HUMAN VACCINES & IMMUNOTHERAPEUTICS
2022, VOL. 18, NO. 6, e2109365 (6 pages)
https://doi.org/10.1080/21645515.2022.2109365

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REVIEW

Adverse events following immunization associated with coronavirus disease 2019 (COVID-19) vaccines: A descriptive analysis from VigiAccess

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ABSTRACT

This study assessed adverse events following immunizations (AEFIs) reported on COVID-19 vaccines in VigiAccess and determined the reporting trends across all continents of the world. The study was cross-sectional quantitative in design. VigiAccess was searched on 10 November 10 2021 for reported adverse events following the introduction of COVID-19 vaccines. After entering the search term, "COVID-19 vaccines" in VigiAccess, AEFIs associated with nine approved brands of COVID-19 vaccines had been documented in the database. Data were captured among age groups, sex, and continents of the world and analyzed using Statistical Package for Social Sciences (SPSS) version 25. Overall, 2,457,386 AEFIs had been reported in VigiAccess at the time of the search. No causal associations could be established between the vaccines and the AEFIs. The public accessing VigiAccess data should therefore be made aware of this in order to not falsely attribute AEFIs to COVID-19 vaccines when assessing the database.

ARTICLE HISTORY
Received 30 May 2022
Revised 20 July 2022
Accepted 1 August 2022

KEYWORDS
Adverse events following immunization; COVID-19 vaccines; pharmacovigilance; spontaneous reporting; VigiAccess

Introduction

Vaccination ranks high among 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] Aside from preventing infectious diseases, vaccines have proven beneficial in achieving herd immunity (personal/direct protection of individuals during infectious disease outbreaks),[4,5] reducing secondary infections that complicate vaccine-preventable diseases,[6] indirectly reducing the incidence of antimicrobial resistance[7] and preventing non-communicable diseases such as cancer due to the fact that infectious agents such as hepatitis B virus are involved in carcinogenesis.[8] Moreover, vaccines have economic benefits such as cost-effectiveness, promotion of health and productivity gains and minimization of the impact of adult illness on family.[6,9,10]

Like pharmaceutical products, vaccines are tested in pre-marketing clinical trials before their approval for use. Phase 1 vaccine trials evaluate the basic safety and immunogenicity of vaccines using a few trial participants; phase 2 trials are larger than phase 1 trials and garner more information on vaccine safety and immunogenicity, whereas phase 3 trials which are larger than the first two phases focus on efficacy and safety of vaccines.[11] Despite the rigor of pre-marketing vaccine trials, 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-world use. Consequently, such data have limitations in their post-market applicability.[4]

It is therefore imperative to report adverse events following immunization (AEFI) after regulatory approval of vaccines for a better understanding of their safety profiles. 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 unfavorable or unintended sign, abnormal laboratory finding, symptom, or disease.[12] 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.[13] AEFI reporting could be passive (spontaneous) or active. In active AEFI reporting, electronic systems are used to monitor AEFIs whereas spontaneous reporting encompasses the voluntary reporting of AEFIs by healthcare professionals (HCPs), patients, and the general public.[14–16] Spontaneous AEFI reporting is more common than active AEFI reporting but is associated with limitations such as difficulty to establish causality between AEFI and a vaccine, under-reporting of less severe AEFIs, misdiagnosis

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of AEFIs and inability to capture late occurring AEFIs after vaccination.[17–19] Despite these shortcomings, passive reporting is very beneficial for characterizing specific AEFIs commonly associated with various vaccines to guide ongoing and future vaccinations so as to prepare for and manage untoward events based on previous experiences.

The COVID-19 which was declared by the World Health Organization (WHO) a global pandemic in March 2020[20,21] has caused a lot of havoc. Following the March 2020 declaration by the WHO, several vaccines have been developed and administered to reduce COVID-19 spread. As of 19 June 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, the United States Food and Drugs Administration (USFDA) and the European Medicines Agency (EMA).[22,23] AEFIs associated with COVID-19 vaccines need to be characterized from spontaneous reports in pharmacovigilance databases. Two such databases developed by the WHO 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 safety information on COVID-19 as they access 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,[24] and the most recent Omicron variant, which had already been detected in 38 countries on 3 December 2021.[25–27] 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. As a result, it is important for a higher percentage of the general public to get vaccinated to reduce morbidity and mortality rates.[28]

As more post-approval COVID-19 vaccine data are being collected, 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.[29,30] This study assessed AEFIs reported on COVID-19 vaccines in VigiAccess and determined AEFI reporting trends across all continents of the world.

Methods

The study followed a cross-sectional quantitative study design. VigiAccess was searched on 10 November 2021 for all reported adverse events following the introduction of COVID-19 vaccines.[31] After entering the search term, "COVID-19 vaccines" in VigiAccess, information on the following brands of COVID-19 vaccines were retrieved from the database: Valneva, MVC-COV1901 (Medigen), Moderna, AstraZeneca UK, Janssen, Pfizer BioNTech, Korea AstraZeneca, MC Pharma, and recombinant adenovirus type 5 vector by Convidecia. Data were captured among age groups, sex, and continents of the world and entered into Statistical Package for Social Sciences (SPSS) version 25. 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 an informed consent process.

Results

After a thorough search of the database, it was observed that the AEFIs were not matched with the vaccines associated with them but were 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.

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.

Continental distribution of AEFIs in VigiAccess

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

Commonly reported AEFIs in VigiAccess

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%),

Table 1. Age group distribution of AEFIs reported in VigiAccess.

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

Table 2. Sex distribution of AEFIs reported in VigiAccess.

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

Table 3. Continental distribution of AEFI.

Continent	Frequency	Percentage
Africa	69,441	3.0
Americas	924,716	38.0
Asia	156,966	6.0
Europe	1,220,042	50.0
Oceania	86,221	4.0
Total	2,457,386	100

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. These top 10 commonly reported AEFI types were System Organ Class (SOC) and the manifestations listed are Preferred Terms from within the SOC. Most of the AEFI types in the top 10 commonly reported were minor events which are self-limiting. However, there were some serious events and these were syncope (nervous system), all investigations with undesirable outcomes (elevated blood pressure and heart rate, positive COVID-19 test, reduced blood pressure and weight loss), pulmonary embolism, and dyspnea (respiratory, thoracic, and mediastinal disorders), and all infections (COVID-19, influenza, herpes zoster, nasopharyngitis, and pneumonia). Table 4 is a description of the top five manifestations of each of the top 10 AEFIs types.

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 post-market adverse events associated with COVID-19 vaccines in 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 2 November 2021, the Centers for Disease Control and Prevention (CDC) recommended that children aged 5–11 years could receive the Pfizer-Bio-NTech pediatric vaccine.[32] 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 crucial vaccine recipient information required for causality assessment 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. The revised WHO AEFI causality assessment protocol introduced in 2013 categorizes AEFI causality into consistent, inconsistent (co-incidental), indeterminate and unclassifiable. AEFI causality assessment involves four processes: determining that the AEFI case satisfies minimum criteria for causality assessment (eligibility), systematically reviewing available information with a checklist, obtaining a trend on causality with the checklist information with an algorithm and categorizing the association of the AEFI to the vaccine.[33] A study conducted in India on the causality assessment of 1037 serious AEFIs revealed that 499 (48%) AEFIs were consistent, 84 (8%) were indeterminate, 323 (31%) were coincidental, and 131 (13%) were unclassifiable. Further investigations revealed that of the 499 causally associated AEFIs, 189 (18%) were causally linked to the vaccine product, 135 (13%) were causally associated with immunization error and 175 (17%) were causally associated with

immunization anxiety. This buttresses the need for causality assessment especially during the rollout of new vaccines like the COVID-19 vaccines to determine the association between vaccines and AEFIs.[34]

On 6 October 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 that has been observed in many parts of the world.[35] This calls for education and clarification on the utility of the VigiAccess database to allay fears and repose confidence in 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.[36–38] Evidence suggests that most developed countries achieved about 90% of the WHO target of 40% COVID-19 vaccine coverage by 31 December 2021, whereas most African countries achieved 10% or less of this target with a cumulative coverage of 250,000 million doses representing 8% coverage.[12,13,39] One reason for the lower AEFI reporting rate for COVID-19 in Africa could be the very low COVID-19 vaccine uptake on the continent as compared to the rest of the world even though the vaccines have been made widely available in Africa. The factors contributing to this are low vaccine nationalism, lack of commitment, low-quality social mobilization and fear and panic about the safety of the vaccines leading to hesitancy.[13]

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 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.[40,41] The MMWR report observed that the majority of these women had a history of allergic reactions. The increased incidence of AEFIs in women could be linked to the higher likelihood of women reporting these events than men as reported in previous studies.[42,43] Another possible reason for the high number of AEFI reports in women than in men could be the high vaccine hesitancy rate in men in comparison to women. A CDC report on 22 June 2021 for instance showed that nearly 9.5 million more women than men had been vaccinated in 42 states of the USA.[44]

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.[45] Vaccine recipients with underlying medical conditions, such as chronic hypertension, diabetes mellitus, asthma, etc., need to inform health officials at vaccination centers for assessment to confirm their eligibility to receive the vaccines due to the possibility of 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.[46] Spontaneous reporting contributes to pharmacovigilance actions taken by local/regional regulators (such as withdrawal of a vaccine where there may be warranted safety concern, or improvement in manufacturing practices) to allow continued safe use of COVID-19 vaccines. Moreover, 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.[47,48] 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.

The major limitation of this study is the use of passive AEFI data from a database which is fraught with some challenges. These challenges include under-reporting, misclassification of AEFI, biases affecting reporting (such as inflated reporting resulting from serious AEFIs from some vaccination clusters elsewhere under discussion in the media space), missing data as observed in the results of the current study where some AEFIs were reported which can neither be attributed to males nor females as well as age groups. Furthermore, it is not possible to use spontaneous AEFI reports to compare the AEFI profiles of vaccines especially in this study where the AEFIs associated with all the vaccines were recorded together without matching them to specific vaccine types.

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. Even though most of the AEFIs were minor and self-limiting there were some serious AEFIs which could lead to hospitalization and even death. 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 to enhance their knowledge of AEFIs associated with COVID-19 vaccines.

Acknowledgement

We wish to acknowledge the WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance in Ghana for providing valuable information on vaccine pharmacovigilance in Africa and the world at large.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Data availability

Data was obtained from an online open access source, VigiAccess. All data retrieved have been presented in the manuscript.

Transparency declaration

The authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

Funding

The author(s) reported there is no funding associated with the work featured in this article.

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