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TRENDS OF COVID-19 VACCINE ADVERSE EVENT FOLLOWING IMMUNIZATION (AEFI): A ONE-YEAR RETROSPECTIVE REVIEW USING THE PASSIVE SURVEILLANCE DATA IN THE NIGERIAN NATIONAL DATABASE (VIGIFLOW).

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ABSTRACT

Since the introduction of the COVID-19 vaccines in Nigeria, NAFDAC has been working with multi-stakeholder groups to ensure efficient utilization of the COVID-19 vaccines and mechanisms for their effective safety monitoring. The safety profile of the vaccines that have been rolled out was based on clinical studies conducted in foreign countries. As these COVID-19 vaccines are novel and with a paucity of data to characterize their safety profile, it is imperative to review their safety data in Nigeria post-authorization hence this study. The study aims to analyze the trends of AEFIs from Passive surveillance reports due to COVID-19 Vaccines in the Nigeria National Database 'Vigiflow" from March 2021 to June 2022.

A retrospective review of all reported AEFIs in the Vigiflow database using passively collected AEFI surveillance data from March 2021 to June 2022 was carried out. Descriptive and inferential statistical methods of analysis were employed. A multivariable logistic regression model was constructed to identify factors associated with any adverse effects (vs no adverse effects). Levels of significance were set at 0.05 with Confidence Interval (CI) at 95%.

A total of 14,959 AEFIs were reported from March 2021 to June 2022. Amongst the AEFIs reported for various COVID-19 vaccines, fever, accounted for most AEFI with 31.8% (n = 7065). Headache and Injection site pain were other common AEFIs to COVID-19 vaccines with 13.2% (n = 2927) and 11.4% (2525) respectively. AstraZeneca brand of the vaccine had the highest number of AEFIs with 64.76% (n= 9687), followed by Moderna brand with 33.08% (n=4948), Pfizer brand, 1.37 (n= 205) and Janssen brand, 0.80%. Fifty-eight (58) AEFIs were identified as serious AEFIs and were investigated in detail by the State Immunization Programme Officers and reviewed by the National Expert Committee (NEC). Six of the top 10 AEFIs namely fever, headache, general body pain, pain at the injection site, tiredness, and local reaction were associated with vaccine brand type. Muscle aches and local reactions were associated with gender while local reactions and pain at the

injection site were associated with vaccine doses. None of the AEFIs were associated with the age group.

A sizeable number of AEFIs were reported in general but the frequency of serious AEFI was low. Overall all four brands of COVID-19 granted emergency use listing approval were well tolerated and no safety concern has been identified so far. Therefore, concluding that the safety benefit of the COVID-19 vaccine outweighs the risks.

Key Points

- There were four COVID-19 vaccine brands in use in Nigeria, these are AstraZeneca, Moderna, Pfizer Biotech, and Janssen. These brands are from conventional vaccine formulations such as mRNA technology and Adeno virus-based vaccines to meet national vaccine demands and needs
- There were 14,959 AEFIs reported at the time of this study, most of which were minor adverse events usually expected following immunization. Out of these, 1180 were reported as serious while 58 serious AEFIs were assessed by the National Expert Committee (NEC).
- The overall AEFI reporting rate ranged from 0.019 to 0.40 per 1000 for the four COVID-19 vaccine products in Nigeria.
- Overall, all four brands of COVID-19 granted emergency use listing approval were well tolerated and no safety concern has been identified so far. Therefore, concluding that the safety benefit of the COVID-19 vaccine outweighs the risks.

INTRODUCTION

Coronavirus Disease (COVID-19) caused by Novel Coronavirus named as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) was declared a pandemic by the World Health Organization (WHO) as a Public Health Emergency of International Concern (PHEIC) on January 30, 2020[1]. The deadly SARS-COV-2 virus that causes COVID-19 disease has spread globally, this has led to more than 3 million deaths with millions of people getting infected. This necessitated the rapid development of vaccines to contain the spread of this virus. At the end of 2020, the first vaccines were granted preliminary approval by the European Medicines Agency (EMA)[2,3]. Also, in December 2020, the first COVID-19 vaccines received emergency use authorization in the United States. Since then, billions of doses of vaccines have been administered worldwide. However, there have been concerns about their safety [4]. The Drugs Controller General of India has so far given its approval to five vaccines for use in India. Covishield (ChAdOx1), COVID-19 vaccine (Covaxin) (BBV152), Sputnik V, Johnson & Johnson, and Zycov are among the vaccines that have been authorized in India.[5]

Several vaccines have been extensively evaluated by the NAFDAC Vaccine Committee with strict regulatory actions and have been given the WHO's Emergency Use Listing (EUL). The Agency takes at least 15 days to carefully review the vaccine dossier or submission package to make sure that the benefits of the vaccine far outweigh the risks and that any side effects are noted for follow-up monitoring by the appropriate NAFDAC and Primary Health Officers after vaccination[6]. The Director General of NAFDAC granted Emergency Use Listing for the first COVID-19 vaccine, Covishield on 20th March 2021.[7] This was followed by Janssen COVID-19 Vaccine on May 17th, 2021[8] and in July 2021, the approval for Moderna and AstraZeneca (Korea) vaccines were granted.[9]

Since the introduction of the COVID-19 vaccines in Nigeria, NAFDAC has been working with multi-stakeholder groups to ensure efficient utilization of the COVID-19 vaccines and mechanisms for their effective safety monitoring. The National Pharmacovigilance Centre (NPC) is domiciled within the National Agency for Food and Drug Administration and Control (NAFDAC) in Nigeria. The Agency regulates and controls the manufacture, importation, exportation, distribution, advertisement, sale, and use of food, drugs, cosmetics, chemicals, detergents, medical devices, and packaged water[10]. The NPC oversees the coordination of all pharmacovigilance activities in Nigeria. It maintains a functional national database 'Vigiflow', receives, documents, follow-ups, analyzes, and evaluates Individual Case Safety Reports (ICSRs), conducts causality assessment of ICSRs in the National database, and periodically sends out alerts on medicine safety concerns.[11]

Adverse events following immunization (AEFI) reports are collected by Active or Passive surveillance. The passive surveillance report is defined as unsolicited reports of adverse events that are sent to a central database or health authority[12]. In Nigeria, these reports are received via several reporting tools and entered into the Nigerian National Database 'Vigiflow'[13]. Passive AEFI surveillance helps to identify population-specific, late-onset, unusual, or unanticipated adverse events that may not have been picked up in pre-licensure vaccination studies[14]. AEFI is any untoward medical occurrence that follows immunization, and which does not necessarily have a causal relationship with the usage of the vaccine. If not rapidly and effectively dealt with, can undermine confidence in a vaccine and ultimately have dramatic consequences for immunization coverage and disease incidence[15].

AEFI is divided into two categories by the World Health Organization (WHO) as Serious and Non-Serious. An AEFI is serious if it causes death, poses a threat to life, necessitates inpatient hospitalization, or extends a current hospitalization and causes a permanent disability. When a reaction happens shortly after injection, subsides quickly, and poses little to no risk, an AEFI is said to be non-serious[16]. Any undesirable or unanticipated sign, aberrant test finding, symptom, or disease may qualify as an adverse event. Reports of adverse events can either be coincidental occurrences that are not directly related to immunization but are temporally related to it or actual adverse events, which are those that are caused by the vaccination or immunization procedure[17]. Country-specific contextualized AEFI definitions could be adopted. Nigeria, however, complies with WHO recommendations. According to the WHO categorization, the five major categories for classification of AEFI could be the Vaccine product related reactions, vaccine quality defects, immunization-error related reactions, immunization-anxiety related reactions and coincidental reactions or events. Some serious AEFIs are reviewed by the National Expert Committee (NEC) on Review of AEFI and Causality Assessment at the national level. It was first inaugurated in 2012 with the objective; To assess causes of serious and unusual AEFI; To provide consultation or recommendation for appropriate actions to be taken (corrective action, communication, feedback and crisis management); It is also involved in the investigation of serious AEFI. The committee's membership is composed of broad expertise, including the following: Public Health Physician, Pediatrician, Neurologist, Immunologist, Infectious disease specialist, Physician, Pathologist, Medical Laboratory scientist, Pharmacists[18].

The COVID-19 pandemic has been a burden in most countries of the world. The fast development and roll-out of the novel COVID-19 vaccines granted EUL to curtail the impact of the disease, the vaccine hesitancy and the corresponding global trend of AEFIs in some cases have been of concerns in so many countries. The safety profile of the vaccines that have been rolled out were based on clinical studies conducted in foreign countries. As these COVID-19 vaccines are novel and with paucity of data to characterize their safety profile, it is imperative to review their safety data in Nigeria post authorization hence this study.

General Objective: To analyze the trends of AEFIs from Passive surveillance reports due to COVID-19 Vaccines in the Nigeria National Database 'Vigiflow" from March 2021 to June 2022.

Specific Objectives:

1. To determine the patterns and seriousness of AEFIs associated with the COVID-19 vaccine.
2. To compare the reported AEFIs of the various COVID-19 vaccine brands
3. To evaluate the demographic and other factors (e.g. sex, age group, vaccine brand etc.) associated with the reported AEFIs

METHODS

Study design:

A retrospective review of all reported AEFIs in the Vigiflow database using passively collected AEFI surveillance data from March 2021 to June 2022 was carried out.

Inclusion Criteria:
All passively reported AEFIs due to COVID-19 Vaccines in the Vigiflow from March, 2021 to June, 2022

Exclusion Criteria:
1. All reported AEFIs not due to COVID-19 Vaccines in the Vigiflow from March 2021 to June 2022
2. All reported AEFIs due to COVID-19 Vaccines not captured in the Vigiflow from March 2021 to June, 2022
3. All AEFIs reports captured by Active CEM surveillance are excluded.
4. All AEFIs that are not properly coded were also excluded.

Data Extraction and Cleaning:
All AEFI surveillance data received between March 2021 and June 2022 entered into Vigiflow were extracted using the search and statistics function of Vigiflow. This function allows query of the database on key parameters of interest.
For this study, the key parameters of interest include; demographics, number of AEFI reported for each type of COVID-19 vaccine and seriousness criteria. The query results were exported to a Microsoft Excel® file for cleaning and analysis.
Reports that did not have the minimum required information for a valid report, i.e. an identifiable reporter (name, location, or professional qualification); an identifiable patient (name or initials, age and/or sex); a suspected medicine (brand or generic name) and description of an AEFI, were removed from the data and excluded from the analysis.
Patterns of non-serious and serious AEFIs were evaluated. A serious AEFI is defined as an adverse event that causes death, poses a threat to life, necessitates in-patient hospitalization, extends a current hospitalization or causes a permanent disability.

Data Analysis
Descriptive and inferential statistical methods of analysis were used for this study. Measures of central tendency for continuous variables were also used to display the various means with their corresponding Standard Deviations, Medians, and interquartile Ranges (Lower and Upper). One-way ANOVA and t-test were used to compare continuous distribution variables. Categorical variables were compared using Chi-Squared and/or Fisher's Exact Test. AEFI reporting rates were calculated using denominator data from the National Primary Healthcare Development Agency.
A multivariable logistic regression model was constructed to identify factors associated with any adverse effects (vs no adverse effects). Levels of significance were set at 0.05 with Confidence Interval (CI) at 95%. The data were analyzed using Jupyter Notebook (Colab) and SPSS 23.0.
Using a logistic regression model to examine the association of demographic (Sex, Age group) and vaccine characteristics (Vaccine brand and Vaccine dose) which was entered into the model simultaneously to determine the factor that is strongly associated with the common AEFIs reported. The first group in each class (i.e. male, age >20, AstraZeneca, and 1st dose) was used as the reference group.

RESULTS
COVID-19 vaccine immunization commenced in Nigeria in March 2021 and 14,959 AEFIs were reported from March 2021 to June 2022. Amongst the AEFIs reported for various COVID-19 vaccines, fever accounted for most AEFIs with 31.8% (n = 7065). Headache and Injection site pain were other common AEFIs to COVID-19 vaccines with 13.2% (n = 2927) and 11.4% (2525) respectively. Others include malaise 7.5% (n=1673), generalized body pain 3.9% (n=863), muscle aches 2.5% (n= 548), chills 2.30% (n=512), joint pain 2.0% (448) and tiredness 1% (n=330). Other

reactions like abdominal pain, dizziness, blurred vision, sleepiness, restlessness, and numbness accounted for the remaining percentage as seen in Table 1 and Fig 1.

From the four vaccines granted emergency use authorization by NAFDAC, AstraZeneca had the highest number of AEFIs with 64.76% (n= 9687), followed by Moderna with 33.08% (n=4948), Pfizer 1.37 (n= 205) and Janssen 0.80% (n=119), see Table 1 and Fig 1 below.

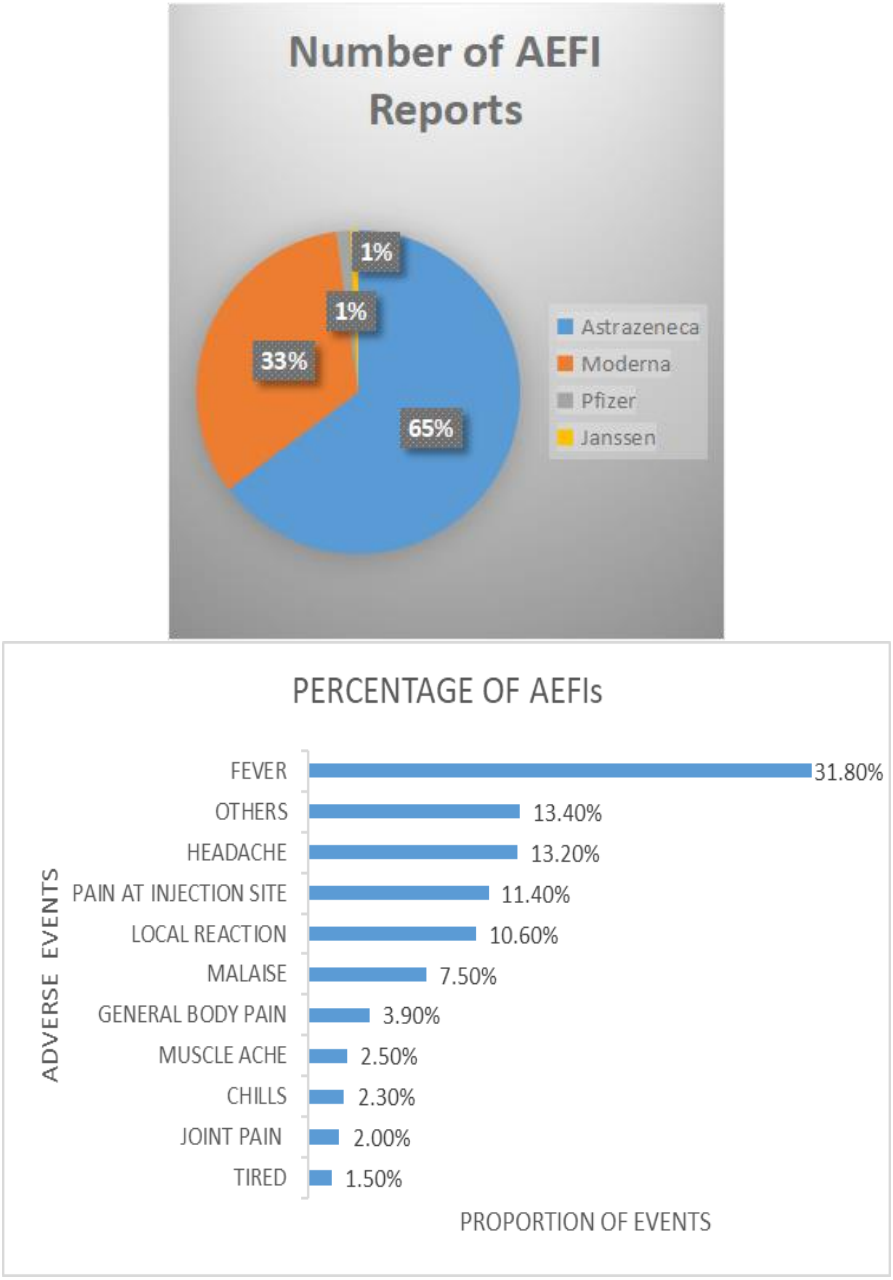

Fig 1: Proportions and Patterns of AEFIs reported in Nigeria

Table 1: Demographic Characteristics, Geographical Locations and Seriousness of AEFIs

Baseline Characteristic	Frequency of AEFI	Percentage (%)
Sex:		
Male	7655	51.173
Female	7304	48.827
Age group		
<20	248	1.658
20-29	1892	12.648
30-39	2216	14.814
40-49	1902	12.715

50-59	1149	7.681
≥60	687	4.593
Not indicated	6865	45.892
Geopolitical Regions		
North Central	2264	15.14
North East	384	2.57
North West	2912	19.47
South East	422	2.82
South West	4021	26.89
South South	1513	10.12
Not indicated	3439	23.00
Total	14955	100
Serious		
Yes	1180	7.888
No	13776	92.092
Not Indicated	3	0.020

The percentage of males with AEFIs was 51.17% (n=7655) slightly higher than the females with 48.83% (n=7304). The age range varied from <20 to ≥60, however in 45.98% (n=6865) of the AEFIs the age was not indicated as shown in Table 1 above. Out of the 14,956 AEFI reports recorded, 7.89% (n=1180) were reported as serious (Table 1), Fifty-eight (58) of these were qualified as serious AEFIs based on the definition. They were thus investigated in detail by the State Immunization Programme Officers and reviewed by the National Expert Committee (NEC). The committee concluded that fifteen (15) reactions were coincidental, thirty-one (31) were due to Vaccine product reaction, four (4) were immunization error related, two (2) were immunization anxiety-related, three (3) temporal relationships were consistent but the evidence was inconclusive, two (2) had conflicting trend of consistency and inconsistency with causal association to immunization while One (1) report is still under investigation. Details can be found in Table 4 (Appendix 1).

Table 2: Proportion of AEFIs due to COVID-19 Vaccine Immunization Reported in Nigeria

Vaccine Brand	Number of AEFI Reports	Number of Serious AEFI*	No of Doses Administered	Reporting Rate (Per 1000)	Serious AEFI Reporting Rate (Per 1000)
AstraZeneca	9687 (64.76%)	882	24,222,570	0.39992	0.03641
Moderna	4948 (33.08%)	267	19,892,432	0.24874	0.01342
Pfizer	205 (1.37%)	21	13,623,678	0.01505	0.00154
Janssen	119 (0.80%)	10	6,212,095	0.01916	0.00161
Total	**14,959**	**1180**	63,950,775		

***This includes those reported from the med safety app**

Table 3: Pattern of AEFIs reported for the COVID-19 vaccine brand used

	Vaccine Name				
AEFI	**AstraZeneca (n/n%)**	**Moderna (n/n%)**	**Pfizer (n/n%)**	**Janssen (n/n%)**	**Total**
Fever	4763 (66.236%)	2146 (%) 29.843	205 (2.851 %)	77 (1.071%)	7191
Chills	276 (53.906%)	234 (45.703%)	0 (0%)	2 (0.390%)	512
Headache	1947 (66.519%)	929 (31.739%)	24 (0.820%)	27 (0.922%)	2927
Joint pain	319 (71.210%)	124 (27.679%)	3 (0.670%)	2 (0.446%)	448
Pain at injection site	1160 (45.941%)	1288 (51.010%)	53 (2.099%)	24 (0.950%)	2525
General Body Pain	558 (64.660 %)	282 (32.677%)	19 (2.202%)	4 (0.463%)	863
Weakness/Malaise	1037 (61.984%)	618 (36.940%)	15 (0.897%)	3 (0.179%)	1673
Local reaction	2340 (99.957%)	11 (0.468%)	0 (0%)	0 (0%)	2351
Tiredness	121 (36.667%)	207 (62.727%)	2 (0.606%)	0 (0%)	330
Muscle aches	351 (64.051%)	196 (35.766%)	1 (0.182%)	0 (0%)	548
Total per Vaccine	12,872	6,035	322	139	**19,368**

Two deaths were recorded as shown in Table 3 above, the deaths were however coincidental after the investigation and review by NEC.

In this study, six of the top 10 AEFIs namely fever, headache, general body pain, pain at the injection site, tiredness, and local reaction were associated with vaccine brand type. Muscle aches and local reactions were associated with gender while local reactions and pain at the injection site were associated with vaccine doses. None of the AEFIs were associated with age group (Table 5, Appendix 2).

Using logistic regression to determine the association of AEFIs with demographic (age group, and gender) and vaccine (vaccine brand and doses) characteristics, headache was strongly associated with the Astra Zeneca and Pfizer vaccines (OR=0.795, 95% C.I =0.634, 0.998, P=0.048). General body pain was strongly associated with the Moderna and AstraZeneca vaccine (OR=0.432, 95% C.I =0.277, 0.675, P=0.000) while pain at the injection site was most strongly associated with the Moderna vaccine (OR= 2.723, 95% C.I. = 2.164, 3.427 P=0.000) Local reaction was associated with Astra Zeneca and Pfizer vaccine (OR=0.003, 95% C.I =0.001, 0.013, P=0.000) while tiredness was strongly associated with the Moderna vaccine (OR=6.397, 95% C.I =3.597, 11.38, P=0.048). For vaccine doses, those who received a second dose were less likely to experience a local reaction (OR = 0.027, 95% C.I = 0.008, 0.084 P=0.000) but more likely to experience pain at the injection site (OR =1.027, 95% C.I =0.610, 1.730 P = 0.000. Concerning gender, females were about 4 times more likely to experience a local reaction (OR= 3.788, 95% C.I. = 3.065, 4.681 P= 0.000), and about 2 times more likely to experience muscle aches (OR=1.6821, 95% C.I = 165, 2.429 P =0.006). (Table 5).

DISCUSSION

Traditionally, data on AEFIs, and more specifically AESIs, are obtained during clinical trials of vaccines before marketing authorization, a larger and more diversified population is immunized during the COVID-19 vaccine deployment, therefore making it possible to study their safety profile in real-life settings[3]. This study described the frequencies and types of AEFIs for the approved COVID-19 vaccines in Nigeria. It also compared AEFI reporting rates among individual vaccines using the Vigiflow database between May 2021 and June 2022. Within this period there were 14,959 AEFIs reported in the Vigiflow. Overall, the AEFIs were generally mild and well tolerated. The overall reporting rate for the different COVID-19 vaccines ranged between 0.019 to 0.39 per 1000 doses. This was comparable to the rate reported in Pakistan (0.29 - 0.79 per 1000)[19] and Ontario[20] (0.60 per 1000) and significantly lower than that of the UK (about 4 per 1000)[21]. Under-reporting is a regular feature of passive surveillance especially in low and middle-income countries. The Nigerian National Pharmacovigilance Centre has continued to organize capacity-building workshops on pharmacovigilance for healthcare professionals (HCPs), the introduction of the Med Safety App in Nigeria around November 2020 enhanced the reporting of AEFIs but there is still a need for more training and awareness creation. Furthermore, active safety surveillance systems[22], like the cohort event monitoring exercise anchored by NAFDAC in collaboration with the University of Maryland, Baltimore (UMB) which is currently ongoing in Nigeria and can detect safety signals in a relatively rapid manner, will provide a more complete and accurate information on the AEFIs. The most reported AEFIs for all four COVID-19 vaccines overall and individually include fever, headache, malaise and injection site pain. Our findings are consistent with previous studies. A recent study using the Vaccine Adverse Event Reporting System (VAERS) database showed that headache, fatigue, chills, pyrexia, and pain were among the top five commonly reported AEFIs for all three COVID-19 vaccines (Pfizer, Moderna and Janssen) studied[23]. Wu et al, showed in a review evaluating the safety profile of COVID-19 vaccines, reported that headache and fatigue were the most common systemic reactions while pain at the injection site was among the most common local reactions[24]. Another study in Europe reported similar findings with the most common AEs reported after the administration of three COVID-19 vaccines (Pfizer, Moderna, and Astra-Zeneca) being myalgia, chills, fatigue, headache, and fever for systemic effects and sore arm

and erythema for non-systemic injection site reactions[25]. These AEs are usually mild and resolve within a short period. Serious AEFIs reports in this study accounted for about 0.39% which is fairly comparable to two US studies, one from an online cohort of 19,586 adults who received COVID-19 vaccination[4] (0.2 - 0.3%) and the other from the VAERS database[23] (<0.1%) but in contrast to a Canadian study of 5.6%[20]. It is however important to note that the 1180 AEFIs that were reported as serious were not truly serious based on the definition of a serious AE. Majority of these reports came in through the Med Safety App, where vaccinees and HCPs (trained and untrained) have the opportunity to report both non-serious and serious AEFIs, thus an AEFI may be reported as serious but does not qualify as a serious AEFI. To buttress the above point, the number of AEFI reports (both non-serious and serious) increased by about 8 folds following the introduction and deployment of the mobile phone reporting software known as the *med safety app*. Only 58 serious AEFIs were identified and the analysis by the NEC confirmed their serious nature. The outcome of the analysis revealed that most of the serious AEFIs were vaccine product-related (31 reports) and some were coincidental (16 reports) this was slightly different from findings from a study in Pakistan where 24 AEFIs were classified as serious out of which 19 cases are coincidental and 5 cases were still under investigation[19.]

Reactogenicity of the four vaccine brands used shows that Janssen and Pfizer vaccine brands were associated with the lowest rate of reactogenicity as compared to the Astra Zeneca vaccine which had the highest rate of reactogenicity and fever was the most reported AEFI. This finding is similar to a Dutch study done across the four vaccine brands[3].

CONCLUSION

This study provides important data on the patterns and determinants of AEFI across sex, age groups, and vaccine brands. Most of the determinants of AEFI had less association with the most commonly reported AEFIs except for vaccine brands. A sizeable number of AEFIs were reported in general but the frequency of serious AEFI was low. Overall, all four brands of COVID-19 granted emergency use listing approval were well tolerated and no safety concern has been identified so far. We therefore conclude that the safety benefit of the COVID-19 vaccine outweighs the risks. Further longitudinal studies will however be needed to further assess and verify our findings given the known limitations associated with the passive spontaneous reporting system.

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