Contextualizing adverse event following immunization data of coronavirus disease 2019 (COVID-19) vaccines in VigiAccess: An approach for reducing COVID-19 vaccine hesitancy

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Abstract

Introduction

Vaccination features high among the public health interventions that have contributed significantly to global health. Following the March 2020 declaration by the World Health Organization that coronavirus 2019 (COVID-19) is a global pandemic, several vaccines have been developed and administered to curb the spread of COVID-19. One of the threats to attaining adequate vaccination uptake for these relatively new vaccines are concerns people have about the adverse event following immunization (AEFI) information. This study sought to assess AEFIs reported on COVID-19 vaccines approved for use so far in VigiAccess and to make a case for why AEFIs data in the database must be interpreted with caution.

Methods

The study followed a cross-sectional quantitative study design. VigiAccess was searched on November 10, 2021 for AEFIs reported so far for all the 12 approved COVID-19 vaccines. Data were captured among age groups, sex and continents of the world. Descriptive data were summarized using tables. Frequencies and percentages were used to categorize descriptive variables. No ethical approval was obtained before the commencement of the study as this was essentially a secondary data analysis of AEFI reports which cannot be linked to any individual. Consequently, there was no need for the informed consent process.

Results

Overall, 2,457,386 AEFIs had been reported in VigiAccess. AEFIs were found to be highest among the 18-44 age group (39.7%) and lowest in vaccine recipients below 12 years (0.1%). AEFIs were more common in females than male vaccine recipients with over two-thirds of the vaccine recipients being females. Among the continents of the world, AEFI reports were highest for Europe (50%) and lowest for Africa (3%). The top 10 commonly reported AEFI types were as follows: general disorders and vaccine administrative site conditions (1,481,549, 60.1%), nervous system disorders (1,046,928, 42.6%), musculoskeletal and connective tissue disorders (704,657, 28.6%), gastrointestinal disorders (495,997, 20.2%), investigations with undesirable outcomes (341,677, 13.9%), skin and subcutaneous tissue disorders (335,932, 13.6%), respiratory, thoracic and mediastinal disorders (262,158, 10.6%), infections and infestations (180,873, 7.3%), vascular disorders (132,533, 5.3%) and injury, poisoning and procedural complications (122,519, 5%).

Conclusion

The study showed that over 2 million COVID-19 AEFIs were spontaneously reported in VigiAccess, however, no causal relationships could be established between the vaccines and the AEFIs. The public accessing VigiAccess data should be made aware of this lack of association so that they may make well informed health decisions.

Introduction

Vaccination ranks high among the public health interventions that have contributed significantly to global health. Between the late 1800s and late 1900s, the leading causes of mortality were attributed to infectious diseases such as pneumonia, meningitis, influenza, tuberculosis, diphtheria, smallpox, pertussis, measles and typhoid fever [1]. However, the discovery and wide use of vaccines contributed significantly to the prevention of many untimely deaths resulting from infectious diseases, particularly in children. In the USA for instance, infectious disease data spanning the period of 1888 to 1924 showed that vaccines prevented approximately 40 million cases of diphtheria, 35 million cases of measles and a total of 103 million cases of childhood diseases [2]. Altogether, vaccines are estimated to prevent at least 6 million deaths, 400 million life years and 97 million disability adjusted life years every year [3].

Vaccines are tested in clinical trials for their safety and efficacy by drug regulatory agencies before approval for use in routine and mass vaccination campaigns. This notwithstanding, the safety of new vaccines is not completely understood from pre-authorization clinical trial data as these trials are conducted in controlled settings different from settings of real time use. Consequently, such data have limitations in their applicability in the wider population [4]. The reason for this limited applicability is as a result of the fact that during clinical trials of vaccines, dozens, hundreds and rarely thousands of participants receive vaccine doses as against millions of people who receive vaccine doses in routine and mass vaccination campaigns. Thus, there is a higher probability of real time vaccine recipients experiencing rare adverse events not recorded during clinical trials. In the wider population, some vaccine recipients may also respond differently to vaccines because of genetic variability, physiological and behavioural differences among other factors [5]. This particularly happens when the vaccines are manufactured and tested within a very short time frame as in the case of coronavirus disease 2019 (COVID-19) vaccines. Evidence from the Global Alliance for Vaccines and Immunizations (GAVI), the funding agency of most of the vaccines used in low and middle income countries (LMICs) for instance shows that the time frame between the introduction of new vaccines in developed countries and their subsequent use in LMICs has reduced considerably [6]. This reduction in time is an indication that safety data from developed countries where the vaccines were first launched may be insufficient at the time of introduction in LMICs necessitating intensive vigilance in the latter countries. Moreover, vaccine trials are conducted in a few days, months and rarely years and consequently, late occurring adverse event following immunizations (AEFIs) may not manifest within that short time frame as against many years of vaccine use in routine and mass vaccination campaigns [7]. Furthermore, the populations in which vaccines are introduced in clinical trials are fixed i.e. vaccines are mostly administered to either children, adolescents, pregnant women or the elderly alone versus the use of most vaccines across all populations in routine and mass vaccination campaigns [8]. As a result, there is the likelihood of some populations who were not represented during the clinical trial phase manifesting adverse events following the administration of vaccines in real time. For these reasons, vaccine surveillance must continue unabated following their marketing approval to ensure patient safety.

The COVID-19 which was declared by the World Health Organization (WHO) a global pandemic in March 2020 [9] has caused a lot of havoc. As of June 19, 2021, over 183 million confirmed cases and approximately 4 million deaths had been reported globally [10]. Following the March 2020 declaration by the WHO, several vaccines have been developed and administered to reduce COVID-19 spread. As of June 19, 2021, 78 candidate vaccines were being studied in clinical trials with 12 of them being approved on Emergency Use Authorization (EUA) basis by the WHO, United States Food and Drugs Administration (USFDA) and the European Medicines Agency (EMA) [11, 12].

Databases for reporting vaccine adverse events are very beneficial for understanding AEFIs associated with COVID-19 vaccines. Two such important databases are Vigibase and VigiAccess. Whilst Vigibase has restricted access, VigiAccess is open to the public and can be accessed online. It is imperative that the public and the scientific community understand the implications of the COVID-19 AEFIs recorded in VigiAccess in order not to exaggerate and misinform the general public about the data in the database. Following the initial COVID-19 pandemic declaration, the SARS-CoV-2 virus, the causative organism has undergone several mutations including Alpha, Beta, Gamma, Delta [13] and the most recent Omicron variant which had already been detected in 38 countries by December 3, 2021 [14–16]. Health experts believe that individuals who have been fully vaccinated against COVID-19 are less likely to suffer from severe illness and complications from this variant should they get infected. It is therefore important for a higher percentage of the general public to get vaccinated to reduce morbidity and mortality rates [17].

As more post-approval data are being collected to elucidate the efficacy of the newly developed vaccines in the larger population, their safety concerns must be investigated to enhance public trust and acceptability. Currently, there have been reports of COVID-19 vaccine hesitancy resulting from exaggeration of AEFIs and myths propagated by conspiracy theorists [18, 19]. This study sought to assess AEFIs reported on COVID-19 vaccines approved for use so far in VigiAccess and make a case for why AEFIs data in the database must be applied with caution.

Methodology

The study followed a cross-sectional quantitative design. VigiAccess was searched on November 10, 2021 for AEFIs reported to date among age groups, sex and continents of the world. Descriptive data were summarized using tables. Frequencies and percentages were used to categorize descriptive variables. No ethical approval was obtained before the commencement of the study as this was essentially a secondary data analysis of AEFI reports which cannot be linked to any individual. Consequently, there was no need for the informed consent process.

Results

After a thorough search of the database, it was observed that the AEFIs were not matched with the individual COVID-19 vaccines but rather lumped together. Additionally, the AEFIs were grouped based on

age bands, sex and continent of the world. It was also observed that the AEFIs were classified based on systems-organ-class, generality and diseases and procedures occurring after vaccine administration.

Age distribution

Overall, 2,457,386 AEFIs had been reported in VigiAccess. AEFIs were highest among the 18-44 age group and lowest in vaccine recipients below 12 years. Table 1 describes the age distribution of vaccine recipients.

Table 1: Age group distribution

Age group	Frequency	Percentage
Below 12 years	3,585	0.1
12-17 years	39,049	1.6
18-44 years	974,453	39.7
45-64 years	758,305	30.9
65-74 years	155,930	6.3
≥75 years	232,113	9.4
Unknown	293,951	12.0
Total	2,457,386	100

Sex distribution

The results show that AEFIs were more common in females than male vaccine recipients with over two-thirds being females. Table 2 is a summary of AEFIs across male and female vaccine recipients.

Table 2: Sex distribution

Sex	Frequency	Percentage
Female	1,684,497	68.5
Male	742,323	30.2
Unknown	30,566	1.3
Total	2,457,386	100

Continental distribution

Among the continents of the world, AEFI reports were highest for Europe and lowest for Africa. This is illustrated in table 3.

Table 3: Continental distribution of AEFI

Continent	Frequency	Percentage
Africa	69,441	3
Americas	924,716	38
Asia	156,966	6
Europe	1,220,042	50
Oceania	86,221	4
Total	2,457,386	100

Commonly reported AEFIs

The top 10 commonly reported AEFI types were as follows: general disorders and vaccine administrative site conditions (1,481,549, 60.1%), nervous system disorders (1,046,928, 42.6%), musculoskeletal and connective tissue disorders (704,657, 28.6%), gastrointestinal disorders (495,997, 20.2%), investigations with undesirable outcomes (341,677, 13.9%), skin and subcutaneous tissue disorders (335,932, 13.6%), respiratory, thoracic and mediastinal disorders (262,158, 10.6%), infections and infestations (180,873, 7.3%), vascular disorders (132,533, 5.3%) and injury, poisoning and procedural complications (122,519, 5%). Moreover, the 10 most commonly reported AEFI manifestations were headache, pyrexia, fatigue, chills, myalgia, nausea, arthralgia, malaise, injection site pain and pain in extremity. Table 4 is a description of the top 5 manifestations of each of these top 10 AEFIs.

Table 4: Description of the top 10 AEFIs and their common manifestations

AEFI types	AEFI manifestation	Frequency	Percentage
General disorders and administrative site conditions	Pyrexia	513,460	20.9
	Fatigue	444,751	18.1
	Chills	342,918	14.0
	Malaise	211,303	8.6
	Injection site pain	179,959	7.3
Nervous system disorders	Headache	636,476	25.9
	Dizziness	196,627	8.0
	Paraesthesia	74,004	3.0
	Hypoaesthesia	50,845	2.1
	Syncope	38,076	1.5
Musculoskeletal and connective tissue disorders	Myalgia	330,119	13.4
	Arthralgia	219,237	8.9
	Pain in extremity	175,673	7.1
	Back pain	38,907	1.6
	Limb discomfort	28,151	1.1
Gastrointestinal disorders	Nausea	279,388	11.4
	Vomiting	88,655	3.6
	Diarrhoea	84,064	3.4
	Abdominal	37,552	1.5
	Upper abdominal pain	24,849	1.0
Investigations with undesirable outcomes	Elevated blood pressure	36,019	1.5
	Elevated heart rate	23,938	1.0
	Positive COVID-19 test	20,491	0.8
	Reduced blood pressure	4,882	0.2
	Weight loss	3,395	0.1
Skin and subcutaneous tissue disorders	Rash	87,608	3.6
	Pruritus	75,647	3.1

	Hyperhidrosis	52,261	2.1
	Erythema	45,127	1.8
	Urticaria	42,127	1.7
Respiratory, thoracic and mediastinal disorders	Dyspnoea	100,081	4.1
	Cough	54,889	2.2
	Oropharyngeal pain	34,203	1.4
	Rhinorrhoea	18,204	0.7
	Pulmonary embolism	17,094	0.7
Infections and infestations	COVID-19	56,052	2.3
	Influenza	4,335	0.2
	Herpes zoster	23,144	0.9
	Nasopharyngitis	16,235	0.7
	Pneumonia	5,979	0.2
Vascular disorders	Hypertension	23,678	1.0
	Flushing	13,635	0.6
	Hot flush	3,582	0.1
	Deep vein thrombosis	12,049	0.5
	Hypotension	11,763	0.5
Injury, poisoning and procedural complications	Inappropriate schedule of product administration	15,367	0.6
	Contusion	13,081	0.5
	Fall	10,491	0.4
	Product storage error	9,488	0.4
	Product administered to patient of inappropriate age	8,944	0.4

Discussion

The present study was conducted to assess the adverse events associated with currently approved COVID-19 vaccines in the VigiAccess database. Globally, efforts are being made to increase the coverage of COVID-19 vaccines whilst generating more safety data on the vaccines so as to include children, adolescents and other special populations in vaccination schedules. For instance on November 2, 2021, the Centers for Disease Control and Prevention (CDC) recommended that children aged 5-11 years could

receive the Pfizer-Bio-NTech pediatric vaccine [20]. Hitherto, this age band was not included in COVID-19 vaccination schedules because of safety concerns.

Amid the rollout of COVID-19 vaccines in different countries, health officials and scientists have utilized national databases such as the Vaccine Adverse Event Reporting System (VAERS) database of USA to detect potential rare and unusual reactions to vaccines. Even though VigiAccess is a good open-access source of AEFI information for the general public, it is difficult to determine vaccine causality from the database as vaccine recipient details such as history of allergy to the vaccine ingredients, existing comorbidities, time of administration of vaccine to time of AEFI manifestation, etc which are typically recorded on individual case report form of vaccine recipients are unavailable in the database. Moreover, AEFI data in VigiAccess requires checks for duplicates and accuracy by health experts before causality assessment is carried out. On October 6, 2021, there were claims on social media by a section of the public/conspiracy theorists that COVID-19 vaccines are unsafe based on AEFI data in VigiAccess. This could have contributed to the COVID-19 vaccine hesitancy currently experienced in many parts of the world [21]. This calls for education and clarification on the utility of the database to allay fears and repose confidence in the COVID-19 vaccines.

The VigiAccess data revealed that half of all the AEFIs were reported from Europe whereas about two-fifths were reported from the Americas. Poor reporting of AEFIs from the African continent has been commonly observed in other studies [22–24]. Since spontaneous reports are beneficial in understanding the profile of AEFIs especially of newly approved vaccines, it is beneficial for all continents to actively get involved in AEFI reporting. One reason for the lower AEFI reporting rate for COVID-19 in Africa could be due to the lower and reduced COVID-19 vaccine uptake in Africa as compared to the rest of the world [25].

According to WHO, 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, and this could be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease [26]. An AEFI could therefore be a vaccine related reaction like fever, rash, injection site pain, abscess and anaphylaxis among others which result from vaccine antigen and human antibody response and are usually temporal in nature [27]. The results show that the 10 most commonly reported AEFI manifestations were headache, pyrexia, fatigue, chills, myalgia, nausea, arthralgia, malaise, injection site pain and pain in extremity. Based on the definition of an AEFI, these may be self-limiting or temporal and therefore not a cause for alarm, however, if the vaccine product is suspected to have caused the event, then causality assessment taking into account other pre-vaccination and post-vaccination risk factors would have to be conducted. Alerting the public of this may strengthen the argument for pro-vaccination, whereby individuals can weigh the risk-benefit of self-limiting adverse events and the serious untoward effects of COVID-19.

AEFIs were commonly reported in females than males and in vaccine recipients aged 18-64 years. This finding is similar to that reported by the Centers for Disease Control and Prevention's (CDC's) Morbidity and Mortality Report (MMWR) in which both anaphylactic allergic and non-anaphylactic allergic reactions were reported after the first dose of the Pfizer Bio-NTech COVID-19 vaccine in women [28, 29]. The MMWR

report observed that majority of these women had a history of allergic reactions, however, this information cannot be verified in the VigiAccess database buttressing the reason not to draw conclusions on AEFI-vaccine relationship from data generated from the database. The increased incidence of AEFIs in women could be linked to the higher likelihood of women reporting these events as reported in previous studies [30, 31]. Another possible reason for the high number of AEFI reports in women than in men in VigiAccess could be due to the high vaccine hesitancy rate in men in comparison to women. A CDC report on June 22, 2021 for instance showed that nearly 9.5 million more women than men had been vaccinated in 42 states of the USA [32].

It is worth noting that AEFIs may also be associated with underlying medical conditions of vaccine recipients (coincidental effects), anxiety of vaccine recipient during vaccination, vaccine administration errors and vaccine quality defects [7]. Vaccine recipients with underlying medical conditions such as chronic hypertension, diabetes mellitus, asthma, etc need to inform health officials at vaccination centres for assessment to confirm their eligibility to receive the vaccines due to the possibility of the manifestation of coincidental AEFIs.

Moreover, an AEFI could be any unexpected event resulting from activities undertaken following an immunization, e.g. road traffic accident of a driver after receiving a vaccine dose. The exact cause of AEFIs such as the latter which may not be associated with the vaccine product is established via causality analyses. AEFI reporting is therefore a very significant component of vaccine pharmacovigilance because it helps to characterize AEFIs associated with specific vaccines for future reference through causality assessment [33]. The investigation could warrant the withdrawal of unwholesome vaccines or even contribute to the improvement in the quality of vaccines if safety is found to be associated with quality defects resulting from bad manufacturing practices. Moreover, healthcare professionals (HCPs) could improve vaccination practices such as injection techniques, storage and transportation of vaccines to maintain their quality when AEFIs are attributed to these factors [34, 35]. The reality of the achievement of global vaccine safety hinges on strengthening national pharmacovigilance systems and the commitment of other stakeholders especially HCPs who have been the major conduits of AEFI reporting.

Conclusions

The study showed that over 2 million COVID-19 AEFIs were spontaneously reported in VigiAccess out of which the 10 most commonly reported AEFI manifestations were headache, pyrexia, fatigue, chills, myalgia, nausea, arthralgia, malaise, injection site pain and pain in extremities. However, no causal relationships could be established between the vaccines and the AEFIs. It is imperative that countries actively engage in active primary vaccine safety studies such as cohort event monitoring to establish causality between AEFIs and vaccines. These findings could also be stored in open-access repositories for the general public, who equipped with the correct knowledge can make well informed health decisions.

Declarations

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Conflict of Interest statement

The authors declare that there is no conflict of interest associated with this study.

Author Contributions

Substantial contributions to the conception or design of the work: PY, NP, VB, FO. Data mining from database: VB, TAM, KBM. Data analysis and interpretation: PY, FO, NP, TAM. Drafting the work or revising it critically for important intellectual content: PY, VB, FO. Proof reading: PY, TAM, NP, KBM. Final approval of the version to be published: PY, KBM, VB, TAM

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