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Adverse events following immunization with Covi-shield ™ vaccine: A descriptive cross-sectional study at a tertiary center, Nepal

Gopal Lama [1], Runa Jha [2], Sagar K Rajbhandari [3], Jenish Neupane [4], Anup Bastola [5]
[1, 2] National Public Health Laboratory, Teku Kathmandu, Nepal
[3-5] Sukraraj Tropical and Infectious Disease Hospital, Teku, Kathmandu, Nepal

Corresponding Author: **Gopal Lama**
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Abstract
Introduction: As the COVID-19 pandemic continues to unfold, rapid global efforts to develop and test vaccines against SARS-CoV-2 have started. Adverse events after immunization are a common issue seen in many vaccines. This study aims at finding the adverse events following the first dose of Covishield™ vaccine administered to the staffs at two health institutions in Kathmandu.
Methods: This was a descriptive cross sectional study conducted among the staffs at National Public Health Laboratory and Sukraraj Tropical and Infectious Disease Hospital, Kathmandu between February to April, 2021. It included 162 participants who had taken the first dose of Covishield™ vaccine. Ethical approval was taken from Nepal Health Research Council. Statistical Package for the Social Sciences were used for analysis.
Results: Various adverse events were seen in 139 (85.8%) participants which were all minor events. None of the participants developed serious adverse events. Very common adverse events experienced were Injection site pain 116 (71.6%), myalgia 76 (46.9%), chills 68 (42%), headache 65 (40.1%), fever 54 (33.3%), dizziness 43 (26.5%) and nausea 20 (12.4%). Similarly, the range of time period from onset to recovery of adverse event was different for different adverse reactions.
Conclusions: The adverse events following first dose of Covishield™ vaccine were all minor reactions with commonest being injection site pain followed by myalgia, chills, headache and fever.

Keywords: COVID-19, Covishield, Injection Site Reaction, Vaccines

Introduction
Since its first identification in Wuhan, China, in December 2019, SARS-CoV-2 has spread worldwide, [1] impacting globally on health, economy and social as well as individual lives, with a substantial number of mortality [2]. Thus, a rapid global efforts to develop and test vaccines against SARS-CoV-2 have started and several of these have shown good safety and immunogenicity [3, 4].
Nepal officially started immunization for COVID-19 on January 27, 2021, with Oxford-Astrazeneca (Covishield™) vaccine [5]. Surveillance of adverse events following immunization (AEFI) is essential to improve vaccine safety, and maintain public trust in immunization programs [6]. Though, safety of this vaccine was demonstrated in a randomized controlled trial, [3] however, its safety and efficacy have not been studied in the context of Nepalese population.
The aim of this study is to find the proportion of adverse reactions after the first dose of Covishield™ vaccine and also to analyze different types of adverse reactions.

Methods
This was a descriptive cross-sectional study conducted at National Public Health Laboratory and Sukraraj Tropical and Infectious Disease Hospital, Kathmandu between February to April, 2021. Ethical Approval was obtained from Nepal Health Research Council (Reference no. 2270). Purposive sampling technique was used and all the employee from these two institutions who had taken the first dose of Covishield™ vaccine and consented to enroll in this study were included in this study. Those employee who did not consent or had not taken the first dose of Covishield™ vaccine were excluded from the study. Participants were followed-up for next four weeks, in person and if not possible, telephonic enquiry were made to some.
In order to avoid bias, various operational definitions were considered based on WHO definitions: [7] any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine were considered AEFI.

Reported adverse events could either be true adverse events – i.e. resulting from the vaccine or immunization process – or coincidental events that were not due to the vaccine or immunization process but was temporarily associated with immunization. Similarly, an AEFI was considered "serious" if it resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/birth defect, or required intervention to prevent permanent impairment or damage. The remaining AEFI were all considered non-serious (minor) events. Similarly, those occurring in >10% were considered very common AEFI, < 10% and ≥ 1% common (frequent), < 1% and ≥ 0.1% uncommon (infrequent) and < 0.1% and ≥ 0.01% rare.

The independent variables in this study were the common adverse events listed in the vaccine information sheet (Injection site pain, swelling, redness, fever, chills, rigor, headache, muscle ache, joint pain, cough, running nose, sore throat, diarrhea, nausea, vomiting, abdominal cramps, loss of appetite, skin rashes, itching, palpitation, dizziness, fainting, shortness of breath). The dependent variables were the previous history of COVID-19 infection and comorbid conditions.

The data were entered in Microsoft excel 2013 and using SPSS version 23, descriptive statistical analysis such as frequencies, percentages and mean were analyzed.

Results

Out of 162 participants who had taken the first dose of Astrazeneca (Covishield™) vaccine, minor adverse events (AEs) were seen in 139 (85.8%) participants, of which 56 were male and 83 were females. None of the participants had serious AEFI (Table 1). Very common AEFI (table 2) were seen in 137 (84.6%) participants with commonest AEFI noted was injection site pain 116 (71.6%) followed by myalgia 76 (46.9 %), chills 68 (42%), headache 65 (40.1%), fever 54 (33.3%), dizziness 43 (26.5%) and nausea 20 (12.4%). Remaining participants had either common AEs such as backache, joint pain, vomiting, malaise, cold extremities, common cold, leg pain and itching, some uncommon AEs or no AEFI at all.

Table 1: Sex distribution of AEFI

Participants	Non-serious AEFI cases n (%)	No AEFI n (%)	Total cases n (%)
Male	56 (34.6)	13 (8.0)	69 (42.6)
Female	83 (51.2)	10 (6.2)	93 (57.4)
Total	139 (85.8)	23 (14.2)	162 (100)

Table 2: Very common AEFI

Local and systemic reactions	N (%)
Pain at injection site	116 (71.6)
Myalgia	76 (46.9)
Chills	68 (42.0)
Headache	65 (40.1)
Fever	54 (33.3)
Dizziness	43 (26.5)
Nausea	20 (12.3)

The onset of AEFI was mainly between 6 – 24 hours with 89.4% developing in the first 24 hours following vaccination. Similarly, 5.3% had developed AEFI between 24 - 48 hours and 5.3% had AEFI after 48 hours of vaccination (Figure 1). Most of these AEFI lasted for less than 72 hours but few had injection site pain lasted for up to 7 days. None of the participants developed serious AEFIs such as anaphylaxis or needed any inpatient treatment.

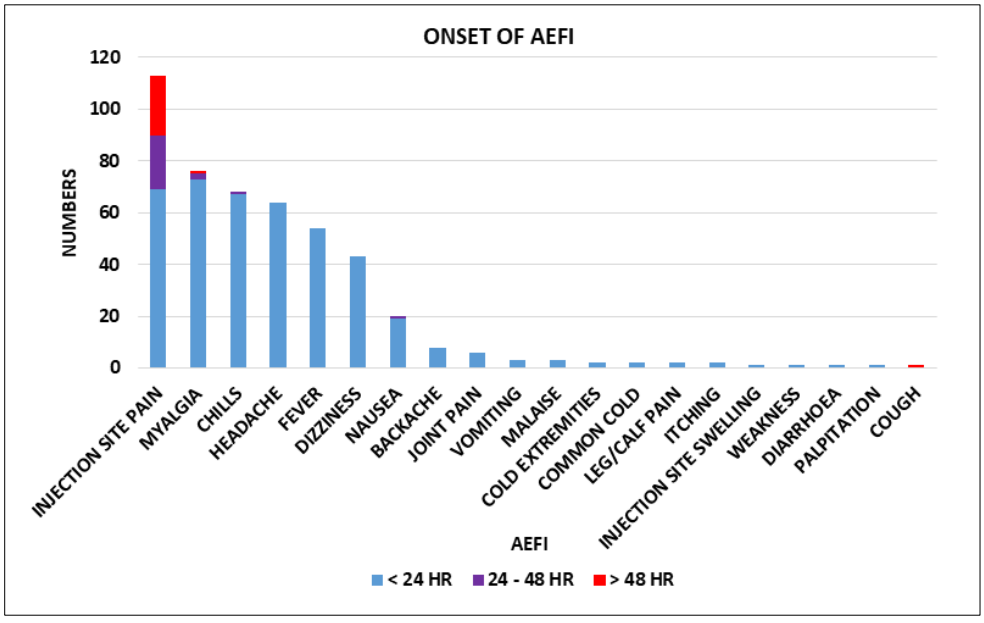

Fig 1: Time frame of onset of different AEFI

Among the total study population, 45 (27.7%) participants had prior COVID-19 infection among which 6 had associated comorbidities. Among the 39 COVID-19 infected only participants, 37 (94.9%) had developed AEFI. Similarly 4 (66.6%) had developed AEFI among the COVID-19 infected participants with associated comorbidities. A total of 19 study participants had associated comorbidities like diabetes, hypertension, hypothyroidism, asthma and ankylosing spondylosis of which 13 had no history of prior COVID-19 infection. Among them, 10 (76.9%) had developed AEFI compared to 3 (23.1%) who did not developed AEFI. Similarly, 104 (64.2%) participants had neither any

comorbidities nor had any history of previous COVID-19 infection and among them, AEFI was seen in 88 (84.6%) participants (Table 3).

Table 3: Proportion of AEFI among different groups of participants

Participants	Total n (%)	AEFI n (%)	No AEFI n (%)
Healthy	104 (64.2)	88 (84.6)	16 (15.4)
Covid-19 infected	39 (27.1)	37 (94.9)	2 (5.1)
Comorbidities	13 (8.0)	10 (76.9)	3 (23.1)
Covid-19 with comorbidities	6 (3.7)	4 (66.6)	2 (33.4)
Total	162 (100)	139 (85.8)	23 (14.2)

Discussion

The COVID-19 disease has emerged as a global crisis within a short period of time with no specific, effective treatment or cure till this date. Many vaccines have been developed rapidly with the belief that immunization with mass vaccination campaign could be the only effective public health interventions to control this pandemic. Since the COVID-19 related vaccines are new, the concern on immunization safety has become as important as the efficacy of vaccines for general public. This study was conducted as a survey to identify adverse events after the first dose of Covishield™ vaccine among participants from a single vaccination center. All the adverse events documented from the time of vaccination to full follow-up period was four weeks. Among the 162 total participants, 85.8% (139) experienced AEFI which is significantly higher compared to the AEFI from other vaccines studies[8] and even much higher to that mentioned in the manufacturer's vaccine sheet.[7] In our study, the proportion of AEFI in female was 51.2% which was higher compared to male (34.6%). This higher incidence in female might be due to the fact that the number of female participants were higher compared to male.

Similarly, one of the early study on Astrazeneca vaccine showed 50% of the participants had injection site pain which is lower compared to our study in which 71.6% had injection site pain. This pain even lasted for up to 7 days in our study, which is contrasting to the previous study. Likewise, in our study, 40.1% had headache and 33.3% had fever which is lower in comparison to that study where 70% and 60%, respectively, had headache and fever [9]. Moreover, none of the participants in our study had immediate development of fever following immunization, with the earliest being 4 hours and majority had onset of fever 8-12 hours post vaccination. Similarly, 47 out of 68 had developed chills between 8-12 hours following immunization.

The AEFI reported in our study may show different results compared to studies done in other countries, which may include other vaccines, [3, 10, 11, 12] or even to manufacturer's safety manuals [13] because this is the first time this vaccine has been given to the Nepalese population and all the previous clinical trials, mostly pre-licensure vaccine trials and studies have been done in other countries. Similarly, this vaccine is authorized for emergency use only [14] and current evidence and studies have been based on certain population or regions only where the vaccine trials and studies had been conducted.

Most of the AEFIs reported can be linked to immunization error or the response to host factors. Improper handling of vaccines, which include contamination during vaccine handling/administration and proper storage including the cold chain maintenance until a subsequent vaccination session or by the use of inappropriate diluents may as well lead to the emergence of adverse events following immunization [15]. Likewise, the vaccine dose as well as the host factor such as age, ethnicity, nutritional factor, immunogenicity of the individuals with regards to the geographical location might impact the development of AEFI among the vaccinated population. Immunization error-related reactions are preventable and immunization workers must be adequately trained and closely supervised to ensure that proper procedures are followed. Thus, immunization safety surveillance is crucial to identify and correct the vaccination errors and related AEFI as they divert attention from the benefit of the immunization program [7].

Careful epidemiological investigation of an AEFI is needed to pinpoint the cause and to correct immunization practices. For this, a large-scale study needs to be conducted in order to obtain a better insight on the vaccine adverse events. However, our study has limitation with smaller sample size and is just a representative data as the participants are from a single vaccination center only.

Conclusions

The AEFIs following first dose of Covishield™ vaccine in this study were all minor adverse reactions. Since immunization could be the most effective way to control the current COVID-19 pandemic, these results showed the vaccine is safe and are encouraging to the general population for adherence to vaccination which could lead to high vaccine coverage rates.

Conflict of Interest

The authors declared no potential conflict of interest with respect to the research, authorship and/or publication of this article.

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