PHARMACOVIGILANCE - POST MARKETING SURVEILLANCE NEWS

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Editor's Note

We wish to thank all our numerous stakeholders who have been working tirelessly with the National Pharmacovigilance Centre (NPC) to ensure the safety of medicines in Nigeria. The NPC is committed to sending out quarterly newsletter to its stakeholders. The objectives of the Newsletter are to disseminate information on Pharmacovigilance activities nationally and globally, to educate stakeholders on drug safety issues, to promote rational use of drugs and to promote spontaneous reporting. This second quarter newsletter focuses on Adverse Events Following Immunization (AEFIs) received during the first phase implementation of MenAfriVac Vaccines in five States in the North (Zamfara, Gombe, Jigawa, Katsina and Bauch) in 2011.

We encourage Health care Professionals and other stakeholders to continue to report all adverse drug reactions. Your valued comments and acknowledgement of receipt of this issue through our email addresses (nafdac_npc@yahoo.com; pharmacovigilance@nafdac.gov.ng) would be most appreciated.

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*Text any DRUG RELATED PROBLEM to the **SHORT CODE 20543 (**For **free** on **MTN, Glo and Etisalat)** for action by the Pharmacovigilance Centre*

PHARMACOVIGILANCE OF VACCINES

The History of Vaccines explores the role of immunization in the human experience and examines its continuing contributions to public health. Protection of the individual and the public from vaccine preventable diseases (VPDs) underscores the goal of immunization. Although modern vaccines are safe, no vaccine is entirely without risk. Safety monitoring of vaccines used in expanded programmes on immunisation is important in all countries, including those with limited resources. As the rates of target diseases decrease, parents become less accepting of even minor common adverse events. Identification, detection, prevention and appropriate communication of adverse events following immunisation (AEFI) are therefore essential to preserve the integrity of immunisation programmes and protect public health (Dodoo, 2007).

Safety of vaccines must be excellent to make vaccine's strategy acceptable, since it usually has a deferred individual benefit but immediate adverse drug reactions (ADRs). (Autret-Leca, 2006). For several reasons, vaccines and biologicals require modified systems of safety monitoring since they are often administered to healthy children and also because of large number of persons who are exposed, frequently compelled by law or regulation to do so because of public health reasons (Schumacher, 1979). This applies particularly to vaccines used within a national immunization programme. In many countries, those exposed to a particular vaccine represent the entire birth cohort and therefore a sizeable part of the entire population. People's expectations of safety are high, and they are reluctant to countenance even a small risk of adverse events. Concerns regarding vaccine safety, real or imagined, may result in loss of confidence in entire vaccine programmes. This can result in poor compliance and a consequent resurgence in morbidity and mortality of vaccine-preventable diseases (Chen, 1999).

Whenever an Adverse Events following immunisation (AEFI) occurs and upsets people to the extent that they refuse further immunizations for their children, the children are much more likely to get a vaccine-preventable disease, become seriously ill, disabled, and even die. Therefore to increase immunization acceptance and improve the quality of services, Nigeria planned to make the surveillance of serious AEFIs, an integral part of all immunization programmes.

A previous attempt at AEFI surveillance in the country was made, just prior to the 2006 Accelerated Measles Campaign, with the inauguration of a National Advisory Committee on Vaccine Safety and AEFI on November 28, 2005 with WHO providing technical support, adhoc committees were also set up at State and LGA levels. Unfortunately, after a few months, these were no longer functional.

The commencement of the ***MenAfriVac™*** campaign against Meningococcal Meningitis A in December 2011 had helped to re-establish the AEFI surveillance in the country to effectively detect, notify, classify AEFI cases, routinely during Routine Immunization services and up to 42 days after mass campaigns. This edition of our newsletter discusses the AEFI reports received during the introduction of MenAfriVac Vaccine in the five phase one States in Nigeria in December, 2011

THE AEFI SURVEILLANCE STRUCTURE IN NIGERIA

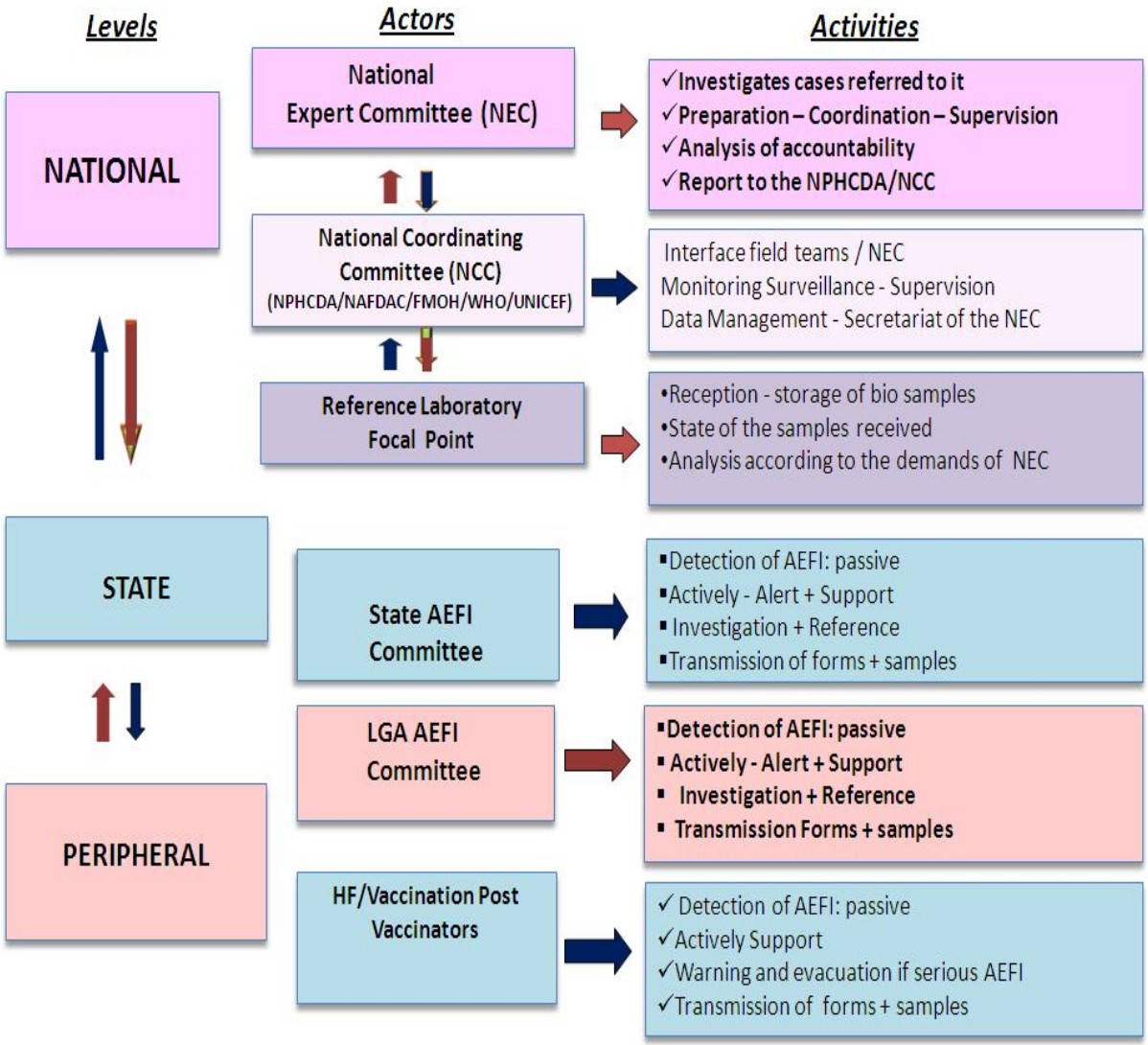
The AEFI surveillance structure was established at the National, State and Peripheral (LGA and Health Facilities) levels as in the figure below

National Level

Immunization safety /AEFI surveillance is a collaborative venture between the National Primary Healthcare Development Agency **(NPHCDA),** in which agency is vested the National Immunization Programme at various levels, and the National Regulatory Authority (NRA) which is the National Agency for Food and Drug Administration and Control **(NAFDAC),** with the Federal Ministry of Health having overall oversight. The NPHCDA is the National focal point for AEFI surveillance. It receives AEFI case reports from sub-national levels, leads investigations and ensures regular analysis and feed results back down the system. It provides support to the states and share all reports and communications with NAFDAC.

NAFDAC, on the other hand, is the technical point of contact for vaccine testing, vaccine licensing and regulation. It receives vaccine samples or initiates collection of samples and advises on vaccine quality and testing. Based on the received AEFI reports, NAFDAC takes informed regulatory decisions on vaccine safety concerns.

Fig 1.0 NIGERIAN AEFI SURVEILLANCE FLOW CHART


Levels
Actors
Activities
NATIONAL
National Expert Committee (NEC)
✓Investigates cases referred to it
✓Preparation – Coordination – Supervision
✓Analysis of accountability
✓Report to the NPHCDA/NCC
National Coordinating Committee (NCC) (NPHCDA/NAFDAC/FMOH/WHO/UNICEF)
Interface field teams / NEC
Monitoring Surveillance - Supervision
Data Management - Secretariat of the NEC
Reference Laboratory Focal Point
•Reception - storage of bio samples
•State of the samples received
•Analysis according to the demands of NEC
STATE
State AEFI Committee
▪Detection of AEFI: passive
▪Actively - Alert + Support
▪ Investigation + Reference
▪Transmission of forms + samples
LGA AEFI Committee
▪Detection of AEFI: passive
▪ Actively - Alert + Support
▪ Investigation + Reference
▪ Transmission Forms + samples
PERIPHERAL
HF/Vaccination Post Vaccinators
✓ Detection of AEFI: passive
✓Actively Support
✓Warning and evacuation if serious AEFI
✓Transmission of forms + samples

MENAFRIVAC VACCINE USE IN NIGERIA

Epidemic meningitis occurs in the sub-Saharan belt from Senegal to Ethiopia. With the specific goal of eliminating Group A meningococcal epidemics in the countries of the Meningitis belt of Africa (Senegal, Gambia, Mali, Burkina Faso, Ghana, Benin, Niger, Nigeria, Cameroun, Chad, Sudan and Ethiopia), WHO and PATH formed the Meningitis Vaccine Project (MVP) and through an innovative consortium a new meningococcal-A conjugate vaccine called ***MenAfriVac***^{TM} was developed by Serum Institute of India and prequalified by WHO in June 2010 (Laforce, 2007 & Bishai, 2011) and is known to induce strong persistent immunological response to group A meningococcus with induction of immunological memory (Sow, 2011).

The vaccine was successfully piloted in Mali, Niger and Burkina Faso in 2010, Nigeria, Chad and Cameroon followed with preventive immunization campaign in 2011. For Nigeria, a phased introduction over 2-3 years has been proposed to ensure wider implementation and coordination of the campaigns. To this end, it is planned that the campaigns will first be introduced in Northern Nigeria and more specifically in the states bordering the Republic of Niger (where the vaccine had already been introduced) in order to optimize the herd immunity effect.

WHO and Uppsala Monitoring Centre (UMC) Sweden conducted a pre-campaign orientation and training on Adverse Events Following Immunisation for Nigerian stakeholders in July, 2011 in Abuja, Nigeria.

The AEFI structure and functions for the country were updated at that meeting with a view to ensuring that the AEFI recorded during the MenAfriVac campaign were reported in line with international standards.

The Federal Government of Nigeria immediately revived and restructured the National committee along these lines pending official inauguration which eventually took place on March 26, 2012. However, the National Coordinating Committee on AEFI as well as the National Expert Committee on AEFI Case Review and Causality Assessment organized a pre-campaign orientation meeting for the 5 phase one MenAfriVac states (Bauchi, Gombe, Jigawa, Katsina, and Zamfara) in Abuja prior to the campaign. The phase one implementing states were chosen by nationally determined criteria through the application of WHO District Prioritization Tool (DPT). After the implementation exercise, AEFI reports were received

from the field and causality assessment were carried on them by the National Expert Committee on AEFI Case Review and Causality Assessment and the reports eventually forwarded to NAFDAC to be captured into the national database.

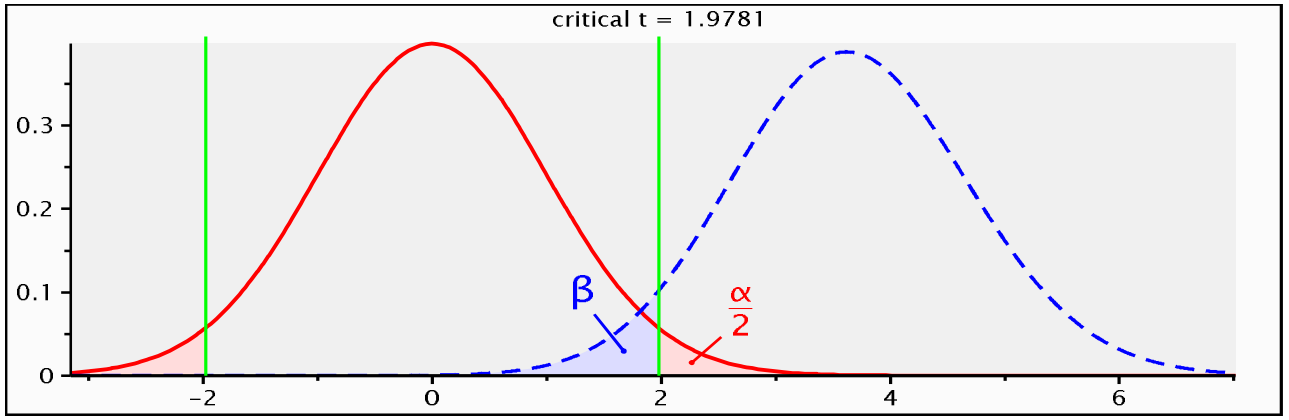
ANALYSIS OF AEFI REPORTS ON MENAFRIVAC VACCINE

Adverse Events Following Immunization data received by the National Pharmacovigilance Center (NPC) are monitored to detect unusual, rare or new vaccine adverse events, to monitor increases in established adverse events following immunization, to identify potential risk factors for particular types of adverse effects and to identify vaccine lots with increased types or numbers of reported adverse events (CDC, 2009). There have been confirmed case reports of Guillain-Barre Syndrome (GBS), a serious neurologic disorder of peripheral nerves amongst adolescents that received conjugate vaccines in the United States (CDC, 2009), while the most alarming reports were from the village of Guoro in Northern Chad of Africa where at least 40 out of five hundred children that received MenAfrivac vaccine aged between 7 and 18 became paralyzed and these children also suffered convulsions and hallucinations (England, 2013). In view of the above, adverse events following MenAfrivac vaccine reported at the NPC were therefore analyzed to establish type of reported reactions and potential risk factors that could predispose individuals to reactions reported.

Multiple Linear Regression Analysis of reported AEFIs

The G* power analysis was calculated a-priori using a medium effect size of 0.5 (Cohen's *d*) so as to ensure that the analysis is accepted with some level of confidence in the pool of subjects that are available (Fig 1.1). An alpha level of 0.05 and a 95% confidence interval was used to detect a likelihood of obtaining any significance between MenAfrivac reaction and the independent variables- age and sex. The non concentrality parameter δ of 3.64 and an actual power of 0.95 gave a total sample size of 134. However, a total of 138 ADRs received on MenAfrivac were analyzed and multiple linear regression was conducted. Based on the available data, the independent variables (age and sex) were analyzed to establish predictors of vaccine reaction (MenAfrivac).

Figure 1.1 G* Power analysis



Source: Generated by the National Pharmacovigilance Center, database management for the purpose of this study

t tests - Means: Difference from constant, one sample case

Analysis: A priori: Compute required sample size

Input:	Tail(s)	=	Two
	Effect size |ρ|	=	0.3
	α err prob	=	0.05
	Power (1-β err prob)	=	0.80
Output:	Noncentrality parameter δ	=	3.6404323
	Critical t	=	1.9780988
	Df	=	132
	Total sample size	=	134
	Actual power	=	0.9509217

Table 1.0 Statistics of variables in the MenAfrivac.sav file

Statistics				
		Age of respondents	Gender of respondents	MenAfrivac reaction
N	Valid	138	138	138
	Missing	0	0	0
Mean		2.18	1.35	1.78
Median		2.00	1.00	1.00
Mode		1	1	1
Std. Deviation		1.336	.478	1.995
Variance		1.784	.228	3.982
Skewness		1.340	.646	2.923
Std. Error of Skewness		.206	.206	.206
Minimum		1	1	0
Maximum		6	2	12
Percentiles	25	1.00	1.00	1.00
	50	2.00	1.00	1.00
	75	3.00	2.00	1.00

Source: Generated by the National Pharmacovigilance Center, database management for the purpose of this study

Variables in the MenAfrivac.sav file (table 1.0). Age of respondents (S.D= 1.336, M= 2.18, Skewness= 1.340), Gender of respondents (S.D= 0.478, M= 1.35, Skewness= 0.646). MenAfrivac reaction (S.D= 1.995, M= 178, Skewness= 2.923).

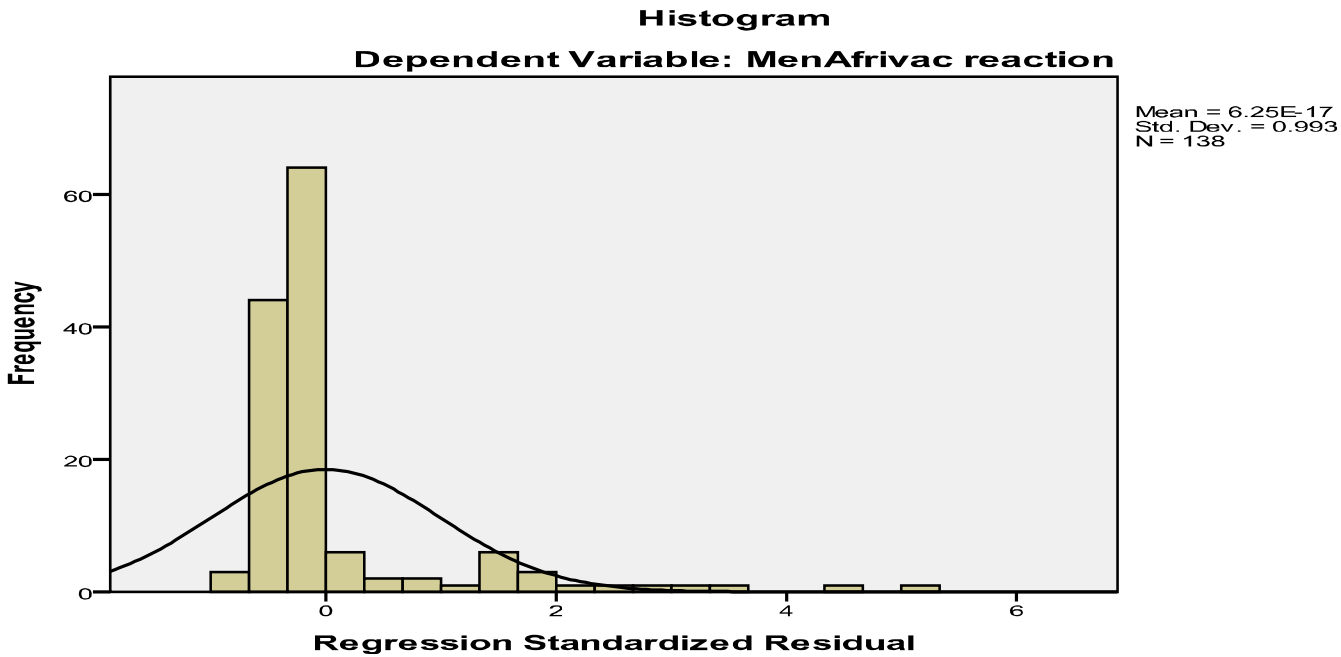
Table 1.1. MenAfrivac reaction in the MenAfrivac.sav file

MenAfrivac reaction					
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	unknown	3	2.2	2.2	2.2
	fever	106	76.8	76.8	79.0
	convulsion	8	5.8	5.8	84.8
	fever/syncope	2	1.4	1.4	86.2
	Git symptoms	3	2.2	2.2	88.4
	local reaction	8	5.8	5.8	94.2
	rashes	2	1.4	1.4	95.7
	headache/local reaction	2	1.4	1.4	97.1
	fever/insomnia	1	.7	.7	97.8
	headache/abscess	1	.7	.7	98.6
	vomiting	1	.7	.7	99.3
	febrile condition	1	.7	.7	100.0
	Total	138	100.0	100.0	

Source: Generated by the National Pharmacovigilance Centre, database management for the purpose of this study

Majority of the adverse drug reactions reported (76.8%, n= 106) were fever. Elevated body temperatures reported ranged from 37.5^0c to 40^0c while both local reaction and convulsions had a valid percentages of 5.8% (n=8). Other reactions reported include GIT symptoms, rashes, vomiting, febrile condition, headache, insomnia, and abscess (table 1.3). The age of respondents in the MenAfrivac.sav file (table 1.0) reflects more than half of the patients (71% n= 98) of whose ADR reports were received were aged 10years and below. This could be attributed to the increased ongoing immunization program for children and public awareness of child vaccination. Approximately 65% (n= 90) of the reports were from male patients while only about 35% (n= 48) of received ADR reports were from female patients (table 1.0).

Figure 1.2 Histogram of MenAfrivac reaction distributions



The histogram was skewed and this indicates an invalid normality of errors assumption (Fig 1.1). The regression standardized residual and frequency obtained reflects 'fever' as the highest number of reactions that was reported.

Multiple Linear Regression

Table 1.2 Coefficients of models in the MenAfrivac.sav file

Coefficients[a]													
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B		Correlations			Collinearity Statistics	
		B	Std. Error	Beta			Lower Bound	Upper Bound	Zero-order	Partial	Part	Tolerance	VIF
1	(Constant)	1.034	.570		1.813	.072	-.094	2.161					
	Age of respondents	.042	.128	.028	.331	.741	-.210	.295	.034	.028	.028	.998	1.002
	Gender of respondents	.487	.357	.117	1.365	.175	-.219	1.193	.118	.117	.117	.998	1.002
a. Dependent Variable: MenAfrivac reaction													

Source: Generated by the National Pharmacovigilance Center, database management for the purpose of this study

The coefficients' table indicated a non-significant relationship between MenAfrivac reaction and age of the respondents (table 1.2). *B*= 0.042, *S.E*= 0.128, *t*= 0.331, *p*= 0.741, 95%C.I (-0.210 – 0.295). There was also no significant relationship between MenAfrivac reactions and Gender of respondents (table 1.4). *B*= 0.487, *S.E*= 0.357, *t*= 1.365, *p*= 0.175, 95% C.I (-

0.219 – 1.193). The findings of the Linear Multiple Regression suggest that reactions experienced by patients after the administration of MenAfrivac vaccine might not be predicted by age and gender of recipients. Although, there was no significant relationship between the variables and MenAfrivac reaction, this could be attributepd to the vast differences in age groups and gender. Data were only analyzed based on received reports.

Conclusion

The Adverse Events Following Immunization (AEFI) so far received by the NPC towards MenAfrivac vaccine did not deviate from reports obtained from the post marketing surveillance of Serum Institute of India (manufactures of MenAfrivac conjugate vaccine) and from those established in literature (CDC, 2012, WHO, 2010). Causality assessments conducted on MenAfrivac reactions such as convulsions, syncope, GIT symptoms, abscess and insomnia established an unlikely relationship. All ADRs reported have been fully resolved with no disability. Although there have been no reports on any form of neurologic disorder or paralysis in Nigeria, increased collaboration between public health programs on immunization and the NPC is highly recommended. In addition, continuous reporting at vaccine centres should be encouraged with intensive follow up in cases of adverse events.

References

1. Autret-Leca E, Bensouda-Grimaldi L, Jonville-Béra AP, Beau-Salinas F. Pharmacovigilance of Vaccines, Arch Pediatr. 2006 Feb; 13(2):175-80. Epub 2005 Dec 15. Review. French. PMID: 16343870 [PubMed - indexed for MEDLINE]

2. Center for Disease Control and Prevention (2012). Possible side effects from vaccines. Retrieved from: http://www.cdc.gov/vaccines/vac-gen/side-effects.htm#mening.

3. Bishai DM, Champion S, Steel ME, Thompson L. Product development partnerships hit their stride: Lessons from developing a meningitis vaccine for Africa. Health Aff (Milwort) 2011; 30 June (6): 1058 – 64

4. Centers for Disease Control and Prevention (2006). Update: Guillain-Barré Syndrome among Recipients for Menactra® Meningococcal Conjugate Vaccine--United States, June 2005-September 2006. *MMWR*; 55(41):1120-1124.

5. Chen R. Safety of Vaccines. In: Plotskin SA, Orenstein WA, eds, Vaccines. Philadelphia, PA: Saunders, 1999; 1144-63

6. Dodoo AN, Renner L, van Grootheest AC, Labadie J, Antwi-Agyei KO, Hayibor S, Addison J, Pappoe V, Appiah-Danquah A. Safety monitoring of a new pentavalent vaccine in the expanded programme on immunisation in Ghana. Nederlands Tijdschrift voor Geneeskunde. 2007 Jan 20; 151(3):172-6.

7. England, C. (2013). Minimum of 40 children paralyzed after new meningitis vaccine. Vactruth.com. Retrieved from: http://vactruth.com/2013/01/06/paralyzed-after-meningitis-vaccine/

8. Faul F., Erdfelder, E., Lang, A.-G. & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, 39, 175-191.

9. Laforce FM, Konte K, Viviani S, Preziosi MP: The Meningitis Vaccine Project. Vaccine 2007: 25 (September Suppl 1) A97-100. Epub. 2007 May

10. Schumacher W, Legal/ethical aspects of vaccination. Dev Biol Stand 1979; 43: 435-8

11. Sow SO, Okoko BJ, Diallo A, Viviani S, Borrow R, Carlone G et al. mmunogenecity and Safety of a meningococcal A conjugate vaccine in Africa. New Engl. J. Med. 2011; 85 (5): 31 -2.

12. World Health Organization (2010). News Release, "Revolutionary new meningitis vaccine set to wipe out deadly epidemics in Africa;" Retrieved from www.who.org

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