Global Journal of Health Science; Vol. 10, No. 11; 2018
ISSN 1916-9736 E-ISSN 1916-9744
Published by Canadian Center of Science and Education

An Assessment of the Reporting Pattern of Adverse Events Following Immunizations in VigiAccess

Peter Yamoah[1, 2, 3] & Frasia Oosthuizen[2]

[1] Komfo Anokye Teaching Hospital, Ghana

[2] College of Health Sciences, University of KwaZulu Natal, Durban, South Africa

[3] Department of Pharmacy Practice, Faculty of Pharmacy and Pharmaceutical Sciences, Kwame Nkrumah University of Science and Technology, Ghana

Correspondence: Peter Yamoah, Box KS13055, Kumasi, Ghana. Tel: 233-24-337-4250. E-mail: pyamoah@gmail.com

Received: July 29, 2018 Accepted: August 17, 2018 Online Published: October 13, 2018

doi:10.5539/gjhs.v10n11p46 URL: https://doi.org/10.5539/gjhs.v10n11p46

Abstract

Purpose: Globally, adverse events following immunization (AEFI) reporting continues to be a challenge. It is estimated that about 95% of AEFIs never get reported after vaccinations necessitating strategies to improve it. The introduction of databases such as VigiAccess in which AEFI data from Pharmacovigilance centres around the world can be assessed is an important step towards improving AEFI reporting and enhancing vaccine safety. This study assessed the reporting pattern of AEFIs from the various continents of the world in VigiAccess, an open-access pharmacovigilance database.

Methods: VigiAccess was thoroughly searched on the 5th of February 2018 for the categories of reported AEFIs and number and types of AEFIs reported for measles vaccine, oral polio vaccine, yellow fever vaccine, pneumococcal vaccine, rotavirus vaccine, meningococcal vaccine, tetanus vaccine and BCG vaccine.

Results: After a thorough search through VigiAccess, 27 categories of reported AEFIs were retrieved. The total number of AEFIs for the 8 vaccines was 813,973. General disorders and administration site conditions were the highest number of AEFIs (251,405 representing 30.9%) followed by skin and subcutaneous tissue disorders (93,011 representing 11.4%) and nervous system disorders (89,077 representing 10.9%). With the continental data, the Americas recorded the highest number of AEFIs followed by Europe, Oceania, Asia and Africa.

Conclusion: General and vaccine administration site conditions were the highest number of AEFIs. The Americas recorded the highest number of AEFIs whereas Africa recorded the least. VigiAccess needs improvement in data synchronization to enhance its reliability.

Keywords: pharmacovigilance, adverse event following immunization, Uppsala Monitoring Centre, VigiAccess

1. Introduction

1.1 Background

The importance of vaccines in preventing deaths resulting from infectious diseases cannot be overemphasized (Lei, Balakrishnan, Gidudu, & Zuber, 2018). Globally, it is estimated that about 2.5 million child deaths alone are prevented by vaccines annually (World Health Organization, 2009). Out of these preventable deaths, a larger proportion is likely to occur in low and middle income countries (LMIC) where more doses of vaccines are used compared to the developed world (WHO, 2012a). As more doses of vaccines are administered, the risk of adverse events following immunization also increases. There is therefore the need to intensify the reporting of AEFIs particularly in LMIC in order to improve vaccine safety.

Vaccines are potent agents which are rigorously tested before approval for disease prevention (Miller, Moro, Cano & Shimabukuro, 2015). However some adverse events associated with them manifest after being used in larger populations following their approval some of which could be fatal if not managed promptly (Chung, 2014; Erlewyn-lajeunesse, Bonhoeffer, Ruggeberg, & Heath, n.d.). Globally, there have been concerns about vaccine safety which have led to dwindling confidence in immunization programs due to news about aftermath of rare but serious AEFIs such as hospitalization and death (Ozawa & Stack, 2013). A classical example is the flaw in the

manufacture of the Salk polio vaccine (improper inactivation of the virus) which led to 40,000 active polio cases causing 51 cases of permanent paralysis and five deaths among vaccinees, and 113 cases of paralysis and five deaths among contacts of vaccinated individuals (Offit, 2005).

To enhance confidence of potential vaccinees in immunization programs it is of utmost importance to develop strategies to document and report AEFIs. A study conducted in 2006 found out that about 95% of AEFIs never get reported after vaccination (Hazell & Shakir, 2006). Current studies have also observed similar trends of reporting. This usually happens because healthcare professionals to whom these AEFIs are reported usually feel that most of the AEFIs are mild and not harmful (Danova, Kocourkova, & Celko, 2017). Moreover, HCPs are more likely to report AEFIs they are already familiar with than unexpected events (Parrella, Braunack-Mayer, Gold, Marshall, & Baghurst, 2013). In a study conducted in the Czech Republic comparing observed AEFIs from a sample of paediatric GP practices with officially reported rate for instance, it was found out that the officially reported rate was far lower than that observed in the study (Danova et al., 2017). This necessitates the education of healthcare professionals on the need to report any unusual events after immunization regardless of how mild they may appear.

AEFI reporting could be active or passive. In active AEFI reporting, electronic systems are used to monitor AEFIs whereas passive reporting encompasses the voluntary reporting of AEFI by healthcare professionals, patients and the general public (Cashman et al., 2017; Li et al., 2014; Parrella, Gold, Braunack-Mayer, Baghurst, & Marshall, 2014). The vast majority of AEFI reports to national pharmacovigilance centres is passive in nature and may have some limitations such as the difficulty to link an adverse event to a vaccine, under-reporting of less severe AEFIs, misdiagnosis of AEFIs and inability to capture late occurring AEFIs after vaccination (Hu et al., 2013; Parrella et al., 2014). Despite these shortcomings, passive AEFI data especially from the public is important to collect in order for them to feel included in vaccine safety monitoring. Moreover, since the public is more likely to report unexpected AEFIs than HCPs their reports could lead to the discovery of rare AEFIs (Clothier et al., 2014; Parrella et al., 2013). Due to this, several studies have suggested that vaccinees and their caretakers (in case of children) must be well equipped to actively partake in AEFI reporting (Hazell, Cornelius, Hannaford, Shakir, & Avery, 2013; Inch, Watson, & Anakwe-Umeh, 2012).

Pharmacovigilance centres are mandated by the WHO to submit adverse drug reaction reports including AEFI reports from various countries to a large pool of adverse drug reaction electronic database called Vigibase (Ampadu et al., 2016). The database system includes the International Conference on Harmonization (ICH) E2B compatible Independent Case Safety Reports (ICSRs) database, the WHO Drug Dictionaries (WHO-DD and -DDE), WHO Adverse Reaction Terminology (WHO-ART), International Classification of Diseases (ICD), and the Medical Dictionary for Regulatory Activities (MedDRA) (Lindquist, 2008). Vigibase categorizes safety data into sex, disease condition for which a particular medicine was given as well as other relevant features on ICSR forms on which safety data of patients are recorded before submission. These features make the database a good resource for the UMC and other stakeholders of pharmacovigilance as it gives an indication of the number of safety reports submitted by each country from the time they joined the PIDM. Vigibase also gives information about the safety profile of medicines and vaccines as well as the quality of reports from the various reporting institutions to the national pharmacovigilance centres (Ampadu et al., 2016). Vigibase may also have the additional advantage of other adverse drug reactions and AEFIs which may not be known in published data as some ADRs and AEFIs are very rare, unsuspecting and late occurring (Yadav, 2008). Despite the relevant information in Vigibase, it is unavailable to the general public. However, the WHO has an alternative database called VigiAccess which is open to the general public and serves as a repository of reported adverse drug reactions and AEFIs (Shankar, 2016). The disadvantage of VigiAccess data is the fact that it does not include country specific adverse reaction and AEFI data but rather, continental adverse drug reaction and AEFI data. Additionally, details of patient data on ICSR forms are also not available in VigiAccess. Despite these disadvantages, VigiAccess can serve as a powerful tool for quick reference of adverse drug reactions and AEFIs by both HCPs and the general public due to its open access nature. This study assessed the reporting pattern of AEFIs from the various continents of the world in VigiAccess. It is hoped that findings from the study will serve as baseline data based on which future researchers will build upon towards improving vaccine safety and the quality of VigiAccess data.

1.2 Study Aim

To assess the reporting pattern of AEFIs in VigiAccess

1.3 Study Objectives

1). To ascertain the categories of reported AEFIs in VigiAccess

2). To quantify the number of the various categories of AEFI in VigiAccess for some selected vaccines

3). To quantify the total number of AEFIs of some selected vaccines in VigiAccess on continental basis

4). To assess the limitations to the use of VigiAccess

2. Methods

2.1 Study Design

The study employed a secondary research design in that existing AEFI data from a database was analyzed and interpreted.

2.2 Data Source

The WHO open access database for reported adverse drug reactions, VigiAccess was the data source for this study. VigiAccess contains adverse drug reaction and AEFI data of 131 full member countries of the WHO Program for International Drug Monitoring [PIDM] (UMC, 2018). The database contains the cumulative number of AEFIs of various vaccines from various countries from the time they joined the PIDM. VigiAccess was thoroughly searched on the 5th of February 2018 for the categories of reported AEFIs. Another search was conducted on the types and number of AEFIs reported for measles vaccine, oral polio vaccine, yellow fever vaccine, pneumococcal vaccine, rotavirus vaccine, meningococcal vaccine, tetanus vaccine and BCG vaccine. These vaccines were randomly selected from a list of 26 vaccines from the website of the Centres for Disease Control and Prevention that are commonly used across the various continents of the world for disease control and prevention (CDC, 2018).

2.3 Data Analysis

Data was periodically entered into SPSS software version 21 and analyzed after full entry. The categories of AEFI were classified based on the body systems and the vaccine product as done at the VigiAccess data interface of the VigiAccess website. The number of AEFIs reported for the vaccines were categorized based on the continents of the world (i.e. Africa, Asia, the Americas, Europe and Oceania). Furthermore AEFI data was categorized based on populations of the various continents of the world to compare population and number of AEFI reports. Tables were used to summarize the categories of AEFI and continental AEFI data and a graph was used to elucidate continental data.

3. Results

3.1 Categories of AEFIs

After a thorough search through VigiAccess, 27 categories of reported AEFIs in the database were retrieved. These included blood and lymphatic system disorders, cardiac disorders, congenital, familial and genetic disorders, ear and labyrinth disorders, endocrine disorders, eye disorders, gastrointestinal disorders, vaccine administration site conditions, hepatobiliary disorders, immune system disorders, infections and infestations, injury, poisoning and procedural complications, metabolism and nutrition disorders, musculoskeletal and connective tissue disorders, neoplasms (benign, malignant and unspecified such as cysts and polyps), nervous system disorders, pregnancy, puerperium and perinatal conditions, psychiatric disorders, renal and urinary disorders, reproductive system and breast disorders, respiratory, thoracic and mediastinal disorders, skin and subcutaneous tissue disorders, social circumstances, surgical and medical procedures and vascular disorders.

3.2 Vaccines versus AEFI Categories

The numbers of vaccinees affected by the various AEFI categories for each vaccine are illustrated in Table 1

From Table 1, the total number of AEFIs for the 8 vaccines was 813,973. General disorders and administration site conditions were the highest number of AEFIs (251,405 representing 30.9%) followed by skin and subcutaneous tissue disorders (93,011 representing 11.4%) and nervous system disorders (89,077 representing 10.9%).

PCV accounted for the highest number of AEFIs (317,208 representing 39.0%) followed by OPV (185,829 representing 22.8%) and MCV (145,447 representing 17.9%). Pneumococcal vaccine and OPV accounted for more than half of the total number of cardiac, congenital, endocrine, eye, general disorders, immune system disorders, infections and infestations, hepatotoxicity, metabolic and nutrition disorders, social circumstances and surgical and medical procedures related AEFIs. The pneumococcal and meningococcal vaccines also accounted for over a half of ear and labyrinth disorders. Additionally over a half of AEFIs associated with the nervous system, pregnancy, and vascular disorders were associated with the pneumococcal vaccine, OPV and meningococcal vaccine whereas over half of the gastrointestinal AEFIs were caused by pneumococcal vaccine, rotavirus vaccine, meningococcal vaccine and OPV. Furthermore, pneumococcal and rotavirus vaccines accounted for over half of injury, poisoning and procedural complications related AEFIs. The BCG vaccine alone caused over a half of lymphatic system related AEFIs. Measles vaccine was the only vaccine that recorded no vaccine product related

AEFIs.

Table 1. Number of reported AEFI categories for the various vaccines

AEFI	Vaccine (N)								
	MV	**OPV**	**YFV**	**PCV**	**RV**	**MCV**	**TV**	**BCG**	**TOTAL**
Blood and lymphatic system disorders	204	1799	391	3456	605	1282	330	8561	16628
Cardiac disorders	95	2861	232	3950	971	1221	192	162	9684
Congenital, familial and genetic disorders	11	238	29	345	186	55	18	28	910
Ear and labyrinth disorders	36	415	172	806	77	680	126	28	2340
Endocrine disorders	1	53	23	95	15	45	18	13	263
Eye disorders	161	2728	448	3503	813	2657	227	200	10737
Gastrointestinal disorders	537	10779	2615	17448	14722	12384	1130	624	60239
General disorders and administration site conditions	2493	63617	6966	105680	13039	43342	9268	7000	251405
Hepatobiliary disorders	21	174	165	404	122	95	35	224	1240
Immune system disorders	519	2286	340	3454	407	1453	612	223	9294
Infections and infestations	797	12702	798	20631	5332	4225	778	10233	55496
Injury, poisoning and procedural complications	198	2416	345	8901	5554	4816	332	726	23288
Investigations	121	4953	829	18047	7257	5641	476	560	37884
Metabolism and nutrition disorders	104	3424	254	5826	2833	1758	128	161	14488
Musculoskeletal and connective tissue disorders	196	4243	1950	17787	730	8483	1656	962	36007
Neoplasms benign, malignant and unspecified	7	123	27	251	39	71	30	225	773
Nervous system disorders	1139	21379	4326	29007	5153	24450	2536	1087	89077
Pregnancy, puerperium and perinatal conditions	19	98	78	91	28	98	33	10	455
Product issues	0	21	5	108	51	134	8	71	398
Psychiatric disorders	196	15067	364	14412	4855	4362	311	212	39779
Renal disorders	25	429	155	814	151	477	84	920	3055
Reproductive system and breast disorders	3	94	75	235	24	168	30	186	815
Respiratory, thoracic and mediastinal disorders	318	6580	918	11630	2474	3905	468	535	26828
Skin and subcutaneous tissue disorders	1720	21782	2535	39401	4368	18150	3174	1881	93011
Social circumstances	2	118	63	713	85	340	47	43	1411
Surgical and medical procedures	8	675	85	2743	1943	472	55	232	6213
Vascular disorders	131	6775	389	7470	1679	4683	679	449	22255
Total	9062	185829	24577	317208	73513	145447	22781	35556	813973

Key: **MV**- Measles vaccine, **OPV**-Oral Polio vaccine, **YFV**-Yellow Fever vaccine, **PCV**-Pneumococcal vaccine, **RV**-Rotavirus vaccine, **MCV**- Meningococcal vaccine, **TV**- Tetanus vaccine and **BCG**- Bacillus Calmette Guerin vaccine.

3.3 Continental AEFI Reports

In the VigiAccess software, the global population is classified based on the five continents of the world including Africa, Americas (north and south), Asia, Europe and Oceania. With the continental data, the Americas recorded the highest number of AEFIs since joining the WHO PIDM program, followed by Europe, Oceania, Asia and Africa. Africa recorded the highest number of yellow fever vaccine AEFIs, the Americas recorded the highest number of OPV, pneumococcal and rotavirus AEFIs, and Europe recorded the highest number of both meningococcal and Tuberculosis (BCG) vaccine AEFIs. Table 2 summarizes the distribution of AEFIs across the various continents of the world.

Table 2. AEFI reports from the various continents of the world

Vaccine	Continent					
	Africa	**Americas**	**Asia**	**Europe**	**Oceania**	**Total**
	N	**N**	**N**	**N**	**N**	**N**
Measles	573	2310	364	1685	212	5144
Oral Polio	1915	79068	4645	4902	1707	92237
Yellow fever	5290	4244	124	2499	243	12400
Pneumococcal	825	97103	5848	34082	9591	147449
Rotavirus	312	18242	3073	6070	3850	31547
Meningococcal	2862	29063	309	34364	5412	72010
Tetanus	197	4262	897	7091	545	12992
Tuberculosis (BCG)	351	3213	4235	16958	621	25378
Total (%)	12325 (3.1)	237505 (59.5)	19495 (4.9)	107651 (27.0)	22181 (5.6)	399157

3.4 Comparison of AEFIs With Current Continental Population

On the 5th of February 2018, when VigiAccess was searched, Asia had the highest population in the world, followed by Africa, the Americas, Europe and Oceania (World Population Review, 2018). Comparing the current population of the various continents with the number of AEFIs associated with the vaccines in this study, 4 in a million AEFI reports were from Asia, 10 in a million AEFI reports were from Africa, 1 in 10,000 AEFI reports were from Europe, 3 in 10,000 AEFI reports were from America and 5 in 10,000 AEFI reports were from Oceania. Table 3 illustrates the comparison of AEFIs across continents of the world.

Table 3. AEFIs versus current continental populations

Continent	**Population**	**Percentage population (%)**	**Number of AEFIs**	**AEFIs per citizen**
Africa	1,281,791,015	17.4	12325	$9.6*10^{-6}$
Americas	754,587,688	10.2	237505	$3.1*10^{-4}$
Asia	4,545,133,094	61.7	19495	$4.2*10^{-6}$
Europe	742,543,873	10.1	107651	$1.4*10^{-4}$
Oceania	41,157,193	0.6	22181	$5.3*10^{-4}$

In comparing population with AEFI reports, Oceania therefore ranks first in reporting followed by the Americas, Europe, Africa and Asia respectively.

4. Discussion

4.1 Categories of Reported AEFIs

An AEFI is any untoward medical occurrence that may present after the administration of a vaccine but which does not necessarily have a causal relationship with the treatment which could be any unfavourable or unintended sign,

abnormal laboratory finding, symptom or disease (CIOMS, 2012). The categories of AEFIs reported as revealed by the search in VigiAccess involved all body systems such as the cardiovascular, respiratory, nervous, skeletal, immune, circulatory, renal, reproductive, endocrine systems, eyes, ears and the skin. AEFIs typically result from immune reactions following immunization and can affect virtually all systems of the body. In all cases, causality assessment is necessary to be conducted on serious AEFIs to establish whether the medical occurrence resulted from the vaccine or not (Williams et al., 2013). However, this may not be necessary in minor AEFIs such as pain, swelling and redness of site of vaccination which are almost always expected after every vaccination. The minor reactions usually occur few hours after vaccination, resolve after a short period of time and poses little danger to the vaccinees (CIOMS, 2012). When properly done, causality assessment could help curb under-reporting and over-reporting of AEFIs. This means that healthcare providers and regulatory authorities must have cutting edge knowledge in the diagnosis and causality assessment of AEFIs. It is claimed that existing disease conditions before immunizations could trigger AEFIs. However, such claims could be verified through safety monitoring or clinical studies to be sure whether the immune response was actually caused by the vaccine (Shimabukuro et al., 2015). For instance, following the emergence of the H1N1 pandemic, mass public vaccination with AS03-adujvanted A (H1N1) pdm09 vaccine was undertaken in Sweden during which many narcolepsy cases were reported (Lakemedelsverket, 2011). Based on available information in the literature at the time, this led to a divided opinion among health experts as to whether the narcolepsy was immune mediated resulting from infections such as streptococcal and H1N1 infection (Aran et al., 2009) or vaccine induced (Han et al., 2011). Consequently a case-control study was conducted to ascertain the actual cause of the narcolepsy. The findings of the study did not support a disease history of narcolepsy before the A (H1N1) pdm09 vaccination and therefore led to the diagnosis of the medical occurrence as a vaccine related AEFI (Lamb et al., 2016).

4.2 Vaccines versus Number of AEFIs

The top 3 AEFIs caused by the vaccines studied were general disorders and administration site conditions, skin and subcutaneous tissue disorders and nervous system disorders. General and nervous system disorders are mainly caused by the immunological response to vaccines. While general disorders are mostly self limiting, neurological disorders are among the most serious, and on rare occasions, life-threatening complications after vaccination (Miravalle, Biller, & Bonwit, 2010). Even though life-threatening neurological cases after vaccination are rare, causality assessment to ensure that there was no pre-existing neurological condition before vaccination is of the essence if it occurs and specialist neurologist care may be appropriate to avert any unforeseen danger to vaccinees (Williams et al., 2011). Administration site conditions and subcutaneous tissue disorders are caused by reaction to components of the vaccines and wrong vaccination technique by the healthcare provider administering the vaccine. Patient profiling to access whether they react fatally to any of the components of the vaccine must be done prior to any vaccination exercise (Chung, 2014). Wrong vaccination techniques such as injecting at the wrong site have often led to abscesses and paralysis when nerves get damaged in the process. It is therefore important that vaccinators are educated periodically on vaccination techniques to prevent these occurrences (Lussier et al., 1999).

The top three vaccines associated with more than half of the recorded AEFIs were pneumococcal, oral polio and meningococcal vaccines. Each of these vaccines recorded general and administration site disorders as the highest number of AEFIs associated with its administration. It is therefore necessary for vaccinators to administer these 3 vaccines in particular with caution. Concurrent administration of these vaccines therefore calls for careful evaluation of risks and benefits as their additive effects could pose a risk to the vaccinees. Pneumococcal vaccine is indicated in patients with sickle cell disease, HIV infection and asthma for prophylaxis against pneumonia in many countries (Crum-Cianflone & Wallace 2014; Han et al., 2015). A study conducted by Han et al., 2015 observed that pneumococcal vaccine (PPSV23) could cause many severe adverse reactions when administered to paediatric and adolescent sickle cell disease patients even though not as much as it does in HIV and asthma patients. The authors suggested that it may be prudent for healthcare providers not to simultaneously administer pneumococcal vaccine (PPSV23) with other vaccines in order not to potentiate AEFIs associated with the pneumococcal vaccine.

4.3 AEFI Reporting Across Continents

The results showed that about 60% of all AEFIs worldwide were reported by the Americas whereas the least number was reported by Africa. These findings were similar to a June 2015 search in Vigibase. In the 2015 search however, reports from Africa were less than 1% as against 3.1% in this study. AEFI reports from the other continents in the 2015 search were America-60%, Europe-28%, Oceania-6% and Asia-5% (UMC, 2015). Even though these results show an improvement in number of AEFIs from Africa, there is still room for improvement. Comparing continental populations per AEFI report, Oceania ranked highest whilst Asia ranked lowest. While it may not be fair to compare AEFIs from continents because various vaccines have been used to different extents

across different continents from the time AEFI reporting began, it is also worth mentioning that since more doses of vaccines are currently being administered in low and middle income countries than developed countries, more AEFI reports are expected from low and middle income countries (WHO, 2012b, 2012c). Africa and Asia together reported about 8% of the global AEFIs. As Africa and Asia contribute to over three quarters of the population of the world, the largest proportion of the world's total AEFI reports was expected to be reported from there. Given the fact that more vaccine doses are administered in most countries in these 2 continents due to the large proportion of low and middle income countries, more needs to be done in maximizing AEFI reporting (WHO, 2012a). These continents need to expand the scope of AEFI reporting to all its countries as well as build capacity of reporting in order for number of AEFIs to be commensurate with the large number of vaccine doses administered.

4.4 Overview of AEFI Reporting and Strengths of Study

This study is the first of its kind to demonstrate the utility of AEFI data in VigiAccess as well as to identify the challenges associated with such data which could be improved in the bid to further vaccine safety.

Even though there has been an improvement in the safety monitoring of vaccines from the beginning of the 21st century, through functional safety monitoring systems there is still room for improvement (Chen et al., 2015). Since the establishment of the WHO Program for International Drug Monitoring (PIDM) in 1968, AEFI reporting had been very slow until the introduction of rigorous monitoring and reporting mechanisms by the WHO and national pharmacovigilance centres from the beginning of the 21st century. These included the Global Vaccine Action Plan (GVAP) and the WHO/UNICEF Joint Reporting Form (JRF) on immunization among others (WHO, 2015; WHO, 2016). GVAP and the WHO/UNICEF JRF for instance recommend the rigorous monitoring of AEFIs by countries and have identified the AEFI reporting ratio (number of AEFI reports per 100,000 surviving infants) as a key indicator for measuring the success of immunization programs. This has challenged many countries to improve vaccine safety in infants.

As of 2010, low and middle income countries were still lagging behind in vaccine safety and AEFI reporting, leading to the development of the Global Vaccine Safety Blueprint by the WHO and its strategic partners in 2011 (WHO, 2012b, 2012c). The goal of the blueprint was to further improve the capacity of regulatory authorities and other stakeholders of pharmacovigilance in low and middle income countries. To augment the efforts of the WHO and its partners in the improvement of vaccine safety, it is important for stakeholders to be abreast with the current situation through regular updates from the WHO and regulatory authorities. Stakeholders of vaccine safety include but not limited to healthcare professionals, academic institutions, vaccine manufacturers, the media, politicians, policy makers, expanded program on immunization (EPI) managers, non-governmental organizations and the general public (Hardt et al., 2013; National Academy of Sciences, 2013). All these groups play unique and significant roles towards improving vaccine safety by way of advocacy, research, reporting and policy formulation on AEFIs. VigiAccess is a good source of information on AEFIs of vaccines and adverse drug reactions (ADRs) in general which stakeholders can easily fall upon for current updates because of its open access nature. Academicians can analyze data in VigiAccess to inform politicians and policy makers on trends in AEFI reporting and ways to improve it. Moreover, vaccine manufacturers could be informed through VigiAccess as to vaccine products and their associated serious AEFIs which could lead to product safety improvement or recalls. Additionally all other stakeholders could join advocates in spreading information on vaccines and their associated AEFIs and the need for reporting.

4.5 Limitations of VigiAccess

In this study, the analysis of the various categories of AEFI in VigiAccess yielded a total number of 813,973 whereas the AEFIs from the various continents were 399,157. This disparity is a major limitation of the study. The disparity raises the concern as to which of the two figures to rely upon for informed decisions or policy formulation on vaccine safety. Even though the disparity did not have an effect on the continental analysis as it affected all continents to the same extent, it would have been better for both data to be same for better comparison between the two. This disparity has been explained at the VigiAccess website as due to the detection and removal of suspected duplicate reports from the VigiAccess dataset by an automatic algorithm called VigiMatch (VigiAccess Q & A, n:d). VigiMatch includes only reports which are complete and deletes those with omitted information on ICSRs from the various continents. Moreover, for suspected duplicate reports only the most complete reports are used in the statistics in VigiAccess. Furthermore, suspected duplicates deleted by vigiMatch could be "false positives", i.e. reports that are not true duplicates, but have been marked as such or "false negatives", i.e. true duplicates that have not been highlighted by the algorithm leading to the disparities.

Duplicates could arise from same AEFI reports on vaccines submitted by different pharmaceutical companies and healthcare institutions (from multiple caregivers of patients and healthcare providers) to national

pharmacovigilance centres. They could also arise via errors during the transfer of AEFI reports between different systems and databases. A thorough data audit therefore needs to be done before sending data to VigiAccess.

5. Conclusion

The study retrieved 27 categories of vaccine AEFIs from the VigiAccess website which involved all body systems. In all 813,973 AEFIs were obtained for all 8 studied vaccines from the search with general and vaccine administration site conditions being the highest number of AEFIs. The continental analysis yielded a total of 399,157 AEFIs out of which the Americas recorded the highest whereas Africa recorded the least. VigiAccess needs improvement in data synchronization to enhance its reliability.

5.1 Recommendations

1). Immunization programs in low and middle income countries must be strengthened and capacity for active surveillance and AEFI reporting improved. Capacity for active surveillance and AEFI could be built into existing health systems, particularly in countries with integrated electronic health information systems to make reporting easier.

2). All areas of immunization including pregnant mothers, infants, teenagers and adults must be improved to increase vaccination coverage.

3). All countries should be supported in the establishment of a process for causality assessment of serious AEFI to avoid misdiagnosis of AEFIs.

4). More rigorous efforts must be made by the Uppsala monitoring centre to reduce AEFI duplication as well as false negatives and positives in the VigiAccess database to repose more public confidence in VigiAccess data.

Acknowledgements

We acknowledge Dr. Didier Nzolo of the National Pharmacovigilance centre of the Democratic Republic of Congo for his valuable information on AEFI reporting pattern in 2015 from Vigibase. We are also grateful to the African Collaborating Centre for Advocacy and training in Pharmacovigilance, Accra Ghana for useful information on the Scope of Pharmacovigilance in Africa.

Competing Interests Statement

The authors declare that there is no conflict of interests regarding the publication of this paper.

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