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RESEARCH PAPER

Reporting of adverse events following immunizations in Ghana – Using disproportionality analysis reporting ratios

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ABSTRACT

Background: Timely reporting of safety information post vaccination is pivotal for the success of any vaccination program. Reports of adverse events following immunization (AEFI) of 6 different vaccinations from Ghana were analysed for signals.

Methods: De-identified data from active surveillance for AEFIs after 2009 AH1N1 influenza, yellow fever, meningitis, measles-rubella, pneumococcal-rotavirus and human papilloma virus vaccinations were used. All vaccinations occurred between January 2010 and December 2013. The ten most occurring events for each vaccination were captured and arranged using Medical Dictionary for Regulatory Authorities (MedDRA) Preferred Term (PT) and System Organ Classification (SOC) codes. Adverse event incidence rates were calculated for each vaccine type, and signals were generated using proportional reporting ratios (PRR).

Results: A total number of 5,141 reports were analysed ranging from 33 (human papilloma virus) to 1958 (measles-rubella). Between 22% and 55% of all AEFIs per vaccine type were collected on the day of vaccination. For each vaccine type, at least 87% of all reported AEFIs occurred in the first 7 days post-vaccination. Multiple reports were received per vaccine type. For the MR vaccine, urticarial recorded the highest attack rate of 6.6 (95% CI 6.2, 7.1) per 100,000 vaccines. The AEFI with the highest PRR for both human papilloma and measles-rubella vaccines was abdominal pain, recording a PRR of 8.15 (95% CI 3.46, 19.23) and 43.75 (95% CI 17.81, 107.45) respectively.

Conclusion: These results underscore the competency of public health systems in sub-Saharan African countries (like Ghana) to identify most frequently occurring and important vaccine related safety issues.

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active surveillance; Ghana; immunization; proportional reporting ratio; safety

Introduction

Vaccination is among the most important interventions in global health. As of 1974 only 5% of children globally, were protected from the six killer diseases, but by early 2017 about 86% were covered.[1] However, vaccines may be associated with unfavourable or unintended events, abnormal laboratory findings, symptoms or disease. Timely reporting of safety information post vaccination is essential for the success of any vaccination program.[2] This may not only help to ascertain the benefit-risk profile of vaccines, it may also encourage prospective vaccinees to avail themselves for vaccine uptake.[2,3] Because most vaccination programs involve large populations as against smaller sample sizes used in their pre-licensor stages, and because some of the events associated with vaccines are rare,[4] have late-onset, are unexpected, or could be population specific,[3] it is important to monitor vaccines post-licensor.

Surveillance systems in immunization in Ghana involve active reporting which involves a systematic search for defined AEFIs in specific populations in an attempt to determine the scope and true incidence of the events (normally done for newly introduced vaccines); passive reporting where the population or healthcare workers (HCW) report any condition they believe could be associated or related to a vaccine event (normally done for all established vaccines); and stimulated passive reporting which is similar to the passive surveillance, except that the system encourages the reporting of events in the community or at the HCW level (useful during national immunization days). For active and stimulated reporting, information is solicited from those vaccinated. Active reporting is a useful tool to conduct near real-time search for potential vaccine adverse events. It helps in the detection of an event temporal to vaccination, irrespective of its severity in its early stages.[5] Spontaneous (unsolicited) reporting systems sometimes may lead to incomplete information in the reports, involving exposures or outcomes, and this may restrict the value of data.[6,7] However, active reporting is expensive. It involves more time and resources,[7] and is therefore not routinely done.[5] The more a particular information is reported concerning a vaccine, the more likely it could be that there is an existing association or a causal relationship.

Signal detection is often used to establish safety signals for new medicines or vaccines and involves both quantitative and qualitative procedures. The most important quantitative signal detection methods involve both Frequentist and Bayesian

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statistical methods.[8] These include the proportional reporting ratios (PRR)[9] used by the European Medicines Agency (EMA)[10] and the Bayesian Confidence Propagation Neural Networks (BCPNN)[11-13] used by the Uppsala Monitoring Center (UMC) which is also the WHO Collaborating Center for international drug monitoring. Using the PRR and BCPNN in a paediatric pharmacovigilance study, Kajungu et al,[14] reported that both data mining methods were equally satisfactory in generating suspected signals.

Quantitative signal detection using databases of AEFI results involving multiple vaccination programs is rare in sub-Saharan Africa. Apart from one multi-site multi-country clinical study using antimalarial drugs in children,[14] there is no study using reports from multi-vaccine adverse events for signal detection. According to the Global Vaccine Safety Blueprint, of the 78 professionals from low and medium income countries (LMIC) who participated in the survey, only 15% reported conducting epidemiological studies using vaccine safety data.[15]

The aim of this study was to identify possible vaccine related safety issues using data of reports of AEFIs after 6 different vaccinations obtained from the Food and Drugs Authority Ghana. PRRs for individually reported adverse events were determined as proof of concept that this is achievable in LMIC.

Results

A total of 5141 AEFI reports were made for the six vaccinations. This comprised of 670 reports after pH1N1 vaccination, 33 reports after HPV vaccination, and 1958 reports after M-R vaccination. The rest were 621 reports after meningitis vaccination, 1028 reports after pneumococcal-rotavirus vaccination, and 831 reports after yellow fever vaccination. The total number of the 10 most reported AEFIs for all the 6 vaccines was 8089.

AEFI reports from females dominated that of males for all the vaccines under consideration (see Table 1). One person (female) and four people (three females and one male) respective died after receiving the pH1N1 and meningitis vaccines. Furthermore, one female died after receiving the yellow fever vaccine. The number of vaccinees with unknown outcome was highest for H1N1 (45.2%). The time to reporting of AEFIs received for all six vaccines are shown in Fig. 1.

AEFI reports for pHIN1 vaccination were received over a period of 40 days; for MR, Prevnar13-Rotavirus, MenAfric, HPV and Yellow fever vaccinations, the AEFI reports were received over a period of 30 days or less. In particular, in the case of MenAfric vaccination, no reports were made after 15 days of surveillance. Between 22% and 58% of all AEFI reports were collected on the day of vaccination. For each vaccination, at least 87% of all reported AEFIs occurred during the first 7 days post-vaccination. Multiple reports were made per person. For meningitis, measles-rubella, HPV, pneumococcal-rotavirus, yellow fever and pH1N1 vaccines the maximum number of reports were 7, 4, 5, 6, 8, and 11 respectively. The lowest for each vaccination type was a single report. Fever recorded the highest attack rate per 100,000 vaccinees for pH1N1, HPV, meningitis, and pneumococcal-rotavirus. For MR vaccine the AEFI with the highest attack rate per 100,000 vaccinees was urticarial which recorded a value of 6.6 (95% CI 6.2, 7.1). These and others are shown on Table 2. The most reported AEFI was fever, followed by urticaria. However, the single most reported AEFI by a vaccine was urticaria due to MR vaccination (768/1958). This was followed closely by fever, also after MR vaccination (710/1958). These and other reported AEFIs are shown on Table 3. The case of fever in Table 3 is described as follows: "for fever, whose preferred term (PT) is pyrexia in MedDRA, a total of 14 reports were obtained from those vaccinated with the HPV vaccine, 710 from those who received MR vaccine, 378 from those who received pH1N1 vaccine, 326 reports from those who were given the meningitis vaccine, 112 from YF vaccinees, and 580 reports from all those vaccinated with the pneumococcal-rotavirus vaccine".

According to Table 4 the highest PRR for pH1N1 vaccine was for dizziness (6.7 (95% CI 5.01, 8.18); $\chi^2 = 216.6$), followed closely by asthenia (5.71 (95% CI 4.52, 7.21); $\chi^2 = 268.7$). The highest PRR for HPV was abdominal pain (8.15 (95% CI 3.46, 19.23); $\chi^2 = 30.2$). Concurrent administration of pneumococcal-rotavirus vaccines (Table 2), led to reports of vomiting, but the PRR was not high enough to be captured as a signal. Watering eyes was a report made only among those vaccinated with pneumonia-rotavirus vaccine. Sensitivity and specificity results for PRRs were 63% and 97% respectively.

Discussion

We reported on adverse events following immunization after active surveillance, and used proportional reporting ratios (as a proof of concept) to detect signals involving six different vaccine types in Ghana. There were multiple reports per vaccinee for all the vaccines studied. Fever, injection site pain and

Table 1. Characteristics of those who reported AEFIs and type of vaccine used.

	H1N1 (N = 670)	HPV (N = 33)	MR (N = 1958)	Meningitis (N = 621)	Pn-Rotavirus (N = 1028)	Yellow fever (N = 831)
Mean age (SD)					(in weeks)	
	33.9 (10.9)	12 (2.4)	5.5 (4.0)	12.7 (8.5)	8.1 (4.6)	33.2 (15.8)
Gender						
Female (%)	463 (69.1)	33 (100)	983 (50.6)	330 (53.4)	537 (52.2)	517 (63.8)
Outcome after event						
Recovered (%)	340 (50.7)	33 (100)	1931 (97.7)	552 (88.9)	942 (91.6)	567 (68.2)
Not recovered* (%)	26 (3.9)	—	3 (0.15)	38 (6.1)	43 (4.2)	135 (16.3)
Death (%)	1 (0.1)	—	—	4 (0.66)	—	1 (0.1)
Unknown (%)	303 (45.2)	—	42 (2.2)	27 (4.35)	43 (4.2)	128 (15.4)
Vaccine ATC code	J07BB02	J07MB01	J07BD53	J07AH10	J07AL01/ J07BH01	J07BL01

*Condition of vaccinee at the time of reporting;

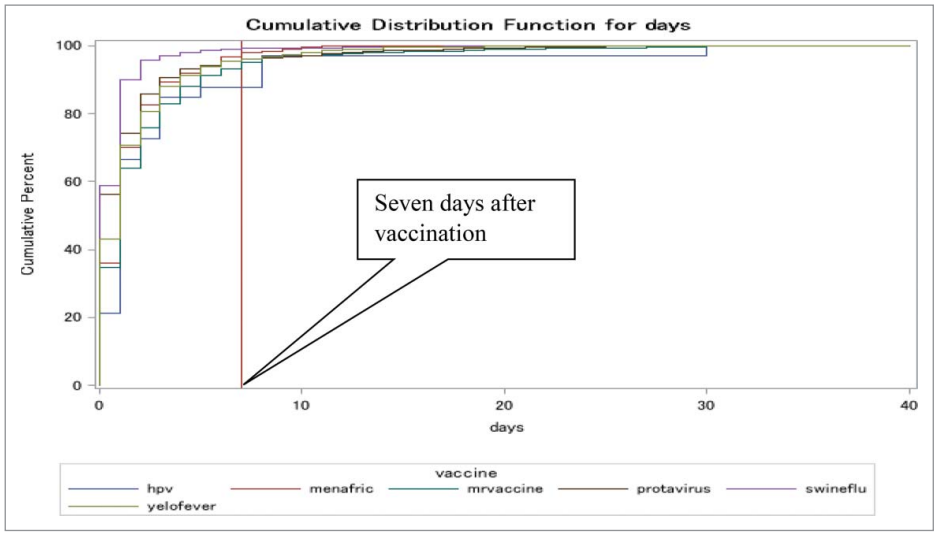

Figure 1. Plot of cumulative density function of AEFIs for all vaccine types. hpv = human papilloma virus vaccine, manafric = meningitis vaccine, mrvaccine = measle-rubella vaccine, protavirus = neumonia/rotavirus vaccine, swineflu = H1N1 vaccine and yelofever = yellow fever vaccine.

injection site abscess, were reported for all the six vaccines studied. Headache, nausea/vomiting were recorded for five of them. Watering eyes was reported among only those vaccinated with the pneumococcal-rotavirus vaccine administered concomitantly. Overall these results are in line with what is known from the SPCs of these vaccines.

Monitoring AEFIs from the day of vaccination is crucial[2] for attainment of results in real time. It is important not to miss any day post vaccination, especially during the first seven days, because most of the AEFIs occurred within this period. Training for field workers should consider this in subsequent immunization programs to improve the data collection process. This study identified multiple reporting of AEFI per vaccinee. Studies[27-29] on other vaccines also made similar observation.

Incidence rates generally agreed with what is in the various SPCs albeit a few instances where AEFIs reported in this study have not been captured in the SPC. Our findings suggest an association between pH1N1 vaccination and headache, myalgia, arthralgia, dizziness, and asthenia. According to the summary of product characteristics (SPC) of Pandemrix,[30] headache, myalgia and arthralgia are very common (affects more than 1 user in 10), dizziness is uncommon affecting 1 to 10 users per 1000. In a related but separate study[31] using a disaggregated data of health care workers from this dataset, it was found that the frequency of occurrence of events in the SPC was higher when compared.

One of the most common AEFIs of HPV vaccine was injection site pain.[32-34] Gastro-enteritis was a severe AEFI that occurred in only about 0.1% of participants.[32] The results on HPV vaccines and associated AEFIs was therefore consistent with current information.

Watering eyes was a report made only among those vaccinated with pneumonia-rotavirus vaccine.

From the summary of product characteristics (SPC) of the yellow fever vaccine,[35] headache is among the most frequently occurring adverse events, and arthralgia and myalgia are commonly occurring. Pruritus, although uncommon in the SPC, occurred frequently in this dataset. This needs to be studied

Table 2. AEFI incidence and incidence rate (with confidence intervals) per 100,000 vacinees for the six types of vaccines.

	HINI (N* = 1,719,256)	HPV (N = 21,525)	MR (N = 11,571,539)	Meningitis (N = 2,999,293)	Pneum/Rotavirus (N = 955,009)	Yellow fever (N = 7,021,423)
Fever	378[22.0 (19.8, 24.2)]	14[63.0 (31, 99.1)]	710[6.1 (5.7, 6.6)]	326[10.9 (9.7, 12.0)]	580[60.7 (55.8, 65.7)]	122[1.7 (1.4, 2.0)]
Headache	249[14.5 (12.7, 16.3)]	8[37.2 (11.4 62.9)]	91[0.8 (0.6, 0.9)]	219[7.3 (6.3, 8.3)]	—	283[4.0 (3.5, 4.5)]
Asthenia	151[8.8 (7.4, 10.2)]	—	—	36[1.2 (1.0, 1.6)]	84[8.8 (6.9, 10.7)]	—
Arthralgia	142[8.3 (6.9, 9.6)]	—	—	—	—	130[1.8 (1.5, 2.2)]
Inj Site abscess	172[10.0 (8.5, 11.5)]	—	—	167[5.6 (4.7, 6.4)]	355[37.2 (33.3, 41.0)]	—
Dizziness	108[6.3 (5.1, 7.5)]	2[9.3 (3.6, 22.2)]	—	71[2.4 (1.8, 2.9)]	—	—
Myalgia	147[8.6 (7.2, 9.9)]	—	—	57[1.9 (1.4, 2.4)]	—	132[1.9 (1.6, 2.2)]
Inj site pain	78[4.5 (3.5, 5.6)]	10[46.4 (17.7, 75.2)]	—	—	310[32.5 (28.8, 36.1)]	40[0.6 (0.4, 0.7)]
Pruritis	36[2.1 (1.4, 2.8)]	—	—	—	—	184[2.6 (2.2, 2.9)]
Nausea/vomiting	35[2.0 (1.4, 2.7)]	3[13.9 (1.8, 29.7)]	302[2.6 (2.3, 2.9)]	—	63[6.6 (4.9, 8.2)]	67[1.0 (0.7, 1.2)]
Urticaria	—	7[32.5 (8.4, 56.6)]	768[6.6 (6.2, 7.1)]	77[2.6 (2.0, 3.1)]	37[3.9 (2.6, 5.1)]	103[1.5 (1.2, 1.8)]
Abdominal pain	—	5[23.2 (2.9, 43.6)]	93[0.8 (0.6, 0.9)]	—	—	—
Cough	—	2[9.3 (3.6, 22.2)]	48[0.4 (0.3, 0.5)]	32[1.1 (0.7, 1.4)]	62[6.5 (4.9, 8.1)]	—
Diarrhoea	—		155[1.3 (1.1, 1.6)]	—	97[10.7 (8.1, 12.2)]	45[0.6 (0.5, 0.8)]
Decreased appetite	—	—	192[1.7 (1.4, 1.9)	103[3.4 (2.8, 4.1)]	45[4.7 (3.3, 6.1)[	—
Stomach ache	—	—	54[0.5 (0.3, 0.60)]	234[7.8 (6.8, 8.9)]	—	50[0.7 (0.5, 0.9)]
Watery eyes	—	—	—	—	51[5.3 (3.9, 6.8)]	—

*Total number vaccinated.

Table 3. Classification of top ten AEFIs associated with each type of vaccine by MedDRA System organ classification (SOC) and Preferred Term (PT).

SOC & adverse event	MedDRA-PT	Type of vaccination (number of events)
General disorders and administrative site conditions		
Fever	Pyrexia	HPV$^{\infty}$ (14) MR$^{\alpha}$ (710) H1N1 (378), Meningitis (326), YF$^{\wedge}$ (112), Pn-Rota* (580)
Injection site abscess	Injection site abscess	H1N1 (172), Pn-Rota (355), Meningitis (167)
Pain/ redness at site	Injection site pain	HPV (10), H1N1 (78), YF (40), Pn-Rota (310)
Weakness	Asthenia	H1N1 (151), Meningitis (36), Pn-Rota (84)
Nervous system disorders		
Headache	Headache	HPV (8), MR (91), H1N1 (249), Meningitis (219), YF (283)
Dizziness	Dizziness	HPV (2), H1N1 (108), Meningitis (71)
Lack of sleep	Insomnia	H1N1 (41)
Musculoskeletal and connective tissue disorders		
Joint pain	Arthralgia	H1N1 (142), YF (130)
Muscle (body) pain	Myalgia	H1N1 (147), YF (132), Meningitis (57)
Gastro-intestinal disorders		
Nausea/vomiting	Nausea/vomiting	HPV (3), MR (302), Pn-Rota, YF , H1N1 (35)
Abdominal pain	Abdominal pain	HPV (5), MR (93)
Diarrhoea	Diarrhoea	HPV (2), MR (48), Pn-Rota (63), YF (67)
Stomach ache	Abdominal pain upper	MR (54), Meningitis (234), YF (50)
Skin and subcutaneous tissue disorders		
Hives	Urticaria	HPV (7), MR (768), Meningitis (77), Pn-Rota (37), YF (103)
Itch	Pruritus	H1N1 (36), YF (184)
Respiratory, thoracic and mediastinal disorders		
Cough	Cough	HPV (2), MR (48), Meningitis (32), Pn-Rota (62)
Metabolism and nutrition disorders		
Loss of appetite	Decreased appetite	MR (192), Meningitis (103), Pn-Rota (45)
Eye disorders		
Excessive eye tearing	Watering eyes	Pn-Rota (51)

$^{\infty}$Human papilloma virus, $^{\alpha}$Measles rubella, $^{\wedge}$Yellow fever, *Pneumococcal-rotavirus

more carefully. Signals generated in this study for measles-rubella vaccine were all consistent with the SPC of measles-mumps-rubella vaccine.[36] Urticaria was classified as a commonly occurring side effect but loss of appetite and gastro-intestinal effects were all captured as uncommonly occurring side effects. Results from meningitis vaccination, and pneumococcal-rotavirus vaccination did not yield any new signals. The concomitant administration of pneumococcal and rotavirus vaccines was the first time in Ghana. Similarly, the meningitis project (using MenAfric vaccine)[37] in the meningitis belt of sub-Saharan Africa was the first time. Other countries in the meningitis belt who received the MenAfric vaccine before Ghana are Burkina Faso[38] and Niger.[39] AEFIs from these two countries[33,34] were similar to those in Ghana. Of the ten most occurring AEFIs in Ghana, 8 were recorded in Burkina Faso[38] and 9 were recorded in Niger.[39] This study follows the Global vaccine safety blueprint's strategic goal of enhancing capacity for vaccine safety assessment in countries that introduce newly developed vaccines or introduce vaccines in settings with novel characteristics.[15]

For regular events sensitivity is expected to be higher[25] compared to rare events. The figure of 63% could be described as acceptable because most sensitivity estimates are lower.[25] High enough sensitivity is required to avoid missing true AEFIs. The specificity of 97% is very good. Specificity is normally higher than sensitivity with adverse events[25,40] so our results conformed to existing practice. This could serve as a quantitative method in addition to current methods of signal detection by regulatory agencies in low and middle income countries most of whom rely on introspection from experts. Notwithstanding, Puijenbroek *et al*[9] have cautioned that the use of sensitivity and specificity could be misleading and should be seen as relative measures. For AEFI monitoring, all events following immunization are reported. This tends to increase the number of reported events but may not represent actual occurrences.[41] Notoriety bias[41] as a result of increased reportage could also play a role in this analysis. The high number of unknown outcomes (condition of vaccinees after AEFI report) for some of the vaccinees could be a limitation that may cause ascertainment bias. It is very possible that such vaccinees fully recovered and decided not to report considering the level of media publication before, during and after the vaccination process.

Conclusion

Almost all the signals generated were well-known and confirmed existing safety knowledge on the vaccines studied. The results underscore the ability of public health systems in Ghana to identify adverse events following immunization and quantify them appropriately. Immunization has been described as one of the best things that happened to our generation because of the associated benefits, but correct quantification of the concomitant risks is essential to provide accurate benefit-risk profiles of vaccines. The study emphasizes the need for more support for vaccine safety surveillance studies in sub-Saharan African countries.

Patients and methods

Setting and selection of data

National de-identified (anonymous) data on AEFIs were used for this study. In Ghana, national AEFI data are collected by the Food and Drugs Authority (FDA) Ghana in collaboration with the Expanded Programme on Immunisation (EPI) Ghana. The researchers were not directly involved with the collection

Table 4. First 10 most reported AEFIs per vaccine per vaccination type, showing PRR (95% confidence interval) and chi squared test results.

AEFI	H1N1 (SWINEFLU)	HPV	MR	Meningitis	Pneumonia-Rotavirus	Yellow fever
Fever	0.98 (0.89, 1.07), 0.2	1.00 (0.64, 1.57), 0.01	1.18 (1.09, 1.27), 16.9	0.93 (0.84, 1.02), 2.28	1.42 (1.32, 1.54), 72.11	0.34 (0.28, 0.40), 187.11
Headache	***1.88 (1.64, 2.15), 81.0***	1.44 (0.76, 2.74), 1.2	0.28 (0.23, 0.35), 166.0	1.78 (1.54, 2.05), 66.67	—	***2.99 (2.63, 3.40), 280.02***
Asthenia	***5.71 (4.52, 7.21), 268.7***	—	—	0.78 (0.55, 1.11), 1.92	1.71 (1.33, 2.20), 17.62	—
Arthralgia	***4.96 3.93, 6.24), 221.7***	—	—	—	—	***5.49 (4.36, 6.91), 257.93***
ISA*	1.49 (1.27, 1.76), 23.2	—	—	1.62 (1.37, 1.91), 33.09	***3.98 3.47, 4.57), 423.75***	—
Dizziness	***6.71 (5.01, 8.18), 216.6***	2, 1.69 (0.43, 6.65), 0.6	—	***3.30 (2.47, 4.43), 70.91***	—	—
Myalgia	***3.53 (2.86, 4.34), 156.3***	—	—	1.05 (0.79, 1.38), 0.10	—	***3.88 (3.15, 4.79), 178.8***
ISP^	0.98 (0.77, 1.25), 0.02	***3.54 (2.01, 6.24), 18.9***	—	—	***9.21 7.55, 11.24), 701.11***	0.60 (0.44, 0.83), 10.06
Pruritus	0.89 (0.62, 1.26), 0.4	—	—	—	—	***30.65 (21.76, 48.45), 887.86***
Urticaria	—	1.08 (0.54, 2.15), 0.04	***8.06 (7.00, 9.29), 1223.3***	0.43 (0.34, 0.54), 60.89	0.15 (0.11, 0.20), 200.30	0.69 (0.57, 0.84), 14.10
Abdominal pain	—	***8.15 (3.46, 19.23), 30.2***	***43.75 (17.81, 107.45), 200.7***	—	—	—
Nausea/Vomit	0.37 (0.26, 0.51), 38.0	0.97 (0.32, 2.93), 0.01	***4.23 (3.52, 5.08), 282.5***	—	0.59 (0.45, 0.76), 16.6	1.00 (0.78, 1.28), 0.01
Diarrhoea	—	—	***2.53 (2.03, 3.16) 71.8***	—	***1.83 (1.44, 2.31), 25.4***	1.06 (0.78, 1.45), 0.2
Cough	—	2.14 (0.54, 8.70), 1.2	1.18 (0.83, 1.66), 0.9	1.46 (0.99, 2.16), 3.7	***2.88 (2.08, 3.98), 44.0***	—
Watering eyes	—	—	—	—	0.97 (0.96, 0.98), 195.2	—
DA+	—	—	***3.05 (2.48, 3.76), 120.3***	***2.22 (1.78, 2.78) 50.5***	0.58 (0.42, 0.79), 12.4	—
Stomach ache	—	—	0.45 (0.34, 0.60), 32.3	***11.51 (9.21, 14.40) 721.6***	—	1.04 (0.78, 1.40), 0.1

*Injection site abscess; ^injection site pain; +Decreased appetite; ***(suspected signals are highlighted and indented***

of the data. They solicited for the data from FDA Ghana. It was therefore a third party data.

To improve the quality of data collection, several training activities on monitoring and evaluation are held prior to any national immunization campaign. AEFIs on six different vaccinations were collected using active surveillance at different times between January 2010 and December 2013. These were:

- 2009 influenza A (H1N1) inactivated monovalent vaccine (pH1N1 vaccine), 2010 – First time in Ghana
- Human papilloma virus (HPV) vaccination, 2013 – First time in Ghana
- Yellow Fever vaccination, 2012
- Meningitis (MenAfric) vaccination, 2012 – First time in Ghana
- Measles Rubella (MR) vaccination, 2013 – First time in Ghana
- Pneumococcal-rotavirus vaccination, 2013. – First time in Ghana

Vaccinations involved different age groups[16] depending on international agreements, groups at risk of exposure, and whether the disease is endemic in the region.[17] For example, for pH1N1, only adults, 18 years old and above were vaccinated.[18] For pneumococcal-rotavirus vaccination AEFIs were captured as though it was one vaccination because the two separate vaccines were administered concurrently. pH1N1 vaccination was introduced in Ghana in 2010 to combat the H1N1 2009 swine flu pandemic that affected many countries globally in 2009.[19] Yellow fever vaccination was as a result of confirmed increase in yellow fever cases[20] and an increased risk of some districts having the disease as a result of risk assessments done. Besides, Ghana is located in a region endemic for yellow fever. Cerebrospinal meningitis is a seasonal outbreak that mostly affects Ghanaians living within the African Meningitis belt with case-fatality rate between 6–14%.[21] Measles, pneumonia and diarrhoeal diseases normally affect children under five years old. Approval to use this third party data was obtained from FDA Ghana.

In Ghana, active surveillance is conducted for any vaccine on its maiden use. In the case of the yellow fever vaccination an active surveillance was conducted because prior to the vaccination there were a few yellow fever related deaths. In effect the data for all the six vaccines were from active surveillances.

Just after every vaccination, the vaccinated person was counselled by public health staff on the need to report any suspected events immediately. They were given mobile numbers to call and names of hospitals to visit immediately they observe any unusual changes. The expected unusual changes were explained to them. Particular referral centres were selected to take care of patients who reported severe AEFIs. At the selected referral sites, physician specialists and consultants with knowledge in the management of the expected AEFIs were selected to be on stand-by in the event of any serious AEFI. A pharmacist with knowledge on AEFIs was selected to ensure that all medicines prescribed for patients who reported any severe AEFI are supplied. A laboratory personnel was also chosen to take care of any laboratory investigations that may be needed. All these personnel were trained before immunization started.

Data analysis

The ten most occurring AEFIs for each vaccination were captured. These were arranged using Medical Dictionary for Regulatory Authorities (MedDRA®) Preferred Term (PT) and System Organ Classification (SOC) codes version 11.1. Median age with corresponding interquartile range was calculated for each type of vaccination. Cumulative density frequencies of all the events were plotted for each vaccine type to identify the most critical period (best time to monitor AEFIs over an acceptable period) to do real-time monitoring. Incidences and incidence (attack) rates per 100,000 vacinees and corresponding 95% confidence intervals were calculated, and the results were compared with the summary of product characteristics (SPC) of the representative vaccine. Denominators for calculating incidence rates were obtained from different sources.[18,22,23]

Proportional reporting ratios for the ten most occurring AEFIs per vaccination and corresponding 95% confidence intervals were calculated. The PRR is a measure of association between the putative factor of interest (in this case the exposed vaccine) and a particular outcome (in this case the reported AEFI). The higher the PRR, the greater the strength of association between the exposure and the outcome.[8,9,24,25] Mathematical formulae for calculating the PRR and its 95% confidence interval are shown on appendix I.

The sensitivity (total number of AEFIs combinations with association and a safety signal divided by the total number of AEFIs combinations with association, multiplied by 100) and specificity (total number of AEFIs combinations without association without a safety signal divided by the total number of AEFIs combinations without association, multiplied by 100)[26] of a safety signal were also calculated. In calculating these figures, the rule of thumb from the EMA guidelines[10] was used. According to EMA guidelines,[10] a signal should be considered if the number of AEFIs reported for an event of interest is greater than or equal to 3, the Chi squared test result is greater than or equal to 4, and the PRR is greater than or equal to 2. Microsoft Excel version 2007 (Microsoft Corporation, Redmond, WA, USA) followed by SAS software version 9.3 (SAS Institute, Cary, NC, USA) were used for the analysis.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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