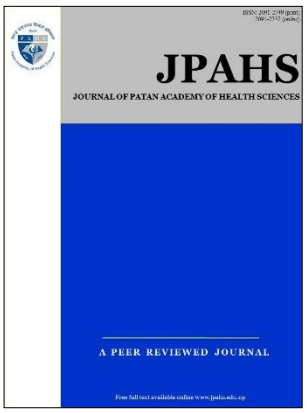

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Adverse events following the first dose of ChAdOx1 nCoV-19 (COVISHIELD) vaccine in the first phase of vaccine roll out in Nepal

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Abstract

Introduction: Nepal started the first phase of COVID-19 vaccination for frontline healthcare workers in January 2021 with the ChAdOx1 nCoV-19 (COVISHIELD) vaccine. We conducted active surveillance of Adverse Effect Following Immunization (AEFI) after the first dose of the vaccine administered at one of the sentinel sites for vaccination, Patan Academy of Health Sciences (PAHS).

Method: All the 5591 first dose 'COVISHIELD' vaccine recipients between 27 Jan -5 Feb 2021 at PAHS, were approached through phone calls to collect data on AEFI. Incidence of common AEFIs in different age groups, gender and those with previous history of COVID-19 were analyzed. Presence of any Adverse Events of Special Interest (AESI) were evaluated.

Result: Out of 5591 vaccines recipient, 3991 (71.3%) responded to the phone call and AEFI was noted in 3394 (85.04%) of them. Minor AEFI was seen in 3391 (84.9%), severe Minor AEFI in 1 (0.02%) and Serious AEFI in 2 (0.05%). Out of 807 vaccine recipients with previous history of COVID-19, 709 (87.9%) had AEFI while of the 3184 with no past history of COVID-19, 2685 (84.3%) had AEFI. However, some of the systemic AEFIs were noted more frequently in those with past COVID-19 infection. A total of 1886 (55.6%) took self-medication for symptom relief, 278 (8.2%) took leave from work while 26 (0.76%) visited health facility for the AEFIs.

Conclusion: Most AEFIs following the first dose of COVISHIELD vaccine were mild and resolved within a few days. Except for one case of anaphylaxis, no other AESI were encountered.

Keywords: adenoviral vector COVID-19 vaccine, AEFI, AESI, COVID-19 vaccine, COVISHIELD, ChAdOx1 nCoV- 19

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Introduction

Coronavirus disease has accounted for 2,664,386 deaths across the globe as of March 17, 2021.[1] There is a possibility of developing herd immunity through acquiring natural immunity via infections. Considering the high morbidity and mortality, the herd immunity as a response strategy for the COVID-19 pandemic response has been flawed by many experts as the death toll could be overwhelming while the impact on the existing health care system and the economy could be disastrous.[2-4] However, the development, and roll-out of the vaccines have opened up the possibility for heard immunity. [4]

As of March 15, 2021, there are 29 vaccines in Phase I trial, 40 in Phase II trial, 27 in Phase III trial, and 13 vaccines have been approved by at least one counry.[5] Nepal officially started first phase of COVID-19 vaccination for frontline health workers on January 27, 2021.[6] COVISHIELD vaccine manufactured by Serum Institute of India and approved in 7 countries[5], was used in the first phase. Safety of this vaccine was demonstrated in Brazil, South Africa and United Kingdom by a randomized controlled trial involving 11363 participants.[7] However, we do not have any published data regarding AEFI of this vaccine in our population. Patan Hospital, Patan Academy of Health Sciences (PAHS) was one of the sites for the vaccination. Adverse events following immunization (AEFI) with the first dose of this vaccine was monitored, through active surveillance. This study presents an analysis of data obtained in the surveillance.

Method

This was a cross-sectional study conducted in February 2021 at Patan Hospital, Patan Academy of Health Sciences (PAHS), Lalitpur, Nepal. The objective of this study was to calculate the incidence of adverse events following immunization (AEFI) observed after the first dose of COVISHIELD vaccine. Ethical approval was taken from Institutional Review Committee (IRC), PAHS.

The frontline health care workers vaccinated in the first phase, who came to Patan Hospital PAHS for vaccination, were enrolled for the study. Data were collected as a part of active surveillance of AEFI. A passive surveillance scheme under the government health system was also in place. The circumstances of the COVID-19 vaccine introduction where a new vaccine is being introduced on a massive scale in a short time interval with inadequate information on serious, rare, and very rare AEFIs, calls for good AEFI surveillance.[10]

The COVISHIELD vaccine was made available by Nepal Government. This vaccine is a recombinant, replication-deficient chimpanzee adenovirus vector vaccine encoding the SARS COV-2 spike glycoprotein. This vaccine contains genetically modified organisms produced in genetically modified human embryonic kidney 293 cells.[11] COVISHIELD vaccine manufactured by Serum Institute of India Pvt Ltd is similar to the COVID-19 Vaccine AstraZeneca (manufactured by AstraZeneca), a ChAdOx1 nCoV- 19 Corona Virus Vaccines and requires two separate doses of 0.5 ml intramuscular (IM) injection, 2nd dose administered between 4 to 6 weeks (up to 12 weeks from studies) after the first dose.[13]

An AEFI is any untoward medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the usage of the vaccine[8] We also looked for presence of any listed Adverse Events of Special Interest (AESI) or any Safety Signals following the vaccine. Signal is the information (from one or multiple sources) which suggests a new and potentially causal association, or a new aspect of a known association, between a vaccine and an adverse event or set of related adverse events, that is judged to be of sufficient likelihood to justify verificatory action.[8] Four tiers of AESI with COVID-19 vaccines have been outlined by SPEAC (Safety Platform for Emergency vACcines).[9]

At the vaccination site, AEFI clinic was established to inform about and to observe for occurrence of any AEFI after vaccination. Following the vaccination, all recipients were observed for 30 minutes. As vaccine recipient were health care workers from different hospitals/health facilities, AEFI focal person for each hospital was designated for quick response. In the event of any severe or serious AEFI, the focal person will divert patient to emergency of Patan Hospital, PAHS.

Information of the health care worker who came for vaccination was taken from the PAHS record section. The records were in electronic form which contained, name, age, sex, name of the institution, and phone number. The vaccine recipients were called after 72 hours of vaccination, through mobile phones. The AEFIs, if any, were recorded in an Excel sheet. Before recording their AEFI, an introduction of the caller was given and the purpose of the query was stated. Basic science faculties with medical background were assigned this task who used a checklist to record the AEFIs. Data from Individuals with missing records, incomplete information or not able to contact were excluded from the analysis.

The collected data from the active AEFI surveillance was analyzed. Independent variables were the common adverse events listed in the vaccine information sheet (Injection site pain, swelling, redness; fever, chills, rigor, sweating, 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, chest tightness).[11] and any other untoward events noted were also documented. The dependent variable was the previous history of COVID-19 infection. Descriptive analysis was done to calculate incidence of AEFI, serious AEFI, and minor AEFI. The common AEFIs in the client who had a previous history of COVID-19 infection were compared with those who did not have COVID-19 infection. A Chi-square test was used to test statistical significance for AEFI in the group who had previous history of COVID-19 versus the group which did not have previous history of COVID-19 infection. A p-value of 0.05 was considered significant.

Result

A total of 5591 vaccine recipients who received the first dose of COVISHIELD vaccine were approached through telephone after 72 hours of vaccination. Out of 5591 only 3991 (71.38%) were reachable and the remaining vaccine recipients either did not respond to the phone call or the phone numbers available from the record were incorrect or unreachable. Of the 3991, there were 1405 (35.2%) male and 2586 (64.8%) female. In this study, AEFI was seen in 3394 (85.04%), minor AEFI in 3391 (84.9%), Serious AEFI requiring hospital admission in 2 (0.05 %) and Severe Minor AEFI requiring medication and a few hours of observation in the hospital in 1 (0.02%). All the three cases (2 serious AEFI and one severe minor AEFI) were females. The five most common Minor AEFIs reported were: Pain at the injection site in 2196 (55%), Fever in 1481 (37.1%), Myalgia in 1201 (30.1%), Lethargy in 1102 (27.6%), and Headache in 1051 (26.3%). The minor AEFIs encountered were categorized as very common, common, and uncommon, based on their percentage of occurrence, Table 1.

Total 1190 (84.7%) males and 2204 (85.2%) females had one or more AEFIs. Chi square test showed no statistically significant difference in the percentage of AEFI seen between males and females (p=0.8). Out of all who had any AEFI, 502 (19.4%) females and 361 (25.6%) males had single symptoms, Figure 1.

The age of the vaccine recipient ranged between 18 to 73 years with a median age of 27 years. Age group was categorized as 18-30 and interval of 10 then after. The chi square test showed that the difference in incidence of AEFI as per age group was statistically not significant (p=0.5).

Of the total 3991 who received the vaccine, 807 (20.2%) had a history of COVID-19 (COVID group) and among them 709 (87.9%) had AEFI. Of the 3184 vaccine recipients with no past

history of COVID-19 (No-COVID group), 2685 (84.3%) had AEFI. The chi square test showed that the difference between two groups was not statistically significant (p=0.4). In both of these groups, most of the vaccine recipients had a single symptom, 699 (22%) in No-COVID group versus 164 (20.3%) in the COVID group. Figure 2.

Out of 3394 who had AEFI, 2876 (84.4%) had symptom onset within 24 hours, 108 (3.1%) had between 24-48 hours, 6 (0.18%) had after 48 hours and 404 (11.9%) were not sure of the exact onset. Similarly, 1660 (48.9%) had symptom resolution between 24-48 hours, 967 (28.5%) had symptom resolution between 48-72 hours, 386 (11.4%) had after 72 hours and 381 (11.2%) were not sure of the time of symptom resolution.

Amongst vaccine recipients, 1886 (55.6%) took over the counter medication for symptom relief. Due to the AEFI 278 (8.2%) took leave from work for a day or more while 26 (0.76%) visited the hospital/health facility for the symptom. Figure 3.

Serious AEFI Case1

A 41 years female with the past history of symptomatic COVID-19 infection, had abdominal cramps and one episode of loose stool within one hour of vaccination. In the second hour, she had a syncopal attack with a significant postural drop in blood pressure and chest tightness without wheeze. The patient was treated in emergency of PAHS with intramuscular Adrenaline 0.5 mg (1:1000), and showed improvement following the treatment, and was discharged after 6 hours of observation. Her next day was uneventful but she presented again after 48 hours with syncope and a significant postural drop in blood pressure. She had no urticarial rashes, cough or wheeze. Her total count, urea, creatinine, electrocardiogram, and echocardiogram were normal. She again received a dose of intramuscular Adrenaline following which she was better but had a recurrence of syncopal attach after 2 hours and received another dose of intramuscular Adrenaline. The patient was then admitted to medical unit of PAHS. She also complained of dizziness and chest tightness on exertion which gradually decreased after 24 hours. Dizziness improved after applying 'deep venous thrombosis (DVT) stocking' while standing and walking. She was discharged after 48 hours with advice for calf muscle squeezing exercise and DVT stocking with an advice to follow up if symptom increases or after one week.

Serious AEFI Case2

A 21-year female presented to emergency of PAHS with abdominal cramps and postural drop within 6 hours post-vaccination. She was treated in emergency with adrenaline intramuscularly and observed for 6 hours and discharged as she was stable. She visited emergency again after 12 hours with the same complaints. On this visit, she had a significant postural drop in blood pressure and was treated with fluid and Adrenaline. Her pain abdomen got better after adrenaline. She was observed for 12 hours in the hospital and discharged. She was stable upon discharge and advised to follow-up if symptom recurred.

Severe Minor AEFI Case 1

A 22-year female presented with urticaria and an episode of syncope within 24 hours of receiving the vaccine. No postural drop in blood pressure or any other abnormal physical signs suggestive of hypoperfusion were observed. Her complete blood count, urea, creatinine, random blood sugar, sodium and potassium was normal. She was also treated with one dose of intramuscular adrenaline, observed for 6 hours, and discharged. No further treatment or follow up visits were required.

There were 10,733 AEFI reported in 3394 vaccine recipients. There were 8075 AEFIs reported amongst 2685 vaccine recipient in No-COVID group and 2744 AEFIs amongst 799 in the COVID group. In the No-COVID group, 1799(22.2%) were local AEFIs and 6276(77.7%) were systemic AEFIs. In the COIVD group501(18.2%) were local and 2243(81.7%) were systemic AEFIs. There was no statistically significant difference between the total incidence of systemic (p=0.7) and local (0=0.8)

AEFIs between the two groups. However, some systemic AEFIs like chills, dizziness, running nose, cough, and abdominal pain were observed more frequently in the COVID group and the difference was statistically significant, Table 2.

Table 1 . Incidence of Minor AEFIs after COVISHIELD (COVID-19) vaccine (N=3991)

Very common (>1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)
Pain at injection site	Joint pain	Sore throat
Fever	Nausea	Abdominal pain
Myalgia	Vomiting	Skin rashes
Lethargy	Sweating	Itching
Headache	Running nose	Shortness of breath
Chills	Swelling at injection site Diarrhoea	Palpitation
Rigor	Cough	Syncope
	Redness at injection site	Chest tightness
	Loss of Appetite	
	Dizziness	

Table 2. Incidence of Systemic AEFIs after COVISHIELD (COVID-19) vaccine in the COVID group (with past history of COVID-19) and Non-COVID group (no history of COVID19)

Symptoms	Non-COVID group N (%)	COVID group N (%)	p-value
Chills	802 (25.2)	215 (26.6)	0.03
Dizziness	281 (8.8)	113 (14.0)	0.00
Running nose	67 (2.1)	15 (1.9)	0.01
Cough	35 (1.1)	11 (1.4)	0.00
Abdominal pain	13 (0.4)	4 (0.5)	0.00

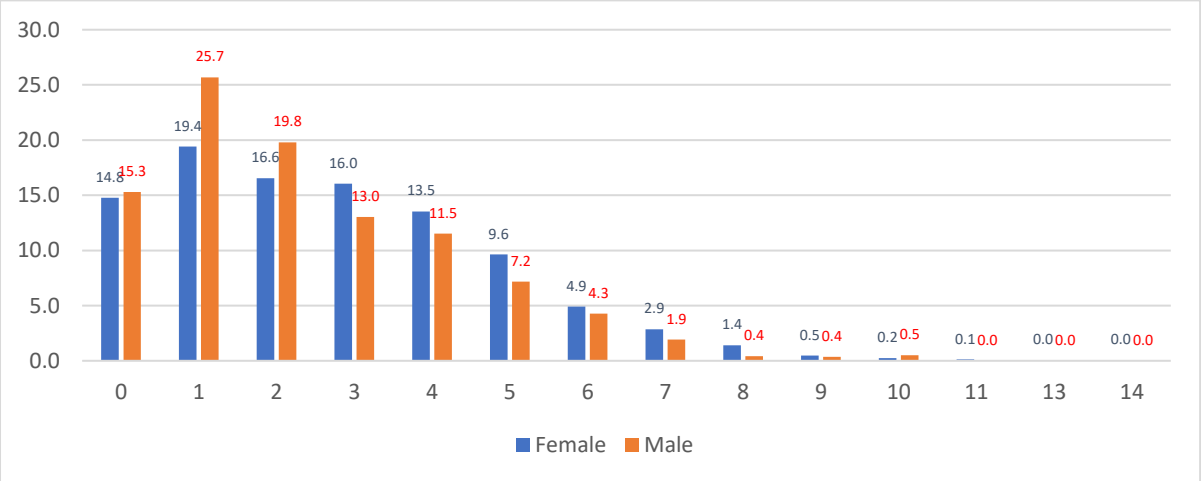

Figure 1. Proportion (Y axis) of total AEFI (X axis) per person after COVISHIELD (COVID-19)vaccine in male and female (N=1190 male and 2192 female)

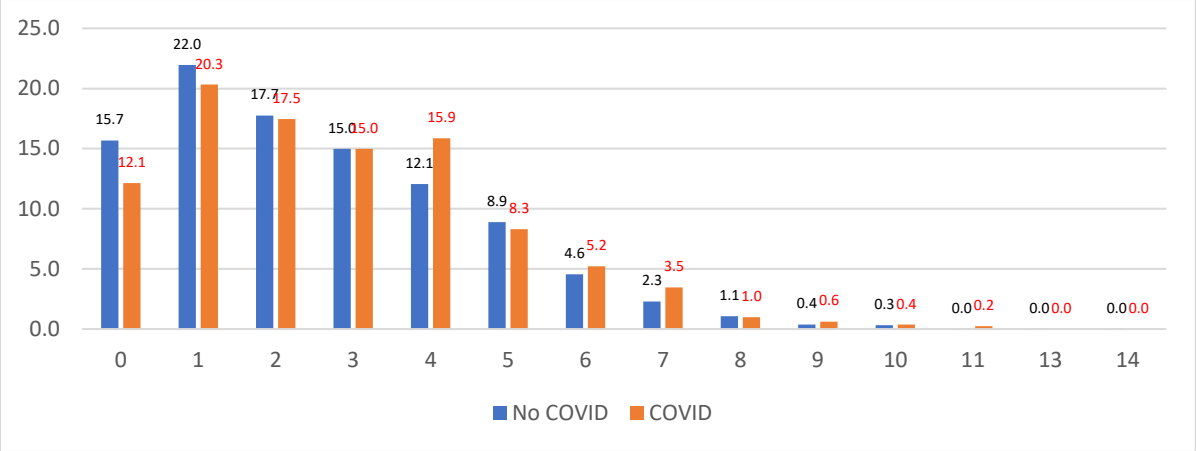

Figure 2. Proportion (Y axis) of total AEFI (X axis) per person after COVISHIELD (COVID-19) in the COVID group (N=709, with past history of COVID-19) and Non-COVID group (N=2685, no history of COVID19)

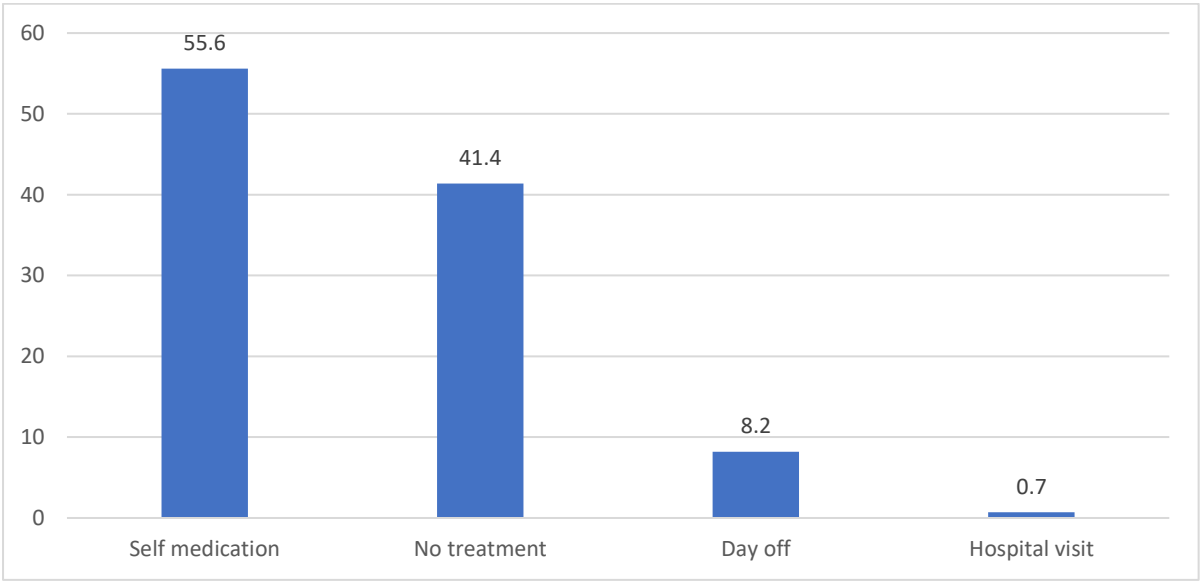

Figure 3. Proportion (Y axis) of vaccine recipient adopting different modality of AEFI management after COVISHIELD (N=3394)

Note: Bar chart represents percentage of incidence, since one person can have two incidence therefore total can be more than 100%.

Discussion

In this study, AEFI was seen in 3394(85.04%). The five most common AEFIs reported were: Pain at the injection site in 2196(55%), Fever in 1481(37.1%), Myalgia in 1201(30.1%), Lethargy in 1102(27.6%), and Headache in 1051(26.3%). The common AEFIs observed in our study and the frequency of occurrence were comparable to the data from the interim analysis of pooled data on adenoviral vector COVID-19 vaccine (Oxford/AZ-ChAdOx1 nCoV-19) from four clinical trials conducted in the United Kingdom, Brazil, and South Africa.[7] The most frequently reported adverse reactions in that data were injection site tenderness (>60%); injection site pain, headache, fatigue (>50%); myalgia, malaise (>40%); pyrexia, chills (>30%); and arthralgia, nausea (>20%).[7] Nausea and injection site swelling reported as 'very common' AEFIs following COVISHIELD vaccine [12] was noted to be only 'common' AEFIs in our survey while dizziness, reported as 'uncommon' AEFI[12] was found to be 'common' AEFI in our cohort. The possibility of some laboratory abnormalities following the adenovirus-based COVID-19 vaccine, like transient neutropenia and lymphopenia

fasting hyperglycemia, have been listed.[14] However, we did not perform any lab tests on our study cohort.

In this survey, Serious Adverse Events (SAEs) were observed in two patients (0.05%) and one (0.02%) patient had Severe Minor AEFI. All three cases had syncopal attacks, two of them had documented postural drop in blood pressure. These cases presenting with syncope and postural drop showed signs of hypoperfusion which can be due to the release of cytokines like IL4, IL17 mediating pro-inflammatory function, and release of interferon-gamma activating inducible nitric oxide synthase (iNOS) responsible for the vasodilatory effect.[15-21] According to the Brighton Collaboration, Anaphylaxis definition, and the SPEAC (Safety Platform for Emergency vACcines) AESI Case Definition Companion Guide for 1st Tier AESI, one of our serious AEFI (Serious AEFI Case 1) meets the level 2 diagnostic certainty for Anaphylaxis.[9,23] The case met one major (cardiovascular) and 3 minor criteria (2 gastrointestinal and one respiratory) for the diagnosis. The symptom onset was within the first two hours of vaccination and had a biphasic course. The onset of anaphylaxis can occur after several minutes but rarely up to two hours of vaccination. Biphasic reactions where symptoms recur 8-12 hours after onset of the original attack, and prolonged attacks lasting up to 48 hours, have been described.[8]

Most of our patients had mild symptoms and the symptoms resolved within a few days which is similar to the finding in the interim analysis of the pooled data.[13] The COVISHIELD was found safe and well-tolerated in phase II/III clinical trial in India and in an interim analysis adverse events after the first dose were comparable to the Oxford/AZ-ChAdOx1 nCoV-19 vaccine. It is reported that no causally related Serious Adverse Events due to the study vaccine has been encountered. [12]Howerver, as of 15 March 2021, a specific form of severe cerebral venous thrombosis associated with thrombocytopenia and bleeding has been identified in seven cases who were vaccinated with COVID-19 AstraZeneca vaccine.[23] There have also been 22 cases reported pulmonary embolism and deep venous thrombosis across United Kingdom and Europe.[24] Therefore, eighteen countries temporarily suspended the AstraZeneca vaccine.[25] No causal relationship has been established between these events and the vaccine till date. The World Health Organization (WHO) has stated that benefits outweigh any potential risk and on March 18, 2021 European Medicine Agency (EMA) came to the same conclusion.[26]

We did not observe a statistically significant difference in the frequency of total AEFI incidence and number of AEFIs in patients with or without previous history of COVID-19 infection. However, a few systemic AEFIs (dizziness, chills, runny nose, cough, and abdominal pain) were noted more frequently in the cohort with a history of COVID-19 infection, and the difference was found statistically significant. Data from the ZOE COVID Symptom Study showed that people with a previous COVID-19 infection are almost twice as likely to experience one or more mild systemic AEFIs compared to people without past COVID-19 infection (33% vs. 19%) from a Pfizer/BioNTech vaccine dose.[27] A significantly higher reactogenicity following SARS CoV-2 mRNA vaccine in those with previous COVID-19 infection was also reported in one another study.[28]

In our study cohort we did not encounter any Neuroinflammatory disorders which is an important Adverse Events of Special interest (AESI). These are reported as very rare events following vaccination with Oxford/AZ-ChAdOx1 nCoV-19 but without an established causal relationship.[11] The data we analyzed did not show any rare or very rare adverse events nor did it point to the occurrence of a new event or signals. Signal detection, verification, and response are important components of AEFI surveillance. Our data was from a single site and signals can best be identified by pooling data from multiple sources.[8]

We have carried out the sentinel surveillance of AEFI at Patan Hospital, PAHS, after the first

dose of the COVISHIELD vaccine in the first phase of vaccine rollout because the safety implications of any new vaccine need to be monitored carefully. It is reported that the information on rare and very rare side effects are insufficient and the vaccine administration on a massive scale with minimum field preparation and training could potentially lead to immunization error-related reactions while insufficient knowledge of potential vaccine quality defects may leave space for possible vaccine component related adverse events.[7] To identify these untoward events active AEFI surveillance via sentinel sites could be very useful.

Conclusion

The active sentinel AEFI surveillance following the first dose of COVISHIELD vaccine in the first phase of vaccination at Patan Hospital, PAHS, Lalitpur, Nepal with a study cohort of 3991 health professionals, showed that the vaccine is safe with the majority of the recipients having only mild AEFIs. Out of 3991 vaccine recipients, 85.04% reported AEFI. There were 10,733 AEFI reported in 3394 vaccine recipients. Minor AEFIs were seen in 85.1% and Serious AEFI was seen in only 0.06% (2 cases) while only 0.03 % (1 case) showed severe minor AEFI. Those with a previous history of COVID-19 infection showed a higher incidence of a few systemic AEFIs compared to those with no past COVID-19 infection. Except for one case of anaphylaxis (Tier 1 AESI) no other AESIs were observed, no deaths encountered nor any safety signals identified.

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Conflict of Interest
None

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Author Contribution
All author contributed substantially. Concept, design, planning- all authors (SS, RD, AS, SA, PR, BS, PP, RS, MG, AR); Literature review- SS, AS; Data Collection/analysis: RD, SA, PR, BS, PP, RS, MG, AR; Draft manuscript: all authors Revision of draft: SS, AS; Final manuscript: all authors; Accountability of the work: all authors.

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