SCHOOL OF PUBLIC HEALTH

COLLEGE OF HEALTH SCIENCES

UNIVERSITY OF GHANA

INCIDENCE OF ADVERSE EVENTS FOLLOWING IMMUNIZATION (AEFIs) OF COVID-19 VACCINES IN GHANA

BY

AMMA FREMPOMAA ASARE

(10934392)

THIS DISSERTATION IS SUBMITTED TO THE UNIVERSITY OF GHANA, LEGON IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE AWARD OF MASTER OF PUBLIC HEALTH DEGREE

FEBRUARY 2023

DECLARATION

I, Amma Frempomaa Asare, declare that this is my work and that the works of other researchers were well acknowledged. The study was undertaken under Dr Harriet Affran Bonful of the Department of Epidemiology and Disease Control, School of Public Health, University of Ghana, Legon. I declare my compliance with good conduct to the principle and guidelines of the ethical review committee. This work has not been previously submitted either in whole or in part for the award of a degree in this institution or elsewhere.

Amma Frempomaa Asare	Dr. Harriet Affran Bonful
(Student)	(Supervisor)
8th February 2023	**8th February 2023**

DEDICATION

This work is dedicated to my parents, Ben and Rita Antwi-Boasiako, and my sons, Owuraku and Kobbie for their encouragement and continuous support in diverse ways throughout my course.

ACKNOWLEDGEMENT

First of all, I would like to thank the Lord God for His sufficient grace and favour throughout my course.

I would also like to thank my supervisor Dr Harriet Affran Bonful for her guidance throughout this project (right from the conceptualization of the topic to the writing of the final dissertation).

Many thanks to all faculty members and the Epidemiology and Disease Control Department staff.

To Mr Yakubu Alhassan, I say thank you for your direction and willingness to assist in the data analyses.

I would like to convey my appreciation to everyone at Food and Drugs Authority for their immense help during the project – the Chief Executive Officer, Mrs Delese Darko; the Deputy CEO for Health Products and Technologies Division, Mr Seth Seaneke; the Head of the Clinical Trials Department, Dr Mrs Yvonne Adu Boahen and the Head of Pharmacovigilance Department, Mr George Sabblah,

Finally, I would want to express my sincere thanks to my colleagues, Mr Richard Osei Buabeng and Ms Abena Asamoa-Amokohene for their unreserved support during my course.

ABSTRACT

Introduction: To fight the COVID-19 pandemic, vaccines form part of an important public health tool in this quest. In Ghana, five (5) COVID-19 vaccines (COVISHIED™ (AstraZeneca), SPIKEVAX™, COMIRNATY™, Gam-COVID-Vac and Janssen) which were given Emergency Use Authorization (EUA) have been used in the mass vaccination campaign since March 2021. Since early phase trials of the vaccines were mostly not conducted in Africans, assessing safety data during their deployment under real-life conditions in the Ghanaian population is important.

Methods: This study was a retrospective study involving secondary safety data analyses of AEFI reports from active (cohort study) and passive surveillance (spontaneous reporting) of the 5 COVID-19 vaccines deployed in the mass vaccination campaign involving adults in Ghana since March 2021. Data obtained from the primary data host institution (FDA) in Microsoft Excel spreadsheets and on paper forms, were cleaned and imported into STATA I/C 16 (Stata Corp LLC, Texas, USA) for analyses. Descriptive characteristics of study participants were done using frequency and percentages for categorical variables, and median and interquartile range for continuous variables. Bar- and pie charts were also used to describe characteristics such as chronic medical conditions, the cumulative incidence of adverse events following immunization (AEFIs), the various forms and number of AEFIs experienced, as well as the latency of AEFIs experienced. For the cohort event study, the cumulative incidence, the incidence rate per 100,000 person days, and the incidence rate ratios were estimated using the dose of vaccines as the unit of analysis. The Pearson chi-square test was used to assess the factors associated with the cumulative incidence of AEFIs among study participants. The Cox-proportional hazard regression model was used to assess the factors associated with the risk of AEFIs among the study participants. For the analysis of the spontaneous (self-reporting) data, descriptive analysis was performed across the various vaccine types. The Pearson chi-square

test was also used to assess the association between the severity of AEFIs experienced and the background characteristics. The binary logistic regression model was also used to assess the factors associated with severe AEFIs and deaths following the occurrence AEFIs among vaccine recipients. Similarly, the outcome of the AEFIs experienced was also described across the background characteristics and the Pearson chi-square test was used to assess the association. All statistical analyses were considered significant with p-values less than 0.05. Approval was obtained on 13th June 2022 from the FDA to use the AEFI data and ethics approval was obtained from the Ghana Health Service Ethics Committee on 18th October 2022.

Results: The overall incidence of AEFIs among the 6,100 vaccine recipients in the cohort study was 14.0% (851/6,100). For the spontaneous reports, of the 10,733,719 vaccinated population, 8,498 AEFIs were reported giving an incidence of about 0.049% (49 per 100,000 persons). In the cohort study, most AEFIs (88.7%) occurred by the following day after vaccination and the proportion of females who experienced AEFIs (15.6%) was higher than that of males (12.4%) and this was statistically significant ($p<0.001$). Also, in both the cohort study and the spontaneous reports, the incidence of AEFIs was higher in the younger age groups compared with those in the 60 years and older age group with the most common AEFIs being headache, body pain, fever and injection site pain. These events were mostly mild and resolved within a few days. The occurrence of AEFIs was found to be dependent on the age, vaccine type, vaccine dose as well as the enrolment site of vaccine recipients in the cohort study. Also, in terms of severity of the AEFIs, age and vaccine type were factors found to be associated with having a severe adverse event in spontaneous reports.

Conclusion: There was a low incidence of AEFIs following all 5 COVID-19 vaccines used in Ghana since the mass immunization with the events being generally mild and resolving within a few days. The public should be made aware that the vaccines are safe and encouraged to get vaccinated to increase vaccine coverage across the country.

Table of Contents

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Events
AEFI	Adverse Events Following Immunization
BCG	Bacillus Calmette–Guérin
BMI	Body Mass Index
CEM	Cohort Event Monitoring
DAIDS	Division of AIDS
EMA	European Medicines Agency
EPI	Expanded Programme on Immunization
ER	Emergency Room
EUA	Emergency Use Authorization
FDA Ghana	Food and Drugs Authority Ghana
GHS	Ghana Health Service
GPS	Global Positioning System
HCW	Health Care Workers
MenACWY	Meningococcal Vaccine
MOH	Ministry of Health
RNA	Ribonucleic Acid
SAE	Serious Adverse Event

US FDA	United States Food and Drug Administration
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization

CHAPTER ONE

INTRODUCTION

1.1 Background

Before the emergence of corona disease, no vaccines for coronaviruses had been made for use in humans (Krammer, 2020). The swift pace of the development of the COVID-19 vaccines as well as the inadequate time for follow-up after vaccination has led to great public anxiety about the safety of the vaccines (Petousis-Harris, 2020). This is especially so since new platforms such as ribonucleic acid (RNA) were used for the development of some of these vaccines (Wu et al., 2021). Results from research by Dodd et al., (2021), indicated that some persons were sceptical about receiving the vaccines with common reasons being given as the safety and possible adverse reactions to these vaccines. These findings are consistent with a cross-sectional online survey conducted among Ghanaian adults, before the rollout of the vaccines in Ghana, which showed that although 51% of respondents were willing to take the vaccine, about 21% were not willing to be vaccinated and 28% were not sure if they wanted to be vaccinated or not (Acheampong et al., 2021).

Following confirmation by the Ministry of Health of the first two cases of the coronavirus disease in Ghana in March 2020, the total number of confirmed cases as of 30th June 2022 was 166,666 with 1,452 deaths (Ghana Health Service, 2022). The total number of COVID-19 vaccine doses administered (AstraZeneca, Moderna, Pfizer, Janssen and Sputnik V) as of 30th June 2022 was 17,409,005 (Ghana Health Service, 2022).

From the literature reviewed, there is not much information publicly available from Africa on post-approval safety monitoring of COVID-19 vaccines. Also, many of the clinical trials conducted during the development of the vaccines were carried out in non-African populations, hence the safety of these vaccines is not well known in Africans. Considering these safety concerns and the rapidly evolving vaccination landscape, this study aims to assess the type of

adverse events associated with the COVID-19 vaccines which were deployed in the mass vaccination in the Ghanaian population. In addition, risk factors related to the occurrence of these events, the time-to-occurrence and their outcomes will be assessed. Any peculiar trends observed in the analyses of the AEFI reports may lead to timely signal detection and evaluation by relevant local and international stakeholders.

1.2 Problem Statement

Vaccines are widely regarded as one of medicine's most impressive success stories in global health. They have significantly reduced the targeted infectious disease in all documented cases, playing an outstanding role in reducing human disease morbidity and mortality (Kaufmann et al., 2014). To end the ongoing COVID-19 crisis, it was important for the approved vaccines to be more widely used (Bong et al., 2020). Unfortunately, just like other drugs, vaccines are associated with adverse reactions or events commonly referred to as adverse events following immunization (AEFIs). An AEFI is any untoward medical occurrence which happens after an immunization and does not necessarily have a causal relationship with the use of the vaccine (Breugelmans et al., 2013; Tozzi et al., 2013). Allergic reactions to vaccines or adverse events following immunizations (AEFIs) may occur as a result of residual non-human protein, and other excipients like preservatives or stabilizers used in formulating the vaccine. AEFIs can be influenced by inherent factors like age, sex, body mass index (BMI), vaccine-related factors such as the brand and adjuvant used, and vaccine administration factors including injection route, and length of the needle (Hervé et al., 2019). Some AEFIs are also believed to be coincidental, accidental or anxiety-related (Siegrist, 2007).

Adverse drug reactions (ADRs) are adverse reactions to a drug that are noxious, unintended, and occur at doses normally used in man (WHO, 2002; Kongkaew et al., 2008). These reactions have been identified as a significant cause of morbidity and mortality across all age groups,

resulting in a significant number of hospital admissions and a significant financial burden on society and healthcare systems (Adisa & Omitogun, 2019). According to a report by Shchory et al., (2020), some studies conducted around the world, have shown that adverse drug reactions (ADRs) account for 3-7 per cent of all hospitalizations, and 10-20 per cent of inpatients experience drug-related adverse reactions. A publication by Kongkaew et al., (2008) revealed that serious adverse drug reactions (ADRs) occur in about 6.7% of hospitalized patients and account for 5 – 9% of inpatient costs in the Americas, Europe and Asia. Again, a study conducted in the UK by Pirmohamed et al., (2004) showed that a total of about 1,225 admissions were related to ADRs, with the ADR directly resulting in hospital admission in 80% of the cases. Adverse events' burden on healthcare is even more pronounced in developing nations, causing financial and economic consequences to individuals and healthcare systems. This may be due to the increase in disease rate, hunger, and insufficient resources in healthcare systems (Bates, 1997).

One significant thing worth noting is that while some ADRs are unforeseeable, many are avoidable with proper planning and monitoring (Coleman & Pontefract, 2016). It is therefore important for persons receiving vaccines and the healthcare professionals involved in the administration of the vaccines to be aware of the possible adverse effects to avoid potential vaccine refusal from the general populace if vaccines are perceived to be unsafe.

1.3 Conceptual Framework

The conceptual framework provides a summary of the host's inherent, vaccine product, vaccine administration-related and other extrinsic factors that can influence the occurrence of AEFIs. This framework was adapted from Hervé et al., 2019 and Zimmermann & Curtis (2019).

Hervé et al., (2019) categorized the factors that can theoretically impact the incidence and severity of local and systemic reaction induced after vaccination under three major groups as

follows; Intrinsic factors (all the conditions that can influence the immune and the endocrine or the hormonal systems of the host); administration factors (all the conditions that can increase tissue stress) and vaccine factors (the components that activate innate immunity inherent in the vaccines).

With Zimmermann & Curtis (2019), factors that can influence vaccine responses were put into eight categories as Intrinsic host factors such as age, sex, genetics, and comorbidities; perinatal factors like gestational age, birth weight, feeding method, and maternal factors; extrinsic factors like preexisting immunity, microbiota, infections, and antibiotics and environmental factors such as geographic location, season, family size, and toxins. In addition to these, there were behavioral factors like smoking, alcohol consumption, exercise, and sleep; nutritional factors such as body mass index, micronutrients, and enteropathy; vaccine factors like vaccine type, product, adjuvant, and dose and vaccine administration factors such as schedule, site, route, time of vaccination, and coadministered vaccines and other drugs.

The choice of this framework (combination of the two) was to ensure that all major categories of the factors were covered or included in this framework. For instance, unknown or coincidental factors are associated with AEFI occurrence which were not captured under by Hervé et al., were captured by Zimmerman & Curtis. Extrinsic factors, environmental or behavioral factors such as place of residence, alcohol, smoking habits also not covered by Hervé et al. were addressed by Zimmerman & Curtis.

As earlier indicated, host's Inherent or intrinsic factors include age, sex, BMI, ethnicity, comorbidities, psychological stress and level of knowledge or education. For instance, age is important when it comes to vaccine reactogenicity. Except for pre-term babies, reactions generally tend to be weaker in younger ages than in older persons (Siegrist, 2007). Again, inflammatory reactions are known to be more common in females than in males. Research has

shown that women exhibit a better immune response that can enable vaccine efficacy, but they also tend to experience more frequent and severe AEs. This may be due to genetic and hormonal differences (Fink & Klein, 2015; Fischinger et al., 2019). Some studies have demonstrated that sex hormones affect immune responses and cytokine levels, with androgens and high doses of oestrogens being immunosuppressive (Hervé et al., 2019).

Environmental or extrinsic factors that can influence how people respond to vaccines include the place of residence (urban or rural) or geographical location, behavioural factors like alcohol consumption and smoking, infections and the use of some antibiotics. Children living in rural areas are reported to have higher antibody responses to tetanus and malaria vaccines than those living in urban areas. However, humoral and cellular responses to the influenza vaccine (TIV) are lower in kids living in countryside areas than in those living in semi-urban areas. Likewise, studies have shown that antibody responses to HepB vaccination and cytokine responses after vaccination with BCG tend to be lower in children and adults living in rural areas (Zimmermann & Curtis, 2019).

Vaccine product factors such as vaccine type and dose, adjuvant type and dose as well as physiochemical properties can also influence immune responses in different ways. For instance, live vaccines usually produce high immune responses resulting in life-long protection even after just one dose, whereas inactivated, subunit, or toxoid vaccines usually necessitate several doses, including booster doses, to achieve similar protection (Zimmermann & Curtis, 2019). A serious reaction may also occur if there is a replication of a live vaccine due to inadequate attenuation of the vaccine strain (Siegrist, 2007).

Vaccine administration factors like schedule, coadministration with other vaccines, needle size, injection site and route, have also been reported to influence AEFI occurrence (Zimmermann & Curtis, 2019). Additionally, errors in the handling of the vaccines, non-adherence to vaccine

use recommendations as well as the requisite administration procedures may likewise result in AEFIs (World Health Organization, 2013). Again, vaccines administered intramuscularly are usually associated with fewer injection site reactions than subcutaneous or intradermal injections and this may probably be because skin and subcutaneous tissues have more pain fibres compared with skeletal muscles (Herzog, 2014; Frösner et al., 2009; Beirne et al., 2018).

In a report by Siegrist (2007), AEFI occurrence could also be coincidental, accidental or a result of anxiety about receiving the vaccine which includes syncope. This could be due to many reasons such as the age of the vaccinee, unfamiliar vaccination environments, and the fact that the vaccines and their administration procedures may be new to the vaccinee (Younus & Al-Jumaili, 2021). That is why it is recommended that vaccine recipients are observed at vaccination centres for at least 15 minutes after immunization (Hause et al., 2021).

It is therefore evident there is the need for healthcare professionals in general to have the requisite knowledge regarding these factors and how they can contribute to the occurrence of AEFIs so that they can prevent avoidable events, diagnose, manage and report vaccination-related reactions (Yamoah et al., 2019). This will go a long way to increase public trust and confidence in vaccination campaigns.

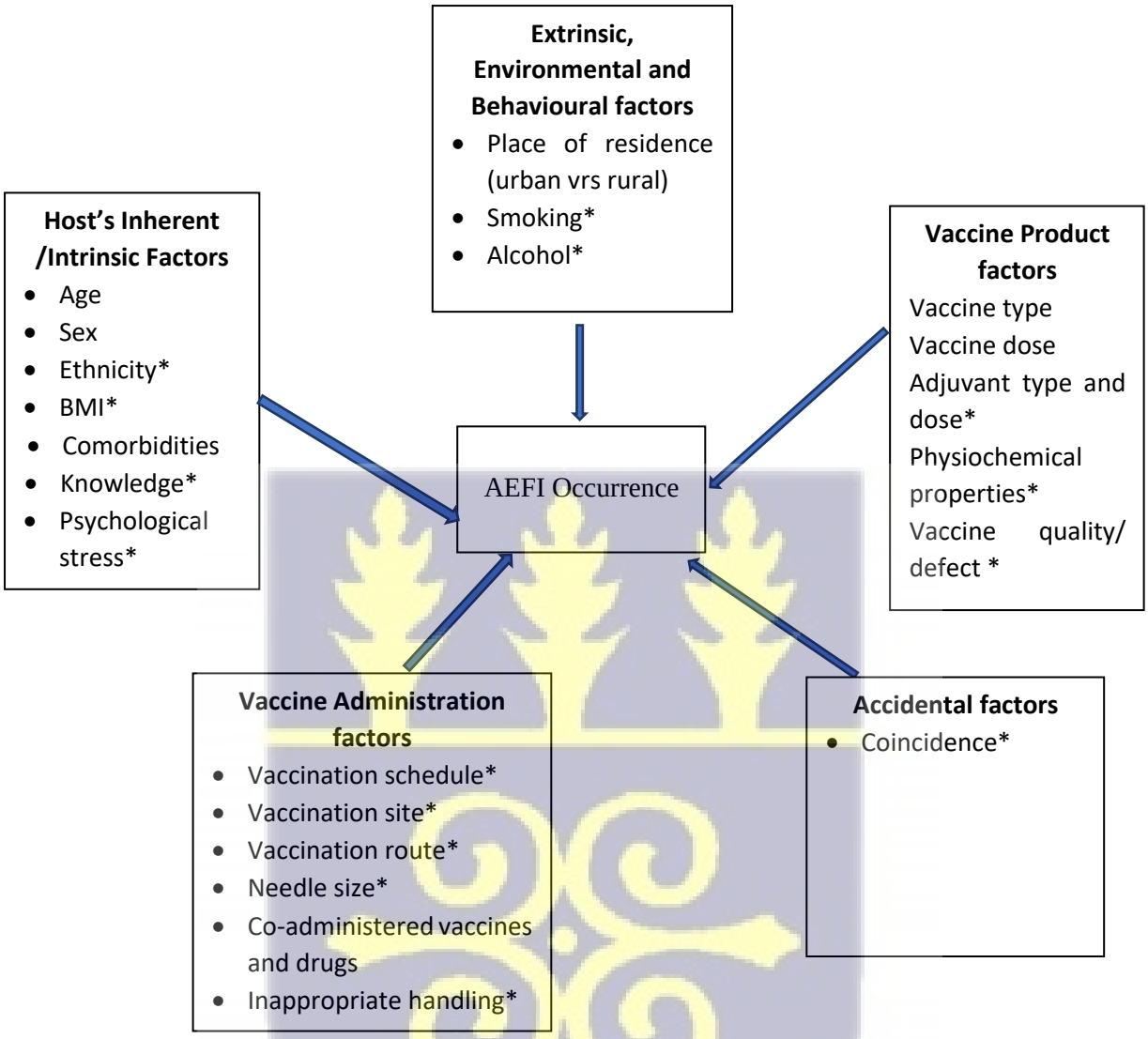


Figure 1.1 Conceptual Framework adapted and modified from Hervé et al., 2019 and Zimmermann & Curtis, 2019.

Note: Factors marked with asterisks (*) were not assessed in this study since no data was collected on these variables.

1.4 Justification

Safety issues in vaccines have the potential to undermine public confidence in vaccination programmes and, eventually, have dire consequences on immunization coverage and increase the incidence of diseases. Novel technologies in vaccines including the use of nucleic acids, micro-organisms genetic modifications, viral vectors or new adjuvants may elicit untoward

reactions different from that of previous technologies (WHO, 2020). It is therefore important to closely monitor the safety of the vaccines being used in Ghana for the mass vaccination campaign due to the underlisted reasons:

First, the vaccines, which were given Emergency Use Authorization (EUA) before the commencement of the mass vaccination in March 2021, are novel with inadequate data on their safety profiles.

Secondly, the early phase clinical trials which were conducted during the developmental stages of the vaccines were not carried out in African populations (which includes Ghana) so there is limited information on the safety of the vaccines in Africans. It is important to assess safety data during their deployment under real-life conditions in the Ghanaian population.

Thirdly, a knowledge of some of the factors associated with the occurrence of AEFIs is important to assist in the avoidance of some preventable events to ease the burden of cost to patients and the health systems.

Finally, from the literature reviewed, there is not much information publicly available from Africa on post-approval safety monitoring of COVID-19 vaccines. Any peculiar trends observed in the analyses of the AEFI reports may lead to timely signal detection and evaluation by relevant local and international stakeholders – the Food and Drugs Authority (FDA), Expanded Programme on Immunization (EPI), Ghana Health Service (GHS), other regulatory agencies and vaccine manufacturers. Sharing the analyses on safety reports from Ghana will help improve the safety of these vaccines.

This study, therefore, assessed secondary safety data from active and passive surveillance for the incidence, rates and types of AEFIs reported from the five (5) COVID-19 vaccines which have been given EUA by the Food and Drugs Authority for use in the mass vaccination since March 2021.

1.5 Research Questions

1. What are the frequencies of reported AEFIs among persons in Ghana after at least one dose of either AstraZeneca, Moderna, Pfizer, Janssen or Sputnik V COVID-19 vaccines since their rollout?
2. What are the types, severity, latency and outcome of the AEFIs among vaccine recipients receiving at least one dose of either AstraZeneca, Moderna, Pfizer, Janssen or Sputnik V COVID-19 vaccines?
3. What are the possible risk factors that are associated with AEFIs?

1.6 Objectives

1.6.1 General Objective

To assess the incidence and factors related to AEFIs among persons who received COVID-19 vaccines in Ghana.

1.6.2 Specific Objectives

1. To estimate the incidences and incidence rates of AEFIs among vaccine recipients who received at least one dose of either AstraZeneca, Moderna, Pfizer, Janssen or Sputnik V COVID-19 vaccines during active and passive surveillance following the commencement of the mass vaccination in Ghana.
2. To identify possible risk factors such as age, sex, demographic, comorbidities, vaccine type and vaccine dose, associated with the AEFIs from these vaccines.
3. To describe the type, severity and latency of the AEFIs experienced by vaccine recipients.
4. To assess the outcomes of the AEFIs among the vaccine recipient

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

COVID-19 is a zoonotic virus known as severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 which emerged late in 2019. SARS-CoV-2 infection can cause a variety of symptoms, ranging from asymptomatic illness to severe acute respiratory distress and death (Folegatti et al., 2020). The virus was given the designation SARS-CoV-2 because it mimicked the coronavirus that causes severe acute respiratory syndrome (SARS-CoV), which is a betacoronavirus (Lu et al., 2020).

2.2 COVID-19 Disease and the Pandemic

COVID-19 disease was discovered when a group of people with unusual pneumonia were traced to a seafood market in Wuhan, China, in December 2019, and were subsequently shown to be infected with 2019-nCoV, a novel coronavirus (Zhu et al., 2020). SARS-CoV-2 virus (Coronavirus) infects humans through droplets and, to a minor extent, aerosols. In symptomatic adults, the disease often manifests as a respiratory illness with fever, cough, headache, myalgia, and, in some cases, digestive symptoms after 2 – 14 days of incubation (Brodin, 2021). Its clinical symptoms range from asymptomatic presentation to severe pneumonia, acute respiratory distress syndrome, respiratory failure, or multiple organ failure (Tsai et al., 2021). COVID-19 risk is higher in older persons as well as people with various health issues such as lung illness, heart disease, diabetes, and cancer (Ali & Alharbi, 2020).

Following its discovery in China and fast spread globally, the disease was declared a pandemic by the WHO on 11th March 2020 (Belete, 2021). Since then, the disease has put a significant strain on healthcare systems that provide treatment to COVID-19 patients and has disrupted non-COVID-19 healthcare services, in addition to having a detrimental impact on the global economy. Additional health implications are expected in the future (Folegatti et al., 2020). The

catastrophic pandemic circumstance has emphasized the importance of safe and effective curative and preventative strategies to decrease disease spread. Recommended preventive measures include keeping a distance of at least 6 feet away from others, wearing suitably fitted facemasks, properly washing hands or using alcohol-based hand sanitisers (National Institutes of Health, 2021). However, because effective antiviral drugs are currently unavailable, immunization is the greatest way to contain the disease outbreak (Belete, 2021).

Vaccination is an essential public health strategy that helps to avert millions of deaths globally each year. Although vaccines are generally safe and effective, and undergo comprehensive safety testing before being used in vaccination programmes, no vaccines, including that for COVID-19, are completely risk-free, and Adverse Events Following Immunization (AEFI) can occur after administration (Laryea et al., 2022). It is therefore of the essence for continuous post-market or post-authorization surveillance to be carried out on vaccines to address safety-related issues. This would build trust in the general public, decrease vaccine hesitancy and sustain efforts through immunization programmes (Siddiqui et al., 2013).

2.3 The AstraZeneca COVID-19 Vaccine Product (COVISHIELD^{TM}) and its associated overall AEFI incidence

The AstraZeneca ChAdOx1 nCoV-19 or AZD1222 is a replication-defective chimpanzee adenovirus-vectored vaccine which expresses the full-length coronavirus spike glycoprotein gene (Ramasamy et al., 2020). The genetically altered organisms used in this vaccine were created in 293 human embryonic kidney cells. The ChAdOx1 nCoV-19 vaccine (manufactured by AstraZeneca), is comparable to the COVISHIELD^{TM} vaccine made by Serum Institute of India Pvt Ltd. Both require two separate doses of 0.5 ml intramuscular (IM) injection, with the second dose administered between 4 and 6 weeks (up to 12 weeks from studies) after the first dose (World Health Organization (WHO), 2022).

According to (Folegatti et al., 2020), a phase 1/2 trial was conducted in the UK, where 1,077 patients were randomly allocated to receive the COVISHIELD^{TM} (n=543) which is COVISHIELD^{TM} as the treatment or MenACWY (n=534) which is a meningococcal vaccine as the control. The study showed pain after vaccination in about 67 per cent and 38 per cent of the experimental and control groups respectively. Despite the experimental vaccination generally having a stronger reactogenicity profile than the control vaccination, data demonstrated that the candidate COVISHIELD^{TM} vaccine given as a single dose was safe and well-tolerated. There were no major side effects from the vaccine. A great proportion of reported AEs was mild to moderate in intensity, and they were all self-limiting.

Another report by Ramasamy et al. in 2020 indicated that local and systemic responses (pain at the injection site, myalgia, headache and feverishness) were more likely in individuals who received COVISHIELD^{TM} in a phase 2/3 trial than in those who received the control vaccination (meningococcal), and events were comparable in character to prior reports.

Following the conduct of some clinical trials in the early developmental phase of the vaccine, it has been used in some countries around the globe. A total of 1,503 healthcare personnel were vaccinated in the Republic of Korea, with 98.1 per cent reporting AEFIs (Jeon et al., 2021) A publication by Kaur et al., (2021) regarding post-approval safety data on COVISHIELD^{TM} use among 804 healthcare practitioners from northern India indicated that AEFIs were detected in 40 per cent of individuals (systemic AEFIs with or without injection site reactions in around 31% of vaccine recipients and 9% of individuals had only local site reactions) following the first dosage. This decreased to about 16 per cent of vaccine recipients following the second dose. Menni et al., (2021) also reported that out of 345,280 vaccine recipients from a prospective observational study conducted in the UK, 33·7% reported systemic side effects and 58·7% also had local side effects.

2.3.1 Common, Serious and Rare AEFIs associated with the vaccine

2.3.1.1 Common AEFIs

Jeon et al., (2021) reported that tenderness at the injection site (94.5%), fatigue (92.9%), pain at the injection site (88.0%), and malaise (83.8%) were the most frequently reported AEFIs following the initial dose of the COVISHIELD™ vaccine among healthcare workers in Korea when vaccinations were initiated in February 2021. Most AEFIs were mild-to-moderate in intensity. There were no significant incidents that necessitated hospitalization, and the majority of AEFIs improved within a few days. These reactions were similar to those reported by Sah et al., (2021) when Nepal initiated their vaccination of healthcare and security personnel in January 2021 and most of these reactions persisted after vaccinations were resolved with paracetamol.

Another cross-sectional study (Subedi et al., 2021) carried out in Nepal in person or through telephone interviews among 1,006 health officials a week after receiving dose one of the COVISHIELD™ also demonstrated that tenderness (60.3%), pain (42.4%), swelling (2.3%) and redness (0.6%) were local reactions experienced. Systemic reactions observed were fever (38.2%), body ache/myalgia (32.2%), headache (28.9%), chills (22.1%), fatigue (17.5%), dizziness (12.0%) and drowsiness (11.0%).

Again, a report by (Kamble et al., 2022) revealed that around 10% of the 836 healthcare professionals of a healthcare institute in Eastern Uttar Pradesh, India, who received the first dose of the vaccination with COVISHIELD™ developed AEFIs. Tenderness or pain at the injection site (59.3%) was the most prevalent event, followed by dizziness or headache (35.3 %), injection site itch or rashes (8.1%), vomiting or nausea (5.8%), and fever or feeling cold (4.7 per cent). The bulk of the AEFIs found (95.3 per cent) were of low intensity, with no significant reactions found according to the severity categorization by WHO.

Side effects of COVISHIELD™ observed in a prospective observational study conducted in the UK indicated that tenderness (49.3%) and pain (19.1%) were the most common local reactions with headache (22.8%), fatigue (21.1%) and rigours (14.7%) being the most common systemic reactions (Menni et al., 2021).

2.3.1.2 Serious AEFIs

In a report by Voysey et al., (2021), the COVISHIELD™ vaccine demonstrated an excellent safety profile throughout four clinical trials earlier conducted in the UK, Brazil, and South Africa. Serious AEs and AEs of special interest were evenly distributed across the research arms. Of the 168 subjects who had SAEs, 79 received COVISHIELD™ (treatment groups, n = 12,021) and 89 received MenACWY (control groups, n = 11,724). Three adverse events which occurred out of the total 175 (84 from the COVISHIELD™ arm and 91 from the control arm), were assessed to be associated with either the experimental or control vaccination.

In a report by Jeon et al., (2021), no serious events occurred that required hospitalization. Thirteen persons with urticaria, injection site discomfort and itching, fever, chills, malaise, headache, disorientation, diarrhoea, tingling feeling, and lower extremity weakness were attended to in the emergency room or outpatient facility. One patient who had dyspnea, nausea, and hypotension within 10 minutes of receiving the immunization, was promptly transferred to the emergency room, given supportive therapy and discharged after the patient progressed spontaneously.

Previous data suggested a relationship between the vaccine and immune-mediated thrombotic thrombocytopenia, comparable to heparin-induced thrombotic thrombocytopenia (HITT) and consequently called VITT (vaccine-induced immune thrombotic thrombocytopenia). However, a case series involving 20 hospitalized patients with thrombocytopenia which happened 1–23 days after receiving the PfizerBioNTech COVID-19 vaccine or the Moderna SARS-CoV-2 vaccine, as well as a fatal intracranial haemorrhage, have also been reported. This suggests that

thrombocytopenia events may occur across the three COVID-19 vaccines, with more events among individuals vaccinated with the AstraZeneca vaccine relative to the PfizerBioNTech vaccine; further data is however required in this regard (Kragholm et al., 2020).

From the results of active surveillance of AEFIs following vaccination of healthcare workers in Nepal, the following was observed; minor AEFIs in 3,391 persons out of 3,991 respondents (84.9 per cent), severe minor AEFIs in 1 (0.02%), and serious AEFIs in 2 people (0.05 per cent). The majority of AEFIs that occurred after the first dose of COVISHIELD^{TM} vaccination were moderate and disappeared within a few days. Apart from one incidence of anaphylaxis, no other AESIs were found (Shrestha et al., 2021).

2.3.1.3 Rare AEFIs

In a report by Voysey et al., (2021), a case of transverse myelitis occurred 4 days after receiving the COVISHIELD^{TM} booster vaccine and according to an independent neurological committee, this was possibly connected to the immunization, with the most likely diagnosis being idiopathic short segment spinal cord demyelination.

Some European countries temporarily halted the administration of the AstraZeneca vaccine on March 11, 2021, following reports of blood clot events and the death of a vaccinated person, notwithstanding assurances from the EMA and the WHO that vaccination was not connected (Mahase, 2021; Wise, 2021). There were 54,571 AE reports from 17 million patients who received the AstraZeneca vaccination, 28 of which were related to thrombotic adverse events. Three deaths were caused by pulmonary embolism and one by thrombosis (Tobaiqy et al., 2021). According to Schafer et al., (2003) however, a rare illness in Europe (AE in this example) is defined as one which affects five out of every 10,000 people, with ultra or very uncommon AE affecting one out of every 50,000 people. These cases of pulmonary embolism would be tentatively labelled as exceedingly uncommon incidents based on a simple calculation of 28 thrombotic events in proportion to 17 million immunized patients who got

the vaccination. Various causal variables for events of thrombosis were unproven and inconclusive, and no definite causal impact could be established.

Given that, the retrospective descriptive assessment of self-reports submitted to the EudraVigilance database concluded that more research was needed to assist national vaccination advisory boards and vaccine-resistant individuals in making more educated, evidence-based decisions (Tobaiqy et al., 2021). This is because several risk factors such as cancer, age, sedentarism, obesity, right heart failure, surgery and some medications (coagulants) have been related to lung or pulmonary embolism (PE) and deep vein thrombophlebitis (DVT) which are major causes of severe illness and death (López et al., 2004). In addition to this, the EMA database revealed incidences of DVT and PE connected to both the Moderna and Pfizer COVID-19 vaccines. No deaths were associated with the Moderna vaccine but for the Pfizer vaccine, of the 11 cases of pulmonary embolism, two deaths were recorded (Tobaiqy et al., 2021).

To contribute to the continuing debate about the safety of the Oxford–AstraZeneca COVID-19 vaccination, Østergaard et al., (2021) studied the Danish population-based data to determine the natural incidence of venous thromboembolism. It was observed that the number of thromboembolic events reported among Europeans who received the Oxford–AstraZeneca COVID-19 vaccine (at least those reported as originating in the venous system) had not increased in terms of the incidence rates from the entire Danish population before the vaccination programme's implementation.

The EMA later declared that despite the likely relationship to rare blood clots with low blood platelets, the benefits of the vaccine are more than the risks since the number of thromboembolic events among vaccinated patients is no more than in the general population (World Health Organization (WHO), 2022; EMA, 2021)

2.3.2 Latency period or time to onset of AEFIs

Jeon et al., (2021) reported that most AEFIs were experienced in the first 24 to 72 hours after taking the vaccine but resolved soon thereafter. A report by Basavaraja et al., (2021) indicated that most AEFIs occurred within 30 minutes to 24 hours following vaccination (322 out of 433 cases). In an article published by Sah et al., (2021) regarding the COVID-19 vaccination programme initiated by the Nepalese Government in January 2021, it was indicated that some health professionals reported irritation in their mood four hours after immunization; others reported myalgia, nausea, soreness at the injection site, and a feverish sensation six hours later. After 12 hours, some also reported temperature rise with chills, which needed to be treated with paracetamol.

In three different districts of central and western Nepal, a cross-sectional study of 1,006 frontline healthcare workers found that the majority of vaccine recipients experienced systemic (73.2%) and localized (65.4%) reactions within 1 – 12 hours of receiving dose 1 of the vaccine. However, these reactions generally resolved in less than 72 hours (Subedi et al., 2021).

The vaccination of the population in a western highland area of Nepal with COVISHIELD™ demonstrated a significant frequency of AEFIs among 276 people who were involved in cross-sectional research by Gautam et al., (2021). The most prevalent AEFIs recorded were discomfort at the injection site, generalized weakness, fever, headache, joint and muscle pain, disorientation, and loss of appetite with the average onset of these symptoms ranging from 9 to 14 hours after immunization.

2.3.3 Effect of Age, Sex and Comorbidities on the incidence of AEFIs

Ciarambino et al., (2021) reported that since the commencement of the pandemic, infected patients range in age from a 4-week-old to >90 years old, with relatively few instances seen in toddlers and babies. Male patients account for 59%–68% of all reported cases with higher fatality rates. In reality, persons who are 75 years old or more have a low immune function and

are more prone to infection and its consequences. COVID-19 patients die at a rate of 2.8 per cent for females and 4.7 per cent for males. As a result, the quality and degree of immunological response may differ between men and women, pre-and post-menopausal women, or adults and children. Additionally, persons with underlying disease conditions or comorbidities such as diabetes, obesity, cardiovascular disease and COPD, have an increased risk for COVID-19 fatality (Mueller et al., 2020).

In a report by Jeon et al., (2021), systemic and local AEFIs were reported more frequently among individuals under the age of 35 years (560 cases out of 566 persons, 98.9%) than among those above the age of 51 years (122 cases out 129 persons, 94.6%). Except for arthralgia and diarrhoea, the occurrence and severity of systemic and localized AEFIs were substantially greater in the younger healthcare worker (HCW) group (35 years or younger) than in the older HCWs group. Ramasamy et al., (2020) discovered that the COVISHIELD^{TM} vaccination was safe and well-tolerated in older individuals, with a reduced reactogenicity profile than in younger adults (reactogenicity reduces with increasing age). These findings were consistent with those of Zhu et al., (2020), who discovered that an adenovirus 5 vector-based vaccination exhibited lower reactogenicity in adults aged 55 and older compared to people aged 18–54 years following a single dose of vaccine.

In a cross-sectional study of 1,006 healthcare workers, Subedi et al., (2021) found that those aged 30 to 44 years had an increased risk of developing AEFIs (adjusted Odds of 1.1) compared to vaccine recipients aged less than 30 years, while persons 44 to 59 years and over 60 years had a lower risk (adjusted Odds Ratio of 0.5 and 0.6 respectively).

On bivariate analysis, Kaur et al., (2021) in their study discovered that the frequency of AEFIs declined with increasing age in their research, with roughly 1.4 times greater odds of acquiring AEFIs among those 18-39 years old compared to those 40 years old. This finding is consistent

with clinical trials examining several viral vector-based vaccinations as per reports by Ramasamy et al., (2020), Sadoff et al., (2021) and Zhu et al., (2020).

The majority of reports indicate that females tend to report more AEFIs. According to Basavaraja et al., (2021), out of the 5,986 healthcare professionals and frontline workers who were given COVISHIELD^{TM} when the COVID-19 vaccination programme began in India in January 2021, 259 persons reported AEFIs, a majority of which were females (193). Again, Kaur et al., (2021), in their report stated that females, those with hypertension, and those with a history of allergy were shown to have a two-fold increased risk of developing AEFIs as compared to men, normotensive vaccine recipients, and those with no history of allergy. Individuals with hypothyroidism had three times the risk of acquiring AEFIs when compared to those with normal thyroid function.

2.4 The Moderna COVID-19 Vaccine Product (SPIKEVAX^{TM}) and its associated overall AEFI incidence

This vaccine is an mRNA vaccine candidate manufactured by Moderna and sold under the brand name Spikevax. It is a lipid mRNA-based vaccine that encodes the S-2P antigen, consisting of the SARS-CoV-2 glycoprotein with a transmembrane anchor and an intact S1-S2 cleavage site (Cattel et al., 2022). The vaccine, mRNA-1273 (100 μg) is administered as a sterile liquid intramuscularly in the deltoid muscle in two doses (0.5 mL each), 28 days apart in the primary series and 0.25 mL in the booster (FDA Briefing Document, 2020; CDC & Ncird, 2022).

Following a phase 1 study conducted on 45 healthy vaccine recipients, 18 to 55 years old, (stratified in 3 groups of 15 vaccine recipients each), it was observed that after dose 1 of the vaccine, systemic AEs were reported by 5 vaccine recipients (33%) in the 25-μg arm, 10 (67%) in the 100-μg arm, and 8 (53%) in the 250-μg arm. After dose 2, AEs of systemic nature were

more common and occurred in 7 of 13 vaccine recipients (54%) in the 25-µg group, all 15 in the 100-µg group, and all 14 in the 250-µg group (Jackson et al., 2020).

In a phase 3 study report by Baden et al., (2021), where 30,420 people from 99 sites across the United States were involved in a clinical trial, it was observed that localized AEs resulted more commonly in the mRNA-1273 group (84.2%) than in the non-active treatment group (19.8%) after the initial dose. This was similar for dose 2 as well where the investigational product group had 88.6% as opposed to the placebo group with 18.8%.

2.4.1 Common, Serious and Rare AEFIs associated with the vaccine.

2.4.1.1 Common AEFIs

In the early developmental stages of the vaccine, a phase 1 open-label clinical trial was conducted using forty-five healthy vaccine recipients who were 18 to 55 years of age. These vaccine recipients, placed in 3 groups, received two vaccinations which were 28 days apart and in a dose of 25 µg, 100 µg, or 250 µg per group. Commonly occurring AEs including pain at the injection site, headache, tiredness, feeling cold and myalgia were observed in greater than half of vaccine recipients. After the second vaccination, systemic AEs were more common, especially within the 250 µg dose group. One participant in the 25-µg group was withdrawn because of transient urticaria, an unsolicited AE, judged to be related to the first vaccination (Jackson et al., 2020).

Similarly, a phase 1, open-label trial of the vaccine was conducted in 40 older adults, who were stratified into 56 to 70 years or ≥71 years age groups. All the vaccine recipients were assigned serially to receive two doses of either 25 µg or 100 µg of the vaccine given 4 weeks apart. Although no serious AEs were reported, solicited events including tiredness, pain at the injection site, headache, chills, and muscle pain which were generally mild or moderate in severity were observed. These events were noted to be dose-dependent and more common after dose 2 of the vaccine (Anderson et al., 2020).

A phase 3 trial of the vaccine was carried out at 99 sites across the United States, involving 30,420 people, including those at high risk of SARS-CoV-2 infection or its complications. According to Baden et al., (2021), the local reactions to the vaccination were generally mild (mostly pain at the injection site). After dose 2, however, about 50% of the vaccine recipients experienced moderate-to-severe systemic side effects such as fatigue, myalgia, arthralgia, and headache. The severity of the solicited systemic events in the vaccine group seemed to increase after the second dose, with a rise in the proportions of grade 2 events (from 16.5 per cent after the first dose to 38.1 per cent after the second dose).

According to Gee et al., (2021), within the first month of the vaccination programme in the US following the granting of Emergency Use Authorization (EUA) for the SPIKEVAX™ vaccine by the US FDA on December 18, 2020, 787,417 persons were given 1 dose of the vaccine. These were healthcare professionals and residents of long-term facilities (LTCF) between the ages of 16 - 110 years. It was observed that 1,373 persons reported AEs with the most frequently solicited local and systemic reactions being injection site pain, fatigue, headache, myalgia, and chills.

A retrospective analysis of spontaneous adverse events recorded in the US VAERS, between 14 December 2020 and 8 October 2021 indicated out of about 604,157 COVID-19 vaccine-related reports received, 284,765 were from the Moderna vaccine. The systemic and local AEs reported (in the order of frequency) included headache, fatigue, chills, pyrexia, pain, pain in extremities, dizziness, nausea, injection site erythema and injection site pain. These reactions were generally mild (Zou et al., 2022).

2.4.1.2 Serious AEFIs

Shimabukuro, (2021) reported that following the implementation of the vaccination programme in the US when the Moderna vaccine was given EUA, 19 cases of severe, potentially life-threatening allergic reactions were reported after administration of the Moderna

vaccine (out of about 7,581,429 doses) were reported administered in the US over a period of 1 month (December 21, 2020-January 10, 2021), indicating a reporting rate of about 2.5 cases per million doses given. Ten of these cases met the case definition level 1 of Brighton Collaboration, with 8 meeting the level 2 case definition and 1 being level 3.

Of the 284,765 AEFIs related to the Moderna vaccine which was recorded in the retrospective analysis of safety reports in the VAERS, there were 3,329 deaths. However, these cases mainly occurred among the elderly with underlying chronic medical conditions, such as diabetes mellitus, high blood pressure and cancer (Zou et al., 2022).

2.4.1.3 Rare AEFIs

Myopericarditis (inflammation of the heart muscle) has been reported as a rare vaccination complication after receipt of mRNA COVID-19 vaccines. According to a report by Rosner et al., (2021), 7 male patients, (<40 years of age and White or Hispanic race/ethnicity), from two US medical centres were hospitalized for acute myocarditis-like illness following COVID-19 vaccination. Six of them received an mRNA vaccine (Moderna or Pfizer/BioNTech), and 1 received the adenovirus vaccine (Janssen).

According to the published preliminary data, all cases of myopericarditis are minor and clinically recover within a few days to a few weeks. Transient myocardial or pericardial inflammation caused by vaccination-related risks is extremely rare and outweighs the risk of cardiac complications caused by SARS-CoV-2 infection (Das et al., 2021).

Between the 3rd week of December 2020, and the second week of January 2021, the VAERS monitored patients and discovered 10 cases of severe, potentially life-threatening allergies following the administration of 4,041,396 first doses of the Moderna COVID-19 vaccine (2.5 cases per million doses administered). The onset of the anaphylaxis occurred 15 minutes or

less after the vaccination in nine of these cases. However, no fatalities attributed to severe, potentially life-threatening allergies were reported (Shimabukuro, 2021).

2.4.2 Latency period or time to onset of AEFIs

In phase 1, an open-label trial of the vaccine involving 40 older adults, who were stratified into 56 to 70 years or ≥71 years age groups revealed that the mild to moderate AEs which were observed following immunization (injection site pain, tiredness, feeling cold, headache, muscle pain) occurred on the vaccination day or 24 hours afterwards and went disappeared quickly (Anderson et al., 2020).

According to a phase 3 trial report by Baden et al., (2021), the side effects which occurred following immunization of over 30,000 vaccine recipients were generally transient, began within 15 hours after vaccination and resolved without sequelae in most vaccine recipients by day 2. A few delayed injection-site reactions, (reactions such as erythema, induration, and tenderness which occurred 8 days or more after injection), were noted in just about 244 vaccine recipients (0.8%) after the first dose and in 68 vaccine recipients (0.2%) after the second dose and resolved over 4 to 5 days.

In the report by Shimabukuro, (2021), 16 anaphylaxis cases out of the 19 reported occurred within 15 minutes of administration of the vaccine.

All 7 cases of myopericarditis according to a report by Rosner et al., (2021) occurred within 3 to 7 days after receipt of the vaccine with acute onset chest pain and biochemical evidence of myocardial injury. In Larson et al., (2021) report, 7 out of the 8 persons who suffered myopericarditis had symptoms presenting on day 3 after the second injection with 5 of them having a fever a day before. Only 1 patient experienced myocarditis after day 1 of vaccination and this patient was said to have been previously infected with COVID-19.

According to the Pentagon Tracking 14 Cases of Heart Inflammation in Troops After COVID-19 Shots | Military.Com, n.d.), fourteen (14) cases of myocarditis, were recorded among some US military persons following vaccination with mRNA vaccines (11 from Moderna and 3 from Pfizer). Apart from 1 person who tested positive for COVID-19 three months before the vaccination and developed myocarditis after their first dose of the vaccine, all others developed myocarditis after their second vaccine doses.

2.4.3 Effect of Age, Sex and Comorbidities on the incidence of AEFIs

Systemic and localized AEs after immunization were observed less frequently among older vaccine recipients (≥65 years of age) than among vaccinees 18 to <65 years of age (Baden et al., 2021).

According to Das et al., (2021), some cases of myocarditis were reported to VAERS following mRNA COVID-19 vaccinations with Pfizer-BioNTech and Moderna. These cases are especially in male adolescents and young adults and usually occur within a week of receipt of dose 2 vaccinations. All 8 individuals who suffered myopericarditis in Larson et al., (2021) report were healthy males between the ages of 21 and 56 years. Likewise, the 7 individuals who according to Rosner et al., (2021) experienced myopericarditis related to the Moderna and Pfizer mRNA vaccines were males more than 40 years old.

2.5 The Pfizer-BioNTech COVID-19 Vaccine Product (COMIRNATY™) and its associated overall AEFI incidence

In response to a bid to stop the spread of COVID-19, which is brought on by SARS-CoV-2 infection, BioNTech and Pfizer developed the Pfizer-BioNTech COVID-19 vaccine (BNT162b2). The vaccine is stabilized in the prefusion conformation and is given intramuscularly (IM) in two doses of 30 g of the diluted vaccine solution (0.3 mL each) 21 days apart (Pfizer-BioNTech, 2020).

A total of 195 healthy adults aged 18 to 55 years and 65 to 85 years participated in a phase 1 trial in the United States, where they were assigned randomly to take either a placebo or one of two vaccine candidates (BNT162b1 and BNT162b2). Vaccine recipients were randomly given two doses of 10 mg, 20 mg, or 30 mg of each of the two candidate vaccines or a placebo, 21 days apart. Others also got a 100-g dose of BNT162b1 or a placebo. BNT162b2 (Pfizer-BioNTech COVID-19 vaccine) was chosen for the pivotal phase 2-3 safety and efficacy trials because it was found to be linked with a lesser occurrence and intensity of systemic reactions than BNT162b1. With an incidence of about 92%, most local reactions (pain, swelling and redness at the site of injection) were generally mild to moderate for both vaccines and none of the vaccine recipients in this study reported a grade 4 systemic or localized event (Walsh et al., 2020).

A total of 43,448 vaccine recipients (≥16 years of age) in a phase 2/3 trial were randomized to receive the two doses of the vaccine 21 days apart; 21,720 received the vaccine (30g), and 21,728 received saline. Similar to the phase 1 study, the immune response was of mild or moderate intensity, along with discomfort at the injection site, exhaustion, and headaches. Although the localized immune response was similar after the two doses, systemic reactogenicity (fever, headache, feeling cold, tiredness, vomiting, diarrhoea, arthralgia and myalgia) was observed to be more frequent and intense after dose 2 than after the first dose. For instance, 4% of vaccine recipients showed signs of severe fatigue, which is higher than what is usual for vaccines recommended for adults (Polack et al., 2020).

2.5.1 Common, Serious and Rare AEFIs associated with the vaccine.

2.5.1.1 Common AEFIs

According to a report by Walsh et al., (2020), mild to moderate pain at the injection site was the main AEFI reported across both vaccinated candidate groups (BNT162b1 and BNT162b2 recipients) in the phase 1 trial of the vaccine. It was observed that systemic events (fever, chills

and fatigue) in the BNT162b2 vaccine recipients were milder than what was reported in BNT162b1 recipients.

The most frequently occurring systemic AEFIs after the second dose, among persons 16 to 55 years old, as per a report by Polack et al., (2020), were fatigue (59%) and headache (52%) with older recipients (more than 55 years old) reporting 51% and 39% respectively. It was also observed that fatigue and headache were reported after dose 2 by quite a number of the younger persons receiving the placebo (23% and 24%, respectively) as well as 17% and 14% respectively of the older placebo recipients' group. In general, localized events were mostly mild-to-moderate in intensity and resolved within 24 to 48 days of receiving the vaccine. Among the younger adult recipient group, pain was reported more frequently (83% after the first dose; 78% after the second 2) than among vaccinees more than 55 years of age who reported 71% and 66% respectively. Fewer vaccinees reported swelling or redness at the injection site and no participant reported a grade 4 localized event. In general, localized events were mostly of mild-to-moderate intensity and resolved within 24 to 48 hours.

Mohammed et al., (2021) in a report indicated that from February 2021 to March 2021, when their mass vaccination campaign was launched, a study involving 386 adult males and females, 18 years old to 65 years old or more, was carried out in Saudi Arabia using a validated modified questionnaire. Localized pain (79.3 per cent), tiredness (42 per cent), myalgia (39.1 per cent), local swelling (27.7 per cent), arthralgia (23.1 per cent), headache (21.8 per cent), fever (21.0 per cent), feeling cold (15.5 per cent), injection site redness (14.8 per cent), and nausea (7.3 per cent) were found to be the most frequently reported local and systemic AEFIs. Additionally, it was observed that dose 2 of the vaccine resulted in more side effects than the primary dose. Only about 12.1% reported severe symptoms and the severity ranged from mild (30%) to moderate (57.9%).

2.5.1.2 Serious AEFIs

Twenty-one (21) cases of anaphylaxis were discovered in the United States from December 14 to December 23, 2020, following the administration of 1,893,360 initial doses of the Pfizer-BioNTech COVID-19 vaccine (11.1 cases per million vaccine doses given), according to Shimabukuro T., (2021). These included seventeen (17) individuals (81%) with a history of allergies, seven (7), of whom had experienced severe life-threatening allergic reactions. The symptoms of 18 anaphylactic cases (86%) began within 30 minutes of the vaccination. Upon follow-up of twenty, all had made full recovery or had been sent home.

2.5.1.3 Rare AEFIs

Myocarditis has been reported as a rare AEFI following mRNA (Pfizer-BioNTech and Moderna) COVID-19 vaccination, particularly after the second dose. The Advisory Committee on Immunization Practices (ACIP), however, reviewed updated risk-benefit analyses following mRNA COVID-19 vaccination in July 2021 and concluded that the advantages outweigh the risks for extremely uncommon serious reactions following COVID-19 vaccination Rosenblum et al., (2021).

2.5.2 Latency period or time to onset of AEFIs

In the phase 1 trial of the vaccine, according to Walsh et al., (2020), localized reactions of mild-to-moderate intensity were reported by the vaccine recipients within 1 week after vaccination.

Polack et al., (2020), also indicated that BNT162b2 (Pfizer-BioNTech COVID-19 vaccine) recipients, who experienced mild-to-moderate pain intensity at the injection site in the global phase 2-3 trial, generally did so within 7 days of vaccination. The systemic AEs also occurred within the first 24 to 48 hours after vaccination and shortly thereafter resolved.

Most AEFIs observed in a cross-sectional study which took place in Saudi Arabia, according to Mohammed et al., (2021), were said to have started at 24 hours (66.3 per cent), and then between 24 and 48 hours (23.2 per cent).

2.5.3 Effect of Age, Sex and Comorbidities on the incidence of AEFIs

Tiredness, headache, rigours, arthralgia and myalgia of severe intensity were reported in a few vaccine recipients in the 18 to 55 years old BNT162b2 group, but no such events were reported by the 65 to 85 years old of this vaccine candidate according to a report on the phase 1 study conducted in the United States (Walsh et al., 2020).

Polack et al., (2020) indicated that in the phase II/III trial of the vaccine, systemic events were higher in those 16 to 55 years of age than in those 55 years of age or more and these events were noted to be higher after dose 2 than dose 1.

In a report on a study which took place from February 2021 to March 2021 in Saudi Arabia, Mohammed et al., (2021) noted that being female and having a history of allergies was significantly associated with the occurrence of AEFIs.

2.6 The Sputnik V COVID-19 Vaccine Product (Gam-COVID-Vac) and its associated overall AEFIs incidence

The Sputnik V vaccine is produced by the Gamaleya National Centre of Epidemiology and Microbiology in Moscow. It contains two discrete types of adenovirus vectors, rAd26 and rAd5, for doses 1 and 2, respectively. The vaccine consists of one intramuscular dose of rAd26-S (0.5 mL) given on day 0 and one intramuscular dose of rAd5-S (0.5 mL) given after 3 weeks (Logunov et al., 2021).

A report by Montalti et al., (2021) from a nationwide study which was conducted in the Republic of San Marino during their COVID-19 vaccination campaign, revealed that out of 2,558 Sputnik V (Gam-COVID-Vac) vaccinees, dose 1 AEFI incidence was 53.3 per cent (of which 42.2% were systemic reactions), whereas the second-dose AEFI incidence was 66.8 per cent (50.4% systemic reactions). In general, 76.0 per cent of those who received two doses experienced some AEFIs after either vaccine dose, with 2.1 per cent experiencing severe

events. In 1,021 60- to 89-year-olds, AEFI incidence was 70.0 per cent, with 53.0 per cent having systemic events and 0.8 per cent experiencing symptoms of severe intensity.

A report by Hasan et al., (2022) indicated that out of 198,890 doses of the Sputnik V vaccine administered in Pakistan when the COVID-19 immunization commenced on 2nd February 2021, only 13 AEFIs were reported, giving a rate of about 0.07 AEFIs per 1,000.

2.6.1 Common, Serious and Rare AEFIs

2.6.1.1 Common AEFIs

The most frequent local reactions observed in a nationwide observational study conducted in the Republic of San Marino (Montalti et al., 2021) were pain (24.8%), lumps (3.7%), warmness (2.2%) and swelling (1.9%). Frequent systemic reactions reported symptoms were muscle weakness (23.8%), headache (18.5%), arthralgia (16.5%), chills (16.5%), myalgia (16%), increase in body temperature (11.9%) and feeling generally uncomfortable (11.8%). These reactions were similar to those observed in the phase 1/2 studies earlier conducted, most of which were mild and no serious AEs were noticed Logunov et al., (2020).

An interim report from the phase 3 study in Russia, which included results for over 21,000 vaccine recipients, 75 per cent of whom were assigned to receive the vaccine, as well as follow-up for adverse events and infection, revealed that no serious adverse events thought to be related to the vaccine were recorded. There were 45 vaccine recipients in the active treatment arm and 23 in the non-active treatment arm who experienced serious adverse events that were unrelated to the vaccine. Unfortunately, 3 persons with severe chronic illnesses in the vaccine group died, and these were ruled unrelated to the vaccine (Logunov et al., 2021; Jones & Roy, 2021).

A total of 469 local reactions were reported in a cohort study of 707 vaccine recipients in Buenos Aires, with 57 per cent reporting pain at the injection site and 11 per cent reporting redness and swelling. A total of 968 systemic reactions were reported, including new or

worsened muscle pain identified in 58% of vaccine recipients, fever in 40%, and diarrhoea in 5%. Thirty-four persons (5%) experienced serious adverse events, with one participant being hospitalized (Pagotto et al., 2021).

2.6.1.2 Serious and rare AEFIs

Cazzola et al., (2021) in a report indicated that the preliminary analysis of the Phase III trial on patients who were given the Sputnik V vaccine in Russia revealed one case of deep vein thrombosis, one case of cerebral circulatory failure, one case of transient ischemic attack, and one case of vascular encephalopathy were recorded. Furthermore, no thromboembolism or thrombocytopenia vasculitis were indicated in the report by Pagotto et al., (2021) where a cohort of 707 vaccinated healthcare professionals in Buenos Aires, Argentina were followed up to investigate the safety of this vaccine.

Nogrady, (2021) noted that despite receiving more than four million doses of the vaccine, Argentina has not reported any clotting events, and Serbia, which has also widely used Sputnik V, has reported no cases of the blood-clotting condition described with other adenovirus vectored vaccines.

2.6.2 Latency period or time to onset of AEFIs

In a report by Montalti et al., (2021), of the 2,556 vaccine recipients who experienced AEFIs, the majority of the events developed within 24 - 48 hours of the injection (85.7%), and less commonly after a few minutes (4.5%), 3 - 5 days (4.2%), and 6 - 7 days (1.4%). Unfortunately, 4.3 per cent of patients who had AEFIs did not give information on the beginning of their reactions.

According to Pagotto et al., (2021), the incident rate of AEFIs following the vaccination of 707 healthcare professionals in a hospital in Buenos Aires was 6.3 per 1,000 patient hours. Systemic and localized reactions occurred on the vaccination day or within 24 hours after and were generally resolved with antipyretics within 1 day.

2.6.3 Effect of Age, Sex and Comorbidities on the incidence of AEFIs

Earlier investigation from a nationwide study which took place in the Republic of San Marino revealed that the Sputnik V has a greater or equivalent tolerability profile in those aged 60 years or more following doses 1 and 2 when compared to other commonly used COVID-19 vaccines Montalti et al., (2021).

Also, Pagotto et al., (2021) revealed that female healthcare workers had a higher AEFI rate after vaccination than their male counterparts (66.4 per cent versus 51.4 per cent; HR 1.38). Workers under the age of 55 also experienced more events than their older colleagues (63.0 per cent versus 28.0 per cent; HR 2.66).

A longitudinal study conducted by Soldà et al., (2022) during the Republic of San Marino COVID-19 vaccination campaign, which used Sputnik V and Pfizer vaccines, found that roughly 6,000 vaccinees were observed for adverse reactions, including subgroups presenting neurological diseases such as Parkinson's Disease (PD) and Multiple Sclerosis (MS). Among all those with the diseases who were followed up on, 61 received the Sputnik vaccination and 21 received the Pfizer vaccine. AEFIs were documented in 67 per cent of the MS cohort, 26 per cent of patients in the PD cohort and 68 per cent in the control cohort after the first dosage. Vaccine recipients reported somewhat higher AEFI rates following the second dose compared to the first, with PD, MS, and control groups reporting 29 per cent, 75 per cent, and 78 per cent, respectively. A majority of the symptoms reported were minor.

2.7 The Johnson & Johnson COVID-19 Vaccine Product (J&J or Janssen COVID-19 Vaccine) and its associated overall AEFI incidence

The Janssen's COVID-19 vaccine uses a human Adenovirus 26 (Ad26) as a vector to express the coronavirus Spike (S) protein and it is administered as a single intramuscular (5×10^{10} viral particles) dose of 0.5ml (Sadoff et al., 2021).

To characterize adverse effects postvaccination with three COVID-19 vaccines that are authorized in the US, including the Janssen vaccine, an analysis of safety data was conducted using VAERS data recorded between January 1, 2021, and April 30, 2021, according to Singh et al., (2022). Following the administration of 8.23 million doses of the vaccine, it was discovered that 51,205 (0.35%) of the 141,208 total analyzable individuals who experienced at least one adverse event after receiving the COVID-19 vaccine belonged to the Janssen vaccine group.

2.7.1 Common, Serious and Rare AEFIs associated with the vaccine

2.7.1.1 Common AEFIs

In a cohort event monitoring study in the Netherlands using patient-reported outcomes, 22,184 vaccine recipients were recruited, out of which 1,508 vaccine recipients received the Janssen COVID-19 vaccine. The most frequent local adverse reaction associated with the Janssen vaccine as reported by Rofles et al., (2022) was injection site pain (48.6%). In terms of systemic AEs, headache (38.9%), tiredness (38.2%), myalgia (33.2%), and nausea (14.2%) were the most frequent.

Sadoff et al., (2021) reported in a double-blinded multinational, randomized, placebo-controlled trial, in which over 43,000 persons 18 years or older were equally assigned to take a single shot of Ad26.COV2.S or placebo, the most common local reaction (48.6% of the vaccine group) was injection-site pain with the most common systemic reactions among the vaccine recipients being headache (in 38.9%), tiredness (in 38.2%), muscle pain (in 33.2%), and nausea (in 14.2%).

According to Singh et al (2022), common AEFIs associated with the Janssen vaccine following safety data analysis of reports from the VAERS in the US include headache (1,217.25 per million doses) and pyrexia (1,036.70 per million doses).

2.7.1.2 Serious and rare AEFIs

The US FDA and the CDC confirmed six cases of cerebral venous thrombosis (CVT) that had been reported in the US on April 13, 2021, and they halted the use of the Janssen vaccine after that. These cases all involved low platelet levels and occurred 6–13 days after vaccination in women between the ages of 18 and 48. This led to the suspension of the vaccine in the EU, South Africa and the USA (Gupta et al., 2021).

Apart from the cases of blood clots with low platelet levels, some cases of Guillain-Barré syndrome have also been documented after receiving the Janssen COVID-19 vaccine. Given this, the Advisory Committee on Immunization Practices (ACIP) made a special recommendation for the use of mRNA COVID-19 vaccines over the Janssen vaccine in all adults in the US in December 2021, following a review of vaccine safety and efficacy data. In cases where receiving the mRNA COVID-19 vaccine is contraindicated, the Janssen vaccine might be an option (Oliver et al., 2022).

2.7.2 Latency period or time to onset of AEFIs

Most solicited local and systemic adverse events reported among the safety subpopulation in the multinational phase 3 trial of the vaccine occurred within 1 to 2 days after the administration of the vaccine and had a median duration of 1 to 2 days (Sadoff et al., 2021).

2.7.3 Effect of Age, Sex and Comorbidities on the incidence of AEFIs

Higher reactogenicity was observed among adults 18 to 59 years of age than those 60 years of age or older during the final analysis of the double-blind multinational, randomized, placebo-controlled trials. Over 43,000 persons 18 years or older were assigned to receive 1 shot of the vaccine or placebo in a 1:1 ratio (Sadoff et al., 2021; Sadoff et al., 2022)

Of the fifty-four (54) cases of blood clots with low platelet counts identified in Janssen COVID-19 vaccine recipients from the beginning of March 2021 to the end of August 2021, in the US, 37 (69%) patients were women. By April 2021, 13 (87%) of the 15 patients with blood clots

with low platelet counts were noted to be women aged 18–49 years. In all, about 48% (26 of 54) of the cases of blood clots with low platelet counts after taking the Janssen COVID-19 vaccine were identified through August 2021 as adult females below 50 years (Oliver et al., 2022).

From the studies conducted on the COVID-19 vaccines, it can be observed that the vaccines are generally safe, with many of the adverse events being mild and resolving within a few days without any interventions. Many of these mild reactions occurred in younger age groups than in the elderly and were also common in females compared to males.

Although there have been few instances of very rare and serious adverse events, as well as deaths associated to the use of some of the vaccines, the advantages of using the vaccines which include reducing the spread of COVID-19 disease and the severity of the disease even if it occurs, far outweigh the risks of these extremely uncommon or rare serious adverse reaction.

CHAPTER THREE

METHODS

3.1 Study Design

This study was a retrospective cohort study involving secondary data analyses of AEFI reports from two sources:

- Active surveillance of AstraZeneca, Moderna and Pfizer COVID-19 vaccines during a prospective cohort event monitoring (CEM) study which took place from March 2021 to June 2022.
- Passive surveillance (spontaneous reporting from all over the country) of the five (5) COVID-19 vaccines deployed for use in the mass vaccination campaign in Ghana from March 2021 to June 2022. These vaccines are AstraZeneca, Moderna, Pfizer, Janssen and Sputnik V.

3.2 Study Population

The study included AEFI data (an exhaustive sampling) of all COVID-19 vaccine-related AEs reported by persons 18 years or older who received at least a dose of any of the vaccines during the CEM study or the nationwide spontaneous reporting from the mass vaccination campaign in Ghana. The sentinel sites for the CEM were:

1. Ejisu Government Hospital (EGH), Ashanti Region
2. Suntreso Government Hospital (SGH), Ashanti Region
3. Kasoa Polyclinic (KPC), Central Region
4. Tamale Central Healthcare (TCH), Savannah Region
5. Holy Family Hospital (HFH), Techiman, Bono East Region
6. Ho Municipal Hospital (HMH), Volta Region
7. Mamprobi Polyclinic (MPC), Greater Accra Region
8. Adabraka Polyclinic (APC), Greater Accra Region

9. Tema General Hospital (TGH), Greater Accra Region

3.2.1 Inclusion criteria

The study included all persons 18 years or older who received at least a dose of any of the 5 COVID-19 vaccines during the CEM study and those who received vaccines in the nationwide mass vaccination campaign in Ghana between 2nd March 2021 to 30th June 2022.

3.2.2 Exclusion criteria

Spontaneous AEFI reports from persons who experienced adverse events from other vaccines which were not COVID-19 vaccines in the FDA's safety database were excluded.

3.3 Study Variables

3.3.1 Outcome (dependent) variables

The study had a primary and secondary outcome (dependent) variable:

- The Primary Outcome Variable for this study was AEFI of COVID-19 vaccines (all vaccine recipients).
- The Secondary Outcomes Variables included (only vaccine recipients who experienced any form of AEFI):
    - The specific AEFIs
        - Local reactions: injection site pain, erythema, swelling, tenderness, etc.)
        - Systemic reactions: fever, headache, myalgia, malaise (feeling tired, irritable or generally unwell), nausea, vomiting, rash, diarrhoea, tightness in the chest muscle, dyspnea, arthralgia etc.
    - The time between vaccination and onset of AEFIs (latency period)
    - The severity of the AEFIs
    - The outcome of the AEFIs (recovery or death)

3.3.2 Independent variables

The Independent Variables for the study were age, sex, region or enrolment site, any known allergies, co-morbidities, concurrent medication at the time of vaccination, dose, schedule and type of vaccine.

Table 3.1 Study Independent Variables

Variable name	Definition	Type of variable	Categories
Sex	Sex of the participant	Categorical	• 0 – male • 1 – female
Age	Age of the participant (in years)	Continuous/Categorical	• < 20 • 20 – 29 • 30 – 39 • 40 – 49 • 50 – 59 • 60 and above
Geographical location or region	Enrolment site (Health facility)	Categorical	• EGH • SGH • KPC • TCH • HFH • HMH • MPC • APC • TGH

Co-morbidities	History of any known illness or disease before receiving the vaccine	Categorical	• Diabetes • Hypertension • Asthma • Others
Allergies	History of allergies to vaccines or vaccine components	Categorical	• Yes • No
Concurrent medication	Drugs being taken at the time of vaccination	Categorical	• Yes • No
Dose	Dose number	Categorical	• First dose • Second dose
Vaccine	Type of vaccine platform (Vectored vaccine or mRNA vaccine)	Categorical	• Covishield/ AstraZeneca • J&J/Janssen • Moderna • Pfizer • Sputnik

3.4 Data Source, Storage and Processing

The two main data sources for this study were identified with the primary data host institution as follows;

- Data from a CEM study (active surveillance) conducted on 3 COVID-19 vaccines (AstraZeneca, Moderna and Pfizer) from 2nd March 2021 to 30th June 2022
- Nationwide spontaneous reports on AEs experienced by vaccine recipients following vaccination in the mass immunization campaign using the COVID-19 vaccines currently

given Emergency Use Authorization (EUA) by FDA in Ghana (AstraZeneca, Moderna, Pfizer, Janssen and Sputnik V).

A password-protected laptop was used to store the secondary data obtained from the primary host institution, FDA. Data from the CEM study was downloaded from the Open Data Kit (ODK), an open-source mobile data collection platform, onto Microsoft Excel spreadsheets. Some of the COVID-19 vaccine-related spontaneous reports from 2nd March 2021 to 30th June 2022 were retrieved from the database following a search on these reports in the FDA's Safety Watch System. This is an online reporting system for AEs on drugs, vaccines and other regulated products. Other spontaneous reports from COVID-19 vaccine recipients which were in hard copies (paper forms) were manually entered into Microsoft Excel spreadsheets.

Based on the study's objectives and variables, the raw data obtained was cleansed by removing unwanted observations such as Ghana Post Digital Addresses or Global Positioning System (GPS) coordinates of health facilities and vaccine recipients, names and other contact details of AEFI reporters and participants, expiry and batch numbers of vaccines, etc. Structural errors were fixed to ensure standardizing of the data by filtering the relevant variable columns and making the necessary correction like removing spaces, correcting wrong spellings in the event names, wrong numerical entries, wrong capitalization of words, etc. Missing information was also addressed by filling in where necessary. For example, the ages of some participants which were missing were filled in given their dates of birth. Some information which was missing such as participant vaccination dates, the brand of vaccine received and time to onset of events were also retrieved from the paper reports or estimated based on other parameters available electronically. All these were done to ensure that the data was in the appropriate format so that any data that was inaccurate, incomplete, incorrectly formatted, duplicated, or even irrelevant to the objectives of the study was removed.

The data was also appropriately recoded to identify each unique vaccine recipient. This was done by filtering the participants' ID column to know those that were inappropriately coded such as missing enrolment site or health facility-specific codes or digits to ensure consistency in the coding system and the number of digits.

Assessment of the severity of AEs was done according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1. This grading table provides an AE severity grading scale ranging from grades 1 to 5 with definitions as follows:

- Grade 1 indicates a mild event; symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated
- Grade 2 indicates a moderate event; symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated
- Grade 3 indicates a severe event; symptoms causing the inability to perform usual social and functional activities with intervention or hospitalization indicated
- Grade 4 indicates a potentially life-threatening event
- Grade 5 indicates death.

For this study, all AEs of grade 3 or more were categorized as 'severe' with grade 1 or 2 being categorized as 'not severe'.

3.5 Statistical Analysis

Data which had been reviewed and appropriately formatted was imported into Stata software STATA I/C 16 (Stata Corp LLC, Texas, USA) and analyzed.

Descriptive characteristics of study participants were done using frequency and percentages for categorical variables, and median and interquartile range for continuous variables. A bar chart was also used to describe selected characteristics such as chronic medical conditions, the cumulative incidence of AEFIs, the various forms of AEFIs experienced and the number of

AEFIs experienced in the study. The pie chart was used to describe the latency of AEFIs experienced.

For the cohort event study, the cumulative incidence, the incidence rate per 100,000 person days, and the incidence rate ratios were estimated using the dose of vaccines as the unit of analysis. Also, the cumulative incidence of AEFIs was estimated using individuals as a unit of analysis. The Pearson chi-square test was used to assess the factors related to the cumulative incidence of AEFIs among study participants. The Cox-proportional hazard regression model was used to assess the factors associated with the risk of AEFIs among the study participants. From the incidence rate ratio (IRRs) analysis of AEFIs by vaccine dose, all variables showed significance and were therefore used in the Cox-proportional hazard regression model. The crude and adjusted hazard rate ratio and the corresponding 95% confidence interval (CI) as well as the p-values were estimated and presented from the Cox-proportional hazard regression models.

For the analysis of the spontaneous (self-reporting) data, descriptive analysis was performed across the various vaccine types. The Pearson chi-square test was used to assess the relationship between the background characteristics and the type of vaccines. The severity of the AEFIs experienced was also described. The Pearson chi-square test was also used to assess the association between the severity of AEFIs experienced and the background characteristics. The binary logistic regression model was used to assess the factors related to severe AEFIs among vaccine recipients in the spontaneous data. Similarly, the outcome of the AEFIs experienced was also described across the background characteristics and the Pearson chi-square test was used to assess the association. The binary logistic regression model was used to assess the factors associated with death outcomes following AEFIs among vaccine recipients in the spontaneous data.

All statistical analyses were considered significant at an alpha of 0.05 level.

3.6 Ethical Considerations

The Ghana Health Service Ethics Review Committee (GHS-ERC) gave ethical approval with number GHS-ERC: 051/09/22 on 18th October 2022 before data analysis (APPENDIX II). Before receiving ethical approval, the FDA (primary data host) approved the use of the data on 13th June 2022. To ensure the confidentiality of vaccine recipients, electronic AEFI data was de-identified (devoid of vaccine recipients' identifying information) by the primary data host before analyses. This data was used for the intended purpose as per the objectives outlined in the proposal. The data was kept safe from unauthorized access in the form of encrypted files on a password-protected laptop while preventing accidental loss or destruction.

This research was self-sponsored or self-funded.

3.7 Quality Control

Data was stored on a computer, protected with a password when it was obtained from the primary data host institution. Before analysis, it was cleansed (transformed into the appropriate format) to ensure its integrity, accuracy, and completeness, appropriately formatted and without duplicates.

CHAPTER FOUR

RESULTS

4.1 Analysis of the Cohort Event Study data

4.1.1 Descriptive Characteristics of Vaccine recipients by Vaccine Dose

A total of 6,723 files were obtained from the cohort data set out of which 6,100 unique vaccine recipients were identified. The remaining 623 files were dropped because they were found to be duplicates. The 6,100 unique vaccine recipients received a total of 9,929 doses of AstraZeneca, Moderna and Pfizer COVID-19 vaccines. All 6,100 vaccine recipients took dose 1 and 3,829 continued to take dose 2. The median age of the 6,100 unique vaccine recipients was 38 years (IQR: 26-55 years). More than half (52.1%) of the vaccine recipients were males. 15.1% of vaccine recipients took the Moderna vaccine, 43.8% took the Pfizer vaccine and 41.1% took the AstraZeneca vaccine. Most vaccine recipients received their vaccines at KPC (20.8%) or MPC (22.3%). More than a third (37.2%) took only the first dose while 62.8%) took both dose 1 & dose 2. (Table 4.1.1)

Table 4.1.1: Descriptive characteristics of vaccine recipients by vaccine dose received

	Unique vaccine recipients	By vaccine dose		
		Total doses	Dose 1	Dose 2
	N=6,100	N=9,929	N=6,100	N=3,829
Age (in years)	38 (26-55)	39 (27-57)	37 (26-54)	43 (30-60)
Age group				
<20 years	748 (12.3)	986 (9.9)	766 (12.6)	220 (5.7)
20-29 years	1,303 (21.4)	2,055 (20.7)	1,318 (21.6)	737 (19.2)
30-39 years	1,238 (20.3)	1,980 (19.9)	1,247 (20.4)	733 (19.1)
40-49 years	883 (14.5)	1,448 (14.6)	886 (14.5)	562 (14.7)
50-59 years	744 (12.2)	1,286 (13.0)	730 (12.0)	556 (14.5)
60+ years	1,184 (19.4)	2,174 (21.9)	1,153 (18.9)	1,021 (26.7)
Sex				
Females	2,919 (47.9)	4,789 (48.2)	2,917 (47.8)	1,872 (48.9)
Males	3,181 (52.1)	5,140 (51.8)	3,183 (52.2)	1,957 (51.1)
History of chronic medical condition				
No	5,079 (83.3)	8,034 (80.9)	5,114 (83.8)	2,920 (76.3)
Yes	1,021 (16.7)	1,895 (19.1)	986 (16.2)	909 (23.7)
Enrolment site				
APC	360 (5.9)	595 (6.0)	360 (5.9)	235 (6.1)
EGH	621 (10.2)	1,203 (12.1)	621 (10.2)	582 (15.2)
HMH	299 (4.9)	389 (3.9)	299 (4.9)	90 (2.4)
HFH	633 (10.4)	1,029 (10.4)	633 (10.4)	396 (10.3)

KPC	1,267 (20.8)	1,811 (18.2)	1,267 (20.8)	544 (14.2)
MPC	1,358 (22.3)	2,124 (21.4)	1,358 (22.3)	766 (20.0)
SGH	630 (10.3)	1,196 (12.0)	630 (10.3)	566 (14.8)
TCH	728 (11.9)	1,319 (13.3)	728 (11.9)	591 (15.4)
TGH	204 (3.3)	263 (2.6)	204 (3.3)	59 (1.5)
Vaccination type				
Moderna	922 (15.1)	1,458 (14.7)	955 (15.7)	503 (13.1)
Pfizer	2,673 (43.8)	3,890 (39.2)	2,714 (44.5)	1,176 (30.7)
AstraZeneca	2,505 (41.1)	4,581 (46.1)	2,431 (39.9)	2,150 (56.2)
Number of vaccine doses taken				
Dose 1 only	2,271 (37.2)	2,271 (22.9)	2,271 (37.2)	0 (0.0)
Dose 1 & 2	3,829 (62.8)	7,658 (77.1)	3,829 (62.8)	3,829 (100.0)

Less than a fifth (16.7%) had a history of chronic medical conditions (Table 4.1.1). Among those with chronic conditions, the most prevalent were hypertension (77.4%), diabetes (26.9%), chronic allergy (6.8%), asthma (5.7%), and ulcers (3.6%). (Figure 4.1)

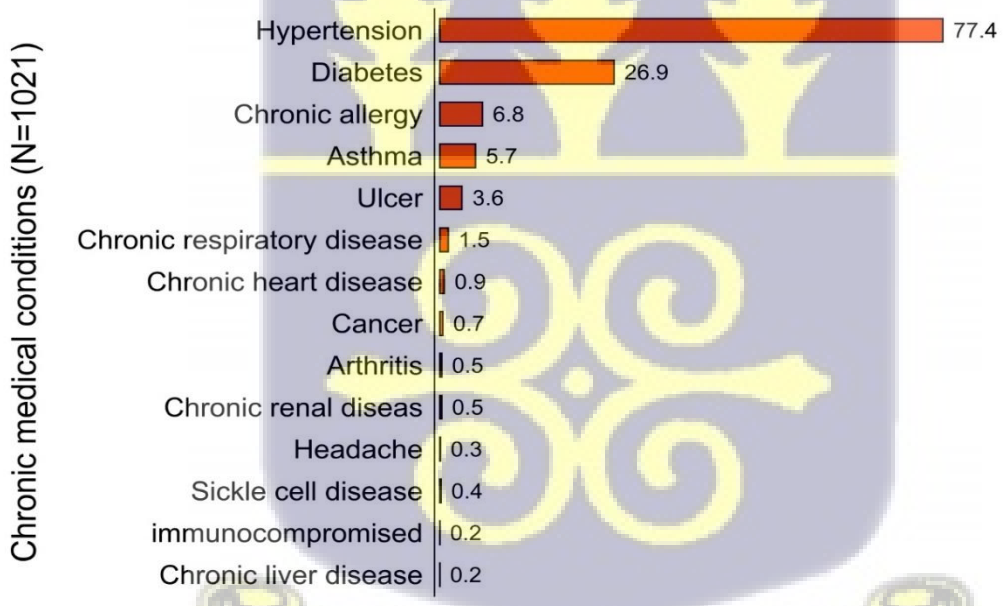


Figure 4.1.1: Specific chronic medical conditions among those with medical conditions

4.1.2 Percentage of Vaccine recipients Experiencing AEFIs by Socio-Demographic Characteristics

Of the 6,100 vaccine recipients in the cohort study, 14% [95% CI: 13.1, 14.8] experienced at least an AEFI with a median age of 39 years (IQR: 27-56). The incidence of AEFIs among the different age categories was statistically significant with a chi-square p-value <0.001. The proportion of females experiencing AEFIs (15.6%) was significantly higher than males (12.4%) with a Chi-square p-value <0.001 (Table 4.1.2).

The proportion of vaccine recipients with a history of chronic medical conditions who experienced an AEFI was higher (18.1%) than those without any chronic medical condition and this was statistically significant with a Chi-square p-value <0.001. The distribution of AEFIs was statistically significant (p-value <0.001) across enrolment sites with HMH recording the highest percentage of AEFIs (35.8%) among vaccinated vaccine recipients (Table 4.1.2).

AEFIs occurred among 14.0% of those who took the Moderna vaccine while 9.7% and 18.5% occurred among those who took the Pfizer and AstraZeneca vaccines respectively. This was statistically significant (p-value <0.001). For AEFIs occurring as per vaccine dose taken, 8.1% of those who took only dose 1 experienced at least an AEFI while 17.4% of those who took both doses 1 and 2 had an AEFI with a Chi-square p-value <0.001.

Table 4.1.2: Percentage of Vaccine recipients Experiencing AEFIs by Socio-Demographic Characteristics

	Experienced AEFI			
	No AEFIs	AEFIs		Chi-square P-value
	n/N (%)	n/N (%)	95% CI	
Overall	5,249/6,100 (86.0)	851/6,100 (14.0)	[13.1, 14.8]	
Age (in years)	37 (26-55)	39 (27-56)		0.015
Age group				<0.001
<20 years	679/748 (90.8)	69/748 (9.2)	[7.4, 11.5]	
20-29 years	1,110/1,303 (85.2)	193/1,303 (14.8)	[13.0, 16.9]	
30-39 years	1,063/1,238 (85.9)	175/1,238 (14.1)	[12.3, 16.2]	
40-49 years	764/883 (86.5)	119/883 (13.5)	[11.4, 15.9]	
50-59 years	617/744 (82.9)	127/744 (17.1)	[14.5, 20.0]	
60+ years	1,016/1,184 (85.8)	168/1,184 (14.2)	[12.3, 16.3]	
Sex				<0.001
Females	2,463/2,919 (84.4)	456/2,919 (15.6)	[14.4, 17.0]	
Males	2,786/3,181 (87.6)	395/3,181 (12.4)	[11.3, 13.6]	
History of chronic medical condition				<0.001
No	4,413/5,079 (86.9)	666/5,079 (13.1)	[12.2, 14.1]	
Yes	836/1,021 (81.9)	185/1,021 (18.1)	[15.9, 20.6]	
Forms of chronic medical conditions				
Hypertension [(M)]	648/836 (77.5)	142/185 (76.8)	-	0.85
Diabetes [(M)]	221/836 (26.4)	54/185 (29.2)	-	0.46
Chronic allergy [(M)]	52/836 (6.2)	17/185 (9.2)	-	0.15
Asthma [(M)]	50/836 (6.0)	8/185 (4.3)	-	0.48
Ulcer [(M)]	29/836 (3.5)	8/185 (4.3)	-	0.52
Chronic respiratory [(M)]	13/836 (1.6)	2/185 (1.1)	-	1.00
Chronic heart disease [(M)]	8/836 (1.0)	1/185 (0.5)	-	1.00

Cancer (M)	7/836 (0.8)	0/185 (0.0)	-	0.36
Arthritis (M)	3/836 (0.4)	2/185 (1.1)	-	0.22
Chronic renal disease (M)	4/836 (0.5)	1/185 (0.5)	-	1.00
Headache (M)	2/836 (0.2)	1/185 (0.5)	-	0.45
Sickle cell disease (M)	1/836 (0.1)	3/185 (1.6)	-	0.020
Immunocompromised (M)	0/836 (0.0)	2/185 (1.1)	-	0.033
Chronic liver disease (M)	1/836 (0.1)	1/185 (0.5)	-	0.33
Enrolment site				<0.001
APC	303/360 (84.2)	57/360 (15.8)	[12.4, 20.0]	
EGH	490/621 (78.9)	131/621 (21.1)	[18.1, 24.5]	
HMH	192/299 (64.2)	107/299 (35.8)	[30.6, 41.4]	
HFH	571/633 (90.2)	62/633 (9.8)	[7.7, 12.4]	
KPC	1,097/1,267 (86.6)	170/1,267 (13.4)	[11.7, 15.4]	
MPC	1,269/1,358 (93.4)	89/1,358 (6.6)	[5.4, 8.0]	
SGH	443/630 (70.3)	187/630 (29.7)	[26.2, 33.4]	
TCH	689/728 (94.6)	39/728 (5.4)	[3.9, 7.3]	
TGH	195/204 (95.6)	9/204 (4.4)	[2.3, 8.3]	
Vaccination type				<0.001
Moderna	793/922 (86.0)	129/922 (14.0)	[11.9, 16.4]	
Pfizer	2,415/2,673 (90.3)	258/2,673 (9.7)	[8.6, 10.8]	
AstraZeneca	2,041/2,505 (81.5)	464/2,505 (18.5)	[17.1, 20.1]	
Number of vaccine doses taken				<0.001
Dose 1 only	2,086/2,271 (91.9)	185/2,271 (8.1)	[7.1, 9.3]	
Dose 1 & 2	3,163/3,829 (82.6)	666/3,829 (17.4)	[16.2, 18.6]	
Dose experienced AEFI among those with 2 doses				
Dose 1 only		361/666 (54.2)	-	
Dose 2 only		246/666 (36.9)	-	
Both doses 1 & 2		59/666 (8.9)	-	

%: Row percentage
(M): Multiple choice (column percentage for multiple choice response)

4.1.3 Cumulative Incidence, Incidence Rate and Incidence Rate Ratio of AEFIs among Vaccine recipients in the First 21 days after Vaccination

Among the 9,929 COVID-19 doses given, 9.2% (95% CI: 8.6% to 9.8%.) of them recorded at least one AEFI within the first 21 days after taking the vaccine. The cumulative incidence of AEFIs was further estimated with the corresponding 95% Confidence interval by age group, sex, enrolment site, vaccine type and vaccine dose. The chi-square association showed a significant difference in the cumulative incidence of AEFIs across the various categories of age group (p=0.010), sex (p=0.003), history of chronic medical condition (p=0.016), enrolment site (p<0.001), vaccination type (p<0.001) and vaccine dose (p<0.001). (Table 4.1.3)

A total of 152,116 person-days was followed up among the 6,100 unique vaccine recipients over a total of 9,929 vaccine doses. The incidence rate of AEFIs was 598 per 100,000 person

days with a 95% confidence interval estimate from 560 to 638 per 100,000 person days. The total person-days, incidence rate and the corresponding 95% CI across the various categories of age group, sex, enrolment sites, vaccination type and vaccine dose are presented in Table 4.1.3.

Using those aged below 20 years as reference, the incidence rate of AEFI was significantly higher among the older age groups with 38% increased risk among those aged 20-29 years (IRR: 1.38, 95% CI: [1.04, 1.82], p=0.024) (Table 4.1.3).

The incidence rate of AEFIs was 15% less among males compared to females (IRR: 0.85, 95% CI: [0.75, 0.97], p=0.015). In comparison with those who received their vaccine dose at TCH, the incidence rate ratio was significantly higher in all the other facilities except MPC. (Table 4.1.3)

Compared with those who received the Pfizer vaccine, the incidence rate of AEFI was 30% significantly higher among those who took Moderna (IRR: 1.30, 95% CI: [1.06, 1.60], p=0.012). The incidence rate of AEFI was 47% less for vaccine dose 2 compared to vaccine dose 1 (IRR: 0.53, 95% CI: [0.45-0.61], p<0.001). (Table 4.1.3)

Table 4.1.3: Cumulative incidence, Incidence rate and Incidence rate ratio of AEFIs among the vaccinated in the first 21 days after vaccination

	Cumulative Incidence of AEFIs			Incidence rate (IR) per 100,000 person days		Incidence rate ratio (IRR)	
Characteristics	**n/N (%)**	**95% CI**	**P-value**	**Total person time in days**	**IR [95% CI]**	**IRR [95% CI]**	**P-value**
Overall	910/9,929 (9.2)	[8.6, 9.8]		152116.1	598.2 [560.6, 638.4]		
Age group			0.010				
<20 years	66/986 (6.7)	[5.3, 8.4]		12681.0	520.5 [408.9, 662.5]	1.00 [reference]	
20-29 years	203/2,055 (9.9)	[8.7, 11.3]		28306.0	717.2 [625.0, 822.9]	1.38 [1.04, 1.82]	0.024
30-39 years	197/1,980 (9.9)	[8.7, 11.4]		29155.0	675.7 [587.6, 777.0]	1.30 [0.98, 1.72]	0.066
40-49 years	138/1,448 (9.5)	[8.1, 11.2]		22845.0	604.1 [511.2, 713.8]	1.16 [0.87, 1.56]	0.320
50-59 years	131/1,286 (10.2)	[8.7, 12.0]		20882.0	627.3 [528.6, 744.5]	1.21 [0.90, 1.62]	0.216
60+ years	175/2,174 (8.0)	[7.0, 9.3]		38247.0	457.6 [394.5, 530.6]	0.88 [0.66, 1.17]	0.372
Sex			0.003				
Females	481/4,789 (10.0)	[9.2, 10.9]		74271.0	647.6 [592.3, 708.2]	1.00 [reference]	
Males	429/5,140 (8.3)	[7.6, 9.1]		77845.0	551.1 [501.3, 605.8]	0.85 [0.75, 0.97]	0.015
History of chronic medical condition			0.016				
No	709/8,034 (8.8)	[8.2, 9.5]		118923.1	596.2 [553.9, 641.7]	1.00 [reference]	
Yes	201/1,895 (10.6)	[9.3, 12.1]		33193.0	605.5 [527.4, 695.3]	1.02 [0.87, 1.19]	0.845
Enrolment site			<0.001				
APC	59/595 (9.9)	[7.8, 12.6]		8872.0	665.0 [515.2, 858.3]	3.64 [2.43, 5.45]	<0.001
EGH	137/1,203 (11.4)	[9.7, 13.3]		20773.0	659.5 [557.8, 779.7]	3.61 [2.53, 5.15]	<0.001
HMH	125/389 (32.1)	[27.7, 36.9]		3554.0	3517.2 [2951.6, 4191.1]	19.25 [13.43, 27.57]	<0.001
HFH	63/1,029 (6.1)	[4.8, 7.8]		2160.0	2916.7 [2278.5, 3733.6]	15.96 [10.71, 23.79]	<0.001
KPC	184/1,811 (10.2)	[8.9, 11.6]		32915.0	559.0 [483.8, 645.9]	3.06 [2.17, 4.32]	<0.001
MPC	89/2,124 (4.2)	[3.4, 5.1]		40946.0	217.4 [176.6, 267.6]	1.19 [0.82, 1.73]	0.366
SGH	205/1,196 (17.1)	[15.1, 19.4]		19322.0	1061.0 [925.2, 1216.6]	5.81 [4.12, 8.18]	<0.001
TCH	39/1,319 (3.0)	[2.2, 4.0]		21341.0	182.7 [133.5, 250.1]	1.00 [reference]	
TGH	9/263 (3.4)	[1.8, 6.5]		2233.0	403.0 [209.7, 774.6]	2.21 [1.07, 4.55]	0.032
Vaccination type			<0.001				
Moderna	134/1,458 (9.2)	[7.8, 10.8]		19258.0	695.8 [587.4, 824.2]	1.30 [1.06, 1.60]	0.012
Pfizer	283/3,890 (7.3)	[6.5, 8.1]		52991.0	534.1 [475.3, 600.0]	1.00 [reference]	
AstraZeneca	493/4,581 (10.8)	[9.9, 11.7]		79867.1	617.3 [565.1, 674.2]	1.16 [1.00, 1.34]	0.052
Vaccine dose			<0.001				
Dose 1	677/6,100 (11.1)	[10.3, 11.9]		91961.0	736.2 [682.8, 793.8]	1.00 [reference]	
Dose 2	233/3,829 (6.1)	[5.4, 6.9]		60155.0	387.3 [340.7, 440.4]	0.53 [0.45, 0.61]	<0.001

CI: confidence interval. IR: Incidence rate. IRR: Incidence rate ratio

4.1.4 Cumulative Incidence of AEFIs from Cohort Study Data by Vaccine Dose

Figure 4.1.2 (A) compares the cumulative incidence of AEFIs from vaccine dose 1 to vaccine dose 2 within age groups. The cumulative incidence of AEFIs was significantly higher for vaccine dose 1 compared to vaccine dose 2 among those aged 20-29 years (12.3% vs. 7.8%, p=0.005), 30-39 years (14.3% vs. 5.7%, p<0.001), 40-49 years (13.4% vs. 6.0%, p<0.001), 50-59 years (14.9% vs. 8.1%, p=0.001) and those aged 60 years and above (12.2% vs. 6.2%, p<0.001). (Figure 4.1.2A)

Figure 4.1.2 (B) compares the cumulative incidence of AEFIs from vaccine dose 1 to vaccine dose 2 among females and also among males. The cumulative incidence of AEFIs was significantly higher for vaccine dose 1 compared to vaccine dose 2 among both females (13.5% vs. 7.8%, p<0.001) and males (11.7% vs. 5.3%, p<0.001). (Figure 4.1.2B)

Figure 4.1.2 (C) compares the cumulative incidence of AEFIs from vaccine dose 1 to vaccine dose 2 among those with and those without chronic medical conditions. The cumulative incidence of AEFIs was significantly higher for vaccine dose 1 compared to vaccine dose 2 among those without chronic medical conditions (11.9% vs. 6.3%, p<0.001) and those with chronic medical conditions (16.0% vs. 7.3%, p<0.001). (Figure 4.1.2C)

Figure 4.1.3 (A) compares the cumulative incidence of AEFIs from vaccine dose 1 to vaccine dose 2 within the health facility where the vaccine was given. The cumulative incidence of AEFIs was significantly higher for vaccine dose 1 compared to vaccine dose 2 in APC (14.6% vs. 4.2%, p<0.001), EGH (22.2% vs. 5.3%, p<0.001), KPC (12.0% vs. 6.9%, p<0.001), MPC (7.4% vs. 0.3%, p<0.001) and TCH (5.7% vs. 0.0%, p<0.001) and TGH (6.4% vs. 0.0%). However, the opposite was observed in HFH where the cumulative incidence was significantly higher for vaccine dose 2 compared to vaccine dose 1 (4.8% vs. 8.1%, p=0.027) (Figure 4.1.3A).

Figure 4.1.3 (B) compares the cumulative incidence of AEFIs from vaccine dose 1 to vaccine dose 2 by vaccine type. The cumulative incidence of AEFIs was significantly higher for vaccine dose 1 compared to vaccine dose 2 for all 3 types of vaccines, Moderna (14.3% vs. 5.7%, p<0.001), Pfizer (8.8% vs. 4.5%, p<0.001) and AstraZeneca (16.1% vs. 7.9%, p<0.001) (Figure 4.1.3B).

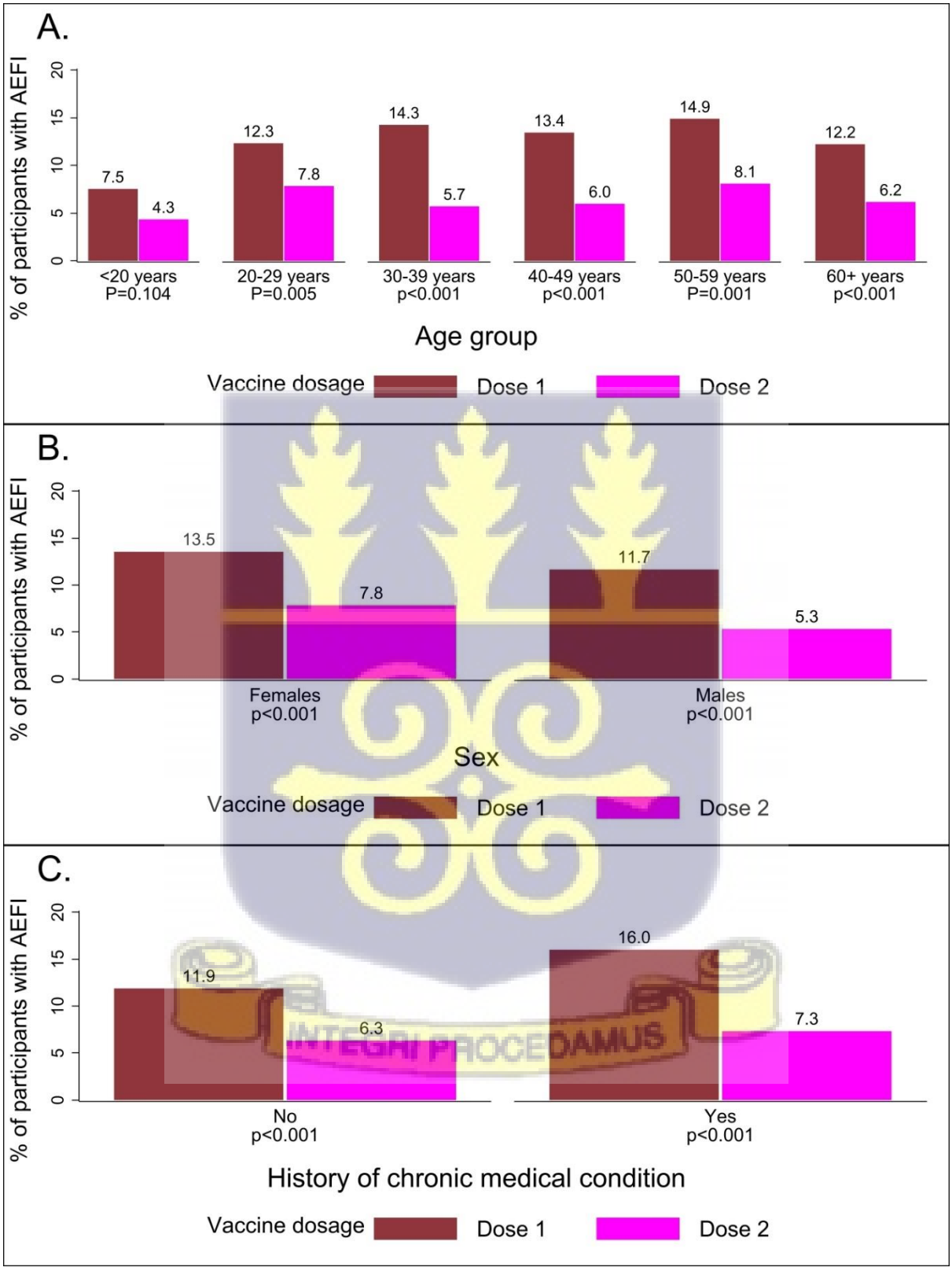


Figure 4.1.2: Cumulative incidence of AEFIs by vaccine dose across characteristics of vaccine recipients (age, sex and chronic medical conditions)

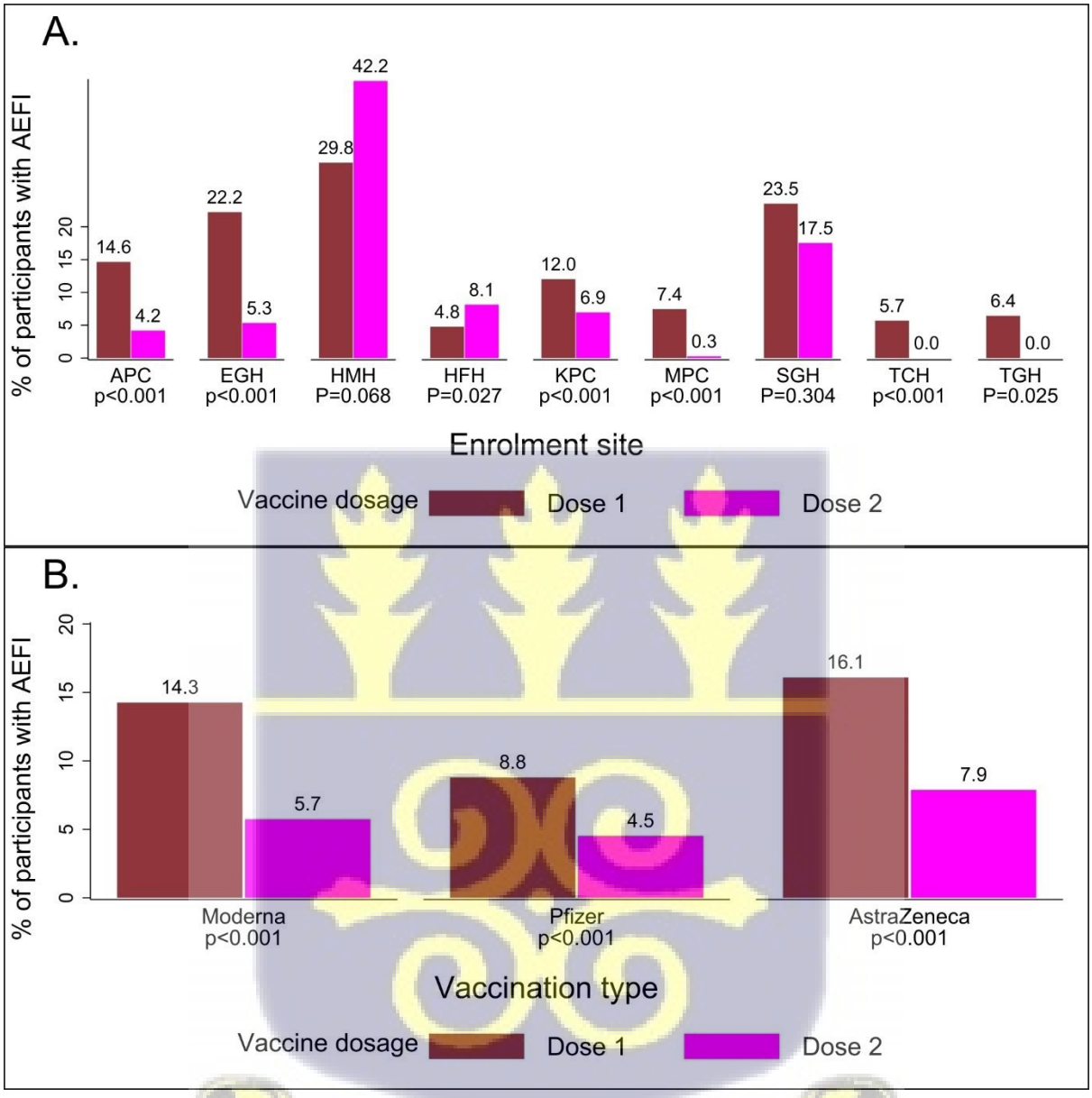


Figure 4.1.3: Cumulative incidence of AEFIs by vaccine dose across health facilities and vaccine type

4.1.5 Incidence Rate Ratio of AEFIs for Vaccine Dose 2 Relative to Vaccine Dose 1

A total of 91,961 person days was observed for vaccine dose 1 with 677 incidences of AEFIs with an incidence rate of 736 AEFIs per 100,000 person days (95% CI: [682, 793]). Also, a total of 60,155 person days was observed for vaccine dose 2 with 233 incidences of AEFI with an incidence rate of 387 AEFIs per 100,000 person days (95% CI: [340, 440]). Overall, the incidence rate of AEFI compared to vaccine dose 1 was 47% less for vaccine dose 2 (IRR: 0.53, 95% CI: [0.45, 0.61], p<0.001). (Table 4.1.4).

Table 4.1.4 also shows the incidence of AEFI after taking vaccine doses 1 and vaccine dose 2 by the age group, sex, enrolment site and vaccine type.

The incidence of AEFI was significantly higher for vaccine dose 2 compared to vaccine dose 1 for those below 20 years (IRR: 1.98, 95% CI: [1.01-3.88], p=0.047). On the other hand, the incidence rate of AEFI was significantly less for vaccine dose 2 compared to vaccine dose 1 for the other age groups, 20-29 years (IRR: 0.67, 95% CI: [0.49-0.91], p=0.011), 30-39 years (IRR: 0.43, 95% CI: [0.30-0.60], p<0.001), 40-49 years (IRR: 0.46, 95% CI: [0.31-0.68], p<0.001), 50-59 years (IRR: 0.48, 95% CI: [0.33-0.70], p<0.001) and those 60 years and above (IRR: 0.47, 95% CI: [0.34-0.64], p<0.001). (Table 4.1.3)

Also, the incidence of AEFIs was significantly less for vaccine dose 2 compared to vaccine dose 1 among both females (IRR: 0.56, 95% CI: [0.46-0.68], p<0.001) and males (IRR: 0.48, 95% CI: [0.38-0.60], p<0.001).

The incidence of AEFIs was significantly less for vaccine dose 2 compared to vaccine dose 1 among those without chronic medical conditions (IRR: 0.56, 95% CI: [0.47-0.66], p<0.001) as well as those with chronic medical conditions (IRR: 0.42, 95% CI: [0.31-0.57], p<0.001).

The incidence of AEFIs was significantly less for vaccine dose 2 compared to vaccine dose 1 for those who received their vaccines at APC (IRR: 0.22, 95% CI: [0.11-0.45], p<0.001), EGH

(IRR: 0.23, 95% CI: [0.15-0.34], p<0.001) and KPC (IRR: 0.49, 95% CI: [0.34-0.71], p<0.001). However, the opposite was observed in HMH where the incidence of AEFIs was significantly higher for vaccine dose 2 compared to vaccine dose 1 (IRR: 1.85, 95% CI: [1.26-2.73], p<0.001). No AEFIs were recorded after taking the second dose in facilities MPC, TCH and TGH (Table 4.1.4).

The incidence of AEFI for vaccine dose 2 compared to vaccine dose 1 was 61% less for Moderna vaccines (IRR: 0.39, 95% CI: [0.26-0.58], p<0.001), 27% less for Pfizer vaccines (IRR: 0.73, 95% CI: [0.54-0.99], p=0.040) and 55% less for AstraZeneca vaccine (IRR: 0.45, 95% CI: [0.37-0.55], p<0.001). (Table 4.1.4)

Table 4.1.4: Incidence rate ratio of AEFIs by vaccine dose

	Vaccine dosage 1			Vaccine dosage 2			The incidence rate ratio of AEFIs for dose 2 relative to dose 1	
Characteristics	**Total person time in days**	**No. with AEFIs**	**IR [95% CI] per 100,000 person-days**	**Total person time in days**	**No. with AEFIs**	**IR [95% CI] per 100,000 person-days**	**IRR [95% CI]**	**p-value**
Overall	91961.0	677	736.2 [682.8, 793.8]	60155.0	233	387.3 [340.7, 440.4]	0.53 [0.45, 0.61]	<0.001
Age group								
<20 years	11631.0	56	481.5 [370.5, 625.6]	1050.0	10	952.4 [512.4, 1770.0]	1.98 [1.01, 3.88]	0.047
20-29 years	18058.0	147	814.0 [692.5, 956.9]	10248.0	56	546.4 [420.5, 710.1]	0.67 [0.49, 0.91]	0.011
30-39 years	18059.0	156	863.8 [738.4, 1010.6]	11096.0	41	369.5 [272.1, 501.8]	0.43 [0.30, 0.60]	<0.001
40-49 years	13384.0	104	777.0 [641.2, 941.7]	9461.0	34	359.4 [256.8, 502.9]	0.46 [0.31, 0.68]	<0.001
50-59 years	11299.0	93	823.1 [671.7, 1008.6]	9583.0	38	396.5 [288.5, 545.0]	0.48 [0.33, 0.70]	<0.001
60+ years	19530.0	121	619.6 [518.4, 740.4]	18717.0	54	288.5 [221.0, 376.7]	0.47 [0.34, 0.64]	<0.001
Sex								
Females	43796.0	346	790.0 [711.0, 877.8]	30475.0	135	443.0 [374.2, 524.4]	0.56 [0.46, 0.68]	<0.001
Males	48165.0	331	687.2 [617.0, 765.4]	29680.0	98	330.2 [270.9, 402.5]	0.48 [0.38, 0.60]	<0.001
History of chronic medical condition								
No	75385.0	536	711.0 [653.3, 773.8]	43538.0	173	397.4 [342.3, 461.2]	0.56 [0.47, 0.66]	<0.001
Yes	16576.0	141	850.6 [721.2, 1003.3]	16617.0	60	361.1 [280.4, 465.0]	0.42 [0.31, 0.57]	<0.001
Enrolment site								
APC	4879.0	50	1024.8 [776.7, 1352.1]	3993.0	9	225.4 [117.3, 433.2]	0.22 [0.11, 0.45]	<0.001
EGH	9327.0	107	1147.2 [949.2, 1386.5]	11446.0	30	262.1 [183.3, 374.9]	0.23 [0.15, 0.34]	<0.001
HMH	2917.0	89	3051.1 [2478.7, 3755.6]	637.0	36	5651.5 [4076.6, 7834.8]	1.85 [1.26, 2.73]	0.002
HFH	980.0	29	2959.2 [2056.4, 4258.3]	1180.0	34	2881.4 [2058.8, 4032.5]	0.97 [0.59, 1.60]	0.916
KPC	22246.0	149	669.8 [570.4, 786.4]	10669.0	35	328.1 [235.5, 456.9]	0.49 [0.34, 0.71]	<0.001
MPC	26192.0	89	339.8 [276.1, 418.3]	14754.0	0	0.00 [-]	0.00 [-]	-
SGH	9980.0	116	1162.3 [968.9, 1394.3]	9342.0	89	952.7 [774.0, 1172.7]	0.82 [0.62, 1.08]	0.158
TCH	13422.0	39	290.6 [212.3, 397.7]	7919.0	0	0.00 [-]	0.00 [-]	-
TGH	2018.0	9	446.0 [232.1, 857.1]	215.0	0	0.00 [-]	0.00 [-]	-
Vaccine type								
Moderna	11236.0	105	934.5 [771.8, 1131.5]	8022.0	29	361.5 [251.2, 520.2]	0.39 [0.26, 0.58]	<0.001
Pfizer	40087.0	229	571.3 [501.9, 650.3]	12904.0	54	418.5 [320.5, 546.4]	0.73 [0.54, 0.99]	0.040
AstraZeneca	40638.0	343	844.0 [759.3, 938.3]	39229.0	150	382.4 [325.8, 448.7]	0.45 [0.37, 0.55]	<0.001

4.1.6 Cox-Proportional Hazard Rate of Risk Factors of AEFIs Among Those Vaccinated Against COVID-19

Table 4.1.5 shows the results for both crude and adjusted hazard rates of AEFIs by characteristics of vaccine recipients from the Cox-Proportional Hazard model.

Compared to those below 20 years, the adjusted hazard rate of AEFIs was over 2 times significantly higher among those aged 20-29 years (aHR: 2.07, 95% CI: [1.56-2.76], p<0.001), 30-39 years (aHR: 2.35, 95% CI: [1.76-3.13], p<0.001) and 40-49 years (aHR: 2.06, 95% CI: [1.51-2.81], p=0.008) and 79% higher among those aged 50-59 years (aHR: 1.79, 95% CI: [1.28-2.50], p=0.001). Except for TCH and TGH, the adjusted model showed a significantly higher adjusted hazard rate of AEFIs among those who took their vaccines from all the other facilities compared to the MPC (Table 4.1.5).

The adjusted hazard rate of AEFI was 31% less among those who received the Moderna vaccine (aHR: 0.69, 95% CI: [0.53-0.90], p=0.006) and 49% less among those receiving Pfizer (aHR: 0.51, 95% CI: [0.39-0.66], p<0.001) compared with those receiving AstraZeneca. Also, the incidence of AEFIs was 52% less among vaccine dose 2 compared to vaccine dose 1 (aHR: 0.48, 95% CI: [0.41-0.55], p<0.001) (Table 4.1.5).

Table 4.1.5: Cox-proportional hazard model of factors associated with the incidence of AEFIs among vaccine recipients

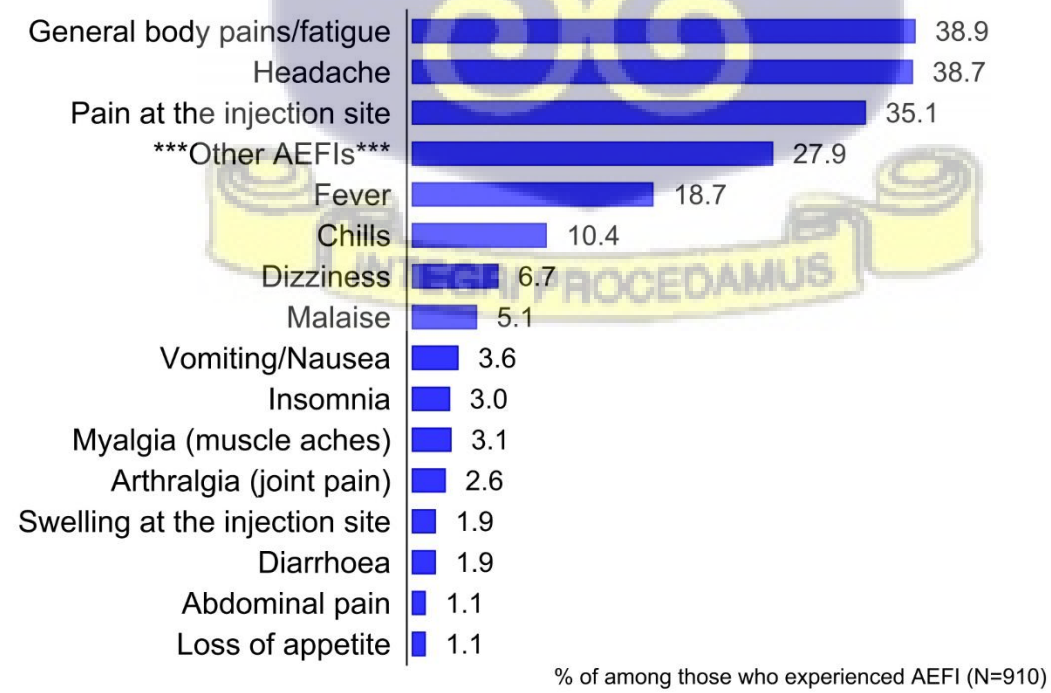
	Unadjusted cox-proportional hazard model		Adjusted cox-proportional hazard model	
Characteristics	**uHR [95% CI]**	**P-value**	**aHR [95% CI]**	**P-value**
Age group				
<20 years	1.00 [reference]		1.00 [reference]	
20-29 years	1.48 [1.13, 1.94]	0.005	2.07 [1.56, 2.76]	<0.001
30-39 years	1.48 [1.13, 1.94]	0.005	2.35 [1.76, 3.13]	<0.001
40-49 years	1.42 [1.07, 1.89]	0.017	2.06 [1.51, 2.81]	<0.001
50-59 years	1.53 [1.15, 2.04]	0.004	1.79 [1.28, 2.50]	0.001
60+ years	1.20 [0.91, 1.58]	0.203	1.30 [0.93, 1.82]	0.125
Sex				
Females	1.21 [1.07, 1.38]	0.003	1.05 [0.93, 1.20]	0.418
Males	1.00 [reference]		1.00 [reference]	
History of chronic medical condition				
No	1.00 [reference]		1.00 [reference]	
Yes	1.19 [1.02, 1.39]	0.026	1.14 [0.96, 1.37]	0.145
Enrolment site				
APC	2.73 [1.97, 3.79]	<0.001	2.41 [1.74, 3.33]	<0.001

EGH	2.76 [2.12, 3.58]	<0.001	3.24 [2.42, 4.33]	<0.001
HMH	8.18 [6.35, 10.53]	<0.001	14.81 [10.69, 20.52]	<0.001
HFH	1.65 [1.21, 2.27]	0.002	2.28 [1.60, 3.26]	<0.001
KPC	2.50 [1.95, 3.22]	<0.001	2.76 [2.14, 3.55]	<0.001
MPC	1.00 [reference]		1.00 [reference]	
SGH	4.53 [3.55, 5.80]	<0.001	4.25 [3.31, 5.46]	<0.001
TCH	0.72 [0.50, 1.04]	0.081	1.27 [0.83, 1.94]	0.269
TGH	0.88 [0.45, 1.73]	0.718	1.15 [0.57, 2.32]	0.688
Vaccine type				
Moderna	0.83 [0.69, 0.99]	0.039	0.69 [0.53, 0.90]	0.006
Pfizer	0.65 [0.57, 0.75]	<0.001	0.51 [0.39, 0.66]	<0.001
AstraZeneca	1.00 [reference]		1.00 [reference]	
Vaccine dose				
Dose 1	1.00 [reference]		1.00 [reference]	
Dose 2	0.54 [0.47, 0.63]	<0.001	0.48 [0.41, 0.55]	<0.001

uHR: unadjusted hazard ratio. aHR: adjusted hazard ratio. CI: confidence interval

4.1.7 Forms of AEFIs Experienced Among Those with at least one AEFI Following Vaccination.

Figure 4.1.4 shows the percentage distribution of the various AEFIs experienced among those with at least one AEFI during the first 21 days after vaccination. General body pains or fatigue (38.9%), headache (38.7%), pain at the injection site (35.1%), fever (18.7%) and chills (10.4%) were some of the common AEFIs experienced among those receiving COVID-19 vaccines. (Figure 4.1.4).



NOTE: *** Combination of AEFIs less than 1% prevalent

Figure 4.1.4: Forms of AEFIs experienced among those who experienced at least one AEFI.

Table 4.1.6 below shows the various forms of AEFIs experienced among those who experienced at least one AEFI distributed by the type of vaccine they received. Except for diarrhoea, loss of appetite and vomiting/nausea, all other forms of AEFIs show statistical significance (Table 4.1.6).

4.1.8 Number of AEFIs Experienced after Receiving COVID-19 Vaccine

Among those who experienced at least some form of AEFI, 36.2% experienced only one AEFI, 36.7% experienced 2 AEFIs, 19.2% experienced 3 AEFIs, 5.5% experienced 4 AEFIs, 1.9% experienced 5 AEFIs and 0.5% experienced 6 AEFIs. (Figure 5)

Table 4.1.6 also shows the number of AEFIs experienced by the vaccine type. (Table 4.1.6)

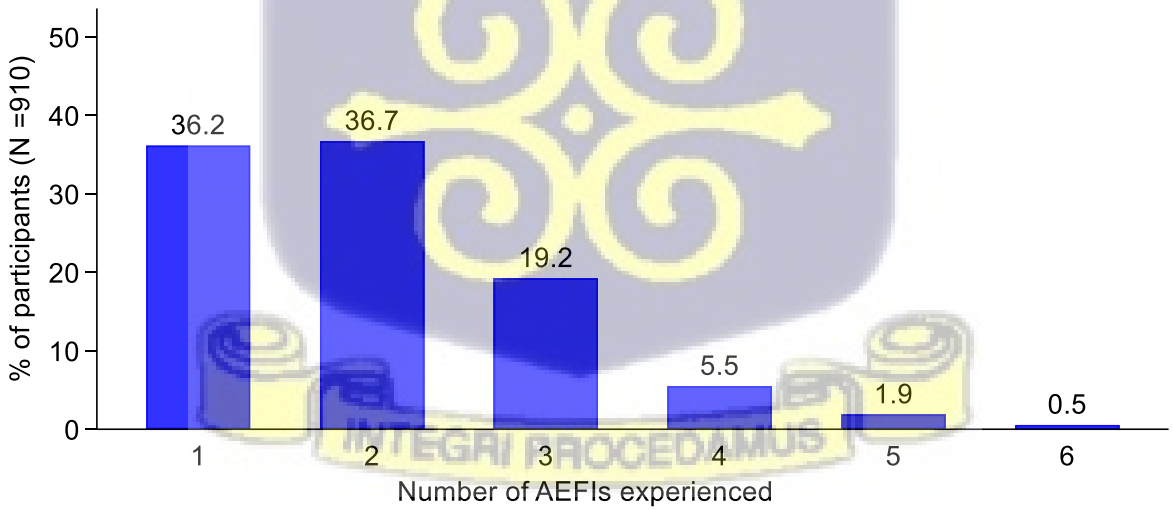


Figure 4.1.5: Number of AEFIs experienced after receiving COVID-19 vaccine dose

4.1.9 Latency of AEFIs Experienced after Receiving COVID-19 Vaccine

Among those who experienced at least some form of AEFI, 46.5% experienced AEFIs on the day of vaccination (day 0), 42.2% the day after vaccination, 7.1% between day 2 and day 7 of vaccination, 1.4% between day 8 and day 14 and 2.7% between day 15 and day 21. (Figure 4.1.6)

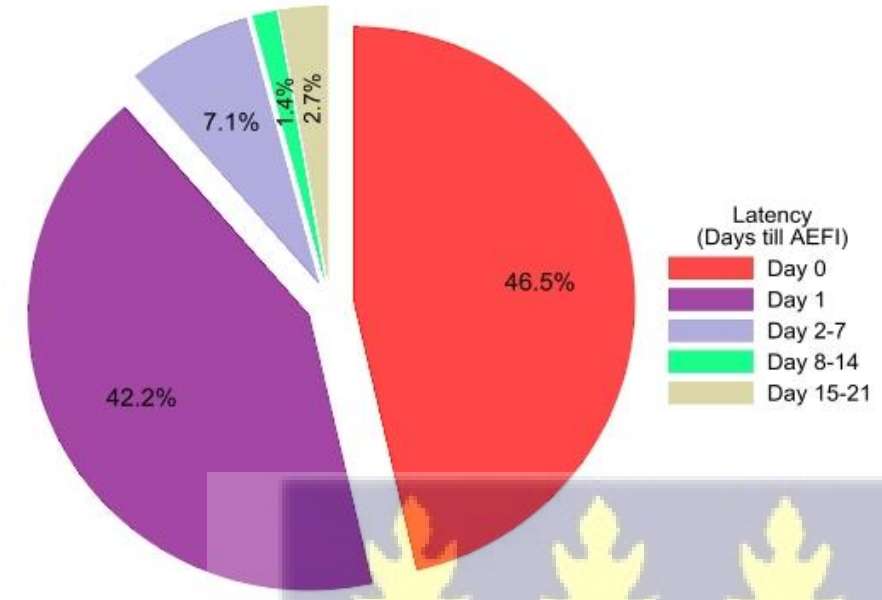


Figure 4.1.6: Latency of AEFIs experienced after receiving COVID-19 vaccine dose

Table 4.1.6 also shows the forms, number and latency of AEFIs experienced in total and individually among the vaccine types. (Table 4.1.6).

Apart from vomiting, diarrhoea and loss of appetite, all other forms of AEFIs were statistically significant.

Generally, and across the 3 vaccines, most vaccine recipients experienced 1 – 3 types of AEFIs following vaccination. This was statistically significant with a p-value of 0.004.

Finally, across all vaccines, most AEFIs occurred on Day 0 (the day of vaccination) and Day 1 (1 day after vaccination) and this was of statistical significance (p<0.001).

Table 4.1.6: Forms, number and latency of AEFIs experienced among those who experienced at least one AEFI by vaccine type

AEFIs experienced	Total N=910	Vaccine type			P-value
		Moderna N=134	Pfizer N=283	AstraZeneca N=493	
	%	%	%	%	
Forms of AEFIs experienced					
General body pains/fatigue	354 (38.9)	31 (23.1)	76 (26.9)	247 (50.1)	<0.001
Headache	352 (38.7)	34 (25.4)	89 (31.4)	229 (46.5)	<0.001
Pain at the injection site	319 (35.1)	85 (63.4)	167 (59.0)	67 (13.6)	<0.001
****Other AEFIs****	254 (27.9)	53 (39.6)	123 (43.5)	78 (15.8)	<0.001
Fever	170 (18.7)	18 (13.4)	30 (10.6)	122 (24.7)	<0.001
Chills	95 (10.4)	27 (20.1)	18 (6.4)	50 (10.1)	<0.001

Dizziness	61 (6.7)	15 (11.2)	13 (4.6)	33 (6.7)	0.048
Malaise	46 (5.1)	0 (0.0)	0 (0.0)	46 (9.3)	<0.001
Vomiting/Nausea	33 (3.6)	4 (3.0)	8 (2.8)	21 (4.3)	0.60
Insomnia	27 (3.0)	2 (1.5)	0 (0.0)	25 (5.1)	<0.001
Myalgia (muscle aches)	28 (3.1)	10 (7.5)	18 (6.4)	0 (0.0)	<0.001
Arthralgia (joint pain)	24 (2.6)	15 (11.2)	7 (2.5)	2 (0.4)	<0.001
Swelling at the injection site	17 (1.9)	8 (6.0)	9 (3.2)	0 (0.0)	<0.001
Diarrhoea	17 (1.9)	2 (1.5)	5 (1.8)	10 (2.0)	1.00
Abdominal pain	10 (1.1)	0 (0.0)	7 (2.5)	3 (0.6)	0.037
Loss of appetite	10 (1.1)	0 (0.0)	1 (0.4)	9 (1.8)	0.11
Number of AEFIs experienced					0.004
1	329 (36.2)	31 (23.1)	94 (33.2)	204 (41.4)	
2	334 (36.7)	57 (42.5)	121 (42.8)	156 (31.6)	
3	175 (19.2)	33 (24.6)	45 (15.9)	97 (19.7)	
4	50 (5.5)	7 (5.2)	16 (5.7)	27 (5.5)	
5	17 (1.9)	4 (3.0)	6 (2.1)	7 (1.4)	
6	5 (0.5)	2 (1.5)	1 (0.4)	2 (0.4)	
Latency (Days till AEFIs)					<0.001
Day 0	423 (46.5)	0 (0.0)	1 (0.4)	422 (85.6)	
Day 1	384 (42.2)	119 (88.8)	264 (93.3)	1 (0.2)	
Day 2-7	65 (7.1)	12 (9.0)	16 (5.7)	37 (7.5)	
Day 8-14	13 (1.4)	2 (1.5)	2 (0.7)	9 (1.8)	
Day 15-21	25 (2.7)	1 (0.7)	0 (0.0)	24 (4.9)	

*** Combination of all AEFIs with overall prevalence <1.0%
%: column percentages

4.1.10 Outcome of AEFIs among vaccine recipients who experienced the events after receiving the COVID-19 vaccine dose

All vaccine recipients (850) but one, who reported AEFIs recovered within a few days. The participant who died received the AstraZeneca vaccine.

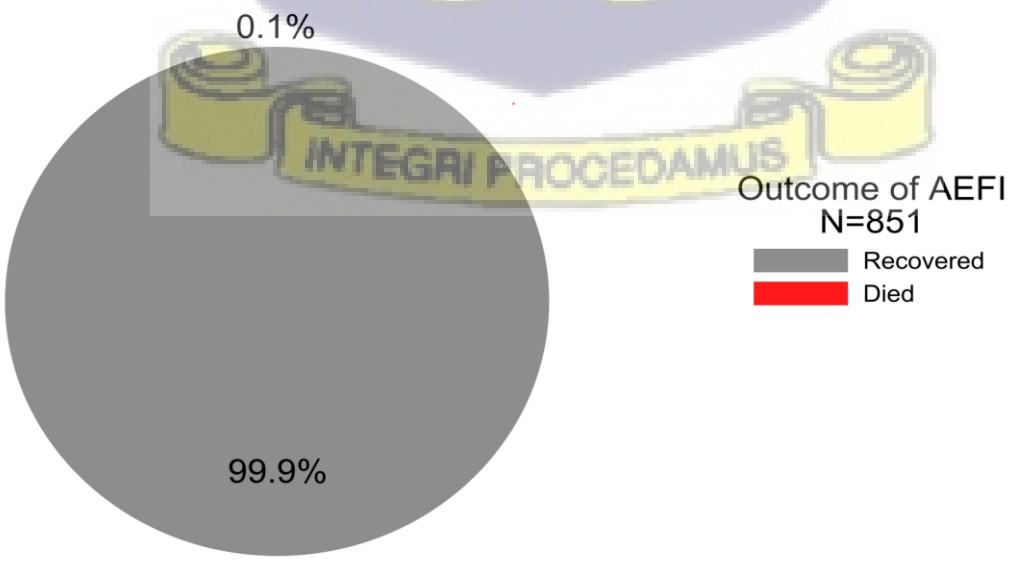


Figure 4.1.7: Outcome of AEFIs among vaccine recipients who experienced the events after receiving the COVID-19 vaccine dose

4.2 Analysis of the spontaneous reporting data

4.2.1 Descriptive Characteristics of Spontaneous Self-reporting Data

A total of 8,498 persons self-reported at least one incidence of AEFI from the commencement of the mass immunization on 2nd March 20 to 30th June 2022. Most of the self-reporting cases were within the age group 20-29 years (26.6%), 30-39 years (29.8%) and 40-49 years (10.3%). Half of those who reported were males (50.1%), 49.4% were females while the sex of 0.4% was not documented. About 1 in 10 (9.2%) reported having an existing medical condition. Among those who reported having an existing medical condition, hypertension (40.6%), allergies (25.6%), ulcers (11.3%), and diabetes (10.8%) were the most common. A few (2.7%) of those who reported were on medication. (Table 4.2.1)

Table 4.2.1 also described the characteristics of the individuals self-reporting AEFIs by the vaccines they received. A total of 4,120 received the AstraZeneca vaccine, 1,673 received the J&J/ Janssen vaccine, 190 received the Moderna vaccine, 57 received Pfizer and 2,458 received Sputnik vaccine. (Table 4.2.1)

Table 4.2.1: Descriptive characteristics of individuals who self-reported AEFIs following COVID-19 vaccination

		Vaccine type					
	Total	**Covishield / AstraZeneca**	**J&J/ Janssen**	**Moderna**	**Pfizer**	**Sputnik**	**P-value**
N	8,498	4,120	1,673	190	57	2,458	
	%	%	%	%	%	%	
Age group							<0.001
<20 years	1.0	0.7	1.5	6.8	15.8	0.4	
20-29 years	26.6	27.3	18.5	27.4	21.1	31.0	
30-39 years	29.8	31.3	16.8	13.7	21.1	37.8	
40-49 years	10.3	11.5	10.3	8.9	1.8	8.7	
50-59 years	6.4	8.4	6.2	4.7	10.5	3.1	
60+ years	6.4	9.7	4.6	7.4	8.8	2.0	
Unknown	19.4	11.1	42.1	31.1	21.1	17.0	
Sex							<0.001
Female	49.4	54.7	49.2	59.5	54.4	39.8	
Male	50.1	45.1	49.2	40.5	45.6	60.0	
Not stated	0.4	0.2	1.6	0.0	0.0	0.2	
Have chronic condition							<0.001
No	90.8	89.6	99.3	99.5	100.0	86.0	
Yes	9.2	10.4	0.7	0.5	0.0	14.0	
Medical condition:							
Asthma	7.3	9.3	18.2	0.0	-	4.4	0.014

Allergies	25.6	2.6	9.1	0.0	-	55.1	<0.001
Hypertension	40.6	58.4	18.2	0.0	-	19.2	<0.001
Cancer	0.6	0.7	9.1	0.0	-	0.3	0.066
Gastritis	0.8	0.5	0.0	0.0	-	1.2	0.470
Hepatitis B	1.8	1.9	0.0	0.0	-	1.7	1.000
HIV	0.1	0.0	0.0	0.0	-	0.3	0.450
Peptic Ulcer	1.3	2.1	0.0	0.0	-	0.3	0.100
Ulcer	11.3	7.2	9.1	0.0	-	16.6	<0.001
Typhoid	0.1	0.2	0.0	0.0	-	0.0	1.000
UTI	0.1	0.2	0.0	0.0	-	0.0	1.000
Diabetes	10.8	17.4	0.0	0.0	-	2.9	<0.001
Sickle cell disease	1.5	2.3	0.0	0.0	-	0.6	0.170
On medication							<0.001
No	97.3	100.0	100.0	100.0	100.0	90.8	
Yes	2.7	0.0	0.0	0.0	0.0	9.2	

Figure 4.2.1 shows the incidence of AEFIs which were self-reported by those who received doses of COVID-19 vaccines at the national level as of 30th June 2022. A total of 17,409,005 doses had been administered as follows; AtraZeneca, 10,096,925; Sputnik-V, 17,982; Moderna, 1,065,357; Pfizer-BioNTech, 3,910,669 and J&J, 2,318,072. The Sputnik vaccine gave the highest incidence of AEFIs (13,669 per 100,000 persons). As of 30th June 2022, the number of persons who had taken at least 1 dose of any of the 5 COVID-19 vaccines was 10,733,719 which represented 47% of the targeted 22.9 million persons (33.8% of the entire Ghanaian population). Out of those who had received at least 1 dose, persons fully vaccinated (received 2 doses) were 7,510,586 which was 32.9% of the targeted 22.9 million (23.7% of the total Ghanaian population). Finally, the number of persons receiving their 1st booster dose was 1,192,595 (Ghana Health Service, 2022)

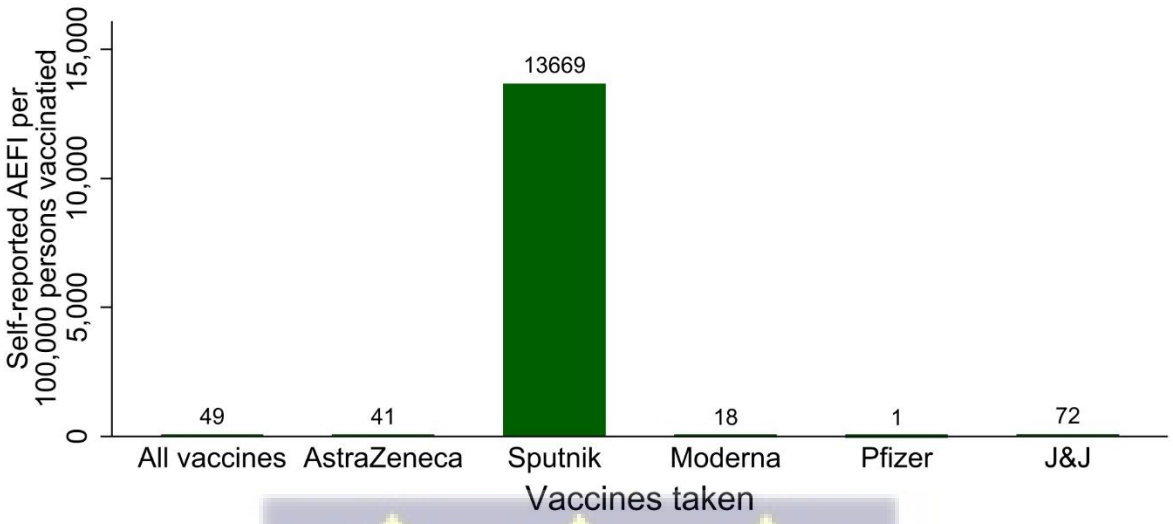
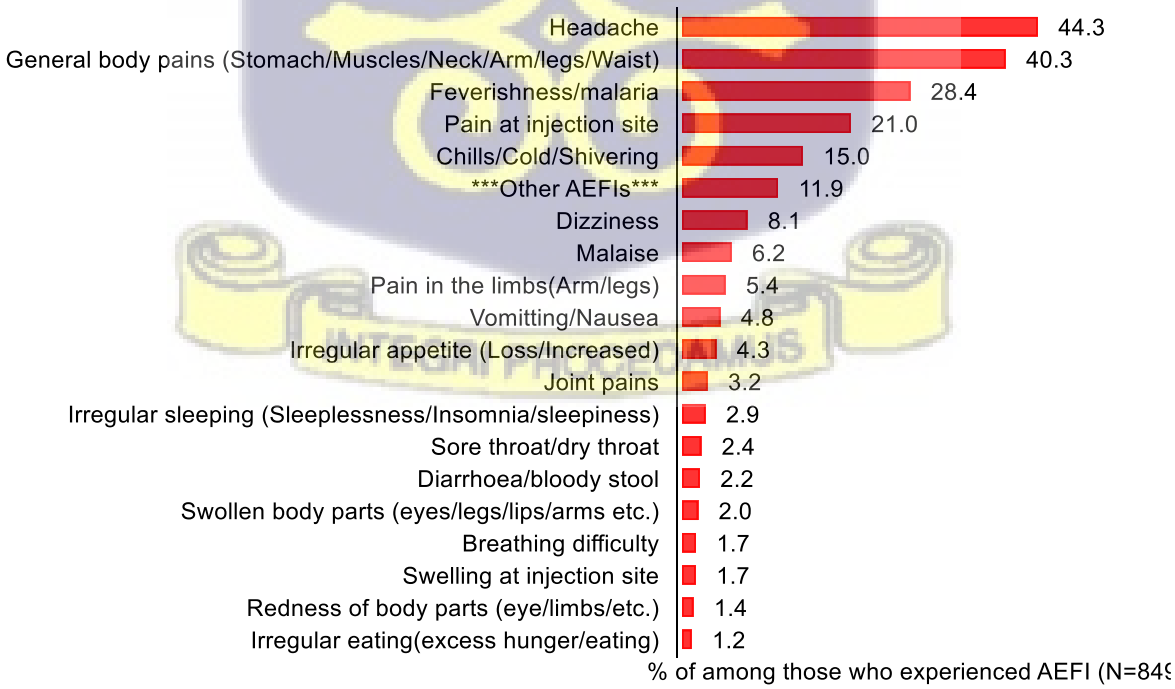


Figure 4.2.1 Incidence of self-reported AEFIs among those receiving vaccine doses in the mass vaccination as of 30th June 2022

4.2.2 Forms of AEFIs among those who self-reported

The most common AEFIs self-reported were headache (44.3%), general body pains (40.3%), fever/malaria (28.4%) pain at the injection site (21.0%) and Chills/cold/shivering (15.0%). (Figure 4.2.2). Table 4.2.2 shows the various AEFIs experienced by vaccine type. (Table 4.2.2)



NOTE: *** Combination of AEFIs less than 1% prevalent

Figure 4.2.2: Forms of AEFIs among those who self-reported

Table 4.2.2: Self-reported AEFIs by vaccine type

	Vaccine type						
	Total	**Covishield/ AstraZeneca**	**J&J/ Janssen**	**Moderna**	**Pfizer**	**Sputnik**	**P-value**
N	**8,498**	**4,120**	**1,673**	**190**	**57**	**2,458**	
	%	**%**	**%**	**%**	**%**	**%**	
Headache	44.3	55.8	33.7	26.3	21.1	34.2	<0.001
General body pains (Stomach/Muscles/Neck/Arm/legs/Waist)	40.3	46.7	39.0	16.3	28.1	32.4	<0.001
Feverishness/malaria	28.4	37.2	27.2	13.7	12.3	16.0	<0.001
Pain at the injection site	21.0	13.8	17.8	56.3	7.0	32.8	<0.001
Chills/Cold/Shivering	15.0	16.7	15.5	5.8	8.8	12.8	<0.001
Other AEFIs	11.9	15.9	8.5	7.4	22.8	7.8	<0.001
Dizziness	8.1	8.3	5.0	7.4	7.0	10.0	<0.001
Malaise	6.2	10.9	1.0	0.5	1.8	2.3	<0.001
Pain in the limbs (Arms/legs)	5.4	5.4	5.5	6.3	14.0	5.0	0.055
Vomiting/Nausea	4.8	7.2	2.9	2.1	10.5	2.1	<0.001
Irregular appetite (Loss/Increased)	4.3	5.7	1.9	3.2	1.8	3.7	<0.001
Joint pains	3.2	4.7	2.0	0.5	3.5	1.7	<0.001
Irregular sleeping (Sleeplessness/Insomnia/sleepiness)	2.9	3.4	2.5	1.1	1.8	2.6	0.061
Sore throat/dry throat	2.4	3.3	1.1	0.0	0.0	1.9	<0.001
Diarrhoea/bloody stool	2.2	2.9	1.7	1.6	8.8	1.3	<0.001
Swollen body parts (eyes/legs/lips/arms etc.)	2.0	3.0	1.1	4.2	10.5	0.6	<0.001
Breathing difficulty	1.7	2.7	1.1	2.1	10.5	0.3	<0.001
Swelling at the injection site	1.7	2.4	1.1	3.7	1.8	0.7	<0.001
Redness of body parts (eye/limbs/etc.)	1.4	1.4	1.6	0.5	0.0	1.4	0.66
Irregular eating (excess hunger/eating)	1.2	1.8	0.7	1.1	1.8	0.5	<0.001

*** Combination of all other AEFIs with overall prevalence <1.0%

4.2.3 Number of AEFIs experienced after receiving COVID-19 vaccine dose

Among those who experienced at least some form of AEFI, 39.5% experienced only one AEFI, 29.5% experienced 2 AEFIs, 18.1% experienced 3 AEFIs, 7.9%experienced 4 AEFIs, 3.2% experienced 5 AEFIs and 1.2% experienced 6 AEFIs. (Figure 8)

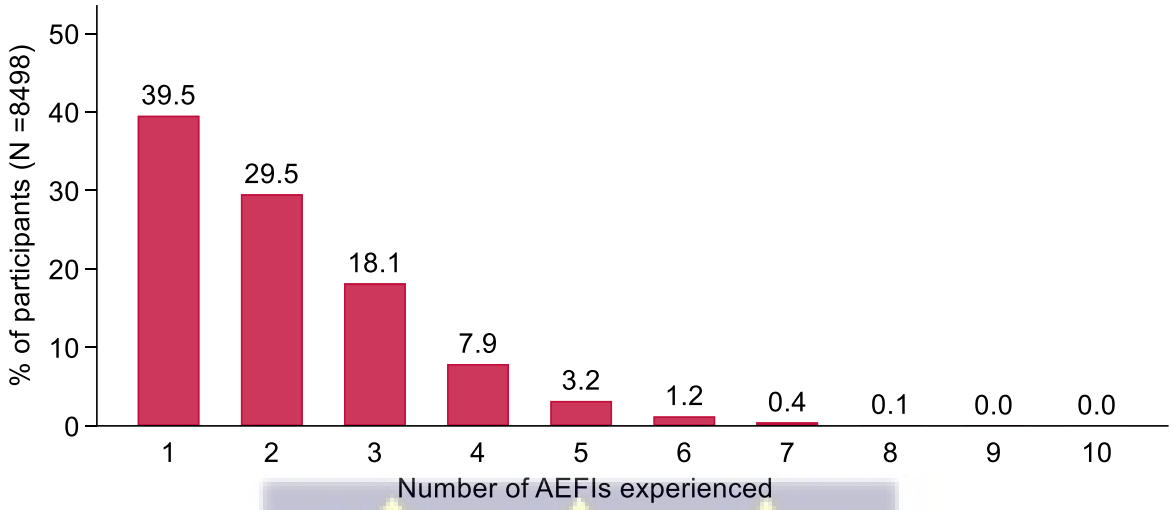


Figure 4.2.3: Number of AEFIs experienced after receiving COVID-19 vaccine dose

Table 4.2.3 below shows the number of AEFIs experienced by the various observed characteristics. (Table 4.2.3)

Table 4.2.3: Number of AEFIs experienced after receiving COVID-19 vaccine dose by characteristics

	Number of AEFIs experienced										
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**p-value**
Characteristics	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	**%**	
Overall	39.5	29.5	18.1	7.9	3.2	1.2	0.4	0.1	0.0	0.0	
Age group											<0.001
<20 years	47.1	31.8	14.1	4.7	1.2	1.2	0.0	0.0	0.0	0.0	
20-29 years	36.2	28.1	20.0	9.7	4.0	1.3	0.5	0.1	0.0	0.0	
30-39 years	36.3	29.7	19.5	8.1	4.0	1.8	0.3	0.1	0.0	0.0	
40-49 years	36.3	32.7	18.4	7.2	3.2	1.3	0.7	0.2	0.0	0.1	
50-59 years	45.2	29.2	16.1	5.5	2.8	0.7	0.6	0.0	0.0	0.0	
60+ years	48.5	30.0	14.0	3.9	2.4	0.6	0.7	0.0	0.0	0.0	
Unknown	45.5	29.2	15.6	7.7	1.3	0.5	0.1	0.0	0.1	0.0	
Sex											<0.001
Female	36.6	28.4	20.0	8.5	4.1	1.5	0.7	0.1	0.0	0.0	
Male	42.5	30.6	16.3	7.2	2.3	0.9	0.2	0.0	0.0	0.0	
Not stated	34.2	23.7	26.3	15.8	0.0	0.0	0.0	0.0	0.0	0.0	
Have an existing medical condition											0.001
No	39.5	29.2	18.5	7.7	3.3	1.3	0.4	0.1	0.0	0.0	
Yes	40.0	32.1	14.3	9.3	2.4	0.8	1.0	0.0	0.0	0.1	
On medication											<0.001
No	39.2	29.5	18.3	8.1	3.2	1.2	0.4	0.1	0.0	0.0	
Yes	52.7	30.5	12.4	1.3	1.8	0.9	0.4	0.0	0.0	0.0	
Vaccine type											<0.001
Covishield/AstraZeneca	25.8	28.6	25.0	11.8	5.6	2.2	0.7	0.2	0.0	0.0	
J&J/ Janssen	50.9	31.1	12.8	4.4	0.5	0.2	0.1	0.0	0.0	0.0	
Moderna	56.8	28.9	10.0	2.1	0.5	0.5	1.1	0.0	0.0	0.0	
Pfizer	45.6	33.3	15.8	3.5	0.0	0.0	1.8	0.0	0.0	0.0	
Sputnik	53.3	29.8	11.0	4.3	1.2	0.3	0.1	0.0	0.0	0.0	

%: row percentage

4.2.4 Severity of AEFIs

Among the 8,498 COVID-19 vaccine recipients who self-reported AEFIs, 0.75% (95% CI: 0.58% to 0.97%) reported severe AEFIs. Severe AEFIs were reported among 0.97% (95% CI: 0.69%-1.3%) of those who received AstraZeneca; 0.42% (95% CI: 0.17%-0.86%) among those who received the J&J vaccine; 2.1% (95% CI: 0.5%-5.3%) among those who received Moderna; 17.5% (95% CI: 8.7%-29.9%) among those who received Pfizer and 0.12% (95% CI: 0.03%-0.3%) among those who received Sputnik V (Figure 4.2.4).

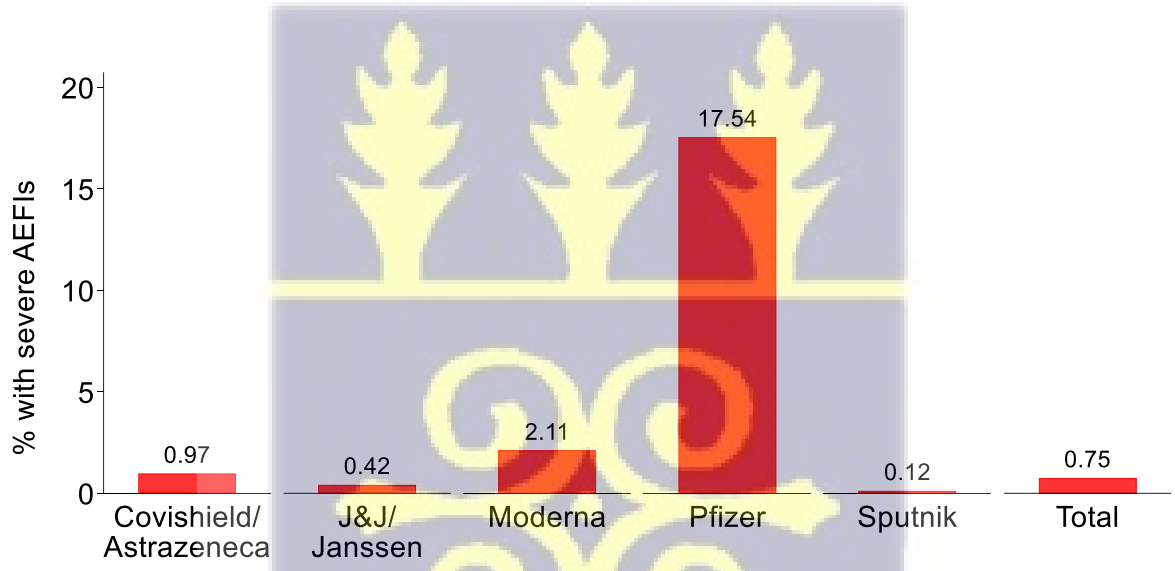


Figure 4.2.4: Prevalence of severe AEFIs among those who self-reported AEFIs

4.2.5 Factors Associated with Severe AEFIs Among Those Who Self-Reported AEFIs

Table 4.2.4 shows the prevalence of severe AEFIs among those who spontaneously reported AEFIs following COVID-19 vaccination by the various characteristics of the vaccine recipients. From the bivariate chi-square test, age group ($p<0.001$), and vaccine type ($p<0.001$) were significantly associated with self-reported severe AEFIs. (Table 4.2.4)

Table 4.2.4 also shows the crude and adjusted odds ratio of severe AEFIs across the observed characteristics of the vaccine recipients. Only 2 variables, age and vaccine type were significantly associated with the outcome in the adjusted analysis. Compared to those below 20 years, the adjusted odds of severe AEFIs were significantly less among those in the other

age group, 20-29 years (AOR: 0.12, 95% CI: [0.04, 0.32], p<0.001), 30-39 years (AOR: 0.18, 95% CI: [0.07, 0.46], p<0.001), 40-49 years (AOR: 0.35, 95% CI: [0.13, 0.98], p=0.046).

Also, the adjusted model showed the odds of severe AEFIs were significantly less in all the other vaccine types when compared to the Pfizer vaccine as follows; AstraZeneca (AOR: 0.05, 95% CI: [0.02, 0.12], p<0.001), J&J/Janssen (AOR: 0.03, 95% CI: [0.01, 0.08], p<0.001), Moderna (AOR: 0.1, 95% CI: [0.03, 0.40], p=0.001) and Sputnik (AOR: 0.01, 95% CI: [0.00, 0.04], p<0.001). (Table 4.2.4)

Table 4.2.4: Factors associated with Severe AEFIs among those who self-reported AEFIs

	Severe AEFIs		Unadjusted logistic regression		Adjusted logistic regression	
Characteristics	**n/N (%)**	**P-value**	**COR [95% CI]**	**P-value**	**AOR [95% CI]**	**P-value**
Age group		<0.001				
<20 years	7/85 (8.2)		1.00 [reference]		1.00 [reference]	
20-29 years	9/2,261 (0.4)		0.04 [0.02, 0.12]	<0.001	0.12 [0.04, 0.32]	<0.001
30-39 years	14/2,535 (0.6)		0.06 [0.02, 0.16]	<0.001	0.18 [0.07, 0.46]	<0.001
40-49 years	10/879 (1.1)		0.13 [0.05, 0.35]	<0.001	0.35 [0.13, 0.98]	0.046
50-59 years	8/542 (1.5)		0.17 [0.06, 0.47]	0.001	0.34 [0.12, 0.96]	0.042
60+ years	12/544 (2.2)		0.25 [0.10, 0.66]	0.005	0.47 [0.17, 1.30]	0.144
Unknown	4/1,652 (0.2)		0.03 [0.01, 0.09]	<0.001	0.07 [0.02, 0.25]	<0.001
Sex		0.097				
Female	38/4,199 (0.9)		1.00 [reference]		1.00 [reference]	
Male	25/4,261 (0.6)		0.65 [0.39, 1.07]	0.091	0.70 [0.41, 1.20]	0.192
Not stated	1/38 (2.6)		2.96 [0.40, 22.13]	0.291	5.20 [0.53, 50.87]	0.157
Have an existing medical condition		0.18				
No	55/7,713 (0.7)		1.00 [reference]		1.00 [reference]	
Yes	9/785 (1.1)		1.61 [0.80, 3.28]	0.185	1.36 [0.55, 3.40]	0.506
On medication		0.18				
No	64/8,272 (0.8)		-		-	
Yes	0/226 (0.0)		-		-	
Vaccine type		<0.001				
Covishield/AstraZeneca	40/4,120 (1.0)		0.05 [0.02, 0.10]	<0.001	0.05 [0.02, 0.12]	<0.001
J&J/ Janssen	7/1,673 (0.4)		0.02 [0.01, 0.05]	<0.001	0.03 [0.01, 0.08]	<0.001
Moderna	4/190 (2.1)		0.10 [0.03, 0.34]	<0.001	0.11 [0.03, 0.40]	0.001
Pfizer	10/57 (17.5)		1.00 [reference]		1.00 [reference]	
Sputnik	3/2,458 (0.1)		0.01 [0.00, 0.02]	<0.001	0.01 [0.00, 0.04]	<0.001

4.2.6 Outcome of AEFIs Among Those Self-Reporting

Among the 8,498 persons who self-reported AEFIs, the outcome of 0.2% was documented as death, 33.4% were still recovering, 58.0% had recovered with 8.4% indicated as unknown. (Figure 4.2.5).

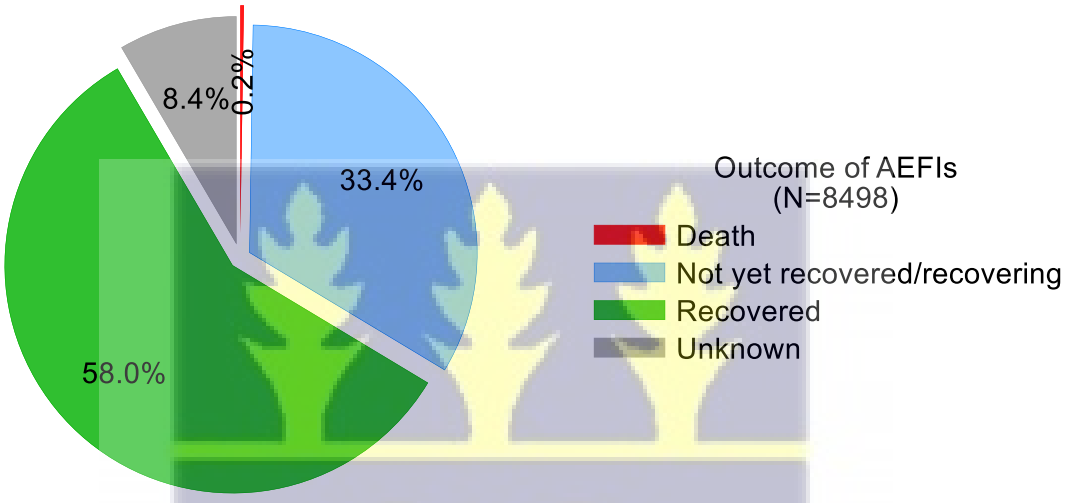


Figure 4.2.5: Outcome of AEFIs among those self-reported AEFIs.

Table 4.2.5 below shows the distribution of the outcomes of AEFIs across the observed characteristics. The bivariate analysis showed a significant association ($p<0.001$) between the outcome of the AEFIs and all the observed characteristics (age group, sex, history of a medical condition, medication, vaccine type and the severity of AEFIs) (Table 4.2.5).

Table 4.2.5: Outcome of AEFIs among those self-reporting

		Outcome of AEFIs				
	Total	**Death**	**Not yet recovered**	**Recovered**	**Unknown**	**p-value**
N	8,498	21	2,836	4,925	716	
	N	n (%)	n (%)	n (%)	n (%)	
Age group						<0.001
<20 years	85	2 (2.4)	34 (40.0)	39 (45.9)	10 (11.8)	
20-29 years	2,261	3 (0.1)	725 (32.1)	1,397 (61.8)	136 (6.0)	
30-39 years	2,535	2 (0.1)	815 (32.1)	1,594 (62.9)	124 (4.9)	
40-49 years	879	2 (0.2)	325 (37.0)	489 (55.6)	63 (7.2)	
50-59 years	542	4 (0.7)	241 (44.5)	261 (48.2)	36 (6.6)	
60+ years	544	7 (1.3)	283 (52.0)	218 (40.1)	36 (6.6)	
Unknown	1,652	1 (0.1)	413 (25.0)	927 (56.1)	311 (18.8)	
Sex						<0.001
Female	4,199	10 (0.2)	1,478 (35.2)	2,321 (55.3)	390 (9.3)	
Male	4,261	10 (0.2)	1,345 (31.6)	2,582 (60.6)	324 (7.6)	
Not stated	38	1 (2.6)	13 (34.2)	22 (57.9)	2 (5.3)	

Have an existing medical condition						<0.001
No	7,713	17 (0.2)	2,516 (32.6)	4,475 (58.0)	705 (9.1)	
Yes	785	4 (0.5)	320 (40.8)	450 (57.3)	11 (1.4)	
On medication						<0.001
No	8,272	21 (0.3)	2,836 (34.3)	4,699 (56.8)	716 (8.7)	
Yes	226	0 (0.0)	0 (0.0)	226 (100.0)	0 (0.0)	
Vaccine type						<0.001
Covishield/AstraZeneca	4,120	16 (0.4)	2,563 (62.2)	1,444 (35.0)	97 (2.4)	
J&J/ Janssen	1,673	1 (0.1)	179 (10.7)	1,045 (62.5)	448 (26.8)	
Moderna	190	1 (0.5)	21 (11.1)	1 (0.5)	167 (87.9)	
Pfizer	57	3 (5.3)	42 (73.7)	8 (14.0)	4 (7.0)	
Sputnik V	2,458	0 (0.0)	31 (1.3)	2,427 (98.7)	0 (0.0)	
Severity of AEFIs						<0.001
Not severe	8,434	3 (0.0)	2,814 (33.4)	4,903 (58.1)	714 (8.5)	
Severe	64	18 (28.1)	22 (34.4)	22 (34.4)	2 (3.1)	

n (%): Frequency (row per cent)

CHAPTER FIVE

DISCUSSION

5.1 Cohort Study Observations

The overall cumulative incidence of AEFIs among those who received the 3 vaccines in the cohort (14.0%) was very low compared to observations made in other similar studies (Kant et al., 2022; Rolfes et al., 2022). This observation of low AEFI incidence was similar across the individual vaccines as well and the overall accidence rate of AEFIs among the cohort was noted as 598 per 100,000 person days.

The AstraZeneca COVID-19 vaccine had an incidence of 18.5% in this study and this was observed to be lower than in early-phase trials and real-world vaccinations. For instance, the phase 1/2 studies conducted in the UK according to Folegatti et al., (2020), recorded an incidence of 67% among 543 vaccine recipients. Jeon et al., (2021) reported an incidence of 98.1% among 1,503 vaccinated healthcare personnel were vaccinated in the Republic of Korea and Subedi et al., (2021) reported an incidence of 79.8% among some vaccinated health workers in Nepal. The most common AEFIs experienced were general body pains/fatigue, headache, fever and pain at the injection site. This was very consistent with reports by Ramasamy et al. (2020) and Jeon et al., (2021).

Those who received the Moderna vaccine recorded an overall cumulative incidence of 14.0% which was also lower than the 67% and 82.4% observed in early-phase trials (Jackson et al., 2020 and Baden et al., 2021 respectively). AEFIs which were most common among the vaccine recipients were pain at the injection site, headache, general body pains/fatigue and chills which is similar to AEFIs recorded from early phase development and real-world administration (Jackson et al., 2020; Anderson et al., 2020; Gee et al., 2021)

Finally, those who received the Pfizer vaccine had an overall incidence of 9.7% which is lower than what was reported (about 92%) in the phase 1 trials by Walsh et al., (2020) or by Polack et al., (2020) in phase 2/3 studies (about 88%). Commonly occurring AEFIs were pain at the injection site, headache, general body pains/fatigue and fever and these were generally similar to events reported by Mohammed et al., (2021).

It was observed that as with other populations globally (Hasan et al., 2022), the incidence of AEFIs varied even across the different selected health facilities in Ghanaian. These differences in the incidences observed which are generally low in Ghana may be a result of the perception, practices and knowledge of those expected to report or their ability to detect AEFIs (Masika et al., 2016; Lv et al., 2022; Aborigo et al., 2022; Gidudu et al., 2020). Another reason for the low AEFI incidence may be due to generally low vaccination coverage in Africa compared to the other countries in the west (Masresha et al., 2022).

Comparatively, significantly more AEFIs were recorded among those who took the AstraZeneca vaccine than those who took the Pfizer or Moderna vaccines. The Pfizer vaccine gave the lowest risk of AEFI occurrence, which was statistically significant in the final adjusted model. Reports by Kant et al., (2022) corroborate this finding.

For all the 3 vaccine types used in the Ghanaian cohort study (AstraZeneca, Moderna and Pfizer), the cumulative incidence of AEFIs was significantly higher for vaccine dose 1 compared to vaccine dose 2 (irrespective of age, sex, enrolment site and history of existing chronic medical conditions). This observation was consistent with reports from early phase trials and real-life administration studies on the AstraZeneca vaccine (Folegatti et al., 2020; Ramasamy et al., 2020; Kaur et al., 2021). For the Moderna vaccine, however, contrary to what was observed in the Ghanaian study,

reports from other studies (Anderson et al., 2020; Baden et al., 2021) indicate an increase in AEFI incidence after dose 2. Similarly for the Pfizer vaccine (also an mRNA vaccine like the Moderna vaccine), studies indicate an increase in AEFIs after the second dose (Mohammed et al., 2021; Menni et al., 2021). Mathioudakis et al., (2021) indicated that this increase in reactogenicity of mRNA vaccines is even more pronounced after a second dose when vaccine recipients have had a prior COVID-19 infection. Unfortunately, information on prior COVID-19 infections among vaccine recipients in the Ghanaian cohort was not obtained at enrolment; hence, the observed disparity cannot be properly assessed. This was a study limitation.

With sex, females reported more AEFIs than males (both cumulative incidence and incidence rates of AEFIs were high) which is consistent with most literature (Green et al., 2022; Fadlilah et al., 2022). This is because women develop higher antibody responses, and stronger innate and cellular immunity, hence experiencing more adverse events after immunization than males (Fink & Klein, 2015). However, after adjusting for all factors in the Adjusted Cox-proportional hazard model, this was not statistically significant, which implies that in the Ghanaian cohort, men and women have about the same risk of developing AEFIs. This is similar to findings from Okeibunor et al., (2022) and Supangat et al., (2021).

Those younger than 60 years old recorded more AEFIs and were at significantly higher risk of experiencing these events. Most studies such as Singh et al., (2022), Vigezzi et al., (2021) and Rolfes et al., (2022) have reported similar trends. In the final adjusted model, this was a factor associated with the incidence of AEFIs.

Although overall, persons with a history of chronic medical conditions like diabetes, hypertension, asthma, sickle cell, etc. experienced a statistically higher cumulative incidence of AEFIs than those

without, among the various forms of chronic medical conditions only those with sickle cell disease and immunocompromised persons showed statistical significance. In the Adjusted Cox-proportional hazard model, the risk of AEFIs occurring in persons with chronic medical conditions was not statistically significant when compared to those without chronic medical conditions.

Most AEFIs occurred on the day of vaccination and the day after vaccination in line with most reports from previous studies including those of Basavaraja et al., (2021) and Mohammed et al., (2021). These reactions were mostly mild to moderate, resolving within a few days except for 1 person who died.

From the Adjusted Cox-proportional hazard model of factors associated with the incidence of AEFIs among people vaccinated against COVID-19, age, enrolment site, vaccine type and dose number were significantly related to the incidence of AEFIs. The occurrence of AEFIs depends on age, vaccine type, vaccine dose as well as enrolment site (geographical location).

The strengths of this study (cohort event monitoring study) include the ample study population and the inclusion of several variables, like the history of chronic diseases, use of concomitant medication and enrolment site (geographical location) of vaccine recipients in the analysis. Also, the availability of the 3 vaccine brands in Ghana allowed for comparison between the vaccines. The inability to have control over the data collection and entry process is a limitation in this study since it was not a prospective one but a retrospective study.

5.2 Spontaneous Reporting Data Observations

The overall cumulative incidence or incidence proportion of AEFIs was about 79 per 100,000 persons. Out of the doses administered, the AEFI incidence for the Sputnik vaccine seemed to be

the highest (13,669 per 100,000 persons) while Pfizer gave the lowest incidence of AEFIs (1 per 100,000 persons). This low incidence of AEFIs in the Pfizer vaccine was also observed in the Ghanaian cohort study with the 3 vaccines (Moderna, Pfizer and AstraZeneca) and is consistent with a report by Kant et al., (2022). In contrast to the high incidence of AEFIs from the Sputnik V vaccine in Ghana, Hasan et al., (2022), reported a rather low incidence of 13 AEFIs following the administration of 198,890 doses (about 7 per 100,000) of the vaccine in Pakistan when their COVID-19 immunization commenced on 2nd February 2021. However, because these are spontaneous/self-reports from the population, this may not be a true reflection of what pertains to Ghana. In addition, the lower incidence in the Pakistani population at the time of the report was attributed to underreporting due to a weak or less established pharmacovigilance system.

The most common AEFIs recorded across the 5 COVID-19 vaccines (in descending order of AEFI incidence) were headache, general body pains, fever, pain at the injection site and chills. These events were usually mild to moderate. This observation was similar to what was observed during the early developmental phase as well as the real-world administration of these vaccines (Zou et al., 2022; Okeibunor et al., 2022).

On the whole, out of the 8,498 persons in Ghana who self-reported at least one incidence of AEFI between 2nd March 2021 and 30th June 2022 during the mass immunization, significantly, most of the cases occurred among persons aged between 20-49. Consistent with most studies, this higher AEFI incidence was also observed individually among these 3 age categories for AstraZeneca, Moderna, Sputnik and Janssen vaccines (Zhu et al., 2020; Pagotto et al., 2021). The Pfizer vaccine recorded the highest AEFI incidence among the 20-29 and the 30-39 age groups with the 40-49 age group recording the least incidence among all the age categories (even those $\geq$50 of age had a much higher AEFI incidence).

The incidence of AEFIs among persons less than 20 years of age (18-19 years) was observed to be generally low and this could be attributed to the number of persons in this age category who received the vaccines nationally within the period. Unfortunately, information on the age of 19.4% of vaccine recipients who reported AEFIs was missing.

With sex, the overall incidence of AEFIs was about the same among males and females; however, individually, the AstraZeneca, Pfizer and Moderna vaccines recorded higher cases among females which is consistent with reports from previous studies such as Jayadevan et al., (2021); Basavaraja et al., (2021); Mohammed et al., (2021); Zou et al., (2022). For the Sputnik vaccine, more males reported a higher incidence of AEFIs while the same number of AEFIs observed among both sexes for the Janssen vaccine was the same. Although this may not be the norm from most literature, Hasan et al., (2022) reported that generally there was a higher incidence of AEFIs in men than in women in Pakistan when they began their mass vaccination. The vaccines rolled out in Pakistan included all the 5 vaccines used in Ghana and overall, more men than women had been fully vaccinated at the time of the report, hence accounting for the higher incidence in males. Unfortunately, information on the gender distribution of the vaccinated population in Ghana (in general and among the individual vaccines) was not available at the time of the study to fully ascertain the proportions of males and females from the entire Ghanaian population reporting AEFIs.

It was also observed that the proportion of females who suffered 3 or more AEFIs was greater than males, however, more males suffered 1 or 2 AEFIs and this was statistically significant. In terms of the severity of the AEFIs, the final adjusted logistic regression model, showed that sex was not associated with the severity of AEFIs and this observation is consistent with that of Okeibunor et al., (2022).

About 1 in 10 persons who reported AEFIs had a history of a chronic medical condition with hypertension, allergies, ulcers, and diabetes as the most common among them. However, in the adjusted logistic regression model, having an existing chronic medical condition was not associated with the severity of the AEFI experienced. Nevertheless, although it is highly recommended to vaccinate these high-risk populations, it is important to closely monitor them. This is because most of the developmental phase studies of the vaccines did not involve such vulnerable populations; hence there is a degree of significant research gaps in this area which may require further studies. The recommendations for vaccinating these special populations against COVID-19 will continue to evolve as research advances (Mohseni Afshar et al., 2021).

Regarding the outcome of AEFIs among those who self-reported, more than half (58%) had fully recovered, and 33.4% were still recovering with 0.2% (21 vaccine recipients) deaths. Unfortunately, the outcome of 8.4% was unknown. Of the 21 persons who died, following causality assessments by the FDA's Technical Advisory Committee on Safety, 12 were considered coincidental since autopsy reports revealed they had underlying or emerging condition(s), or condition(s) caused by exposure to something other than the vaccine. These conditions included ischaemic heart disease, chronic liver disease and bilateral massive pulmonary embolism. Six (6) persons were ineligible for assessment since no autopsies were performed due to traditional beliefs or their family's refusal. One (1) was classified as a temporal relationship to the vaccine, however, there was insufficient definitive evidence for the vaccine causing the event. Finally, the autopsy reports for 2 persons were pending at the time of data analyses for this study. The causality assessment was done using the WHO's Causality Assessment Scale.

From the Adjusted logistic regression model of factors associated with the severity of AEFIs among people who self-reported AEFIs following vaccination against COVID-19, age and vaccine type were factors found to be associated with the odds of having a severe adverse event.

The strengths of this study on spontaneous reports include the ample study population from across different parts of the country and the inclusion of various variables, like the history of chronic medical conditions, use of concomitant medication and the availability of different vaccine brands in Ghana which allowed for comparison. Self-reported symptoms may sometimes be subjective (information bias) and may not depict the real adverse events experienced which may pose as a limitation of the study. Although the possibility of underreporting of especially mild AEFIs could have been a limitation, this was mitigated by the data from the CEM.

Public Health Implications and Directions for Future Research

The COVID-19 vaccines are safe and continued vaccination will offer protection against COVID-19-related morbidity and mortality that far exceeds the anticipated rates of rare and serious AEFIs. It is therefore important to disseminate this information to the relevant stakeholders including healthcare professionals and the general public. Information of such nature would increase public trust (decrease vaccine hesitancy) in vaccination programmes (current and future) and ensure that many people get vaccinated to prevent incidence of the COVID-19 disease. However, there is a need for enhanced sensitization and the implementation of enhanced pharmacovigilance activities to increase timely reporting of adverse events from the vaccines so as not to miss any potential safety signals.

CHAPTER SIX

CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

There was a low incidence of AEFIs following immunization of all 5 COVID-19 vaccines used in Ghana so far since the mass immunization with the events being generally mild and resolving within a few days. The incidence of AEFIs was higher among the young population (below 60 years) and also in females.

Headache, general body pains, fever and injection site pain were the most common AEFIs associated with the COVID-19 vaccines among those vaccinated.

The occurrence of AEFIs was found to be dependent on the age, vaccine type, vaccine dose as well as enrolment site (geographical location) of vaccine recipients in the cohort study. Also, in terms of severity of the AEFIs, age and vaccine type were factors found to be associated with the odds of having a severe adverse event in the spontaneous reports.

Since most of the AEFIs which occurred in both the cohort study and the spontaneous reports are mild and resolved quickly, it could be inferred that the vaccines are safe. Making the public aware of the nature, type of side effects and the factors associated with greater odds of these side effects (AEFIs) would build confidence in the vaccines. Vaccine hesitancy among the public would be overcome and this would result in a further increase in vaccine uptake or coverage across the country.

6.2 Recommendations

The following recommendations are being made for consideration:

1. The EPI/GHS could make use of this study's findings to make all stakeholders, including the general public, aware and assure them of the safety of the COVID-19 vaccines. This would build confidence in the vaccines, encourage vaccine uptake and increase coverage across the country.
2. There is a need for the EPI/GHS to also have data on the gender distribution of the vaccines in the general population to enable further assessments of the effects of the vaccines in relation to gender.
3. There is also the need for sensitization of the vaccinated persons to be able to identify and report AEFIs. This would help identify very rare adverse events of safety concerns within the population.
4. The FDA should continue to assess the safety of these vaccines in the general adult population as well as conduct similar analyses in the ongoing vaccination of pregnant women and persons 15 – 17 years of age.

REFERENCES

Aborigo, R. A., Welaga, P., Oduro, A., Shaum, A., Opare, J., Dodoo, A., Ampadu, H., & Gidudu, J. F. (2022). Optimising reporting of adverse events following immunisation by healthcare workers in Ghana: A qualitative study in four regions. *PloS One*, *17*(12), e0277197. https://doi.org/10.1371/journal.pone.0277197

Acheampong, T., Akorsikumah, E. A., Osae-Kwapong, J., Khalid, M., Appiah, A., & Amuasi, J. H. (2021). Examining vaccine hesitancy in sub-Saharan Africa: A survey of the knowledge and attitudes among adults to receive covid-19 vaccines in ghana. *Vaccines*, *9*(8). https://doi.org/10.3390/vaccines9080814

Adisa, R., & Omitogun, T. I. (2019). Awareness, knowledge, attitude and practice of adverse drug reaction reporting among health workers and patients in selected primary healthcare centres in Ibadan, southwestern Nigeria. *BMC Health Services Research*, *19*(1), 1–14. https://doi.org/10.1186/s12913-019-4775-9

Ali, I., & Alharbi, O. M. L. (2020). COVID-19: Disease, management, treatment, and social impact. *Science of the Total Environment*, *728*, 138861. https://doi.org/10.1016/j.scitotenv.2020.138861

Anderson, E. J., Rouphael, N. G., Widge, A. T., Jackson, L. A., Roberts, P. C., Makhene, M., Chappell, J. D., Denison, M. R., Stevens, L. J., Pruijssers, A. J., McDermott, A. B., Flach, B., Lin, B. C., Doria-Rose, N. A., O'Dell, S., Schmidt, S. D., Corbett, K. S., Swanson, P. A., Padilla, M., … Beigel, J. H. (2020). Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. *New England Journal of Medicine*, *383*(25), 2427–2438. https://doi.org/10.1056/nejmoa2028436

Baden, L. R., el Sahly, H. M., Essink, B., Kotloff, K., Frey, S., Novak, R., Diemert, D., Spector, S. A., Rouphael, N., Creech, C. B., McGettigan, J., Khetan, S., Segall, N., Solis, J., Brosz, A., Fierro, C., Schwartz, H., Neuzil, K., Corey, L., … Zaks, T. (2021). Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *New England Journal of Medicine*, *384*(5), 403–416. https://doi.org/10.1056/nejmoa2035389

Basavaraja, C. K., Sebastian, J., Ravi, M. D., & John, S. B. (2021). Adverse events following COVID-19 vaccination: first 90 days of experience from a tertiary care teaching hospital in South India. *Therapeutic Advances in Vaccines and Immunotherapy*, *9*(March 2020), 1–12. https://doi.org/10.1177/25151355211055833

Bates, D. W. (1997). The Costs of Adverse Drug Events in Hospitalized Patients. *JAMA: The Journal of the American Medical Association*, *277*(4), 307. https://doi.org/10.1001/jama.1997.03540280045032

Beirne, P. v., Hennessy, S., Cadogan, S. L., Shiely, F., Fitzgerald, T., & Macleod, F. (2018). Needle size for vaccination procedures in children and adolescents. *Cochrane Database of Systematic Reviews*, *2018*(8). https://doi.org/10.1002/14651858.CD010720.pub3

Belete, T. M. (2021). Review on up-to-date status of candidate vaccines for COVID-19 disease. *Infection and Drug Resistance*, *14*, 151–161. https://doi.org/10.2147/IDR.S288877

Bong, C. L., Brasher, C., Chikumba, E., Mcdougall, R., Mellin-Olsen, J., & Enright, A. (2020). The COVID-19 Pandemic: Effects on Low- And Middle-Income Countries. *Anesthesia and Analgesia*, *131*(1), 86–92. https://doi.org/10.1213/ANE.0000000000004846

Breugelmans, J., Lewis, R. F., Agbenu, E., Veit, O., Jackson, D., Domingo, C., Böthe, M., Perea, W., Niedrig, M., Gessner, B. D., Yactayo, S. & YF AEFI group. (2013). Adverse events

following yellow fever preventive vaccination campaigns in eight African countries from 2007 to 2010. Vaccine, 31(14), 1819-1829.

Brodin, P. (2021). Immune determinants of COVID-19 disease presentation and severity. *Nature Medicine*, *27*(1), 28–33. https://doi.org/10.1038/s41591-020-01202-8

Cattel, L., Giordano, S., Traina, S., Lupia, T., Corcione, S., Angelone, L., la Valle, G., de Rosa, F. G., & Cattel, F. (2022). Vaccine development and technology for SARS-CoV-2: Current insight. *Journal of Medical Virology*, *94*(3), 878–896. https://doi.org/10.1002/jmv.27425

Cazzola, M., Rogliani, P., Mazzeo, F., & Matera, M. G. (2021). Controversy surrounding the Sputnik V vaccine. *Respiratory Medicine*, *187*(June), 106569. https://doi.org/10.1016/j.rmed.2021.106569

CDC, & Ncird. (2022). *COVID-19 Vaccine Interim COVID-19 Immunization Schedule for 6 Months of Age and Older*. www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-

Ciarambino, T., Para, O., & Giordano, M. (2021). Immune system and COVID-19 by sex differences and age. *Women's Health*, *17*. https://doi.org/10.1177/17455065211022262

Coleman, J. J., & Pontefract, S. K. (2016). Adverse Drug Reactions. *CME CLINICAL PHARMACOLOGY*, *16*, 481–486.

Das, B. B., Moskowitz, W. B., Taylor, M. B., & Palmer, A. (2021). *Vaccination : What Do We Know So Far ?*

Dodd, R. H., Cvejic, E., Bonner, C., Pickles, K., McCaffery, K. J., Ayre, J., Batcup, C., Copp, T., Cornell, S., Dakin, T., Isautier, J. M., & Nickel, B. (2021). Willingness to vaccinate against

COVID-19 in Australia. *The Lancet Infectious Diseases*, *21*(3), 318–319. https://doi.org/10.1016/S1473-3099(20)30559-4

EMA. (2021). *EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR VAXZEVRIA (ChAdOx1-S [RECOMBINANT])*. *1*(101).

Fadlilah, S., Setiawan, D. I., Muflih, M., Amigo, T. A. E., Susanto, R., & Pujianto, A. (2022). *Factors Associated with Adverse Events Following the First Dose of COVID-19 Immunization in Indonesia*. *34*(3), 249–257.

FDA Briefing Document. (2020). FDA Briefig Document Moderna COVID-19 Vaccine. *Fda*, 1–54. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM583779.pdf

Fink, A. L., & Klein, S. L. (2015). Sex and gender impact immune responses to vaccines among the elderly. *Physiology*, *30*(6), 408–416. https://doi.org/10.1152/physiol.00035.2015

Fischinger, S., Boudreau, C. M., Butler, A. L., Streeck, H., & Alter, G. (2019). Sex differences in vaccine-induced humoral immunity. *Seminars in Immunopathology*, *41*(2), 239–249. https://doi.org/10.1007/s00281-018-0726-5

Folegatti, P. M., Ewer, K. J., Aley, P. K., Angus, B., Becker, S., Belij-Rammerstorfer, S., Bellamy, D., Bibi, S., Bittaye, M., Clutterbuck, E. A., Dold, C., Faust, S. N., Finn, A., Flaxman, A. L., Hallis, B., Heath, P., Jenkin, D., Lazarus, R., Makinson, R., … Yau, Y. (2020). Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary

report of a phase 1/2, single-blind, randomised controlled trial. *The Lancet*, *396*(10249), 467–478. https://doi.org/10.1016/S0140-6736(20)31604-4

Frösner, G., Steffen, R., & Herzog, C. (2009). Virosomal hepatitis a vaccine: Comparing intradermal and subcutaneous with intramuscular administration. *Journal of Travel Medicine*, *16*(6), 413–419. https://doi.org/10.1111/j.1708-8305.2009.00351.x

Gautam, A., Dangol, N., Bhattarai, U., Paudel, S., Poudel, B., Gautam, S., Sharma, P., Uranw, S., & Sharma, S. K. (2021). ChAdOx1 nCoV-19 vaccine and its self-reported adverse events: a cross-sectional study from Western Nepal. *Journal of Global Health Reports*, *5*, 1–7. https://doi.org/10.29392/001c.25471

Gee, J., Shimabukuro, P. M., Su, J., Tom, G. M. C., Sotir, R., Mark, g L., Jazwa, T. M., Amelia, N. N., Licata;, S. M., Clark;, T., Markowitz;, L., Lindsey;, N., & Zhang;, B. C. (2021). First Month of COVID-19 Vaccine Safety Monitoring — United States, *MMWR. Morbidity and Mortality Weekly Report*, *70*(8), 283–288.

Ghana Health Service. (2022). COVID-19 : Vaccination Updates. *Nuhs*, 1–15. https://www.nuhs.edu.sg/For-Patients-Visitors/COVID-19/Pages/COVID-19-Vaccination-Updates.aspx

Gidudu, J. F., Shaum, A., Dodoo, A., Bosomprah, S., Bonsu, G., Amponsa-Achiano, K., Darko, D. M., Sabblah, G., Opare, J., Nyaku, M., Owusu-Boakye, B., Oduro, A., Aborigo, R., Conklin, L., Welaga, P., & Ampadu, H. H. (2020). Barriers to healthcare workers reporting adverse events following immunization in four regions of Ghana. *Vaccine*, *38*(5), 1009–1014. https://doi.org/10.1016/j.vaccine.2019.11.050

Green, M. S., Peer, V., Magid, A., Hagani, N., Anis, E., & Nitzan, D. (2022). *Gender Differences in Adverse Events Following the Pfizer- BioNTech COVID-19 Vaccine*. 1–12.

Gupta, A., Sardar, P., Cash, M. E., Milani, R. v, & Lavie, C. J. (2021). Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information. *Progress in Cardiovascular Diseases*, *67*(January), 105–107.

Hasan, S. S., Rashid, A., Osama, S., Mustafa, Z. U., & Merchant, H. A. (2022). Covid-19 Vaccine safety and adverse event analysis from Pakistan. *Clinical Immunology Communications*, *2*(May), 91–97. https://doi.org/10.1016/j.clicom.2022.05.003

Hause, A. M., Gee, J., Johnson, T., Jazwa, A., Marquez, P., Miller, E., Su, J., Shimabukuro, T. T., & Shay, D. K. (2021). Anxiety-Related Adverse Event Clusters After Janssen COVID-19 Vaccination — Five U.S. Mass Vaccination Sites, April 2021. *MMWR Recommendations and Reports*, *70*(18), 685–688. https://doi.org/10.15585/mmwr.mm7018e3

Hervé, C., Laupèze, B., del Giudice, G., Didierlaurent, A. M., & da Silva, F. T. (2019). The how's and what's of vaccine reactogenicity. *Npj Vaccines*, *4*(1). https://doi.org/10.1038/s41541-019-0132-6

Herzog, C. (2014). Influence of parenteral administration routes and additional factors on vaccine safety and immunogenicity: A review of recent literature. *Expert Review of Vaccines*, *13*(3), 399–415. https://doi.org/10.1586/14760584.2014.883285

Jackson, L. A., Anderson, E. J., Rouphael, N. G., Roberts, P. C., Makhene, M., Coler, R. N., McCullough, M. P., Chappell, J. D., Denison, M. R., Stevens, L. J., Pruijssers, A. J.,

McDermott, A., Flach, B., Doria-Rose, N. A., Corbett, K. S., Morabito, K. M., O'Dell, S., Schmidt, S. D., Swanson, P. A., … Beigel, J. H. (2020). An mRNA Vaccine against SARS-CoV-2 — Preliminary Report. *New England Journal of Medicine*, *383*(20), 1920–1931. https://doi.org/10.1056/nejmoa2022483

Jayadevan, R., Shenoy, R., & TS, A. (2021). Survey of symptoms following COVID-19 vaccination in India. *Public and Global Health*, Preprint. https://www.medrxiv.org/content/10.1101/2021.02.08.21251366v1%0Ahttps://www.medrxiv.org/content/10.1101/2021.02.08.21251366v1.abstract%0Ahttps://www.medrxiv.org/content/10.1101/2021.02.08.21251366v1%0Ahttps://www.medrxiv.org/content/10.1101/2021.02.08.212

Jeon, M., Kim, J., Oh, C. E., & Lee, J. Y. (2021). Adverse Events Following Immunization Associated with Coronavirus Disease 2019 Vaccination Reported in the Mobile Vaccine Adverse Events Reporting System. *Journal of Korean Medical Science*, *36*(17), 1–8. https://doi.org/10.3346/jkms.2021.36.e114

Jones, I., & Roy, P. (2021). The Sputnik V COVID-19 vaccine candidate appears safe and effective. *The Lancet*, *397*(10275), 642–643. https://doi.org/10.1016/S0140-6736(21)00191-4

Kamble, B., Bashar, Md. A., & Mishra, C. P. (2022). Incidence, Pattern and Severity of Adverse Events Following Immunization (AEFIs) Associated With Chadox1 nCOV-19 Corona Virus Vaccine (Recombinant) Among the Healthcare Workers of a Tertiary Care Institute of Eastern Uttar Pradesh, India. *Cureus*, *14*(2), 1–8. https://doi.org/10.7759/cureus.21848

Kant, A., Jansen, J., Balveren, L. van, & Hunsel, F. van. (2022). Description of Frequencies of Reported Adverse Events Following Immunization Among Four Different COVID-19 Vaccine Brands. *Drug Safety*, *45*(4), 319–331. https://doi.org/10.1007/s40264-022-01151-w

Kaufmann, S. H. E., Juliana McElrath, M., Lewis, D. J. M., & del Giudice, G. (2014). Challenges and responses in human vaccine development. *Current Opinion in Immunology*, *28*(1), 18–26. https://doi.org/10.1016/j.coi.2014.01.009

Kaur, U., Ojha, B., Pathak, B. K., Singh, A., Giri, K. R., Singh, A., Das, A., Misra, A., Yadav, A. K., Kansal, S., & Chakrabarti, S. S. (2021). A prospective observational safety study on ChAdOx1 nCoV-19 coronavirus vaccine (recombinant) use in healthcare workers- first results from India. *EClinicalMedicine*, *38*, 101038. https://doi.org/10.1016/j.eclinm.2021.101038

Kongkaew, C., Noyce, P. R., & Ashcroft, D. M. (2008). Hospital admissions associated with adverse drug reactions: A systematic review of prospective observational studies. *Annals of Pharmacotherapy*, *42*(7–8), 1017–1025. https://doi.org/10.1345/aph.1L037

Kragholm, K., Sessa, M., Mulvad, T., & Porsborg, M. (2020). *Thrombocytopenia after COVID-19 vaccination*. *January*, 2020–2022.

Krammer, F. (2020). SARS-CoV-2 vaccines in development. *Nature*, *586*(7830), 516–527. https://doi.org/10.1038/s41586-020-2798-3

Larson, K., Larson, K. F., Ammirati, E., Adler, E. D., Cooper Jr, L. T., Hong, K. N., Saponara, G., Couri, D., Cereda, A., Procopio, A., Cavalotti, C., Oliva, F., Sanna, T., Antonio Ciconte, V., Onyango, G., Holmes, D. R., & Borgeson, D. D. (2021). Circulation Myocarditis After

BNT162b2 and mRNA-1273 Vaccination. *Circulation*, *144*, 506–508. https://doi.org/10.1161/CIRCULATIONAHA.121.055913

Laryea, E. B., Frimpong, J. A., Noora, C. L., Tengey, J., Bandoh, D., Sabblah, G., Ameme, D., Kenu, E., & Amponsa-Achiano, K. (2022). Evaluation of the adverse events following immunization surveillance system, Ghana, 2019. *PLoS ONE*, *17*(3 March), 1–13. https://doi.org/10.1371/journal.pone.0264697

Logunov, D. Y., Dolzhikova, I. v., Shcheblyakov, D. v., Tukhvatulin, A. I., Zubkova, O. v., Dzharullaeva, A. S., Kovyrshina, A. v., Lubenets, N. L., Grousova, D. M., Erokhova, A. S., Botikov, A. G., Izhaeva, F. M., Popova, O., Ozharovskaya, T. A., Esmagambetov, I. B., Favorskaya, I. A., Zrelkin, D. I., Voronina, D. v., Shcherbinin, D. N., … Gintsburg, A. L. (2021). Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. *The Lancet*, *397*(10275), 671–681. https://doi.org/10.1016/S0140-6736(21)00234-8

Logunov, D. Y., Dolzhikova, I. v., Zubkova, O. v., Tukhvatullin, A. I., Shcheblyakov, D. v., Dzharullaeva, A. S., Grousova, D. M., Erokhova, A. S., Kovyrshina, A. v., Botikov, A. G., Izhaeva, F. M., Popova, O., Ozharovskaya, T. A., Esmagambetov, I. B., Favorskaya, I. A., Zrelkin, D. I., Voronina, D. v., Shcherbinin, D. N., Semikhin, A. S., … Gintsburg, A. L. (2020). Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia. *The Lancet*, *396*(10255), 887–897. https://doi.org/10.1016/S0140-6736(20)31866-3

López, J. A., Kearon, C., & Lee, A. Y. Y. (2004). Deep venous thrombosis. *Hematology / the Education Program of the American Society of Hematology. American Society of Hematology. Education Program*, 439–456. https://doi.org/10.1182/asheducation-2004.1.439

Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., Wang, W., Song, H., Huang, B., Zhu, N., Bi, Y., Ma, X., Zhan, F., Wang, L., Hu, T., Zhou, H., Hu, Z., Zhou, W., Zhao, L., … Tan, W. (2020). Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The Lancet*, *395*(10224), 565–574. https://doi.org/10.1016/S0140-6736(20)30251-8

Lv, H., Pan, X., Wang, Y., Liang, H., & Yu, H. (2022). Barriers to healthcare workers reporting adverse events following immunization in Zhejiang province, China. *Human Vaccines and Immunotherapeutics*, *18*(5). https://doi.org/10.1080/21645515.2022.2083865

Mahase, E. (2021). AstraZeneca vaccine: Blood clots are "extremely rare" and benefits outweigh risks, regulators conclude. *BMJ (Clinical Research Ed.)*, *373*(April), n931. https://doi.org/10.1136/bmj.n931

Masika, C. W., Atieli, H., & Were, T. (2016). Knowledge, Perceptions, and Practice of Nurses on Surveillance of Adverse Events following Childhood Immunization in Nairobi, Kenya. *BioMed Research International*, *2016*. https://doi.org/10.1155/2016/3745298

Masresha, B., Poy, A., Weldegebriel, G., Mbuyita, S., Fussum, D., Bwaka, A., Paluku, G., Atuhebwe, P., Mihigo, R., & Impouma, B. (2022). Progress with COVID-19 vaccination in the WHO African Region in 2021. *The Pan African Medical Journal*, *41*(May), 8. https://doi.org/10.11604/pamj.supp.2022.41.2.34102

Mathioudakis, A. G., Ghrew, M., Ustianowski, A., Ahmad, S., Borrow, R., Papavasileiou, L. P., Petrakis, D., & Bakerly, N. D. (2021). *Self-Reported Real-World Safety and Reactogenicity of COVID-19 Vaccines: A Vaccine Recipient Survey*. 1–13.

Menni, C., Klaser, K., May, A., Polidori, L., Capdevila, J., Louca, P., Sudre, C. H., Nguyen, L. H., Drew, D. A., Merino, J., Hu, C., Selvachandran, S., Antonelli, M., Murray, B., Canas, L. S., Molteni, E., Graham, M. S., Modat, M., Joshi, A. D., … Spector, T. D. (2021). Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. *The Lancet Infectious Diseases*, *21*(7), 939–949. https://doi.org/10.1016/S1473-3099(21)00224-3

military.com. (n.d.). *Pentagon Tracking 14 Cases of Heart Inflammation in Troops After COVID-19 Shots | Military.com*. Retrieved July 11, 2022, from https://www.military.com/daily-news/2021/04/26/pentagon-tracking-14-cases-of-heart-inflammation-troops-after-covid-19-shots.html

Mohammed, R. A., Garout, R. M., Wahid, S., Ayub, F., Firas Zin Alddin, L. M., & Sultan, I. (2021). A Survey on the Side Effects of Pfizer/BioNTech COVID-19 Vaccine Among Vaccinated Adults in Saudi Arabia. *Cureus*, *13*(11). https://doi.org/10.7759/cureus.19222

Mohseni Afshar, Z., Babazadeh, A., Janbakhsh, A., Mansouri, F., Sio, T. T., Sullman, M. J. M., Carson-Chahhoud, K., Hosseinzadeh, R., Barary, M., & Ebrahimpour, S. (2021). Coronavirus disease 2019 (Covid-19) vaccination recommendations in special populations and patients with existing comorbidities. *Reviews in Medical Virology*, *August*. https://doi.org/10.1002/rmv.2309

Montalti, M., Soldà, G., di Valerio, Z., Salussolia, A., Lenzi, J., Forcellini, M., Barvas, E., Guttmann, S., Messina, R., Poluzzi, E., Raschi, E., Riccardi, R., Fantini, M. P., la Fauci, G., & Gori, D. (2021). ROCCA observational study: Early results on safety of Sputnik V vaccine (Gam-COVID-Vac) in the Republic of San Marino using active surveillance. *EClinicalMedicine*, *38*, 4–10. https://doi.org/10.1016/j.eclinm.2021.101027

Mueller, A. L., McNamara, M. S., & Sinclair, D. A. (2020). Why does COVID-19 disproportionately affect older people? *Ageing*, *12*(10), 9959–9981.

National Institutes of Health. (2021). Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19). *NIH*, *2019*, 1–243. https://www.covid19treatmentguidelines.nih.gov/.%0Ahttps://www.covid19treatmentguidelines.nih.gov/

Nogrady, B. (2021). Mounting evidence suggests the Sputnik COVID vaccine is safe and effective. *Nature*, *595*(7867), 339–340. https://doi.org/10.1038/d41586-021-01813-2

Okeibunor, L., Id, O., Babatunde, Y., & Id, M. (2022). *Adverse events following COVID-19 vaccination in Kwara State, North-central*. *2019*(March 2020), 1–10. https://doi.org/10.1371/journal.pgph.0000835

Oliver, S. E., Wallace, M., See, I., Mbaeyi, S., Godfrey, M., Hadler, S. C., Jatlaoui, T. C., Twentyman, E., Hughes, M. M., Rao, A. K., Fiore, A., Su, J. R., Broder, K. R., Shimabukuro, T., Lale, A., Shay, D. K., Markowitz, L. E., Wharton, M., Bell, B. P., … Daley, M. F. (2022). Use of the Janssen (Johnson & Johnson) COVID-19 Vaccine: Updated Interim Recommendations from the Advisory Committee on Immunization Practices — United

States, December 2021. *MMWR. Morbidity and Mortality Weekly Report*, *71*(3), 90–95. https://doi.org/10.15585/mmwr.mm7103a4

Østergaard, S. D., Schmidt, M., Horváth-Puhó, E., Thomsen, R. W., & Sørensen, H. T. (2021). Thromboembolism and the Oxford–AstraZeneca COVID-19 vaccine: side-effect or coincidence? *The Lancet*, *397*(10283), 1441–1443. https://doi.org/10.1016/S0140-6736(21)00762-5

Pagotto, V., Ferloni, A., Soriano, M. M., Díaz, M., Golde, M. B., González, M. I., Asprea, V., Staneloni, I., Vidal, G., Silveira, M., Zingoni, P., Aliperti, V., Michelangelo, H., & Figar, S. (2021). Active Surveillance of the Sputnik V Vaccine in Health Workers. *MedRxiv*, 2021.02.03.21251071. https://doi.org/10.1101/2021.02.03.21251071

Petousis-Harris, H. (2020). Assessing the Safety of COVID-19 Vaccines: A Primer. *Drug Safety*, *43*(12), 1205–1210. https://doi.org/10.1007/s40264-020-01002-6

Pfizer-BioNTech. (2020). Pfizer-Biontech Covid-19 Vaccine (Bnt162, Pf-07302048) Vaccines and Related Biological Products Advisory Committee Briefing Document. *Elsevier*, *23*(December), 92. https://www.fda.gov/media/144246/download

Pirmohamed, M., James, S., Meakin, S., & Green, C. (2004). Adverse drug reactions as cause of hospital admission: Authors' reply. *BMJ*, *329*(7463), 460. https://doi.org/10.1136/bmj.329.7463.460-a

Polack, F. P., Thomas, S. J., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Perez, J. L., Pérez Marc, G., Moreira, E. D., Zerbini, C., Bailey, R., Swanson, K. A., Roychoudhury, S., Koury, K., Li, P., Kalina, W. v., Cooper, D., Frenck, R. W., Hammitt, L. L., … Gruber, W. C. (2020).

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *New England Journal of Medicine*, *383*(27), 2603–2615. https://doi.org/10.1056/nejmoa2034577

Ramasamy, M. N., Minassian, A. M., Ewer, K. J., Flaxman, A. L., Folegatti, P. M., Owens, D. R., Voysey, M., Aley, P. K., Angus, B., Babbage, G., Belij-Rammerstorfer, S., Berry, L., Bibi, S., Bittaye, M., Cathie, K., Chappell, H., Charlton, S., Cicconi, P., Clutterbuck, E. A., … Zizi, D. (2020). Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial. *The Lancet*, *396*(10267), 1979–1993. https://doi.org/10.1016/S0140-6736(20)32466-1

Rolfes, L., Härmark, L., Kant, A., van Balveren, L., Hilgersom, W., & van Hunsel, F. (2022). COVID-19 vaccine reactogenicity – A cohort event monitoring study in the Netherlands using patient-reported outcomes. *Vaccine*, *40*(7), 970–976. https://doi.org/10.1016/j.vaccine.2022.01.013

Rosenblum, H. G., Hadler, S. C., Moulia, D., Shimabukuro, T. T., Su, J. R., Tepper, N. K., Ess, K. C., Woo, E. J., Mba-Jonas, A., Alimchandani, M., Nair, N., Klein, N. P., Hanson, K. E., Markowitz, L. E., Wharton, M., McNally, V. v., Romero, J. R., Talbot, H. K., Lee, G. M., … Oliver, S. E. (2021). Use of COVID-19 Vaccines After Reports of Adverse Events Among Adult Recipients of Janssen (Johnson & Johnson) and mRNA COVID-19 Vaccines (Pfizer-BioNTech and Moderna): Update from the Advisory Committee on Immunization Practices — United States, July 202. *MMWR Recommendations and Reports*, *70*(32), 1094–1099. https://doi.org/10.15585/mmwr.mm7032e4

Rosner, C. M., Genovese, L., Tehrani, B. N., Atkins, M., Bakhshi, H., Chaudhri, S., Damluji, A. A., de Lemos, J. A., Desai, S. S., Emaminia, A., Flanagan, M. C., Khera, A., Maghsoudi, A., Mekonnen, G., Muthukumar, A., Saeed, I. M., Sherwood, M. W., Sinha, S. S., O'Connor, C. M., & Defilippi, C. R. (2021). Myocarditis Temporally Associated with COVID-19 Vaccination. *Circulation*, *144*(6), 502–505. https://doi.org/10.1161/CIRCULATIONAHA.121.055891

Sadoff, J., Gray, G., Vandebosch, A., Cárdenas, V., Shukarev, G., Grinsztejn, B., Goepfert, P. A., Truyers, C., Fennema, H., Spiessens, B., Offergeld, K., Scheper, G., Taylor, K. L., Robb, M. L., Treanor, J., Barouch, D. H., Stoddard, J., Ryser, M. F., Marovich, M. A., … Douoguih, M. (2021). Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. *New England Journal of Medicine*, *384*(23), 2187–2201. https://doi.org/10.1056/nejmoa2101544

Sadoff, J., Gray, G., Vandebosch, A., Cárdenas, V., Shukarev, G., Grinsztejn, B., Goepfert, P. A., Truyers, C., van Dromme, I., Spiessens, B., Vingerhoets, J., Custers, J., Scheper, G., Robb, M. L., Treanor, J., Ryser, M. F., Barouch, D. H., Swann, E., Marovich, M. A., … Douoguih, M. (2022). Final Analysis of Efficacy and Safety of Single-Dose Ad26.COV2.S. *New England Journal of Medicine*, *386*(9), 847–860. https://doi.org/10.1056/nejmoa2117608

Sadoff, J., le Gars, M., Shukarev, G., Heerwegh, D., Truyers, C., de Groot, A. M., Stoop, J., Tete, S., van Damme, W., Leroux-Roels, I., Berghmans, P.-J., Kimmel, M., van Damme, P., de Hoon, J., Smith, W., Stephenson, K. E., de Rosa, S. C., Cohen, K. W., McElrath, M. J., … Schuitemaker, H. (2021). Interim Results of Phase 1–2a Trial of Ad26.COV2.S Covid-19

Vaccine. *New England Journal of Medicine*, *384*(19), 1824–1835. https://doi.org/10.1056/nejmoa2034201

Sah, R., Shrestha, S., Mehta, R., Sah, S. K., Raaban, A. A., Dharma, K., & Rodriguez-Morales, A. J. (2021). AZD1222 (Covishield) vaccination for COVID-19: Experiences, challenges, and solutions in Nepal. *Travel Medicine and Infectious Disease*, *40*(February), 101989. https://doi.org/10.1016/j.tmaid.2021.101989

Schafer, A. I., Levine, M. N., Konkle, B. A., & Kearon, C. (2003). Thrombotic disorders: diagnosis and treatment. *Haematology / the Education Program of the American Society of Hematology. American Society of Hematology. Education Program*, 520–539. https://doi.org/10.1182/asheducation-2003.1.520

Shchory, M. P., Goldstein, L. H., Arcavi, L., Shihmanter, R., Berkovitch, M., & Levy, A. (2020). Increasing adverse drug reaction reporting-how can we do better? *PLoS ONE*, *15*(8 August), 1–15. https://doi.org/10.1371/journal.pone.0235591

Shimabukuro, T. (2021). Allergic reactions including anaphylaxis after receipt of the first dose of Moderna COVID-19 vaccine — United States, December 14–23, 2020. *American Journal of Transplantation*, *21*(3), 1332–1337. https://doi.org/10.1111/ajt.16516

Shimabukuro T. (2021). *MMWR, Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine — United States, December 14–23, 2020*. https://doi.org/10.1016/j.vaccine.2007.02.064

Shrestha, S., Devbhandari, R. P., Shrestha, A., Aryal, S., Rajbhandari, P., Shakya, B., Pandey, P., Shrestha, R. K., Gupta, M., & Regmi, A. (2021). Adverse events following the first dose of the ChAdOx1 nCoV-19 (COVISHIELD) vaccine in the first phase of vaccine rollout out in

Nepal. *Journal of Patan Academy of Health Sciences*, *8*(1), 9–17. https://doi.org/10.3126/jpahs.v8i1.36242

Siddiqui, M., Salmon, D. A., & Omer, S. B. (2013). Epidemiology of vaccine hesitancy in the United States. *Human Vaccines and Immunotherapeutics*, *9*(12), 2643–2648. https://doi.org/10.4161/hv.27243

Siegrist, C. A. (2007). Mechanisms Underlying Adverse Reactions to Vaccines. *Journal of Comparative Pathology*, *137*(SUPPL. 1), 46–50. https://doi.org/10.1016/j.jcpa.2007.04.012

Singh, A., Khillan, R., Mishra, Y., & Khurana, S. (2022). The safety profile of COVID-19 vaccinations in the United States. *American Journal of Infection Control*, *50*(1), 15–19. https://doi.org/10.1016/j.ajic.2021.10.015

Soldà, G., Barvas, E., Lenzi, J., di Valerio, Z., la Fauci, G., Guttmann, S., Riccardi, R., Fantini, M. P., Salussolia, A., Montalti, M., & Gori, D. (2022). Gam-COVID-Vac (Sputnik V) and Pfizer-BioNTech Vaccines Adverse Events Following Immunization in Patients Affected by Parkinson's Disease and Multiple Sclerosis: A Longitudinal Study. *Vaccines*, *10*(3). https://doi.org/10.3390/vaccines10030370

Subedi, P., Yadav, G. K., Paudel, B., Regmi, A., & Pyakurel, P. (2021). Adverse events following the first dose of Covishield (ChAdOx1 nCoV-19) vaccination among health workers in selected districts of central and western Nepal: A cross-sectional study. *PLoS ONE*, *16*(12 December), 1–15. https://doi.org/10.1371/journal.pone.0260638

Supangat, Sakinah, E. N., Nugraha, M. Y., Qodar, T. S., & Mulyono, B. W. (2021). *COVID-19 Vaccines Programs : adverse events following immunization (AEFI) among medical Clerkship Students in Jember, Indonesia*. *4*, 1–7.

Tobaiqy, M., Elkout, H., & Maclure, K. (2021). Analysis of thrombotic adverse reactions of covid-19 AstraZeneca vaccine reported to Eudravigilance database. *Vaccines*, *9*(4), 1–8. https://doi.org/10.3390/vaccines9040393

Tozzi, A. E., Asturias, E. J., Balakrishnan, M. R., Halsey, N. A., Law, B., & Zuber, P. L. (2013). Assessment of causality of individual adverse events following immunization (AEFI): a WHO tool for global use. Vaccine, 31(44), 5041-5046.

Tsai, P. H., Lai, W. Y., Lin, Y. Y., Luo, Y. H., Lin, Y. T., Chen, H. K., Chen, Y. M., Lai, Y. C., Kuo, L. C., Chen, S. D., Chang, K. J., Liu, C. H., Chang, S. C., Wang, F. der, & Yang, Y. P. (2021). Clinical manifestation and disease progression in COVID-19 infection. *Journal of the Chinese Medical Association*, *84*(1), 3–8. https://doi.org/10.1097/JCMA.0000000000000463

Vigezzi, G. pietro, Lume, A., Minerva, M., Nizzero, P., Gianfredi, V., Odone, A., Signorelli, C., & Moro, M. (2021). *Safety surveillance after BNT162b2 mRNA COVID-19 vaccination : results from a cross-sectional survey among staff of a large Italian teaching hospital*. *92*. https://doi.org/10.23750/abm.v92iS6.12217

Voysey, M., Clemens, S. A. C., Madhi, S. A., Weckx, L. Y., Folegatti, P. M., Aley, P. K., Angus, B., Baillie, V. L., Barnabas, S. L., Bhorat, Q. E., Bibi, S., Briner, C., Cicconi, P., Collins, A. M., Colin-Jones, R., Cutland, C. L., Darton, T. C., Dheda, K., Duncan, C. J. A., … Zuidewind, P. (2021). Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *The Lancet*, *397*(10269), 99–111. https://doi.org/10.1016/S0140-6736(20)32661-1

Walsh, E. E., Frenck, R. W., Falsey, A. R., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Neuzil, K., Mulligan, M. J., Bailey, R., Swanson, K. A., Li, P., Koury, K., Kalina, W., Cooper,

D., Fontes-Garfias, C., Shi, P.-Y., Türeci, Ö., Tompkins, K. R., … Gruber, W. C. (2020). Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. *New England Journal of Medicine*, *383*(25), 2439–2450. https://doi.org/10.1056/nejmoa2027906

WHO. (2020). Covid-19 vaccines: safety surveillance manual - Stakeholders. In *World Health Organization*.

Wise, J. (2021). Covid-19: European countries suspend use of Oxford-AstraZeneca vaccine after reports of blood clots. *BMJ (Clinical Research Ed.)*, *372*(March), n699. https://doi.org/10.1136/bmj.n699

World Health Organization. (2013). Causality Assessment of an Adverse Event Following Immunization (AEFI). *World Health Organization*, 8. http://www.who.int/vaccine_safety/publications/aevi_manual.pdf

World Health Organization (WHO). (2022). Interim recommendations for use of the ChAdOx1-S [recombinant] vaccine against COVID-19 (AstraZeneca COVID-19 vaccine AZD1222, SII Covishield, SK Bioscience). *World Health Organization*, *19*, 1–8. https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-AZD1222-2021.1

Wu, Q., Dudley, M. Z., Chen, X., Bai, X., Dong, K., Zhuang, T., Salmon, D., & Yu, H. (2021). Evaluation of the safety profile of COVID-19 vaccines: a rapid review. *BMC Medicine*, *19*(1), 1–16. https://doi.org/10.1186/s12916-021-02059-5

Yamoah, P., Bangalee, V., & Oosthuizen, F. (2019). Knowledge and perceptions of adverse events following immunization among healthcare professionals in Africa: A case study from Ghana. *Vaccines*, *7*(1), 1–15. https://doi.org/10.3390/vaccines7010028

Younus, M. M., & Al-Jumaili, A. A. (2021). An Overview of COVID-19 Vaccine Safety and Post-marketing Surveillance Systems. *INNOVATIONS in Pharmacy*, *12*(4), 8. https://doi.org/10.24926/iip.v12i4.4294

Zhu, F. C., Guan, X. H., Li, Y. H., Huang, J. Y., Jiang, T., Hou, L. H., Li, J. X., Yang, B. F., Wang, L., Wang, W. J., Wu, S. P., Wang, Z., Wu, X. H., Xu, J. J., Zhang, Z., Jia, S. Y., Wang, B. sen, Hu, Y., Liu, J. J., … Chen, W. (2020). Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. *The Lancet*, *396*(10249), 479–488. https://doi.org/10.1016/S0140-6736(20)31605-6

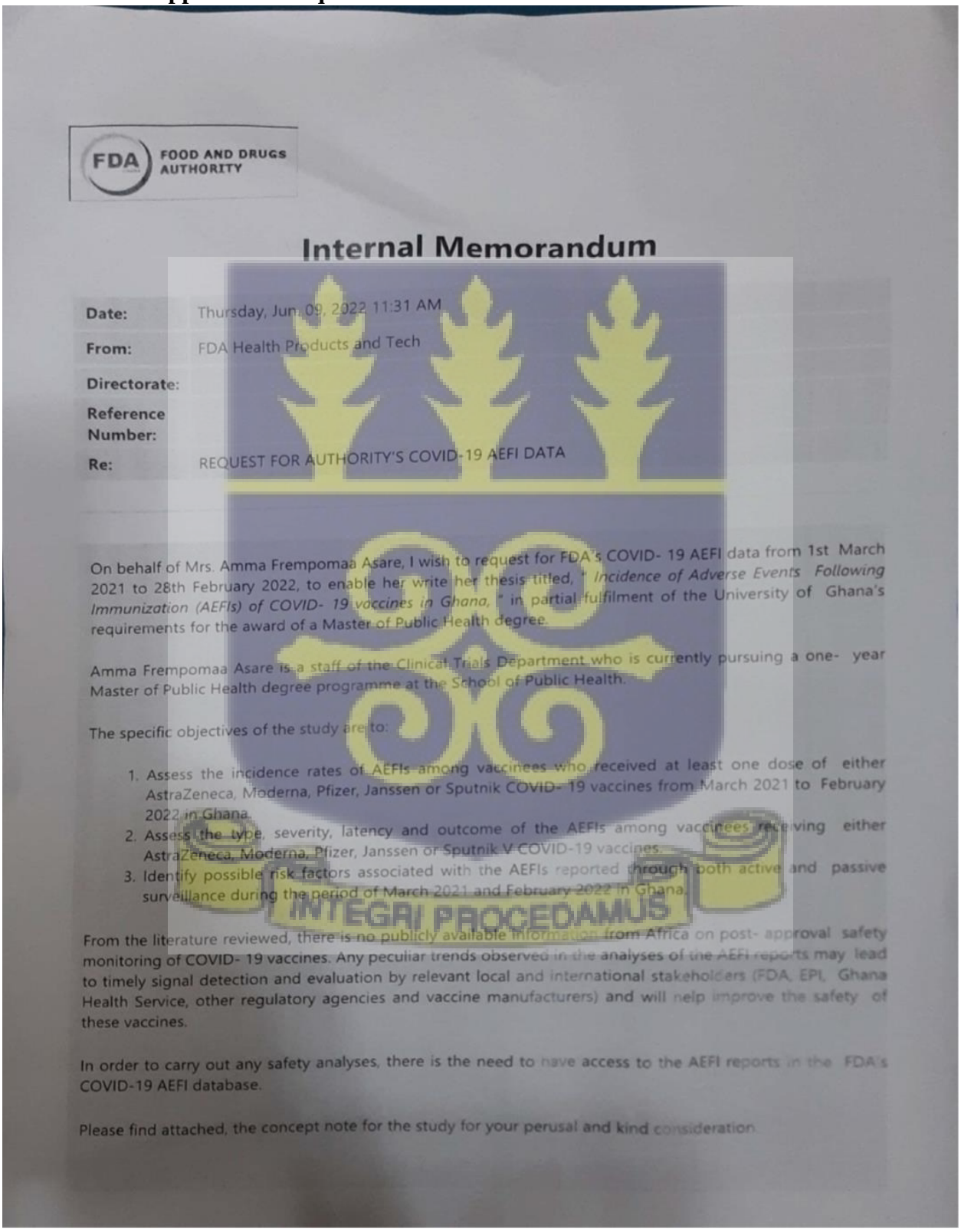
Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R., Niu, P., Zhan, F., Ma, X., Wang, D., Xu, W., Wu, G., Gao, G. F., & Tan, W. (2020). A Novel Coronavirus from Patients with Pneumonia in China, 2019. *New England Journal of Medicine*, *382*(8), 727–733. https://doi.org/10.1056/nejmoa2001017

Zimmermann, P., & Curtis, N. (2019). Factors that influence the immune response to vaccination. *Clinical Microbiology Reviews*, *32*(2), 1–50. https://doi.org/10.1128/CMR.00084-18

Zou, C., Xue, X., & Qian, J. (2022). Characteristics and Comparison of Adverse Events of Coronavirus Disease 2019 Vaccines Reported to the United States Vaccine Adverse Event Reporting System Between 14 December 2020 and 8 October 2021. *Frontiers in Medicine*, *9*(April). https://doi.org/10.3389/fmed.2022.826327

APPENDICES

APPENDIX I Approval of Request to FDA to AEFI Data on COVID-19 Vaccines



FDA FOOD AND DRUGS AUTHORITY

Internal Memorandum

Date:	Thursday, Jun 09, 2022 11:31 AM
From:	FDA Health Products and Tech
Directorate:	
Reference Number:	
Re:	REQUEST FOR AUTHORITY'S COVID-19 AEFI DATA

On behalf of Mrs. Amma Frempomaa Asare, I wish to request for FDA's COVID- 19 AEFI data from 1st March 2021 to 28th February 2022, to enable her write her thesis titled, " *Incidence of Adverse Events Following Immunization (AEFIs) of COVID- 19 vaccines in Ghana,* " in partial fulfilment of the University of Ghana's requirements for the award of a Master of Public Health degree.

Amma Frempomaa Asare is a staff of the Clinical Trials Department who is currently pursuing a one- year Master of Public Health degree programme at the School of Public Health.

The specific objectives of the study are to:

1. Assess the incidence rates of AEFIs among vaccinees who received at least one dose of either AstraZeneca, Moderna, Pfizer, Janssen or Sputnik COVID- 19 vaccines from March 2021 to February 2022 in Ghana.
2. Assess the type, severity, latency and outcome of the AEFIs among vaccinees receiving either AstraZeneca, Moderna, Pfizer, Janssen or Sputnik V COVID-19 vaccines.
3. Identify possible risk factors associated with the AEFIs reported through both active and passive surveillance during the period of March 2021 and February 2022 in Ghana.

From the literature reviewed, there is no publicly available information from Africa on post- approval safety monitoring of COVID- 19 vaccines. Any peculiar trends observed in the analyses of the AEFI reports may lead to timely signal detection and evaluation by relevant local and international stakeholders (FDA, EPI, Ghana Health Service, other regulatory agencies and vaccine manufacturers) and will help improve the safety of these vaccines.

In order to carry out any safety analyses, there is the need to have access to the AEFI reports in the FDA's COVID-19 AEFI database.

Please find attached, the concept note for the study for your perusal and kind consideration.

Seth Seaneke To **Delese Mimi Darko**
Thursday, Jun. 09, 2022 07:19 PM
Comments : Pls for your kind approval

Delese Darko To **Seth Kwaku Seaneke**
Monday, Jun. 13, 2022 11:57 AM
Comments : Approved

Seth Seaneke To **Edwin Nkansah**
Monday, Jun. 13, 2022 06:30 PM
Comments : Pls fyna

Edwin Nkansah To **Yvonne Ayongo Adu Boahen**
Tuesday, Jun. 14, 2022 01:31 PM
Comments : Please for your necessary action Thank you

Yvonne Adu-Boahen To **Amma Frempomaa Asare**
Tuesday, Jun. 14, 2022 12:35 PM
Comments : Amma, Pls fyka

Completed by **Amma Frempomaa Asare**
Tuesday, Jun. 14, 2022 01:30 PM
Comments : Received and well-noted with much thanks.

APPENDIX II Ghana Health Service Ethic Review Committee Approval

GHANA HEALTH SERVICE ETHICS REVIEW COMMITTEE

In case of reply the number and date of this Letter should be quoted.

My Ref. GHS/RDD/ERC/Admin/App 122/479
Your Ref. No.

Research & Development Division
Ghana Health Service
P. O. Box MB 190
Accra
Digital Address: GA-050-3303
Mob: +233-50-3539896
Tel: +233-302-681109
Email: ethics.research@ghs.gov.gh
18th October, 2022

Amma Frempomaa Asare
School of Public Health,
P. O. Box LG 571,
University of Ghana, Legon-Accra, Ghana

The Ghana Health Service Ethics Review Committee has reviewed and given approval for the implementation of your Study Protocol.

GHS-ERC Number	**GHS-ERC: 051/09/22**
Study Title	Incidence of Adverse Events Following Immunization (AEFIs) of COVID-19 Vaccines in Ghana
Approval Date	18th October, 2022
Expiry Date	17th October, 2023
GHS-ERC Decision	**Approved**

This approval requires the following from the Principal Investigator

- Submission of a yearly progress report of the study to the Ethics Review Committee (ERC)
- Renewal of ethical approval if the study lasts for more than 12 months,
- Reporting of all serious adverse events related to this study to the ERC within three days verbally and seven days in writing.
- Submission of a final report after completion of the study
- Informing ERC if study cannot be implemented or is discontinued and reasons why
- Informing the ERC and your sponsor (where applicable) before any publication of the research findings.

You are kindly advised to adhere to the national guidelines or protocols on the prevention of COVID -19

Please note that any modification of the study without ERC approval of the amendment is invalid.

The ERC may observe or cause to be observed procedures and records of the study during and after implementation.

Kindly quote the protocol identification number in all future correspondence in relation to this approved protocol

SIGNED.....
Dr. Naa-Korkor Allotey
(Ag. Head, Ethics & Research Management Department)

Cc: The Director, Research & Development Division, Ghana Health Service, Accra