Pharmacovigilance during mass immunization campaign with MenAfrivac™ in Cameroon

INAUGURALDISSERTATION

zur

Erlangung der Würde eines Doktors der Philosophie

vorgelegt der Philosophisch-Naturwissenschaftlichen Fakultät

der Universität Basel

von

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aus Yaounde, Kamerun

Basel, 2016

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät auf Antrag von

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Basel, den 23 Juni, 2015

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List of abbreviations and acronyms

ADR: Adverse Drugs Reaction

AE: Adverse Events

AEFI: Adverse Events Following Immunization

EPI: Expanded Program on Immunization

GACVS: Global Advisory Committee on Vaccine Safety

GVSI: Global Vaccine Safety Initiative

LMIC: low- and Middle-Income Countries

MedDRA: The Medical Dictionary for Regulatory Activities terminology

MEER: Maximum Experimentwise Error Rate

MDG: Millennium Development Goals,

MOH: Ministry of Public Health

MVP: Meningitis Vaccine Project

LTD: Private Limited Company

NRA: National Regulatory Authority

PATH: Program for Appropriate Technology in Health

PIDM: Program for International Drug Monitoring

PS: Polysaccharide

SMS: Short Message Service (SMS)

SOC: System Organ Class

UMC: Uppsala Monitoring Centre

VPD: Vaccine Preventable Diseases

WHO: World Health Organization

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Acknowledgement

First and foremost thanks goes to my almighty God, the pathway through this PhD thesis would have never been possible without his grace and blessings – praise and honor to your holiness forever amen.

There are many people I would like to express my sincere gratitude for their great role in supporting this work. First of all, I express my heartfelt gratitude to my supervisor Prof. Blaise Genton, for his tireless and superb academic and scientific supports. Thank you for trusting me. I really learned from you and only God can thank you properly.

I would also like to thank Prof. Marcel Tanner, the director of Swiss TPH for being my faculty representative and to ensure all my financial and academic matters are settled accordingly. Special thanks go to Christine Mensch and Doris Stamm our students' administrators for their joyful and motivating monitoring of my academic, financial affairs and journeys. Many thanks to all my academic lecturers during course work, fellow students and friends in Basel. You all made my studies and my stay in Basel a happy moment.

I am very grateful to Dr. Beat Stoll for overseeing the field activities of this PhD project, for his highly stimulating scientific discussions, and for showing me the path between the Faculty of Medicine and Biomedical Sciences of the University of Yaounde1 where you met me and Swiss TPH.

I acknowledge the support I acquired from the country WHO office of Cameroon, Cameroon Ministry of Public Health which financially supported field activities of this project; of the Swiss Foundation for Excellence and Talent in Biomedical Research who funded trips, TRREE (Training and Resources in Research Ethics Evaluation), the University of Dschang and the Cameroon based NGO: M.A. SANTE (Meilleur Access aux Soins de Santé) which funded trips for protocol development, lectures, manuscripts and thesis drafting.

Special thanks to the manager of the Expanded Program on Immunization, Cameroon Ministry of Public Health (MOH); the head of department of drugs, pharmacy and laboratory, MOH; members of AEFIs surveillance expert committee for the 2012 MenAfrivac™ campaign; Adamaoua and North West regional Delegations of Public Health; All the 27 health districts (Adamaoua and North West Health regions); regional and districts AEFI focal points for the 2012 MenAfrivac™ campaign who accepted the integrate field activities of this project in the campaign activities.

My sincere thanks also goes to Prof. Koulla Shiro Sinata, secretary General at the Ministry of Public Health, Cameroon; Prof. Anaclet Fomethe, Rector University of Dschang; Prof. Mpoame Mbida, Head of Department Biomedical Sciences, University of Dschang; Prof. Anne Cecile BISSECK, Head of the Division of Health Operations Research, Ministry of Public Health; Prof. Dominique Sprumont, Institut de Droit de la Santé, University of Neuchatel; Prof. Watcho Pierre, Coordinator, Department of Biomedical Sciences, University of Yaoundé 1; Dr Nguefack Georges, Department of Public Health, Faculty of Medicine and Biomedical sciences, University of Yaoundé I, Cameroon, and Dr Genevieve Decosterfor their precious and helpful advices.

I'm greatly indebted to my children Karel, Dora, Armel, Juan, Whenever, Nicolas, Tina Franky and Vanelwho used to complain persistently whenever I was away for studies, especially at times when they need me most.

Special thanks and dedication to my parents Mr. Dieumo Antoine and MrsNguekeng Helene, for giving birth to me, Showing me the way and the importance of school and sciences and supporting me spiritually throughout my life.

I am grateful to my beloved wife Doris for your warm support and taking care of the family aloneduring my distant stay in the field sites and in Basel. Special thanks go to my late brothers and sisters, Zeofack Jean Robert and Dongmo Christaline for their moral assistance.

Last but not the least, I would like to thank my friends: Marc, Assare, Dominic, Abas, my students and colleagues: Stephanie, Walter, Martin, Sonia, Fabrice, Marcelin, Celestin for their supports.

Summary

Background.Immunization is one of the most cost effective public health interventions and is estimated to have greatly reduced diseases, disabilities, deaths, and inequities worldwide. To date, it has allowed totally eradicating one disease and putting more than 7 others under control. After testing in clinical trials, only vaccines that meet the requirements of safety and effectiveness are registered and authorized by competent authorities to be used in routine and mass immunization campaigns. However, it is known that whatever may be the performances, clinical phases of a vaccine cannot detect all related adverse events following immunization (AEFIs). This is supported by the fact that the sample size of clinical trials is insufficient to detect rare AEFIs; a given fraction of AEFIs occurring in the marketed phase of vaccine is related to behavioral and biological particularities of vaccinees as they are not rigorously selected as in clinical trials patients, others are related to program errors such as non-compliance to vaccines storage or administration procedures. Thus, AEFIs may occur following administration of licensed vaccines and constitute a risk of damage on the health of patients or a reason for immunization refusal since vaccine safety gets more public attention than vaccination effectiveness.

To anticipate on potentially damaging effects of AEFIs on the health of vaccinees and the adherence of population to immunization, it has been recommended that each vaccination program develops a vaccine pharmacovigilance system to firstly detect, report, investigate, and respond to AEFI and, secondly share information on AEFIs, needed to update the safety profile of each licensed vaccine. Currently published studies show that for a number of reasons, vaccines pharmacovigilance systems are limited to reach their goals in developing countries such as Cameroon. Consequently, several million doses of vaccines are administered to children and pregnant women in routine EPI (Expanded Program on Immunization) and to many other specific groups in immunization campaigns with little information on vaccines safety generated and made available.

The overall goal and specific objectives: This PhDaimed to contribute in securing access to immunization by assessing efficient interventions that can be used to improve the pharmacovigilance of licensed vaccine. Its activities were embedded in the vaccination campaign against meningococcal meningitis A, organized in two health region of Cameroon in 2012, with the newly introduced conjugate meningococcal meningitis A vaccine (MenAfrivac™). The objectives of this thesis were i) to investigate the safety profile of the vaccine MenAfrivac™ in the mass immunization campaign against meningococcal meningitis organized in Adamaoua and North West Health regions of Cameroon; ii) to assess the effect on AEFI reporting, after the meningitis vaccination campaign with MenAfrivac™, of sending a weekly standardized SMS to

health workers in charge of AEFI surveillance in health facilities or conducting standardized supervision of these personnel using skilled supervisors; and iii) to compare the incidence and distribution of MenAfrivac™AEFIs reported during clinical trial phases to that reported during immunization campaigns.

Method. Three different study designs were used independently to respond to different specific objectives of this thesis. The first was a descriptive and analytical study based on data collected from AEFIs report forms using a preconceived grid. Passive and stimulated AEFIs 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.The second was an open randomized controlled design with three arms. Health facilities that met the inclusion criteria were randomly assigned to receive: i) a weekly standardized SMS asking them to report all medical events occurring during the intervention period in persons immunized during the campaign, ii) a weekly standardized supervisory visit by trained health district focal points for AEFI detection and reporting processes, or iii) no intervention besides routine training and sensitization of health facility teams during health districts coordination meetings (the control group). The primary outcome was the incidence of AEFIs per 100 health facilities per week reported to the Regional Delegation of Public Health rate from week 5-8 after the immunization campaign. The third was a systematic review conducted to identify all published studies reporting adverse events following MenAfrivac™ administration during clinical trials and immunization campaigns. The incidence rate (IR) of overall, local, systemic, serious and types of reported AEFIs were estimated and compared between clinical trials and immunization campaigns studies using the incidence rate difference (IRd).

Findings.

Safety profile of MenAfrivac™in immunization campaign

Of 2'093'381 persons vaccinated in Adamaoua and North West health regions in 2012, 1'352 AEFIs were reported. Of these, 228 (16.9%) were excluded because they did not meet inclusion criteria. Among the remaining 1'124 (83.1%), the incidence rate was 53.7 AEFIs/100'000 doses administered/8 weeks. Of 82 serious AEFIs reported, 52 (63.4%) met the case definition. Twenty-three (28.1%) were investigated, of which 4 (17.4%) were probably related to the vaccination (incidence rate: 0.2 AEFIs/100'000 doses administered/8 weeks). Fever was the commonest AEFI with 626 cases (incidence rate: 31.4 AEFIs/100'000 doses administered/8 weeks). Proportions of subjects with different primary SOC (system organ class) disorders varied by age group, gastro-

intestinal and respiratory being more frequent in children aged <4 years and neurological and general conditions more in adults for example.

***Effects of SMS or supervision on AEFI reporting*.**

A total of 348 (77.2%) of 451 health facilities were included, and 116 assigned to each of three groups. The incidence rate of reported AEFIs per 100 health facility per week was 20.0 (15.9-24.1) in the SMS group, 40.2 (34.4-46.0) in supervision group and 13.6 (10.1-16.9) in the control group. Supervision led to a significant increase of AEFI reporting rate compared to SMS [adjusted RR=2.1 (1.6-2.7; p<0.001] and control [RR=2.8(2.1-3.7); p<0.001)] groups. The effect of SMS led to some increase in AEFI reporting rate compared to the control group, but the difference was not statistically significant [RR =1.4(0.8-1.6); p=0.07)].

Safety profile of MenAfrivac^{TM} in clinical trials and vaccination campaigns

Seven studies were included from 6 publications including 4 clinical trials and 3 immunization campaigns. The overall AEFI IR was 4.6 (4.5-4.7) per 100'000 doses administered per week. In clinical trials studies, the IR per 100'000 doses administered per week of overall, local, and systemic AEFIs were 10'047, 11'499, and 17'248 respectively. In immunization campaigns, these values for overall, local, and systemic AEFIs were 4.0, 0.59, and 3.12 respectively. None of 10 serious AEFIs reported during clinical trials was related to the vaccine. Of 41 serious AEFIs reported during immunization campaigns, 5 were probably related to vaccine. IR of AEFIs were higher in clinical trials than in immunization campaigns studies, the difference (IRd) for overall AEFIs being of 10043 (95% CI 10042-10044) per 100'000 doses per week, for local of 11'498 (11'498-11'498), for systemic of 17'245 (17'245-17'245)] and for serious AEFIs of 1.55 (1.54-1.56). The AEFI IR decreased by more than 99.9% for overall, local, systemic and 99.5% for serious AEFIs from clinical trials to immunization campaigns.

Conclusion

Neither new safety signal nor increased incidence of serious AEFIs compared to previous mass immunization campaign withMenAfrivac^{TM}was observed. There were age differences in incidence and type of AEFIs that are probably related to different background incidence of diseases and different susceptibilities or reporting rates in these different age groups.

Supervision was more effective than SMS or routine training in improving AEFI reporting rate. It should be part of any AEFI surveillance system. SMS could be useful in improving AEFI reporting rates but strategies need to be found to improve its effectiveness, and thus maximize its benefits.

The magnitude of the difference between IR of AEFI as evaluated in the controlled setting of clinical trials and more pragmatic approach of mass vaccination campaigns was huge. IR of AEFIs was more than 99% lower in vaccination campaigns than in clinical trials, including for the

reporting of serious ones. Although the objective of pharmacovigilance is not to identify all minor AEFIs, sustainable strategies including for example standardization of hospital registries with information on vaccination status to improve active case detection in hospitals to allow better reporting and investigation of causality and stimulation of reporting using adequate supervision and communication technologies such as SMS reminders need to be put in place.

Résumé

Contexte. . La vaccination est l'une des interventions de santé publique les plus efficiente qui contribue à la diminution de la morbidité, mortalités et des inégalités dans le monde entier. À ce jour, elle a permis d'éliminer une maladie et de contrôler plus de 7 autres. Après avoir été testés lors d'essais cliniques, seuls les vaccins qui répondent aux exigences de sécurité et d'efficacité sont enregistrés et autorisés par les autorités compétentes pour être utilisés dans les programmes de vaccination de routine et lors des campagnes de vaccination. Toutefois, il est connu que quelles que soient leurs performances, les phases de développement cliniques d'un vaccin ne peuvent pas détecter toutes les manifestations adverses post immunisation (MAPI). Ceci s'expliquerait par le fait que la taille d'échantillon des essais cliniques est limitée pour détecter les MAPI rares; une fraction donnée de ces MAPI est liée à des particularités comportementales et biologiques des personnes vaccinées qui ne sont pas rigoureusement sélectionnées comme lors des essais cliniques ; une autre est liée aux erreurs programmatiques associées au non-respect des procédures de conservation et d'administration des vaccins. Ainsi, des MAPI peuvent survenir après l'administration de vaccins homologués et constituer un risque de dommages sur la santé des patients ou une raison de refus de la vaccination, d'autant plus que l'attention du public est plus facilement attirée par les problèmes de sécurité des vaccins que par leur efficacité.

Pour anticiper sur les effets potentiellement néfastes des MAPI sur la santé des personnes vaccinées et l'adhésion de la population à la vaccination, il a été recommandé que chaque programme de vaccination développe un système de pharmacovigilance afin d'une part de détecter, notifier, investiguer et répondre aux MAPI et d'autre part, rendre disponibles les données de la surveillance des MAPI pour la mise à jour du profil de sécurité de chaque vaccin homologué. Actuellement les études publiées montrent que, pour un certain nombre de raisons, les systèmes de pharmacovigilance ne sont pas très performants, et ne permettent pas de ce fait d'atteindre leurs objectifs dans les pays en développement comme le Cameroun. Par conséquent, plusieurs millions de doses de vaccins sont administrés aux enfants et aux femmes enceintes dans le cadre du PEV (Programme élargi de vaccination) de routine et aux groupes spécifiques variés lors des campagnes de vaccination. Très peu d'informations en sont disponibles et accessibles sur les MAPI survenues.

Objectifs. Cette thèse a pour objectif d'améliorer la performance du système de pharmacovigilance en évaluant l'efficience de nouvelles interventions dans le contexte d'une

vaccination de masse. Ses activités ont été intégrées dans la campagne de vaccination contre la méningite à méningocoque A, organisée dans deux régions du Cameroun en 2012, avec le vaccin conjugué nouvellement introduit contre la méningite à meningocoque A (MenAfriVac™). Les objectifs de cette thèse sont i) d'étudier le profil de sécurité du vaccin MenAfriVac ™ lors de la campagne de vaccination de masse contre la méningite à méningocoques A organisée dans les régions de l'Adamaoua et du Nord-Ouest du Cameroun ii) d'évaluer l'effet de l'envoi d'un SMS hebdomadaire standardisé aux personnels de santé en charge de la surveillance des MAPI dans les formations sanitaires ou de la supervision de ces personnels de santé par des superviseurs qualifiés sur la notification des MAPI, après les campagnes de vaccination contre la méningite avec MenAfriVac™ ; et iii) de comparer l'incidence et la distribution des MAPI MenAfriVac™ signalées lors des phases d'essais cliniques à celles rapportées lors des campagnes de vaccination.

Méthodologie. Trois différents types d'étude ont été utilisés de façon indépendante pour répondre à chacun des trois objectifs spécifiques de cette thèse. Le premier était une étude descriptive et analytique basée sur des données recueillies sur les fiches de notification des MAPI à l'aide d'une grille préconçue. Une surveillance passive stimulée a été menée dans les formations sanitaires et dans les sites de vaccination sur une période de deux semaines au cours de la campagne de vaccination et pendant les six semaines qui suivaient la fin de la campagne. Les incidences et les types de MAPI ont été décrits en fonction du délai de survenue après l'administration des vaccins, du groupe d'âge, et de la région. La deuxième étude était une étude randomisée et contrôlée avec trois groupes. Les formations sanitaires qui répondaient aux critères d'inclusion ont été assignées au hasard à recevoir: i) un SMS hebdomadaire standardisé leur demandant de signaler tous les événements médicaux survenus pendant la période d'intervention chez les personnes immunisées durant la campagne, ou ii) une visite de supervision hebdomadaire par le point focal surveillance des MAPI du district de santé, ou iii) aucune intervention autre que la formation de routine et de sensibilisation au cours des réunions de coordination des districts de Santé (groupe de contrôle). Le principal effet mesuré était l'incidence des MAPI pour 100 formations de sanitaires par semaine rapportée à la délégation régionale de la Santé Publique, de la semaine 5 à la semaine 8 après la campagne de vaccination.

Le troisième type d'étude était une revue systématique portant sur toutes les études publiées dans lesquelles les MAPI survenant après l'administration du MenAfriVac™ au cours des essais cliniques et des campagnes de vaccination ont été notifiés. Les taux d'incidences (TI) de l'ensemble des MAPI, des MAPI locales, systémiques et graves, ainsi que les types de MAPI

notifiées ont été estimés et comparés entre les essais cliniques et les études menées lors des campagnes de vaccination à l'aide de la différence de taux d'incidence (IRD).

Résultats.

Sécurité du MenAfriVac^{TM} lors de la campagne de vaccination

Des 2'093'381 personnes vaccinées dans les régions de l'Adamaoua et du Nord-Ouest en 2012, 1'352 MAPI ont été notifiées. Parmi celles-ci, 228 (16,9%) ont été exclues parce qu'elles ne répondaient pas aux critères d'inclusion. Pour les 1'124 (83,1%) restantes, le taux d'incidence des MAPI était de 53,7 MAPI/100'000 doses administrées/8 semaines. Des 82 MAPI graves notifiées, 52 (63,4%) répondaient à la définition de cas. Vingt-trois (28,1%) ont été investiguées, dont 4 (17,4%) étaient probablement liées à la vaccination (taux d'incidence: 0,2 MAPI/100'000 doses administrées/8 semaines). La fièvre était la MAPI notifiées la plus fréquente avec 626 cas (taux d'incidence: 31,4 MAPI/100'000 doses administrées/8 semaines). Les proportions de personnes présentant un syndrome caractérisant chaque SOC (system organ class) identifié variaient en fonction des groupes d'âge. Les affections gastro-intestinales et respiratoires étant les plus fréquentes chez les enfants âgés de <4 ans et les troubles neurologiques et généraux plus fréquents chez les adultes.

Effets du SMS ou de la supervision sur la notification des MAPI.

348 (77,2%) des 451 formations sanitaires recensées ont été incluses et 116 attribuées à chacun des trois groupes. Le taux d'incidence de MAPI signalées pour 100 établissement de santé par semaine était de 20,0 (15,9 à 24,1) dans le groupe de SMS, de 40,2 (34,4 à 46,0) dans le groupe de supervision et de 13,6 (10,1 à 16,9) dans le groupe contrôle. La supervision a entrainé une augmentation significative du taux de notification des MAPI comparativement au groupe recevant le SMS [RR ajusté = 2,1 (1,6 -2.7; p <0,001] et au groupe contrôle [RR = 2,8 (2.1-3.7); p <0,001)]. L'envoi des SMS entraîne une certaine augmentation des taux de notification des MAPI par rapport au groupe de contrôle, mais la différence n'a pas été statistiquement significative [RR = 1,4 (1.0-1,9); p = 0,51)].

Sécurité de MenAfrivacTM lors des essais cliniques et des campagnes de vaccination

Sept études ont été incluses à partir de 6 publications dont 4 essais cliniques et 3 études menées lors des campagnes de vaccination. Le taux d'incidence global des MAPI était de 4,6 (4,5-4,7) par 100'000 doses administrées par semaine. Dans les essais cliniques, les TI par 100'000 doses administrées par semaine de MAPI globales, locales et systémiques étaient de 10'047, 11'499 et 17'248 respectivement. Lors des campagnes de vaccination, ces valeurs pour les MAPI globales, locales et systémiques étaient de 4,0 ; 0,59 et 3,12 respectivement. Aucunes des 10 MAPI graves

notifiées lors des essais cliniques n'était liée au vaccin. Des 41 MAPI graves notifiées lors des campagnes de vaccination, 5 étaient probablement liées au vaccin. Le TI des MAPI étaient plus élevés lors des essais cliniques que lors des campagnes de vaccination, la différence des TI concernant les MAPI global étant de 10'043 (IC à 95%= 10'042-10'044) pour 100'000 doses par semaine, de 11'498 (11'498-11'498), 17'245 (17'245-17'245)] et 1,55 (1,54 à 1,56) pour les MAPI locales, systémiques et graves respectivement. Le TI des MAPI a diminué de plus de 99,9% en ce qui concerne les MAPI globale, locales, systémiques et de 99,5% pour les MAPI graves, quand on passe des essais cliniques aux études menées lors des campagnes de vaccination.

Conclusion. Aucune augmentation de l'incidence des MAPI graves n'a été observée comparativement aux précédentes campagnes de vaccination de masse avec le MenAfriVac™. Il y avait des différences d'incidence et de type da MAPI selon l'âge, différences probablement liées à des différences d'incidences des maladies et des sensibilités ou des différences de taux de notification parmi les différents groupes d'âge.

La supervision a été plus efficace que le SMS ou la surveillance de routine sur l'amélioration du taux de notification des MAPI. Elle devrait faire partie de tout système de surveillance des MAPI. Le SMS pourrait être utile pour améliorer les taux de notification des MAPI mais les stratégies doivent être trouvées pour améliorer son efficacité, et donc maximiser ses avantages.

L'ampleur de la différence entre les TI des MAPI dans le cadre d'essais cliniques et lors des approches plus pragmatiques des campagnes de vaccination de masse était considérable. Le TI de MAPI était de plus de 99% inférieur lors des campagnes de vaccinations par rapport aux essais cliniques, y compris le taux de notification des MAPI graves. Bien que l'objectif de la pharmacovigilance n'est pas d'identifier toutes les MAPI mineures, des stratégies pérennes, telles que la standardisation des registres des formations sanitaires incluant au moins une variable sur les antécédents de vaccination par exemple pourrait améliorer la détection active des cas dans les formations sanitaires et permettre une meilleure notification et l'investigation des cas de MAPI; la stimulation de la notification en utilisant la supervision et les technologies de communication telles que des rappels par SMS devraient être mis en place.

Zusammenfassung

Kontext.Impfungen gehören zu den effizientensten Public Health Interventionen und trugen in grossem Ausmass weltweit dazu bei, Krankheiten, Behinderungen, Todesfälle sowie auch Ungerechtigkeiten zu reduzieren. Bis heute konnte eine Krankheit total ausgerottet werden, und mehr als sieben weitere sind unter Kontrolle. Einzig Impfstoffe, welche die Bestimmungen betreffend Sicherheit und Wirksamkeit in klinischen Versuchen unter Beweis stellen konnten, erhalten die Bewilligung der kompetenten Behörden, in Routineprogrammen oder Massenimpfkampagnen angewendet zu werden. Wir wissen aber auch, dass trotz nachgewiesener Leistung diese klinischen Versuche nicht alle mit der Impfung im Zusammenhang stehenden unerwünschten Nebenwirkungen (AEFIs - Adverse Events Following Immunization) entdecken können. Dies erklärt sich aus der Tatsache, dass die Stichproben dieser klinischen Versuche oft zu klein sind, um seltene AEFIs zu entdecken. Dazu kommt, dass ein gewisser Anteil der AEFIs, welche in der Vermarktungsphase der Impfstoffe auftreten, im Zusammenhang mit Besonderheiten im Verhalten und in biologischen Faktoren der geimpften Personen stehen, da diese eben nicht gleichermassen sorgfältig wie in klinischen Studien ausgewählt werden. Andere AEFIs wiederum werden durch Fehler im Impfprogramm hervorgerufen, wie zum Beispiel das Nichtbeachten der idealen Lagerungsbedingungen oder gar bei der Verabreichung der Impfungen. Deswegen können AEFIs auch bei registrierten Impfstoffen auftreten und bergen stets ein gewisses Risiko für die Gesundheit der Patienten. Sie werden auch als Gründe der Ablehnung eines gewissen Impfstoffes in den Vordergrund gestellt, da in der Bevölkerung der Sicherheit von Impfstoffen manchmal eine grössere Beachtung geschenkt wird wie der Wirksamkeit des Produktes. Um nun solchen potentiell für die Gesundheit der Geimpften schädigenden Effekte vorzubeugen, und um damit auch eine bessere Compliance einer gegebenen Bevölkerung zu erreichen, wurde empfohlen, dass jedes Impfprogramm ein Meldesystem entwickelt mit den Zielen, einerseits AEFIs früh zu entdecken, zu registrieren, zu untersuchen und zu beheben und andrerseits die AEFIs Information zu verarbeiten, damit das Sicherheitsprofil eines jeden lizensierten Impfstoffes angepasst werden kann. Publizierte Studien zeigen, dass die Impfmeldesysteme von Entwicklungsländern wie Kamerun die gesteckten Ziele aus verschiedenen Gründen nicht ganz erreichen. Folglich werden in den Routine Impfprogrammen (EPI – Expanded Program on Immunization) mehrere Millionen Impfdosen an Kinder, schwangere Frauen und viele andere spezifische Gruppen verabreicht ohne dass die Sicherheit weiter untersucht wird und die Resultate dann auch zugänglich sind.

Diese PhD Forschung beabsichtigt, zu vermehrter Sicherheit im Zugang zu Impfstoffen beizutragen, indem sie mehrere effiziente Interventionen kritisch betrachtet, welche zu einer Verbesserung des Meldesystems von bereits zugelassenen Impfstoffen geeignet wären. Ihr Blick richtet sich vorwiegend auf die Meningokokken-Meningitis A Schutzimpfung, welche in zwei Regionen von Kamerun im 2012 eingeführt wurde. Es handelt sich um den neu eingeführten Meningokokken Meningitis A Impfstoff mit dem Namen MenAfrivac™. Die Ziele dieser Doktorarbeit sind i) das Sicherheitsprofil von MenAfrivac™ in Massenimpfkampagnen gegen Meningitis zu untersuchen, welche in den beiden kamerunesischen Gesundheits-Regionen Adamaoua und Nord-West organisiert wurden und ii) dabei die Wirksamkeit des AEFI Meldesystems zu evaluieren, bei welchem nach der Impfung mit MenAfrivac™ entweder wöchentlich standardisierte SMS an das mit dem AEFI Meldesystem betraute Gesundheitspersonal in den verschiedenen Gesundheitszentren versandt wurden oder aber eine standardisierte Supervision derselben durch ausgebildete Fachleute vor Ort durchgeführt wurde und schliesslich iii) die Inzidenz und Verteilung der MenAfrivac™ AEFIs der Impfkampagnen mit jenen der publizierten Daten aus den klinischen Feldversuchen zu vergleichen.

Methode. In dieser Forschung fanden je nach den verschiedenen spezifischen Zielsetzungen und unabhängig voneinander, drei verschiedene Studien-Designs Anwendung.Das erste war eine deskriptiv analytische Studie, welche sich auf Daten berief, welche aus den vorgegebenen Formularen des AEFI Meldesystem konstituierte. Dabei handelte es sich um ein passives- aber auch um ein aktiv gefördertes AEFI Meldesystem, welches in den Gesundheitszentren und anderen Orten, wo Impfungen durchführt wurden, über einen Zeitraum von zwei Wochen während der Impfkampagnen und bis sechs Wochen danach funktionierte. Die Inzidenz und Typologie der AEFI wurden beschrieben nach dem Zeitpunkt deren Auftretens nach der Impfung, nach Altersgruppe der betroffenen Person und nach der Gesundheitsregion, wo die AEFI auftraten. Das zweite Design war eine offene randomisierte Studie mit drei Gruppen. Jene Gesundheitszentren, welche die Einschlusskriterien erfüllten wurden zufällig zugeordnet, um i) wöchentlich standardisierte SMS zu erhalten, welche danach fragten, alle während der Impfkampagne an geimpften Personen beobachteten medizinischen Ereignisse zu melden, oder ii) eine wöchentliche, standardisierte Supervision mit speziell zur Erkennung und Meldung von AEFIs ausgebildetem Fachpersonal zu erhalten oder aber dann iii) von gar keiner spezifischen Intervention berücksichtigt wurden ausser der routinemässig durchgeführten Ausbildung und Sensibilisierung der Teams im Gesundheitszentrum anlässlich von Distrikt-Koordinations-Sitzungen (dies war die Kontroll-Gruppe). Der Primary Outcome war die AEFI Inzidenz pro 100 Gesundheitszentren pro Woche, welche an die Regionale Public Health Delegation zwischen

Woche 5 bis 8 nach der Impfkampagne gemeldet wurden. Das dritte Design war eine Systematic Review, welche alle publizierten Studien über gemeldete AEFI identifizierte, die im Zusammenhang mit den klinischen Studien zu MenAfrivac™ und den Impfkampagnen durchgeführt wurden. Dabei wurde dann die Inzidenzrate (IR) aller, der lokalen, systemischen, und als schwerwiegend geltenden AEFI und deren Natur hochgerechnet und diese von klinischen Studien mit jenen der Impfkampagnen verglichen, was dann die Inzidenzraten-Differenz ergab (IRD).

Resultate.

Sicherheitsprofil von MenAfrivac™ in Impfkampagnen

Im Jahre 2012 wurden von den in den Gesundheitsregionen Adamaoua und Nord-West geimpften 2'093'381 Personen insgesamt 1'352 AEFIs gemeldet.Anschliessend mussten 228 (16.9%) wegen Nichterfüllens der Enschlusskriterien ausgeschlossen werden. Unter den Verbliebenen 1'124 (83.1%) AEFIs errechnet sich somit eine Inzidenzrate von 53.7 AEFIs/100'000 verabreichten Impfungen/8 Wochen.Von den 82 sogenannt schwerwiegend gemeldeten AEFIs, erfüllten 52 (63.4%) die erforderliche Definition. Dreiundzwanzig (28.1%) wurden untersucht, und 4 (17.4%) davon standen wahrscheinlich in einem Zusammenhang mit der Impfung (Inzidenzrate: 0.2 AEFIs/100'000 applizierten Impfungen /8 Wochen). Fieber war der häufigste AEFI mit 626 Fällen (Inzidenzrate: 31.4 AEFIs/100'000 applizierten Impfungen /8 Wochen). Die Anteile von Personen, welche von verschiedenen primären Organsystem Störungen betroffen waren, variierten nach Altersgruppe. Gastrointestinale- und den Atemapparat betreffende Störungen wurden zum Beispiel häufiger bei Kindern unter 4 Jahren und neurologische und allgemeine Erscheinungen häufiger bei Erwachsenen beobachtet.

Auswirkung auf die AEFI Melderate durch SMS Stimulation verglichen mit direkter Supervision

Insgesamt wurden 348 (77.2%) der 451 Gesundheitszentrern eingeschlossen und je 116 zu je einer Gruppe zugeordnet. Die Inzidenzrate der gemeldeten AEFI Fälle per 100 Gesundheitszentren pro Woche war20.0 (15.9-24.1) in der SMS Gruppe, 40.2 (34.4-46.0) in der Gruppe mit direkter Supervision und 13.6 (10.1-16.9) in der Kontrollgruppe. Die Supervision führte zu einem signifikanten Anstieg der gemeldeten AEFI Fälle verglichen mit der SMS Gruppe [bereinigtes RR=2.1 (1.6-2.7; p<0.001] oder der Kontrollgruppe [RR=2.8(2.1-3.7); p<0.001)]. Die SMS Stimulation führte zu einem gewissen Anstieg der gemeldeten AEFI Fälle verglichen mit der Kontrollgruppe, aber der Unterschied fiel statistisch nicht signifikant aus [RR =1.4(0.8-1.6); p=0.07)].

Sicherheitsprofil von MenAfrivac^{TM} in klinischen Studien und Impfkampagnen

Es wurden 7 Beobachtungen eingeschlossen, welche in 6 Publikationen beschrieben wurden – 4 klinische Versuche und 3 Impfkampagnen.Insgesamt beobachtete man einen AEFI IR von 4.6 (4.5-4.7) pro 100'000 applizierten Impfungen pro Woche.Studien zu klinischen Versuchen rapportierten eine IR pro 100'000 applizierten Impfungen pro Woche betreffend aller, der lokalen und der systemischen AEFIs von 10'047, 11'499, und 17'248 beziehungsweise. In den Impfkampagnen waren die Werte betreffend aller, der lokalen und der systemischen AEFIs 4.0, 0.59, and 3.12 beziehungsweise. Kein einziger der in den klinischen Versuchen als schwerwiegend gemeldeten Fälle konnte der Impfung zugeordnet werden. Von den 41 als schwerwiegend gemeldeten AEFIs, welche im Laufe von Impfkampagnen auftraten, wurden 5 als wahrscheinlich im Zusammenhang mit der Impfung gebracht. Die IR von AEFIs waren höher in den klinischen Studien als in den Impfkampagnen. Somit ist die Differenz (IRD) für alle AEFIs 10'043 (95% CI 10'042-10'044) pro 100'000 verabreichten Impfungen pro Woche, für lokale 11'498 (11'498-11'498), für systemische 17'245 (17'245-17'245) und für als schwerwiegend geltende AEFIs 1.55 (1.54-1.56). Die AEFI IR verringerte sich somit um mehr als 99.9% für alle, die lokalen und die systemischen AEFIs und um 99.5% betreffend die als schwerwiegend geltende AEFIs ausgehend von den klinischen Versuchen zu den Impfkampagnen.

Vergleicht man mit vorhergehenden Massenimpfkampagnen von MenAfrivac^{TM}, so wurden weder neue Sicherheitssignale noch eine erhöhte Inzidenz von als schwerwiegend geltendnen AEFIs verzeichnet. Es bestehen altersabhängige Unterschiede im Auftreten und der Art der AEFIs, welche wahrscheinlich vor dem Hintergrund einer verschiedenen Inzidenz von Krankheiten und verschiedenen Anfälligkeitsprofilen oder auch unterschiedlichen Melderaten für diese verschiedenen Altersgruppen zu sehen sind. Die direkte Supervision ist wirksamer als SMS Stimulation oder ein Routine Training Kurs bezüglich der Verbesserung der Melderate von AEFIs. Die Supervision sollte somit Teil eines jeden AEFI Meldesystems werden. Die SMS sind eventuell nützlich bei der Verbesserung der Melderate von AEFIs. Es braucht jedoch neue Strategien, um die Wirkung zu erhöhen und so den Nutzen zu maximieren.

Die Grösse der Differenz zwischen der AEFI IR, wie sie einerseits in kontrollierten Settings der klinischen Studien und andrerseits mit einem mehr pragmatischen Ansatz der Massenimpfkampagnen evaluiert wurde, war enorm. Die AEFI IR der Massenimpfkampagnen war mehr als 99% niedriger als jene der klinischen Versuche, einschliesslich der Meldungne von als schwerwiegend geltenden AEFIs. Obwohl die Pharmakovigilanz nicht primär alle leichten AEFIs zu identifizieren sucht, braucht es eine Entwicklung nachhaltiger Strategien wie zum Beispiel eine

Standardisierung von Spitalregistern, welche die Information des Impfstatus beinhalten, damit eine aktive Erkennung der Fälle in den Spitälern mit darauf folgender Untersuchung einer eventuellen Kausalität möglich wird. Die Förderung der Melderate durch angepasste Supervision und Integration von Kommunikationstechnologie wie SMS muss ausgebaut und fortgesetzt werden.

Chapter 1: Introduction

Effectiveness of immunization as a public health intervention

Vaccination is an intervention that has been proven efficient in preventing child mortality worldwide. It is estimated that it saves every year at least 6 million deaths, 400 million life years and 97 million disability adjusted life years and has helped to control many diseases (1). Compared to other public health interventions, it is among interventions with lowest investment risk in human per capita development with proven economic impact (1).

Vaccines development and safety assessment

Eachvaccineis developed in threephases including thepreclinical, clinical, and post registration phases,in which itssafety, reactogenicity and efficacyare evaluated(2). International and national guidelinesfor the regulation ofclinical trials(3; 4) present recommendationsfor safety assessment during vaccines clinical development, registration and prequalification phases(5; 6).Recommendations to ensure the quality and safety of the vaccine when it is marketed are also presented in appropriate guidelines(7; 8; 9).

Importance of post registration AEFI surveillance

Vaccines used in the Expanded Programme on Immunization (EPI) are generally prequalified by WHO following a rigorous and standardized procedures (5).What so evertheprequalificationprocedure, itmust be knownthat exposureto the vaccinecan induce,beside expected effects, adverse events (AE).

The assessment of drug safety inclinical trials is limited to detect all potential adverse events following immunization (AEFIs). Reasons behind these limitations include: i) the non-implementation of the standardization of the monitoring andreporting ofAEFIsin clinical trials (10; 11); ii) a given fractionofAEFIthat occurin vaccine post registration phase arerelated to patients behavioral, biological differencesof targeted populations, failure to comply to contra-indications, vaccine storage, transportation, administration and may not be detectedby clinicaltrials; iii) sample sizesof clinical trials often lackthenecessarypower to detectrare AEFI(12). It is thus essential that national monitoring and reporting systems for vaccine safety be planned as part of immunization programmes and/or of pharmacovigilance systems, be efficiently and adequately supplied with needed minimum resources, implemented and coordinated.

A minority of persons who are vaccinated may experience AEFIs that are related to the vaccine, most of which are mild and time-limited but can also, in rare cases be serious. The update onthese

categories of AEFI isnecessaryto guidedecisions andplans of National regulatory authorities (NRA), EPIofficials, policy makers and the pharmaceutical industry.

Whether relatedto the vaccineor not,AEFIscanhandicap theadhesion of the populationto vaccination(15; 16).This mustbe preventedsothat vaccinationcontinues to playits role indisease control.

Postregistration AEFIsurveillanceis thus essential and recommended to countries implementing routine EPI and supplementary immunization activities EPI(17; 18).It allows the updating of information on vaccinesafety profile. This informationbeing essentialto those involvedfor the continuous improvement ofservice delivery in terms ofvaccination andto ensure theinterest and demandof the populationfor vaccination.

AEFI case definition

An AEFI is any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine (9). The adverse event may be any unfavorable or unintended sign, symptom or disease, or abnormal laboratory finding. It can be serious or mild. A serious AEFI is a reaction that results in death, hospitalization or prolongation of hospitalization, permanent or significant disability, causes congenital abnormality or requires intervention to prevent damage or impairment (9). A cluster of AEFIs is two or more cases of the same adverse event related in time,place or vaccine administered. Following AEFIs are recommended eligible for investigation: serious AEFI;cluster AEFI;suspected signal; suspected immunization error;it appears on the list of events defined for AEFI investigation or; it causes significant parental or public concern.The ultimate goal of an investigation is to determine whether the vaccine or immunization process is responsible for the reported event(s) or to find another cause and correct it if possible, and reassure the public. There are 5 possible causes of AEFI (9). These include: i) vaccine product-related reaction: an AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product; ii) vaccine quality defect-related reaction: an AEFI that is caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product, including its administration device as provided by the manufacturer; iii) immunization error-related reaction (formerly “programme error”): an AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable; iv) immunization anxiety-related reaction: an AEFI arising from anxiety about the immunization; v) coincidental event: an AEFI that is caused by something other than the vaccine product. Cluster of AEFIs are usually due to immunization error-related reactions. To promote comparability of reported AEFI, cases definition and clinical classification of cases should be done following the Brighton

Collaboration and The Medical Dictionary for Regulatory Activities terminology (MedDRA) respectively (74, 77).

Goal of AEFI surveillance

Immunization safety surveillance aims at early detecting, reporting, investigation and appropriately responding to adverse events in order to lessen the negative impact on the health of the individuals and on the immunization programme. Appropriate vaccine surveillance is an indicator of immunization programme quality (9). It also enhances programme credibility and can provide actual country data on vaccine risks. In Cameroon, all AEFI are recommended to be detected at health facilities and reported to the EPI through the health district service and regional delegation of public health and then to Department of Pharmacy, Drugs and Laboratory (80). During campaigns, all AEFI are recommended to be detected at vaccination sites and health facilities and reported to the EPI through the health district service and regional delegation of public health and then to experts committee in charge of AEFIs monitoring.

Activities for better immunization safety at global level

Since 1999,vaccine safetyhas been identifiedas a priority projectby the World Health Organization (WHO)(19).Aproject aiming to improve the global vaccine safety was launched andfocused on: insuring vaccine safety from clinical trials up to point of use; conducting research and development to insure safer and simpler delivery systems; improving access to safer and more efficient systems for vaccine delivery and sharps waste management; and identifying and managing risks related to immunization. One of the main supporting activitiesimplementedby WHO forthe latter was the establishment of a Global Advisory Committee on Vaccine Safety (GACVS) to provide support needed to improve AEFI surveillance in countries (20; 21).In theseperspectives,a number ofactionshave already beentakenincluding the productionand provisionofguidelines onsetting up and running a vaccinepharmacovigilance system and implementing its activities(18; 22; 23).Also, to contribute in establishing effective vaccine pharmacovigilance systems in all countries, the WHO is developing a global vaccine safety blueprint (24). Preliminary activities of this initiative included identifying local experience, available infrastructures, needs and priorities of vaccine safety monitoring expressed in Low- and Middle-Income Countries (LMIC) (25).

Developing AEFI surveillance system at country level

Thebasic elementsforthe establishmentof AEFIs surveillance and management ofpharmacovigilance centersin generalhave been described ininternational guidelines(28).These guidelinesdetail the AEFIs surveillance objectives, the minimum informationexpected in an AEFI reporting form, thedetection, reporting investigatingand data analysis procedures, and the required mechanisms for collaboration

and coordinationactivities among institutions involved. The minimum needed equipment,human resourcesand activitiesare also described. It underlines that the choiceof the local institutions tohost thepharmacovigilanceand AEFI surveillance servicesis crucial for the success of its activities. A recent survey of vaccine safety stakeholders with different professional backgrounds in LMIC identified following as actions to be implemented to improve existing vaccine safety systems in LMIC:improve the quality of existing vaccine safety data, to enhance local analytic capacity, to establish health-care databases and to enhance information sharing within and across countries (25).

Challenges of AEFI surveillance in vaccine clinical trials

The detection, reporting and investigation ofAEFI as well as results presentation on vaccine safety during clinical trials are notalways done as recommendedin guidelines (3).A review published in 2005 underlined number of weaknesses: methods of many clinical trials lacked information on AEFIs case definition, procedures of AEFI detection, reporting, investigation, duration and periodicity of AEFI follow up.Inconsistency between presented results and described methodology and lack of standardization of AEFI surveillance procedures among clinical trials were other weaknesses pointed out (29). About half of articles reporting clinical trials failed to disclose result on drug safety. Anotherreview on clinical trials conducted in developing countries and publishedin 2012underlined the need to harmonize safety reporting procedures and to implement standardized AEFIs case definitions (31).The above mentionedchallenges need to be addressed in order to ensure the reliabilityof informationonvaccine safetypresentedin clinical trial reports.Italsounderlines the importantroleto be playedbyvaccines post licensure pharmacovigilance in the monitoringof vaccinesafety profile.

Challenges of AEFIs surveillance in routine and immunization

The establishmentand the functioningof a credible vaccine pharmacovigilance system are essential forthe monitoring of the safety profileof vaccinesused inthe EPIand supplementaryimmunization activities (SIAs)(18). But thecurrent landscape ofnational pharmacovigilance systemsdoes not meet yetexpectations.Published studies conducted in 55 LMIC countries highlighted number of challenges:halfof the countries donot yethavea pharmacovigilance systemin place;only about 45% of these countries have trained human resources andbudget allocated for pharmacovigilance (32); till as recently as in 2005, there were stillcountries whereimmunization activitieswere carried out withoutany plan to conduct AEFI surveillanceand countries where initiatives aimed at the standardization of AEFI case definitions were unknown (33).In a numberof countries, remarkable progresses arenoted. As the example of Burkina Faso where basic structures for

pharmacovigilanceand AEFI surveillance activities have been established but the system still lacksregulation andspecificguidelines for adequateorganization andcoordination of activities(34).

At health facilities level, AEFI underreportinghas been identified as one ofmajorweakness(35; 36; 37; 38).

Asurvey recently conductedbyWHOidentifiedtheperceivedand documented needs to address in order to improve vaccine safety systems in countries(25).

Challenges of AEFI surveillance in immunization campaigns

Mass vaccination campaignsare organized eitherto prevent an epidemic, in responseto an epidemic, or to improve the coverage ofroutine EPI.For over 10yearsat least 5campaigns are organized in Cameroun yearly targeting ina very few daysa large number ofpeople.Tovaccinatea largenumber of people,health personalunaccustomedto vaccinationare solicited to complement tosupplement regular EPI staff. Thus, immunization campaignsinvolve inexperienced staffinimmunization activities, thelarge number of doses given over a short period of time leading to many occurring AEFIs including coincidental events (23).Immunization activitiesare oftenconducted inoutreach, mobile, or door to door strategies andlimit the possibilitiesto maintain thecoldchain.This situation is known to predispose to an increased incidence of program errors.In addition, it is fertile grounds for rapid expansion ofrumors that can lead torefusalor decreasedadhesionof the populationsto vaccination(23).

Underreporting and described related factors

Several studies havedescribedfactors associated withpoor performancesof pharmacovigilancein generalandAEFIsreporting in particular.Thesefactors may act either at the level ofimmunization programs,health facilitiesor the community.

At immunization program level, factors influencing AEFI reporting arepoorly described. Thereporting ratemay depend on theavailability ofguidelines and procedures, resources, surveillance design, frequency and qualityoftraining and supervisionimplementedin the framework of AEFI monitoring(39; 40; 41).

At health facilities level, the main determinants of underreporting are related to service delivery and particularly to health care staff. Work overload, privileged professional categories (physician); ignorance, fear of being accused of ignorance, beliefs and perceptions, doubt on the case definition and period of surveillance, lack of interest and indifference resulting from inadequate training have been identified as main determinantsassociated with underreporting (15; 42; 43; 44). We did not find studies describing the relationship betweenthe availability of regulations, resources, guidelines, standard operating procedures, reporting forms, incentives and adverse events reporting rates.

At community level, limited knowledge, awareness and perceptions of persons vaccinated have beenidentified as factors influencing the AEFI reporting rates (45; 46; 47). The geographical and financial accessibility of health facilities to communities, and communities' perceptions regarding service delivery in health facilities can be other factors influencing AEFI reporting.

The main consequence of underreporting is that a considerable proportion of serious adverse events, program errors and AEFIs that cause concern to the public are not detected and investigated.

Interventions to improve AEFI surveillance

To the best of our knowledge no intervention hasyet been tested or implemented to assess effects of improvingthe regulation,resources, guidelines or equipment on rate and/or quality AEFI reported.The direct impact ofthe international initiativeslike Programme for International Drug Monitoring (PIDM)andGlobal vaccine safety blueprint have not yet been assessed(48; 26).

At the operational level interventions have been mainly targeting patients but not health facilities. The most tested intervention has been the use of short message service (SMS) tostimulate AEFI reporting. (50; 51; 52). This strategy has been shown effective in improving AEFIsdetection and reporting rates (53).

Many other alternatives have been assessed (55; 56; 57). These included among other the use of phones, fax, worldwide web or e-mail reporting. These channels have been limited as they require adequate equipment, internet network coverage and permanent power supply.Training has been proven to improve the AE reporting but this has been limited to certain category of health personnel

Supervision has been proven, during masses immunization campaigns organized in Cameroon, to contribute in improving AEFIs reporting rate and the completeness of reporting forms (56).But this result could not be generalized since there was not appropriate control intervention and the supervision procedure was not rigorously standardized in different sites.

Supervision has various definitions and ways of implementation.In health domain, it includes more qualified health personnel interacting with generally less qualified ones to verify and insure that their tasks and activities are implemented following predefined guidelines (57). It is part of the district health system like in Cameroon. In this country, basic health care is often provided by nurses and in some case general practitioners in Integrated Health Centers under the supervision of the health district staff. The health district staffs are supervised from the regional staff which is also supervised by the ministerial staff. Supervision is part of clinical practice activities and health programmes but is not implemented in all health facilities and programs because of lack of human

and financial resources and of poor planning. Health programs like EPI implement it more rigorously and regularly.

A review of nine controlled studies comparing supervision versus no supervision showed a significant positive effect in two out of three studies; enhanced supervision significantly improved health worker performances in two out of five studies. In one study, there was no effect of decreasing supervision frequency on service utilization (54). In this review, types of procedures and implementation of supervision, study sites, study power, targeted population and activities as well as outcome type and assessment were very diverse.

Communicating via mobile phone using Short Message System (SMS) is a cheap mean of communication. It can be used to strengthen the health system by speeding the exchange of information between health facilities and health structures.The WHO is promoting the use of new technologies including SMS as strategy to improve health delivery in resource-limited settings (58).The effect of this policy is taking ground in Cameroon with mobile telephones and free communication offered by WHO to all health facilities involved in surveillance activities since December 2013.Since then, SMS is being used to stimulate AEFI reporting but its benefits are still limited since it is neither systematic nor generalized.There arealsoattempts to useSMSfor cases reporting but initiativesin this direction arestill isolated.In other setting, it has been demonstrated to significantly improve the mobilization of anesthesia personnel in response to mass casualty incidentswith some limitations though (59). A portionof persons targeted by SMS targetsdid not read it intimeandeveryone readingthe message did notreactin time. The present study offers an opportunity to test efficacy of SMS compared to that of supervision over routine AEFI monitoring practiceson AEFI reportingamong health workers during a vaccination campaign against meningococcal meningitis A using the vaccine MenAfrivac™.

The burden of meningitis in Africa

Infectious meningitis can be viral, fungal, parasitic or bacterial but Neisseria meningitidis is the predominant cause of bacterial meningitis epidemic and is the most frequent worldwide. For over 100 years, the disease has affected all continents. The strains associated with outbreaks include: A, B, C, and W135 and X (60). The meningitis A strain is the most common, morbid and rife in twenty-twoSahelian Africa countries (from Senegal to Ethiopia) called meningitis belt of Africa with the population at risk estimated at over 400 million. Outbreaks typically occur in the dry season with an estimated annual incidence of 1000-1200 cases per 100,000 habitants per epidemic (60). The baseline incidence varies between 10-20 cases per 100 000 habitants. In the period 1993-2012, close to one million cases occurred causing about 100,000 deaths. Treatmentcostsare aboveincome of

severalaffected families andconstitutean obstacle to development (61). From the time MenAfrivac™has been used in immunization campaigns to prevent the disease, the incidence and specific mortality related to Meningococcal meningitis A have been rapidly decreasing (63). Cameroon is one of the countries affected by the disease.Table 1, presents the number of cases of Meningococcal meningitis and deaths reported in Cameroon from 2009 to 2012. We have to underline that low proportion of cases and deaths are reported due to poor performances of the epidemiological surveillance.

Table I: Number of cases of Meningococcal meningitis and deaths reported in Cameroon from 2009 to 2012 (source: department of disease control, Cameroon Ministry of Public Health).

Year	Case	Deaths	Lethality
2009	1001	122	12,2%
2010	835	71	8,5%
2011	2733	191	7%
2012	671	74	11%

The Meningitis Vaccine Project (MVP)

Meningitis epidemics raging in Africa for a long time could not be controlled in spite of reactive mass vaccination of the population at risk with meningococcal polysaccharide (PS) vaccines (64). The efficiency of this vaccine was indeed hampered because of its limited efficacy in infants and young children.Also, it did not decrease carriage, neither conferred herd immunity (64).Inspired by successful experiences of conjugate vaccines against Haemophilus B and Meningococcal meningitis C (67), the WHO called in 2000, for a group of experts to assess the feasibility ofdeveloping an affordable meningococcal A or A/C conjugate vaccine to control meningitis as public health problem in Africa (66). After assessment, the group reached the conclusion that this project was feasible.An initiative involving the partnership between WHO and Program for Appropriate Technology in Health (PATH), funded by the Bill and Melinda Gates Foundation,with supports ofdelegations of African ministries of health and a group of international experts called Meningitis Vaccine Project (MVP) was thus born with the aim to develop, test, and license MeningococcalMeningitis A Conjugate vaccines for Sub-Saharan Africa. The meningococcal meningitis Aconjugate vaccine (MenAfrivac™) was then developed by the Serum Institute of India LTD (64).Clinical phases began in 2005 and were implemented in India and Africa. At the end of these phases, the vaccine was proven effective and safe and marketed in India in 2009 (66). It was then introduced in Burkina Faso in 2010 (68). Till 2012, over 100 million persons have been vaccinated during mass preventive vaccination campaigns

in 10 countries with this vaccine (66). The epidemiological surveillance following these campaigns has not reported a case of meningitis A detected in a vaccinated person. The incidence and specific mortality of meningococcal meningitis Aare therefore considerably decreasing but outbreaks of meningococcalmeningitis W135are still persisting (60). From AEFI surveillance, there is no reason for concern regarding the safety of the vaccines (38).

Description ofMenAfrivac™

MenAfrivac™ (Meningococcal A Conjugate vaccine) is a lyophilized vaccine made of purified meningococcal A polysaccharide covalently bound to tetanus toxoid (TT), which acts as a carrier protein. The vaccine consists of purified group-specific bacterial polysaccharide from *Neisseria meningitidis* group A (72). It satisfies the WHO recommendations to assure vaccine quality, safety and efficacy (73). It is indicated for active immunization against invasive meningococcal disease caused by Neisseria meningitidis group A. It does not protect against other forms of invasive disease caused by other meningococcal groups (such as Groups B, C, W135, and Y).

MenAfrivac™ has shown adverse reactions during clinical trials in the 4 days following immunization, namelylocal reaction includinginjection site tenderness in 2% to 30% and induration in less or equal to 2%; and systemic reactions including, diarrhea in less or equal to 13% of children and adults 1 to 29 years of age, irritability in less than or equal to 12% of children 1 to 10 years of age, headache inless than or equal to 11% of children and adults 11 to 29 years of age, vomiting; loss of appetite and lethargy in less than or equal to 10% of thevaccine recipients and fatigue, fever (body temperature = 38°C) in 2% to7%, and myalgia, arthralgia in less than or equal to 1% (72). All adverse reactions following immunization were transient and resolved without sequelae.

The vaccine must not be administered to subjects with known hypersensitivity to any component of the productor to subjects having shown hypersensitivity after previous administration of the vaccine. It should not be used insubjects with acute infectious diseases and/or ongoing progressive illnesses. In case of fever with temperature of at least 38°C or active infection immunization should be delayed. Pregnant women should not be immunized since effects of vaccine on the fetus are unknown. Lactating women also should not be given the vaccine since it is not known whether the vaccine is excreted in human milk. Administration of the vaccine to subject with impaired immune responses may not induce an effective response.

After a pilot phase, the vaccine was introduced in three African countries in 2010. These included Burkina Faso, Mali and Niger covering a total population of 18 million persons. The AEFI surveillance was passive and active in one health district in Burkina Faso (38; 71). Passive surveillance revealed a

total of 1807 AEFIs, including 44 serious events reported from 18.4 million people vaccinated in the 3 countries during introduction. This corresponds to a reporting rate of 9.8 AEFIs per 100 000 people vaccinated. Fever (39.2%) and local reactions (28.4%) were most commonly reported AEFIs. Based on a review by national expert committees in each country, only 3/44 serious AEFIs were classified as possibly or probably related to vaccination (1 case each of acute exanthematous pustulosis, bronchospasm, and vomiting). In addition, during the pilot phase another 4 serious events were classified as possibly or probably related to vaccination (bronchospasm, meningitis-like syndrome, vomiting, and urticarial).

Active surveillance for 12 pre-identified syndromes was conducted for 52 days (10 days during the vaccination campaign and 42 days after) in 16 health-care facilities in which approximately100 000 people had been vaccinated (71). A total of 71 episodes of these syndromes were investigated, of which the most common were convulsions (32 cases), urticaria (18) and bronchospasm (14). The national expert committee of Burkina Faso classified these cases as coincidental.A total of 2022 pregnant women vaccinated in Burkina Faso and Mali have also been followed to collect data on AEFIs and pregnancy outcomes.

AEFI surveillance as part of pharmacovigilance in Cameroon

The Republic of Cameroon, with a population of about 20 million in 2012 is situated in central Africa. It is organized in 10 health regions and was subdivided into 181 functional health districts in 2012, each of them having a given number of health areas (78). Each health district and health area has a district hospital and Integrated Health Centers respectively. The quality of health care is generally low. Major health problems include reproductive health problems, malaria, HIV/AIDS, tuberculosis, other infectious diseases and cardiovascular diseases.The main barriers limiting access to health care services include inadequacy of human, material and financial resources, poor planning, geographic and cultural inaccessibility to health care and a poor health information system. Strategies to overcome these barriers include reinforcing the health system, preventing maternal and child mortality, health promotion, and diseases control through health programs.

Pharmacovigilance is part of the health system in Cameroon. It is in charge to organize continuous surveillance of safety and efficacy of drugs and vaccines used in clinical practice and in public health programs but its activities are still very limited (79). Presently only the EPI is implementing pharmacovigilance as part of its activities (80). Even there, the minimum resources to adequately insure surveillance activities are provided only for a given proportion of vaccination campaigns and mostly by international partners.This should be a point from where to learn in order to build the

system in other health programs and in clinical practices. From previous campaigns surveillance activities; low reporting and investigation rate, ignorance, lack of motivation, and lack of training have been identified as main barriers to AEFI surveillance.Among other interventions, supervision has been judged to be the most efficient in improving the training, the awareness as well as AEFIs reporting and investigation rates (78). Figure 1 shows the AEFI reporting and the investigation system framework in Cameroon.

The vaccination campaign against meningitis A that took place in 2012 had as part of its activities AEFI surveillance. It targeted more than 2 million persons aging 1 to 29 years old in all 27 health districts of Adamaoua and North West health regions. The AEFI surveillance was implemented for 56 days including 14 during the campaign and 42 after the campaign.

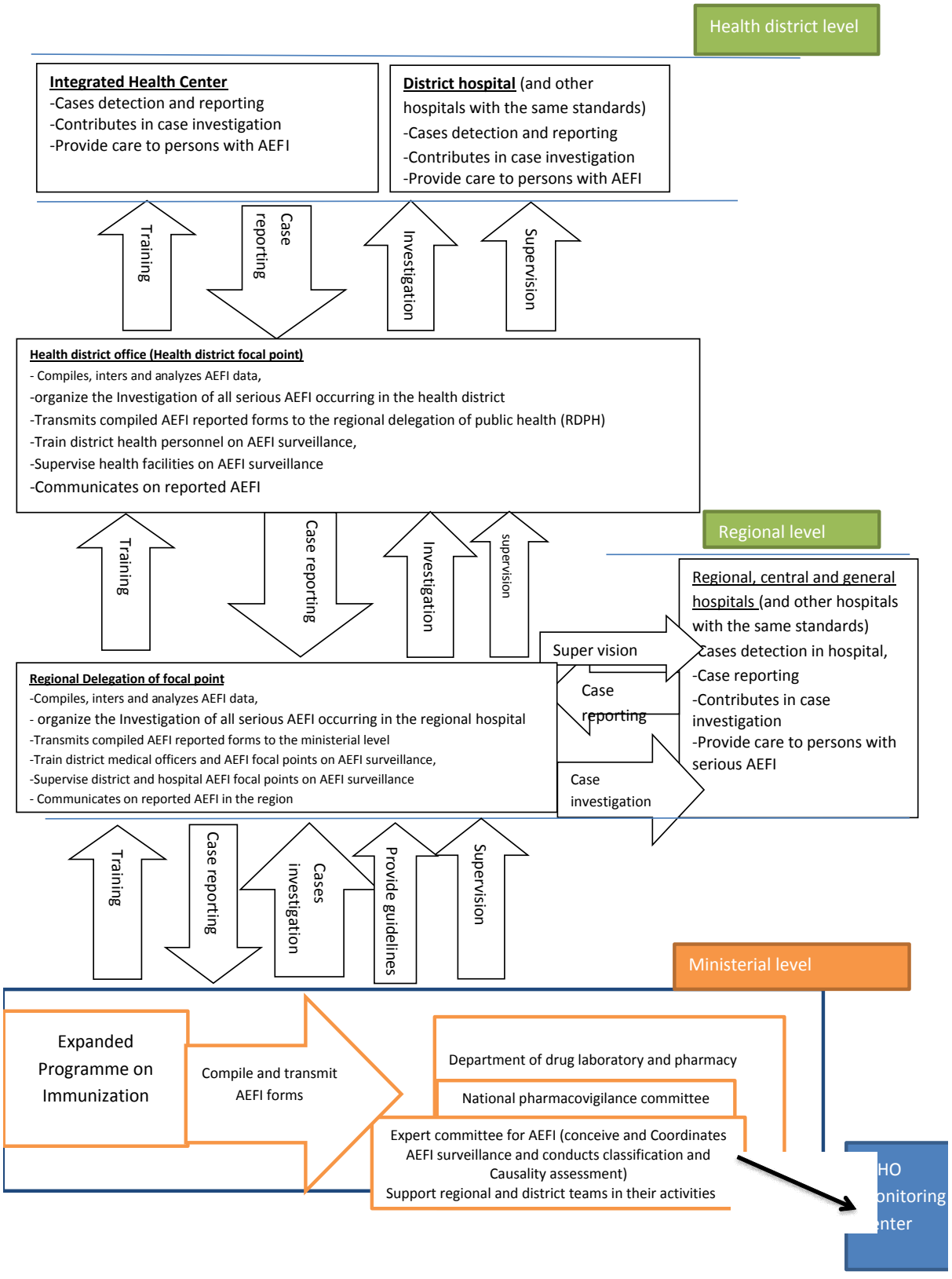
Health district level
Integrated Health Center
-Cases detection and reporting
-Contributes in case investigation
-Provide care to persons with AEFI
District hospital (and other hospitals with the same standards)
-Cases detection and reporting
-Contributes in case investigation
-Provide care to persons with AEFI
Training
Case reporting
Investigation
Supervision
Health district office (Health district focal point)
- Compiles, inters and analyzes AEFI data,
-organize the Investigation of all serious AEFI occurring in the health district
-Transmits compiled AEFI reported forms to the regional delegation of public health (RDPH)
-Train district health personnel on AEFI surveillance,
-Supervise health facilities on AEFI surveillance
-Communicates on reported AEFI
Regional level
Training
Case reporting
Investigation
supervision
Super vision
Case reporting
Case investigation
Regional, central and general hospitals (and other hospitals with the same standards)
Cases detection in hospital,
-Case reporting
-Contributes in case investigation
-Provide care to persons with serious AEFI
Regional Delegation of focal point
-Compiles, inters and analyzes AEFI data,
- organize the Investigation of all serious AEFI occurring in the regional hospital
-Transmits compiled AEFI reported forms to the ministerial level
-Train district medical officers and AEFI focal points on AEFI surveillance,
-Supervise district and hospital AEFI focal points on AEFI surveillance
- Communicates on reported AEFI in the region
Training
Case reporting
Cases investigation
Provide guidelines
Supervision
Ministerial level
Expanded Programme on Immunization
Compile and transmit AEFI forms
Department of drug laboratory and pharmacy
National pharmacovigilance committee
Expert committee for AEFI (conceive and Coordinates AEFI surveillance and conducts classification and Causality assessment)
Support regional and district teams in their activities
HO
onitoring
nter

Figure 1: Flow of detection, reporting and investigation of AEFIs during vaccination campaigns in Cameroon

Chapter 2: Rationale and Research Question

Vaccination is one of the health care interventions with the most favorable cost-effective and risk ratios. Vaccines used as the prevention of vaccine-preventable diseases are those that have proven effectiveness and safe in clinical trials and those satisfyingthe WHO criteria for prequalification. Whatever the performances of clinical development phases of a vaccine are, these cannot detect all vaccine-related AEFIs. While it is unrealistic to think that post-registration monitoring can detect all AEFI occurring during this phase, it is recommended that it should detect, report, investigate and respond to all serious AEFIs, cluster AEFI, suspected signal, suspected immunization error and those that cause concern to the community.

In Cameroon, AEFI surveillance is part of the expanded immunization program and pharmacovigilance system but these activities are mainly implemented in vaccination campaigns. Even during these campaigns, available resources are insufficient to adequately cover minimum planned activities. The national laboratory drug quality control is not able to conduct quality assessment of vaccines and diluents.Very little importance and rigor are given to staff's training and results of AEFI surveillance. In routine EPI, about 600,000 pregnant women and more than 800,000 children receive yearly 12 antigens with 9 of these antigens being administered in three doses.Less than 50 AEFIs cases have been reported in EPI for each of the 3 past years and in all of these years neither timeliness nor the completeness was satisfactory.Each year, at least five immunization campaigns are conducted with an estimate of about 15 million doses administered to children, women of child bearing age, and other groups.During these campaigns, underreporting, low completeness, timeliness and investigation rates characterize AEFIs surveillance. So, at the end of a campaign, it is very difficult to conduct proper data analyses and causality assessment and draw conclusions about vaccine safety profile.

The described landscape highlights the need to identify interventions that can help improve performances of AEFI surveillance.We believe that theseinterventions can havea better effect on vaccines pharmacovigilance if ittargetstheoperational level of thehealth system andtheAEFI reporting.

The present PhD was conducted to evaluate the performances of AEFIs monitoring during vaccination campaigns in Cameroon, the safety profile of the new vaccine during immunization

campaign and the effectiveness of efficient supervision of health personnel of sending SMS to health personnel to improve performances of monitoring AEFIs.

The results could be used to improve post registration AEFI surveillance and increase the availability of information on vaccine safety during this phase and the opportunities to properly respond to when needed. The MenAfriVac^{TM}isanewly developed and introduced in Africa.It is known to be safe given itssafety profile described from clinical trials results but verylittle informationisavailable to update itssafety profile since it is being used for immunization campaigns.

The study collected information from avaccination campaignwhich took placein Cameroonin December 2012and frompublished data of the clinical trial phases of the MenAfriVac^{TM}and on safetyof the vaccineduring otherimmunizationcampaigns conducted in the African belt with this vaccine.

The research questions were as follows;

1. What was the safety profile of the MenAfriVac^{TM} vaccine in the vaccination campaign organized in Cameroon in December 2012
2. Does sending a weekly standardized SMS to health workers in charge of AEFI surveillance in health facilities or conducting standardized supervision of these personnel using skilled supervisors result in higher AEFI reporting rates than the routine AEFI surveillance activities (i.e., “no intervention”)?
3. What is the magnitude of the difference in the AEFI reporting rates between clinical trials and vaccination campaigns with MenAfriVac^{TM} vaccine? What are the implications of this magnitude in the safety profile of the vaccine described in immunization campaigns?

Chapter 3: OBJECTIVES

3.1 General objective

To assess the safety profile of MenAfrivac™and identify sustainable interventions that can contribute to improvepharmacovigilance during mass immunization campaign in Cameroon.

3.2 Specific objectives

1. To investigate the safety profile of the vaccine MenAfrivac™ in the mass immunization campaign against meningococcal meningitis organized in Adamaoua and North West Health regions of Cameroun in December 2012
2. to assess the effect on AEFI reporting, after the meningitis vaccination campaigns with MenAfrivac™,of sending a weekly standardized SMS to health workers in charge of AEFI surveillance in health facilities or conducting standardized supervision of these personnel using skilled supervisors
3. To comparethe incidence and distribution of MenAfrivac™AEFIsreported during clinical trial phases to that reported during immunization campaigns

Chapter 4: Methodology

4.1 Study areas

4.1.1 The field phase

The field phase of this study was conductedduring the immunization campaign organized in Adamaoua and North West health regions in Cameroon in December 2012 and January 2013.In 2012**,** the Adamaoua health region had 8 health districts and 73 health areas.In the same period, the North West Health region had 19 health districts and 213 health areas.Figure 2 presents the location of the two targeted health regions on the Cameroon map.

Table II: Distribution of health districts and immunization campaign targeted population in the Adamaoua health region (Source: EPI, MOH, Cameroon)

N°	Health district	Number of health areas	Targeted population
01	Bankim	06	82’643
02	Banyo	07	137’783
03	Djohong	04	61’722
04	Meiganga	11	131’162
05	Ngaoundéré rural	14	167’594
06	Ngaoundéré urbain	04	207’019
07	Tibati	15	156’645
08	Tignère	12	97’472
TOTAL		**73**	1’042’040

Table III: Distribution of health districts and immunization campaign targeted population in the North West health region (Source: EPI, MOH, Cameroon)

N°	Health District	Number of health areas	Targeted population
01	Ako	06	43’210
02	Bafut	13	30’645
03	Bali	06	44’000
04	Bamenda	17	23’072
05	Batibo	13	230’442
06	Benakuma	08	55’272
07	Fundong	11	38’164
08	Kumbo East	19	87’714
09	Kumbo West	19	119’788
10	Mbengwi	16	64’464
11	Ndop	15	37’435
12	Ndu	09	142’298
13	Njikwa	06	56’172
14	Nkambe	14	12’634
15	Nwa	05	84’323
16	Oku	10	40’383
17	Santa	09	60’366
18	Tubah	10	48’916
19	Wum	12	36’870
TOTAL		218	1’218’733

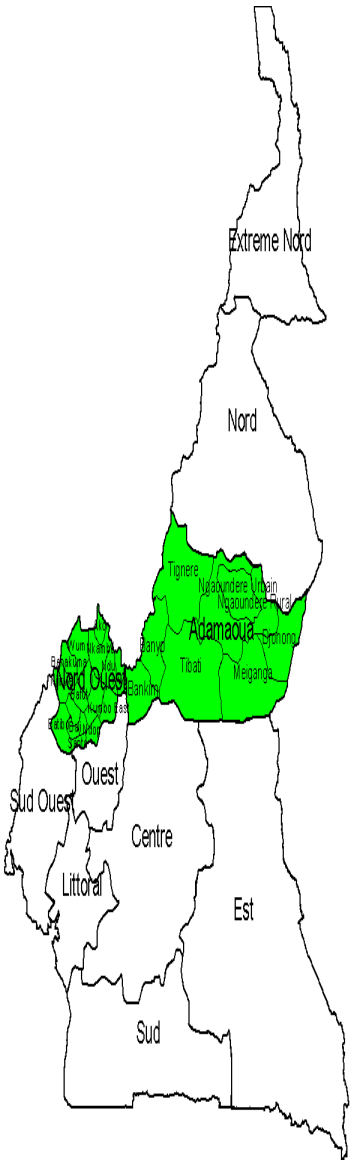
Extreme Nord
Nord
Adamaoua
Nord Ouest
Ouest
Sud Ouest
Centre
Littoral
Est
Sud

Figure 2: Cameroon map highlighting the two Health Regions targeted by the study: The Adamaoua and North West regions.

4.1.2:The Office phase

Preparatory activities and data management were conducted by the Cameroon Ministry of public health in Yaounde at the Departmentof drugs and pharmacy and the Division of Health Operations Research, and by Swiss TPH, Basel, Switzerland. One part of the study involved a systematic review of the safety profile of MenAfriVac^{TM} with information collected from themeningitis vaccine project website,the Medline (PubMed) and Embase data bases.

4.2 Study population anddesign

4.2.1 AEFI incidence and distribution duringMenAfrivac^{TM} immunization campaign in Cameroon

The target population of the study was all persons aged between 1-29years that were vaccinatedin the Adamawa and North West health regions. This population was estimated at 2'054'989 (756’350 in the Adamaoua region and 1 298 639 in the North West region) representing about 70% of the total population.

The detection of AEFI was done athealth facilityand community levels.It was a passive detection with one thirdof the health facilities stimulated through supervision andone third using standardized SMS.The reporting formsof allreported caseswere reviewedusinga validated gridto collect dataon health facility, patient, immunization and AEFI characteristics.

4.2.2 Effects of SMS or supervision on AEFI reporting rates

Officially created and functional health facilities, covered by at least one mobile telephone network with at least one health personnel appointed for AEFI surveillance, were included. Health personnel working in the included health facilities and designated in charge of AEFI surveillance in the MenAfrivac^{TM} campaign were targets of interventions.

The study wasa randomized, controlled trialinvolving threegroups.

i) The SMS group: In which standardized SMS were sent once in English and once in French on weekly basis to AEFIs focal points in health facilities. The ‘’delivery report’ ’function of the mobile phone was used to verify if the message was received and viewed.

ii) Supervision group: each week, a trained nurse (on supervision and AEFI surveillance) visited each health facility assigned to the supervision group on Monday or Tuesday to supervise the focal points of AEFI detection and reporting using a standardized grid. Weaknesses were corrected by supervisors using standardized guidelines. The supervision visits were verified

by checking stamps and signatures of the heads of the health facility on supervisor's mission orders.

iii) The control group: health facilities received no additional AEFI-related interventions apart from what all health facilities normally receive during a vaccination campaign, namely pre-campaign training on AEFIs surveillance, passive AEFI monitoring during the campaign and 42 days after and monthly sensitization of health facility teams during health district coordination meetings.

The endpoint was the AEFI incidence rate.

4.2.3. Comparison of AEFI incidence and distribution between clinical trials and immunization campaigns

This was a systematic review in which all study participants exposed to MenAfrivac^{TM}in clinical trials or immunization campaigns were targeted.

All published studies reporting adverse events following MenAfrivac^{TM} administration during clinical trials and immunization campaigns were searched from the Meningitis vaccine project website, Medline and Embase. Data were selected using a grid on study and participants' characteristics, immunization and surveillance procedures and characteristics of reported AEFIs. The incidence rate (IR) of the general, local, systemic, serious AEFIs and types of reported AEFIs were estimated and compared between clinical trials and immunization campaign studies using the incidence rate difference (IRd).

4.3. Study procedures

Surveillance guidelines and tools were adapted from those developed and used during previous campaigns(38, 65, 71). 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 diluent 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.

During the immunization campaign, baseline information was collected per health facility on the health region, health district, category of health facility (e.g., integrated health center vs. other), and type and position of health professionals designated as the AEFIs focal point. Information on mobile telephone network coverage was also obtained and districts supervisors selected. In addition, the number of AEFIs reported before the interventions were implemented was collected at North West

and Adamaoua Regional Delegations of Public health. During the two-week period following the campaign, districts focal points were trained and assignment of health facilities to intervention groups proceeded. Interventions were implemented and outcomes assessed as described in chapter 6.

For the systematic review, data were extracted using a validated grid from a previous study(26) Data were extracted by one reviewer and compiled in an excel table. A second reviewer cross-checked one by one all extracted data comparing data in the excel table to filled data extraction forms and full texts of articles. In case of discrepancies, corrections were made from the full text article. The following characteristics were extracted from each article: characteristics of the study (study design, year of publication, study country, health care setting, type of resource available, source of the report, name of the first author), characteristic of the study population (size, age group, inclusion criteria, exclusion criteria, number of pregnancies exposed), phase of the vaccine development (phase 1, 2, 3, 4 clinical trials, mass immunization campaign, routine EPI), characteristics of the vaccination (antigen, dose, administration procedure, other vaccine or drugs concomitantly administered, first or second dose), characteristics of the AEFI surveillance system (case definition of AEFI, case definition of serious AEFI, type of surveillance (active, passive stimulated or not), surveillance duration, type of AEFI investigated), characteristics of reported AEFIs [total number, number of serious, number of local reaction, number of systemic reaction, number of AEFIs per age group, number of AEFI per type, number of clusters AEFIs, number and type of AEFIs among pregnant women, number of serious AEFIs investigated, number of vaccine product-related reaction, number of vaccine quality defect-related reaction, number of immunization error-related reaction (formerly “program error”), number of immunization anxiety-related reaction, number of coincidental events].

4.4. Statistical methods

For each objective,data wereextractedeither from AEFIs report forms orfrom published articlesusinga grid.These datawereenteredeither onEpiInfoversion3.5.3orin Excel 2010, crosschecked, cleanedandanalyzedeitherdirectly ortransferred toStata10(Texas,2009)or19IBM SPSSfor analysis.

The MenAfrivac^{TM}safety profile during vaccination campaigns was described by estimatingthe incidence rateof overall and types of AEFIby time after injection, age group and health region. AEFIs symptoms were aggregated in SOC (System Organ Class) and their proportions were estimated and compared per age group, health region, vaccine and diluent batch. This comparison was made firstly by performing unadjusted relative risk with 95% confidence interval. Multivariate logistic regression

was further used to adjust for potential confounding variables. To control MEER (maximum experimentwise error rate) due to multiple testing, p-values were adjusted based on Bonferroni method.

To assess the effects of SMS or supervision on AEFI reporting rates, the incidence rate of reported AEFIs was estimated per study group. The effect of interventions was compared between study groups by estimating the rate ratio (RR) and the risk relationship. The significance of the difference was estimated using the Z test, confidence intervals and p value. Poisson regression model was used to estimate the effect of interventions on reported AEFI on incidence rates, after adjusting for potential confounders, namely the cumulative number of AEFIs reported from Week 1-4, the health region, the type of health facility and position of the health professionals acting as the AEFI focal points

In the study aiming at Comparing AEFI incidence and distribution between clinical trials and immunization campaigns; theincidencesof overall, local, systemic, serious and types of AEFIs were estimated and compared between clinical trial phases and immunization campaignwith MenAfrivac™.The comparison was made by estimating incidence rate difference with 95% IC.

More Details of statistical methods are presented in chapters 5, 6 and 7.

4.3 Ethical consideration

The work was conducted according to the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and the 2008 version of the Declaration of Helsinki.

The confidentiality and privacy of the patients were maintained, as the variables that could lead to their identification in the AEFI source documents were not transferred into the data extraction forms.

In order to fully comply with ethics in clinical research, before being included in a study, all participants (hospital focal points for AEFI surveillance) were informed and consented prior to their inclusion. All studies were approved by the Cameroon National Ethics Committee (approval number: 208/CNE/SE/2012) and the randomized trial was registered into the Pan African Clinical Trial Registry database with a unique identification number PACTR201201000454298 (www.pactr.org).

Chapter 5: Incidence and type of adverse events during mass campaign with a conjugate group a meningococcus meningitis vaccine (MenAfrivac™) in Cameroon

AUTHORs: Jerome ATEUDJIEU, Beat STOLL, Georges NGUEFACK-TSAGUE, Marcellin NIMPA MENGOUO, Blaise GENTON.

ABSTRACT

Purpose

To describe the incidence and type of adverse events following immunization (AEFIs) with a new conjugate vaccine againstmeningitis A (MenAfrivac™)in a Cameroonian vaccination campaign.

Methods

The campaignwas heldin December 2012 and the AEFIs surveillancefrom December-January 2013. This was both a passive and stimulated surveillance. Incidence rates of overall and serious AEFIs were estimated as well as AEFIs incidence rates by type, age group and region. AEFIs symptoms were aggregated in SOC.

Results

Of 2'093'381 persons vaccinated, 1'352 AEFIs were reported. Of these 228 (16.9%) were excluded because they did not meet inclusion criteria.Among the remaining 1'124 (83.1%), the incidence rate was 53.7 AEFIs/100'000 doses administered/8weeks. Of 82 serious AEFIs reported, 52 (63.2%) met the case definition. Twenty-three (28.1%) were investigated, of which 4 (17.4%) were probably related to the vaccination (incidence rate: 0.2 AEFIs/100'000 doses administered/8weeks). Fever was the commonest AEFI with 626 cases (incidence rate: 31.4 AEFIs/100'000 doses administered/8weeks). Proportions of subjects with different primary SOC disorders varied by age group, gastro-intestinal and respiratory being more frequent in children aged <4years and neurological and general conditions more so in adults for example.

Conclusion

This studydid not detect any new safety signal norincreased incidence of seriousAEFIs compared to previous mass immunization campaign withMenAfrivac™**.** There were age differences in incidence and type of AEFIs that are probably related to different background incidence of diseases and different susceptibilities or reporting in these different age groups.

Key words: AEFI incidence, immunization campaign, MenAfrivac™,Meningitis A, Cameroon

BACKGROUND

AEFIs (Adverse Events Following Immunization) 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; 2; 3; 4). Surveillance of AEFIsis thus an integralpart of anyimmunization activity.(32; 90; 91).But expectations are still not met because of underreporting, low completeness, untimelinessand poor data quality (8; 9). Consequently available informationon marketed vaccine safety is limited. A number ofstudiesidentifiedinterventionsandstrategies to improvethe situation(10; 11; 12; 13; 14). More operational research is needed, particularly in Africa, to identify effective interventions for AEFI surveillance performance(15; 16; 17; 18).

Since its introduction in 2010, more than 100 million doses of MenAfrivac^{TM}have been administered to people in10 African countriesofthe meningitis belt by the end of 2012(19). However, published information on AEFIs distribution covers onlyabout 18million people vaccinated(20). Disseminating information onvaccine safetyfor allvaccinated casesis highly recommended as this guides actions aiming at improving safety of the vaccine, and hence overall benefit.

The objective of the present studywas to describe the incidences and type ofAEFIsreported in the 2012 mass immunization with MenAfrivac^{TM}againstmeningitisAin Cameroon.

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 active stimulated AEFIs 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. AEFIs symptoms were aggregated in SOC and their proportions were estimated and compared per age group, health region, vaccine and diluent batch.

Preparatory activities

Members of the AEFI multidisciplinary Monitoring Committee were appointed by the Ministerof Public Health. They updated AEFI surveillance guidelines, ordered necessary supplies, trained central, regional and district supervisors.

Case definition and selection criteria

AEFI case definitions were adapted from those used during previous campaigns(21; 22; 23). Allcases reported from North West and Adamaoua health regions during the surveillance period were

eligible.Cases with a report form lacking record of symptom,date of vaccination orsymptomonset wereexcluded. Caseswith datesofsymptoms onset prior tovaccination and variables with ambiguous, confusing or unintelligible description of symptoms, dates or health districts regions were excluded too.

Surveillance and data collection tools

Surveillance guidelines and tools were adapted from those developed and used during previous campaigns(21; 22; 23). 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 diluent 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 health facility, then district, region and central level. Regions, districts, health facilities and vaccination teams were supervised by supervisors from central, regional and district levels. Regional delegations of public health and district health services were in charge ofreceiving anddistributing surveillanceresources,collecting,compiling and sending AEFI reports to upper levels and 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 cases during consultation and in registers, reporting these cases and investigating serious ones. Focal points of two third of health facilities were stimulated for the last four weeks of surveillance using enhanced supervision or SMS (11).

At the community level, surveillance activities included sensitizing people two weeks before and during the surveillance period to detect AEFI and what to do if it occurs. At this level, AEFIs reporting was conducted by vaccination teams in vaccination sites during the two weeks of the vaccination campaign.

At the central level, weekly meetings of the AEFI monitoring committee were held to review report forms, stimulate reporting, ensure that all serious AEFIs were investigated and causality assessment performed.

Statistical analysis

The AEFIs incidence rate was estimated over a period of 8-week post-injection per 100'000 vaccine doses administered. Overall and serious AEFIs incidence rates were estimated; as were AEFI incidence rates per, type, time after injection, age group, and region. The Medical Dictionary for Regulatory Activities (MedDRA) was used to code and retrieve reported events (24; 25). For each

AEFI, each sign or symptom (low level terms) was assigned to a Preferred Term (PT). The process was implemented by a qualified physician. 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 (25). Each SOC was considered as a dependent variable, and modelled including the following exploratory variables: age group, region, vaccine and diluent batch. A bivariate analysis was performed first using unadjusted relative risk with 95% confidence interval. Multivariate logistic regression was further used to adjust for potential confounding variables. When the variable of interest was one of the above repressors, the others were considered as confounders in the corresponding regression model. The strength of risk in multivariate regression was then quantified using adjusted relative risk with 95% confidence interval. P-values were computed using Chi-squared test; and since age group was ordinal variable, Gamma test of association was used. To control MEER (maximum experimentwise error rate) due to multiple testing, p-values was adjusted based on Bonferroni method (26). Data were entered in Epi-Info version 3.5.3, and analyzed using Stata version 10 and IBM SPSS version 19.

RESULTS

I. Incidence of reported AEFIs

AEFI surveillance activities started with the campaign on December 3, 2012 and ended on January 27, 2013. In total, 2'093'381doses of MenAfrivac^{TM}were reported to have been administered in 27 health districts. Table 4 presents the batches and number of doses of vaccines and diluents used. The 1'352 reported AEFIs included 1'144 (84.6%) from the North West region and 206 (15.2%) from the Adamaoua region. For 2 (0.2%) AEFIs, the region were not specified. Table 5 presents the distribution of reported AEFI per health district and region.

In total228 (16.3%)AEFIswere excludedfor the following reasons: date of vaccination missing (120; 10.5%), date of symptom onset missing (33; 2.9%), no symptom was reported (22; 2.0%), symptom onset was prior to vaccination date (53; 4.7%). 1'124 (83.1%) reported AEFIs were analyzed (53.7 AEFI/100'000 doses administered/8 weeks). Of 1'101 with the gender variable filled, 507 (46.1%) were males and 594 (53.9%) females. Seven (1.2%) AEFIs occurred inpregnantwomen .

Table IV: distribution of number of doses of vaccines and diluents used per batch

Vaccine/diluent batch	Batch number	Number of doses used	Percentage of the total of doses used
Vaccine			
Batch A	127O20100Z	69'410	3
Batch B	127O20110Z	845'500	37
Batch C	127O20120Z	882'310	38
Batch D	127O20130Z	520'180	22
Total		**2'317 '400**	**100**
Diluent			
Batch A	10812006CZ	1'185'720	51
Batch B	10812006BZ	1'131'680	49
Total		**2'317'400**	**100**

Table V: Distribution of reported AEFI per health district and health region

District	Number of doses administered	Number of AEFI reported	Incidence rate/100'000 doses administered/8weeks
Adamaoua			
Bankim	61'686	25	40,5
Banyo	94'704	18	19.0
Djohong	59'605	28	47.0
Meiganga	105'648	6	5.7
Ngaoundere Rural	140'985	26	18.4
Ngaoundere Urbain	164'180	59	35.9
Tibati	114'484	40	34.9
Tignere	71'394	4	5.6
Total	812'686	206	25.4
North West			
Ako	33'528	21	62.6
Bafut	43'058	18	41.8
Bali	16'765	55	328.1
Bamenda	218'561	83	37.9
Batibo	49'803	220	441.7
Benakuma	38'227	62	162.2
Fundong	85'426	36	42.1
Kumbo East	117'033	12	10.3
Kumbo West	68'465	40	58.4
Mbengwi	38'493	16	41.6
Ndop	148'028	14	9.5
Ndu	52'863	11	20.8
Njikwa	13'621	13	95.4
Nkambe	83'230	179	215.1
Nwa	39'993	22	55.0
Oku	55'589	70	125.9
Santa	49'911	20	40.1
Tubah	43'109	24	55.7
Wum	84'992	168	197.7
Health district missing		60	
Total	1'280'695	1'144	89.3

II. Distribution of reported AEFIs

a) Incidence of serious AEFIs reported

AEFIs seriousness was reported for 1’120 (99.6%). Of these, 82 (7.3%) serious AEFIs were reported leading to an incidence rate of 3.9/100’000 doses administered/8weeks. After review by the monitoring committee, 30/82 (36.6%) were considered minor AEFIs. Of the remaining 52 (2.5AEFIs/100’000 doses administered/8weeks), 29 (55.7%) were not assessed for causality because of insufficient information. The vaccine relatedness was thus conducted on 23/52 (44.2%) serious AEFIs among which 4 (incidence rate: 0.2 AEFI/100’000 doses administered/8weeks) were classified as probably related to the vaccine and 19 unrelated (coincidental). The 4 probably related cases included one case of hypersensitivity and 3 cases of anaphylactic shock. The 19 unrelated cases were classified as coincidental.

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

Table 6 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 1’811 (90.9%) systemic reactions, summing up to 1’994. Fever had the highest incidence rate. Some report forms included more than one AEFI type. Figure 3 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 withimmunization activities.

Table VI: Incidence rates of signs and Symptoms 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/8weeks
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 injectedlimb	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	7 7	3.9
Convulsions	18	0.9
Sudden faintness afterinjection	05	0.3
Unconsciousness	4	0.2
Other symptoms	351	17.6
Total	1'811	90.8
Total reported symptoms	1'994	100.0

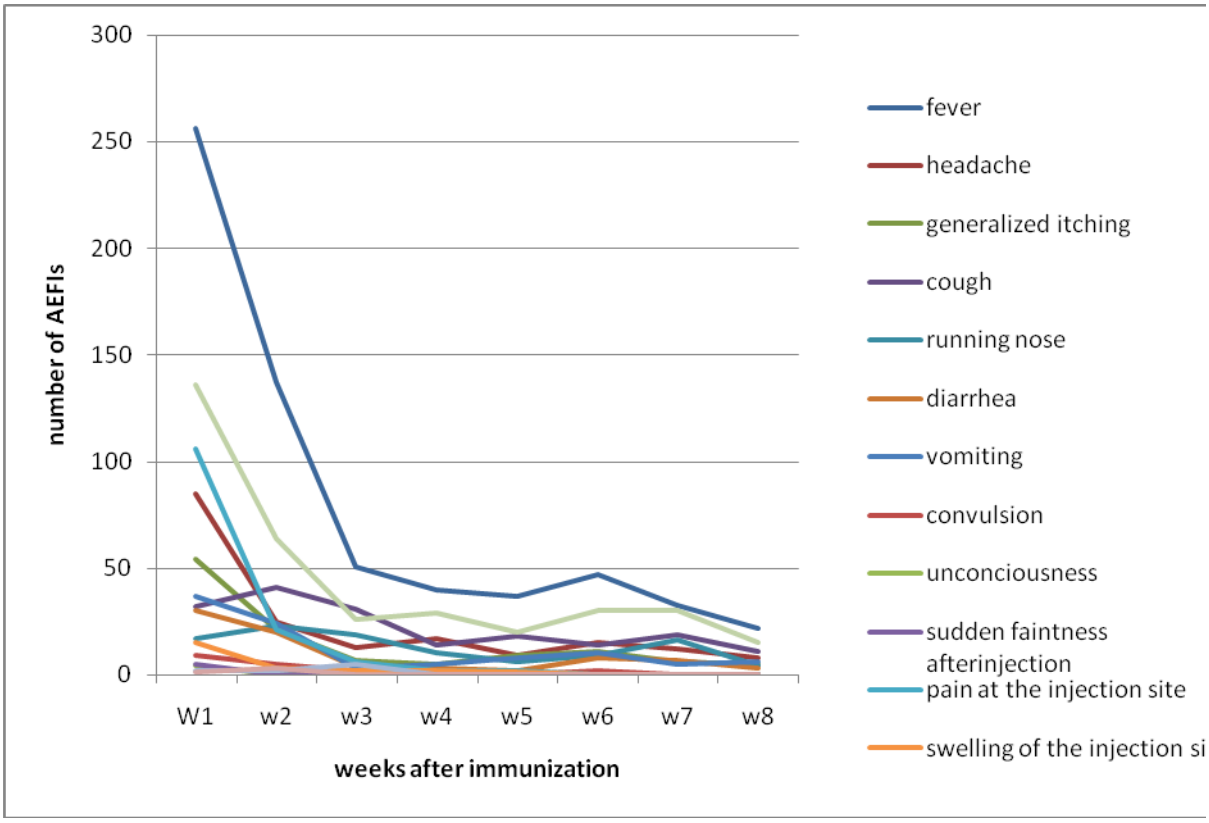

Figure 3: Weekly number of the different types of AEFI during the surveillance period

Legend: W: week

c) Distribution of reported AEFIs categorized by SOC

Table 7 shows the distribution of AEFIs per SOC. The SOC 'infection and infestation' had the highest rate (17.4/100'000 doses administered/8weeks) followed by 'Nervous system disorders' (9.8/100'000 doses administered/8weeks).

Table VII: Incidence of reported AEFIs categorized by SOC

N°	SOC	Frequency	Cumulative incidence /100'000 doses/8 weeks administered
3	Infections and infestations	364	17.4
2	Nervous system disorders	206	9.8
3	Respiratory, thoracic and mediastinal disorders	203	9.7
4	Gastrointestinal disorders	162	7.7
2	General disorders and administration site disorders	139	6.6
7	Immune system disorders	127	6.1
5	Pregnancy, puerperium and perinatal conditions	2 (2/7)	NA*

* 7 cases of pregnancies were reported.

d) Distribution of AEFIs reported per age group

A total 422, 320, 260 and 25 AEFIs were reported in age groups 1-4 years, 5-15 years, 16-29 years and ≥ 30 years respectively. 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 AEFI incidence rate per 100'000 doses administered/8weeks was thus 100.0, 38.8 and 30.6 for age groups 1-4, 5-15 and 16-29 respectively. Taking the age group 1-4 years as reference, the AEFIs incidence rate was lower in age groups 5-15 years [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 5 shows the distribution of AEFIs reported per health district and region. 206 AEFIs were reported in the Adamaoua region for 812'692 doses administered (25.4/100'000 doses administered/8weeks) and 1'144 for 1'280'695 doses in the North West region (89.3/100'000 doses administered/8weeks). The incidence rate of AEFIs for the North West region was higher than that for the Adamaoua [RR=3.6 (2.8-3.8), p<0.0001].

III) Comparison of proportions of AEFIs categorized by SOC reported between age groups

Table 8 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 years than in age group 1-4 years [aRR=0.55(95% CI 0.33-0.91) and 0.47(0.29-0.77) respectively]. The same was true for the proportion of reported 'Respiratory, thoracic and mediastinal disorders' [aRR= 0.47 (0.29-0.74) and 0.19 (0.11-0.33) respectively]. Proportions of 'General disorders' and 'administration site conditions' were significantly higher in age group 16-29 [aRR= 3.00(1.69-5.34)]. Lastly the proportion of 'Nervous System Disorders' was higher in age groups 5-15 and 16-29 years [aRR=2.36 (1.44-3.88) and 2.07(1.28-3.37) respectively].

Table VIII: Comparison of proportions of AEFIs (categorized by SOC) reported per age group.

SOC	Age groups							Total SOC (%)
	[1-4]	[5-15]			[16-29]			
			P-value	Bonferroni adjusted p value		P-value	Bonferroni adjusted p value	
Gastrointestinal disorders								
Number n (n/N%)	85/464 (18.3)	38/343 (11.1)			35/362 (9.7)			158/1'169 (13.5)
RR (95%CI)	1	0.53 (0.35-0.81	0.003		0.43 (0.28-0.65)	<0.001		
aRR (95%CI)	1	0.55 (0.33-0.91)	0.020	0.040	0.47 ((0.29-0.77)	0.003	0.006	
General disorders and administration site conditions								
Number n (n/N %)	25/464 (5.4)	34/343 (9.9)			76/362 (21.0)			135/1'169 (11.5)
RR (95%CI)	1	1.893 (1.10-3.23)	0.020		4.25 (2.64-6.85)	<0.001		
aRR (95%CI)	1	1.64 (0.87-3.12)	0.130		3.00 (1.69-5.34)	<0.001	<0.002	
Infections and infestations								
Number n (n/N%)	146/464 (31.5)	107/343 (31.2)			106/362 (29.3)			359/1'169 (30.7)
RR (95%CI)	1	0.95 (0.7 (0-1.29)	0.740		0.7 (9 (0.58-1.07)	0.130		
aRR (95%CI)	1	1.00 (0.68-1.46)	0.990		0.84 (0.58-1.21)	0.340		
Nervous system disorders								
Number n (n/N %)	44/464 (9.5)	80/343 (23.3)			77 /362 (21.3)			201/1'169 (17.2)
RR (95%CI)	1	2.86 (1.92-4.28)	<0.001		2.34 (1.57-3.49)	<0.001		
aRR (95%CI)	1	2.36 (1.44-3.88)	<0.001	<0.002	2.07 (1.28-3.37)	0.003	0.006	
Immune system disorders								
Number n (n/N %)	36/464 (7 .8)	41/343 (11.9)			44/362 (12.2)			121/1'169 (10.4)
RR (95%CI)	1	1.58 (0.98-2.53)	0.060		1.49 (0.94-2.38)	0.090		
aRR (95%C	1	1.53 (0.85-2.76)	0.160		1.67 (0.96-2.92)	0.070		
Respiratory, thoracic and mediastinal disorders								
Number n (n/N %)	128/464(27.6)	43/343 (12.5)			24/362 (6.6)			195/1'169 (16.7
RR (95%CI)	1	0.36 (0.24-0.52)	<0.001		0.16 (0.10-0.26)	<0.001		
aRR (95%CI)	1	0.47 (0.29-0.74)	<0.001	<0.002	0.19 (0.11-0.33)	<0.001	<0.002	
Total age group (N)	464	343			362			1'169

RR (95%CI): Relative risk with 95% confidence interval; aRR (95%CI): adjusted Relative risk with 95% confidence interval. N: Total age group. n: number of cases categorized by SOC. SOC: System Organ Class. The p value was adjusted using the Bonferroni method after persistence of significance in multivariate logistic regression; the adjusted variables being region, vaccine batch and diluent batch

IV ***Comparison of proportions of AEFIs categorized by SOC between regions and vaccine and diluent batch***

As presented in tables 9, 10 and 11, proportions of AEFIs categorized by SOC did not significantly differbetween regions, vaccine batches nor diluent batches, except for 'Gastrointestinal disorders' which affected more individual cases exposed to diluent batch B compared to batch A [aRR=1.93(1.06-3.51)].

Table IX: Comparison of proportion of AEFI reported per region, categorized by SOC

SOC	Adamaoua	North West		Total SOC (%)
			P value	
Gastrointestinal disorders				
Number n (n/total region (N)%)	19/134 (14.2)	139/1'035 (13.4)		158/1'169 (13.5)
RR (95%CI)	1	0.95 (0.56-1.59)	0.830	
aRR (95%CI)	1	0.08 (0.01-0.57 ()	0.010	
General disorders and administration site conditions				
Number n (n/N%)	38/134 (28.4)	97/1'035 (9.4)		135/1'169 (11.5)
RR (95%CI)	1	0.26 (0.17 (-0.40)	0.000	
aRR (95%CI)	1	0.83 (0.27 (-2.56)	0.750	
Infections and infestations				
Number n (n/N%)	33/134 (24.6)	326/1'035 (31.4)		359/1'169 (30.7)
RR (95%CI)	1	1.43 (0.94-2.17	0.090	
aRR (95%CI)	1	1.65 (0.63-4.33)	0.310	
Nervous system disorders				
Number n (n/N%)	25/134 (18.7)	176/1'035 (17.0)		201/1'169 (17 .2)
RR (95%CI)	1	0.90 (0.56-1.43)	0.650	
aRR (95%CI)	1	0.32 (0.07-1.44)	0.140	
Immune system disorders				
Number n (n/N%)	13/134 (9.7 ()	108/1'035 (10.4)		121/1'169 (10.4)
RR (95%CI)	1	1.09 (0.60-2.00)	0.780	
aRR (95%CI)	1	0.32 (0.07 (-1.44)	0.950	
Respiratory, thoracic and mediastinal disorders				
Number n (n/N%)	6/134 (4.5)	189/1'035 (18.3)		195/1'169 (16.7)
RR (95%CI)	1	4.85 (2.10-11.18)	0.000	
aRR (95%CI)	1	0.24 (0.02-2.79)	0.260	
Total health regions (N)	134	1'035		1'169

RR (95%CI): Relative risk with 95% confidence interval ;aRR (95%CI): adjusted Relative risk with 95% confidence interval. N: Total health region. n: number of cases categorized by SOC . SOC: System Organ Class. The adjusted variables were age group; vaccine and diluent batch.

Table X: Comparison of proportion of reported AEFIs per vaccine batch that were categorized by SOC

SOC	Vaccines batch number		Total SOC (%)						
	Batch A	Batch B			Batch C		Batch D		
			P value	Bonferroni adj. p value		P value		P value	
Gastrointestinal disorders									
Number n (n/N %)	7/44 (15.9)	18/145 (12.4)			67/534 (12.5)		55/385 (14.3)		147/1'108 (13.3)
RR (95%CI)	1	0.78 (0.30-2.01)	0.61		0.82 (0.35-1.90)	0.64	1.08 (0.46-2.54)	0.86	
aRR (95%CI)	1	0.16 (0.03-1.08)	0.06		0.94 (0.18-4.7)	0.94	1.18 (0.22-6.13)	0.85	
General disorders and administration site conditions									
Number n (n/N%)	3/44 (6.8)	43/145 (29.7)			50/534 (9.4)		38/385 (9.9)		134/1'108 (12.1)
RR (95%CI)	1	6.02 (1.77 -20.49)	0.01		1.51 (0.45-5.06)	0.50	1.81 (0.53-6.12)	0.34	
aRR (95%CI)	1	2.22 (0.41-12.14)	0.36		0.51 (0.10-2.44)	0.40	0.91 (0.18-4.51)	0.91	
Infections and infestations									
Number n (n/N %)	16/44 (36.4)	37/145 ((25.5)			17/534 (0 (31.8)		118/385 (30.6)		341/1'108 (30.8)
RR (95%CI)	1	0.63 (0.31-1.30)	0.21		0.90 (0.47 -1.7)	0.7	1.00 (0.52-1.91)	0.99	
aRR (95%CI)	1	0.64 (0.19-2.17)	0.24		0.51 (0.10-2.44)	0.27	0.58 (0.20-1.69)	0.32	
Nervous system disorders									
Number n (n/N%)	3/44 (6.8)	26/145 (17 (.9)			94/534 (17.6)		7/385 (1.8)		194/1'108 (17.5)
RR (95%CI)	1	3.11 (0.90-10.82)	0.07		3.14 (0.95-10.35)	0.06	3.81 (1.15-12.65)	0.03	
aRR (95%CI)	1	0.7 (6 (0.13-4.65)	0.7		2.13 (0.42-10.65)	0.36	1.98 (0.38-10.25)	0.42	
Immune system disorders									
Number n (n/N%)	8/44 (18.2)	16/145 (11.0)			57/534 ((10.7 ()		39/385 (10.2)		120/1'108 (10.8)
RR (95%CI)	1	0.58 (0.23-1.47)	0.25		0.58 (0.26-1.30)	0.19	0.62 (0.27 -1.42)	0.25	
aRR (95%CI)	1	0.96 (0.15-6.03)	0.96		0.85 (0.18-4.00)	0.83	1.42 (0.29-6.95)	0.68	
Number n (n/N %)	7/44 ((15.9)	5/145 (3.5)			96/534 (18.0)		64/385 (16.6)		70/1'108 (15.5
RR (95%CI)	1	0.20 (0.06-0.66)	0.01		1.25 (0.54-2.88)	0.60	1.30 (0.55-3.04)	0.55	
aRR (95%CI)	1	0.07 ((0.008-0.7 (0)	0.02	0.06	1.84 (0.39-8.70)	0.45	1.02 (0.21-5.13)	0.97	
Total vaccine batch nuber (N)	44	145			534		385		1'108

RR (95%CI): Relative risk with 95% confidence interval; aRR (95%CI): adjusted Relative risk with 95% confidence interval. N: total vaccine batch. n: number of cases categorized by SOC. SOC: System Organ Class. The p value was adjusted using the Bonferroni method after persistence of significance in multivariate logistic regression; the adjusted variables being age group; region, and diluent batch.adj: adjusted

Table XI: Comparison of proportion of reported AEFIs per diluent batch that were categorized by SOC

SOC	BATCH A	BATCH B		
			P value	Total SOC (%)
Gastrointestinal disorders				
Number n (n/N %)	32/281 (11.4)	7/530 (13.2)		110/811 (13.6)
RR (95%CI)	1	1.44 (0.93-2.24)	0.10	
aRR (95%CI)	1	1.93 (1.06-3.51)	0.03	
General disorders and administration site conditions				
Number n (n/N %)	42/281 (14.9)	56/530 (10.6)		98/811 (12.1)
RR (95%CI)	1	0.7 (2 (0.47-1.10)	0.13	
aRR (95%CI)	1	1.48 (0.78-2.83)	0.23	
Infections and infestations				
Number n (n/N %)	81/281 (28.8)	17/530 (31.1)		252/811 (31.1)
RR (95%CI)	1	1.29 (0.94-1.7 (7 ()	0.12	
aRR (95%CI)	1	1.10 (0.7 (5-1.62)	0.61	
Nervous system disorders				
Number n (n/N %)	51/281 (18.2)	89/530 (16.8)		140/811 (17.3)
RR (95%CI)	1	0.98 (0.67-1.43)	0.90	
aRR (95%CI)	1	1.08 (0.67 (-1.7 (3)	0.7 (4	
Immune system disorders				
Number n (n/N %)	34/281 (12.1)	54 /530 (10.2)		88/811 (10.9)
RR (95%CI)	1	0.88 (0.56-1.39)	0.58	
aRR (95%CI)	1	0.82 (0.47-1.42)	0.47	
Respiratory, thoracic and mediastinal disorders				
Number n (n/N %)	41/281 (14.5)	82/530 (15.5)		123/811 (15.2)
RR (95%CI)	1	1.15 (0.7 (6-1.73)	0.50	
aRR (95%CI)	1	0.7 (3 (0.46-1.17)	0.19	
Total diluent batch (N)	281	530		811

RR (95%CI): Relative risk with 95% confidence interval aRR (95%CI): adjusted Relative risk with 95% confidence interval. N: Total diluent batch. n: number of cases categorized by SOC. SOC: System Organ Class. The adjusted variables were age group, region, and vaccine batch.

DISCUSSION

The overall incidence rateofAEFIs, reported during the mass immunization campaign against meningitis A held in Cameroon in 2012 was 53.7AEFI/100'000 doses administered/8weeks). It was 3.9 AEFI/100'000 doses administered/8weeks for serious AEFIs with four (0.2 AEFI/100'000 doses

administered/8weeks) classified as probably related to the vaccine. The incidences and types of AEFIs varied according to age group and region.

The estimated incidence rate ofAEFIswashigher in this campaign than in previous ones organized in Cameroon or in other countries using the same vaccine(21; 22; 27; 23). There are several possible reasons for that: i) suboptimal vaccine storage conditions or administration procedures, ii) coincidental epidemic illnesses during the campaign surveillance period, or iii) improvedmonitoring system. Vaccinesused werepre-qualified by the WHOand this was confirmed by the competent departmentsof the Ministry ofPublic HealthofCameroon. Cold chain, vaccine transport and administration procedures were closely supervisedand no irregularity was reported(28). Thus the high incidence of AEFIs was unlikely due to vaccine quality or program errors. Noepidemicwasreportedin any of the targeted regions that could have increased the incidenceofAEFIs. The high incidence rate ofAEFIin this campaign was thus morelikely due to the improvementof the detection and monitoring system. Indeed,unlike othercampaigns, two thirds ofhealth facilitiesinvolved inthis campaignwerestimulated to report AEFIs weekly during thelast fourweeks of the surveillance by supervising the health personnel concerned, and sending SMSto AEFIs focal pointsin health facilities(11). This reporting enhancement contributed to an increase in AEFI reporting rate in the second half of themonitoringperiodduring which the rateis oftenlow. Interventions contributing to improve AEFIs reporting rates should bepromoted during immunization activities in order to improve thesensitivityof the surveillance and the likelihoodto detectnew AEFIs andall seriousAEFIsones.

The incidence rate of seriousadverse eventsreported was in thesame rangeas that in previousstudies. However, less than a thirdof these caseswere investigated because either they did not meetthe case definition or they lackednecessaryinformationto be appropriately assessed. The proportion of coincidental cases(82%)was similar to that reported during campaigns inBurkina Faso and Mali (29). Four cases including one case of hypersensitivity reaction and three cases of anaphylactic shock were probably related to the vaccine based on the case definition, time lapse after immunization, time window of increased risk, the favorable course after adrenaline administration, the biological plausibility and exclusion of other causes. These cases were allergic reactions, as reported in previous studies (29). Information on these caseswas rather limited; they werereported based on symptoms by the vaccination teamsthat were notin a position toperform athorough clinical examination because of the emergency of the situation.

Regarding AEFIs types, reported local reactions were minorwiththe highest incidence duringthe first week ofsurveillance and the lowest (zero) after week 4 post-immunization(Figure 1). Incidence rate was higher than that observed during previous campaigns but lower than that recorded during

clinical trials., Indeed, monitoring oflocal reactionsis importantsince it allowsearly detection and prevention of some program errors and somaintains populationadhesion to immunization. (22; 21; 32; 30; 31; 23). Regarding systemic reactions, fever wasthemost frequenteventin our studyfollowed byheadache andrunning nose. Thefrequencies and ranking of the different types ofAEFIs were not always the samein previous campaigns. Feverwas the commonestsystemic symptomreportedfortwo out of three campaigns and the secondfor the last onewhileheadachewas the first symptomreported foroneout of three campaignsand thesecondin one out of three(23; 22; 21; 32; 30; 31).The type of AEFI, thetemporarysequenceof their occurrence after vaccination,and the course with a gradual decline over the eight weeks of surveillance suggest that a given proportion of thesesymptoms and signs was probably related tovaccination.

Standardization of procedures to aggregate reported events in medically meaningful groupings is essential totrace AEFIsin vaccines clinical development and marketed phase, among different manufacturers, andto shareinformationbetween actors involvedinthesafety of vaccines. We aggregated reported AEFIs in SOCs following MedDRA(25; 24). To the best of our knowledge, no previous study has presented reported AEFIs following administration of the vaccine MenAfrivac^{TM}in SOCs**.** Proportions of 'Gastrointestinaldisorder' and 'Respiratory, thoracic and mediastinal disorders' reported in age group1-4years were higher than in older age groups. Thiscan be explained by the higher background incidence of diarrhea and cough inyounger children.

The incidence of AEFIs reported from theNorth Westregion was at leastthreetimes higher than in theAdamaoua. Similarly,the incidence rate was about 100 times higher in Batibo Health Districtthan 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 unequalspatialdistribution of reported AEFIshas already been observedin other countries ((33; 22; 21). Information onthe geographic distribution ofreported AEFIis necessaryto monitorsurveillance activities.Areas with low reporting rate should be stimulatedto do better by adopting good practices. The low AEFI reporting rate in the Adamaouaregion can be explained by thelimited geographical accessibility ofhealth facilities and different health seeking behavior(28; 34; 35). Thistrend has also been observed for other health outcomes. For example, results of the 2011 national health demographic survey shows that only 46% of women delivered in a health facilityin theAdamaoua Regionwhile this percentage was93% intheNorthWest one (35). One of the possible responses to this low reporting rate could be the establishment of acommunity-based AEFIs surveillance which has been proven to improve AEFI reporting rate(36).

The interpretation of the above findings should be taken with some caution since up to16% of reported AEFIs and 55% of serious ones could not be analyzeddue tolowcompleteness

orincoherentdata. The number of persons vaccinated was not detailed in days or weeks and could not allow to estimating AEFI incidence rate per week.

CONCLUSION

Theincidence rates of overall and serious AEFIsreported from the vaccination campaign against meningococcalmeningitisAheld inCameroonin December2012 were higherthan inpreviouscampaigns, probablybecause of the intensified monitoring system put in place. Theincidencedeclined over the surveillance period and varied according to age group, health districts and regions. The distribution of theseAEFIsand review ofpreviousdataon MenAfrivac^{TM}safety supports the assumption that a given fractionof theseAEFIswas probably related to immunization. The present assessment did not detect any newserious AEFI and did not note any increase in serious AEFI rate compared to previous mass immunization campaign withMenAfrivac^{TM}. This supports the large-scale use of this vaccine to prevent meningitis A epidemics and mortality in Africa.

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

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Acknowledgements

We sincerely thank:

- The country WHO office of Cameroon and Cameroon Ministry of Public Health who financially supported from the immunization campaign budget, the budget for the study implementation;
- The Cameroon based NGO: M.A. SANTE (Meilleur Accès aux soins de Santé) / BAHCARE (Better Acces to Health Care) that funded trips during the manuscript drafting;
- NJIMBIA CHEBE Anthony who contributed in editing this manuscript

Chapter 6: Vaccines safety; effect of supervision or SMS on reporting rates of adverse events following immunization (AEFIS) with meningitis vaccine (MenAfrivac™): a randomized controlled trial

Abstract

Authors: Jérôme ATEUDJIEU, Beat STOLL, Georges NGUEFACK-TSAGUE, Christophe TCHANGOU, Blaise GENTON

Background. To ensure vaccines safety, given the weaknesses of the national pharmacovigilance system in Cameroon, there is a need to identify effective interventions that can contribute to improving AEFIs reporting.

Objective.To assess the effect of: i) sending weekly SMS, or ii) weekly supervisory visits on AEFI reporting rate during a meningitis immunization campaign conducted in Cameroon in 2012 using the meningitis A conjugate vaccine (MenAfriVac™).

Methods. Health facilities that met the inclusion criteria were randomly assigned to receive: i) a weekly standardized SMS, ii) a weekly standardized supervisory visits or iii) no intervention. The primary outcome was the reported AEFI incidence rate from week 5-8 after the immunization campaign. An intention-to-treat approach was used to assess outcomes. All missing values were crosschecked and data were retrieved from the regional delegations by the study teams before data entry. The incidence rate of reported AEFIs was estimated per study group. The effect of interventions was compared between study groups by estimating the rate ratio (RR) and the attributable risk. The significance of the difference was estimated using the Z test, confidence intervals and p value. The Poisson regression model was used to estimate the effect of interventions on reported AEFI on incidence rates, after adjusting for potential confounders, namely the cumulative number of AEFIs reported from Week 1-4, the health region, the type of health facility and position of the health professionals acting as the AEFI focal points. Data were entered in epi info version 3.5.3 and analyzed using Stata version 10(Texas, 2009) and IBM SPSS 19. The level of confidence of our estimates was 95%.

Results

A total of 348 (77.2%) of 451 health facility wereincluded, and 116 assigned to each of three groups. The incidence rate of reported AEFIs per 100 health facility per week was 20.0 (15.9-24.1) in the SMS group, 40.2 (34.4-46.0) in supervision group and 13.6 (10.1-16.9) in the control group. Supervision led to a significant increase of AEFI reporting rate compared to SMS [adjusted RR=2.1 (1.6-2.7;

p<0.001] and control [RR=2.8(2.1-3.7); p<0.001)] groups. The effect of SMS led to some increase in AEFI reporting rate compared to the control group, but the difference was not statistically significant [RR =1.4(0.8-1.6); p=0.07)].

Conclusion

Supervision was more effective than SMS or routine training in improving AEFI reporting rate. It should be part of any AEFI surveillance system. SMS could be useful in improving AEFI reporting rates but strategies need to be found to improve its effectiveness, and thus maximize its benefits.

Registration number: PACTR201201000454298

Key words: SMS, supervision, AEFI surveillance, immunization campaign, meningitis, Cameroon.

BACKGROUND

The major goal of immunization safety surveillance is to detect and respond appropriately to Adverse Events Following Immunization (AEFIs) in order to reduce its potential negative impact on the success of immunization programmes (17).

An AEFI is medical incidence occurring after immunization and believed to be caused by immunization (2). Types, seriousness and frequency of AEFI depend on the product and the medical history of the vaccine recipient (3; 4). AEFIs are susceptible to cause minor or serious harm to individuals, as well as negatively affect to the national immunization program, including a reduction in the population's use of the program (5). During vaccination campaigns, risk of AEFIs occurring is higher since a very large number of people are vaccinated at the same time and rumors can have damaging consequences on vaccine uptake (6; 7).

In Cameroon, AEFI surveillance is an integral part of the EPI (8). It is part of the national pharmacovigilance system which is based in the Directorate of Pharmacy, Medicine and Laboratories (9). Weaknesses in this system include insufficient motivation and training of personnel at different levels; limited coordination and resources; and low AEFI and ADR (Adverse Drugs Reactions) reporting, investigation, completeness and timeliness rates. The system is implemented within routine EPI activities but is much more active and supported during immunization campaigns. For example, all immunization campaigns conducted in the last four years included AEFI surveillance (10; 11). Reports from these activities highlighted the same weaknesses as the national pharmacovigilance activities as well as a positive effect of supervision on these parameters. For example, during a yellow fever immunization campaign that took place in 2009 in 62 health districts in Cameroon, 362 AEFIs were reported, including 53 serious cases. Ninety-two of the cases or 25% of all reported AEFIs were detected as a result of supervision conducted in only 20% of the target

health districts during the last week of AEFI surveillance. These included eight serious cases (28.8% of all serious AEFIs reported).

Supervision is the standard recommended intervention in Cameroon to ensure that AEFIs monitoring, reporting, and cases investigation take place (8). However, the efficiency of supervisionis limitedsince it requires a lot of resources in terms of personnel, coordination, funding and logistics to sustainably contribute to the monitoring of field activities (12; 13; 14). Short Messages Services (SMS) has been shown to improve health outcomes among patients in African countries by increasing health workers' adherence to guidelines (15; 16; 17). It is thereforea potentially valuable tool to remind health professionals to identify and report AEFIs. The coverage of mobile phone networks in Cameroon was estimated in 2011 to be more than 90% (18).

This paper describes research conducted in conjunction with meningitis A immunization campaign that took place from 3rd -16th December 2012 in two health regions in Cameroon (Adamaoua and North West) that are part of the African belt (19). The campaign used the new conjugate vaccine against group A Meningococcus (**MenAfriVac™**) produced bySerum Institute of India. This vaccine has been shown to be efficacious and extremely safe (132; 133; 134; 135).

The aim of the study was to assess the effect on AEFI reporting, after the meningitis vaccination campaigns, of sending a weekly standardized SMS to health workers in charge of AEFI surveillance in health facilities or conducting standardized supervision of these personnel using skilled supervisors. We hypothesized that either of these interventions would result in higher AEFI reporting rates than the routine AEFI surveillance activities (i.e., "no intervention").

METHODS

Registration

The study was approved by the Cameroon National Ethics Committee and registered in the Pan African Clinical Trial Registry (www.pactr.org) database with PACTR201201000454298 as the unique identification number.

Study design.

The study used an open randomized controlled design with three arms. All health facilities that were registered in health districts targeted in the 2012 meningitis A campaigns and that met the inclusion criteria were randomly assigned to receive: i) a weekly standardized SMS asking them to report all medical events occurring during the intervention period in persons immunized during the campaign, ii) a weekly standardized supervisory visit by trained health district focal points for AEFI detection

and reporting processes, or iii) no intervention besides routine training and sensitization of health facility teams during health districts coordination meetings (the control group). The primary outcome was the incidence of AEFIs per 100 health facilities per week reported to the Regional Delegation of Public Health. Informed consents of all health workers were obtained after the nature and possible consequences of the studies had been fully explained to them.

Participating health facilities

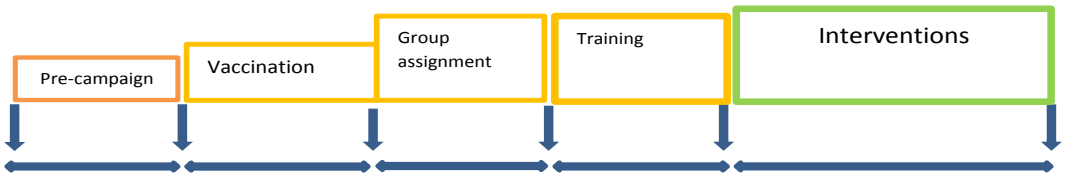
Inclusion criteria for health facilities in the study included the existence of at least one health professional appointed or accepting to be the health facility focal point for AEFIs during the meningitis A campaign surveillance period, their ownership of a mobile telephone and their commitment to be present during the study period. Non-functional health facilities, those not covered by at least one of national mobile telephone networks, those with AEFI focal point who expected to be absent for at least one week or during one of interventions were excluded from the study.

The study targeted health facilities that were officially registered in all 27 health districts of the health regions of Adamaoua (8 health district) and North West (19 health districts). The official document mapping out Cameroon's health facilities indicates that there were 468 health facilitiesin these two health regions in 2011, including 136 in the Adamaoua region, and 332 in the North West region (24).

Interventions

Pre-intervention procedures

Field activities conducted in all health districts before intervention are shown in Figure 4.



Period	November 26-28, 2012	December 03-16, 2012	Dcember18-25, 2012	December 27-28, 2012	December 31, 2012 to January 28, 2013
Field activities	Training of all personnel involved in AEFI surveillance	-Vaccination, -Routine AEFI Surveillance -Informed consent and enrollment of Health personnels and Health workers	enrolment of health facilities and randomized allocation of interventions - Routine AEFI Surveillance	Trainings of supervisors and pre-testing of interventions -Routine AEFI Surveillance	-Weekly sending of SMS -Weekly supervision -Routine AEFI Surveillance -Follow up of research interventions

Figure 4: Flow diagram of field activities during the implementation of the study

Interventions

iv) SMS: Mobile phone numbers of AEFIs focal points in health facilities in the SMS groups were cross-checked by calling each owner. Messages to be sent were taped, crosschecked and saved onto a mobile telephone. Each week for four consecutive weeks, standardized SMS were sent to all AEFIs focal points in the SMS group at 8:00 a.m. on Monday in one language (French or English) and on Tuesday in the other language (the order was alternated from one week to the other) to all AEFIs focal points in SMS health facility group at 8:00 AM. The content of the messages was the same each week and included a reminder of the MenAfriVac™ AEFI surveillance period, case definition of an AEFI and a recommendation to actively detect and report all occurring AEFI on a daily basis. The ‘’delivery report’ ’function

of the mobile phone was used to verify if the message was received and opened.

v) Supervision: Each week, a nurse trained in supervision and AEFI surveillance visited on Monday or Tuesday each health facility to supervise the focal point on AEFI detection and reporting using a standardized grid. This grid included structured questions to check if the supervisee had included AEFI surveillance in his or her daily time table and if he/she knew the AEFI case definition, the AEFI surveillance period, how to detect and report a case and what to do with a serious AEFI case. Weaknesses were corrected by supervisors using standardized guidelines. The supervisory visits were verified by checking the stamps and signatures of the head of the health facility on supervisor's mission orders.

Control

Health facilities in the control group received no additional AEFI-related interventions apart from what all health facilities normally receive during a vaccination campaign, namely pre-campaign training on AEFIs surveillance, passive AEFI monitoring during the campaign and 42 days after and monthly sensitization of health facility teams during health district coordination meetings.

Outcomes

The primary outcome was the incidence rate of reported AEFIs per 100 health facility per week during the intervention period, (Week 5-8 after immunization (31 December 2012 to 27 January 2013). The numerator was the sum of reported AEFIs and the denominator was the number of health facilities multiplied by the number of weeks of the intervention. The secondary outcome was the reported incidence rate of serious AEFIs.

For each health facility, baseline information was collected on the health region, health district, category of health facility (e.g., integrated health center vs. other), and type and position of health professionals designated as the AEFIs focal point. In addition, the number of AEFIs reported before the interventions were implemented was collected at North West and Adamaoua Regional Delegations of Public health.

Sample size

The sample size calculation was based on the test of the null hypothesis that there is no difference between supervision or SMS on AEFI reporting rate compared to no intervention. The level of significance was set at 0.05 with 2-tailed test. The sample size was calculated using the WHO publication on Sample Size Determination in Health Studies (25). Assuming equal numbers of health facilities in each of the three groups, 150 health facilities or 50 per group were needed to give 80% power to detect a 5% increase in reported AEFI per health facility per week. To account for a

compliance rate of 80% and 20% drop-out rate, the sample size was increased to 300 health facilities.

Randomization

Health districtsthat had health facilities included in the study wereranked in alphabetic order from A to Z using the filter function of Excel 2010. The health facilities were also ranked in the same order per health district. All its key variables (health region, health district, type of health facility, type and position the focal point) except its name were hidden during the assignment process. The facilities were then randomly assigned to the SMS, supervision and control arms in blocks of three following a 1:1:1allocation ratio. All combinations of blocks were listed and a number assigned to each combination. Numbers were generated from Table XXXIII of Fisher and Yates(26) as follow: an arbitrary starting point was chosen in the table and from that point; numbers were read row by row across pages.

Statistical analysis

An intention-to-treat approach was used to assess outcomes. All missing values were crosschecked and data were retrieved from the regional delegations by the study teams before data entry. The incidence rate of reported AEFIs was estimated per study group. The effect of interventions was compared between study groups by estimating the rate ratio (RR) and the risk relationship. The significance of the difference was estimated using the Z test, confidence intervals and p value. The Poisson regression model was used to estimate the effect of interventions on reported AEFI on incidence rates, after adjusting for potential confounders, namely the cumulative number of AEFIs reported from Week 1-4, the health region, the type of health facility and position of the health professionals acting as the AEFI focal points. Data were entered in epi info version 3.5.3 and analyzed using Stata version 10(Texas, 2009) and IBM SPSS 19. The level of confidence of our estimates was 95%.

RESULTS

Recruitment, participants' flow and baseline data

During the first half of December 2012, a total of 451out of 468 registeredhealth facilities (96.4%) in the two health regions were visited and asked to participate in the study. One hundred and three (22.8%) were excluded, including 39 (37.9%) in the Adamaoua and 64 (62.1%) in the North West health regions. Reasons for exclusion included absence of a cell phone networks (77 (74.8%), the health facility was non-functional (21 (20.4%)) and other reasons (5(4.9%)). A total of 348 (77.2%) health facilities were included, and 116 were assigned to each of three groups. Three health facilities, including two in the SMS group and one in the supervision group, withdrew before the interventions started because the health professionals selected to receive intervention were not

available and could not be replaced. Figure 5 shows the enrolment and assignment processes of health facilities in the flow in the study. Table 12 shows the characteristics of health facilities and health professionals by study groups.

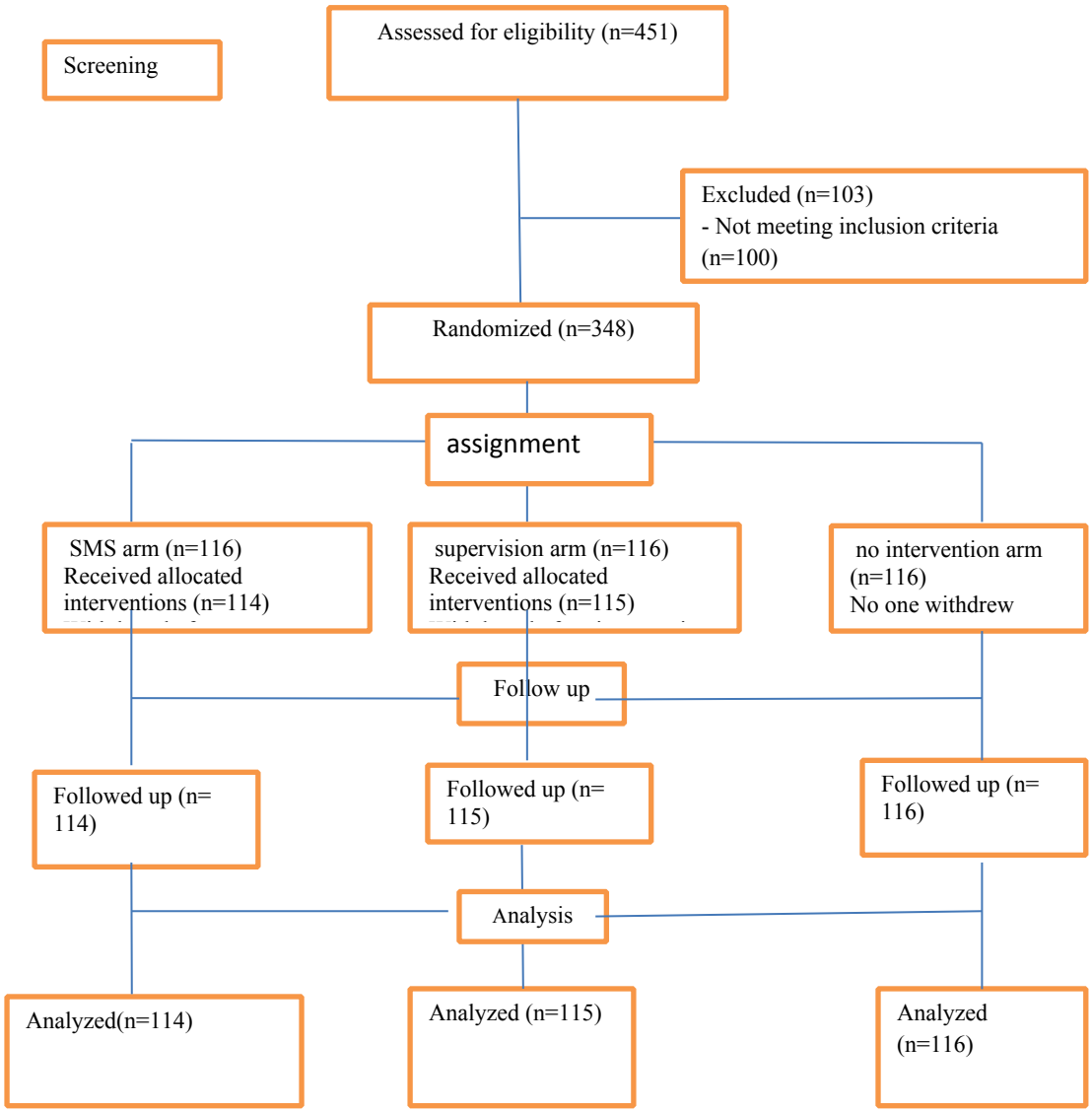

Screening
Assessed for eligibility (n=451)
Excluded (n=103)
- Not meeting inclusion criteria (n=100)
Randomized (n=348)
assignment
SMS arm (n=116)
Received allocated interventions (n=114)
supervision arm (n=116)
Received allocated interventions (n=115)
no intervention arm (n=116)
No one withdrew
Follow up
Followed up (n= 114)
Followed up (n= 115)
Followed up (n= 116)
Analysis
Analyzed(n=114)
Analyzed (n=115)
Analyzed (n=116)

Figure 5: Flow diagram of the study

Table XII: Characteristics of health facilities and Health professionals included in the study, by intervention group

Characteristics	Total		SMS group		Supervision group		Control group		
	n	%	n	%	n	%	n	%	P value
Health facilities									
By region									
North West region	263	76.2	87	33.1	87	33.1	89	33.8	0.980
Adamaoua Region	82	23.8	27	32.9	28	34.2	27	32.9	0.980
By type of health facility:									
Integrated Health Centers	231	66.9	79	34.2	74	32.0	78	33.8	0.870
Other health facilities	114	33.1	35	30.7	41	36.0	38	33.3	0.700
Health personnel									
By position within the facility:									
Head of integrated health centers	216	62.6	79	36.6	72	33.3	65	30.1	0.360
Other position in the health facility	129	37.4	35	27.2	43	33.3	51	39.5	0.110
By types of health professional									
Nurses	325	94.2	107	33.0	110	33.8	108	33.2	0.970
Other	20	05.8	7	35.0	5	25.0	8	40.0	0.590

Outcomes and risks estimation

Figure 6 presents the evolution of the number of AEFI reported before intervention (weeks 1-4) and during intervention period (weeks 5-8) in the different groups. During the intervention period, 339 AEFIs were reported from participating health facilities, including 91 from the SMS group, 185 from the supervision group, and 63 from the control group. The number of health facility -weeks observed was 456 in the SMS group, 460 in the supervision group and 464 in the control group. The incidence rates of reported AEFI were 20.0 (15.8-24.1) AEFIs per 100 health facilities per week in the SMS arm, 40.2 (34.4-46.0) in the supervision arm and 13.6 (10.1-16.9) in the control arm.

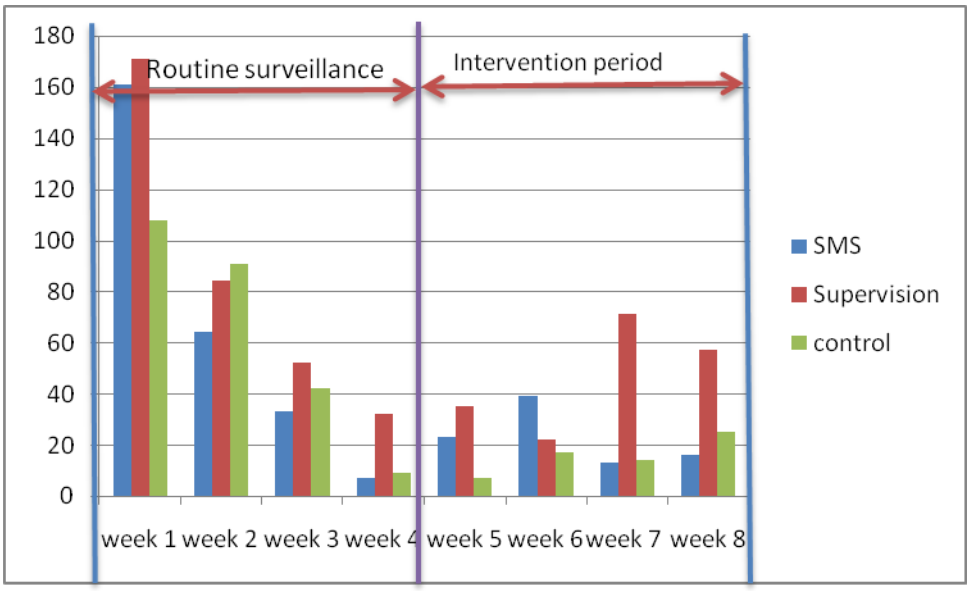


Figure 6: Number of AEFI reported before the interventions (Week 1-4) and during the intervention period (Weeks 5-8) in the different intervention groups

The crude incidence rate of AEFI reporting rates of the interventions groups compared to the control groups is shown in Table 13 The incidence rates of reported AEFIs in SMS and supervision groups were superior to that of the control group. The AEFI reporting rate in the supervision group was also superior to that in the SMS group. The attributable risk of AEFIs reporting per 100 health facilities per week in the SMS and supervision groups compared to the control group were 6.38 (0.1-12.8) and 26.6 (9.9-33.3) respectively. This rate in the supervision group compared to the SMS group was 20.3 (13.3-27.3).

Table 14 presents the incidence rates of the interventions groups compared to the control group after adjustment for the cumulative number of AEFI reported during the four weeks prior to the intervention, the health region, type of health facility, and type and position of thehealth professionals serving as AEFI focal points. The incidence rate of reported AEFIs in SMS group was superior but not statistically different to that of the control group [RR =1.4 (0.8-1.6; p=0.070)], while

the incidence rate of reported AEFIs in supervision group remained significantly superior to that of the SMS [adjusted RR=2.1 (1.6-2.7; p<0.001] and control group [RR=2.8 (2.1-3.7; p<0.001)].

A total of 17 serious AEFIs were reported during the intervention period including seven from the SMS, 9 from the supervision and 1 from the control groups. This resulted in incidence rate of 1.53 serious AEFIs per 100 health facility per week in the SMS group, 1.95 in the supervision group and O.22 in the control group.

Table XIII: Crude incidence (RR) rate comparing AEFI reporting rates of the interventions groups to that of the control group using simple Poisson regression.

Group	RR	95% IC RR	P value
SMS	1.5	(1.1-2.0)	0.022
Supervision	2.9	(2.2-3.9)	<0.001
Control	1		

Table XIV: Adjusted rate ratios comparing outcomes in interventions groups to that of the control group using multiple Poisson regression

Group allocation	**RR**	**95% IC RR**	**P value**
Groups			
SMS	1.4	(0.8-1.6)	0.07
Supervision	2.8	[2.1-3.7)	<0.001
Control	1		
Regions			
Adamawa	0.3	(0.2-04)	<0.001
North west	1		
Type of health facility			
Integrated health centers	1.6	(1.2-2.2)	<0.001
District and other hospitals	3.1	(2.0-4.9)	<0.001
Private health center	1		
Type of health professional receiving the intervention			
Nurses	3.7	(1.0-9.8)	0.024
Lab technician	4.9	(1.3-18.0)	0.017
Other health professionals	1		

Health professionals' position

Head of health facility	2.0	(1.5-2.7)	<0.001
Not heading the health facility	1		
Cumulative number of AEFI reported prior to the interventions (Weeks 1-4 following immunization)	1.04	(1.04-1.06)	<0.001

AEFI: Adverse Events Following Immunization.DISCUSSION

Results of this study show thatweekly supervision of health professionals in charge of AEFI surveillance in health facilities significantly improved the reporting rate compared to sending standardized SMS to these health professionals or to the standard practices. Sending SMS to remind health professionals about AEFI surveillance improved AEFIs reporting rates compared to the control group but not significantly. This studyis unique in that it is the first measure the effects of supervision and SMS on AEFI reporting rate.

A benefit of supervision in increasing AEFIs reporting rate, timeliness and completeness of AEFI reporting have already been observed during previous AEFI surveillance conducted following immunization campaigns in Cameroon (10). These results are also in line with other studies of different health activities that showed benefits of supervision in improving job satisfaction, knowledge, skills and performances of health workers (13; 27; 28). Unlike recommended in someguidelines, weekly supervision was done bynurses who were not superior to those they were supervising in terms of rank or qualifications (i.e., peers), but who were well trained andhadtimeand resourcesto do their job properly. The supervision was interactive, and included responses to knowledge gaps. Thus, it was expected to not only remind supervisees about AEFI reporting, but also to improve their ability to detect and report AEFIs. This approach has been shown from previous studies to be more efficient and less costly, as well as to have a broader reachthan routine supervision typically conducted on a less frequent basis by higher level health personnel who are not necessary trained to supervise the tasks in question (27; 29; 30)

The fact that the effect of weekly SMS on AEFI reporting rates was not statistically different to that of control group does not mean that SMS has no effect on AEFIs reporting. Our study, in fact, showed that the rates of reporting serious AEFIs were quite similar in the supervision and SMS groups and both much higher than in the control group. A beneficial effect of SMS on AEFI reporting has been shown in Cambodia, but the study lacked acontrol group(31)**.** Studies conducted in various settings of the efficacy of SMS in improving health care delivery have had varying results (32; 16; 33). Optimal circumstances and strategies for the use of SMS to remind health workers about AEFIs reporting are still to be clearly defined (34; 35). The SMS in this study were designedto remind

thetargeted health workers about the AEFIcase definition, the surveillance period, and the reporting process, with the expectation thatall suspected AEFI cases would be reported and all serious cases investigated. The fact thatthere wasno interactionbetween thesender and receiversof the SMS could have contributed to reduce the effectiveness ofSMScompared to face-to-facesupervision.Receiving, reading and understanding aSMSmay not necessarilylead to the expected response, especially if the personreceiving itis notconstrained ormotivatedto do so. Previous studies have reported high response rate among health professionals after having incentives added to the SMS reminder although this optionraises the question ofsustainability when implemented in a routine program(36; 37).

Supervision is already recognized as a useful intervention when successfully integrated into health activities and programs (40; 41; 42; 27; 39). However, its effects are often below expectations because of the limitations of the health system to conduct it properly (41). The concern is not only to determine how to set up supervision to make it more efficient, but also to identify the most efficient interventions that can replace or be associated with it in order to improve the monitoring of health interventions. One of the interesting findings of the present study is that it has shown that nurses can supervise other nurses on AEFI reporting at the district level. Further studies could be designed to evaluate the effectiveness and efficiency of different supervision strategies on AEFI reporting at all levels of the health system. It could also be useful to compare the efficiency of using nurses as peer supervisors to that of more typical supervision strategies using supervisorsofhigher level professionalsand to determine the circumstances in which SMS can help to improve AEFI monitoring. Other interventions and modes of delivery could be tested such as sending letters, using incentives, sensitizing vaccinated populations using mobile phones or the internet, and training that have been shown to improve health program performance (43; 44; 45; 46; 47).

Though health facilities participating in this study were sampled from only two of the ten health regions of Cameroon, the characteristics and distribution of these health facilities and the health professionals working in them were similar to those in Cameroon as a whole (38; 31). This suggests that our findings are applicable to the country as a whole and to other health systems with similar characteristics (39).

This study has some limitations. Data on some important variables that could have been included in the regression model to adjust for confounding were not collected. These included number of newpatient visits made during theintervention periodperhealth facility and the immunization coverage rate of the population served by the health facility. The number of patient visits was not collected because patient registration forms and procedures are not standardized in the participating health facilities. The immunization coverage rate was not collected since immunization

activities were conducted both in health facilities and communities and reported per health area, but not per health facility. In addition, the completion rate of AEFI reporting formswas very lowand some important variables such as, the date of consultation, were missing on the forms. These weaknesses didnot allow us to estimate some important parameters of AEFI surveillancesuch as promptness and identification of all serious AEFIs.

CONCLUSION

The results of this study show that weekly supervision of health professionals in charge of AEFI surveillance in health facilities significantly improved the AEFI reporting rate compared to sending standardized SMS to these health professionals or to routine AEFI-related activities. Sending weekly standardized SMS to remind health professionals on AEFI surveillance improved only slightly overall AEFI reporting rate. This study also demonstrates that it is feasible to effectively supervise health staff at the district level using nurses. Ifthis approach can be confirmed to be sustainable over time, it should be scaled up to improve themonitoring health programmes and activities in Cameroon and in other countries with similar health system.

We recommend that when planning AEFI surveillance during vaccination campaigns, supervision should be included as an intrinsic part of the program. Strategies need to be identified to improve the effectiveness of supervision to maximize its benefits. More work needs to be done to determine whether regular SMS can contribute to improvements in the rate of AEFI reporting, and if so, how and in which circumstances the impact can best be achieved. Other interventions such as alternating SMS and supervision or sending SMS to the vaccinated persons or their parents should also be tested.

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Acknowledgements:

We sincerely thank:

- The country WHO office of Cameroon and Cameroon Ministry of Public Health who financially supported field activities
- The Swiss Foundation for Excellence and Talent in Biomedical Research who funded trips during the manuscript drafting
- Denise DeRoeck to have edited this paper

Chatter 7: Safety profile of the meningococcal conjugate vaccine (MenAfrivac™) in clinical trials and vaccination campaigns: a systematic review

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ABSTRACT

Background

Adverse event following immunization (AEFI) surveillanceis requiredin allphases of vaccines development. However, the rigor inthe implementation of thisrequirement differs fromclinical trialphases to mass immunizationcampaigns.

Objective

To compare the AEFIs incidence between clinical trials and vaccinationcampaignswith the new conjugate meningitisAvaccine (MenAfrivac™).

Methods

This is a systematic review ofstudieson MenAfrivac™ safety in clinical trialsandvaccination campaigns. The search was conducted for the period 2001-2014 in English in the meningitis vaccine project website and by consulting the list of publications in Medline (PubMed) and Embase (Ovid) using following terms: ''meningococcal meningitis A''AND ''conjugate vaccine'' AND ''safety'' in

Medline; ''*meningococcus*'' OR ''*Neisseria meningitidis* group A'' AND ''conjugate vaccine'' AND ''safety'' in Ovid. AEFIs incidence rates (IR) were estimated and compared between MenAfrivac™ clinical trials and immunization campaigns and incidence rate difference (IRd) is reported.

Results

Seven studies were included from 6 publications including 4 clinical trials and 3 immunization campaigns. The overall AEFI IR was 4.6 (4.5-4.7) per 100'000 doses administered per week. In clinical trials studies, the IR per 100'000 doses administered per week of overall, local, and systemic AEFIs were 10'047, 11'499, and 17'248respectively. Pains at the injection site had the highest IR among local reactions and diarrhea the highest IR of systematic reactions. In immunization campaigns, the IR per 100'000 doses administered per week, for overall, local, and systemic AEFIs were 4.0, 0.59, and 3.12 respectively. The highest IR among local reactions was pain at injection site and among systematic reactions fever. None of 10 serious AEFIs reported during clinical trials was related to the vaccine. Of 41 serious AEFIs reported during immunization campaigns, 5 were probably related to vaccine. IR of AEFIs were thus higher in clinical trials than in immunization campaigns studies, the difference (IRd) for overall AEFIs being of 10043 (95% CI 10042-10044) per 100'000 doses per week, for local of 11'498 (11'498-11'498), for systemic of 17'245 (17'245-17'245)] and for serious AEFIs of 1.55 (1.54-1.56). The AEFI IR decreased by more than 99.9% for overall, local, systemic and serious AEFIs from clinical trials to immunization campaigns.

Conclusion

As expected, the incidence of AEFIs after MenAfrivac™ vaccination was lowerin mass immunization campaigns than in clinical trials studies. The magnitude of the difference was huge. Although the objective of pharmacovigilance is not to identify all minor AEFIs, sustainable strategies mustbe developed to improve the detection and reporting of significant AEFI during mass immunization campaigns in order to have an accurate picture of vaccine safety, and potentially identify program errors.

Key words: MenAfrivac™ safety, AEFI surveillance, clinical trials, immunization campaign,

BACKGROUND

In clinical trials, themonitoring of vaccines anddrugs safety is mandatory and harmonized. Assessing vaccine's safety is the mainobjectiveofphase Iclinical trials but the number ofparticipantsislimited and does not allow the detection of rareadverse events(1). The gradual increase insample size of participants inphases 2, 3, and 4clinicaltrials remains suboptimal todetect rare adverse events following immunization 'AEFIs)compared tothe marketed phase of vaccines(2; 3).

Post-licensure surveillance of AEFIs is expected to improve vaccines safety by detecting and investigating new, rare, program errors or delayed-onset AEFI not detected in pre-licensure clinical trials or when new vaccine schedules are adopted (4; 5). Itprovides useful informationto anticipate orrespond to public concernsabout the safety ofvaccinesand thus contributes inincreasingthe adherence of thepublicto vaccination(5; 6). Thecurrently publishedstudies indicate thatAEFIs surveillanceisbelow expectationsdue toweaknessessuch as lowdetection, reporting and investigation rates(7; 8; 9; 10). Comparing thegeographical distribution ofAEFIsurveillance dataprovided usefulinformation to monitorvaccinessafety and to map some weaknesses of AEFIs surveillance systems(11). The comparisonof the incidence and type ofAEFI collected during vaccine clinical development phases and post-marketing surveillance, and an estimation of the magnitude of the difference could be useful to evaluate the amount of rare AEs that are missed in clinical trials as well as the amount of AEs that are not considered sufficiently important to be reported by either vaccinees themselves or health professionals during immunization campaigns or routine implementation.

ThePSA-TT vaccine (MenAfrivac™) was developedtorespond to MeningococcalmeningitisA outbreaks ragingin more than 21African countries(12). Clinical trials phases of the vaccine showed the vaccine to be safe and effective (13; 14; 15). It was thus licensedin India in 2009 andpre-qualified by WHOa year later(12). Fromits introduction inBurkina Fasoin 2010 to 2012,10African countries have beentargetedby vaccination campaigns,immunizingmore than 100million individuals(12). AEFI surveillance has been part of these campaigns and its results have been published in three countries (16; 17; 18; 19).

With an aim to contribute in providing useful information for better planning and monitoring of AEFIs surveillance activities during MenAfrivac™campaigns, this study has as objective to comparethe incidence and distribution of AEFIsreported during clinical trial phases to that reported during immunization campaigns.

Our hypotheses were that i) AEFIs incidence gradually decreasefrom Phase 1toPhases 2, 3, 4 and vaccinationcampaign due to the factthat AEFIs surveillance progressively loses its place as central question over thesephases; ii) fromphase 1tophases 4 clinical trials and to vaccination campaigns, thenumber of peoplevaccinatedgradually increases, the immunized population is thus diversifiedand allows the detection of rareseriousAEFI and eventually AEFI that only occur in specific populations; moreover conditions ofstorage and useof the vaccine areless likely to be complied to,predisposing toa potentialincrease ofAEFIs incidence.

METHODS

2.1**.** Study design

A review was conducted to identify all published studies reporting adverse events following MenAfrivac**™** administration during clinical trials and immunization campaigns. The incidence rate (IR) of overall, local, systemic, serious and types of reported AEFIs were estimated and compared between clinical trials and immunization campaigns studies using the incidence rate difference (IRd).

2.2. Study settings

Studies conducted in all sites were included.

2.3. Study population

Were included studies reporting adverse events following immunization with meningococcal group A conjugate vaccine from male and female subjects aging 1 to 35 years old. These were age groupstargeted byclinical trials andvaccination campaigns MenAfrivac™.

2.4. Literature search

Theliterature searchwasbased onthreestrategies that included:

i) Safety information from the web site of meningitis vaccine project

The web site of the meningitis vaccine(20) project was accessed to collect reports and references of studies reporting AEFIs in clinical trials and in mass immunization with MenAfrivac™. For full text of reports missing in this website, the search was conducted by its title or first author's name in Medline (PubMed) and Embase (Ovid).

ii) Systematic search in Medline (PubMed) and Embase (Ovid)

A systematic literature search was conducted in PubMed and Ovid using the following combinations: ''meningococcal meningitis A''AND ''conjugatevaccine''AND ''safety'' in Medline; and

''meningococcus'' OR "Neisseria meningitidis group A'' AND ''conjugate vaccine'' AND ''safety'' in Ovid.

iii) Consultation of article references

An additional manual search was conducted in reference lists of eligible articles. The search was conducted from February 15th 2015 to March 17th 2015.

2.5. Eligibility criteria

Were eligible, phase 1, 2, 3 clinical trials studies, and mass immunization campaigns studies reporting AEFIs after exposure to MenAfrivac™.

2.6. Selection criteria

Were included: studies in English language and reports published from 2001 (when the MenAfrivac™ was launched) to 2014, reporting AEFIs following exposure to the vaccine MENAFRIVAC™.Study participants exposed to MAfrivac™ were included. The definition of AEFI was based on the WHO definitions (21; 1).

Were excluded: **i)** unpublished reports**,** reports not published in peer reviewed scientific journal, ii) publications reporting AEFIs following concomitant exposure of participants to MenAfrivac™and anothervaccine or drugs; iii) duplicates (case where more than one publication reports AEFIs from the samepopulation overthe same period); iv) publications with AEFIs reported in preclinical phase of MenAfrivac™development; v) publicationsforwhich the full textwas not available;and vi) abstractsofconferences. Were also excluded participants to whom the vaccine administered was not done following manufacturer dose, administration or storage procedures.

The selection was conducted by two reviewers independently, following a two-step process: first, assessing the title and abstract, and second, assessing the full text, using the selection criteria. All disagreements were resolved by consulting full text of articles.

2.7. Data extraction

A data extraction grid used fora previous study was adapted (11). Data were extracted by one reviewer and compiled in an excel table. A second reviewer cross-checked one by one all extracted data comparing data in the excel table to filled data extraction forms and full texts of articles. In case of discrepancies, corrections were made from the full text article. The following characteristics were extracted from each article: characteristics of the study (study design, year of publication, study country, health care setting, type of resource available, source of the report, name of the first

author), characteristic of the study population (size, age group, inclusion criteria, exclusion criteria, number of pregnancies exposed), phase of the vaccine development (phase 1, 2, 3, 4 clinical trials, mass immunization campaign, routine EPI), characteristics of the vaccination (antigen, dose, administration procedure, other vaccine or drugs concomitantly administered, first or second dose), characteristics of the AEFI surveillance system (case definition of AEFI, case definition of serious AEFI, type of surveillance (active, passive stimulated or not), surveillance duration, type of AEFI investigated), characteristics of reported AEFIs [total number, number of serious, number of local reaction, number of systemic reaction, number of AEFIs per age group, number of AEFI per type, number of clusters AEFIs, number and type of AEFIs among pregnant women, number of serious AEFIs investigated, number of vaccine product-related reaction, number of vaccine quality defect-related reaction, number of immunization error-related reaction (formerly "program error"), number of immunization anxiety-related reaction, number of coincidental events].

2.8. Outcomes

The primary outcome was the incidence rate difference (IRd) of overall AEFIs between clinical trials and mass campaign studies. Secondary outcomes were the IRd comparing local, systemic, serious and types of AEFIs between clinical trials and mass campaign studies.

2.9. Quality assessment

To assess the methodological quality of studies, we assessed procedures of participants' selection, the adopted cases definition of AEFIs, procedures of AEFIs detection, reporting and investigation. The quality assessment was independently conducted by two reviewers. Any discrepancy was resolved through discussions.

2.10. Data analysis

IR per 100'000 doses administered per week of overall, local, systemic, and serious and types of AEFIs in clinical trials and mass campaigns were estimated. The numerator of the incidence rate was the sum of cases of AEFI reported and its denominator, the sum of persons exposed to the vaccine multiplied by the duration of follow up. AEFI IRs in clinical trials were compared to that of post registration phases by estimating the IRd and its 95% confidence interval. Data were entered in Microsoft excel 2010 analyzed using the same software and Stata version 10 (Texas, 2009).

RESULTS

3.1. Study selection

The search identified 123 titles including 53 (43.1%) from the Meningitis Vaccine Project (MVP) web site, 58 (47.2%) from Medline, 10 (8.1%) from Ovid and 2 (1.6%) from references of articles. After duplicates were removed, 108 titles and abstracts were screened of which 9 full texts were selected and 6 included in the study. Three were excluded because presenting too aggregated summaries on reported AEFIs (22; 23; 24). Figure 7 presents details of selection process. In total 11'476'276 doses of MenAfrivac™ including 1'190 in clinical trials and 11'475'086 in immunization campaigns were reported in included articles to have been administered following manufacturer recommendations.

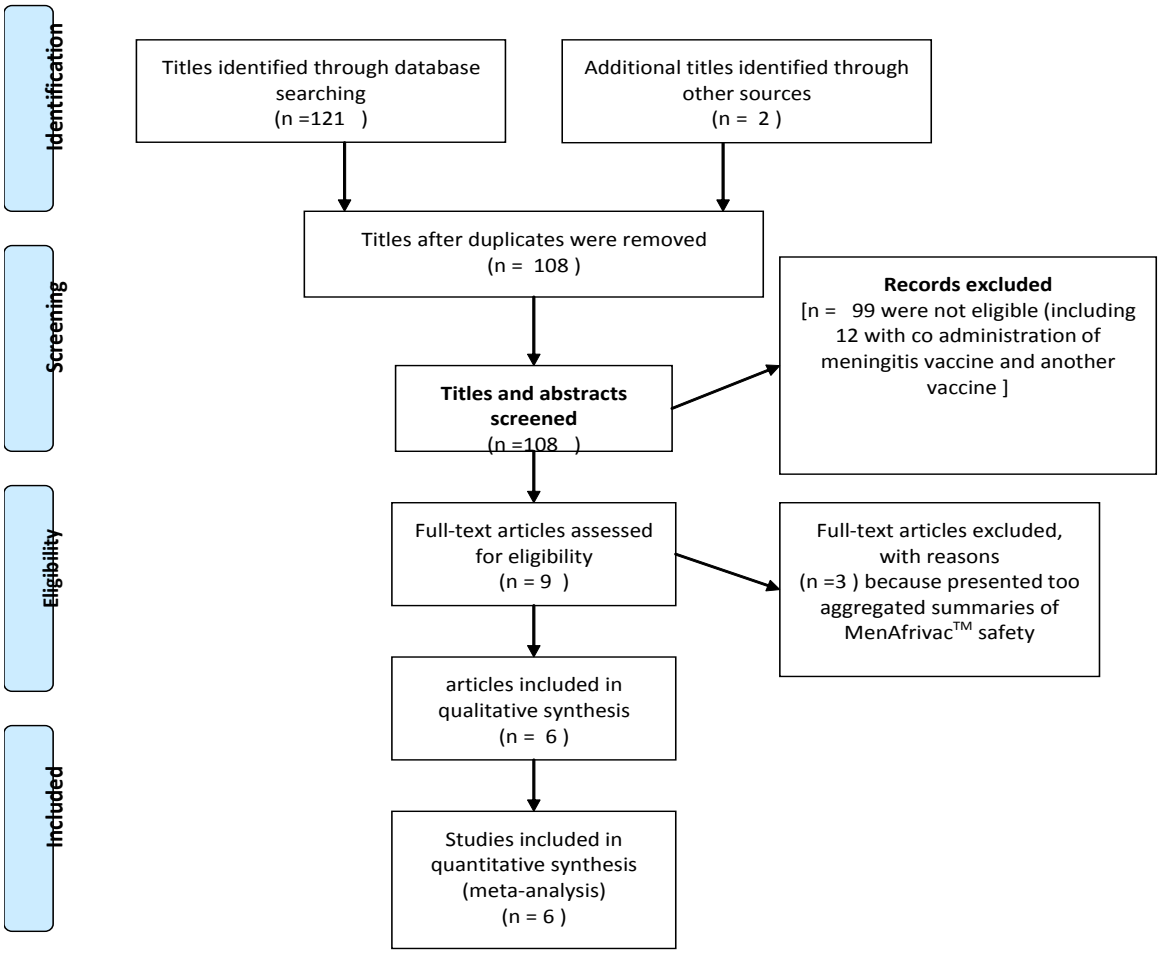

Figure 7: Flow diagram of the study selection

3.2. Study characteristics

Characteristics of included articles are presented in Table 15. Three articlesreported clinicaltrialsand included4studies (13; 15; 14); two articles reported two studies on AEFI surveillance during immunization campaign and one article reported a phase 4 field trial study assessing MenAfrivac^{TM} safety when delivered in a controlled temperature chain(18; 17; 25). Characteristics of AEFIs surveillance are presented in Table 16.

Table XV: Characteristics of included studies

Author: year of Publication; country (reference)	Study period	Region/ or site	Phase of vaccine development	Age group (years)	Number of persons exposed to PsA-TT	Dose of PsA-TT administered	Number of administered doses per person	Vaccine manufacturer
Kshirsagar, 2007, India (13)	2005-2006	King Edward Memorial (KEM) Hospital, Mumbai; (2) Nizam's Institute of Medical Sciences, Hyderabad; (3) BYL Nair Charitable Hospital, Mumbai.	phase I clinical trial	18-35	24	0.5 ml	One	Serum Institute of India Ltd.
Sow; 2011; Gambia, Mali Senegal (14), (A)	2006-2009	Centre pour le Développement des Vaccins in Bamako, Mali ; Medical Research Council ; Laboratories in Basse, Gambia and ; Institut de Recherche pour le Développement in Niakhar, Senegal	Phase II clinical trial	1-2	201 exposed to primary dose and 192 exposed to booster	0.5 ml	primary vaccination and booster	Serum Institute of India Ltd.
Sow; 2011; Gambia, Mali Senegal (14), (B)	2007-2009	Centre pour le Développement des Vaccins in Bamako, Mali ; Medical Research Council ; Laboratories in Basse, Gambia and ; Institut de Recherche pour le Développement in Niakhar, Senegal	Phase II-III clinical trial	2-29	604 exposed including 203 in age group 2-10, 202 in age group 11-17, and 199 in age group 18-29	0.5 ml	One	Serum Institute of India Ltd.
Hirve ; 2012; India (15)	2007-2008	Shirdi Sai Baba Hospital, Pune, India	Phase II-III clinical trial	2-10	169	0.5 ml	One	Serum Institute of India Ltd.
Maman; 2012; Niger (17)	September–November 2010.	Niger, the district of Filingué,	Post registration (immunization campaign)	1-29	356'532	0.5 ml	One	Serum Institute of India Ltd.
Ouandaogo, 2012, Burkina Faso (18)	September –December 2010	The whole country	Post registration (immunization campaign)	1-29	11'117'555	0.5 ml	One	Serum Institute of India Ltd.
Steffen; 2014 ; Benin (25)	November –December 2012	Four villages in Banikoara (vaccine use in CTC[1]) and four villages in Kandi (vaccine in recommended ranged of cold chain)	Post registration (Phase IV)	1-29	1000 in CTC and 999 in the non-CTC group	0.5 ml	One	Serum Institute of India Ltd.

[1:] CTC: controlled temperature chain (exposing vaccine at temperatures of up to 40°C for up to four days)

Table XVI: Characteristics of AEFI surveillance

Study	Did case definition of minor AEFI comply with WHO guidelines	Did case definition of serious AEFI comply with WHO guidelines	Was the case detection active(a) or passive (b) or both (c)	Did allvaccinated persons have the same probability to be detected in case of AEFI	Was the reporting procedure standardized	Were serious AEFI investigated	Who was in charge of serious AEFI investigation	What was the total duration in days of AEFI surveillance for each person exposed
Kshirsagar 2007 (13)	Minor AEFI not defined	Serious AEFI not defined	c	Yes	Yes	Yes	Research team	Observed for 3h after vaccination, actively followed up for 7 days for solicited reaction, 28 for unsolicited reactions, 365 for serious AEFIs
Sow 2011(A) (14)	Minor AEFI not defined	serious AEFI not defined	c	Yes	Not described	Yes	Research team	28 days including 30mn observation and 4 days active monitoring, 280 days for serious AEFI and 450 for serious after booster
Sow 2011(B) (14)	Minor AEFI not defined	serious AEFI not defined	c	Yes	Not described	Yes	Research team	28 days including 30mn observation and 4 days active monitoring, 280 days for serious
Hirve: 2012 (15)	Minor AEFI not defined	serious AEFI not defined	c	Yes	Yes	Yes	Research team	28 AEFI surveillance including 30 mn observation after vaccination, 4 days active monitoring, 365 surveillance of serious AEFIs
Maman 2012 (17)	Yes	Yes	b	No (case detection was health facility-based and access to health facility was not presume to be equal for all people vaccinated)	Yes	Yes	The Committee in charge	42 days
Ouandaogo 2012 (18)	Yes	yes	c	No (case detection was health-facility based and access to health facility was not presume to be equal for all people vaccinated)	yes	Yes	The Committee in charge	42 days
Steffen 2014 (25)	Minor AEFI not defined	serious AEFI not defined	c	Yes	Not described	Yes	The Committee in charge	5 days

3.3 Incidence of AEFI in clinical trials and in immunization campaign studies

IR of overall AEFI in clinical trials and immunization campaigns studies are presented in table 17 The AEFI IRs of clinical trials, mass immunization campaigns and overall were 10’047.0 (10’046-10’048), 4.0(3.9-4.1) and 4.6 (4.5-4.7) AEFIs per 100’000 doses administered per week respectively

Table XVII: Incidence rate (IR) of overall reported studies in clinical and campaign studies

Study	Vaccine development phase	Number of AEFIs reported	Number of doses administered	Duration of AEFIS surveillance in days	Duration of surveillance in persons week	IR (number of AEFI per 100’000 doses administered per week)
Kshirsagar 2007 (13)	phase 1clinical trial	27	24	7	24	112’500.0
Sow 2011(A) (14)	Phase 2 clinical trial	179	393	28	1’572	11’387.0
Sow 2011(B) (14)	Phase 2-3clinical trial	110	604	28	2’416	4’553.0
Hirve: 2012 (15)	Phase 2-3 clinical trial	155	169	28	676	22 928.9
Total clinical trials		**471**	**1’190**		**4’688**	**10’047.0**
Maman 2012 (17)	Phase 2-3 clinical trial	356	356’532	42	2’139’192	16.6
Ouandaogo 2012 (18)	Post registration (immunization campaign)	2’008	11’466’950	42	68’801’700	2.9
Steffen 2014 (25)	Post registration (immunization campaign)	439	999	5	713,57	61’522.0
Total campaign studies	Post registration (Phase 4)	2’803	11’824’481		7’0941’606	4.0
Overall clinical trials and campaign studies		3’274	11’825’671		70’946’294	4.6

AEFI incidence in clinical trials

For the majorityof clinical trials, details on the type of AEFIs were available onlyforthe 4-7 days ofsurveillance;thus,onlythis period wastaken into accountin estimating IR of AEs per type and characteristics (local or systemic) in clinical trials studies. Table 18 presents AEFI IR in clinical trials studies. The IR per 100'000 doses administered per week, of local and systemic AEFIs were 11'499, and 17'248 respectively. The highest IR among local AEFIs was for pain at injection site and among systematic AEFIs was diarrhea.

AEFI incidence in mass vaccination campaigns

The IRs of AEFIs reported during studies in vaccination campaigns are presented in table 19 In immunization campaigns, the IR per 100'000 doses administered per week of local and systemic AEFIs were 0.59, and 3.12 respectively. The highest IR among local reactions was for pain at injection site and among systematic for fever.

Table XVIII: Incidence of different types of AEFIs following Menafrivac™ in clinical trials studies

AEFI type	Kshirsagar 2007 (13)		Sow 2011(A) (14)		Sow 2011(B) (14)		Hirve: 2012 (15)		Overall		
	Number of cases reported	Time of surveillance in person week (1)	Number of cases reported ((2)	Time of surveillance in person week	Number of cases reported (2)	Time of surveillance in person week	Number of cases reported (2)	Time of surveillance in person week	Number of cases reported	Time of surveillance in person week	Incidence rate (number of AEFI per 100'000 doses administered per week)
Pain at the injection site	18	24	17	225	30	345	Ag[1]	676	65	1'270	5'119
Induration/ redness injection site	3	24	17	225	7	345	Ag[1]	676	27	1'270	2'126
Swelling injection site	2	24	0	225	0	345	Ag	676	2	1'270	158
Abcess	0	24	0	225	0	345	0	676	0	1'270	0.00
Total local reaction	**23**	**24**	**34**	**225**	**37**	**345**	**52**	**676**	**146**	**1'270**	**11'499**
Fever	0	24	13	225	18	345	0	676	31	1'270	2'441
Headache	1	24	0	225	45	345	0	676	46	1'270	3623
convulsion	0	24	0	225	0	345	0	676	0	1'270	0.00
Cough	0	24	0	225	0	345	0	676	0	1'270	0.00
Running nose	0		0	225	0	345	0	676	0	1'270	0.00
Vomiting	0	24	7	225	8	345	0	676	15	1'270	1'181
Diarrhea	0	24	40	225	6	345	0	676	46	1'270	3'623
Loss of appetite	0	24	14	225	1	345	0	676	15	1'270	1'181
Irritability	0	24	4	225	0	345	0	676	5	1'270	315
Asthenia	1	24	0	225	10	345	0	676	11	1'270	866
Pruritus	0	24	0	225	0	345	0	676	0	1'270	0.00
Sudden fainting	0	24	0	225	0	345	0	676	0	1'270	0.00
Myalgia	0	24	0	225	3	345	0	676	3	1'270	236
Arthralgia	1	24	0	225	2	345	0	676	3	1'270	236
Other	1	24	0	225	0	345	0	676	1	1'270	79
Total systemic	**4**	**24**	**78**	**225**	**93**	**345**	**44**	**676**	**219**	**1'270**	**17'248**

(1): Considered duration of surveillance; 7 days; (2): Considered duration of surveillance: 4 days; Ag: aggregated

Table XIX: Incidence of types of AEFIs following Menafrivac™ in vaccination campaign studies after 42 days surveillance

AEFI type	Maman 2012 (17)		Ouandaogo 2012 (18)		Steffen: 2014 (25)		Overall		
	Number of cases reported	Time of surveillance in person week	Number of cases reported	Time of surveillance in person week	Number of cases reported	Time of surveillance in person week	Number of cases reported	Time of surveillance in person week	Incidence rate (number of AEFI per 100'000 doses administered per person week)
Pain at the injection site	4	2'139'192	Ag	68'801'700	155	714	159	70'946'886	0.22
Induration injection site	0	2'139'192	Ag	68'801'700	11	714	11	70'946'886	0.00
Swelling injection site	0	2'139'192	0	68'801'700	0	714	0	70'946'886	0.03
Abscess	7	2'139'192	16	68'801'700	2	714	25	70'946'886	0.04
Total local reaction	**11**	2'139'192	**243**	68'801'700	**168**	**714**	**421**	70'946'886	**0.59**
Fever	53	2'139'192	779	68'801'700	103	714	935	70'946'886	1.32
Headache	25	2'139'192	310	68'801'700	33	714	368	70'946'886	0.52
Convulsion	22	2'139'192	17	68'801'700	0	714	39	70'946'886	0.06
Cough	3	2'139'192	0	68'801'700	0	714	0	70'946'886	0.00
Running nose	0	2'139'192	0	68'801'700	0	714	0	70'946'886	0.00
Gastrointestinal disorders (Ag)	37		265	68'801'700	35	714	320	70'946'886	0.45
		2'139'192		68'801'700		714		70'946'886	
		2'139'192		68'801'700		714		70'946'886	
Irritability	0	2'139'192	0	68'801'700	4	714	4	70'946'886	0.01
Asthenia	0	2'139'192	15	68'801'700	32	714	47	70'946'886	0.07
Pruritus	22	2'139'192	84	68'801'700	21	714	127	70'946'886	0.18
Dizziness or Sudden fainting	3	2'139'192	120	68'801'700	0	714	123	70'946'886	0.18
Myalgia	3	2'139'192	96	68'801'700	27	714	126	70'946'886	0.18
Arthralgia	1	2'139'192	24	68'801'700	7	714	34	70'946'886	0.05
Other	4	2'139'192	55	68'801'700	0	714	59	70'946'886	0.08
Total systemic	**170**	2'139'192	**1765**	68'801'700	**281**	**5994**	**2216**	70'946'886	**3.12**

1 Ag: aggregated

Serious AEFI in clinical trials and vaccination campaign studies

A total 51 serious AEFI were reported including 10 (1.56 serious AEFIs per 100'000 doses administered per week) in clinical trials studies and 41 (0.08 serious AEFIs per 100'000 doses administered per week) during mass vaccination campaigns studies. Types and etiologies of serious AEFIs in clinical trials and vaccination campaigns are presented in tables 20 and 21 respectively. Types of AEFI reported during clinical trials studies differed to that reported during vaccination campaign studies. None of serious AEFIs reported during clinical trials was related to the vaccine after causality assessment of all reported cases. Causality assessment was conducted for 40 out 41 reported serious AEFIs in vaccination campaign studies and 5 were probably related to vaccine (12.5%) and 5 (10%) were not classified because of lack of information

Table XX: Type and etiology of serious MenAfrivac™ AEFIs in clinical trials

Study	duration of surveillance in days	number of vaccine doses administered	Type of AEFI (symptom/sign or preferred term	Delay between vaccination and AEFI occurrence	SOC where indicated	Causality relationship with the vaccine	Number of cases	Outcome
Kshirsagar 2007 (13)	365 (one year)	24	toothache	6days	Not indicated	Unrelated	1	Not indicated
Sow 2011(A) primary vaccination (36)	730 (Two years)	201	Note indicated	Not indicated	Infections an infestations	Unrelated	1	Recovered
			Acute Gastroenteritis	Not indicated	Infections an infestations	Unrelated	1	Death
			Protein energy malnutrition	Not indicated	Metabolism and nutritional disorder	Unrelated	1	Death
Sow 2011(A) Booster (14)	730 (Two years)	192	Injury	Not indicated	Injury, poisoning and procedural complications	Unrelated	1	Death
			Note indicates	Note indicated	Vascular disorders		1	Recovered
Sow 2011(B) (14)	365	604			Injury and poisoning and procedural complications	Unrelated	1	Recovered
					Pregnancy, puerperium and perinatal conditions	Unrelated	1	Recovered
Hirve 2012 (15)	365	169	Acute lymphoblastic leukemia	23 days	Not indicated		1	Remission (under chemotherapy)
			Chronic tonsillitis	More than 28 days after	Not indicated	Unrelated	1	Recovered
Total							10	

SOC: System Organ Class

(A) : study A in the article; (B) study B in the article

Table XXI: Types and causes of serious AEFIs following administration of MenAfrivac™ in vaccination campaigns

Study	duration of surveillance in days	number of vaccine doses administered	Type of AEFI (symptom/sign or diagnosis)	Delay between vaccination and AEFI occurrence	SOC	Causality relationship with the vaccine	Number of cases	Outcome
Maman 2012 (17)	42	356'532	Severe malaria (13 were reported to have fever, 8 convulsions, 8 gastrointestinal disorders and all 14 have positive malaria smear)	Not indicated	Severe malaria	None was related (Coincidence)	14	Not clear
			Vomiting, diarrhea, hypothermia (35°C), convulsion and coma	1 day	Not indicated	Not conducted	1	The child died two hours after admission
			Allergic reaction: rash and intense pruritus, bronchospasm and erythematous and edematous plaques on all the body	30 minutes	Not indicated	Probably related to the vaccine	1	Not clear
Ouandaogo 2012 (18)	42	11'466'950	Exanthematous pustulosis	Not indicated	Not indicated	Probably related to the vaccine	1	Not clear
			Angioedema	Not indicated	Not indicated	Probably related to the vaccine	1	Not clear
			Bronchospasm	Not indicated	Not indicated	Probably related to the vaccine	1	Not clear
			Vomiting	Not indicated	Not indicated	Probably related to the vaccine	1	Not clear
			Not indicated	Not indicated	Not indicated	Coincidence	17	Not clear
			Not indicated	Not indicated	Not indicated	unclassified	4	Not clear
Steffen: 2014 (25)	5	999					0	
total							41	

3.4. Comparing AEFI incidence rate in clinical trials and vaccination campaign studies

The IRds of local, systemic, types and serious AEFI are presented in table 22 IR of AEFIs were higher in clinical trials than in immunization campaigns studies, the difference (IRd) for overall AEFIs being of 10043 (95% CI 10042-10044) per 100'000 doses per week, for local of 11'498 (11'498-11'498), for systemic of 17'245 (17'245-17'245)] and for serious AEFIs of 1.55 (1.54-1.56). The IRd of some types of AEFI is not presented due to the fact that some studies opted to aggregate data on some type of AEFIs. Headache had the highest IRd [3'622 (3'622-3'623)]. The IR decreased by more than 99.9% for overall, local and systemic AEFIs and by 99.5% for serious from clinical trials to immunization campaigns

Table XXII: Incidence rate difference of types of AEFI between clinical trials and immunization campaigns

Type of AEFI	Incidence rate in clinical trial (number of AEFI per 100'000 doses administered per person week)	Incidence rate immunization campaigns (number of AEFI per 100'000 doses administered per week)	Incidence rate difference (number of AEFI per 100'000 doses administered per week)	[95% Conf. Interval]
Pain at the injection site	5'119.26	0.22	Ag	
Induration :redness injection site	2'126.46	0.00	Ag	
Swelling injection site	157.52	0.02	Ag	
Abscess	0.00	0.04	-0.04	[-0.05—0.03]
Total local reaction	**11498.65**	**0.59**	**11498.06**	**[11'498.02-11'498.09]**
Fever	2441.49	1.32	2440.18	[2'440.17-2'440.19]
Headache	3622,86	0.52	3622.35	[3'622.34-3'622.36]
convulsion	0.00	0.06	-0.06	[-0.08--0.04]
Cough	0.00	0.00	0.00	
Running nose	0.00	0.00	0.00	
Vomiting	1'181.37	0.44	5'985.16	[5'985.09-5'985.23]
Diarrhea	4'252.93			
Loss of appetite	1'417.64			
Gastro intestinal disorder	5'986.60			
Irritability	315.30	0.01	315,02	[314.94-315,10]
Asthenia	866.34	0.07	866,27	[866.25-866.29]
Pruritus	0.00	0.17	-0.17	[-0.19- -0.13]
Dizziness or Sudden fainting	0.00	0.18	-0.18	[-0.20- -0.14]
Myalgia	236.27	0.18	236,10	[236.09-236.10]
Arthralgia	236.27	0.05	236,23	[236.22-236.24]
Other	78.76	0.08	78,66	[78.65-78.67]
Total systemic	**17'247.97**	**3.12**	**17'244.85**	**[17'244.80-17'244.90]**

Ag: At least one study had the number of aggregated in a syndrome

3.5. Risk of bias within studies

Table 23 presents the assessment of risk of bias in included studies. Information on participants' selection in clinical trial studies was not sufficiently detailed for a thorough assessment of the risk of selection bias in these studies. Cases definitions of minor and serious AEFIs were not presented for all clinical trials and limited the assessment of detection bias. The duration and detection procedures of AEFI surveillance and of serious AEFI surveillance were not the same in all included studies and predisposed to an increase risk of detection bias across studies. There was also a risk of detection bias in studies conducted in immunization campaigns as all vaccinated populations did not have the same geographic access to AEFI surveillance. In some of the included studies, AEFI were only presented in syndrome or in systemic organ class without prior presentation of symptom or sign. This predisposed to an increased risk of reporting bias in and across studies. Available information was limited to rule out the risk-attribution bias for 6 out of 7 included studies as nothing was mentioned on how each study participants were followed up till the end of the surveillance period. The causality assessment of serious AEFIs was not clearly described in clinical trials studies while it was conducted by a multidisciplinary committee in campaign studies. This could increase the risk of bias across studies regarding classification of serious AEFIs.

Table XXIII: Risks of bias for included studies

Study	Is there a risk of selection bias?	Is there a risk of detection bias?	Is there attrition bias?	Is there a risk of reporting bias?	Is there a risk of bias in assessing the etiology of serious AEFI
Kshirsagar 2007 (13)	Unclear[1]	No[4]	Unclear[6]	Unclear[8]	Unclear[9]
Sow 2011(1) (14) (A)	Unclear[1]	No[4]	Unclear[6]	Unclear[8]	Unclear[9]
Sow 2011(2) (14) (B)	Unclear[1]	No[4]	Unclear[6]	Unclear[8]	Unclear[9]
Hirve: 2012 (15)	Unclear[1]	No[4]	Unclear[6]	Unclear[8]	Unclear[9]
Maman 2012 (17)	No[2]	Yes[5]	Unclear[6]	Unclear[8]	Unclear[9]
Ouandaogo 2012 (18)	Yes[2]	Yes[5]	Unclear[6]	Unclear[8]	Unclear[9]
Steffen 2014 (25)	Yes[3]	No[5]	No[7]	Unclear[8]	Unclear[9]
Across studies	Yes[10]	Yes[10]	Yes[10]	Yes[10]	Yes[10]

1: procedure of participants selection and enrolment not detailed; 2 : all eligible people in covered health districts were targeted by the vaccination campaign and AEFI surveillance; 3: study villages were selected by the Benin Ministry of Health; 4: the detection and reporting processed of AEFI were standardized; 5: Access to AEFI surveillance expected to differed among persons vaccinated; 6: the number of participants followed up till the end of surveillance period was not indicated; 7: all participant were followed up till the end of the five days surveillance period; 8: information about the supervision or the monitoring of reporting are not presented . 9: Processes of serious AEFI causality assessment were not presented; 10: the selection and follow up of participants, the AEFIs detection, reporting and investigation process differed from one study to

DISCUSSION

To the best of our knowledge this is the first systematic review comparing incidence rates of AEFIs between clinical trials phases and immunization campaigns with Menafrivac™, but also with any other vaccines. It gives an insight on the magnitude of difference in incidence rates of overall, local, systemic, serious and types of AEFI when assessed in the rather controlled setting of clinical trials, especially in Phase 1 and 2, and just pragmatic during mass immunization campaigns. As expected, the incidence of AEFI was much higher in clinical trials than in mass campaign studies with a decrease of more than 99% for all AEFIs from different phases of clinical trials to immunization campaigns. None of the serious AEFIs reported in clinical trials studies was related to the vaccine while 5 out of 40 serious AEFIs investigated in immunization campaign studies were probably related to the vaccine.

Since the objectives of clinical trials are completely different than those of mass immunization campaigns, the first one being primarily to assess the safety and reactogenicity of a new product, the second one being to protect a whole population from a disease, it is not expected to have equivalent IR of AEFIs. However, since the safety of a vaccine cannot be ascertained by clinical trials only due to the small sample size that hinders detection of rare significant AEFIs, it is highly desirable that a good surveillance system is put in place when a new product is distributed at large scale. Our observation of new serious probably vaccine-related AEFIs in mass immunization campaigns shows that there is a necessity to have a monitoring of safety in place during such enterprise, and that it can work. What this review does not show is the number of such events that were missed during campaigns. There are certainly many since the IR of serious AEFI was more than 99% lower in mass campaigns than in clinical trials. This observation is worrying.

There are several reasons that can explain the magnitude of this difference. They can be categorized into two groups, namely one related to methodological differences and the second to the surveillance system in place. For the first one, the duration of observation may have played a role. Indeed, the surveillance period in clinical trials was shorter than in mass campaigns. This leads to a higher overall IR since AEFIs are mainly observed in the first or second week post vaccination. The numerator is therefore much higher. Diversity in vaccine safety monitoring procedures, surveillance periods as well as AEFI reporting and analysis have been identified to contribute in reducing accurate scientific information on vaccine safety (26). To maximize scientific progress on immunization safety, standardization of AEFI surveillance period in clinical trials and mass campaigns after registration is essential. The second reason for this big IRd is linked to the poor performance of the surveillance system in place during mass campaign to capture AEFIs. There are many challenges that have been

largely described in previous studies (27). Under-detection and under-reporting of AEFIs in mass campaigns are well known and intrinsic to an activity that is not focused on safety assessment. In clinical trials, the detection, reporting and investigation of AEFIs are part of the TOR of a well-trained monitored, supervised and audited research team. On the other hand, in mass vaccination campaigns, there is limited number of health personnel trained to supervise AEFI surveillance, detect, report and investigate cases of AEFI. From our experience in Cameroon, one focal point per health district is designated and trained for AEFI surveillance supervision and one focal point per health facility is designated and trained for the detection, reporting and investigation of cases of AEFIs. One person only to supervise surveillance in the whole district and one only in a big hospital is clearly not sufficient. Indeed, in a hospital where many serious cases are treated, and in different wards, at different times of the day and night, it is difficult to detect those that can be the result of an SAE. The consultation registers are not standardized and do not allow the detection of cases of AEFI after the consultation. They do not include variables on vaccination history. Thus, cases of AEFIs consulted in the absence of focal point have very little chance of being detected. Also, for lack of resources, the training of supervisors and focal points is often made in cascade and is integrated into the training of other campaign activities. The duration is often very short and decreases drastically when applied from central to operational level. Similarly competence of trainers decreases since one trainee cannot deliver better training than that received in a shorter time. Improvements can however be made such as by i) revising the patient registration system to include at least one variable for active case detection, ii) ensuring that all health workers receive initial or continuing training enabling them to implement the minimum AEFIs monitoring activities at the operational level, iii) sensitizing head of health facilities to include in TOR of all health personnel involved in care, the detection and reporting of AEFI, and this being even more important in hospitals, iv) to use efficient interventions such as continuous supervision and even SMS messages to remind health staff of their surveillance duty (24)).

The poor performance of AEFI surveillance in mass campaign is worrying in terms of safety of vaccines because i) it misses local AEFIs such as abscesses for example that may be a key indicator of program error such as compliance with vaccine storage, transportation and administration procedures, ii) it misses severe local AEFIs which are preventable and are likely to draw the attention of the public and spread rumors and refusals for vaccination, iii) it misses serious AEFIs and compromises causality assessment and possibilities to appropriately respond to.

To understand whether such differences of AEFIs reporting between clinical trials and mass vaccination were inherent to MenAfrivac™ or were common to all vaccines, we made a rough

estimate of the magnitude of the difference in IR of AEFIs between clinical trials and post registration immunization using the new pneumococcal conjugate vaccine 13. For 5308 doses of the vaccine administered during clinical trials, 5004 AEFIs were reported, including 1803 local and 3201 systemic (28; 29; 30; 31). While in post registration, 871 vaccine doses were administered and 550 AEFIs were reported including 236 local and 314 systemic (32). IRd per 100 000 doses per week between clinical trials and post registration vaccination were 19’089, 5'423, 13'666 and for overall, local, and systemic AEFIs reported respectively. Thus AEFI incidence decreased from clinical trials to post registration vaccination studies by 52%, 37%, and 53% for overall, local, and systemic AEFI respectively. This relatively low difference can be explained by the fact that in the post registration study, AEFI monitoring was more rigorous, which increased the chance of detecting AEFIs than during studies conducted during the vaccination campaigns with MenAfrivac^{TM}. Also vaccinees were closely monitored for AEFIs by telephone throughout the monitoring period. Lastly, the vaccinated population was made up of people of older age in a European country.

Conclusion

This systematic review highlights the magnitude of the difference between IR of AEFI as evaluated in the controlled setting of clinical trials and more pragmatic approach of mass vaccination campaigns. IR of AEFIs was more than 99% lower in vaccinations campaigns than in clinical trials, including for the reporting of serious ones. Since the objectives might not be the same, safety and reactogenicity being the most important outcome in clinical trials, and detection of rare severe and serious events in mass campaign, there is no expectation of IR to be equivalent in the two settings. However, there is definitely room for improvement of the surveillance system in mass campaign and post registration implementation, including for example standardization of hospital registries with information on vaccination status, better case detection in hospitals to allow better investigation of causality, sufficient number of trainees and dedicated health staff in health facilities and hospitals, and adequate supervision, even with new technologies such as SMS reminders.

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Chapter 8: General Discussion, Conclusion andRecommandations

8.1. General discussion

The main goal of this thesis is to identify sustainable interventions that can contribute to improvethe performancesof pharmacovigilance during mass immunization campaign with MenAfrivac^{TM} in Cameroon. To this end, three studies were conducted and results are presented in Chapters 5, 6 and 7. This chapter discusses main findings and presents general thesis recommendations on practical application and potential further studies based on the main study findings.

8.1.1: Improving AEFI reporting rates of immunization campaign

Chapters 5 and7of this thesisshowthatunderreporting ofAEFIsis a major obstacleto theupdate ofvaccinesafetyinformation and for the appropriate response to AEFIs in immunization campaigns. Chapter 6shows thatsupervisionof health staffor reminding them using SMS improvethe reporting rateofAEFIs. Taking into account these results when planning and implementingroutine or massimmunization have been recommended to improve AEFI reporting rate and to define apharmacovigilance system. Given thenecessary resources,thesustainableimprovement of pharmacovigilance includingvaccine pharmacovigilancealso depends on otherinitiativesand actions at different levels such as global level, health care system, pharmaceutical industry, scientific communityand on otherparameters that canaffect the qualityofinformationdescribing vaccine safety profile.

Since 1961, WHO has taken initiatives to enhance drug safety; and to support public health programs for the effective assessment of the risk-benefit profile of medicines.Vaccine safety isa priority targetfor thisactivity since 1999 through the establishment of the Global Advisory Committee on Vaccine Safety (GACVS) (183). A number of actions have been conducted in these perspectives focusing on strengtheningthe capacities of countriesinsetting up an efficient pharmacovigilance systems and boosting the international and national collaboration on drug and vaccine safety. Examples of these actions included setting up the Program for International Drug Monitoring, to collect reports of suspected adverse drug reactions to be incorporated into the WHO database and analyze; developing and sharing guidelines on drug and vaccine pharmacovigilance and developing training programs (190). This resulted in substantial progresses in some countries although improvement is still required as recent published reports revealed a rather slow progress in somecountries in the developmentandimplementationof vaccine pharmacovigilance system (33).

The number of countries collaborating with the WHO Program for International Drug Monitoring has substantially increased in recent years (81).In some countries there is willingness of decision makersto put in place basic structuresof the pharmacovigilance system (34).In general, in LMIC, the minimum resources, infrastructure,regulations, and guidelines to implement the pharmacovigilance activities are still lacking, limiting the capacity of generating the required information to assess the risk-benefit ratio of marketed vaccine (25, 32). To the best of our knowledge, no publication has focused on the reason for the poorimplementation of the WHO initiativein LMIC. From our experience in Cameroon, this can be explained by low coverage of staff needed to implement the initiative. Training programs that are offered in this context invite only a small proportion of people involved in AEFIs monitoring. These people often do not have the resources to organize training sessions and share their knowledge with their colleagues and other stakeholders. Guidelines developed by WHO are hardly solicited since those who should do so, are not trained on AEFIs surveillance and are not aware of it utility. Efforts to improve regulations usually target only the health staff while drafting documents and approving these documents often involve other people from other backgrounds and other sectors. Most health program managers are still unaware of the importance of pharmacovigilance. For example, one study showed that even when resources for pharmacovigilance are made available by Global Fund, only 27% of proposals included it in the request for funding (191). Improvementsmight be possiblein pharmacovigilance in general,if training on vaccine pharmacovigilance is included inbasic training of health personnel; if headof EPIand otherhealth programsusingdrugsare trained inpharmacovigilance, ifactions to improve regulationinvolve all key stakeholders,ifresources areallocatedto train a sufficient number ofhealthpersonnel at alllevels of the health system in pharmacovigilanceand if theminimum infrastructure, equipment, resources provided and guidelines are developed and made available.

Guidelines forthe creationand functioning ofa pharmacovigilance centerdo not definethe roles of governmentin the process (192).No other document, to the best of our knowledge does it.Declaration of Alma-Ata precises that Governments have a responsibility for the health of their people which can be fulfilled only by the provision of adequate health and social measures (193). It can be deduced that the Government has the responsibility to setup a functional pharmacovigilance system in each country. It should therefore be the responsibility of the government to creating and assigning objectives of pharmacovigilance centers, developing regulations and guidelines, allocating resources and infrastructure, appointing staff and evaluating the results of activities. Published studies indicate that in several countries, especially in LMIC, these initial steps are still not taken and no study to the best of our knowledge has attempted to describe the reasons (25, 32).In Cameroon, a Presidential Decree organizing the Ministry of Public Health creates the pharmacovigilance service

and assigns specific missions (79). The assigned tasks are matched to provide information necessary for the assessment of risks and benefits of medicines and vaccines. These tasks are almost not performed but no assessment has been done to explore the reasons. From our experience, the plausible explanations would includeinsufficient resources since to date no budget is planned for the implementation of pharmacovigilance activities. Ignorance also characterizes those responsible of health programs that involve drug use because no head of health programs including the EPI managersincludes pharmacovigilancein the yearly budget of their activities. Inadequate qualification and background of persons appointed to manage pharmacovigilance service is one of constraints because since this service exists, only nurses are appointed to operate. They usually lack necessary leadership, bravery and expertise to interact with health programs, health regions, health facilities, their hierarchy and international organizations; the lack of decentralization of pharmacovigilance units in the health regions and health programs; dependence on donors for fundingleading to unsustainability of activities. Improvement would be possible by appointing head of pharmacovigilance services sufficiently qualified and motivated persons to plan, mobilize local and external resources, stimulate the participation of key stakeholders, implement and assess key activities; creating pharmacovigilance units in all health programs, health regions, health districts and hospitals; allocating minimum local resources and equipment including computers and software for data management; and putting in place an AEFIs data management and analysis system.

The role of the pharmaceutical industry in investigating drugs and vaccine safety during clinical trials is well described (3). In Cameroon as in other countries, this role is not described for registered and marketed vaccines and drugs. The WHO Guidelines for setting up and running a pharmacovigilance center limit their role to receiving from pharmacovigilance services or the national regulatory authority reported cases of AE and AEFI occurring after exposure to drugs or vaccines produced by the concerned pharmaceutical company. This is reasonable as extending their role to support pharmacovigilance promotion or activities could directly or indirectly put pharmacovigilance centers in conflicts of interest in the assessing drugs risk benefit ratio.Their contribution couldbe beneficial in using reported AEFI or AE to generate and share information on drugs and vaccines safety profile especially in countries with poor pharmacovigilance system, to regularly update drugs and vaccine information sheets, and to identify, support or conduct research projects in order to clarify AEFI and immunization causal relationship which is imprecise after AEFI investigation.

Given therelatively highcost of supervisionand the relativelylowefficacy ofSMSon improvingAEFIs reporting rates, it is necessary to explored new horizonsinorder to identify strategies that can be

used for sustainable improvement of AEFIs reporting rate. In Cameroon, the standardized EPI guidelines recommend supervision as the standard available intervention to ensure that tasks planned for each activity are performed following procedures as instructed (80).Supervision is known to be expensive and usually requires high expertise. Theseconstraints limitthe expectedcontribution ofsupervisionin improvinghealthinterventions outcomes. Chapter 6 of this thesis shows strategies to improve its efficiency. Other strategies could be tested to reduce it the cost. For example the assignment and training of AEFIs supervisors in health facilities or assignment of area supervisors to cover a given number of health facilities not distant from each other. Thus, bringing supervisors closer to supervisees could make it less expensive because the distance costs will be reduced. The integration of activities to be supervised could also reduce the costs of supervision as integration is known to increase the efficiency of health interventions (195). For example, in routine EPI, the supervision of AEFIs surveillance could be integrated in the supervision of epidemiological surveillance of EPI preventable diseases such as measles, yellow fever, materno-neonatal tetanus, and acute flaccid paralysis. The surveillance of these diseases is regularly funded. Supervision of AEFI surveillance activities may be included at no additional cost. The AEFI reporting could also be improved by combining SMSand supervision to remind and train health personnel on AEFI reporting. Future studiescould thus test whetheralternatingSMS withsupervisioncould improvethenotification rateofAEFIs at low cost. We could alsoevaluate the effectof stimulatingmore than one personperhealth facility using SMS, hopingthat at least one of them reacts and that it results inan increase in theAEFIs reporting rate.SendingSMSto the communityhas been shown to be effectivein improvingthe detection ofAEFI(196).The combination ofsending SMSto thosevaccinatedandhealth personnelin chargeofAEFIsurveillance couldimprove SMS effectiveness in improving AEFI reporting rate and should beevaluatedin futurestudies.

Another way to improve the AEFIs detection and reporting rates is to target care seeking points.A study conducted in south Sudan showed that the therapeutic itinerary of patients with fever included the following:home, traditional healers, magicians, private formal and informal medicine vendors and health centers (198).In Cameroon, despite the differences in culture, these points are the same. A system could be set up where staffs working in these health care points alert health workers of the closest health facility in case an AEFI is detected. This system is being evaluated in Cameroon whether it can improve case detection and reporting of EPI preventable diseases under epidemiological surveillance. Traditional healers are involved in epidemiological surveillance and are asked to alert the health centers in case they detect a suspected case of any disease under surveillance. This is still under evaluation. On the same line, an unpublished study conducted in

Cameroon showed that the telephone warning system by ‘‘ beeb "(a short phone call not picked up) sent by parents of vaccinated children(followed by a phone call from the health center to collect additional needed data)significantly improved the AEFI reporting rates compared to the control group in which in case of AEFI, parents were advised to bring the child to hospital (199). Further studies could assess effects of intervention like ‘‘beeb’’ or SMS sent from the community, pharmacy vendors or traditional healers, magician in case of an AEFI in improving AEFI reporting rate.

Anyinterventions thathave been proven effectiveinimprovingvaccine pharmacovigilanceusingSMS,''beeb’’ or phone calls is not expected to encounterdifficultyduring implementation in Cameroon. Topromoteepidemiological surveillance, the WHO has made availabletoall health facilitiesfrom referral hospitalsto health centersmobile telephones and a network in whichmessages andcalls are free of charge.This greatlyreducesthe costsof interventionsand improves its feasibility.The concern ishow toensure sustainabilitywhenthe resources made availableby WHOwill be exhausted.

The integration of AEFI detection and reporting in a systemcollectingcommunity-basedinformation at a knownfrequencyis likely to improve AEFIsdetection and reportingrates at low cost. A study conducted inTanzania showedthat it is feasibleto integratethesurveillance of pregnant women exposuretodrugs within the health and demographic surveillance (HDS) platform (200). This integration included monthly visit of pregnant women and is presumed to improveAEFIreporting ratesas it increases number of health worker and patient contact.

In Cameroon,AEandAEFIare notthe onlyhealth eventsunder surveillance(201). About thirty diseases are targeted by epidemiological surveillance. Incidences of cases reported for diseases under surveillance are by far lower than expected due to underreporting. The resultsof interventionstestedin Chapter 6could be appliedto improve thereportingof these diseases. This should be easy since the detection, reporting and investigation procedures in epidemiological surveillance and in vaccine pharmacovigilanceare the same.Given that both surveillances lack the human, material and financial resources for their activities, the integration of both activitiescouldimprove the results ofeach. For example further study could assess the feasibility and cost-effectiveness of integrating activities of AEFI surveillance to that of epidemiological surveillance.

8.1. 2 Improving other parameters of AEFI surveillance

The reporting rate is not the only parameter that needs improvement to ensure proper monitoring of vaccine safety. Other parameters may need to be improved to insure that good information is used to describe vaccine safety profiles. These wouldinclude; case definition, types of AEFI detected,

reported and investigated, the causality assessment, completeness and timeliness of reporting forms, reporting and investigation of cases, developing and training on AEFI pharmacovigilance, andhow to evaluate the AEFI surveillance system.

The AEFI case definition in vaccine clinical trials or in the post registration phases conditions the specificity and the sensitivity of the surveillance system which is the capacity of the system to detect the true suspected event in the population under observation (203). This definition is important in the monitoring system since its modification can change significantly, the number of detected cases.It is in this light that one must ask the question whether AEFIs case definitions used in clinical trials and post registration are sensitive enough, understood and used by the entire chain involved in monitoring? In WHO guidelines, aconstant evolution has been notedin the direction ofimprovingthe sensitivity ofAEFIs case definition. Thus, this definition evolved from “medical incident that takes place after an immunization and is believed to be caused by the immunization” (17) '' to “any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine (18) '' From field experience, the first definition is not sufficiently accurate as the expression “believed to be caused by the immunization” can leadto indecisionwhen a suspect case of AEFI is detected. The second definition which is the latest is easier to be taught, more easily understood and used by the health staff. But community volunteers and traditional healers who have important role in the therapeutic itinerary of patients in Cameroon and in many African countries are expected to have difficulties to understand and use the definition.
Indeed, the expression 'medical occurrence' 'is not accurate and can have different interpretations. We believe that this definition should be assessed regularly and updated to ensure that it can be used by all categories of persons involved in AEFI surveillance.

Identification of adverse events following immunization in clinical trials, routine immunization or during immunization campaigns requires a clear and standardized definition of these events that is easy to be used by people involved. To date, the standardization of the definition of all events is still ongoing. Describing events using non standardized cases definitions can lead to non-homogeneous sensitivity and specificity of AEFIs surveillance system in clinical trials and post registration phases of vaccines development. The Brighton collaboration is an initiative that works to improve the assessment of the safety of vaccines with a very significant contribution in the development of formats and standardized case definition of signs and symptoms likely to occur after exposure to vaccines as well as the development of guidelines for data collection, analysis and presentation during AEFIs monitoring (77). The framework provides three levels of precision for each AEFI and

indicates the context of use for each. It is true that the sensitivity and specificity of definitions presented in three levels of accuracy was tested but in routine immunization and vaccination campaigns, these definitions are not easily applicable. For example fever definition seems very applicable regardless of the level of care but the required data collection details are more applicable in clinical trials setting where everything is standardized and closely monitored than in routine immunization (205).Details required to describe the thermometer used to assess the temperature are difficult to be provided since required details are not provided with thermometers sold in Cameroon. Providing practical training on required details per sign and symptom, ensuring the supervision of its implementation, and data collection would be very difficult during vaccination campaigns where the time allocated for training is short, the work load is very high for medical staff and some of cases are usually detected by non-medical staff. This may explain why in the results of the systematic review presented in Chapter 7The incidence of fever in clinical trials was different to that of immunization campaigns.

Completeness of reporting forms, timeliness, proportion of appropriately investigated serious AEFIs cases, and the reliability of the data in the AEFI report form are other key parameters that need to be monitored (206). Where needed, these parameters could be improved concomitantly with the underreporting using the same strategies.

In clinical trials, it is mandatory to collectquantify anddescribe eachAEFI (3). In themarketed phase, any AEFI that is of concern to the parents or to the health-care workers should be reported; particularly serious AEFIs, signals and events associated with a newly introduced vaccine, AEFIs that may have been caused by an immunization error-related reaction, significant events of unexplained cause occurring within 30 days after vaccination, and events causing significant parental or community concern (18).It is reasonable not to recommend reporting all types of AEFIs for marketed vaccines. If the monitoring system set up is sensitive enough, it would be unrealistic to report all cases. For example during the vaccination campaign against meningococcal meningitis A organized in Cameroon in 2012, over 2 million people were vaccinated, meaning about 70% of the population. National statistics indicate that fever for example can affect over 40% of the population in a month (207)In this population if 70% of people are vaccinated, it could happen that several cases of fever coinciding with the AEFI surveillance period occur. In this case, at least 100’000 case of fever would have occurred.It would not have been feasible to report all these cases which meet AEFI case definition. Given that it is required to monitor each event in order to assess the safety profile of the vaccine used, it would be more efficient to meet the earlier WHO recommendation in terms of type

of AEFI to be reported at marketed phase of vaccines and to develop a monitoring system that would randomly select either consultation days or patients consulting during the surveillance period of AEFIs to estimate the incidence of minor AEFI.

With the aim to update key information for vaccines safety Profile and the assessment of the risk benefit ratio, the detection, reporting, investigation and description of the causal relationship between serious AEFI and immunization is one of the main objectives of AEFIs monitoring (18). In Chapter 7 of this thesis, we noted that in clinical trials, the standardization procedures for detecting, reporting, investigation, analysis of causality is not always implemented. For post registration immunization, the reporting rate of serious AEFI was very low compared to clinical trials. Similarly, the low reporting rate, and poor qualityof investigation are common and this limits possibilities to draw conclusions regarding relatedness at the end of the causality analysis process. From field experience, the following explanations are plausible. Insufficiency of qualified and motivated human resources resulting in insufficient coverage ofhospitalized and monitoring period and the non-detection of certain cases of AEFI due to ignorance of the case definition. Besides that, financial resources are often inadequate to acquire sufficient amount of supplies for samples collection and to ensure transportation of samples from peripheral areas to the reference laboratory. Reported forms are received by the expert committee very late and incomplete to help improve the quality of investigation. The communication between the periphery and the committee is not sufficiently regular to support remote assistance in order to improve case investigation. Improvement is possible by increasing the duration of training and promoting the use of case studies. More frequent and closer supervision or sending SMS could also improve the AEFI detection and the quality of investigation. Minimum necessary consumables for sample collection should be supplied during campaigns. A rapid transfer of information using emails for example where possible could improve the timeliness and allow completion of the investigation when the patient is still hospitalized. In health facilities, anAEFIfocal pointshould be assignedin eachcare team.The guidelines onclinical trials shouldbe reviewed tostandardizeprocedures for detecting, reporting, and investigation ofAEFIsin clinical trials (3). On the same line, the improving the monitoring of clinical trials implementation by ethical committees or/and NRA can improve the compliance of research teams to clinical trials guidelines and to dear research protocols and SOP (standard operating procedures)

Training onpharmacovigilance is one intervention that is expected to contribute in improving national capacities in implementing pharmacovigilance activities. Actually it is mainly promotedby WHO.It aims to strengthen and maintain capacity for national vaccine pharmacovigilance through

the delivery of E-learning courses, basic training, advanced trainings, the development of trainer resources, the creation of pool of national, regional and global experts in capacity building, and the respond to requests for training courses (190). The diversity of the program is expected to improve knowledge and practices of people involved in pharmacovigilance in countries. But the fact that several studies identified inadequate training as a major handicap in the ability of countries to conduct pharmacovigilance activities means that either the programs do not respond to training needs of those involved in pharmacovigilance, or the coverage of targeted population remainslow. As it was the case in strengthening capacities of African countries in research ethics evaluation, the program can be readjusted if needed by conducting a study to identify priorities in term of training objectives and targets (208). Periodic evaluation of these programs could also be useful to assess its efficiency (209). The discrepancy between the varieties of training opportunities and insufficient training could be justified by the fact that health personnel have limited access to these programs. Because very few perceive the need to be trained in pharmacovigilance since they are ignorant of the need. They are in this case unlikely to visit the indicated web site to download training resources or solicit training. Those who participate in training seminars are regularly those in charge of centers. At the end of these training, no resources are planned to replicate the training to other health personnel in health facilities, health program, health regions, and health districts and hospitals.It is thus unrealistic to think that the training offered by WHO can help to build the capacity of all health personnel in each developing country. Local training opportunities are offered during immunization campaigns and are too brief to impact a significant strengthening of pharmacovigilance among health personnel. A sustainable capacity building can be done by pleading to competent authorities for training on pharmacovigilance to be included in the basic training curricula of health personal. Ongoing training could have a better result through an increase in the promotion of E-learning in pharmacovigilance and decentralization of the planning and implementation of training seminar in country through calls for grant.

8.1.3 Safety profile of the vaccine MenAfrivac^{TM} in mass immunization campaign

The safety profileof a marketedvaccine, as that of any drug,interestshealth personnel, managers of immunization programs,pharmaceutical industry,thepublic, thenationaldrugregulatory authority, non-governmental and international organizations involvedinvaccination; as it isan important parameterin the analysisof the risk-benefit ratio andin the decision-making process to develop and register vaccines, plan immunization activities, adherenceto vaccination program,and to plan responses to AEFIs occurring during immunization.

It is therefore essentialthat allefforts be made toensure that afterany mass immunization campaign orimmunization activity, information on vaccination coveragebe accompaniedwith the details,on vaccine safety.

Results of the study presented in chapter 6 supported that MenAfrivac^{TM} is safe. This conclusion islogical looking at comparisons of the distribution of overall, local, systemic, serious,and of types of AEFIs reported in the targeted campaign to that of previous campaigns(38). The conclusion would have been less reassuring about the safety of vaccines if it included details about shortcomings of the reporting process. As in this case a fifthofreportedAEFIwas notincluded in the analysisbecause of thepoorquality of reporting, the analysisof causalitywas notdone onmore than halfof seriousAEFIfor the same reasons, all newAEFIsdetectedwere notinvestigatedfor the same reasonsand that theincidence rate ofreportedAEFIwasthree times higherinone healthregion than the other and 100times higher in one healthdistrictwith respectto another. This means that itisdifficult to makestatements aboutthe safety profileof avaccineused during avaccination campaign without the criteria validate the quality of the surveillance that generated the information. If not,a lowerstandard surveillancewillfail todetect someseriousAEFIsandwe believe that thenon-detectionof these AEFIsdoesnot confirm itsabsence.

Almost all studies previously publishedon Menafrivac^{TM} safety profile during mass campaigns support that the vaccine is safe but are more or less affected with the sameweaknesses. Inaddition, theaggregated anddetailed data onthe vaccine safety profile cover onlyone fifth and onetenth of100 milliondosesadministeredbetween 2010 and 2012.These deficiencieson the qualityand completenessofAEFIdatacast doubtwhen reporting the vaccine safety and limit evidence baseline information when planning AEFIs surveillance.

8.1.4: Magnitude and implications of AEFIs incidence rate difference between clinical trials and immunization campaigns

Mass campaigns increase the risk of AEFIs occurrence as campaigns often involves the use of less experienced personnel for vaccine administration, administering a large number of doses over a short periods of time, less chance to respect restrictions , contra-indication and drug interactions. The likelihood of detecting, reporting and investigation of AEFIs is higher in clinical trials since its research team members are better trained and monitored in their task and therefore likely to better comply with AEFI reporting and investigation procedures.

In campaigns several parameters contribute to reduce the capacity of the health system to ensure proper AEFIs surveillance (38).The consequence is low AEFIs reporting rate. Ourconcern isthe magnitudeof the IRd between clinical trials and immunization campaigns that can beconsidered acceptable. Resolving this concern is expected to result in an indicator that can be used to judge the value of AEFI reporting rate in post licensure vaccination. To the best of our knowledge, this preoccupation has not yet been discussed in publications.

It is utopian to expect zero AEFIs IRd between clinical trials and post registration vaccination. But, in order not to jeopardize the adhesion of the people to vaccination, each monitoring system should work to keep the AEFIs IRd close to zero for serious, local and those AEFIs that concern populations. With the hope that this performance would allow the detection and reporting of programme errors, rare AEFI and those related to group with particular physiological or pathological conditions. A review conducted with results presented in chapter 7, found that AEFI IRd between clinical trials and mass campaigns with MenAfrivac^{MT} regarding local, systemic and serious AEFI was very high with the IR decreasing by more than 99% from clinical trials to mass campaigns. Although the acceptable values for these differences are not known, a simple judgment can deduce that they are large enough to cast doubt on the assertions about AEFIs safety profile based on AEFI surveillance data.

We recommend that the Cameroon MOH should initiate the process leading to use the AEFI IRd between clinical trials and post registration vaccinations as an indicator of post registration AEFIs surveillance performance. This could be one of key indicator to be used in order to assess and monitor performances ofAEFissurveillance system putin placeduring immunizationcampaigns or supplementaryimmunization activities in Cameroun.

8.2 Conclusions

- The supervision of health facilities by trained health district nurses on AEFIs surveillance, significantly increases the reporting rate of AEFIs compared to routine AEFI surveillance practices during immunization campaigns
- The standardized SMS sent to remind health personnel on AEFIs surveillance increases, the AEFIs reporting rates compared to routine AEFI surveillance practices during immunization campaign
- The supervision of health facilities by trained health district nurses on AEFI surveillance, increases AEFIs reporting rate better than sending the SMS, during immunization campaigns

- Neither new nor increase incidence of serious AEFIs relate to MenAfrivac™ were detectedin the mass immunization campaign organized in Cameroon in December 2012 and thus supports that MenAfriVac™ vaccine is safe and should continue to be used in mass vaccination campaigns
- The incidence rate of AEFI reported in mass immunization campaign organized in Cameroon in December 2012 varied by health district and health region
- The incidence rate of overall, local, and systemic, reported AEFIs during immunization campaigns was at least 99% lower than that reported in clinical trials and that of serious AEFI at 95% lower than that of clinical trials.
- The underreporting is one of the main barriers to the achievement of the objectives of AEFI surveillance during immunization campaign with MenAfrivac™ in Cameroon

8.3 Recommendations

What can be directly translated into public health policy?

- Key indicators should be defined for the monitoring of performances of vaccine pharmacovigilance during immunization campaigns. For example, using as indicator, the incidence rates differences of reported and investigated serious AEFIs between clinical trials and immunization campaigns
- During immunization campaigns, AEFI surveillance should anticipate the underreporting by stimulating AEFIs reporting using standardized SMS sent to health personnel and supervising health personnel using trained district nurses.
- Results of AEFI monitoring should be regularly published by the authorities in charge, to facilitate the compilation and analysis of data on vaccine safety,
- Monitoring and reporting procedure should be standardized between the phases of clinical trials, and post registration vaccination, countries, manufacturers and vaccination campaigns to facilitate comparison and monitoring of vaccine safety profile. The most sensitivecase definitionshould beused for allsuspected AEFIsandforseriousonesthe case definition should be standardized and adapted to the standard of care or laboratory as recommended by the Brighton collaboration.
- The authorities in charge should design and validate respective training modules and objectives for supervisors and health workers involved in AEFIs monitoring.
- Head of health facilities should review the patients' registration system to incorporate at least one variable on vaccination history to facilitate active detection of AEFIs cases.

- The number of needed AEFIs supervisors in health districts and health facilities must be estimated and provided during immunization campaigns.
- The head of health facility have to include monitoring of AEFIs in the TOR of all health staff,
- Minimum needed supplies and resources for AEFI cases detection, reporting, investigation as well as samples collection and transportation, data analysis should be provided by authorities in charge.
- Coordination of activities between the EPI and the department of drugs, pharmacy and laboratory has to be improved
- To improve it efficiencies, vaccine pharmacovigilance activities should be integrated in epidemiological surveillance activities and demographic health surveillance platforms where it exists.
-

Research needed in the future

- Identify strategies to improve the effectiveness of SMS on AEFI reporting rate. For example testing the effect of stimulating the reporting of AEFI detection and reporting by sending concomitantly, SMS to health personnel in charge of AEFI surveillance and at community level to parents of children vaccinated
- Identify strategies to reduce the cost of supervision as intervention to improve AEFI reporting rate. For example, assessing the feasibility and cost effectiveness of using hospital and health area supervisors vs district supervisors on AEFI reporting rate
- Identify key indicators for the monitoring of AEFIs surveillance during immunization campaign, Determining the acceptable incidence rate difference of reported and investigatedserious AEFIs between clinical trials phases, and immunization campaign and between clinical trials phase and routine immunization
- Identify sustainable interventions to improve other parameters of AEFI reporting like the completeness of reporting forms and the AEFI investigation ratefor example, testing the use internet on improving the timeliness of serious AEFIs reporting and investigation

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