY-CRM-primed vs Naïve group and 10.59% for MenACWY-D-primed vs Naïve group. Group differences in terms of percentages of participants with hSBA titers ≥1:8 against MenC, MenW, and MenY at Day 1 ranged from 14.14% (MenW) to 27.78% (MenC) for MenACWY-CRM-primed vs Naïve group, and from 14.72% (MenY) to 20.40% (MenC) for MenACWY-D-primed vs Naïve group. At Day 1, hSBA GMTs against MenA were slightly higher in primed participants than in the Naïve group. hSBA GMTs against MenC, MenW, and MenY at Day 1 were higher in primed participants than in the Naïve group (Table 3).

3.3. Safety and reactogenicity of a booster or first dose of MenACWY-CRM

The most commonly reported solicited local AE during the 7-day follow-up after vaccination was injection-site pain, experienced by 36–41% of participants across groups (Fig. 4). The most frequently reported solicited systemic AEs were fatigue (38% in the pooled primed group and 20% in the Naïve group) and headache (31% in the pooled primed group and 22% in the Naïve group) (Fig. 4). No cases of fever with a body temperature ≥40 °C were reported during the entire study period. Solicited AEs were reported with a grade 3 intensity (severe) by ≤4% of participants across groups.

Overall, during the 29-day period post-vaccination, 25% of primed and 22% of vaccine-naïve participants reported at least one unsolicited AE, and 8% and 11% at least one possibly vaccine-related unsolicited AE (Table 4). The most frequently reported at least possibly vaccine-related unsolicited AEs in either the pooled primed or the Naïve group were fatigue (2% of primed participants), injection site erythema (4% of naive participants), and injection site pruritus (2% of naive participants).

During the entire study period (Day 1 to Day 181), 8 participants reported 13 SAEs, none of which were considered as related to vaccination (Table 4). Three SAEs were reported in the MenACWY-CRM-primed group (1 case of major depression with suicide attempt, 1 case of intentional overdose with suicide attempt, and 1 participant with abdominal pain, tonsillitis, respiratory disorder, and septic shock); 2 SAEs were reported in the MenACWY-D-primed group (1 suicide attempt and 1 suicidal ideation); and 3 SAEs were reported in the Naïve group (1 case of diabetic ketoacidotic hyperglycaemic coma, 1 case of diverticulitis, and 1 spontaneous abortion). Medically-attended AEs were reported in 30% of primed and 19% of vaccine-naive participants. At least possibly vaccine-related medically attended AEs were reported in 1 participant in the MenACWY-CRM-primed group (lymphadenopathy with onset on day 3), in 3 participants in the MenACWY-D-primed group (urticaria with onset on day 10 and day 130, fatigue and headache with onset on day 1 followed by myalgia with onset at day 4, and anxiety with onset on day 22), and in 1 participant in the Naïve group (pyrexia with onset on day 1). There were no AEs leading to withdrawal from the study, and no deaths during the study.

4. Discussion

In this study, approximately 1 month after a single booster dose of the MenACWY-CRM vaccine, percentages of participants with hSBA seroresponse ranged from 95.49% to 96.86% in the MenACWY-CRM-primed group and between 93.24% and 96.45% in the MenACWY-D-primed group, across the four meningitis serogroups, and met the predefined criterion for the assessment of the sufficiency of immune responses. Approximately one month after the booster dose administration, almost all primed participants demonstrated a seroresponse and had hSBA titers ≥1:8. Similar immune response rates were observed after a booster dose of MenACWY-CRM given 3 years after priming with the MenACWY-CRM or the MenACWY-D vaccine in a previous phase III trial in adolescents [19]. These results suggest that one dose of the MenACWY-CRM vaccine can be administered as a booster at 16–18 years of age as recommended by the US ACIP, irrespective of either MenACWY-CRM or MenACWY-D vaccine used for priming [20,21].

A group of vaccine-naïve participants was added to the study design to evaluate the rapidity and magnitude of the booster response to the MenACWY-CRM vaccine in primed individuals and of the primary response in naïve individuals. Following administration of a single dose of the MenACWY-CRM vaccine, hSBA titers for each vaccine serogroup were higher in primed participants than in naïve individuals, showing that the immune response to the booster dose of the MenACWY-CRM vaccine was anamnestic. Similar results were obtained in 2 previous clinical trials: a phase III study in adolescents, where a booster dose of the MenACWY-CRM vaccine was given 3 years after primary vaccination with either the MenACWY-CRM or the MenACWY-D vaccine [19], and a phase II study, where the MenACWY-CRM vaccine

Table 3
Percentages of participants with hSBA titers ≥1:8 and hSBA GMTs against MenA, MenC, MenW and MenY at Days 1, 4, 6 and 29 after a booster (MenACWY-CRM- and MenACWY-D-primed groups) or a primary (Naïve group) dose of MenACWY-CRM vaccine (Per Protocol Set, Day 29).

	MenACWY-CRM-primed			MenACWY-D-primed			Naïve		
Timepoint	N	% of participants with hSBA titers ≥1:8 (95% CI)	GMT (95% CI)	N	% of participants with hSBA titers ≥1:8 (95% CI)	GMT (95% CI)	N	% of participants with hSBA titers ≥1:8 (95% CI)	GMT (95% CI)
MenA									
Day 1	289	12.46 (8.88–16.83)	2.81 (2.54–3.11)	282	14.89 (10.95–19.59)	2.95 (2.67–3.27)	93	4.30 (1.18–10.65)	2.27 (1.90–2.71)
Day 4	144	11.11 (6.49–17.42)	2.83 (2.43–3.29)	138	13.04 (7.92–19.83)	3.00 (2.57–3.51)	48	4.17 (0.51–14.25)	2.25 (1.73–2.93)
Day 6	146	53.42 (44.99–61.71)	12.87 (9.63–17.19)	140	47.14 (38.66–55.75)	10.17 (7.57–13.66)	44	9.09 (2.53–21.67)	2.48 (1.46–4.20)
Day 29	290	98.62 (96.51–99.62)	210.10 (181.07–243.78)	282	98.94 (96.92–99.78)	236.69 (203.56–275.20)	93	70.97 (60.64–79.92)	32.11 (24.70–41.76)
MenC									
Day 1	288	61.11 (55.22–66.77)	16.11 (13.28–19.54)	281	53.74 (47.72–59.68)	10.72 (8.82–13.03)	93	33.33 (23.89–43.87)	5.06 (3.60–7.10)
Day 4	144	70.83 (62.68–78.10)	22.96 (17.31–30.45)	138	60.14 (51.47–68.38)	14.29 (10.71–19.07)	48	43.75 (29.48–58.82)	6.69 (4.10–10.90)
Day 6	145	87.59 (81.09–92.47)	92.27 (68.91–123.56)	139	92.09 (86.28–95.98)	90.06 (66.84–121.35)	44	43.18 (28.35–58.97)	6.71 (3.95–11.40)
Day 29	290	100 (98.74–100)	1159.93 (977.33–1376.63)	281	99.64 (98.03–99.99)	1057.66 (888.74–1258.68)	93	87.10 (78.55–93.15)	59.70 (44.12–80.78)
MenW									
Day 1	289	75.43 (70.05–80.29)	22.07 (18.54 26.29)	282	76.95 (71.59–81.74)	23.46 (19.66–28.00)	93	61.29 (50.62–71.22)	12.21 (8.98 –16.62)
Day 4	144	81.94 (74.67–87.85)	25.90 (20.13–33.32)	138	82.61 (75.24–88.53)	33.87 (26.18–43.82)	48	62.50 (47.35–76.05)	13.80 (8.92–21.35)
Day 6	146	93.84 (88.62–97.14)	112.49 (86.26–146.71)	140	97.86 (93.87–99.56)	143.75 (109.61–188.54)	44	63.64 (47.77–77.59)	15.98 (9.85–25.93)
Day 29	290	100 (98.74–100)	1394.65 (1176.59–1653.11)	281	100 (98.70–100)	1883.96 (1585.12–2239.15)	92	84.78 (75.79–91.42)	55.31 (40.90–74.80)
MenY									
Day 1	287	54.01 (48.05–59.88)	9.24 (7.81–10.94)	281	46.98 (41.02–52.99)	8.22 (6.93–9.75)	93	32.26 (22.93–42.75)	4.56 (3.39–6.13)
Day 4	143	55.24 (46.71–63.56)	10.87 (8.26–14.32)	138	55.80 (47.10–64.24)	12.12 (9.16–16.04)	48	33.33 (20.40–48.41)	4.63 (2.88–7.44)
Day 6	145	85.52 (78.72–90.81)	63.30 (47.73–83.95)	140	87.86 (81.27–92.76)	61.56 (46.18–82.05)	44	45.45 (30.39–61.15)	6.44 (3.86–10.76)
Day 29	290	100 (98.74–100)	1066.66 (900.67–1263.25)	281	99.64 (98.03–99.99)	1007.62 (848.53–1196.54)	93	77.42 (67.58–85.45)	37.40 (27.75–50.42)

MenACWY-CRM-primed, participants previously vaccinated with the MenACWY-CRM vaccine; MenACWY-D-primed, participants previously vaccinated with the MenACWY-D vaccine; Naïve, participants who were not previously vaccinated with any meningococcal vaccine; hSBA, human serum bactericidal assay; N, number of participants; CI, confidence interval; GMT, geometric mean titer.

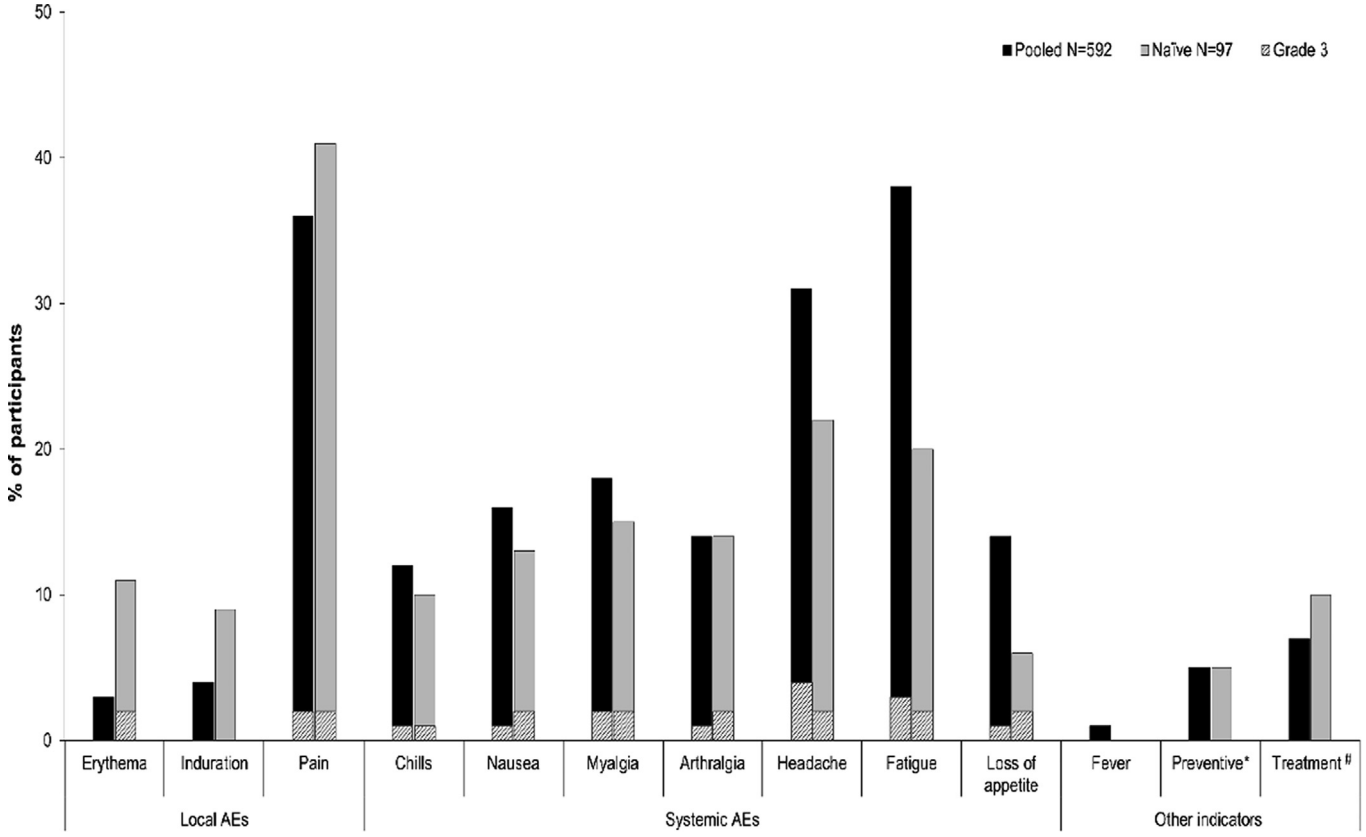

Fig. 4. Percentage of participants with solicited local and systemic AEs reported during the 7-day period following vaccination (Safety Set). Pooled, pooled data for MenACWY-CRM-primed and MenACWY-D-primed cohorts; MenACWY-CRM-primed, participants previously vaccinated with the MenACWY-CRM vaccine; MenACWY-D-primed, participants previously vaccinated with the MenACWY-D vaccine; Naïve, participants who were not previously vaccinated with any meningococcal vaccine; AEs, adverse events; N, number of participants. *Preventive use of antipyretics/analgesics; #Treatment with antipyretics/analgesics.

Table 4
Overview of unsolicited AEs and SAEs after a booster (MenACWY-CRM- and MenACWY-D-primed groups) or a primary (Naïve group) dose of MenACWY-CRM vaccine (Unsolicited Safety Set).

AE	Pooled primed group (N = 601) n (%)	Naïve group (N = 100) n (%)
Any AE	152 (25)	22 (22)
At least possibly related AE	50 (8)	11 (11)
Any SAE	5 (1)	3 (3)
At least possibly related SAE	0	0
Medically attended AEs	181 (30)	19 (19)
Possibly related medically attended AEs	4 (1)	1 (1)
AE leading to premature withdrawal	0	0
Death	0	0

Pooled primed group: participants previously vaccinated with the MenACWY-CRM or the MenACWY-D vaccine; Naïve, participants who were not previously vaccinated with any meningococcal vaccine; N, number of participants; n (%), number (percentage) of participants within the category; AE, Adverse Event; SAE, Serious Adverse Event.

was administered at approximately 5 years after previous vaccination with the MenACWY-CRM vaccine (or a licensed meningococcal polysaccharide vaccine) [22]. In the present study, the booster response to the MenACWY-CRM vaccine in primed participants was also more rapid than the response to primary vaccination in naïve participants. In the primed groups, substantial increases in percentages of participants with hSBA titers ≥1:8 and in hSBA GMTs against the four vaccine serogroups were already observed at 5 days after the administration of the booster dose of the MenACWY-CRM vaccine, while antibody titers remained similar to pre-vaccination levels at 3 days post-booster vaccination. Considerable increases in the percentage of participants with hSBA titers ≥1:8 after 6 and 8 days post-booster vaccination have been reported previously [22,23]. Thus, as has already been established [24], this time interval necessary to observe a rise in protective antibody titers is of particular importance from a public health perspective in cases of outbreak, as antibiotic prophylaxis may still need to be administered to close contacts of patients with IMD, in addition to a booster dose of the MenACWY-CRM vaccine.

Prevailing antibody titers 4–6 years after priming with MenACWY-CRM and MenACWY-D vaccines were also evaluated. The proportions of primed participants with hSBA titers ≥1:8 against MenC, MenW, and MenY ranged between 47.24% and 76.63%. For MenA, 12.46% and 15.46% of participants primed with the MenACWY-CRM and MenACWY-D vaccines, respectively, showed hSBA titers ≥1:8. Our observation is consistent with previous studies where antibody persistence following administration of a single dose of the MenACWY-CRM vaccine or other meningococcal conjugate vaccines was also lower for MenA compared with the other serogroups at 3 or 5 years after vaccination [19,22,25–27].

The safety and tolerability profile of the MenACWY-CRM vaccine was acceptable and was similar in primed and naïve participants in this study. No new safety concerns were raised. These results are in line with those of previous clinical trials showing that a booster dose of the MenACWY-CRM vaccine had a similar tolerability and safety profile to that observed after primary vaccination [25].

This study was the largest trial evaluating booster responses to the MenACWY-CRM vaccine and was adequately powered to demonstrate the sufficiency of the immune response induced in primed participants. Nevertheless, the limitations of this study included its open-label design, the absence of randomization to the treatment since all participants received the MenACWY-CRM vaccine and were assigned to the study groups based on their prior vaccination status. This study was also limited by the fact that the mean age of the participants in the Naïve group was higher compared to that of the primed participants, which is a consequence of the ACIP recommendation in the US for an universal vaccination of adolescents with quadrivalent meningococcal conjugate vaccines. The differences in the mean age of the groups was also reflected in the higher proportion of medically attended AEs reported in primed versus naïve participants, which was an expected finding since, according to what is a common finding in clinical practice, adolescents may be more likely to consult their physician when they are sick and may be more likely to have concomitant infectious diseases compared with adults.

5. Conclusions

This phase IIIb study showed that a booster dose of the MenACWY-CRM vaccine induced a sufficient immune response in adolescents and adults, irrespectively of either MenACWY-CRM or MenACWY-D vaccine administered 4–6 years earlier for priming. As expected, immune responses induced by a single dose of the MenACWY-CRM vaccine were higher in primed compared with naïve participants, showing that the booster dose induced an anamnestic response. The immune response was also more rapid in primed than in naïve participants, with meaningful increases in hSBA titers observed at 5 days post-vaccination. The MenACWY-CRM vaccine had a clinically acceptable safety and tolerability profile, and no safety concerns were raised. Our results suggest that MenACWY-CRM can effectively boost individuals primed with a quadrivalent conjugate meningococcal vaccine 4–6 years earlier.

Trademark statement

Menveo is a trademark owned by the GSK group of companies. Menactra is a registered trademark of Sanofi Pasteur Inc.

Data sharing statement

The results summary for this study (GSK study number 205352–NCT02986854) is available on the GSK Clinical Study Register and can be accessed at www.gsk-clinicalstudyregister.com. For interventional studies that evaluate our medicines, anonymized patient-level data will be made available to independent researchers, subject to review by an independent panel, at www.clinicalstudydatarequest.com within six months of publication. To protect the privacy of patients and individuals involved in our studies, GSK does not publicly disclose patient-level data.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Maria Lattanzi, Thembile Mzolo, Silvia Barbi, Michele Pellegrini, Pavitra Keshavan are employed by GSK group of companies. Michele Pellegrini and Pavitra Keshavan hold shares in the GSK group of companies. Dr. Stanley Block reports grants from GSK during the conduct of the study.

Acknowledgments

The Authors thank all participants involved in the study, study nurses and study investigators: Darrell Herrington, William Seger, Brandon Essink, Nicola Klein, Earl Franklin, James Peterson, William Douglas, Donna De Santis, Jennifer Kay, William Kirby, Franck Eder, Linda Murray, Donald Hurley, Earl Martin, Adam Kaplan, Isaac Marcadis, Madhavi Ampajwala, Shelly Senders, Mary Tipton, Scott Kaiser, William Simon, Louis Hiotis, and Mark Johnson. The Authors also thank Teresa Bolduc and Massimo Bianchini (GSK) for coordinating the study conduct, Valerio Romolini and Lisette Moelard (GSK) for performing data analysis, Cristel Stalens, Sophie Eugène and Jacqueline Möbius (GSK) for laboratory analyses, and Igor Smolenov (ex-Novartis) and Carlo Curina (GSK) for their contribution to the study. The authors would also like to thank Modis platform for editorial assistance and manuscript coordination, on behalf of GSK. Claire Verbelen (Modis, on behalf of GSK) provided medical writing support.

Author's contribution

MT, SLB, SS and WD were investigators in the study; SB, TM, ML, MP and PK analyzed the data; MP and PK drafted the manuscript; all authors critically reviewed the manuscript and contributed to its contents. All authors have approved the final version of the manuscript.

Funding

This study and related publication were sponsored by GlaxoSmithKline Biologicals S.A.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.08.065.

References

[1] Hoffman O, Weber RJ. Pathophysiology and treatment of bacterial meningitis. Ther Adv Neurol Disord 2009;2:1–7. https://doi.org/10.1177/1756285609337975.
[2] Khatami A, Pollard AJ. The epidemiology of meningococcal disease and the impact of vaccines. Expert Rev Vaccines 2010;9:285–98. https://doi.org/10.1586/erv.10.3.
[3] Borrow R, Alarcon P, Carlos J, Caugant DA, Christensen H, Debbag R, et al. The Global Meningococcal Initiative: global epidemiology, the impact of vaccines on meningococcal disease and the importance of herd protection. Expert Rev Vaccines 2017;16:313–28. https://doi.org/10.1080/14760584.2017.1258308.
[4] Jafri RZ, Ali A, Messonnier NE, Tevi-Benissan C, Durrheim D, Eskola J, et al. Global epidemiology of invasive meningococcal disease. Popul Health Metr 2013;11:17. https://doi.org/10.1186/1478-7954-11-17.
[5] Pelton SI. The global evolution of meningococcal epidemiology following the introduction of meningococcal vaccines. J Adolesc Health 2016;59:S3–S11. https://doi.org/10.1016/j.jadohealth.2016.04.012.
[6] Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. Vaccine 2009;27(Suppl 2):B51–63. https://doi.org/10.1016/j.vaccine.2009.04.063.
[7] MacNeil JR, Blain AE, Wang X, Cohn AC. Current epidemiology and trends in meningococcal disease-United States, 1996–2015. Clin Infect Dis 2018;66:1276–81. https://doi.org/10.1093/cid/cix993.
[8] Christensen H, May M, Bowen L, Hickman M, Trotter CL. Meningococcal carriage by age: a systematic review and meta-analysis. Lancet Infect Dis 2010;10:853–61. https://doi.org/10.1016/S1473-3099(10)70251-6.
[9] Dwilow R, Fanella S. Invasive meningococcal disease in the 21st century-an update for the clinician. Curr Neurol Neurosci Rep 2015;15:2. https://doi.org/10.1007/s11910-015-0524-6.
[10] Halperin SA, Bettinger JA, Greenwood B, Harrison LH, Jelfs J, Ladhani SN, et al. The changing and dynamic epidemiology of meningococcal disease. Vaccine 2012;30(Suppl 2):B26–36. https://doi.org/10.1016/j.vaccine.2011.12.032.
[11] Cohn AC, MacNeil JR, Harrison LH, Hatcher C, Theodore J, Schmidt M, et al. Changes in *Neisseria meningitidis* disease epidemiology in the United States,

1998–2007: implications for prevention of meningococcal disease. Clin Infect Dis 2010;50:184–91. https://doi.org/10.1086/649209.
[12] US Food and Drug administration. Package Insert – Menveo: highlights of prescribing information, 2013.
[13] Halperin SA, Gupta A, Jeanfreau R, Klein NP, Reisinger K, Walter E, et al. Comparison of the safety and immunogenicity of an investigational and a licensed quadrivalent meningococcal conjugate vaccine in children 2–10 years of age. Vaccine 2010;28:7865–72. https://doi.org/10.1016/j.vaccine.2010.09.092.
[14] Klein NP, Reisinger KS, Johnston W, Odrljin T, Gill CJ, Bedell L, et al. Safety and immunogenicity of a novel quadrivalent meningococcal CRM-conjugate vaccine given concomitantly with routine vaccinations in infants. Pediatr Infect Dis J 2012;31:64–71. https://doi.org/10.1097/INF.0b013e31823dce5c.
[15] Reisinger KS, Baxter R, Block SL, Shah J, Bedell L, Dull PM. Quadrivalent meningococcal vaccination of adults: phase III comparison of an investigational conjugate vaccine, MenACWY-CRM, with the licensed vaccine. Menactra Clin Vaccine Immunol 2009;16:1810–5. https://doi.org/10.1128/CVI.00207-09.
[16] Tregnaghi M, Lopez P, Stamboulian D, Grana G, Odrljin T, Bedell L, et al. Immunogenicity and safety of a quadrivalent meningococcal polysaccharide CRM conjugate vaccine in infants and toddlers. Int J Infect Dis 2014;26:22–30. https://doi.org/10.1016/j.ijid.2014.03.1390.
[17] Cohn A, MacNeil J, Clark T, Ortega-Sanchez I, Briere E, Meissner H, et al. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). Recommendat Rep 2013;62(RR-2):1–28.
[18] Snape MD, Perrett KP, Ford KJ, John TM, Pace D, Yu LM, et al. Immunogenicity of a tetravalent meningococcal glycoconjugate vaccine in infants: a randomized controlled trial. JAMA 2008;299:173–84. https://doi.org/10.1001/jama.2007.29-c.
[19] Baxter R, Reisinger K, Block SL, Izu A, Odrljin T, Dull P. Antibody persistence and booster response of a quadrivalent meningococcal conjugate vaccine in adolescents. J Pediatr 2014;164(1409–15):. https://doi.org/10.1016/j.jpeds.2014.02.025e4.
[20] Centers for Disease Control and Prevention (CDC). Updated recommendations for use of meningococcal conjugate vaccines – Advisory Committee on Immunization Practices (ACIP), 2010. MMWR Morb Mortal Wkly Rep 2011;60:72–6.
[21] Centers for Disease Control and Prevention (CDC). Licensure of a meningococcal conjugate vaccine for children aged 2 through 10 years and updated booster dose guidance for adolescents and other persons at increased risk for meningococcal disease – Advisory Committee on Immunization Practices (ACIP), 2011. MMWR Morb Mortal Wkly Rep 2011;60:1018–9.
[22] Jacobson RM, Jackson LA, Reisinger K, Izu A, Odrljin T, Dull PM. Antibody persistence and response to a booster dose of a quadrivalent conjugate vaccine for meningococcal disease in adolescents. Pediatr Infect Dis J 2013;32:e170–7. https://doi.org/10.1097/INF.0b013e318279ac38.
[23] Robertson CA, Greenberg DP, Hedrick J, Pichichero M, Decker MD, Saunders M. Safety and immunogenicity of a booster dose of meningococcal (groups A, C, W, and Y) polysaccharide diphtheria toxoid conjugate vaccine. Vaccine 2016;34:5273–8. https://doi.org/10.1016/j.vaccine.2016.09.003.
[24] McNamara LA, MacNeil JR, Cohn AC, Stephens DS. Mass chemoprophylaxis for control of outbreaks of meningococcal disease. Lancet Infect Dis 2018;18:e272–81. https://doi.org/10.1016/S1473-3099(18)30124-5.
[25] Baxter R, Keshavan P, Welsch JA, Han L, Smolenov I. Persistence of the immune response after MenACWY-CRM vaccination and response to a booster dose, in adolescents, children and infants. Hum Vaccin Immunother 2016;12:1300–10. https://doi.org/10.1080/21645515.2015.1136040.
[26] Baxter R, Reisinger K, Block SL, Percell S, Odrljin T, Dull PM, et al. Antibody persistence after primary and booster doses of a quadrivalent meningococcal conjugate vaccine in adolescents. Pediatr Infect Dis J 2014;33:1169–76. https://doi.org/10.1097/INF.0000000000000438.
[27] Baxter R, Baine Y, Kolhe D, Baccarini CI, Miller JM, Van der Wielen M. Five-year antibody persistence and booster response to a single dose of meningococcal A, C, W and Y tetanus toxoid conjugate vaccine in adolescents and young adults: an open, randomized trial. Pediatr Infect Dis J 2015;34:1236–43. https://doi.org/10.1097/INF.0000000000000866.