Impact of the Serogroup A Meningococcal Conjugate Vaccine, MenAfriVac, on Carriage and Herd Immunity

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(See the Editorial Commentary by Maiden on pages 364–6.)

Background. The conjugate vaccine against serogroup A *Neisseria meningitidis* (NmA), MenAfriVac, was first introduced in mass vaccination campaigns of 1–29-year-olds in Burkina Faso in 2010. It is not known whether MenAfriVac has an impact on NmA carriage.

Methods. We conducted a repeated cross-sectional meningococcal carriage study in a representative portion of the 1–29-year-old population in 3 districts in Burkina Faso before and up to 13 months after vaccination. One district was vaccinated in September 2010, and the other 2 were vaccinated in December 2010. We analyzed 25 521 oropharyngeal samples, of which 22 093 were obtained after vaccination.

Results. In October–November 2010, NmA carriage prevalence in the unvaccinated districts was comparable to the baseline established in 2009, but absent in the vaccinated district. Serogroup X *N. meningitidis* (NmX) dominated in both vaccinated and unvaccinated districts. With 4 additional sampling campaigns performed throughout 2011 in the 3 districts, overall postvaccination meningococcal carriage prevalence was 6.95%, with NmX dominating but declining for each campaign (from 8.66% to 1.97%). Compared with a baseline NmA carriage prevalence of 0.39%, no NmA was identified after vaccination. Overall vaccination coverage in the population sampled was 89.7%, declining over time in 1-year-olds (from 87.1% to 26.5%), as unvaccinated infants reached 1 year of age. NmA carriage was eliminated in both the vaccinated and unvaccinated population from 3 weeks up to 13 months after mass vaccination (*P* = .003).

Conclusions. The disappearance of NmA carriage among both vaccinated and unvaccinated populations is consistent with a vaccine-induced herd immunity effect.

Keywords. *Neisseria meningitidis*; meningitis belt; conjugate vaccine; carriage; herd immunity.

Meningococcal disease is a major public health challenge in countries of sub-Saharan Africa lying in the meningitis belt [1, 2]. The causative agent, *Neisseria meningitidis* normally lives in a commensal relationship with humans, colonizing the nasopharynx [1, 3, 4], and is transmitted between healthy persons by close contact. Only exceptionally it enters the bloodstream and causes meningitis and/or septicemia. In the meningitis belt,

N. meningitidis of serogroups A (NmA), W135 (NmW135), and X (NmX) have caused outbreaks [5–7], but NmA has been responsible for all but one of the major epidemics.

In spite of extensive use of polysaccharide vaccines, epidemics are still occurring [8]. Conjugate vaccines, developed by coupling a carrier protein to the polysaccharide antigen, elicit strong and long-lasting immune responses, including children <2 years old [3, 9] and may confer herd immunity by interrupting transmission of the pathogens [10–14]. Meningococcal conjugate vaccines against serogroups A, C, Y, and W135 are marketed in industrialized countries [3], but for most African countries, they are not affordable [15].

MenAfriVac, a safe, immunogenic and affordable conjugate vaccine [16] was developed especially to eliminate NmA epidemics in the meningitis belt and was first introduced in Burkina Faso, Mali, and Niger in 2010 [15, 17, 18]. Mass vaccination of 10.8 million 1–29-year-olds was done in Burkina Faso from 5 to 15 December 2010. When vaccination coverage is not complete, however, the ability to achieve herd immunity in addition to protecting vaccinated individuals will be an essential benefit of the vaccine. Although many conjugate vaccines have been shown to interrupt carriage of the pathogen, this remained to be demonstrated for a NmA conjugate vaccine.

To evaluate the potential for herd immunity after MenAfriVac vaccination, we studied its impact on NmA carriage in a multicenter repeated cross-sectional carriage study in Burkina Faso. Baseline NmA carriage was estimated to 0.39% in Burkina Faso in 2009 [19]. The impact of MenAfriVac on NmA carriage up to 13 months after vaccination and evidence of a herd immunity effect is presented here.

METHODS

Ethics
The study obtained ethical clearance from the Norwegian Regional Committee for Medical Research Ethics, Southern Norway, the Ethical Committee for Health Research in Burkina Faso, and the Institutional Review Board at Centers for Disease Control and Prevention, Atlanta, Georgia.

Study Design and Oversight
The study was conducted as a multicenter repeated cross-sectional survey in 3 health districts in Burkina Faso; the urban district of Bogodogo, counting roughly 616 000 inhabitants and in 2 rural districts, Dandé (215 000 inhabitants) and Kaya (500 000 inhabitants), as described elsewhere [19]. Multiple sampling campaigns were conducted simultaneously in all 3 districts, and for each campaign a representative portion of the 1–29-year-olds was included within a 4-week period. We used a multistage cluster design and performed a new random selection of households for each sampling campaign.

All healthy 1–29-year-olds residing the selected households were invited to participate in a survey and to provide a swab specimen, independently of vaccination status and participation in previous campaigns. Informed consent was obtained from each participant or guardian if the subject was <18 years old. Household leaders and participants answered a structured questionnaire that included information on risk factors for carriage and MenAfriVac vaccination. All data were entered on personal digital assistants.

Prevaccination carriage prevalence was determined in 4 sampling campaigns (S1–S4) performed every 3 months in 2009 [19]. As part of a phased vaccine introduction, a safety study of MenAfriVac was conducted in Kaya, one of the study sites, from 18 to 24 September 2010 when all 1–29-year-olds were immunized. Three weeks later, carriage study S5 started in all 3 districts and was conducted in October–November 2010; S5 documented the carriage prevalence in nonvaccinated districts immediately before vaccination and also represented the first postvaccination campaign in Kaya.

The 1–29-year-olds in the rest of Burkina Faso were vaccinated with MenAfriVac in the period of 5–15 December 2010 [17]. Four postvaccination carriage campaigns were then done in the 3 study sites every 3 months through 2011 in the same way as before vaccine introduction. Campaigns S6, S7, S8, and S9 were conducted in February–March, May, August, and October–November 2011, respectively.

Sample Collection and Analysis
Oropharyngeal samples were obtained from each participant and analyzed at the Centre Hospitalier Universitaire Pédiatrique Charles de Gaulle for the district of Bogodogo, at the Centre Hospitalier Régional de Kaya for the district of Kaya, and at the Centre Hospitalier Universitaire Souro Sanou for the district of Dandé, as described elsewhere [19]. The Norwegian Institute of Public Health (NIPH), Oslo, Norway, received all presumptive meningococcal isolates for confirmatory analyses. The serogroup of confirmed *N. meningitidis* was determined by slide agglutination using A, B, C, X, Y, Z, W135, and 29E antiserum (Remel). For nonserogroupable isolates, the serogroup obtained by capsule gene polymerase chain reaction [20] was used as the final result. The quality of the laboratory analysis in Burkina Faso was monitored through a laboratory quality control (QC) system, as described elsewhere [21]. In addition to internal QC of reagents, media, and incubation conditions, a subset of presumptive *N. meningitidis*–negative samples were retrieved from 2 of the analytical steps and controlled at the NIPH as part of the external QC [21].

Data Management and Statistical Analyses
Field and laboratory data were combined. Samples with missing or duplicate links between the person and the

laboratory identification or between the person and the household were excluded. Data management was done with R v.2.14.1 and statistical analysis with Stata v.11.1. Bivariable comparisons were performed using Rao-Scott corrected χ^2 tests, and odds ratios were calculated by logistic regression, using survey methods accounting for the cluster sampling design. Statistical significance was defined as P values <.05 and as 95% confidence intervals not including null.

RESULTS

Study Population

During the sampling campaigns S5–S9, a total of 28 625 persons were asked to participate, and 27 012 (94.4%) accepted (Table 1). Of these, 25 940 (96.0%) reached the swabbing station where an oropharyngeal swab specimen was obtained from 25 726 (99.2%). A total of 205 (0.8%) samples were excluded due to lack of traceability. Among the 205 excluded participants 14 (6.8%) were carriers, but none were carriers of NmA (13 NmX and 1 NmY). Of the 25 521 participants with data correctly registered in all databases (range, 5071–5169 per campaign), 22 093 were enrolled after vaccine introduction and therefore included when comparing pre- [19] and postvaccination carriage prevalence. The remaining 3428 samples were taken from the districts of Bogodogo and Dandé in S5, just before vaccine introduction. With 20 326 samples obtained in the baseline study [19], the total sampling size of the carriage study reaches 45 847.

In the postvaccination sampling campaigns, 43.4% of the participants were male, and 51.9% were <10 years old. The overall vaccine coverage estimated from the participant's responses was 89.7% for the first assessments possible after mass vaccination (S6), but coverage varied by districts (93.6%, 83.8%, and 91.8% for Bogodogo, Dandé, and Kaya, respectively). Vaccine coverage was age dependent in a consistent way; coverage was lowest in the 16–29-year age group at about 85% but remaining stable over time, and coverage of 1-year-olds declined over time from 87.1% in S5 to 26.5% in S9, as unvaccinated children reached 1 year of age.

Overall Meningococcal Carriage Prevalence

A total of 1649 carriers were identified, of whom 1536 were from the 22 093 participants enrolled after mass vaccination (6.95%) (Table 2). Carriage prevalence in the 3 districts decreased gradually, from 10.31% in S5 to 3.29% in S9 (Figure 1). In each campaign, prevalence was highest in the district of Kaya, and lowest in Bogodogo. There was a higher prevalence during the 2011 dry season (S6 and S7) than during the rainy season (S8 and S9) ($P < .001$).

NmA Carriage Before and After Vaccination

In campaign S5, NmA carriage prevalence in Dandé (0.24%) was comparable to the overall 2009 prevalence (0.21%) in that district. In Bogodogo, no NmA was found in S5, but NmA carriage was also intermittent and low in the baseline study. Thus, campaign S5 demonstrated that NmA was still circulating in unvaccinated districts at the same magnitude as during the baseline study in 2009 [19].

Table 1. Enrolled Participants and Collected Samples in Carriage Study Performed in 3 Districts in Burkina Faso, 2009–2011

	Prevaccination		Postvaccination			
	2009	2010	2010	2011	Total S5–S9	Postvaccination Total[d]
	S1–S4[a]	S5 (Bogodogo, Dandé)[b]	S5 (Kaya)[c]	S6–S9		
No. of persons						
Asked to participate	23 097	3779	1877	22 969	28 625	24 846
Agreeing to participate	21 583	3567	1825	21 620	27 012	23 445
Meeting at swabbing station	20 676	3480	1716	20 744	25 940	22 460
Providing swab specimen	20 470	3444	1704	20 578	25 726	22 282
No. of samples						
Excluded[e]	144	16	61	128	205	189
Included in analysis	20 326	3428	1643	20 450	25 521	22 093

[a] Baseline study of meningococcal carriage [19].

[b] S5 in Bogodogo and Dandé: last carriage study campaign before vaccination.

[c] S5 in Kaya: first postvaccination carriage study campaign.

[d] Samples taken in Bogodogo and Dandé during S5 (before MenAfriVac vaccination in those districts) are not included.

[e] Samples without full traceability were excluded.

Table 2. Meningococcal Carriage Before and After MenAfriVac Vaccination in Burkina Faso

	Prevaccination Total[a] (n = 20 326)	Sampling Campaign						Postvaccination Total[d] (n = 22 093)	OR (95% CI)	P
		S5 (B, D)[b] (n = 3428)	S5 (K)[c] (n = 1643)	S6 (n = 5169)	S7 (n = 5096)	S8 (n = 5106)	S9 (n = 5079)			
Serogroup										
A	80 (0.39)	4 (0.12)	0	0	0	0	0	0	NA[e]	.003
B	0	0	0	0	0	1 (0.02)	0	1 (0.01)	NA[e]	.341
C	4 (0.02)	2 (0.06)	1 (0.06)	1 (0.02)	0	1 (0.02)	0	3 (0.01)	0.69 (.11–4.53)	.697
W135	70 (0.34)	9 (0.26)	0	7 (0.14)	26 (0.51)	35 (0.69)	24 (0.47)	92 (0.42)	1.21 (.69–2.13)	.506
X	90 (0.44)	51 (1.49)	388 (23.62)	311 (6.02)	240 (4.71)	138 (2.70)	100 (1.97)	1177 (5.33)	12.65 (6.88–23.25)	<.001
Y	457 (2.25)	36 (1.05)	15 (0.91)	66 (1.28)	37 (0.73)	43 (0.84)	30 (0.59)	191 (0.86)	0.38 (.25–.57)	<.001
NG[f]	108 (0.53)	11 (0.32)	6 (0.37)	16 (0.31)	15 (0.29)	22 (0.43)	13 (0.26)	72 (0.33)	0.61 (.41–.90)	.014
Total	809 (3.98)	113 (3.30)	410 (24.95)	401 (7.76)	318 (6.24)	240 (4.70)	167 (3.29)	1536 (6.95)	1.80 (1.37–2.38)	<.001

Unless otherwise specified, data represent No. (%) of carriers.

Abbreviations: CI, confidence interval; NA, not applicable; NG, nonserogroupable; OR, odds ratio.

[a] Baseline study of meningococcal carriage, campaigns S1–S4 in 2009 [19].

[b] S5 in Bogodogo and Dandé: last carriage study campaign before vaccination.

[c] S5 in Kaya: first postvaccination carriage study campaign.

[d] Samples taken in Bogodogo and Dandé on S5 (before MenAfriVac vaccination in those districts) are not included.

[e] Not applicable, because no NmB was found before vaccination, and no NmA was found after vaccination.

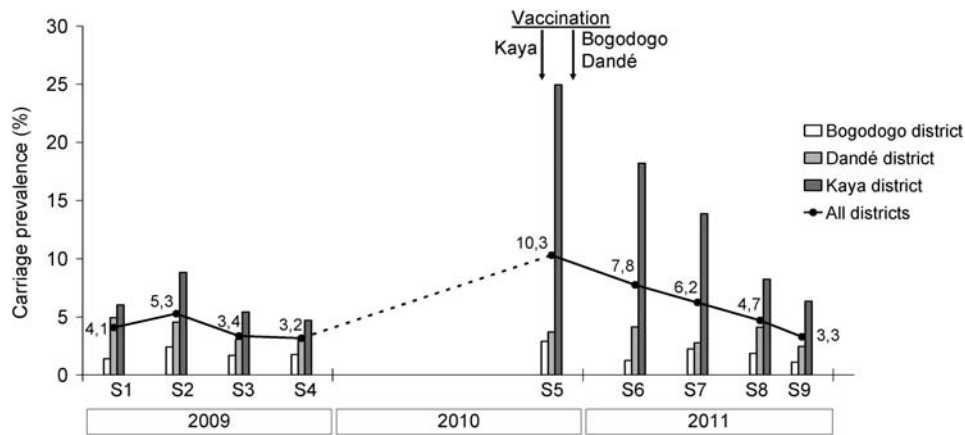[f] Nonserogroupable *Neisseria meningitidis*.

Figure 1. Carriage prevalence of *Neisseria meningitidis* in 3 districts in Burkina Faso at 9 sampling time points, S1–S9 (2009–2011) before and after MenAfriVac mass vaccination.

In the district of Kaya, where MenAfriVac vaccination campaign had ended 3 weeks before the carriage sampling S5 started, none of the 1643 persons enrolled during S5 carried NmA. The postvaccination carriage study campaigns S6–S9, conducted simultaneously in all 3 districts in 2011, enrolled an additional 20 450 persons, and none were carriers of NmA (Table 2; Figure 2). Elimination of NmA after mass vaccination was statistically significant when all 3 districts were considered together as well as when each district was considered separately ($P < .05$) (Figure 2).

Herd Immunity
Of 2241 unvaccinated participants, the expected number of NmA carriers was calculated to be 8.74 when we considered

the overall baseline carriage of 0.39% or 6.84 when age-specific carriage prevalence was considered. No NmA carrier was found after vaccination and the difference was significant ($P < .05$).

Serogroup Distribution
In all 5 sampling campaigns S5–S9, NmX was dominant with an overall prevalence of 4.81%. NmX carriage decreased over time in all 3 districts and overall prevalence declined from 8.66% in S5 to 1.97% in S9 (Table 2). NmX was dominant in Kaya and represented 85.3%–94.6% of all meningococcal isolates; it represented 21.1%–63.3% of the isolates in Bogodogo and 9.5%–33.3% in Dandé (Figure 3). NmX prevalence was highest at S5 in Kaya (23.6%), but NmX was present in
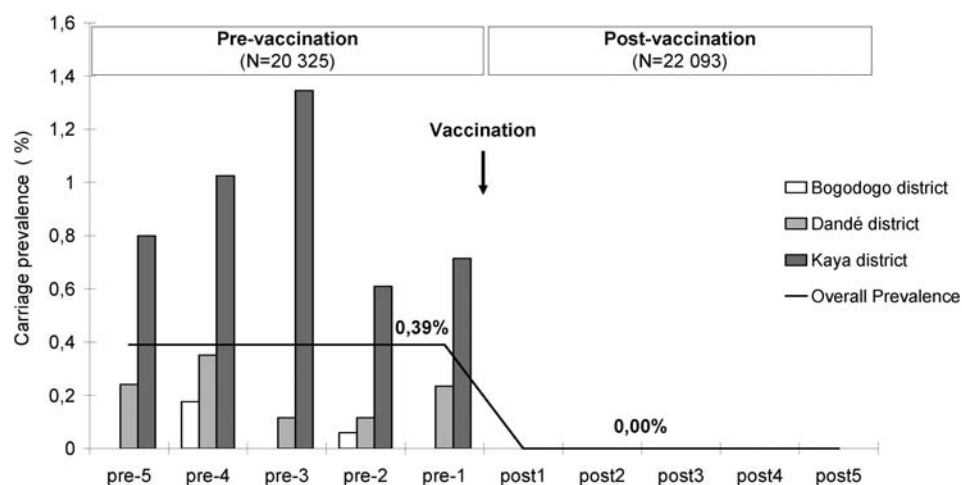

Figure 2. Carriage of serogroup A *Neisseria meningitidis* at 5 timepoints before (pre-5 to pre-1) and 5 timepoints after (post1 to post5) MenAfriVac vaccination.
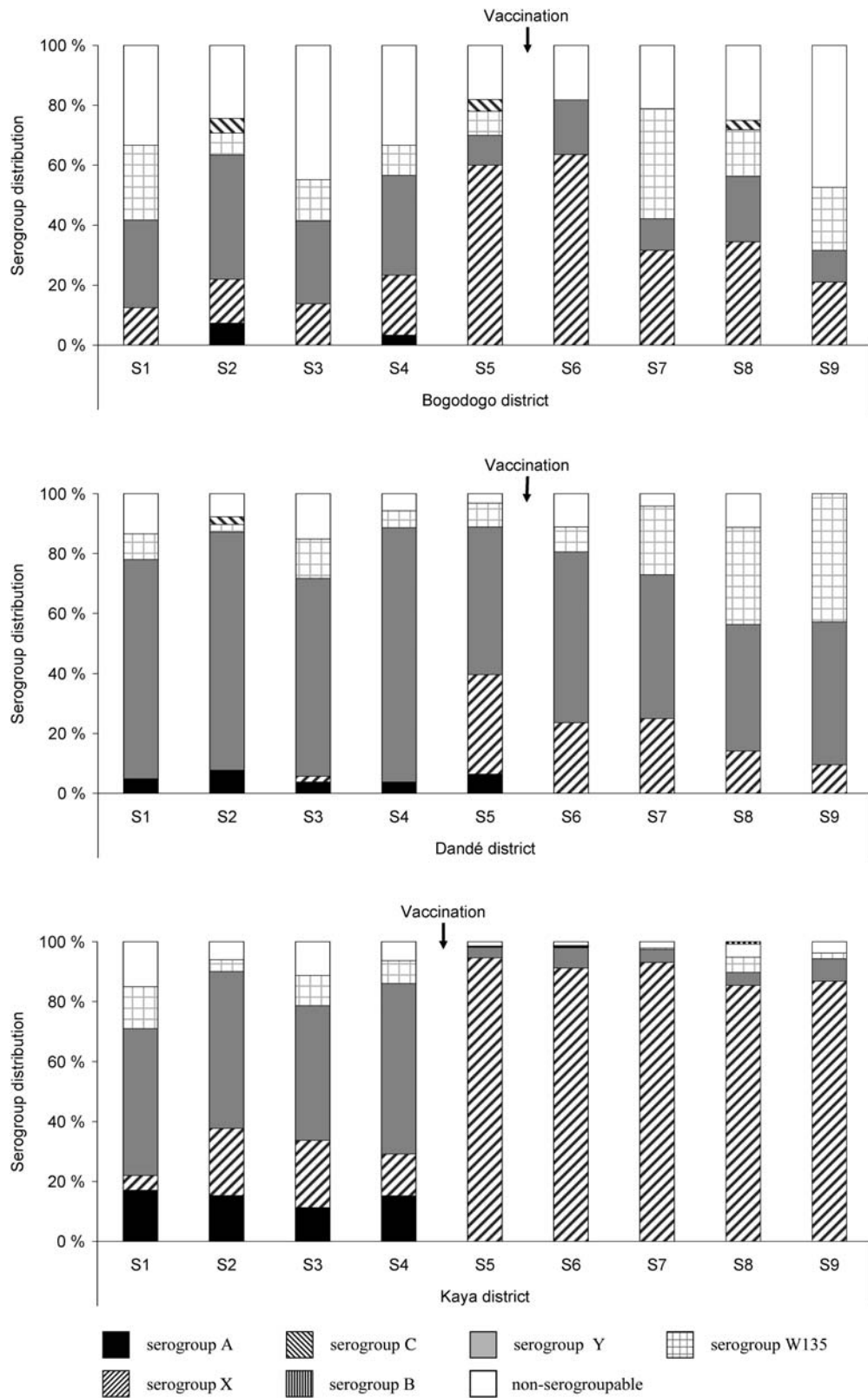
Figure 3. Serogroup distribution of meningococcal carriage isolates in 3 districts in Burkina Faso at 9 sampling time points, S1–S9 (2009–2011), before and after MenAfriVac mass vaccination.
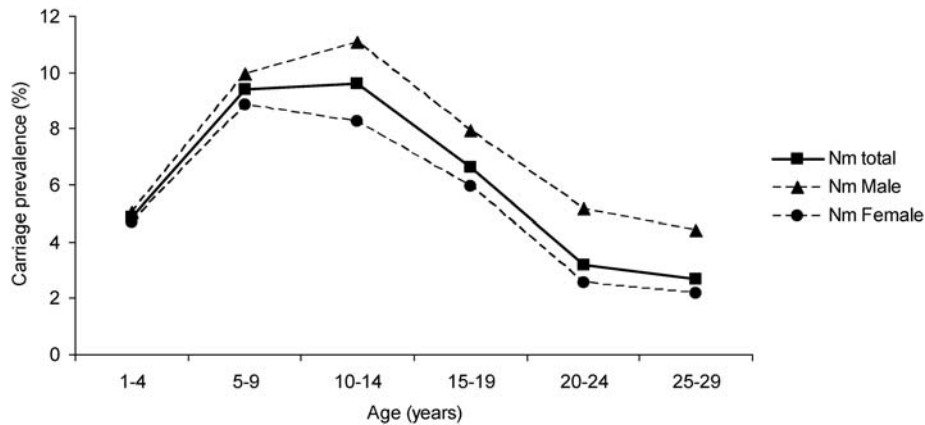
Figure 4. Carriage prevalence of *Neisseria meningitidis* by age group and sex. Abbreviation: Nm, *Neisseria meningitidis*.

unvaccinated districts (1.74% in Bogodogo; 1.23% in Dandé), at higher rates compared with 2009 data ($P < .001$ for both comparisons). NmX was the dominant serogroup in Bogodogo in S5 and S6 (Figure 3).

The proportion of nongroupable isolates was highest in Bogodogo, whereas NmY dominated in Dandé (Figure 3). Overall, NmY carriage was low (0.86%), and its prevalence by campaign declined through the study period (Table 2). NmW135 was almost nonexistent in Kaya, but it represented up to 36.8% and 42.9% of the isolates from Bogodogo and Dandé, respectively (Figure 3). Overall, NmW135 carriage prevalence reached a maximum in S8 (0.69%) and then declined in S9 (0.47%) (Table 2). Comparison of carriage prevalence before and after vaccination shows a significant reduction in NmA, NmY, and nonserogroupable carriage and a significant increase in NmX carriage (Table 2).

Age and Sex Distribution of Meningococcal Carriers

For the 20 092 participants providing swab specimens after MenAfriVac vaccination, carriage prevalence was higher for male participants (8.11%) than female participants (6.06%; $P < .001$). The highest prevalence was found among 10–14-year-olds for male and 5–9-year-olds for female participants (Figure 4). Carriage prevalence varied substantially with age only for NmX, with a maximum carriage in the age groups of 5–9 years (7.59%) and 10–14 years (7.48%) (Figure 5).

Laboratory QC

Five meningococcal isolates were found among the 1155 presumptive *N. meningitidis*–negative QC samples [21] retrieved from all the postvaccination campaigns. Of these 2 were NmX and 3 were nongroupable. Considering the proportion of samples tested in the 2 analytical steps included in the external
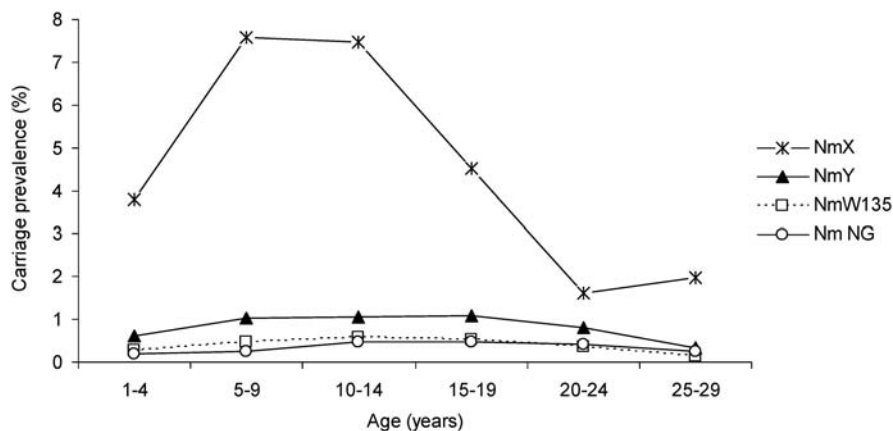

Figure 5. Carriage prevalence of dominating serogroups of *Neisseria meningitidis* by age. Abbreviations: NG, nonserogroupable; Nm, *Neisseria meningitidis*.

QC, we extrapolated that the number of false-negative samples was 58, whereas the number of true-negative samples was 20 419. Of 1616 presumptive meningococcal isolates sent to the NIPH 1531 were confirmed as *N. meningitidis* (true positive) and 85 were not (false positive). Using standard formulas, the overall sensitivity of meningococcal isolation and identification in Burkina Faso after mass vaccination was 96.3% (range, 92.4%–100% for each campaign), and the overall specificity was 99.6% (range, 98.8%–99.8% for each campaign).

DISCUSSION

The study demonstrated that NmA carriage was eliminated after a successful mass vaccination campaign with MenAfriVac in Burkina Faso. The effect was seen in both vaccinated and unvaccinated persons and persisted throughout the 13-month postintroduction period.

The introduction of MenAfriVac, originally planned for the end of 2009, was delayed by 1 year. Because of lack of funds, we had to interrupt the repeated carriage samplings initiated in 2009 [19] until study S5, performed in October–November 2010, when NmA still circulated in unvaccinated districts at levels comparable to the 2009 baseline.

The age and sex of participants in the study were similar to those in the baseline study (43.7% male; 54% <10 years old) [19]; we assumed thus that the populations sampled were comparable. Study workers were largely the same as during the baseline study, the studies were identical in methodology, and retraining was provided before the study began. The QC system [21] documented excellent performance of the laboratories in Burkina Faso; the underestimation of meningococcal carriage was lower than during the baseline study (0.24% vs 0.49%), and 95% of the isolates sent to the NIPH were confirmed as *N. meningitidis*, compared with 77% in the baseline study. Moreover, none of the QC samples contained NmA. Hence, we feel confident that carriage prevalence before and after mass vaccination can be compared and that the disappearance of NmA carriage was not related to methodological changes or lapses in quality of the work performed.

We studied the 1–29-year-old age group, targeted for MenAfriVac vaccination. Consequently, some participants in the postvaccination carriage study were not vaccinated because they were either too young at time of vaccination or did not receive or accept the vaccine (mainly the 16–29-year-olds). If the vaccine did not interrupt transmission, the unvaccinated population would be at the same risk of carrying NmA as before vaccination. Our study demonstrated that NmA carriage was eliminated in the unvaccinated group. The herd effect was probably a result of high antibody titers demonstrated during the development and testing of the vaccine [16].

After the vaccination campaign, the dramatic decrease in NmA disease in Burkina Faso in 2011 and 2012 is also consistent with a strong herd effect [22]. In comparison, immunization of teenagers with NmC conjugate vaccines in the United Kingdom reduced carriage of serogroup C meningococci by 66% after 1 year [10], and the attack rate in unvaccinated was reduced by 66% [13]. Polysaccharide-protein conjugate vaccines against other pathogens have also been shown to reduce carriage and generate herd immunity. Vaccination of young children with pneumococcal conjugate vaccines has contributed to significant reduction of carriage and disease in older children and adults [14, 23, 24]. Conjugate vaccines against *Haemophilus influenzae* type b infection have enabled the control of this disease, and in some countries its elimination, an accomplishment partly attributed to the vaccine's ability to protect against colonization [11, 25]. Achieving herd immunity is an essential benefit of MenAfriVac and might contribute to significant reduction of meningitis epidemics.

Serogroup replacement, as demonstrated after the use of pneumococcal conjugate vaccines [24, 26], is always a concern when a new vaccine is introduced. A notable increase in NmX cases and a high NmX carriage prevalence was seen in 2011 [22]. However, NmX was already circulating in the eastern districts of Bogodogo and Kaya in 2009, occupying a larger ecological niche than NmA [19]. NmX started to cause disease in 2009 [27], and in the epidemic season of 2010, before vaccine introduction, about 20% of the tested isolates were confirmed as NmX [22]. The significantly higher NmX carriage prevalence in October-November 2010 seemed unrelated to vaccination as it was observed in both vaccinated and unvaccinated districts. Waning of NmX carriage in the course of 2011 suggests increasing immunity against this serogroup. Altogether, these data suggest that vaccine-induced serogroup replacement with NmX did not occur and that the increase of NmX cases in 2011 was due to a wave of NmX that had already started in 2009, as observed elsewhere [28].

Geographic variations in the meningococcal carriage rates were similar to those observed during the baseline study [19], with the district of Kaya having the highest prevalence. Seasonal variation was also similar, with lowest carriage in the rainy season.

The age distribution of meningococcal carriage, very much dominated by NmX, showed a maximum carriage in younger age groups compared with the prevaccination study [19]. Carriage of serogroups other than NmX varied little with age. Thus, age distribution of each serogroup was different from the baseline study, but in both studies, the dominant serogroup varied significantly by age, whereas the other serogroups did not. Age distribution of meningococcal carriage might therefore depend on the epidemiological context and the dominant serogroup.

Our study showed no NmA circulation after vaccine introduction. We hypothesize that NmA colonization was impeded such that the effective reproduction number (R) fell to <1 and the pathogen disappeared [29]. Detailed analysis of the NmC circulation in the United Kingdom before the introduction of MenC conjugate vaccines estimated a basic reproduction number (R_0) at 1.36, lower than had been suspected [30]. Given the low NmA carrier rate in Burkina Faso before immunization it is likely that NmA R_0 in Africa may also be very low. If that supposition is correct, even modest coverage rates with NmA conjugate vaccine should have a major impact, assuming that complete population mixing is taking place [31]. Better data on NmA R_0 in Africa are sorely needed, as well as more detailed information on the length of protection after a dose of MenAfriVac.

The accepted theory for conjugate vaccines is that the high immunoglobulin G titers produced in blood leak onto the mucosal epithelium of the nasopharynx, thus preventing carriage acquisition [32]. Our study showed that MenAfriVac prevented acquisition but also possibly interrupted ongoing carriage, because unexpected rapid elimination of NmA carriage was seen in the district of Kaya. The possibility that MenAfriVac may be a therapeutic vaccine should be further explored.

In summary, NmA carriage was eradicated in both vaccinated and unvaccinated populations in Burkina Faso from 3 weeks up to at least 13 months after mass vaccination with MenAfriVac. Our findings are consistent with a vaccine-induced herd immunity effect. With herd immunity, the progressive implementation of MenAfriVac ultimately encompassing the whole of the meningitis belt may be expected to progressively eliminate NmA. Protecting the unvaccinated, especially the young children until the vaccine is integrated into child immunization programs, is clearly beneficial for the populations. To better understand the impact of a major public health intervention such as the introduction of MenAfriVac, in addition to continued surveillance, the dynamic of clearance, and the long-term protection of the vaccine against disease and carriage should be further explored.

Notes

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