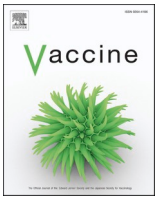
Vaccine 42 (2024) 126460

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine



Safety of mRNA COVID-19 vaccines among persons 15- years and above in Ghana: A cohort event monitoring study

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ARTICLE INFO

Keywords:
COVID-19 vaccine
Cohort event monitoring
Adverse event following immunization

ABSTRACT

Introduction: The development of COVID-19 vaccines during the pandemic occurred with an unprecedented speed, requiring extraordinary post-approval safety monitoring to facilitate ongoing evaluation of their benefit-risk profile. In Ghana, the Food and Drugs Authority granted emergency use authorization to six of these vaccines including the two mRNA COVID-19 vaccines, namely, Pfizer-BioNTech and Moderna COVID-19 vaccines.

The objective of the study was to estimate the incidence of adverse events following immunization (AEFIs) and adverse events of special interest (AESIs) in persons vaccinated with mRNA COVID-19 vaccines, and to identify factors associated with the development of AEFIs.

Methods: We conducted a prospective cohort event monitoring study in seven selected static vaccination center in six of Ghana's 16 regions. The choice of regions was based on their geographical locations and the incidence rate of COVID-19 at the time of the study. The study was conducted with people aged 15 years and older who were vaccinated with mRNA COVID-19 vaccines, including pregnant women.

Study participants were recruited starting in November 2021, with the last participant followed up in August 2022. Persons vaccinated were followed up on days 1, 7, and 28 post-dose 1 and up to 91 days after dose 2.

AEFIs were described with the most specific, or lowest-level, term using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.1. Frequencies of AEFIs after each vaccine dose and vaccination center were determined. Cox-proportional hazard regression was used to assess the independent risk factors associated with the incidence of AEFI among the participants.

Results: Overall, 4678 persons who received Pfizer-BioNTech or Moderna COVID-19 vaccines from the seven vaccination centers were enrolled in the study.

The mean age of participants was 32.9 years (SD ± 14.4). A total of 17.4 % (95 % CI: 16.3 % to 18.5 %) of participants experienced AEFI, with a higher incidence among Moderna COVID-19 vaccine recipients (20.4 %) compared to Pfizer-BioNTech COVID-19 vaccine recipients (14.0 %). The top five common AEFIs included injection site pain, headache, dizziness, fatigue, and fever. No serious AEFIs were reported during the study. Factors such as vaccination center and history of chronic medical conditions influenced the risk of experiencing an AEFI. Cox-proportional hazard regression revealed a 37 % lower risk of AEFI with the Pfizer-BioNTech COVID-19 vaccine compared to the Moderna COVID-19 vaccine.

Conclusion: The study on mRNA COVID-19 vaccines in Ghana showed that the vaccines are tolerated well with no significant safety concerns. Reports of systemic and local events were consistent with those reported in the

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https://doi.org/10.1016/j.vaccine.2024.126460
Received 8 April 2024; Received in revised form 10 September 2024; Accepted 14 October 2024
Available online 23 October 2024

summary of product characteristics of the two vaccines. The study's outcome showed that there were no safety issues with mRNA COVID-19 vaccines in Ghana. The results of this study can be used as a crucial advocacy tool to address vaccine hesitancy as countries plan to routinize COVID-19 vaccines. Additionally, the active monitoring study serves as a model for such studies in low- to middle-income countries (LMICs) with weak pharmacovigilance systems during future pandemics.

1. Background

Globally, the coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulted in over 660 million confirmed cases and over 6 million deaths [1,2]. Immunization is a public health measure that is both cost-effective and life-saving, was employed as one of the major interventions to curtail the pandemic. Vaccines alone have saved around 14.4 million lives worldwide between 2020 and 2021, according to recent estimates [3]. The advancement of vaccines that are both safe and effective in preventing diseases that result in significant illness and death has been a prominent achievement in scientific progress during the 21st century [4,5].

The global effort to develop and deliver effective COVID-19 vaccines has resulted in a variety of safe and effective choices. The development of the COVID-19 vaccines during the pandemic occurred with unprecedented speed. The development and approval of vaccines usually takes 10 years; however, multiple vaccines were developed within a year of the onset of the pandemic [6]. This contributed to increased perceived safety concerns of COVID-19 vaccines among the population, which drives rumours and misinformation [7,8]. As of December 2022, 50 COVID-19 vaccines had been issued with emergency use authorization (EUA) or full marketing authorization for use across the globe [9]. About 13.6 billion doses of COVID-19 vaccines have been administered globally as of November 2023 with only 33 % of the population living in low- and middle-income countries (LMICs) receiving at least one dose compared with about 80 % in high-income countries [8].

In Ghana, the Food and Drugs Authority (FDA) is mandated to issue marketing authorization and monitor the safety of vaccines. The FDA granted EUA to six COVID-19 vaccines used in response to the pandemic. These were Sputnik V (Gam-COVID-Vac), Covishield (Oxford/AstraZeneca formulation), Vaxzevria (Oxford/AstraZeneca formulation), COVID-19 Vaccine Janssen (Ad26.COV2-S [recombinant]), Comirnaty (Pfizer-BioNTech COVID-19 vaccine), and Spikevax (Moderna COVID-19 vaccine) [10].

Ghana was the first country to receive COVID-19 vaccines from the COVID-19 Vaccine Global Access (COVAX) facility in Africa to start its vaccination drive in March 2021 [11]. The initial choice of vaccine types and prioritization of the population for deployment of the limited available vaccines were guided by the technical recommendations of the National Immunization Technical Advisory Group. These recommendations were updated by the group as the epidemiology of the COVID-19 evolved, cold chain capacity was boosted, and more data on the safety profile of the vaccines became available.

Systematic and efficient vaccine surveillance is essential for establishing the benefit-risk profile of vaccines, especially for novel products like those for COVID-19 [9]. Common adverse events with a short time to onset are often identified during randomized clinical trials. However, rare adverse events with delayed onset are most likely detected once large populations have been immunized with the vaccine [2].

Safety monitoring of registered vaccines is conducted by the Ghana FDA in collaboration with the Ghana Health Service (GHS) through the Expanded Program on Immunization (EPI) to ensure the safety of vaccine recipients. Two safety monitoring systems, active safety surveillance (cohort event monitoring) and spontaneous reporting, were employed to monitor the safety of COVID-19 vaccines.

Cohort event monitoring (CEM) is a prospective, observational (non-interventional) cohort study that may be conducted early in the post-marketing phase to monitor the safety of any new drug or vaccine. The methodology was developed to comprehensively document all adverse events that occur within a specified group of participants who are exposed to a drug or vaccine. By encompassing all clinical events, irrespective of causal suspicion, CEM possesses the capability to detect adverse drug reactions (ADRs) that were so far unidentified and unanticipated. The cohort data is utilized as a denominator in calculating the incidence rates. Additionally, risk factors for certain ADRs may be identified due to the collection of underlying health information at the initiation of treatment [12].

Acquiring better knowledge of real-world vaccination safety is especially crucial in an LMIC setting where clinical trials have been conducted. This is because of the differences in demographic, genetic, and environmental factors that may influence vaccine safety profiles [13]. Accurate information on safety of mRNA COVID-19 vaccines in the real world is required to influence public health decisions, direct future research work, and create public confidence in vaccination.

We conducted a CEM study to evaluate e real-world safety data on the mRNA COVID-19 vaccines used in Ghana. The objective of the study was to estimate the incidence of AEFIs and AESIs in persons vaccinated with mRNA COVID-19 vaccines and to identify factors associated with the development of AEFIs.

2. Methods

2.1. Study design and participants

We conducted a CEM in selected static vaccination centers in seven health facilities in six of Ghana's 16 regions. Two sites were in the Greater Accra region and the rest were one each in Ashanti, Central, Volta, Bono East and the Northern regions. The regions were selected based on the incidence of COVID-19 disease and to cover all three ecological zones of the country to show national representativeness. We purposely selected a facility in each selected region; Northern zone: Tamale Central Hospital (RCH); Middle zone: Ejisu Government Hospital (EGH), Holy Family Hospital (HFH); Coastal zone: Ho Municipal Hospital (HMH); Kasoa Polyclinic (KPC); Mamprobi Polyclinic (MHP); Tema General Hospital (TGH).

The facilities were selected based on their COVID-19 vaccination performance and robustness of disease/AEFI surveillance system. The high vaccination coverage and robust surveillance system ensured.

that the target enrollment is achieved and follow up of enrolled participants was successful.

Fig. 1 shows the map of Ghana indicating the 16 regions by ecological zones and six regions where the sentinel sites were located.

The study was conducted in persons who were 15 years who consented to participate and be followed up for the duration of the study. Of the two mNRA vaccines being deployed in Ghana during the.

study period, Ghana's Ministry of Health had recommended the Pfizer/BioNTech vaccines in persons from 15 years and above including pregnant women [14]. Individuals who had received at least a dose of any of the COVID-19 vaccines before the study were excluded and those who had received other brands of COVID-19 vaccines during the study were also excluded.

2.2. Sampling and data collection

We planned to sample 5000 participants in this study with a

minimum recruitment of 720 per site. We consecutively enrolled consenting participants who had received at least a first dose of the authorized mRNA vaccines at the participating sites. Data collection followed up participants on days 1, 7, and 28 post-dose 1 and up to 91 days after dose 2. Study participants were recruited and followed up from November 2021 to August 2022 when the last participant was followed-up. We considered all participants who were not successfully reached via phone call after three consecutive days as lost to follow-up. Data collectors were trained on the use of the reporting tools which included: a line listing form, an enrollment form and a follow-up form. The tools were developed and pre-tested in health facilities other than those used for the study. Ghana's AEFI reporting form was used to capture reported events. The main outcome variable was AEFI defined any untoward medical occurrence that follows immunization and that does not necessarily have a causal relationship with the usage of the vaccine. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom, or disease [15]. A serious AEFI is an AEFI that is life threatening, results in death, hospitalization or prolongation of existing hospitalization, disability, congenital malformation [15].

The list of nineteen COVID-19 AESIs monitored were as recommended by WHO Surveillance Manual on Monitoring and Responding to AESIs [16].

2.3. Data Management and analysis

The collected data was entered into Open Data Kit (ODK) collect. The study data was analyzed using Stata MP version 18 (Stata Corp., College Station, TX, USA). Baseline characteristics of the study participants were described by vaccine type using frequency and percentages for categorical variables. The mean and standard deviation were used to summarize the baseline age of the study participants.

Comparison of the baseline characteristics of the cohort by vaccine type was done using Pearson chi-square test for categorical variable and the Welch's *t*-test for continuous variables.

The cumulative incidence and the corresponding 95 % confidence interval of AEFI among the cohort were estimated.

The incidence rate and the corresponding 95 % confidence interval of AEFI was also estimated considering the total person-time and the number of people experiencing AEFI. The incidence rate was reported as the number of AEFI per 1000-person-follow-up days. Comparison of incidence rate between groups was performed using the incidence rate ratio and significance of the difference in incidence rate was reported using the *p*-value. The Kaplan-Meier plot was used to display the risk of AEFI over time (days after vaccination) among the participants on selected background characteristics of the study cohort. The Log-rank test was used to test the difference in survival rate (risk-rate) across groups.

The cox-proportional hazard regression model was used to estimate the hazard rate ratio of the incidence of AEFI across the baseline characteristics of the cohort. Both the crude and adjusted hazard ratio and their corresponding 95 % confidence interval and *p*-values were reported. Variables that were significantly associated with the risk of AEFI among the cohort were determined using the adjusted cox-proportional hazard regression models. All statistical significance in this study was set at $\leq$0.05 level of significance.

2.4. Ethical consideration

Study participation was strictly voluntary, and participants were free to withdraw at any stage of the study. The study protocol and procedure was approved by the Ghana FDA's Joint COVID-19 Vaccine Safety Review Committee, a multi-disciplinary committee set up to among other things advice the Authority on the post-approval safety monitoring of COVID-19 vaccines [17].

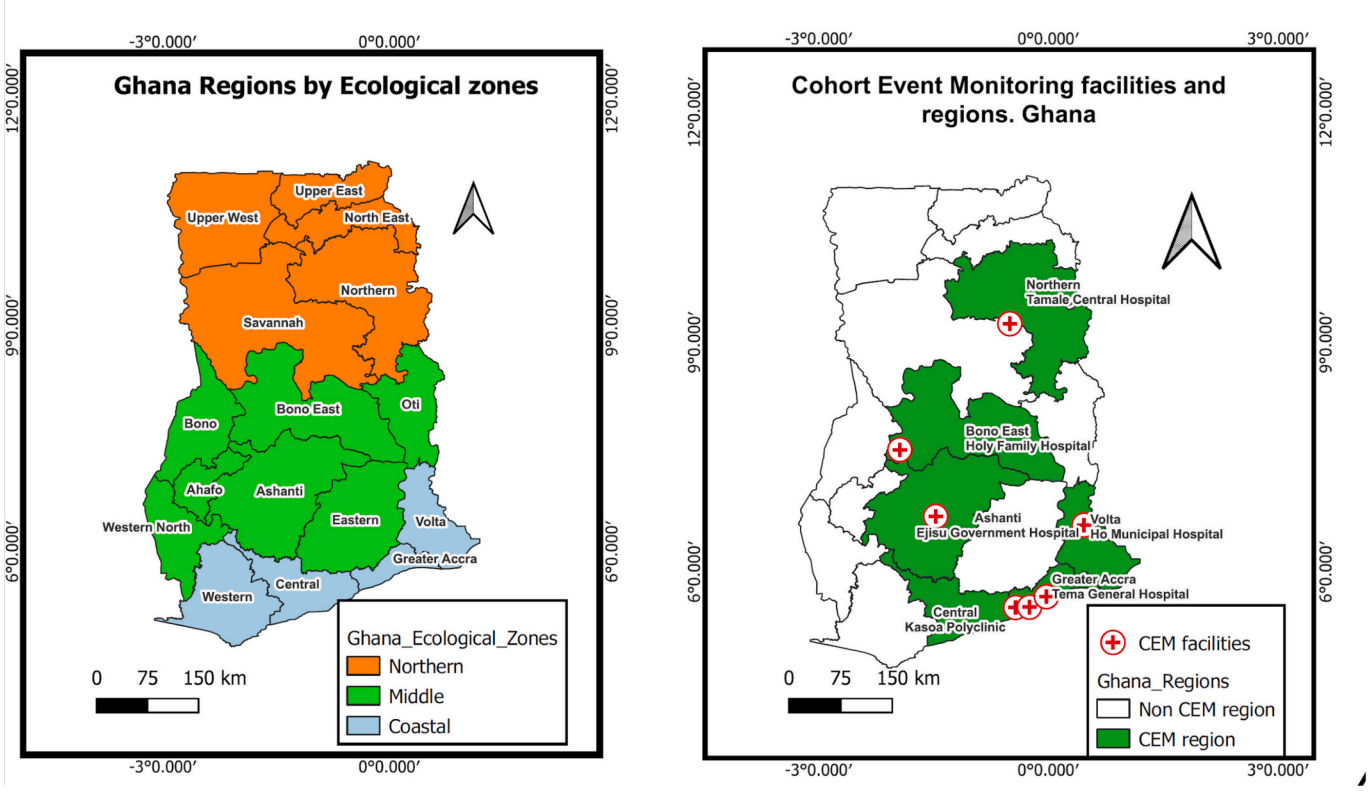

Fig. 1. A map of Ghana indicating the 16 regions based on ecological zones (left), with the six regions where the sentinel sites were located in green (right).

3. Results

3.1. Study population and participants

The study involved a cohort of 4678 participants from the seven sentinel sites who received the mRNA COVID-19 vaccines, namely the Pfizer-BioNTech COVID-19 vaccine (2226 participants) and the Moderna COVID-19 vaccine (2452 participants).

The mean age of participants was 32.9 (SD ± 14.4) years with those receiving the Moderna COVID-19 vaccine on average older than those receiving Pfizer/BioNTech COVID-19 vaccine (36.6 yrs. vs. 28.7 yrs., $p < 0.001$). The majority (57.6 %) of the participants were females with a higher proportion of those receiving Pfizer-BioNTech COVID-19 vaccine being female compared to those receiving Moderna COVID-19 vaccine (59.6 % vs. 55.8 %, $p < 0.009$).

The history of chronic medical conditions was 4.0 % among the cohort. Table 1 shows the baseline characteristics of the study participants.

3.2. Cumulative incidence of AEFIs experienced by study participants

Among the 4678 participants, 17.4 % (95 % CI: 16.3 % to 18.5 %) recorded at least one AEFI incidence during the follow-up. The cumulative incidence of AEFI was significantly higher among those receiving the Moderna vaccine (20.4 %) compared to those receiving the Pfizer vaccine (14.0 %) ($p < 0.001$) as Fig. 2 shows.

3.3. The frequency and incidence of AEFIs experienced by participants

Among the 4678 participants, 11.7 % experienced a single AEFI, 4.4 % experienced two distinct AEFIs, 1.0 % experienced three AEFIs, 0.3 % experienced four AEFIs, and < 0.1 % experienced five AEFIs.

In terms of the specific AEFI experienced, the five most common AEFIs classified by the Lower Level Term using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.1 [18]] were pain at the injection site (64.5 %), headache (19.1 %), dizziness (12.9 %), fatigue (9.5 %), and fever (6.9 %), as Table 2 shows. (See Table 3.)

3.4. Bivariate association between AEFIs and background characteristics of participants

The cumulative incidence of AEFI significantly differed across vaccination centers with the three top cumulative incidences among those who were vaccinated at HMH (61.2 %), EGH (40.5 %), and TGH (15.1 %). Among the women, none who were pregnant recorded any AEFI compared to 17.4 % AEFI incidence among those who were not pregnant. The difference was however not significant due to the small number of pregnant women.

3.5. Incidence and incidence rate of AEFI among people receiving COVID-19 vaccines

The incidence rate of AEFI per 1000 person days after COVID-19 vaccination was 3.51 (95 % CI; 3.27 to 3.76). The incidence rate per 1000 person days was higher among the cohort receiving Moderna vaccine (IR: 4.29, 95 % CI: 3.9–4.7) compared to those who received Pfizer vaccine (IR: 2.61, 95 % CI: 2.3–2.9). No serious AEFIs were reported during the study.

The incidence rate of AEFI significantly varied across the centers of vaccination with the highest incidence recorded among the cohort receiving vaccine at the HMH (IR: 48.26, 95 % CI:42.74–54.50) and the least incidence rate recorded at RCH (IR: 0.60, 95 % CI: 0.44–0.83). The log-rank test showed significant variation of risk of AEFI by vaccination center ($p < 0.001$).

The incidence rate was higher in cohorts after dose 1 (IR: 9.23, 95 % CI: 8.32–10.25) compared to dose 2 (IR: 2.32, 95 % CI: 2.12–2.55).

Table 1
Baseline characteristics of study participants by vaccine type in Ghana.

Characteristics	Total	Vaccine type		P-value
		Moderna	Pfizer/ BioNTech	
Total	*N* = 4678	*N* = 2452	*N* = 2226	
Age in years, Mean [±SD]	32.9 [±14.4]	36.6 [±13.8]	28.7 [±13.9]	<0.001[w]
Age group (years)				<0.001
15–24	1561 (33.4)	489 (19.9)	1072 (48.2)	
25–34	1248 (26.7)	756 (30.8)	492 (22.1)	
35–44	843 (18.0)	537 (21.9)	306 (13.7)	
45–54	522 (11.2)	347 (14.2)	175 (7.9)	
55+	404 (8.6)	277 (11.3)	127 (5.7)	
Non-response	100 (2.1)	46 (1.9)	54 (2.4)	
Sex				0.009
Female	2694 (57.6)	1368 (55.8)	1326 (59.6)	
Male	1984 (42.4)	1084 (44.2)	900 (40.4)	
Vaccination center				<0.001
EGH	600 (12.8)	468 (19.1)	132 (5.9)	
HFH	651 (13.9)	403 (16.4)	248 (11.1)	
HMH	425 (9.1)	122 (5.0)	303 (13.6)	
KPC	764 (16.3)	86 (3.5)	678 (30.5)	
MHP	791 (16.9)	402 (16.4)	389 (17.5)	
RCH	731 (15.6)	499 (20.4)	232 (10.4)	
TGH	716 (15.3)	472 (19.2)	244 (11.0)	
Received dose 2				0.64
No	1984 (42.4)	1032 (42.1)	952 (42.8)	
Yes	2694 (57.6)	1420 (57.9)	1274 (57.2)	
Currently pregnant				<0.001
No	2340 (86.9)	1163 (85.1)	1177 (88.8)	
Yes	81 (3.0)	1 (0.1)	80 (6.0)	
Unknown	272 (10.1)	203 (14.8)	69 (5.2)	
Currently breastfeeding				<0.001
No	2645 (98.2)	1331 (97.3)	1314 (99.1)	
Yes	49 (1.8)	37 (2.7)	12 (0.9)	
History of COVID-19 infection				<0.001
Had a positive test forcovid19	10 (0.2)	9 (0.4)	1 (0.0)	
Never infected by covid19	4441 (94.9)	2432 (99.2)	2009 (90.3)	
Probable case but no lab confirmation	227 (4.9)	11 (0.4)	216 (9.7)	
History medical condition				<0.001
No	4,489 (96.0)	2,291 (93.4)	2,198 (98.7)	
Yes	189 (4.0)	161 (6.6)	28 (1.3)	
Chronic respiratory disease or asthma	19 (0.5)	15 (0.7)	4 (0.2)	0.013
Chronic heart disease	3 (0.1)	2 (0.1)	1 (0.0)	0.58
Chronic liver disease	2 (0.0)	2 (0.1)	0 (0.0)	0.16
Chronic renal disease	2 (0.0)	1 (0.0)	1 (0.0)	0.99
Diabetes	38 (0.9)	33 (1.5)	5 (0.2)	<0.001
Immunocompromised/ immunosuppressed	2 (0.0)	2 (0.1)	0 (0.0)	0.16

(*continued on next page*)

Table 1 (*continued*)

Characteristics	Total	Vaccine type		P-value
		Moderna	Pfizer/ BioNTech	
Obesity	0 (0.0)	0 (0.0)	0 (0.0)	
Chronic allergy	3 (0.1)	3 (0.1)	0 (0.0)	0.087
Hypertension	135 (3.2)	117 (5.5)	18 (0.9)	<0.001
Arthritis	4 (0.1)	4 (0.2)	0 (0.0)	0.057
Peptic Ulcer	17 (0.4)	15 (0.6)	2 (0.1)	0.003

Key: Ejisu Government Hospital (EGH); Holy Family Hospital (HFH); Ho Municipal Hospital (HMH); Kasoa Polyclinic (KPC); Tamale Central Hospital (RCH); Mamprobi Polyclinic (MHP); Tema General Hospital (TGH).

[W] Welch's t-test. All other tests are from the Pearson's chi-square test. Welch BL. The generalization of 'STUDENT'S'problem when several different population varlances are involved. Biometrika. 1947 Jan 1;34(1-2):28-35.

Participants without chronic medical conditions were over 3 times more likely to experience an AEFIs than those without chronic medical (IRR: 3.05, 95 % CI: 2.01–2.89, p < 0.001).

3.6. Cox-proportional hazard regression model of factors associated with incidence of AEFI among people receiving COVID-19 vaccine

The Cox-proportional hazard regression model was used to assess the independent risk factors of AEFI incidence among the cohort. From the adjusted model, the risk of AEFI was 37 % less among those who received Pfizer vaccine compared to those who received the Moderna vaccine (aHR: 0.63, 95 % CI: 0.53–0.75, $p < 0.001$). Compared to those who received vaccine at EGH, the adjusted risk of AEFI was more than twice as high among those who received vaccine at HMH (aHR: 2.41, 95 % CI: 2.04–2.85, p < 0.001), but significantly less among those who received vaccine at HFH (aHR: 0.21, 95 % CI: 0.16–0.27, p < 0.001), KPC (aHR: 0.20, 95 % CI: 0.14–0.27, $p < 0.001$), MHP (aHR: 0.14, 95 % CI: 0.10–0.19, p < 0.001), RCH (aHR: 0.09, 95 % CI: 0.06–0.13, p < 0.001), and TGH (aHR: 0.44, 95 % CI: 0.34–0.59, $p = 0.007$). Table 4 shows risk factors for the crude and adjusted HR for other variables.

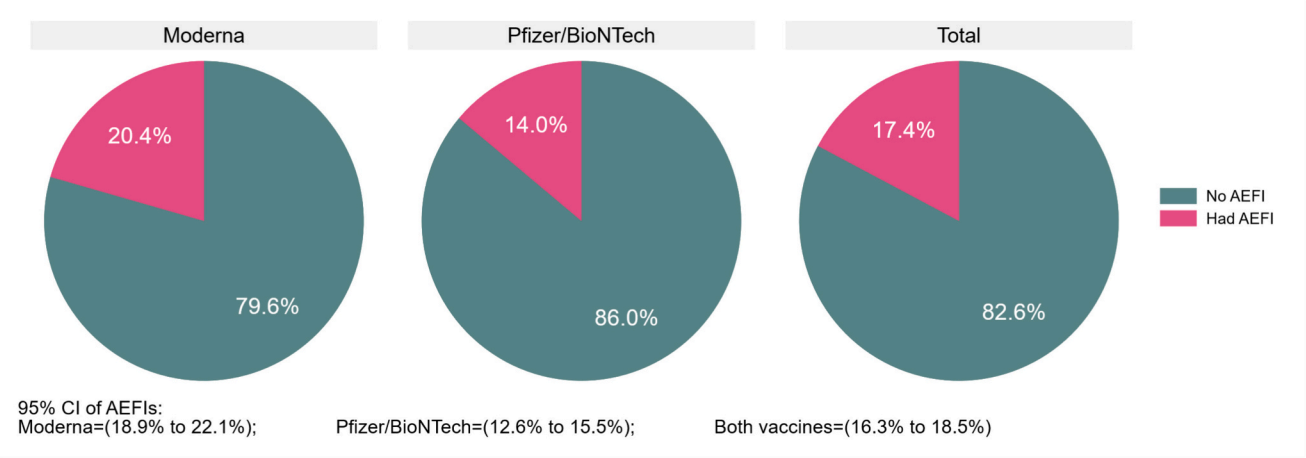

Fig. 2. Cumulative incidence of AEFI among people vaccinated against COVID-19.

Table 2
Cumulative incidence of AEFIs and specific AEFI experience by vaccine type by participants.

AEFIS	Both Vaccines		Moderna		Pfizer/BioNTech		P-value
	n/N	% (95 % CI)	n/N	% (95 % CI)	n/N	% (95 % CI)	
Any AEFI	812/4678	17.4 (16.3, 18.5)	501/2452	20.4 (18.9, 22.1)	311/2226	14.0 (12.6, 15.5)	<0.001
Specific AEFI:							
Injection site pain	524/812	64.5 (61.1, 67.8)	331/501	66.1 (61.7, 70.2)	193/311	62.1 (56.4, 67.5)	0.246
Headache	155/812	19.1 (16.4, 22.0)	102/501	20.4 (16.9, 24.2)	53/311	17.0 (13.0, 21.7)	0.242
Dizziness	105/812	12.9 (10.7, 15.4)	84/501	16.8 (13.6, 20.3)	21/311	6.8 (4.2, 10.1)	<0.001
Fatigue	77/812	9.5 (7.6, 11.7)	52/501	10.4 (7.8, 13.4)	25/311	8.0 (5.3, 11.6)	0.268
Fever	56/812	6.9 (5.3, 8.9)	39/501	7.8 (5.6, 10.5)	17/311	5.5 (3.2, 8.6)	0.205
Chills	31/812	3.8 (2.6, 5.4)	19/501	3.8 (2.3, 5.9)	12/311	3.9 (2.0, 6.6)	0.962
Muscle pain	29/812	3.6 (2.4, 5.1)	26/501	5.2 (3.4, 7.5)	3/311	1.0 (0.2, 2.8)	0.002
Joint pain	25/812	3.1 (2.0, 4.5)	22/501	4.4 (2.8, 6.6)	3/311	1.0 (0.2, 2.8)	0.006
Injection site swelling	24/812	3.0 (1.9, 4.4)	12/501	2.4 (1.2, 4.1)	12/311	3.9 (2.0, 6.6)	0.231
Pain	24/812	3.0 (1.9, 4.4)	20/501	4.0 (2.5, 6.1)	4/311	1.3 (0.4, 3.3)	0.027
Injection site abscess	13/812	1.6 (0.9, 2.7)	4/501	0.8 (0.2, 2.0)	9/311	2.9 (1.3, 5.4)	0.021
Abdominal pain	10/812	1.2 (0.6, 2.3)	7/501	1.4 (0.6, 2.9)	3/311	1.0 (0.2, 2.8)	0.587
Loss of appetite (anorexia)	10/812	1.2 (0.6, 2.3)	9/501	1.8 (0.8, 3.4)	1/311	0.3 (0.0, 1.8)	0.064
Injection site redness	8/812	1.0 (0.4, 1.9)	2/501	0.4 (0.0, 1.4)	6/311	1.9 (0.7, 4.2)	0.032
Diarrhea	5/812	0.6 (0.2, 1.4)	3/501	0.6 (0.1, 1.7)	2/311	0.6 (0.1, 2.3)	0.937
Nausea	4/812	0.5 (0.1, 1.3)	3/501	0.6 (0.1, 1.7)	1/311	0.3 (0.0, 1.8)	0.583
Limb weakness	3/812	0.4 (0.1, 1.1)	1/501	0.2 (0.0, 1.1)	2/311	0.6 (0.1, 2.3)	0.311
Irregular menstruation	3/812	0.4 (0.1, 1.1)	3/501	0.6 (0.1, 1.7)	0/311	#VALUE!	0.172
Vomiting	3/812	0.4 (0.1, 1.1)	2/501	0.4 (0.0, 1.4)	1/311	0.3 (0.0, 1.8)	0.859
Allergic reaction	2/812	0.2 (0.0, 0.9)	1/501	0.2 (0.0, 1.1)	1/311	0.3 (0.0, 1.8)	0.733
Bleeding	2/812	0.2 (0.0, 0.9)	1/501	0.2 (0.0, 1.1)	1/311	0.3 (0.0, 1.8)	0.733
Cough	2/812	0.2 (0.0, 0.9)	2/501	0.4 (0.0, 1.4)	0/311	0.0 (0.0, 1.2)	0.265

Table 3
Incidence rate of AEFI by characteristics of study participants in Ghana.

Characteristics	Total person days	No. with AEFI	Incidence rate per 1000 person days	Incidence rate ratio	
			IR (95 % CI)	IRR (95 % CI)	P-value
Total	231,483	812	3.51 (3.27, 3.76)		
Vaccine					
Moderna	116,697	501	4.29 (3.9, 4.7)	1.00 (reference)	
Pfizer/ BioNTech	119,377	311	2.61 (2.3, 2.9)	0.61 (0.52, 0.71)	<0.001
Age group					
15–24	77,897	270	3.47 (3.08, 3.91)	1.00 (reference)	
25–34	64,869	221	3.41 (2.99, 3.89)	0.98 (0.81, 1.20)	0.865
35–44	43,587	141	3.23 (2.74, 3.82)	0.93 (0.74, 1.17)	0.552
45–54	27,775	88	3.17 (2.57, 3.90)	0.91 (0.70, 1.20)	0.514
55+	21,455	77	3.59 (2.87, 4.49)	1.04 (0.78, 1.38)	0.811
Non-response	522	15	28.74 (17.32, 47.67)	8.29 (4.46, 15.41)	<0.001
Sex					
Female	141,844	458	3.23 (2.95, 3.54)	1.00 (reference)	
Male	94,261	354	3.76 (3.38, 4.17)	1.16 (1.00, 1.36)	0.058
Vaccination center					
EGH	18,812	243	12.92 (11.39, 14.65)	1.00 (reference)	
HFH	39,874	64	1.61 (1.26, 2.05)	0.12 (0.09, 0.17)	<0.001
HMH	5388	260	48.26 (42.74, 54.50)	3.74 (2.82, 4.95)	<0.001
KPC	52,790	55	1.04 (0.80, 1.36)	0.08 (0.06, 0.11)	<0.001
MHP	38,799	44	1.13 (0.84, 1.52)	0.09 (0.06, 0.12)	<0.001
RCH	62,654	38	0.61 (0.44, 0.83)	0.05 (0.03, 0.07)	<0.001
TGH	17,789	108	6.07 (5.03, 7.33)	0.47 (0.36, 0.62)	<0.001
Received vaccine dose 2					
No	38,128	352	9.23 (8.32, 10.25)	1.00 (reference)	
Yes	197,977	460	2.32 (2.12, 2.55)	0.25 (0.22, 0.29)	<0.001
Currently pregnant					
No	134,745	458	3.40 (3.10, 3.72)	–	
Yes	7005	0	0 (–)	–	
Currently breastfeeding					
No/Unknown	138,972	448	3.22 (2.94, 3.54)	1.00 (reference)	
Yes	2872	10	3.48 (1.87, 6.47)	1.08 (0.53, 2.20)	0.831
History of COVID-19 infection					
Never infected	222,892	773	3.47 (3.23, 3.72)	1.00 (reference)	
Probably/ tested positive	13,213	39	2.95 (2.16, 4.04)	0.85 (0.60, 1.20)	0.358
History of chronic medical condition					
No	228,041	733	3.21 (2.99, 3.46)	1.00 (reference)	<0.001
Yes	8064	79	9.80 (7.86, 12.21)	3.05 (2.24, 4.15)	

4. Discussion

We set out to determine the incidence of AEFIs and AESIs in all enrolled persons vaccinated with the mRNA COVID-19 vaccine, specifically Pfizer BioNTech (Comirnaty) and Moderna (Spikevax) in Ghana, and to identify factors associated with the development of AEFIs.

Occurrence of adverse events following COVID-19 vaccination have been reported in studies across the world [19,20]. We observed that overall, few (17.4 %) vaccinees experienced at least one adverse event, with recipients of Moderna COVID-19 vaccine experiencing higher incidence of adverse events (20.4 %) compared to Pfizer-BioNTech COVID-19 vaccinees (14.0 %). This is consistent with studies in which a higher percentage of subjects who received the Moderna vaccine reported AEFIs compared to the Pfizer-BioNTech vaccines [20,21]. Data from Europe and Canada revealed that though the Pfizer and Moderna COVID-19 vaccines had lower incidence rates compared to other COVID-19 vaccines, the total AEFI incidence rates for Moderna COVID-19 was relatively higher as compared to Pfizer/BioNTech vaccines [22,23]. The relatively low incidence of AEFI observed is a departure from the high incidence rate of 52.6 % reported among an African cohort of 1284 Nigerians [24]. The data from these studies also showed that serious AEFIs and AESIs were reported; remarkably, in our current study, no serious AEFIs or AESIs as listed by WHO were reported among the 4678 cohort.

Regarding the type of the AEFIs, the top five commonly reported AEFIs were pain at injection site, headache, dizziness, fatigue, and fever. These AEFIs have been documented in the Summary of Product Characteristics (SmPC) for Moderna COVID-19 vaccine [25] and Pfizer/ BioNTech COVID-19 vaccine [26] as well as studies conducted with mRNA-based COVID-19 vaccines [21,22]. Meo et al. listed the five top reported AEFIs for both vaccines as pain at injection site, fatigue, headache, muscle pain, chills and joint pain [22], whereas a European study mentioned the top five events as injection site pain, headache, myalgia, injection site swelling, and malaise for Moderna vaccine and injection site pain, fatigue, myalgia, headache, and malaise for the Pfizer vaccine [23]. The type of AEFIs reported were similar to events already listed in the SmPCs.

The occurrence and reporting of AEFIs are dependent on multiple factors, including sociodemographic, health systems, disease and vaccine-related factors. Regarding disease-related factors, a positive association between comorbid conditions such as hypertension, diabetes, asthma, arthritis, and lung or cardiovascular diseases and the occurrence of AEFI has been observed in studies in Czech Republic, Iraq, and Saudi Arabia [19,20,27]. Injection site redness, for example, was significantly associated with the total number of NCDs ($p = 0.010$), and the total number of medical treatments ($p = 0.031$) [20]. Our study finding is consistent with these observations, and this could be partly explained by the selective rollout of vaccines in older populations, who have an increased burden of comorbidities.

Table 4
Cox-proportional hazard regression model of factors associated with incidence of AEFI among people receiving COVID-19 vaccine in Ghana.

	Unadjusted model		Adjusted model	
Variables	uHR [95 % CI]	P-value	aHR [95 % CI]	P-value
Vaccine type				
Moderna	1.00 [reference]		1.00 [reference]	
Pfizer/BioNTech	0.66 [0.57, 0.75]	<0.001	0.63 [0.53, 0.75]	<0.001
Age group				
15–24	0.90 [0.71, 1.15]	0.396	0.95 [0.73, 1.24]	0.713
25–34	0.93 [0.73, 1.20]	0.594	1.17 [0.91, 1.52]	0.223
35–44	0.88 [0.67, 1.15]	0.344	1.05 [0.80, 1.38]	0.707
45–54	0.89 [0.67, 1.20]	0.451	1.06 [0.79, 1.40]	0.707
55+	1.00 [reference]		1.00 [reference]	
Sex				
Female	1.00 [reference]		1.00 [reference]	
Male	1.06 [0.93, 1.21]	0.392	0.97 [0.85, 1.10]	0.597
Site				
EGH	1.00 [reference]		1.00 [reference]	
HFH	0.20 [0.15, 0.26]	<0.001	0.21 [0.16, 0.27]	<0.001
HMH	1.68 [1.44, 1.97]	<0.001	2.41 [2.04, 2.85]	<0.001
KPC	0.15 [0.11, 0.20]	<0.001	0.20 [0.14, 0.27]	<0.001
MHP	0.12 [0.09, 0.17]	<0.001	0.14 [0.10, 0.19]	<0.001
RCH	0.10 [0.07, 0.14]	<0.001	0.09 [0.06, 0.13]	<0.001
TGH	0.39 [0.32, 0.49]	<0.001	0.44 [0.34, 0.59]	<0.001
Received vaccine dose 2				
No	1.00 [reference]		1.00 [reference]	
Yes	0.82 [0.72, 0.95]	0.007	1.39 [1.18, 1.63]	<0.001
History of chronic medical condition				
No	1.00 [reference]		1.00 [reference]	
Yes	2.74 [2.22, 3.38]	<0.001	1.47 [1.17, 1.84]	0.001
History of COVID-19 infection				
Never infected	1.00 [reference]		1.00 [reference]	
Probable/tested positive	0.90 [0.66, 1.22]	0.489	1.07 [0.67, 1.69]	0.779

Several studies have reported an increased risk of developing an AEFI in individuals with a previous COVID-19 infection [19,27]. The study by Menni et al. reported that systemic and local AEFIs were more common in individuals with a past COVID-19 infection [27].

In the current study, however, incidence of AEFIs was independent of COVID-19 infection history. This mirrors the finding from a study among healthcare workers in Ghana, where the risk of developing an AEFI to Covishield COVID-19 vaccine among those with a history of COVID-19 infection did not significantly differ from the COVID-19 naïve health workers [19,27]. During the early phase of the pandemic, uptake of COVID-19 testing was limited, coupled with widespread promotion of non-pharmacologic treatment of COVID-19-like illnesses in Ghana. It is highly plausible that individuals could have been unknowingly infected with mild to moderate forms of COVID-19 disease.

We found that vaccination center, vaccine type, and dose received were associated with increased risk of AEFI among the cohort. For example, residency in Kurdistan Region of Iraq was identified as a statistically significant risk factor for developing severe symptoms P-value <0.0001 [19]. Our study provides consistent evidence pointing to a strong association between the site of vaccination and the number of AEFIs reported. Specifically, compared to those who were vaccinated at EGH, the adjusted risk of AEFI was over two times higher among those who received vaccines at HMH but significantly lower among those who were vaccinated at the remaining sites. This could be explained by community members' lack of trust in clinical research due to the experience with the clinical trials of Ebola vaccine in 2015 in the Volta region of Ghana where the HMH site is located [28,29]. Additionally, the targeted rollout of vaccines to the most affected areas with increased incidence of the COVID-19 could account for the observation. It is also postulated that the difference by immunization site can be due to disparities in the levels of awareness creation, which could have led some sites to report more AEFIs compared to others.

Age was not associated with an increased risk of AEFI among the vaccinees in the current study. This can be compared to the results of Almohaya et al., 2021 [30], in a cross-sectional study that assessed early adverse events (AEs) following Pfizer/BioNTech vaccination in Saudi Arabia. In contrast, studies have reported that people older than 55 years are less likely to suffer from adverse effects [31]. This could be because elderly people may also be on chronic pain medication which would have masked the symptoms of pain, headache, fatigue and fever. Alternatively, higher incidence of AEFIs in people aged ≥55 years could be due to the fact that most persons aged 55 years and above are likely to have comorbid conditions such as hypertension and diabetes and presence of comorbid conditions is significantly associated with incidence of AEFIs.

Our regression analysis demonstrates that sex was not independently associated with the likelihood of reporting more AEFIs. 17 % of females experienced AEFI compared to 18 % of males; although the majority of the vaccinees were females, this is at variance with reports from elsewhere [19,20,27]. For example, injection site swelling was significantly more prevalent among female health workers in a prevalence study of Pfizer/BioNTech COVID-19 vaccine side effects in the Czech Republic ($p = 0.021$) [20].

It is important to interrogate further the factors that could have contributed to the observed increased reporting rate of AEFI from the Volta region particularly. Due to the vaccination policy in Ghana, which restricts individuals under age 15 from receiving Pfizer/BioNTech vaccines and those under age 18 from receiving Moderna COVID-19 vaccines [14], we excluded individuals who were younger than 15 years. There is, therefore, a need to investigate AEFI among this age group. Again, recognizing that there could be long-term AEFI, long-term surveillance studies on sections of vaccinees may be required [32].

4.1. Implications for policy

Our findings offer strong real-world evidence supporting the promotion of new vaccines, especially mRNA COVID-19 vaccines in Ghana. With the WHO declaring the end of COVID-19 as a global health emergency and countries transitioning to routine COVID-19 vaccination, this study's results will be used to advocate for and address vaccine hesitancy in Ghana.

Second, active monitoring of adverse events is useful for detecting signals for new vaccines and other health products, particularly in lower- to middle-income countries with weak pharmacovigilance systems. The design and experience from this study serves as a model to be used in future introduction of new vaccines and other health products, and during a pandemic.

4.2. Strengths and limitations of the study

To the best of our knowledge, this is the first cohort event monitoring study in Africa to provide data on the safety of mRNA COVID-19 vaccines in an African population.

The careful selection of study sites across the ecological zones in Ghana and use of a Cohort Event Monitoring study design offered distinctive advantages in the real-world assessment of vaccine safety which include the ability to produce higher reporting rates, rapid results, early detection of signals, fewer missing data in reports and less reporting bias [12,23]. While regulatory authorities have well established routine spontaneous reporting systems in most African countries, our study may be among the few active pharmacovigilance systems that provided data to support the uptake of the COVID-19 vaccination in Africa during the COVID-19 pandemic.

Despite this strength, the authors acknowledge the limited sample size. This is because the WHO guideline on Cohort Event Monitoring (CEM) for Safety Signal Detection after Vaccination with COVID-19 Vaccines requires that to detection of adverse events that occur at a frequency of less than one case per 10,000 vaccinated individuals with at least 95 % confidence, requires a sample size of 30,000 persons are to be vaccinated with at least one dose of the COVID-19 vaccine [33].

5. Conclusion

We conclude that the overall incidence of AEFI following vaccination is low, with recipients of Moderna COVID-19 experiencing higher incidence of adverse events compared to Pfizer-BioNTech COVID vaccinees. The authors did not identify any significant safety concerns regarding mRNA vaccination in real-world settings. The overall safety profile patterned a lower risk of serious AEFI following mRNA vaccines. The strong real-world evidence provided by the study could help promote the roll out of new vaccines while the design and experience from this study serve as a model to be used in future introduction of new vaccines and other health products, and also during a pandemic.

Funding information

This project is funded by USAID's Promoting the Quality of Medicines Plus (PQM+) program led by USP.

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Declaration of competing interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This project is funded by USAID's Promoting the Quality of Medicines Plus (PQM+) program led by USP, grant number: 7200AA19CA00025.

Data availability

The data that has been used is confidential.

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