ORIGINAL ARTICLE

Meningococcal ACWYX Conjugate Vaccine in 2-to-29-Year-Olds in Mali and Gambia

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ABSTRACT

BACKGROUND

An effective, affordable, multivalent meningococcal conjugate vaccine is needed to prevent epidemic meningitis in the African meningitis belt. Data on the safety and immunogenicity of NmCV-5, a pentavalent vaccine targeting the A, C, W, Y, and X serogroups, have been limited.

METHODS

We conducted a phase 3, noninferiority trial involving healthy 2-to-29-year-olds in Mali and Gambia. Participants were randomly assigned in a 2:1 ratio to receive a single intramuscular dose of NmCV-5 or the quadrivalent vaccine MenACWY-D. Immunogenicity was assessed at day 28. The noninferiority of NmCV-5 to MenACWY-D was assessed on the basis of the difference in the percentage of participants with a seroresponse (defined as prespecified changes in titer; margin, lower limit of the 96% confidence interval [CI] above −10 percentage points) or geometric mean titer (GMT) ratios (margin, lower limit of the 98.98% CI >0.5). Serogroup X responses in the NmCV-5 group were compared with the lowest response among the MenACWY-D serogroups. Safety was also assessed.

RESULTS

A total of 1800 participants received NmCV-5 or MenACWY-D. In the NmCV-5 group, the percentage of participants with a seroresponse ranged from 70.5% (95% CI, 67.8 to 73.2) for serogroup A to 98.5% (95% CI, 97.6 to 99.2) for serogroup W; the percentage with a serogroup X response was 97.2% (95% CI, 96.0 to 98.1). The overall difference between the two vaccines in seroresponse for the four shared serogroups ranged from 1.2 percentage points (96% CI, −0.3 to 3.1) for serogroup W to 20.5 percentage points (96% CI, 15.4 to 25.6) for serogroup A. The overall GMT ratios for the four shared serogroups ranged from 1.7 (98.98% CI, 1.5 to 1.9) for serogroup A to 2.8 (98.98% CI, 2.3 to 3.5) for serogroup C. The serogroup X component of the NmCV-5 vaccine generated seroresponses and GMTs that met the prespecified noninferiority criteria. The incidence of systemic adverse events was similar in the two groups (11.1% in the NmCV-5 group and 9.2% in the MenACWY-D group).

CONCLUSIONS

For all four serotypes in common with the MenACWY-D vaccine, the NmCV-5 vaccine elicited immune responses that were noninferior to those elicited by the MenACWY-D vaccine. NmCV-5 also elicited immune responses to serogroup X. No safety concerns were evident. (Funded by the U.K. Foreign, Commonwealth, and Development Office and others; ClinicalTrials.gov number, NCT03964012.)

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THE GLOBAL ROAD MAP FOR THE DEFEATing Meningitis by 2030 program was endorsed by the World Health Assembly in November 2020. This strategy aims to eliminate epidemic bacterial meningitis and to reduce the rate of vaccine-preventable disease by 50% and mortality by 70% before the end of the decade.[1]

In 2019, there were estimated to be more than 2.5 million cases of meningitis worldwide, which resulted in more than 236,000 deaths.[2] The highest incidences of meningitis and death from the disease occur across the African meningitis belt, which stretches from Gambia and Senegal in the west to Ethiopia in the east, where meningitis epidemics, predominantly caused by *Neisseria meningitidis*, occur on a background of high rates of endemic disease.[2,3] Although six serogroups of meningococcus (A, B, C, W, X, and Y) can cause invasive disease, serogroup A has historically been the most important cause of disease in the meningitis belt. However, after mass vaccination campaigns with MenAfriVac, a conjugate vaccine developed to address this burden, that were conducted by means of a partnership among the Serum Institute of India, the World Health Organization (WHO), and PATH (formerly known as the Program for Appropriate Technology in Health), serogroup A disease has been virtually eliminated.[4-6]

Nonetheless, countries in the meningitis belt continue to record high rates of disease due to other serogroups. Large epidemics of meningitis caused by meningococcal serogroup C have occurred in Niger and northwestern Nigeria, and serogroup C disease continues to predominate in countries such as Burkina Faso, Chad, Mali, and Togo, from which surveillance data are available.[6-11] Epidemic serogroup W disease has also been reported in Ghana and Togo, and serogroup X disease has additionally emerged with epidemic potential in the meningitis belt and elsewhere.[8,9,12-15]

Although four quadrivalent meningococcal ACWY conjugate vaccines have been licensed and prequalified by the WHO, their use in the African meningitis belt has been limited by supply and cost constraints.[14] Furthermore, there are currently no licensed vaccines against meningococcal serogroup X.[13,14] Thus, building on the success of the Meningitis Vaccine Project (which developed MenAfriVac), the Serum Institute of India and PATH developed a pentavalent meningococcal ACWYX conjugate vaccine (NmCV-5) with the goal of eliminating meningococcal disease in sub-Saharan Africa. Supportive data on the safety and immunogenicity of NmCV-5 have been reported from a phase 1 trial involving persons 18 to 45 years of age in the United States and a phase 2 trial involving children 12 to 16 months of age in Mali.[16,17]

Here, we report the results of a phase 3 trial of the NmCV-5 vaccine in participants 2 to 29 years of age, the target age group for meningococcal outbreak–response campaigns, in Mali and Gambia. The trial aimed to show the safety and immunologic noninferiority of the NmCV-5 vaccine as compared with a licensed, WHO-prequalified, quadrivalent meningococcal conjugate vaccine (MenACWY-D [Menactra, Sanofi Pasteur]). This trial was intended to provide the required data for the licensure and WHO prequalification of the vaccine for future epidemic control.

A Quick Take is available at NEJM.org

METHODS

TRIAL DESIGN AND PARTICIPANTS

We conducted a two-center, phase 3, double-blind, randomized, active-controlled, noninferiority trial in Mali and Gambia. After undergoing screening for eligibility on the basis of prespecified inclusion and exclusion criteria (see the Supplementary Appendix, available with the full text of this article at NEJM.org), 600 participants were enrolled in one of three groups according to age: 2 to 10 years, 11 to 17 years, and 18 to 29 years. All the participants 18 years of age or older, and the parents or guardians of participants younger than 18 years of age, provided written informed consent. Participants who were at least 13 years of age (in Mali) or at least 12 years of age (in Gambia) also provided written assent.

Full details of the trial conduct are provided in the protocol, available at NEJM.org. The responsibilities of the authors for the design and conduct of the trial, the analysis of the data, and the writing of the manuscript are outlined in the Supplementary Appendix. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

OVERSIGHT

The trial was conducted in accordance with the principles of the Declaration of Helsinki and with Good Clinical Practice guidelines. The pro-

tocol was approved by the research ethics committee of the Faculté de Médecine, de Pharmacie et d'Odonto-Stomatologie, in Mali; the institutional review board of the University of Maryland School of Medicine; the Gambia Government–Medical Research Council Joint Ethics Committee in Gambia; and the Western Institutional Review Board. Regulatory approval was obtained from the Directorate of Pharmacy and Medicine, Mali, and the Medicines Control Agency, Gambia. A data and safety monitoring board oversaw the trial.

RANDOMIZATION AND BLINDING

Eligible participants within each age group were randomly assigned in a 2:1 ratio to receive either the NmCV-5 vaccine (400 participants) or the MenACWY-D vaccine (200 participants). Randomization was undertaken with the use of a Web-based system, according to a permuted block randomization scheme. Randomization and the preparation and administration of the vaccines were undertaken by personnel who were aware of the trial-group assignments; these personnel were not involved in other participant-related procedures or the collection of end-point data. Parents and guardians, participants, and all other trial staff were unaware of the trial-group assignments.

VACCINES

A single 0.5-ml dose of NmCV-5 contains 5 μg of meningococcal serogroup A and X polysaccharides conjugated to tetanus toxoid and 5 μg of meningococcal serogroup C, W, and Y polysaccharides conjugated to recombinant cross-reactive material 197 (a nontoxic mutant of diphtheria toxin). A single dose of MenACWY-D contains 4 μg each of meningococcal A, C, W, and Y polysaccharides conjugated to diphtheria toxoid (see the Supplementary Appendix). The vaccines were administered by injection into the deltoid muscle with the use of a 23-gauge, 25-mm needle.

OBJECTIVES AND END POINTS

The trial had two primary objectives: first, to show that the immune responses to meningococcal serogroups A, C, W, and Y that were generated by the NmCV-5 vaccine were noninferior to those generated by the MenACWY-D vaccine; and second, to show that the immune responses to meningococcal serogroup X that were generated by NmCV-5 were noninferior to the lowest immune response generated by MenACWY-D to serogroups A, C, W, and Y. Comparison with the lowest response that was generated by the MenACWY-D serogroups was made after a regulatory agreement in the absence of a licensed serogroup X comparator vaccine. Serum samples that were obtained before vaccination (day 0) and on day 28 after vaccination were tested with a serogroup-specific serum bactericidal antibody (SBA) with rabbit complement.[18,19]

Immune responses were defined in terms of two primary end points: the serogroup-specific SBA seroresponse and the geometric mean titer (GMT) measured 28 days after vaccination. For the analysis of seroresponse, we assessed the percentage of participants with a postvaccination SBA titer of at least 32 in those with a prevaccination titer of less than 8 or a titer that was at least four times as high as the prevaccination titer in those with a prevaccination titer of at least 8. Secondary end points included the percentages of participants with SBA titers of at least 8 and at least 128 before vaccination and on day 28 after vaccination, as well as data related to the safety profile of NmCV-5 as compared with that of MenACWY-D. Details of the visit schedule are provided in the Supplementary Appendix.

Data on solicited injection-site and systemic adverse events were collected, and events were graded for severity on the day of vaccination and for a further 6 days after vaccination by means of home visits conducted by trained fieldworkers. Data on unsolicited adverse events were collected by trial clinicians from the day of vaccination and for a further 28 days after vaccination, and events were graded for severity. Solicited systemic events and unsolicited events were judged by the investigator for relatedness to vaccination. Data on serious adverse events were collected for 168 days after vaccination (see the Supplementary Appendix).

STATISTICAL ANALYSIS

The immunologic noninferiority of NmCV-5 as compared with that of MenACWY-D was assessed on the basis of the criteria set for either of the two primary end points. A prospective

alpha-allocation scheme was used for multiplicity adjustment. One-sided significance levels of 0.02 and 0.0051 were applied to noninferiority testing for seroresponse with a margin of –10 percentage points and for GMT with a margin of 0.5, respectively. The between-group difference (NmCV-5 group minus the MenACWY-D group) in the percentage of participants with a serogroup-specific seroresponse was calculated with a two-sided 96% confidence interval, which was obtained by means of the Miettinen and Nurminen method.[20] The ratios of the GMTs between the two groups (NmCV-5 group divided by the MenACWY-D group) against each serogroup were calculated with a two-sided 98.98% confidence interval. For each serogroup, the $\log_2$-transformed SBA titers were used to construct a two-sided 98.98% confidence interval for the mean between-group difference with the use of analysis of covariance with $\log_2$-transformed baseline titers as a covariate. Participant age, sex, and trial site were evaluated for inclusion in the model with the use of stepwise selection. The mean difference and corresponding limits of the 98.98% confidence interval were exponentiated to obtain the ratio of GMTs and the corresponding 98.98% confidence interval.

The sample-size and power calculations are provided in the Supplementary Appendix. The primary immunogenicity analysis was conducted in the per-protocol population, which included all the participants who underwent randomization and vaccination, who had serologic results available, and who had no protocol deviations that would have been considered likely to have an effect on the immunogenicity assessment. The safety analyses were conducted in the safety population, which included all the participants who received one dose of NmCV-5 or MenACWY-D and provided any safety data. All the statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

TRIAL POPULATION

The first participants were recruited in August 2019. Safety follow-up to 168 days after vaccination was completed in June 2021. Informed consent was provided for 1869 participants, of whom 1800 were eligible and underwent randomization and vaccination (Fig. S1 in the Supplementary Appendix). In each age group, 400 participants received NmCV-5 and 200 received MenACWY-D (safety population).

Overall, 50.7% of the participants were female, all were African, and 43.4% were in the Mandinka–Malinke ethnic group (Table 1). There were no notable between-group differences in the demographic or anthropometric characteristics of the participants in any age group. The trial participants were considered to be representative of the target population for NmCV-5 vaccination (Table S1).

IMMUNOGENICITY

Overall, the percentages of participants with a seroresponse to serogroups A, C, W, and Y at 28 days after vaccination with NmCV-5 ranged from 70.5% (95% confidence interval [CI], 67.8 to 73.2) for serogroup A to 98.5% (95% CI, 97.6 to 99.2) for serogroup W (Table 2). A total of 97.2% (95% CI, 96.0 to 98.1) of the participants had a serogroup X response. The percentages of participants with a seroresponse after vaccination with MenACWY-D, for the four included serogroups, ranged from 50.0% (95% CI, 45.8 to 54.2) for serogroup A to 97.4% (95% CI, 95.6 to 98.6) for serogroup W.

Because the lowest percentage of participants with a seroresponse after vaccination with MenACWY-D was for serogroup C, this serogroup was used as the comparator for the purposes of the noninferiority analysis for serogroup X in the NmCV-5 group. The between-group difference in the percentage of participants with a seroresponse for the four shared serogroups ranged from 1.2 percentage points (96% CI, –0.3 to 3.1) for serogroup W to 20.5 percentage points (96% CI, 15.4 to 25.6) for serogroup A. The between-group difference in the percentages of participants with a serogroup X response in the NmCV-5 group and a serogroup A response in the MenACWY-D group was 47.2 percentage points (96% CI, 42.8 to 51.6). The lower limit of the 96% confidence interval was above the noninferiority margin of –10 percentage points for all the serogroups, both in the overall population (Fig. 1A) and in each age group. Thus, the noninferiority of the NmCV-5 vaccine as compared with the MenACWY-D vaccine was shown on the basis of seroresponse.

Table 1. Demographic and Anthropometric Characteristics of the Participants, in Overall Population and According to Age Group (Safety Population).*

Characteristic	Overall, 2 to 29 Yr		2 to 10 Yr		11 to 17 Yr		18 to 29 Yr	
	NmCV-5 (N = 1200)	MenACWY-D (N = 600)	NmCV-5 (N = 400)	MenACWY-D (N = 200)	NmCV-5 (N = 400)	MenACWY-D (N = 200)	NmCV-5 (N = 400)	MenACWY-D (N = 200)
Median age (range) — yr	13 (2–29)	13 (2–29)	6 (2–10)	5 (2–10)	13 (11–17)	13 (11–17)	22 (18–29)	21 (18–29)
Female sex — no. (%)	606 (50.5)	307 (51.2)	179 (44.8)	94 (47.0)	187 (46.8)	102 (51.0)	240 (60.0)	111 (55.5)
Black race — no. (%)†	1200 (100)	600 (100)	400 (100)	200 (100)	400 (100)	200 (100)	400 (100)	200 (100)
Ethnic group — no. (%)†								
Mandinka–Malinke	523 (43.6)	258 (43.0)	174 (43.5)	87 (43.5)	167 (41.8)	87 (43.5)	182 (45.5)	84 (42.0)
Bambara	234 (19.5)	123 (20.5)	92 (23.0)	41 (20.5)	84 (21.0)	42 (21.0)	58 (14.5)	40 (20.0)
Fula–Peulh	151 (12.6)	78 (13.0)	55 (13.8)	30 (15.0)	52 (13.0)	26 (13.0)	44 (11.0)	22 (11.0)
Other	292 (24.3)	141 (23.5)	79 (19.8)	42 (21.0)	97 (24.2)	45 (22.5)	116 (29.0)	54 (27.0)
Height — cm	145.3±26.5	144.4±27.0	113.5±17.3	111.3±16.4	154.9±11.6	155.0±11.5	167.4±8.9	166.9±8.7
Weight — kg	41.9±20.5	41.5±20.6	19.4±6.8	18.5±5.8	44.4±12.8	44.2±12.1	61.8±12.0	61.7±12.5

* Plus–minus values are means ±SD. The safety population included participants who received one dose of the pentavalent ACWYX meningococcal conjugate vaccine NmCV-5 or the quadrivalent meningococcal conjugate vaccine MenACWY-D and provided any safety data. Percentages may not total 100 because of rounding.
† Race and ethnic group were reported by participants 18 years of age or older or by the parent or guardian for those younger than 18 years of age.

The overall serogroup-specific SBA GMT 28 days after vaccination with NmCV-5 ranged from 5587.2 (95% CI, 5123.7 to 6092.5) for serogroup C to 31,290.4 (95% CI, 29,222.2 to 33,505.1) for serogroup X (Table 2). The serogroup-specific SBA GMT at 28 days after vaccination with MenACWY-D for the four included serogroups ranged from 1854.9 (95% CI, 1619.6 to 2124.4) for serogroup C to 12,294.6 (95% CI, 10,778.9 to 14,023.4) for serogroup W.

Because the lowest SBA GMT after vaccination with MenACWY-D was to serogroup C, we used this serogroup as the comparator for the purposes of the noninferiority analysis with serogroup X in the NmCV-5 group. The adjusted SBA GMT ratio for the four shared serogroups ranged from 1.7 (98.98% CI, 1.5 to 1.9) for serogroup A to 2.8 (98.98% CI, 2.3 to 3.5) for serogroup C. The adjusted GMT ratio for the comparison of serogroup X in the NmCV-5 group with serogroup C in the MenACWY-D group was 9.5 (98.98% CI, 7.1 to 12.8). The lower limit of the 98.98% confidence interval was above the noninferiority margin of 0.5 for all the serogroups, both in the overall population (Fig. 1B) and in each age group. Thus, the noninferiority of the NmCV-5 vaccine as compared with the MenACWY-D vaccine was shown on the basis of the SBA GMTs. Hence, the two primary objectives of the trial were met in each age group on the basis of both seroresponse and GMT.

The percentages of participants who had baseline and postvaccination serogroup-specific SBA titers of at least 8 and at least 128 are provided in Table S3. The geometric mean factor increases after NmCV-5 vaccination tended to be higher than those after MenACWY-D vaccination for all serogroups and in all age groups (Table S4). Although there were no notable differences in the distribution of SBA titers at baseline, the percentage of participants with results above any given titer tended to be higher after NmCV-5 vaccination than after MenACWY-D vaccination (Fig. 2).

SAFETY

Overall, solicited adverse events were assessed in 1199 participants in the NmCV-5 group and in 599 in the MenACWY-D group. A total of 312 participants (26.0%) in the NmCV-5 group and 115 (19.2%) in the MenACWY-D group had at least one solicited injection-site reaction (P=0.001)

(Table 3). Pain was the most common reaction, occurring in 311 participants (25.9%) in the NmCV-5 group and in 115 (19.2%) in the MenACWY-D group (P=0.001). Overall, 133 participants (11.1%) in the NmCV-5 group and 55 (9.2%) in the MenACWY-D group had a solicited systemic adverse event. All the solicited events were mild or moderate in severity and resolved with no more than simple analgesia.

Unsolicited adverse events were assessed in the full safety population of 1800 participants. After vaccination with NmCV-5, 189 participants (15.8%) had a mild or moderate unsolicited adverse event, as compared with 99 participants (16.5%) after vaccination with MenACWY-D. None of the unsolicited events were judged by the investigators to be related to vaccine. Overall, the most common unsolicited events were upper respiratory tract infection, malaria, and pharyngitis, which occurred in 4.6%, 1.3%, and 0.8% of the participants, respectively (Table S5).

Three serious adverse events occurred after vaccination in each vaccine group, none of which were deemed by the investigator to be related to vaccine. One 18-year-old participant in the MenACWY-D group died after trauma unrelated to the trial.

A total of 13 pregnancies were reported during trial follow-up. Eleven women had normal deliveries without congenital anomalies, and 2 women chose to terminate their pregnancies.

DISCUSSION

This phase 3 trial showed the immunologic noninferiority of the NmCV-5 vaccine as compared with the licensed, WHO-prequalified, quadrivalent meningococcal conjugate vaccine MenACWY-D. Noninferiority was shown in all three age groups on the basis of both seroresponse and GMT. The NmCV-5 vaccine had a safety profile similar to that of the licensed vaccine. These data are expected to support the licensure and WHO prequalification of NmCV-5 as a pentavalent meningococcal conjugate vaccine, including for serogroup X.

The licensure of meningococcal conjugate vaccines, including those targeting new serogroups, on the basis of immunogenicity rather than efficacy end points, is a well-established approach.[21,22] Serum bactericidal antibodies, measured with the use of human complement, were originally defined as a correlate of protection against invasive serogroup C disease in U.S. military recruits.[23,24] However, the standardized assay with rabbit complement was subsequently used to support the licensure and introduction of serogroup C conjugate vaccines in the United Kingdom.[21,25-27] The short-term, one-dose efficacy of 97% among teenagers and 92% among toddlers supported the validity of this approach in the United Kingdom, and an SBA titer of at least 8 and an increase by a factor of at least 4 in titers were identified as markers of vaccine-induced protection against this serogroup.[26,28] In the United Kingdom and elsewhere, effectiveness of between 91% and 96% within 12 months after vaccination has been shown in all age groups, with protection being sustained more consistently in those vaccinated after infancy.[29,30]

A similar approach was used for the licensure of the meningococcal serogroup A conjugate vaccine MenAfriVac.[21,22,31] In the absence of a defined correlate of protection and in the context of high baseline antibody titers, the requirement for an increase in SBA titer by a factor of 4 was used as the primary end point.[31] According to enhanced surveillance leading up to and after the rollout of the vaccine across the African meningitis belt, the incidence of meningitis has substantially decreased, and serogroup A disease has all but disappeared. Burkina Faso recorded a 71% reduction in the incidence of meningitis and a 99.8% reduction in the incidence of serogroup A meningitis in the year after the MenAfriVac campaign.[32] A 94% reduction in the incidence of meningitis was also recorded in Chad within 4 to 6 months after vaccination.[33] A study that was conducted across nine countries in the meningitis belt showed a 57% reduction in the incidence of suspected meningitis and a decrease of more than 99% in the incidence of serogroup A meningitis that were associated with mass vaccination campaigns.[4] Serogroup C and A conjugate vaccines also generate herd protection, which indicates an effect on nasopharyngeal carriage as well as on invasive disease.[34-37]

There are now early data on the effectiveness of the MenACWY-D vaccine and other quadrivalent vaccines, which were also licensed on the basis of immunogenicity results. In an analysis of serogroup C and Y breakthrough cases after the introduction of single-dose vaccination with MenACWY-D in adolescents in the United States,

Table 2. Noninferiority Analyses of Immunogenicity on the Basis of Seroresponse and Geometric Mean Titers (Per-Protocol Population).*

Analysis and Serogroup	Overall Analysis		Seroresponse Difference (96% CI) or GMT Ratio (98.98% CI)			
	NmCV-5	MenACWY-D	Overall	2 to 10 Yr	11 to 17 Yr	18 to 29 Yr
Seroresponse						
A						
No. with response/total no.	814/1154	286/572				
Percent with response (95% CI)	70.5 (67.8 to 73.2)	50.0 (45.8 to 54.2)	20.5 (15.4 to 25.6)	13.2 (4.7 to 21.9)	28.1 (19.2 to 36.7)	20.6 (11.6 to 29.4)
C						
No. with response/total no.	1109/1133	531/556				
Percent with response (95% CI)	97.9 (96.9 to 98.6)	95.5 (93.4 to 97.1)	2.4 (0.6 to 4.7)	1.6 (–1.0 to 5.5)	1.9 (–0.3 to 5.8)	3.6 (–0.5 to 8.9)
W						
No. with response/total no.	1081/1097	520/534				
Percent with response (95% CI)	98.5 (97.6 to 99.2)	97.4 (95.6 to 98.6)	1.2 (–0.3 to 3.1)	–0.2 (–2.0 to 2.5)	1.7 (–0.3 to 5.5)	2.0 (–1.4 to 6.7)
Y						
No. with response/total no.	1019/1051	494/537				
Percent with response (95% CI)	97.0 (95.7 to 97.9)	92.0 (89.4 to 94.1)	5.0 (2.5 to 7.9)	5.3 (1.8 to 10.3)	8.1 (3.5 to 14.1)	1.6 (–2.5 to 6.8)
X						
No. with response/total no.	1099/1131	48/507				
Percent with response (95% CI)	97.2 (96.0 to 98.1)	9.5 (7.1 to 12.4)	47.2 (42.8 to 51.6)†	38.1 (30.9 to 45.7)†	54.4 (46.8 to 61.7)†	49.2 (41.4 to 56.8)†
GMT						
A						
No. of participants	1172	583				
GMT (95% CI)	8009.9 (7631.7 to 8407.0)	4729.7 (4420.0 to 5061.2)	1.7 (1.5 to 1.9)	1.7 (1.4 to 2.0)	2.0 (1.7 to 2.4)	1.5 (1.2 to 1.8)
C						
No. of participants	1190	588				
GMT (95% CI)	5587.2 (5123.7 to 6092.5)	1854.9 (1619.6 to 2124.4)	2.8 (2.3 to 3.5)	2.7 (2.0 to 3.7)	2.8 (2.0 to 3.9)	3.1 (2.2 to 4.5)

W						
No. of participants	1185	589				
GMT (95% CI)	28,963.4 (26,804.6 to 31,295.9)	12,294.6 (10,778.9 to 14,023.4)	2.5 (2.1 to 3.0)	2.4 (1.8 to 3.4)	2.4 (1.7 to 3.4)	2.4 (1.7 to 3.4)
Y						
No. of participants	1186	591				
GMT (95% CI)	10,844.8 (10,260.2 to 11,462.8)	4815.6 (4380.9 to 5293.4)	2.2 (1.9 to 2.5)	2.3 (1.9 to 2.9)	2.1 (1.7 to 2.7)	2.0 (1.6 to 2.6)
X						
No. of participants	1187	523				
GMT (95% CI)	31,290.4 (29,222.2 to 33,505.1)	737.1 (641.3 to 847.4)	9.5 (7.1 to 12.8)‡	17.5 (8.4 to 36.6)‡	9.9 (6.3 to 15.6)‡	4.9 (3.3 to 7.2)‡

* Shown are the immunogenicity results according to age group and the complete vaccine-specific data for the overall analysis; complete vaccine-specific data for the age-specific analyses are provided in Table S2. Seroresponse was defined as a postvaccination titer of serum bactericidal antibody (SBA) with rabbit complement of at least 32 in participants with a prevaccination SBA titer of less than 8 or as an increase by a factor of at least four over baseline in the postvaccination SBA titer in participants who had a prevaccination SBA titer of at least 8. The analysis was based on the number of participants with an SBA seroresponse between prevaccination and day 28 after vaccination, divided by the number of participants with evaluable data. In the overall analysis, the 95% confidence intervals for the percentages of participants with a seroresponse were calculated by the Clopper–Pearson method. The two-sided 96% confidence intervals for the between-group difference in the percentages of participants with a response (NmCV-5 group minus the MenACWY-D group) were constructed by the Miettinen and Nurminen method. Postvaccination geometric mean titers (GMTs) and 95% confidence intervals were calculated by exponentiating the corresponding $\log_2$-transformed mean and its two-sided 95% confidence interval. The $\log_2$-transformed SBA titers were used to construct a two-sided 98.98% confidence interval for the mean between-group difference with the use of analysis of covariance (ANCOVA). The mean difference and the limits of the corresponding 98.98% confidence interval were exponentiated to obtain the GMT ratios (GMT in the NmCV-5 group divided by that in the MenACWY-D group) and the corresponding 98.98% confidence intervals. ANCOVA included $\log_2$-transformed baseline titers, age, sex, and trial site as a covariate. Interaction terms for trial group and baseline titers, trial group and age, trial group and trial site, baseline titers and age, and baseline titers and trial site were also included in the model. The per-protocol population included all the participants who underwent randomization and vaccination and who had serologic results available, in the absence of protocol deviations that would have been considered likely to have an effect on the immunogenicity assessment.

† For the analysis of seroresponse, the difference between the percentage of participants with a serogroup X response after NmCV-5 vaccination and the lowest percentage with a seroresponse to serogroups A, C, W, and Y after MenACWY-D vaccination (i.e., serogroup A in all cases) was calculated.

‡ The ratio of the serogroup X GMT after vaccination was compared between the GMT in the NmCV-5 group and the lowest GMT to serogroups A, C, W, and Y in the MenACWY-D group (i.e., serogroup C in all cases).

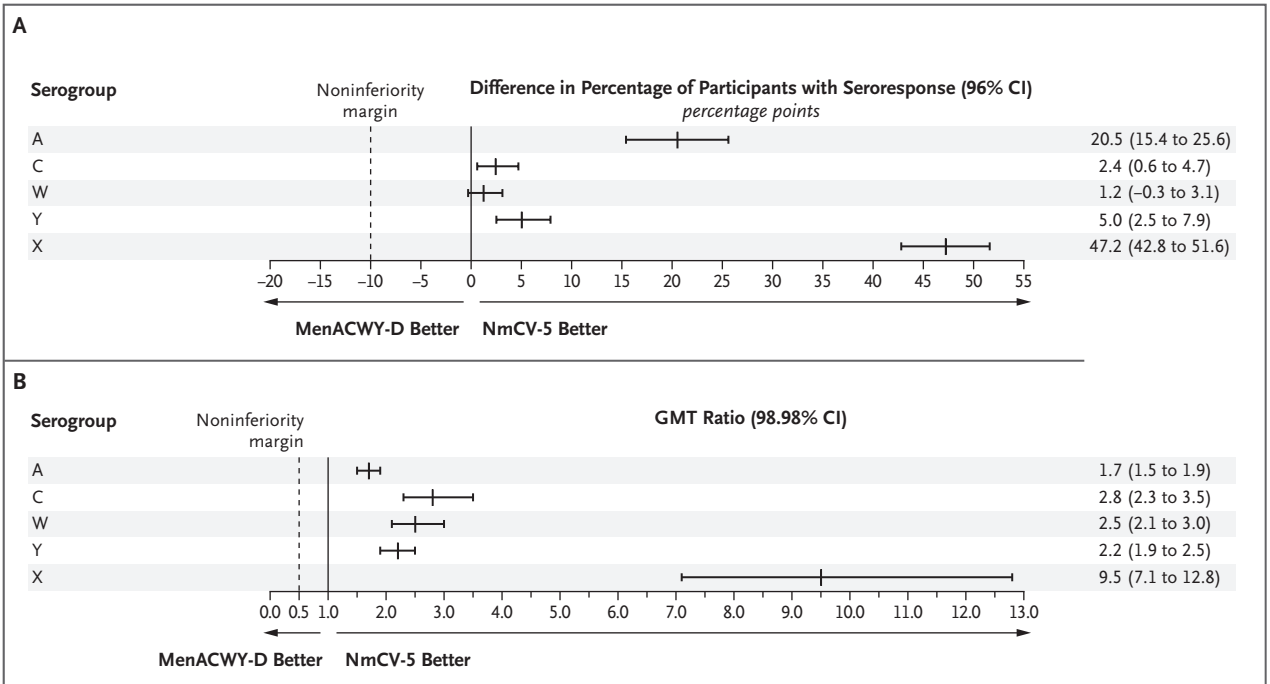

Figure 1. Overall Noninferiority Analysis of Immunogenicity on the Basis of Seroresponse and Geometric Mean Titers at 28 Days after Vaccination.

Shown are the comparisons of the pentavalent ACWYX meningococcal conjugate vaccine NmCV-5 with the quadrivalent meningococcal conjugate vaccine MenACWY-D with regard to seroresponse (Panel A) and geometric mean titer (GMT). Seroresponse was defined as a postvaccination titer of serum bactericidal antibody (SBA) with rabbit complement of at least 32 in participants with a prevaccination SBA titer of less than 8 or as an increase by a factor of at least four over baseline in the postvaccination SBA titer in participants who had a prevaccination SBA titer of at least 8. For serogroup X, the comparisons are shown between the seroresponse and GMT generated against this serogroup by the NmCV-5 vaccine and the lowest seroresponse and GMT generated by the MenACWY-D vaccine against the four serogroups it contains (serogroup A for seroresponse, and serogroup C for GMT). The analyses were conducted in the per-protocol population, which included all the participants who underwent randomization and vaccination, who had serologic results available, and who had no protocol deviations that would be considered likely to affect the immunogenicity assessment.

vaccine effectiveness was estimated to be between 80% and 85%.[38] A case–control study that was conducted in the same setting estimated a vaccine effectiveness of 79% within 1 year and of 69% between 1 year and 3 years after vaccination. Vaccine effectiveness was 79% against serogroup C and 51% against serogroup Y up to 8 years after vaccination.[39] After the introduction of a quadrivalent vaccine program that predominantly used MenACWY-TT (Nimenrix, Pfizer) in adolescents in the United Kingdom, an overall vaccine effectiveness of 94%, including effectiveness of 94% against serogroup W and 82% against serogroup Y, was recently shown.[40] The program has also been shown to reduce pharyngeal carriage of meningococcus and is expected to generate herd protection.[41]

Thus, strong postimplementation data support the licensure of meningococcal conjugate vaccines on the basis of immunogenicity rather than efficacy end points. The availability of such effectiveness data and the extensive use of the MenACWY-D vaccine, which was the first quadrivalent conjugate vaccine to be licensed, including as part of an outbreak response in West Africa, support the choice of the vaccine as the comparator in this trial. Some differences in the immunogenicity of the four currently licensed quadrivalent vaccines have been reported. However, data are lacking to suggest that these immunogenicity differences translate into differences in effectiveness.[42] The generally higher immune responses to NmCV-5 over the licensed

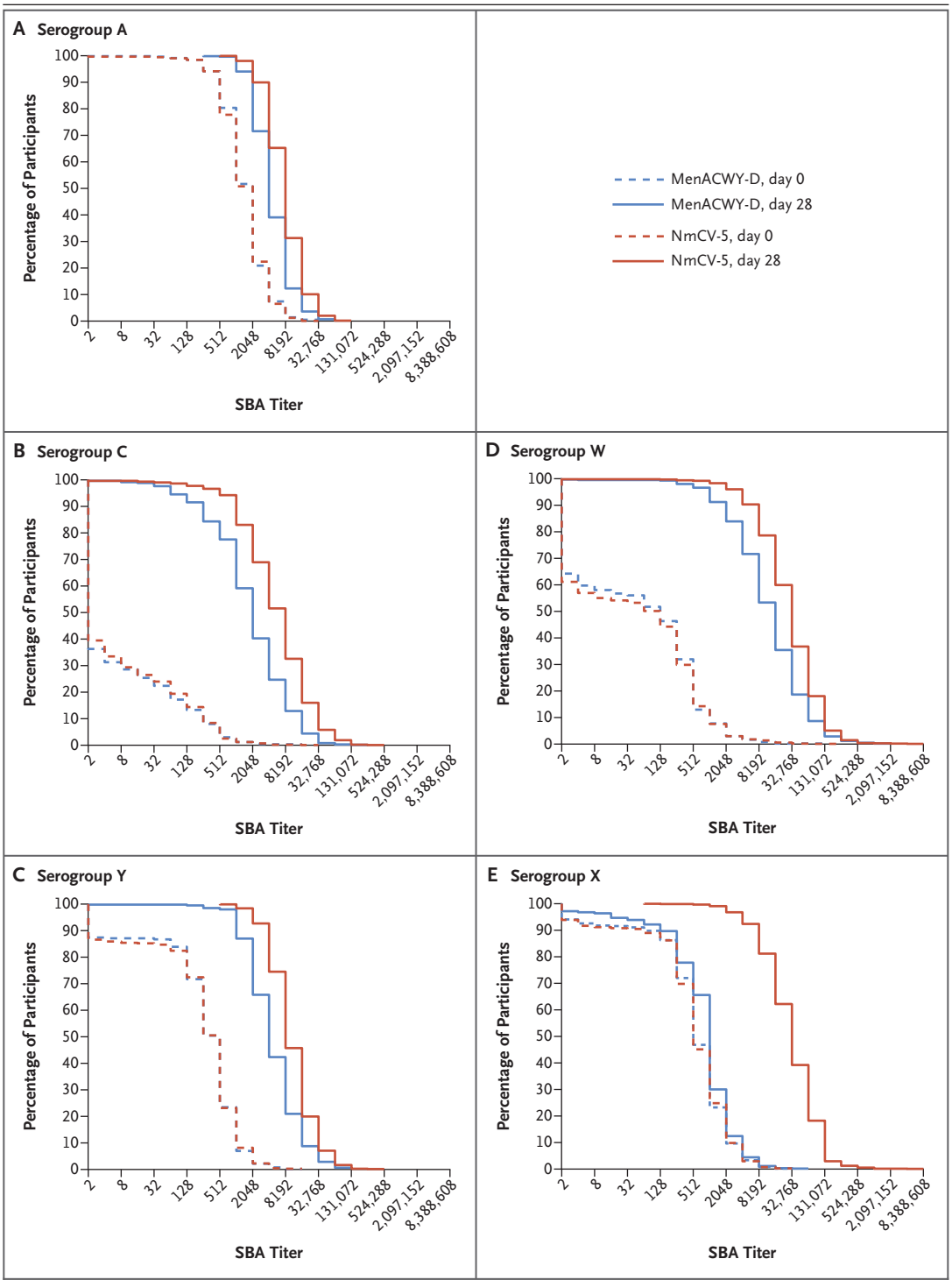

Figure 2. Reverse Cumulative Distribution Curves before Vaccination and 28 Days after Vaccination, According to Meningococcal Serogroup.

The prevaccination value was assessed before the vaccine was administered on day 0.

Table 3. Solicited and Unsolicited Adverse Events, in Overall Population and According to Age Group (Safety Population).

Event	Overall		2 to 10 Yr		11 to 17 Yr		18 to 29 Yr	
	NmCV-5 (N=1200)	MenACWY-D (N=600)	NmCV-5 (N=400)	MenACWY-D (N=200)	NmCV-5 (N=400)	MenACWY-D (N=200)	NmCV-5 (N=400)	MenACWY-D (N=200)
Solicited adverse events*								
Injection-site adverse event — no./total no. (%)								
Any event†	312/1199 (26.0)	115/599 (19.2)	80/399 (20.1)	19/200 (9.5)	114/400 (28.5)	45/200 (22.5)	118/400 (29.5)	51/199 (25.6)
Any grade ≥3 event	0/1199	0/599	0/399	0/200	0/400	0/200	0/400	0/199
Pain†	311/1199 (25.9)	115/599 (19.2)	79/399 (19.8)	19/200 (9.5)	114/400 (28.5)	45/200 (22.5)	118/400 (29.5)	51/199 (25.6)
Swelling or induration	4/1199 (0.3)	2/599 (0.3)	3/399 (0.8)	1/200 (0.5)	0/400	0/200	1/400 (0.2)	1/199 (0.5)
Systemic adverse event — no./total no. (%)								
Any event	133/1199 (11.1)	55/599 (9.2)	30/399 (7.5)	8/200 (4.0)	50/400 (12.5)	24/200 (12.0)	53/400 (13.2)	23/199 (11.6)
Any grade ≥3 event	0/1199	0/599	0/399	0/200	0/400	0/200	0/400	0/199
Distribution								
<6 Yr of age								
Fever	2/185 (1.1)	1/110 (0.9)	2/185 (1.1)	1/110 (0.9)	—	—	—	—
Drowsiness	3/185 (1.6)	0/110	3/185 (1.6)	0/110	—	—	—	—
Irritability	4/185 (2.2)	1/110 (0.9)	4/185 (2.2)	1/110 (0.9)	—	—	—	—
Anorexia	2/185 (1.1)	2/110 (1.8)	2/185 (1.1)	2/110 (1.8)	—	—	—	—
Diarrhea	2/185 (1.1)	1/110 (0.9)	2/185 (1.1)	1/110 (0.9)	—	—	—	—
≥6 Yr of age								
Fever	13/1014 (1.3)	4/489 (0.8)	5/214 (2.3)	0/90	7/400 (1.8)	2/200 (1.0)	1/400 (0.2)	2/200 (1.0)
Fatigue	38/1014 (3.7)	16/489 (3.3)	2/214 (0.9)	0/90	11/400 (2.8)	4/200 (2.0)	25/400 (6.2)	12/200 (6.0)
Headache	73/1014 (7.2)	29/489 (5.9)	14/214 (6.5)	2/90 (2)	32/400 (8.0)	17/200 (8.5)	27/400 (6.8)	10/200 (5.0)
Myalgia	22/1014 (2.2)	13/489 (2.7)	3/214 (1.4)	1/90 (1)	11/400 (2.8)	3/200 (1.5)	8/400 (2.0)	9/200 (4.5)
Arthralgia	13/1014 (1.3)	3/489 (0.6)	2/214 (0.9)	0/90	5/400 (1.2)	1/200 (0.5)	6/400 (1.5)	2/200 (1.0)
Anorexia	13/1014 (1.3)	7/489 (1.4)	1/214 (0.5)	1/90 (1)	5/400 (1.2)	1/200 (0.5)	7/400 (1.8)	5/200 (2.5)
Diarrhea	8/1014 (0.8)	1/489 (0.2)	1/214 (0.5)	0/90	4/400 (1.0)	1/200 (0.5)	3/400 (0.8)	0/200

Unsolicited adverse events‡								
Any event — no. (%)	189 (15.8)	99 (16.5)	81 (20.2)	36 (18.0)	44 (11.0)	25 (12.5)	64 (16.0)	38 (19.0)
Any grade ≥3 event — no. (%)	0	0	0	0	0	0	0	0
Serious adverse events§								
Any event — no. (%)	3 (0.2)	3 (0.5)	0	2 (1.0)	0	0	3 (0.8)	1 (0.5)
Vaccine-related event — no. (%)	0	0	0	0	0	0	0	0

* Data on solicited injection-site and systemic adverse events were collected for 7 days after vaccination. Data on solicited injection-site and systemic adverse events were missing for two participants: one in the 2-to-10-year-old age group who received the NmCV-5 vaccine and one in the 18-to-29-year-old age group who received the MenACWY-D vaccine.
† The overall incidence of injection-site reactions and of pain at the injection site was higher in the NmCV-5 group than the MenACWY-D group ($P=0.001$ for both comparisons by Fisher's exact test).
‡ Data on unsolicited adverse events were collected for 28 days after vaccination.
§ Data on serious adverse events were collected for 168 days after vaccination.

comparator provide further reassurance in this regard.

This trial has several strengths. Both Mali and Gambia are in the African meningitis belt and are thus representative of a key future target population for vaccination with NmCV-5, and the findings are likely to translate to other settings. The consistency of the immune responses across age groups is also reassuring. Finally, the technology that is used in the production of the NmCV-5 vaccine is based on cost-effective methods for carrier protein production, polysaccharide fermentation and purification, and chemical conjugation. Thus, the vaccine is expected to be made available at a cost lower than that of the existing quadrivalent vaccines.

The limitation of product licensure on the basis of immunogenicity is acknowledged, and the generation of effectiveness data regarding the NmCV-5 vaccine, particularly against serogroup X disease, will be important. Data on the persistence of immune responses at 6 months and 12 months will be necessary, particularly considering the potential future routine use of NmCV-5 outside the epidemic response.

In addition, the high baseline GMTs for serogroup A, which reflect outcomes of previous MenAfriVac campaigns and routine immunization programs in Mali and Gambia, limited the percentage of participants with a serogroup A response. Nonetheless, postvaccination titers were considerably higher than those that have been shown to provide protection against this serogroup, and more than 95% of previously unvaccinated toddlers had a serogroup A response.[17]

In this trial, we found that the NmCV-5 vaccine elicited immune responses that were noninferior to those for all four serotypes in common with the MenACWY-D vaccine, as well as to serogroup X, without evident safety concerns. On the basis of these trial data, NmCV-5 may emerge as a tool to support meningococcal disease control, particularly across the meningitis belt of sub-Saharan Africa, and thus may contribute to epidemic elimination and the other goals of the global road map for the Defeating Meningitis by 2030 program.

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APPENDIX

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