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ORIGINAL REPORT

# Incidence and types of adverse events during mass vaccination campaign with the meningococcal a conjugate vaccine (MENAFRIVAC™) in Cameroon

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## ABSTRACT

**Purpose** A new vaccine against meningitis A was introduced in Africa meningitis belt in 2010. This study was planned to describe the incidence and types of adverse events following immunization (AEFIs) with a new conjugate vaccine against meningitis A (MenAfrivac™) in a Cameroonian vaccination campaign.

**Methods** The campaign was conducted in Adamawa and North West regions in December 2012 and the AEFIs enhanced surveillance from December 2012 to January 2013. Incidence rates (IR) of overall and serious AEFIs were estimated as well as AEFI incidence rates by type, age group and region. AEFI symptoms were aggregated in System Organ Class (SOC).

**Results** Of 2 093 381 persons vaccinated, 1352 AEFIs were reported. Of these, 228 (16.9%) were excluded because of not meeting inclusion criteria and 1124 (83.1%) included (IR: 53.7/100 000 doses administered/8 weeks). Of the 82 serious AEFIs reported, 52 (63.2%) met the case definition. 23 (28.1%) were investigated, of which 4 (17.4%) were probably vaccine product-related reactions (IR: 0.2/100 000 doses administered/8 weeks). Fever was the most common reported AEFI with 626 cases (IR: 31.4/100 000 doses administered/8 weeks). The proportion of people with the SOC "Gastrointestinal disorders" was significantly lower in ages 5–15 and 16–29 years than 1–4 years [aRR = 0.63(0.42–0.93) and 0.54(0.36–0.81) respectively].

**Conclusion** Incidence and types of AEFI reported during MenAfriVac™ vaccination campaign organized in Cameroon in 2012 did not suggest concern regarding the vaccine safety. Differences in frequency of AEFIs types per age group could guide the monitoring of AEFIs frequency in future campaigns. Efforts are needed to improve the investigation rate of serious AEFIs. Copyright © 2016 John Wiley & Sons, Ltd.

KEY WORDS—AEFI incidence; vaccination campaign; MENAFRIVAC™; meningitis A; Cameroon; pharmacoepidemiology

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## BACKGROUND

AEFI surveillance is essential to ensure vaccine safety. It is expected to provide information on incidence, distribution and risk factors for expected and unexpected serious and minor AEFIs.[1] Surveillance of AEFIs is thus an integral part of any immunization activity.[1] In Africa, the capacity of AEFI surveillance systems in providing the information needed to evaluate and update vaccines risks benefits ratio is still limited. This results from insufficient training of involved health personnel, poor planning and limited resources leading to AEFIs underreporting, low completeness of reporting forms, poor data quality and investigation capacity.[2,3] A number of studies have assessed the efficacy and effectiveness of interventions to improve the situation[2,4–6] but more still needs to be done.[7–9]

MenAfrivac™ (Meningococcal A Conjugate vaccine) is indicated for active immunization against invasive meningococcal disease caused by Neisseria

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meningitidis group A in individuals ages 1–29.[10] It was licensed in December 2009 by India, prequalified by WHO in 2010 and introduced at public health scale targeting individuals 1–29 years of age in Burkina Faso, Mali and Niger.[11] Since the introduction of the vaccine, over 217 million people ages 1–29 have been vaccinated.[12] Since early 2015, the vaccine is recommended by WHO in routine immunization to be administered to children 9 months or older.[12]

AEFI reported in MenAfrivac™ clinical trials were described as transient and resolved withoutsequelae.[11] The distribution of AEFI reported in MenAfrivac™ mass vaccination campaign was described during its introduction in Burkina Faso, Niger and Mali in a surveillance that lasted 42 days after immunization.[13–15] Passive surveillance revealed a cumulated incidence of 9.8/100 000 people vaccinated and 3/44 serious AEFIs classified as possibly or probably related to vaccination.[13] The frequency and distribution of these AEFIs supported that the vaccine is safe when used on a public health scale. The active surveillance targeted 12 pre-identified syndromes from approximately 100 000 people vaccinated in Burkina Faso.[13–15] A total of 71 episodes of these syndromes were investigated and classified coincidental.

This study describes AEFI report during a mass immunization campaign organized in Cameroun in 2012, in Adamawa and North West health regions, targeting over two million people ages 1–29. AEFI monitoring was different from that of Burkina Faso, Mali and Niger as it was enhanced by weekly supervision of AEFIs focal points in one third of health facilities, by weekly Short Message Service (SMS) in the second third and the remaining one third was the control group operating as in the routine with irregular supervision of AEFI surveillance during the campaign and passive post campaign surveillance.[5]

The objective of the present study was to describe the incidences and types of AEFIs reported in the 2012 mass immunization with MENAFRIVAC™ in Cameroon and to provide additional information to update the status of the MenAfrivac™ risk benefit ratio when used at a large scale.

## METHODS

### *Ethical review*

This study was approved by the Cameroon National Ethics Committee with 208/CNE/SE/2012 as ethical clearance number.

### *Study design*

This was a descriptive and analytical study based on data collected from AEFIs report forms using a preconceived grid. Passive and enhanced AEFI surveillance were conducted in health facilities and in vaccination sites over a period of two weeks during the vaccination campaign and six weeks thereafter. Incidence and types of AEFIs were described by time after injection, age group and health region. AEFI symptoms were aggregated in System Organ Class (SOC) and their frequency compared per age group, health region, and vaccine and diluents batches.

### *Preparatory activities*

Members of the AEFIs Experts Monitoring Committee (AEMC) were appointed by the Minister of Public Health. This was a multidisciplinary committee including 10 members with the following specialties: clinical biology, pharmacy, nursing, communication, public health, epidemiology, pathology, neurology and internal medicine. All of them had been trained and familiarized to AEFI surveillance for at least three previous immunization campaigns. This committee met to update the AEFI surveillance guidelines and tools as well as to identify and order necessary supplies. They also organized the training of central, regional and district supervisors. Each district received copies of AEFIs surveillance guidelines, report and investigation forms and supplies.

### *Case definition and selection criteria*

AEFI case definitions were adapted from guidelines and those used during previous campaigns.[14–16] Anyone who received the Meningococcal A Conjugate vaccine during the mass immunization campaign organized in Adamawa and North West regions of Cameroon from 3 December 2012 to 17 December 2012 was eligible. A minor AEFI was any event occurring within 42 days following vaccine administration and not putting the patient's life in danger or not involving hospitalization. A serious AEFI was any event occurring within 42 days following vaccine administration which causes or leads to a life-threatening illness, patient's hospitalization, prolongation of an existing hospitalization, a significant or persistent disability or death. Cases with dates of symptoms onset prior to vaccination, lacking the date of vaccination or symptom onset and with a report forms lacking record of symptom, with



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Table 1. Incidence rates of signs and symptoms s of reported AEFIs during the surveillance period (over an 8-week period)

| Signs and symptoms | Number of AEFI cases with the symptom or sign | Cumulative incidence/ 100 000 doses administered/8 weeks |
|---|---|---|
| **Local** | | |
| Pain at the injection site | 137 | 6.8 |
| Pain in the injected arm | 05 | 0.3 |
| Swelling of the injection site | 37 | 1.8 |
| Swelling of the injected limb | 04 | 0.2 |
| Total | 183 | 9.2 |
| **Systemic** | | |
| Fever | 626 | 31.4 |
| Headaches | 184 | 9.2 |
| Running nose | 180 | 9.0 |
| Cough | 150 | 7.5 |
| Generalized pruritus | 118 | 5.9 |
| Vomiting | 98 | 4.9 |
| Diarrhea | 77 | 3.9 |
| Convulsions | 18 | 0.9 |
| Sudden faintness after injection | 05 | 0.3 |
| Unconsciousness | 4 | 0.2 |
| Other symptoms | 351 | 17.6 |
| Total | 1811 | 90.8 |
| Total reported symptoms | 1994 | 100.0 |

ambiguous, confusing or unintelligible description of symptoms were excluded. Table 1s presents case definitions of expected AEFI adapted from experience of previous campaigns and Brighton Collaboration.[14,15,17]

### *Surveillance and data collection tools*

Surveillance guidelines and tools were adapted from those developed and used during previous vaccination campaigns organized in Cameroon. Report forms were standardized in English and French. Data were extracted from these forms using a grid conceived to collect information on the reporting health facility, patient's age and sex, vaccine and diluents batch number, administration procedures, dates of vaccination, symptom onset and of reporting, exposure to other drugs, actions taken to manage AEFI, outcome and seriousness of the AEFI and status of the reporting health personnel.

### *Surveillance activities*

AEFI surveillance activities followed a path from the vaccination site to the district, region or central health facility. Regions, districts, health facilities and vaccination teams were managed by supervisors from central, regional and district levels. Regional delegations of public health and district health services were in charge of receiving and distributing surveillance resources and the collecting, compiling and sending AEFI reports to upper levels and those investigating serious AEFIs.

At the health facility level, surveillance was conducted over the two weeks of the campaign and six weeks after. It included detecting and reporting AEFI cases during medical consultation and in patient registers. The detection and reporting processes were enhanced by weekly supervision of one third of AEFIs health facilities focal points or weekly reminding of one third of them by SMS while the remaining one third was the control group operating as in the routine with irregular supervision of AEFI surveillance during the campaign and passive post campaign surveillance[5].

At the community level, surveillance activities included sensitizing people two weeks before and during the surveillance period to detect AEFIs and what to do if they occur. At this level, AEFI reporting was conducted by vaccination teams in vaccination sites during the two weeks of the vaccination campaign. Case status (serious or not serious) was assigned by the AEFI focal point in each health facility. This was reviewed by the AEMC.

At the central level, weekly meetings of the AEMC were held to review report forms, stimulate the reporting and investigation and conduct causality assessment.

Serious AEFI, unexpected increase of AEFI incidence rate, cluster and events causing community or health personnel concern were eligible for causality assessment. The casualty assessment process was adapted from the 2013, WHO guidelines.[18] The causality assessment was conducted on a single case based by the AEMC. Outcome of clinical and laboratory investigation, AEFI history and time frame, the exclusion of other possible explanations and biological plausibility were used to assess the link between immunization and the event under investigation. Outcome of causality assessment included vaccine product-related reaction, vaccine quality defect-related reaction, vaccination error-related reaction, vaccination anxiety-related reaction or coincidental events.

### *Statistical analysis*

The AEFIs incidence rate (IR) was estimated over a period of 8-week post-injection per 100 000 vaccine



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doses administered. Overall and serious AEFIs IR were estimated by type, time after injection, age group and region. The Medical Dictionary for Regulatory Activities (MedDRA) was used to code and retrieve reported events.[19,20] For each AEFI, each sign or symptom (low level terms) was assigned to a Preferred Term (PT). Each PT was automatically assigned to primary SOC using Stata software. PTs that were only represented in one SOC were automatically assigned that SOC. When a PT was linked to more than one SOC, it was assigned to a primary SOC selected as recommended in MedDRA Guideline.[19,20]

Each SOC was considered as a dependent variable, and modeled including the following exploratory variables: age group, region and vaccine and diluent batches. A bivariate analysis (univariate log-binomial) was performed first using unadjusted relative risk with 95% confidence interval. Multivariate log-binomial regression was further used to adjust for potential confounders variables. When the variable of interest was one of the above regressors, the others were considered as potential confounders in the corresponding regression model after backward selection. The strength of risk in multivariate log-binomial regression was then quantified using adjusted relative risk with 95% confidence interval. *P*-values were computed using Chi-squared test, and because age group was ordinal variable, Gamma test of association was used. To control maximum experiment wise error rate (MEER) because of multiple testing, *p*-values were adjusted using the Bonferroni method.[21] Data were entered in Epi-Info version 3.5.3 and analyzed using Stata version 12 and IBM SPSS version 19.

## RESULTS

### *I. Incidence of reported AEFIs*

AEFI surveillance activities started with the campaign on 3 December 2012 and ended on 27 January 2013. The immunization campaign targeted 2 128 374 people including 797 450 in Adamawa and 1 330 924 in the North West region. In total, 2 093 381doses of MENAFRIVAC™ were administered (administrative coverage (AC): 98.4%) including 812 686 (AC: 101.9%) in Adamawa and 1 280 695 (AC: 96.2%) in the North West region.

Table 2s presents the batch and number of doses of vaccines and diluents used. Of 1352 AEFIs reported, 1144 (84.6%) were from the North West, 206 (15.2%) from Adamawa and 2 (0.2%) had no specification of the region. Table 3s presents the distribution of reported AEFI per health district and region.

Figure 1 presents the flow chart of the reporting and classification of AEFI cases. In total, 228 (16.3%) AEFIs were excluded for the following reasons: date of vaccination missing (120; 10.7%), date of symptom onset missing (33; 2.9%), no symptom reported (22; 2.0%) and symptom onset was prior to vaccination date (53; 4.7%). A total of 1124 (83.1%) reported AEFIs were analyzed (53.7/100 000 doses administered/8 weeks). Of these, 1101 had the gender variable filled as 507 (45.1%) were males and 594 (52.8%) were females. Seven (0.3%) minor AEFIs occurred among women who were pregnant. The incidence of AEFIs reported was lower in the group that did not receive weekly reminding by SMS or by supervision[5]

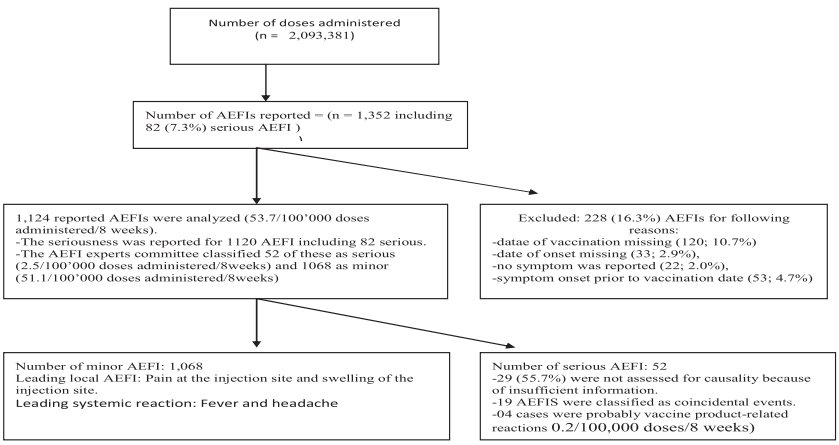


Figure 1. Flow chart of the reporting and classification of AEFIs cases during the Menafrivac™ mass immunization campaign organized in Cameroon in December 2012



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## *II. Distribution of reported AEFIs*

### a) *Incidence of serious AEFIs reported*

AEFIs seriousness was reported for 1120 (99.6%). Among the 1124 AEFIs reported, 82 were initially reported as serious and 1038 as minor (i.e. four AEFIs could not be categorized by seriousness). Following a review by the AEMS, 30 out of the 82 serious AEFIs were reclassified as minor resulting in a serious AEFI incidence rate of 2.5 /100 000 doses administered /8 weeks. The incidence rate for minor AEFIs ($n = 1068$) was calculated at 51.1/100 000 doses administered/8 weeks. Among the remaining 52 (2.5/100 000 doses administered/8 weeks), 29 (55.7%) were not assessed for causality because of insufficient information. The vaccine relatedness was thus conducted on 23/52 serious AEFIs among which 4 (incidence rate: 0.2/100 000 doses administered/8 weeks) were classified as probably vaccine product-related reaction and 19 classified as coincidental events. The four probable vaccine product-related reactions included one case of hypersensitivity (0.05/100 000 doses administered /8 weeks) and three cases of anaphylactic shock (0.2/100 000 doses administered/8 weeks). The 19 unrelated cases were classified as coincidental. These included six cases of meningitis, six cases of severe malaria, two cases of febrile enteritis, two cases of septicemia, one case of abdominal trauma, one case of systemic salmonellosis and one case of arthritis. Table 4s presents the summary of relatedness assessment of serious AEFIs.

### *b) Distribution of AEFIs per type and time from vaccination*.

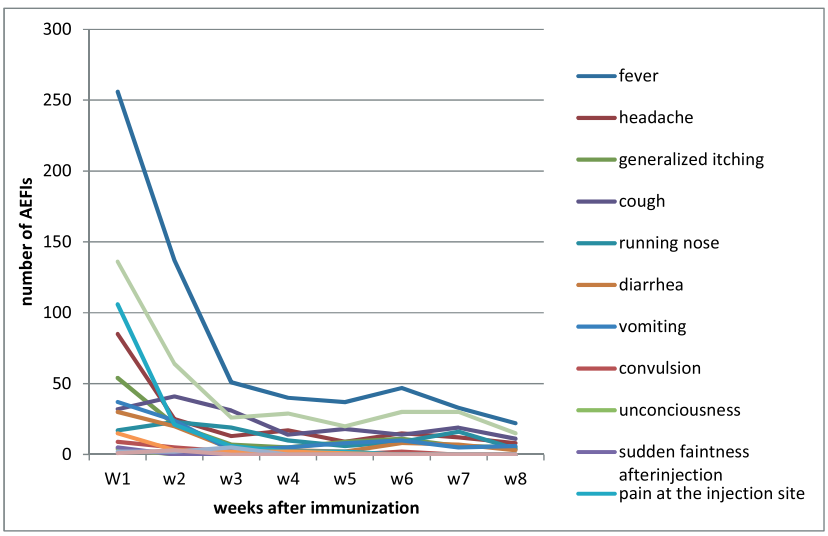
Table 1 shows the types of AEFIs (symptoms and signs) reported during the surveillance period and their incidence rates. These included 183 local reactions (10.1%) and 1811 (90.9%) systemic reactions, summing up to 1994, with fever having the highest incidence rate. Some report forms included more than one AEFI type. Figure 2 shows the number and types of AEFIs reported per week. The number was highest in the first weeks of surveillance. The first two weeks of surveillance were overlaid with immunization activities.

### *c) Distribution of reported AEFIs categorized by SOC*

Table 5s shows the distribution of AEFIs per SOC. The SOC "infection and infestation" had the highest rate (17.4/100 000 doses administered/8 weeks) followed by "Nervous system disorders" (9.8/100 000 doses administered/8 weeks).

### *d) Distribution of AEFIs reported per age group*

A total of 422, 320, 260 and 25 AEFIs were reported in age groups 1–4, 5–15, 16–29 and ≥30 respectively. A total of 422 277, 824 067 and 847 037 doses of MENAFRIVAC™ were administered to the age groups 1–4, 5–15 and 16–29 respectively. The number of doses administered to the age group ≥ 30 was not reported. The AEFI incidence rate per 100 000 doses administered/8 weeks was thus 100.0, 38.8 and 30.6 for age groups 1–4, 5–15 and 16–29 respectively.




Legend: W: week

Figure 2. Weekly number of the different types of AEFI during the surveillance period



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Taking the age group 1–4 years as reference, the AEFI incidence rate was lower in age groups 5–15 [RR = 0.39 (0.34–0.45), $p < 0.001$] and 16–29 years [RR = 0.30 (0.26–0.35), $p < 0.001$].

### *e) Distribution of AEFIs reported by health region*

Table 3s shows the distribution of AEFIs reported per health district and region. A total of 206 AEFIs were reported in Adamawa for 812 692 doses administered (25.4/100 000 doses administered/8 weeks) and 1144 for 1 280 695 doses in the North West region (89.3/100 000 doses administered/8 weeks).The incidence rate of AEFIs for the North West region was higher than that for Adamawa [RR = 3.6 (2.8–3.8), $p < 0.001$].

### *III. Comparison of proportions of AEFIs categorized by SOC reported between age groups*

Table 6s presents the comparisons of proportions of reported AEFIs categorized by SOC between age groups. The proportion of reported "Gastrointestinal disorders" was significantly lower in age groups 5–15 and 16–29 than in age group 1–4 [aRR = 0.63 (95% CI 0.42–0.93) and 0.54(0.36–0.81) respectively]. The same was true for the proportion of reported "Respiratory, thoracic and mediastinal disorders" [aRR = 0.57 (0.40–0.81) and 0.26 (0.16–0.41) respectively]. Proportions of "General disorders" and "administration site conditions" were significantly higher in age group 16–29 [aRR = 2.53 (1.53–4.18)]. Last, the proportion of "Nervous system disorders" was higher in age groups 5–15 and 16–29 [aRR = 2.03 (1.34–3.09) and 1.84(1.22–2.79) respectively].

### *IV. Comparison of proportions of AEFIs categorized by SOC between regions and vaccine and diluents batch*

Proportions of AEFIs categorized by SOC did not significantly differ between regions, vaccine batch nor diluents, except for "Gastrointestinal disorders" which affected more individual cases exposed to diluents batch B compared to batch A [aRR = 1.79 (1.06–3.05)]; and was less frequent in Nord West Region compared to Adamawa [aRR = 0.10 (0.03–0.43)].

## DISCUSSION

The overall IR of AEFIs, reported during the mass immunization campaign against meningitis A held in Cameroon in 2012, was 53.7/100 000 doses administered/8 weeks. It was 2.5/100 000 doses administered/8 weeks for serious AEFIs with 4 (0.2/100 000 doses administered/8 weeks) classified as probably related to the vaccine. The incidences and types of AEFIs varied according to age group and region.

The estimated IR of AEFIs was higher in this campaign than in previous ones organized in Cameroon or in other countries.[14,15,22] There are several possible reasons for that which include suboptimal vaccine storage conditions or administration procedures, coincidental epidemic illnesses during the campaign surveillance period or improved monitoring system. Vaccines used were pre-qualified by WHO, and this was confirmed by the competent departments of the Ministry of Public Health of Cameroon. Cold chain, vaccine transport and administration procedures were closely supervised and no irregularity was reported.[22] Thus the high incidence of AEFIs was unlikely because of vaccine quality or program errors. No epidemic was reported in any of the targeted regions that could have increased the incidence of AEFIs. The high AEFI IR in this campaign was thus most likely because of the improvement of the detection and monitoring system. Indeed, unlike other campaigns, two thirds of health facilities involved in this campaign were reminded to report AEFIs weekly during the last four weeks of the surveillance by supervising one third of health personnel or sending SMS to AEFIs.[5] This reporting enhancement contributed to an increase in AEFI reporting rate in the second half of the monitoring period during which the rate is often low. Interventions contributing to improve AEFIs reporting rates should be promoted during immunization activities in order to improve the sensitivity of the surveillance and the likelihood to detect new AEFIs and all serious AEFIs.

The IR of serious adverse events was in the same range as that in previous campaigns.[14,15] However, less than a third of these cases were investigated because either they did not meet the case definition or they lacked necessary information to be appropriately assessed. The proportion of coincidental cases (82%) was similar to that reported during campaigns in Burkina Faso and Niger.[14,15] Four cases including one case of hypersensitivity reaction and three cases of anaphylactic shock were classified as probable vaccine product-related reactions based on the case definition, time lapse after immunization, the favorable course after adrenaline administration, the biological plausibility and exclusion of other causes. These cases were allergic reactions, as reported in previous campaigns.[13] Information on these cases was rather limited because they were reported based



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on symptoms by the vaccination teams that were not in a position to perform a thorough clinical examination because of the emergency of the situation.

Regarding AEFI types, reported local reactions were minor with the highest incidences during the first week of surveillance and the lowest (zero) after week 4 post-immunization (Figure 2). IR was higher than that observed during previous campaigns but lower than that recorded during clinical trials.[14,15,23–25] Monitoring of local reactions is important because it allows early detection and prevention of some program errors and maintains population adhesion to immunization. Regarding systemic reactions, fever was the most frequent event in our study followed by headache and running nose. The frequencies and ranking of different types of AEFIs were not always the same in previous campaigns. Fever was the most common systemic symptom reported for two out of three campaigns and the second for the last one while headache was the first symptom reported for one out of three campaigns and the second in one out of three.[19,20] The type of AEFI, the temporary sequence of their occurrence after vaccination and the course with a gradual decline over the eight weeks of surveillance suggest that a given proportion of these symptoms and signs were probably related to vaccination.

Standardization of procedures to aggregate reported events in medically meaningful groupings is essential to trace AEFIs in the clinical development of vaccines and post-licensure phase, among different manufacturers, and to share information between actors involved in vaccines safety. We aggregated AEFIs in SOCs following MedDRA guidelines.[19,20] Proportions of "Gastrointestinal disorder" and "Respiratory, thoracic and mediastinal disorders" reported in ages 1–4 were higher than in older age groups. This can be explained by the higher background incidence of diarrhea and cough in younger children.

The IR of AEFIs reported from the North West region was at least three times higher than in Adamawa. Similarly, the IR was about 100 times higher in Batibo Health District than that estimated in the Tignere health district. No difference in AEFI types as categorized by SOC was detected when comparing proportions of types of AEFIs in each region. The unequal spatial distribution of reported AEFIs has already been observed when comparing AEFI IR in previous campaigns.[14,15] Information on the geographic distribution of reported AEFI is necessary to monitor surveillance activities. Areas with low reporting rate should be stimulated to do better by adopting good practices. The low AEFI reporting rate in Adamawa can be explained by the limited geographical accessibility of health facilities and different health seeking behavior. This trend has also been observed for other health outcomes. For example, results of the 2011 national health demographic survey showed that only 46% of women delivered in a health facility in Adamawa while this percentage was 93% in the North West one.[26]One of the possible responses to this low reporting rate could be the establishment of a community-based AEFI surveillance which has been proven to improve AEFI reporting rate.[27]

The interpretation of the above findings should be taken with some caution because up to 16% of reported AEFIs and 55% of serious ones could not be analyzed because of low completeness or in-coherent data. The number of persons vaccinated was not detailed in days or weeks and could not allow to estimating AEFI incidence rate per week.

## CONCLUSION

The present assessment did not detect any new serious AEFI and did not note any increase in serious AEFI rates compared to previous mass immunization campaigns with MENAFRIVAC™. This supports the large-scale use of this vaccine to prevent meningitis A epidemics and mortality in Africa.

The incidence declined over the surveillance period and varied according to age group, health districts and regions. The distribution of these AEFIs supports the assumption that a given fraction was probably related to immunization.

Observed age group differences in incidence and types of AEFI could be explained by different background incidence of diseases and different susceptibilities or reporting in these different age groups.

During future vaccination campaigns, actions should be taken to ensure that, AEFI reporting accuracy and completeness as well as AEFIs reporting and investigation rates reach in all targeted regions, the minimal level to allow the updating of vaccine risk–benefit ratio and to detect and prevent in time, program errors.

## CONFLICT OF INTEREST

Summarizing the information from each author (see section 4): Neither authors of this manuscript nor their family members have worked, received any funding or support from the project "Developing a meningococcal A conjugate vaccine".



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KEY POINTS

- Incidence and types of AEFI reported during MenAfriVac™ vaccination campaign organized in Cameroon in 2012 did not suggest concern regarding the vaccine safety;
- Differences in frequency of AEFIs types per age group could guide the monitoring of AEFI frequency in future campaigns;
- In the next vaccination campaigns, actions should be taken to insure that all reported AEFIs match case definition and that AEFIs reporting and investigation forms are correctly and completely filled;
- The analysis of reported AEFIs by type, time, age group and geographic area, completeness, timeliness is necessary for better monitoring of the AEFI detection and reporting process;
- Standardization of procedures to aggregate reported AEFIs in medically meaningful groupings is essential for the monitoring of the distribution of AEFI by population categories, vaccine batches, immunized geographical areas and other parameters that might influence its incidence and seriousness.

## ETHICS STATEMENT

The work was conducted according the 2008 version of the Declaration of Helsinki.

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