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Adverse Events Following Immunization (AEFI) of COVISHIELD Vaccination Among Healthcare Workers in Ghana

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Abstract

Objective: To describe the incidence of adverse event following immunization (AEFI) and determine factors that affect the onset and duration of AEFI after COVISHIELD vaccination among healthcare workers.

Design: Prospective cohort study.

Setting: Tertiary healthcare Korle-bu, Ghana

Participant: Three thousand and twenty two healthcare workers over 18 year and not ill were follow-up for both first and second of COVISHEILD vaccination. Healthcare workers filled out an online questionnaire on the previous history of COVID-19 infection, age, sex, occupation or profession, department, and history of allergy.

Primary outcome: The occurrence of the AEFI were identified by self-reporting to the AEFI team members.

Results: A total two thousand one hundred and thirty two healthcare work (70.6%, incidence rate of 706 per 1000 doses) had least one AEFI with 70.3% (incidence rate of 706 per 1000 doses) non-serious and 0.33% (incidence rate of 3.3 per 1000 doses) serious AEFI. Most commonly reported systemic adverse events were headache (48.6%), fever (28.5%), weakness (18.4%) and body pains (17.9%). The estimated median time-to-onset of the AEFI following the first dose vaccination was 19 hours and median time to recovery was 56 hours or two days. Age, sex, previous SARS Cov 2 infection, history of allergies and comorbidity were not significantly associated with the onset and duration of AEFI. However, participants who use paracetamol seem to be significantly protected (HR [95% CL]:0.15[0.14, 0.17]) from having a long duration of AEFI.

Conclusion: In conclusion, the results of our study indicate that the rate of non-serious AEFI is higher and serious AEFI is low with COVIDSHIED vaccination in healthcare workers. The rate of AEFI was high in the first dose as compare to the second dose. The sex, age, previous SARS CoV 2 infection, allergies and comorbidity were not significantly associated with the onset and duration of AEFI.

Strengths and limitations of this study

- This is the largest prospective cohort of AEFI among Healthcare workers, estimating time to occurrence and recovery of AEFI.
- The study had the advantage of collecting information on possible risk factors before the occurrence of AEFI
- The incidence rate of AEFI decreases after the second dose vaccination.
- Previous SARS COV 2 infection and demographic characteristics have no association with AEFI.
- Our study is composed of health workers, who may have different sociodemographic characteristics compared with the general population, which may limit the generalizability of the study

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus -2(SARS COV 2) is an unprecedented public health emergency affecting the lives of everyone and the social fabric of the world. This infection was first reported in Wuhan, China, in December 2019, has rapidly spread across the globe. As of January 2022, COVID-19 has infected over 200 million people and over 4 million deaths [1 2]. To overcome this pandemic, vaccination strategy to prevent COVID-19 infection remains an essential tool as the world searches for effective treamtment. There are many myths surrounding vaccine use, especially in Africa, and any false report on the safety may increase vaccine hesitancy.

As of January 2022, about 53.0% of the world population has been vaccinated with at least one dose of the COVID-19 vaccine [3]. In Ghana, the Expand immunisation program (EPI) has administered over 4 million doses, with the majority being AstraZeneca (COVISHIELD). Only 8.4% of Ghana's population has been vaccinated - 2.6 % fully vaccinated and 5.7% partially vaccinated[3].

COVSHIELD, a DNA vaccine developed by Oxford University and AstraZeneca, consists of a non-replicating chimpanzee adenovirus that carries Deoxyribonucleic acid (DNA) encoding (instructions) for the spike protein of SARS-CoV-2 to the human cells [4]. The DNA is released into the cytoplasm and then to the nucleus, where it is transcribed into the Messager Ribonucleic acid (mRNA). The mRNA is then translated by ribosome into spike protein which then elicits the immunogenic response.

However, this vaccine is without adverse events. World Health Organization (WHO) define an adverse event following immunisation (AEFI) as any untoward medical occurrence following immunisation and which may not have a necessary causal relationship with the usage of vaccines [5]. AEFI are classified into two: serious and non-serious. An AEFI is considered serious if it results in death or is life-threatening, such as inpatient hospitalisation or prolonging existing hospitalisation. An AEFI is deemed to be non-serious when a reaction occurs within a few hours of injection, resolves shortly and poses little or no damage

To our knowledge, there have been no prospective studies of adverse events following immunisation of COVISHEILD vaccine. Most of these studies found in the literature were cross-sectional studies that collected information retrospectively. Thus unable to estimate the duration of the adverse event following COVISHEILD vaccination. We conducted a prospective study to describe the incidence of AEFI and determine factors that affect the onset and duration of AEFI after COVISHIELD vaccination among a cohort of healthcare workers in a Teaching Hospital.

Materials and Methods

Participants and recruitment

The study recruited 4000 healthcare workers across the various department of Korle-bu Teaching Hospital, Korle-bu, Accra. Recruitment took place between 24 February and 2nd march 2021. To be eligible, a Health Care worker had to be 18 and over years, not infected with COVID-19 at the time of recruitment or very ill, had no allergy against the component of the COVISHIELD vaccine and completed the consent form. Healthcare workers were excluded if they tested positive for SARS COV 2 before entering the study or had medical contraindication against the vaccine. Details of the study, PCR COVID-19 testing, and vaccination procedure were explained to each healthcare worker after written informed consent was obtained.

Data Collection and Follow-up

At baseline, healthcare workers COVID-19 status were tested using a GeneXerpt PCR. Healthcare workers filled out an online questionnaire on the previous history of COVID-19 infection, age, sex, occupation or profession, department, and history of allergy. The baseline data were collected and managed using REDCap (Electronic Data Capturing System)[6 7]. Three thousand and twenty-two out of four thousand healthcare workers were followed-up for two months. All participants had both the First and Second dose COVISHIELD vaccine.

The average follow-up time is 56 days (median: 58) after baseline. Participants were asked to record the time of onset and end of AEFI. During the follow-up, participants were asked to report any symptoms after the COVISHIELD vaccination to the hospital AEFI team members. Participants were called daily during the week after vaccination (first or second dose), followed by a weekly call for three weeks.

Outcomes

Study participants were asked to record the occurrence of an AEFI to the AEFI team, which was made of 4 physicians, a pharmacist with experience in pharmacovigilance, and four nurses with experience in AEFI. Participants were called periodically about the occurrence of AEFI by phone. All self-reported AEFI were confirmed based on the WHO operational definition. The AEFI were classified into non-serious and serious AEFI.

Statistical analysis

Statistical analyses were performed using the SPSS software. Kaplan-Meier curves were used to plot the survival function between the group. Survival functions were compared using the log-rank test. Cox proportional models were used to determine the effect of covariates on onset and duration AEFI.

Patient and Public Involvement

Patients or the public were not involved in the design or conduct, or reporting, or dissemination plans of our research.

Results

A total of 3022 staff and students were enrolled on the study. Table 1 shows a summarise of the study participants characteristics. The mean age was 36.2 (SD = 9.7) years. The majority of the participants were between 30 to 39 years. Nurse and Doctors were the most predominant profession. Few of the participants had previous SARS Cov 2 infections.

Adverse event Following Immunisation

The prevalence of AEFI was 70.6% (incidence rate of 706 per 1000 doses) , with the majority being non-serious (70.3%, incidence rate of 703 per 1000 doses) and fewer people with serious AEFI (0.33%, incidence rate of 3.3 per 1000 doses). The occurrence of AEFI was lower in the second dose(20%, incidence rate of 200 per 1000 doses) compared with the first dose (62.4%, incidence rate of 624 per 1000 doses) regardless of the interval between the two doses. 50.1% of participants had first dose AEFI only, 8.1% had second dose AEFI and 12.3% had both first and second dose AEFI. The most symptomatic combination was the flu-like or COVID-like symptoms occurring in both the first and second dose. The

occurrence of AEFI increased with increasing age in the first dose; however, there were no adverse events in the age groups greater than 50 years in the second dose vaccination.

Types of Adverse Events Following Immunisation

The most common local AEFI was pain at the injection site. No other local AEFI such as swelling were reported. The most commonly reported systemic adverse events were headache (48.6%), fever (28.5%), weakness (18.4%) and Feeling body pains (17.9%) (Figure 1). This pattern of AEFI for the second dose was similar to that of the first dose (Figure 1).

Table 1:Study Participants Characteristics

Variables	(N = 3022)
Age group	
< 30.0	814 (26.9%)
30.0 - 39.9	1335 (44.2%)
40.0 - 49.9	528 (17.5%)
50.0 - 59.9	276 (9.1%)
60.0 and over	69 (2.3%)
Sex	
Female	1751 (57.9%)
Male	1271(42.1%)
Profession	
Doctor	916 (30.2%)
Nurse	1053 (34.8%)
Pharmacist	102 (3.4%)
Medical laboratory	93 (3.1%)
Physiotherapy	36 (1.2%)
Dietician	19 (0.6%)
Administrator	116 (3.8%)
Accountant	73 (2.4%)
Heathcare Assistant	41 (1.4%)
Orderly	48 (1.6%)
Security	38 (1.3%)
Clinical Psychologist	48 (1.6%)
Medical student / National Service person	96 (3.2%)
Others	345 (11.4%)
Previous COVID-19 Infection	
No	2559 (84.6%)
Yes	466 (15.4%)
AEFI First Dose	
No	1125 (37.2%)
Non serious	1887 (62.4%)
Serious	10 (0.33%)
AEFI Second Dose	
No	2406(76.6%)
Non serious	617 (20.4%)
Serious	0 (0.0%)
History of allergies	
Yes	304 (10.0%)
No	2718 (90.0%)

Onset and Duration of Adverse Events Following Immunisation

The estimated median time-to-onset of the AEFI following the first dose vaccination was 19 hours, indicating that 50% of the AEFI occurs within a day (Figure 2). Median time to developing the second dose AEFI could not be estimated from the Kaplan mere curve since less than 50% of the study participants experienced AEFI after second dose vaccination. From Figure 3, majority of the participants developed an AEFI within 24 hours (91.1% for first dose and 92.1% for Second dose); while delay onset of AEFI occurred in 1.3% of the participants.

The median time to recovery was 56 hours or approximately two days (Figure 4). The duration of AEFI was significantly shorter in those who reportedly took paracetamol (56 hours) than those who did not take paracetamol (349 hours approximately 14 days) (Figure 5). This indicates that paracetamol reduced the time to recovery by 294 hours (12 days).

Intervention Use in Managing Adverse Events Following Immunisation

Various interventions were administered to help participants who were experiencing AEFI. Sixty-six (66.4%) of AEFI participants reported the use of paracetamol (antipyretic). However, 26% reported not taking any treatment or intervention. Only 2% of the participants reported to the hospital.

Factors Affect Onset and Duration of Adverse Events Following Immunisation

A multivariate cox regression model was used to identify factors that predicted the onset of AEFI independently of the other variables under consideration. Our analysis shows that age, sex, previous SARS Cov 2 infection, history of allergies and comorbidity did not reach statistical significance (Table 2). In the multivariate analysis (Table 3), participants who use paracetamol seem to be significantly protected (HR [95% CL]:0.15[0.14, 0.17]) from having a long duration of AEFI. However, other variables like age, sex, history of allergies, and comorbidity were not statistically significant.

Table 2: Multivariate Adjusted hazard ratio (and 95% confidence interval) for associations between selected characteristics and the onset of AEFI

	Hazard Ratio (95% CL)	P.value
Age (years)	1.00 (0.99 - 1.00)	0.265
Sex		
Female	1	
Male	0.95 (0.87 - 1.05)	0.324
Previous Infection		
No	1	
Yes	1.11 (0.93 -1.19)	0.562
History of Allergies		
No	1	
Yes	0.99 (0.86-1.15)	0.912
Comorbidity		
No	1	
Yes	1.02 (0.87 -1.21)	0.775

Table 3: Multivariate Adjusted hazard ratio (and 95% confidence interval) for associations between selected characteristics and the duration of AEFI

	Hazard Ratio (95% CL)	P.value
Age (years)	1.00 (0.99 - 1. 00)	0.421
Sex		
Female	1	
Male	1.03 (0.94 - 1.13)	0.507
Previous Infection		
No	1	
Yes	1.05 (0.93 -1.19)	0.432
Antipyretic (paracetamol)		
No	1	
Yes	0.15 (0.14 -0.17)	0.00
History of Allergies		
No	1	
Yes	0.99 (0.86 - 1.16)	0.984
Comorbidity		
No	1	
Yes	1.01 (0.85 - 1.18)	0.929

Discussion.

We found that the incidence rate of AEFI was 70.6% after the COVISHIELD vaccination. Non-serious AEFI was 70.3%, and serious or life-threatening AEFI was 0.3%. However, the incidence of AEFI decreases from 62.4% to 20% after the second dose of COVISHIELD vaccination. Our results confirmed previous reports[8-10] on the rare occurrence of serious or life-threatening AEFI and the high prevalence of non-serious AEFI. No serious adverse events were reported after the second dose vaccination of COVISHIELD. The rate of AEFI varies from study to study. The studies from UK (75% [11]), India (57.0%), Togo (75% [12]), and Ethiopian (43.4%[13]) reported finding that were consistent with our results. These differences may be due to ethnicity, genetic factors and study design.

Previous studies in adverse event following COVID-19 vaccination have reported that reactogenicity increases with preexisting natural immunity leading to increased risk of the adverse event among those with previous SARS Cov 2 infection[14 15]. Our hazard ratio of 1.11 (0.93 -1.19), although not significant is consistent with these studies. On the other hand, A survey study by Bardeheir et al [8] found that preexisting natural immunity from SARS CoV 2 infection did not increase the risk of adverse event following immunisation. This study not finding this association is due to the relative small number of study participants with previous SARS Cov 2 infection.

Contrary to previous study, we found that second dose of COVISHIELD was associated with a lower number of adverse events (20%) compared with first dose vaccination. Menni etal (2021) reported that high reactogenicity following the second dose is related to post first vaccination immunogenicity [11].

Our result found that the median time to onset of AEFI was 19 hours after vaccination. Most AEFI started within 24 hours (92.1% for first and 91.8% for second doses). The rate of AEFI tends to decline with

time, with no incidence being recorded after a week. Our results differ from two survey studies that reported that the most adverse events occur within 48 hours [9 10]. The delayed onset of adverse events after 72 hours (three days) was 0.3% for the first dose and 0.1% for the second dose.

Analysing the effect of demographics characteristics on adverse effects following COVISHIELD vaccination, we found no effect of sex and age on adverse effects. Our results indicates that the rate of adverse effects was similar for males and females. This is consistent with previous studies findings [8 9].

The most common systematic adverse event was headaches (48.6% in the first dose and 48.8% in the second). This value was higher than in these studies (27%[10] , 21.0% [13]), but lower than values found in other studies (58.5% [9], 59.0%[16]). The differences in these results are due to different populations and the study design. The studies reporting lower values than our results were survey studies which are usually subject to recall bias. In contrast, the most common local AEFI was pain at the injection site (51.0% in First dose and 52.2% in second dose) and is consistent with the studies found in the literature [8-10 16]. The variation of the pain perception is due to psychological, sociocultural and genetic factors, which may be explained by the difference in the rate of pain at the site of injection from others studies [8-10 16].

The use of antipyretics such as paracetamol to ameliorate adverse events following vaccination was perversive among the healthcare worker. Sixty nine percent (69.0%) of those who experienced adverse events took paracetamol. Paracetamol was effective in reducing the recovery time. However, paracetamol is known to suppress vaccine effectiveness through various mechanisms [17], and unnecessary use of it should be avoided, especially during vaccination.

This prospective study had the advantage of collecting information on possible risk factors before the occurrence of AEFI. Therefore it prevents recall bias once the adverse event has occurred. All participants were from the hospital, therefore, eliminating the hospital as a variation. One strengthen of this study is the large sample size with AEFI. Because of limited resources, we did not collect information on all possible risk factors. In addition, it should be emphasised that we did focus on health care workers, not the general population.

In conclusion, the results of our study indicate that the rate of non-serious AEFI is higher and serious AEFI is low with COVIDSHIELD vaccination in healthcare workers. The rate of AEFI was high in the first dose as compare to the second dose. The sex, age, previous SARS CoV 2 infection, allergies and comorbidity were not significantly associated with the onset and duration of AEFI. However, antipyretic (paracetamol) was able to speed up AEFI recovery, and its use is encouraged in the event of unbearable symptoms.

Contributors:

KM, AS, FA and EO conceived and designed the original protocol. All authors were involved in amending the protocol. K M, YM, ElO, and DD conducted the study, including staff recruitment and data collection. Data entry was carried out by JZ, ELO, HM and EA. KM, DD and HM carried out the data cleaning and preliminary analysis. KM analysed the data. KM wrote the first draft of the manuscript with EO, AS and YM. All authors contributed to subsequent and final drafts. KM and AS are guarantors for the paper.

Competing interests: None declared

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Data sharing statement: The data for this article are available upon reasonable request from the corresponding authors.

Ethics approval: This study received ethics approval from the Korle-bu Teaching Hospital institutional review boards (IRD: KBTH-ADM/00014/2022) in Ghana**.**

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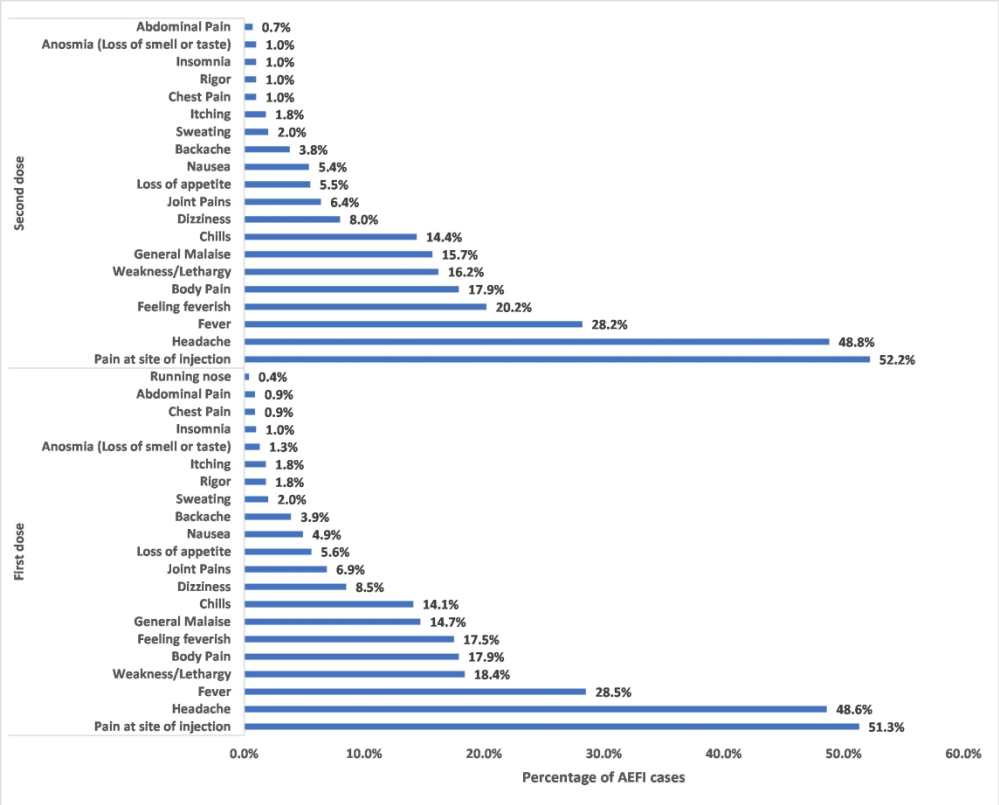

Figure 1: Various of type AEFI after First and Second doses of COVISHIELD Vaccination

276x222mm (240 x 240 DPI)

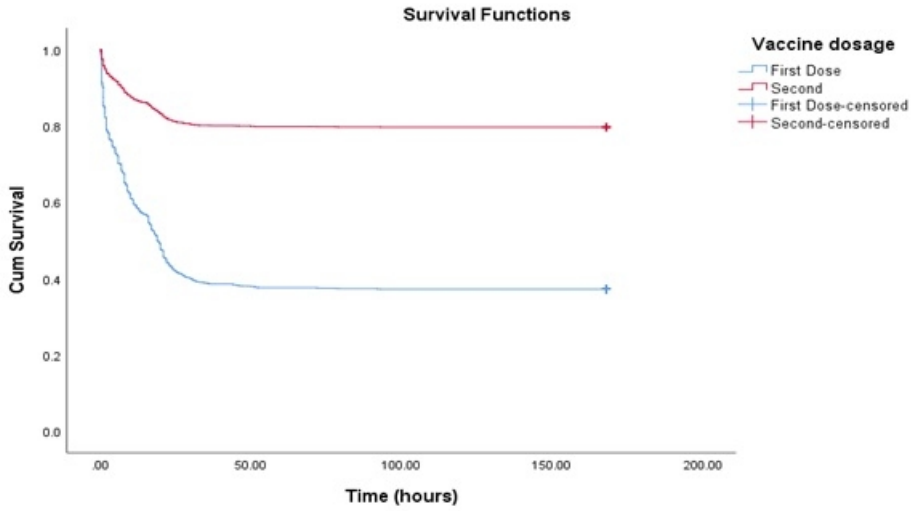

Figure 2: Comparison of the Kaplan mere survival curve of AEFI onset between First and Second dose of COVISHIED vaccination

66x34mm (240 x 240 DPI)

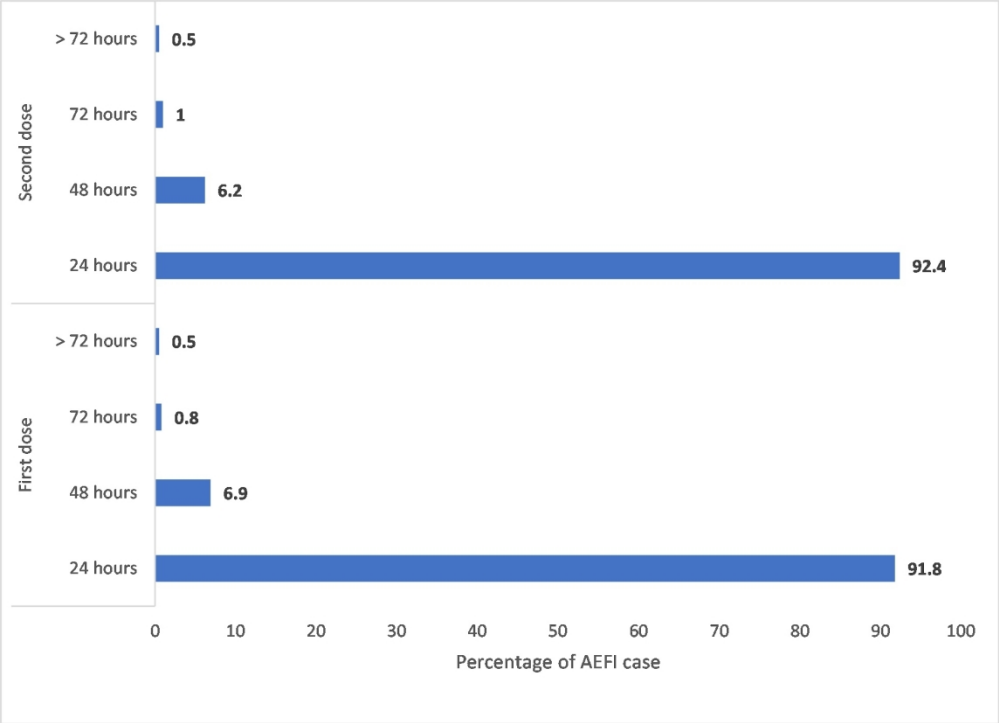

Figure 2: Onset of AEFI by the various time of the day.

207x150mm (240 x 240 DPI)

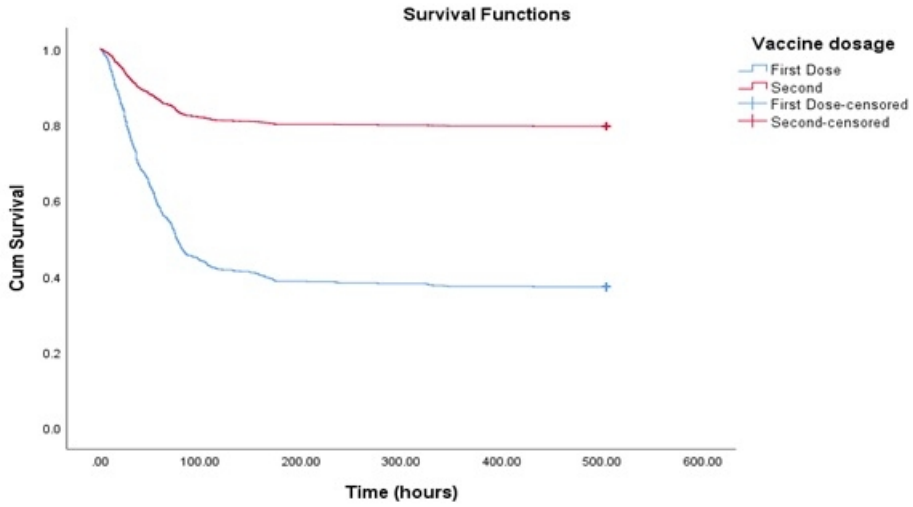

Figure 4: Comparison of the Kaplan meirre survival curve of AEFI duration between First and Second of COVISHIED vaccination

66x34mm (240 x 240 DPI)

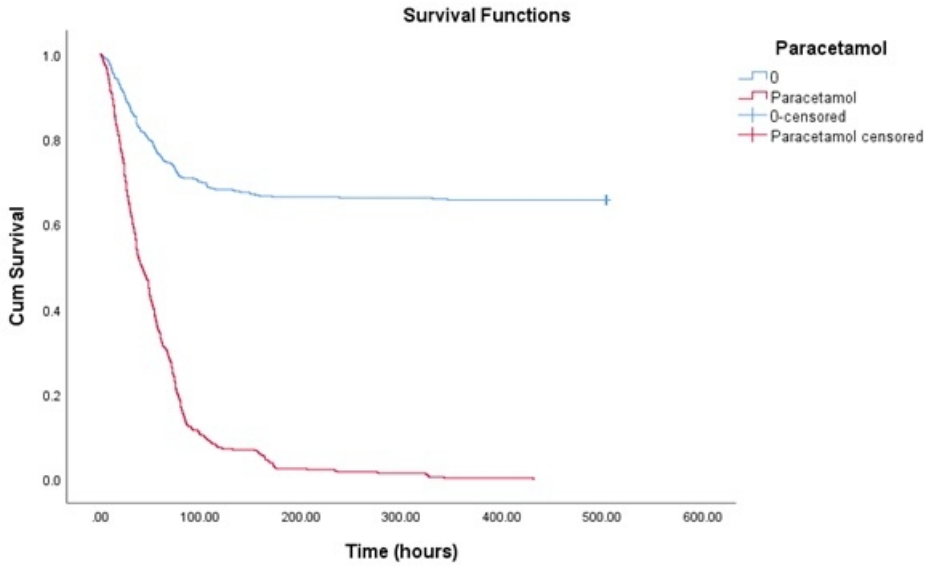

Figure 5: Kaplan mere survival curve shows the effect of paracetamol on the AEFI duration

66x38mm (240 x 240 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1/2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	4
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	4
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	Report numbers of outcome events or summary measures over time	6

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Adverse Events Following Immunization (AEFI) of COVISHIELD Vaccination Among Healthcare Workers in Ghana

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Abstract

Objective: To describe the incidence of adverse events following immunization (AEFI) and determine the factors that affect the onset and duration of AEFI after COVISHIELD vaccination among healthcare workers.

Design: Prospective cohort study.

Setting: Tertiary healthcare Korle-bu, Ghana

Participant: Three thousand and twenty-two healthcare workers at least 18 years of age were followed up for two months after receiving two doses of the COVISHEILD vaccine.

Primary outcome: The occurrence of the AEFI was identified by self-reporting to the AEFI team members.

Results: A total of 3022 healthcare workers had at least one AEFI (incidence rate of 706.0 (95% CI: 676.8 – 736.1) per 1000 doses) with an incidence rate of 703.0 (95% CI: 673.0 – 732.0) per 1000 doses for non-serious and an incidence rate of 3.3 (95% CI: 1.6 – 6.1) per 1000 doses for serious AEFI. The most commonly reported systemic adverse events were headache (48.6%), fever (28.5%), weakness (18.4%) and body pains (17.9%). The estimated median time-to-onset of the AEFI following the first-dose vaccination was 19 hours and the median AEFI duration was 40 hours or two days. Delayed-onset AEFI occurred in 0.3% after first dose and 0.1% after second dose. Age, sex, previous SARS-CoV-2 infection, history of allergies and comorbidity were not significantly associated with the onset and duration of AEFI. However, participants who used paracetamol seemed to be significantly protected (HR 0.15; 95% CI:0.14, 0.17) from having a long duration of AEFI.

Conclusion: The results of our study indicate a high incidence of non-serious AEFI and the rare occurrence of serious AEFI after COVIDSHIELD vaccination in healthcare workers. The rate of AEFI was higher after the first dose than after the second dose. Sex, age, previous SARS-CoV-2 infection, allergies and comorbidity were not significantly associated with the onset and duration of AEFI.

Strengths and limitations of this study

- Our study is a large-scale prospective cohort with comprehensive monitoring of AEFI among healthcare workers.
- The study had the advantage of collecting information on risk factors before the occurrence of AEFI.
- The method of self-reporting AEFI symptoms by healthcare workers is inherently associated with reporting bias and residual confounding.
- Our study is composed of health workers, who may have different sociodemographic characteristics compared with the general population, which may limit the generalizability of the study.
- A prospective cohort with a good response of 75.5% of the original participants for two months

Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an unprecedented public health emergency affecting people's lives and the world's social fabric. This infection was first reported in Wuhan, China, in December 2019 and has rapidly spread across the globe. As of January 2022, COVID-19 has infected over 200 million people and has caused over 4 million deaths [1 2]. To overcome this pandemic, the vaccination strategy to prevent COVID-19 infection remains an essential tool as the world searches for an effective treatment. There are many myths surrounding the use of vaccines, especially in Africa, and any false report on its safety may increase vaccine hesitancy.

COVSHIELD, a DNA vaccine developed by Oxford University and AstraZeneca, consists of a non-replicating chimpanzee adenovirus that carries Deoxyribonucleic acid (DNA) encoding (instructions) for the spike protein of SARS-CoV-2 to the human cells [3]. The DNA is released into the cytoplasm and then to the nucleus, where it is transcribed into the Messager Ribonucleic acid (mRNA). The mRNA is then translated by ribosome into spike protein, eliciting the immunogenic response.

As of January 2022, about 53.0% of the world population has been vaccinated with at least one dose of the COVID-19 vaccine [4]. In Ghana, the Expanded immunization program (EPI) has administered over 4 million doses, with the majority being AstraZeneca (COVISHIELD). Only 8.4% of Ghana's population have been vaccinated - 2.6 % fully vaccinated and 5.7% partially vaccinated[4]. However, this vaccine is not without adverse events. To our knowledge, there have been no prospective studies of adverse events following immunization of the COVISHEILD vaccine. Most of these studies found in the literature were cross-sectional or retrospective cohort studies that could not estimate the duration of the adverse events after a COVISHEILD vaccination. Thus we conducted a prospective study that aims to describe the incidence of AEFI and determine factors that affect the time to onset and duration of AEFI after COVISHIELD vaccination among a cohort of healthcare workers in a Teaching Hospital.

Materials and Methods

Study Design and Setting

This is a prospective cohort study involving healthcare workers to determine the incidence of Adverse events following COVISHIELD vaccination. The study was conducted at Korle-bu Teaching Hospital in Ghana. With a 2000-bed capacity and over seven thousand healthcare workers, the hospital is one of Ghana's treatment centres for SARS-CoV-2 infected patients.

Participants and recruitment

The study recruited 4000 healthcare workers across the various department of Korle-bu Teaching Hospital, Korle-bu, Accra. Recruitment took place between 24th February and 2nd march 2021. After the ethical approval, the study was publicized on all hospital's noticeboards and social media platforms. All healthcare workers in the hospital were sensitized about the new COVISHIELD vaccination.

All eligible healthcare workers were invited to participate in the study after indicating their willingness to be vaccinated by preregistration at the vaccination centres. A healthcare worker was defined as a person employed by the Ghana's Ministry of Health to work in Korle-bu Teaching hospital. To be eligible, a Healthcare worker had to be at least 18 years of age, an employee of Korle-bu Teaching Hospital and have

completed the consent form. Healthcare workers were excluded if they had been partially vaccinated (with any vaccine), tested positive for SARS-CoV-2 infection at the time of recruitment, very ill, refused to be vaccinated, or had medical contraindications or allergies to the vaccine (COVISHIELD). Details of the study, PCR COVID-19 test, and vaccination procedure were explained to each healthcare worker after written informed consent was obtained. COVISHIELD vaccines were provided to all eligible healthcare workers because it was the only COVID-19 vaccine approved by Ghana's Ministry of Health.

Data Collection and Follow-up

All eligible healthcare workers were tested for SARS-CoV-2 infection using a GeneXerpt PCR Machine. Those that were positive for SARS-COV-2 infection were excluded from the study. At the baseline, pre-vaccination online questionnaire was to obtain information about employee identification number, age, sex, occupation or profession, department, previous history of COVID-19 infection, preexisting medical condition (comorbidity), and history of allergy. The baseline data were collected and managed using REDCap (Electronic Data Capturing System)[5 6]. Among the 3237 healthcare workers who completed the pre-vaccination baseline questionnaire, we restricted the analysis to 3022 healthcare workers who took both the first and second doses of the COVISHIELD vaccine. The 3022 healthcare workers were followed up for two months – one month after receiving the first dose and another month after receiving the second dose. Figure 1 shows participants flow in the study.

Vaccination (first or second doses) of the healthcare workers were conducted by the nurses from the Public health unit. All the healthcare workers received two separate doses of 0.5ml of COVISHIELD vaccine intramuscularly. The interval between the first and second doses was 6 to 8 weeks. To verify healthcare workers who received the first dose of the COVISHIELD vaccine, their employee identification number provided at the baseline was used to retrieve their vaccination information from the national vaccination registry. Any unmatched employee identification number indicated that the healthcare worker was not available for the first dose vaccination and was excluded from the study. The second-dose vaccination intake was verified by entering the vaccination card number into the national vaccination registry before follow-up. All healthcare workers whose vaccination status indicated the first dose only from the national vaccination registry were excluded from the study.

During the follow-up, participants were asked to report any symptoms after the COVISHIELD vaccination to the hospital's AEFI team members; and record the time of onset and end of AEFI. Participants were called daily during the week after the first dose of vaccination, followed by a weekly call for three weeks. The daily and weekly calls were repeated after the second dose of vaccination.

Outcomes

Study participants were asked to record the occurrence of the AEFI to the AEFI team, which was made up of 4 physicians, a pharmacist with experience in pharmacovigilance, and four nurses with experience in AEFI. Participants were contacted periodically via phone calls about the occurrence of AEFI. All self-reported AEFI were confirmed based on the WHO's operational definition. The AEFI is defined as any untoward medical occurrence that follows immunization and does not necessarily have a causal relationship with the usage of the vaccine[7]. The AEFI were classified into non-serious and serious AEFI based on the WHO's definition. Non-serious adverse events were defined as any event that is not serious and does not pose a potential risk to the health of the recipient. Serious adverse events were defined as events involving hospitalization, prolongation of existing hospitalization, life-threatening illness, or permanent disability or death**.**

Statistical analysis

Statistical analyses were performed using SPSS software. Kaplan-Meier curves were used to plot the survival function between the group. Survival functions were compared using the log-rank test. Cox proportional models were used to determine the effect of covariates on the onset and duration AEFI.

Patient and Public Involvement

Patients or the public were not involved in our research's design, conduct, reporting, or dissemination plans.

Results

A total of 3022 healthcare workers who received the first and second doses of COVISHIELD vaccine were followed up for two months. The average follow-up time was 56 days (median: 58) after baseline. Table 1 shows the descriptive characteristics of the study's participants. The age of the 3022 healthcare workers ranged from 30 to 39 with a mean of 36.2 (SD = 9.7) years. Nurse and Doctors were the most predominant profession. Almost 15.1% reported having previous SARS-CoV-2 infection, 10.0% had a history of allergies, and 8.0% had preexisting medical conditions.

Adverse event Following Immunization

The incidence of AEFI was 706.0 (95% CI: 676.8 – 736.1) per 1000 doses , with a higher incidence of non-serious (incidence rate of 703.0 (95% CI: 673.0 – 732.0) per 1000 doses) compared with serious AEFI (incidence rate of 3.3 (95% CI: 1.6 – 6.1) per 1000 doses). The occurrence of AEFI was lower in the second dose(incidence rate of 204.1 (95% CI: 188.4 – 220.9) per 1000 doses) compared with the first doses (incidence rate of 627.3 (95% CI: 599.8 – 656.7) per 1000 doses) regardless of the interval between the two doses. 62.8% (1897/3022) of participants had adverse events after the first dose. Among the participants who experienced adverse events after the first dose, 19.6% (372/1897) developed adverse events after second-dose vaccination. Of these participants, most (68.7%, 256/372) developed second-dose adverse events early than their first-dose adverse events. 8.1% (245/3022) had adverse events after the second dose but had no adverse events after the first dose. The most common AEFI symptom combination was the flu-like or COVID-like symptoms experienced by Healthcare workers after the first and second doses. The occurrence of AEFI increased with age in the first dose; however, no adverse events were reported among age groups greater than 50 years during the second-dose vaccination.

Types of Adverse Events Following Immunization

The most common local AEFI was pain at the injection site. No other local AEFI such as swelling, were reported. In the case of systemic adverse events, headache (48.6%), fever (28.5%), weakness (18.4%) and feeling of body pains (17.9%) were the most commonly reported adverse events (Figure 2). The type of AEFIs observed after the first-dose vaccination was clinically similar to that observed after the second-dose vaccination(Figure 2).

Table 1:Study Participants Characteristics

Variables	(N = 3022)
Age group	
< 30.0	814 (26.9%)
30.0 - 39	1335 (44.2%)
40.0 - 49	528 (17.5%)
50.0 - 59	276 (9.1%)
60.0 and over	69 (2.3%)
Sex	
Female	1751 (57.9%)
Male	1271(42.1%)
Profession	
Doctor	916 (30.2%)
Nurse	1053 (34.8%)
Pharmacist	102 (3.4%)
Medical laboratory	93 (3.1%)
Physiotherapy	36 (1.2%)
Dietician	19 (0.6%)
Administrator	116 (3.8%)
Accountant	73 (2.4%)
Heathcare Assistant	41 (1.4%)
Orderly	48 (1.6%)
Security	38 (1.3%)
Clinical Psychologist	48 (1.6%)
Medical student / National Service person	96 (3.2%)
Others	345 (11.4%)
Previous COVID-19 Infection	
No	2559 (84.6%)
Yes	466 (15.4%)
AEFI First Dose	
No	1125 (37.2%)
Non serious	1887 (62.4%)
Serious	10 (0.33%)
AEFI Second Dose	
No	2406(76.6%)
Non serious	617 (20.4%)
Serious	0 (0.0%)
History of allergies	
Yes	304 (10.0%)
No	2718 (90.0%)
Comorbidity	
Yes	242(8.0%)
No	2780 (92.0%)

Onset and Duration of Adverse Events Following Immunization

The estimated median time-to-onset of the AEFI following the first-dose vaccination was 19 hours, indicating that 50% of the AEFI occurs within a day (Figure 3). The median time to developing AEFI after second-dose vaccination could not be estimated from the Kaplan mere curve since less than 50% of the study participants experienced AEFI. From Figure 4, most participants developed AEFI within 24 hours (91.1% for the first dose and 92.1% for the second dose), while the delayed-onset AEFI that started after 7 days, occurred in 0.3% and 0.1% of the participants after administration of first and second doses respectively.

The median duration after the onset of AEFI was 40 hours or approximately two days (Figure 5). First-dose adverse events had a mean duration of 55.5 hours and were similar to the second-dose adverse events (54.9 hours). Regarding the association between the duration of AEFI and vaccine doses, the Log-rank test revealed that vaccine doses had no association with the duration of adverse events. This indicates that AEFIs after the first and second doses were similar in the adverse event duration. Although there was a high number of recoveries after first-dose vaccination, this was proportional to the number of adverse events reported.

Healthcare workers who reportedly took paracetamol (56 hours) had a significantly shorter adverse event duration than those who did not take paracetamol (349 hours, approximately 14 days) (Figure 6). This indicates that paracetamol shortens the duration of adverse events by 294 hours (12 days).

Intervention Used in Managing Adverse Events Following Immunization

Various interventions were administered to help participants who were experiencing AEFI. About Sixty-six percent (66.4%) of AEFI participants reported the use of paracetamol (antipyretic) for treatment. However, 26% reported not taking any treatment or intervention. Only 2% of the participants reported to the hospital.

Factors Affecting Onset and Duration of Adverse Events Following Immunization

A multivariate cox regression model was used to identify factors that predicted the onset of AEFI independently of the other variables under consideration. Our analysis shows that age, sex, previous SARS-CoV-2 infection, history of allergies and comorbidity did not reach statistical significance (Table 2). Table 3 shows the hazard ratio for several factors associated with the duration of AEFI. In the multivariate analysis (Table 3), participants who used paracetamol were significantly protected (HR 0.15; 95% CI: 0.14, 0.17) from having long adverse event duration . However, other variables like age, sex, history of allergies, and comorbidity were not significantly associated with the duration of AEFI recovery.

Table 2: Multivariate Adjusted hazard ratio (and 95% confidence interval) for associations between selected characteristics and the onset of AEFI

	Hazard Ratio (95% CI)	P.value
Age (years)	1.00 (0.99 - 1.00)	0.265
Sex		
Female	1	
Male	0.95 (0.87 - 1.05)	0.324
Previous Infection		
No	1	
Yes	1.11 (0.93 -1.19)	0.562
History of Allergies		
No	1	
Yes	0.99 (0.86-1.15)	0.912
Comorbidity		
No	1	
Yes	1.02 (0.87 -1.21)	0.775

Table 3: Multivariate Adjusted hazard ratio (and 95% confidence interval) for associations between selected characteristics and the duration of AEFI

	Hazard Ratio (95% CI)	P.value
Age (years)	1.00 (0.99 - 1. 00)	0.421
Sex		
Female	1	
Male	1.03 (0.94 - 1.13)	0.507
Previous Infection		
No	1	
Yes	1.05 (0.93 -1.19)	0.432
Antipyretic (paracetamol)		
No	1	
Yes	0.15 (0.14 -0.17)	0.00
History of Allergies		
No	1	
Yes	0.99 (0.86 - 1.16)	0.984
Comorbidity		
No	1	
Yes	1.01 (0.85 - 1.18)	0.929

Discussion.

We found that the incidence rate of AEFI was 706 per 1000 doses after the COVISHIELD vaccination. Non-serious AEFI was 703 per 1000 doses, and serious or life-threatening AEFI was 3.3 per 1000 doses. However, the incidence of AEFI decreases from 627.3 per 1000 doses after first-dose vaccination to 204.1 per 1000 doses after the second-dose vaccination. Our results confirmed the previous reports[8-10] on the rare occurrence of serious or life-threatening AEFI and the high incidence of non-serious AEFI associated with COVISHEILD vaccine. No serious adverse events were reported after the second-dose of COVISHIELD vaccination. The rate of AEFI varies from study to study due to differences in study methodologies, population, and context. The studies from the UK (75% [11]), India (57.0%[12]), Togo (75% [13]), and Ethiopian (43.4%[14]) reported findings that were consistent with our results.

Previous studies in adverse events following the COVID-19 vaccination have reported that reactogenicity increases with preexisting natural immunity leading to an increased risk of adverse events among those with previous SARS-CoV-2 infection[15 16]. Although not significant, our hazard ratio of 1.11 (0.93 -1.19) is consistent with these studies. On the other hand, A survey study conducted by Bardeheir et al [8] found that preexisting natural immunity from SARS-CoV-2 infection did not increase the risk of adverse events following immunization. This study did not find this association due to the relatively small number of participants with previous SARS-CoV-2 infection.

Contrary to a previous study, we found that the second-dose vaccination of the COVISHIELD vaccine was associated with a lower number of adverse events (200 per 1000 doses) than the first-dose vaccination. Menni etal (2021) reported that high reactogenicity following the second-dose vaccination is related to post-first-dose vaccination immunogenicity [11].

Our results found that the median time to onset of AEFI was 19 hours after vaccination. Most AEFIs started within 24 hours (92.1% for the first and 91.8% for the second dose) after innoculation. The rate of AEFI tends to decline with time, with no incidence being recorded after a week. Our results differ from two survey studies that reported that most adverse events occur within 48 hours [9 10]. The delayed onset of adverse events (after seven days) was 0.3% for the first-dose vaccination and 0.1% for the second-dose vaccination.

Analyzing the effect of demographic characteristics on adverse events following COVISHIELD vaccination, we found no effect of sex and age on adverse events. Our results indicate that the rate of adverse events was similar for males and females. This is consistent with the findings from previous studies [8 9].

The most common systematic adverse event was headaches (48.6% in the first dose and 48.8% in the second). Our results indicate that the occurrence of headaches was higher than studies reporting 27%[10] and 21.0% [14] but lower than studies reporting 58.5% [9] and 59.0%[17]. The differences in these results are due to different populations and research methods. Studies reporting lower values than our results were survey or cross-sectional studies which are usually subject to recall bias. In contrast, studies reporting higher values than our results were cohort studies or studies that used both passive and active surveillance

The most common local AEFI was pain at the injection site (51.0% in the first dose and 52.2% in the second dose) and this is consistent with the studies found in literature [8-10 17]. Pain perception is subjective and depends on personal exposures like psychological, sociocultural and genetic factors, which may be explained by the slight differences in our rate of pain at the injection site compared with other studies [8-10 17]. Among those who developed AEFI, most healthcare workers had two or more adverse event symptoms. Although the COVISHIELD vaccine is known to increase the risk of thrombosis [10], our study did not find any coagulopathy like deep vein thrombosis, cardiovascular accident (stroke), neurological deficits, etc.

among healthcare workers. The use of antipyretics such as paracetamol to ameliorate adverse events following vaccination was pervasive among healthcare workers. Sixty-nine percent (69.0%) of those who experienced adverse events took paracetamol. Paracetamol was effective in reducing the recovery time. However, paracetamol is known to suppress vaccine effectiveness through various mechanisms [18], and unnecessary use of it should be avoided, especially during vaccination.

This prospective study had the advantage of collecting information on possible risk factors before the occurrence of AEFI. Therefore it prevents recall bias once adverse events have occurred. All participants were from the hospital, eliminating the hospital as a variation. One strength of this study is the large sample size with AEFI. Because of limited resources, we did not collect information on all possible risk factors. We found that those who took the first dose only, relatively experienced severe symptoms that may deter them from receiving the second dose. The method of self-reporting AEFI symptoms by healthcare workers is inherently associated with reporting bias and residual confounding. In addition, it should be emphasized that we did focus on healthcare workers, not the general population.

In conclusion, the results of our study indicate that the rate of non-serious AEFI is higher and serious AEFI is low with COVIDSHIELD vaccination in healthcare workers. The rate of AEFI was higher in the first-dose vaccination compared to the second-dose vaccination. Sex, age, previous SARS-CoV-2 infection, allergies, and comorbidity were not significantly associated with the onset and duration of AEFI. However, antipyretic (paracetamol) was able to speed up AEFI recovery, and its use is encouraged in the event of unbearable symptoms.

Contributors:

KM, AS, FA and EO conceived and designed the original protocol. All authors were involved in amending the protocol. K M, YM, ElO, and DD conducted the study, including staff recruitment and data collection. Data entry was carried out by JZ, ELO, HM and EA. KM, DD and HM carried out the data cleaning and preliminary analysis. KM analyzed the data. KM wrote the first draft of the manuscript with EO, AS and YM. All authors contributed to subsequent and final drafts. KM and AS are guarantors for the paper.

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Ethics approval: This study received ethics approval from the Korle-bu Teaching Hospital institutional review boards (IRD: KBTH-ADM/00014/2022) in Ghana**.**

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Figure Legend

Figure 1: Participants Flow in the Study.

Four thousand healthcare workers were invited to participate in the AEFI COVISHELD vaccination Study. Three thousand and twenty-two out of the original participant received the first and second doses of the COVISHIELD vaccine after a two-month follow-up. About 978 healthcare workers were excluded from the study: 80 were partially vaccinated, 135 refused vaccinations, 223 missing information, and 540 participants did not meet eligibility criteria.

Figure 2: Various types of AEFI after First and Second doses of COVISHIELD Vaccination.

Study participants presented with various types of adverse events after vaccination. The adverse events observed after first-dose vaccination were similar to those observed after second-dose vaccination. The only local adverse event reported by half (52%, 51%) of the participants was pain at the injection site. The six most commonly reported systematic adverse events in descending order of percentage were headache, fever, weakness, body pains, feeling feverish and generalized malaise.

Figure 3: Onset of AEFIs by time interval after inoculation.

The onset of AEFIs after inoculation was similar in both vaccinations (first and second doses). The majority of adverse events occurred within 24 hours after vaccination. The delayed onset of adverse events was rare (0.1%, 0.3%) among the participants.

Figure 4: Comparison of the Kaplan-Meier survival curves of AEFI onset between first and second doses of COVISHIED vaccination.
A Kaplan-Meier curve that demonstrates the onset of AEFI after COVISHIELD vaccination. After first-dose vaccination, the median time-to-onset of AEFI was 19.0 [95% CI: 18.0 – 20.0] hours. The median time to onset after the second-dose vaccination could not be estimated. There was a significantly higher incidence of adverse events after the first-dose vaccination than after the second-dose vaccination ($p < 0.00$).

Figure 5: Comparison of the Kaplan Meier survival curve of AEFI duration between first and second doses of COVISHIED vaccination.
Kaplan Meier curves show the duration of AEFI after the onset. The estimated median duration of AEFI was 76 hours [95% CI: 70.8 – 81.1] (approximately 3 three days). There was no difference in duration between the first and second dose

Figure 6: Kaplan mere survival curve shows the effect of paracetamol on the AEFI duration.
The participants who took paracetamol had significantly shorter recovery times than those who did not. Statistical significance between this group was evaluated using the log-rank test.

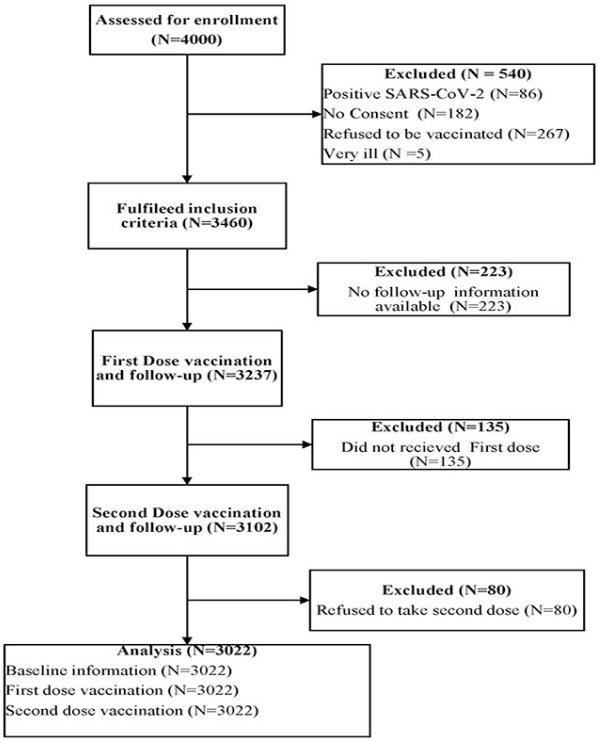

Figure 1: Participants Flow in the Study.

375x375mm (72 x 72 DPI)

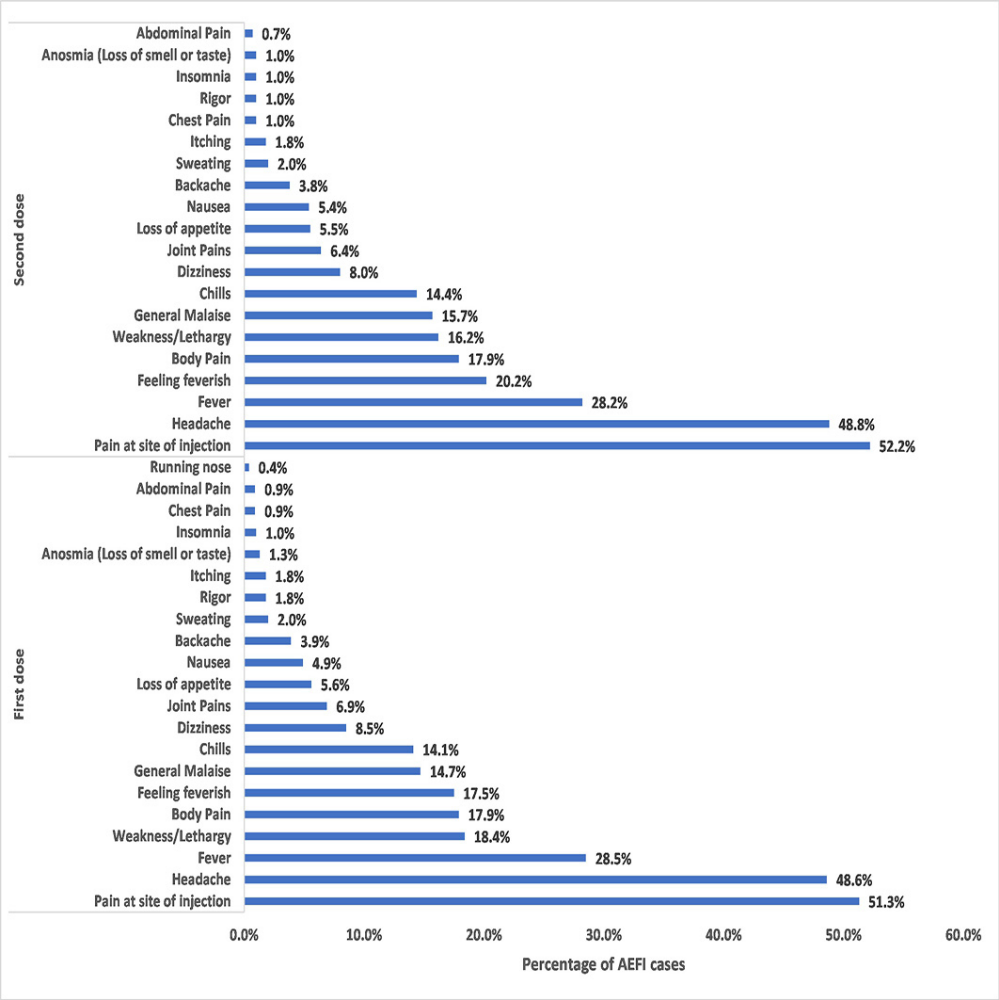

Figure 2: Various types of AEFI after First and Second doses of COVISHIELD Vaccination.

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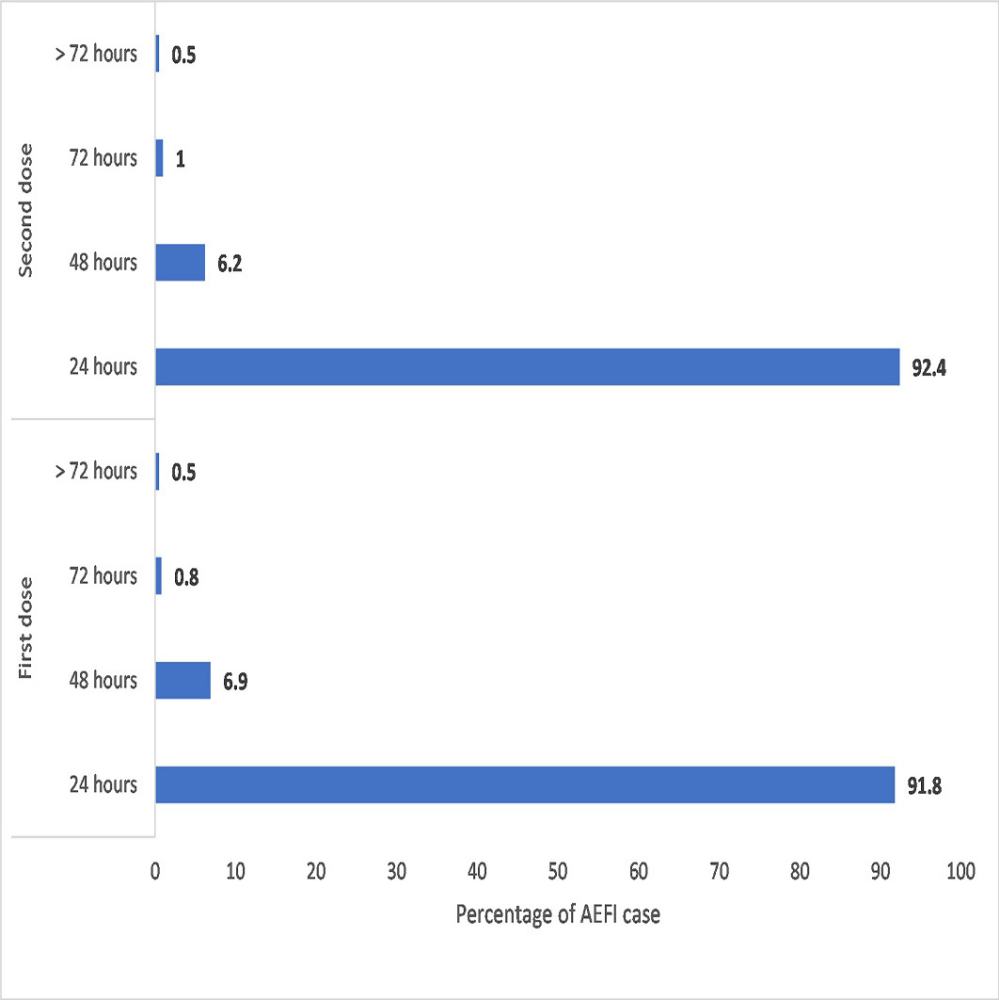

Figure 3: Onset of AEFIs by time interval after inoculation.

375x375mm (72 x 72 DPI)

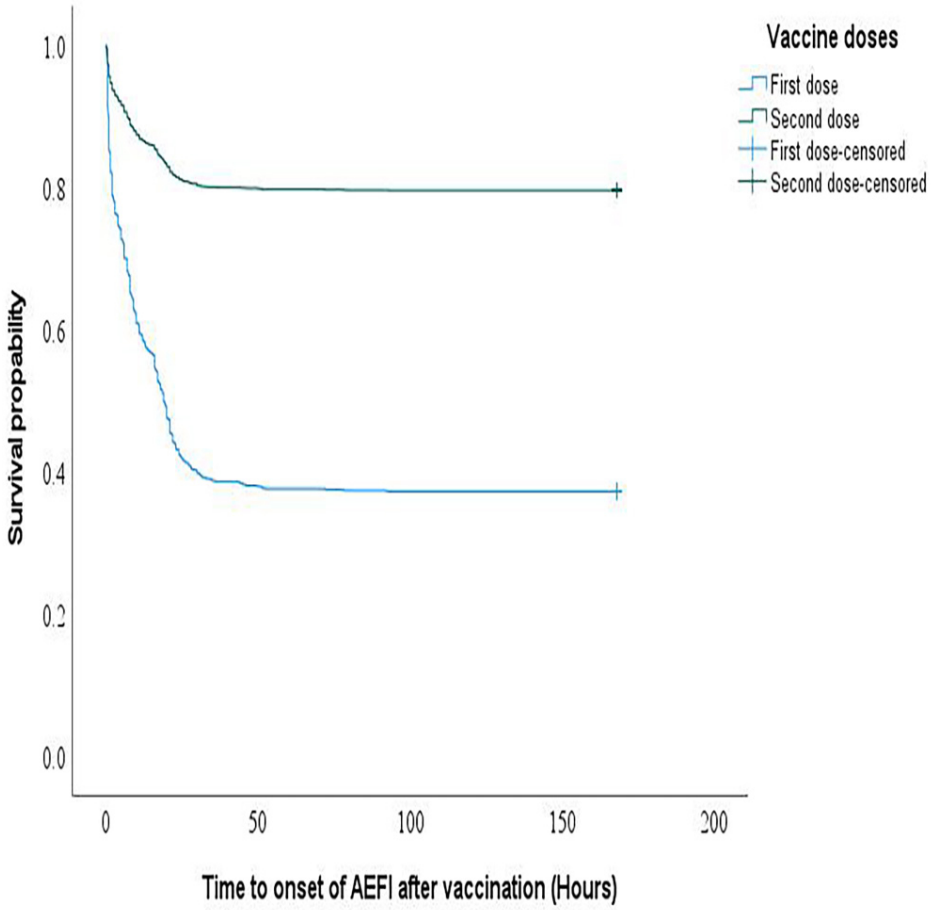

Figure 4: Comparison of the Kaplan-Meier survival curves of AEFI onset between first and second doses of COVISHIELD vaccination.

375x375mm (72 x 72 DPI)

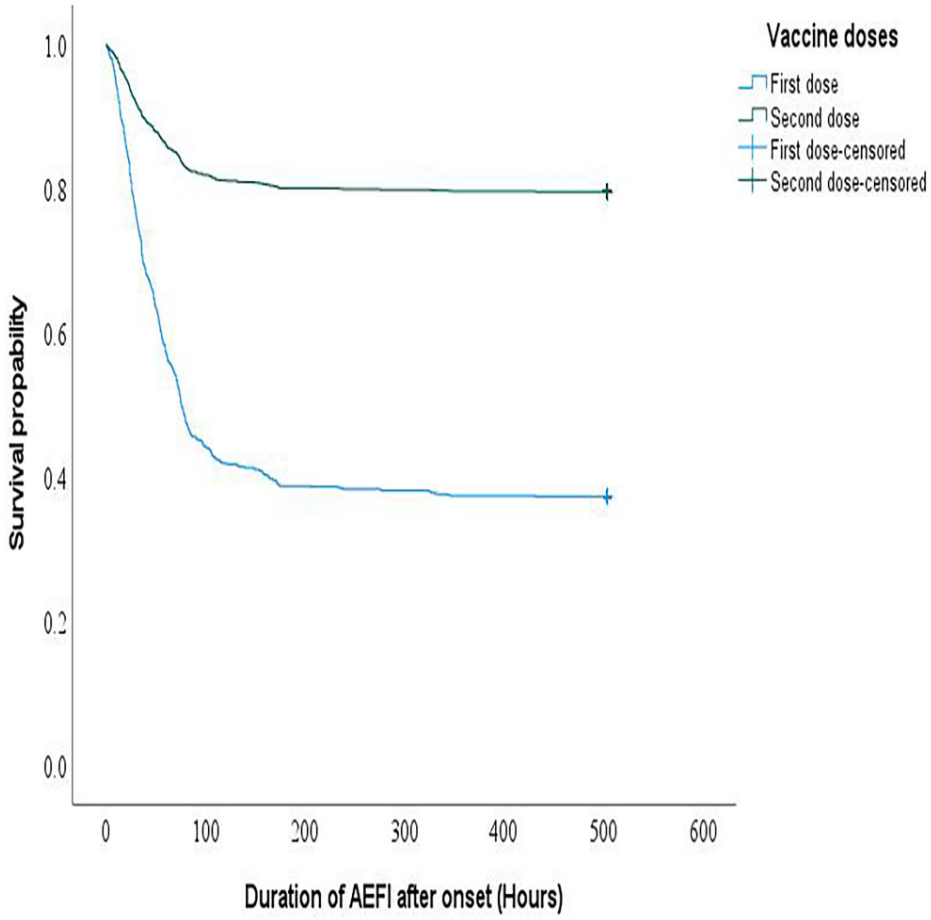

Figure 5: Comparison of the Kaplan Meier survival curve of AEFI duration between first and second doses of COVISHIED vaccination.

375x375mm (72 x 72 DPI)

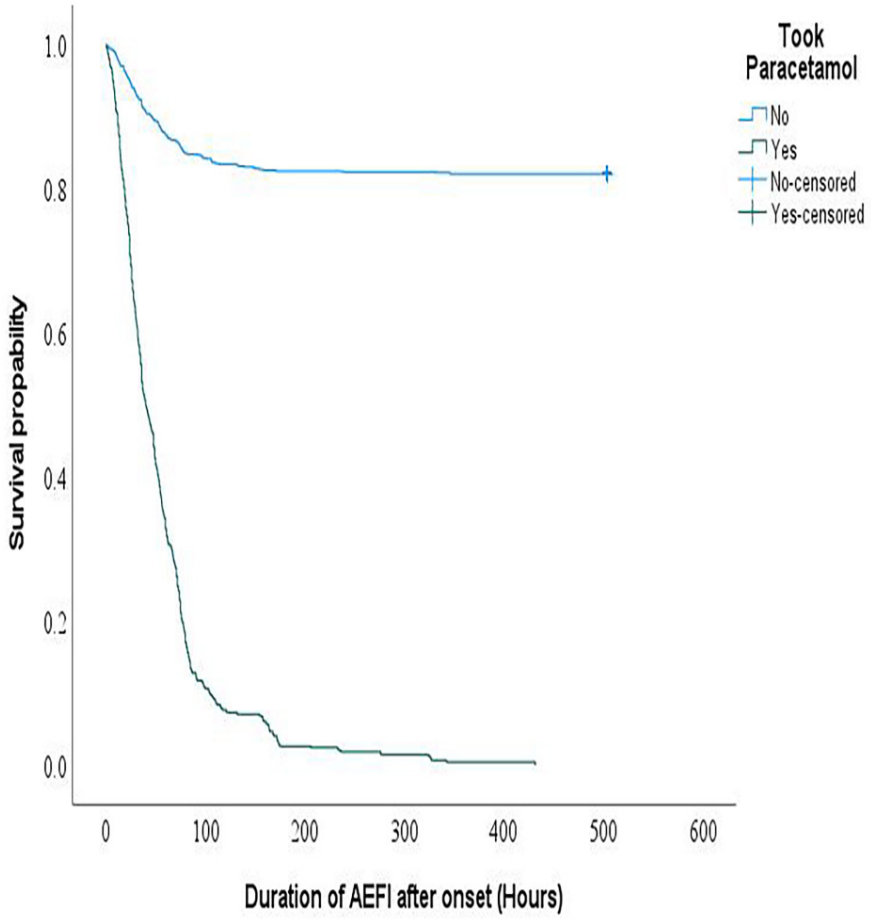

Figure 6: Kaplan mere survival curve shows the effect of paracetamol on the AEFI duration.

375x375mm (72 x 72 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1/2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	3/4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	5
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	5
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	5
Outcome data	15*	Report numbers of outcome events or summary measures over time	5/6

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.