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A study to determine adverse event following immunization using COVISHIELD vaccine for prevention of COVID-19 infection in a field practice area of urban health center

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ABSTRACT

Background: The COVID-19 vaccination program was introduced in India on 16 January 2021. The Government-issued fact sheet was the only source of information regarding Adverse Events Following Immunizations (AEFIs) for these vaccines. **Aims and Objectives:** The objective of this study was to assess the AEFI reported following COVISHIELD vaccination in an urban health center. **Materials and Methods:** The spontaneous reporting method was used for data collection for 3 months. A data collection form was designed to collect the data from the study population who reported adverse events. Collected data were analyzed and categorized by severity and seriousness. The causality assessment was done using the World Health Organization's causality assessment algorithm. **Results:** A total of 3,486 doses of COVISHIELD vaccine were administered at the study site during the study period. In all, 306 AEFIs were reported from 190 subjects with an incidence rate of 5.45%. The majority of the subjects with AEFIs belonged to the age group of 18–45 years. Out of the total 306 AEFIs, 287 AEFIs were expected as per the fact sheets. Most of the AEFIs (59.47% [n = 182]) were observed at the system organ class of "General disorders and administration site conditions." After the causality assessment, out of 433 AEFIs to COVISHIELD vaccine, 94.22% (n = 287) of events were categorized to have "consistent causal association with immunization." All of them recovered from their adverse events without any sequelae. **Conclusion:** Most common AEFI after COVISHIELD vaccination was found to be general disorders and administration site conditions. No severe AEFI reported.

Key words: AEFIs of COVID-19 vaccine; COVID-19 vaccination; COVISHIELD

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INTRODUCTION

Adverse events following immunization (AEFI) are defined as any untoward medical occurrence that follows immunization and that does not necessarily have a causal relationship with the usage of a vaccine.[1] The AE may be any unfavorable or unintended sign, abnormal laboratory finding, symptom, or disease. In India, two COVID-19 vaccines received Emergency Use Authorization on January 3, 2021. These were COVISHIELD (AstraZeneca's vaccine manufactured by Serum Institute of India Private Limited, Pune, India) and Covaxin (Bharat Biotech Limited, Hyderabad, India). The vaccines were in phase III clinical trials.[2,3]

Healthcare worker and frontline workers were given the first priority for vaccination initially as they were at the highest risk of exposure. From March 2021, the second phase of vaccination was started. Vaccines were made available first for people aged above 60 and above 45 with comorbidities. This was expanded on April 1, 2021, to cover everyone above 45 years. In the third phase, vaccines

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were made available for people above 18 years of age. The vaccination program started at the immunization clinics at hospitals, followed by vaccination drives hosted at outreach sites. The guideline document released by the Government of India mentioned management plans for AEFI and recording of the same through the COVID Vaccine Intelligence Network (CoWIN) software.[4,5]

The Government of India constituted the National Expert Group on Vaccine Administration for COVID-19 to oversee all aspects of the introduction of the COVID-19 vaccine in India. Two vaccines that were approved for restricted use in an emergency situation by the Central Drugs Standard Control Organization in India are COVISHIELD™ (AstraZeneca's vaccine manufactured by Serum Institute of India) and COVAXIN™ (manufactured by Bharat Biotech Limited).[6]

As per the operational guidelines, each beneficiary needs to be observed at the immunization center for a minimum of 30 min for AEFIs or AEs of special interest. After 30 min, the beneficiaries are free to report the development of any AEs to the vaccination center whenever they develop any.[7] This study was conducted with an objective to assess the AEs following COVID-19 vaccinations at the study site.

Aims and objectives

The objective of this study was to assess the adverse event following immunisation reported following COVISHIELD vaccination in an urban health centre.

MATERIALS AND METHODS

The study site was an urban health center under a tertiary care teaching hospital. The study was a prospective observational Study. Study duration was 90 days (March 12, 2021 to July 29, 2021).

Ethical clearance

Ethical clearance was taken from the Institutional Ethical Committee (letter number GMCD/IEC/Community-medicine/02/2021, dated 18/04/2021).

The participants included were the vaccination beneficiaries who reported any AEs following COVID-19 vaccination using COVISHIELD vaccine. Every vaccinated subject at urban health center was observed for a period of 30 min following vaccination. Posters of the possible AEFIs were made available in the vaccination and observation area to educate the beneficiaries on possible AEFIs. Furthermore, the vaccination team informed the beneficiaries to report back if they develop any kind of AEs. Information such as demographic details (age, gender, and contact details) of the beneficiary, date and time of vaccination, vaccine details (name, batch number, and dose number), details of pre-existing medical condition, and details of AE was collected in the suitably designed data collection form after taking informed consent from each beneficiary. All the reported events were categorized to its system organ classification (SOC) as per the Medical Dictionary for Regulatory Activities SOC classification. The reported events were subjected to causality assessment as per the new algorithm developed by the safety and vigilance department of the WHO.[8] Furthermore, reported events were categorized by severity, seriousness, type of medical intervention for the AEs, and the outcome of the event.

SPSS version 22 was used for data analysis using proportion methods, and central tendencies.

RESULTS

The total number of COVISHIELD vaccine doses administered at the study site was 3486. About 1925 (55.22%) beneficiaries of the COVISHIELD™ vaccine completed their vaccination schedule (2 doses) and 1,561 (44.77%) have partially completed (one dose) their schedule.

The number of subjects who reported AE was 190 and the calculated incidence rate of AEs following COVISHIELD vaccination was 5.45% (total number of subjects who developed AEFIs/total number of beneficiary's × 100).

Females (n=140) developed more AEFIs when compared with males (n=50). In all, 1.09% of the study population developed AEFIs during the observation period following the vaccination. The majority of the study population with AEFIs belong to the age group of 18–45 years (83.45%, n=159) followed by 46–60 years (7.8%, n=14) and above 60 years (8.75%, n=17; L). The incidence of AEFI occurrence in the age group of 18–45 years was 5.67% (159 AEFIs in 2800 beneficiaries). The incidence of AEFIs in the age group of 46–60 years was 6.57% (14 AEFIs in 213 beneficiaries). Similarly, the incidence of AEFIs in the age group of above 60 years was 3.59% (17 AEFIs in 473 beneficiaries). A total of 167 subjects developed AEFIs within 24 h, 12 between 24 and 48 h, five between 48 and 72 h, 22 between 72 and 96 h, and 1 after 4 days. A detailed description of time temporal relationship of vaccine with AEFIs is given in Table 1.

a: AEFI reactions that occurred according to WHO factsheet for Covishield first dose[8]

b: AEFI reactions that occurred according to WHO factsheet for Covishield second dose.[8]

A total of 306 AEFIs occurred among 190 subjects, that is, 1.6 AEFIs per person with a range of 1–7 AEFIs. A total of 52.64% (n=100) of beneficiaries reported single AE,

Table 1: Timeline of manifestation of AEFI after COVISHIELD vaccination

Time (h)	COVISHIELD™ (n=190)									
	1st dose (n=183)					2nd dose (n=09)				
	Subjects who developed AEFIs		Number of AEFIs (n=297)[a]		Total number of AEFIs after 1st dose (n=297)[a]	Subjects who developed AEFIs		Number of AEFIs (n=09)[b]	Total no. of AEFIs after 2nd dose (n=09)[b]	
	Male (n=47)	Female (n=136)	Male (n=64)	Female (n=233)		Male (n=3)	Female (n=4)	Male (n=3)	Female (n=4)	
≤30 min	6 (3.3%)	27 (13.8%)	8	22	30	2 (1.1%)	3 (1.5%)	4	5	9
≥30 min to 24 h	33 (17.1%)	96 (50.2%)	51	195	246	–	–	–	–	–
25–48 h	5 (1.9%)	7 (4.5%)	4	12	16	–	–	–	–	–
49–72 h	1 (0.4%)	4 (1.5%)	0	3	3	–	–	–	–	–
73–96 h	2 (0.7%)	–	1	0	1	–	–	–	–	–
≥97 h	–	1 (0.4%)	0	1	1	–	–	–	–	–

[a]AEFI reactions that occurred according to WHO factsheet for Covishield first dose.[8] [b]AEFI reactions that occurred according to WHO factsheet for Covishield second dose[8]

37.2% (n=71) of beneficiaries reported 2 AEs, 8.8% (n=17) of beneficiaries reported 3 AEs, 1.36% (n=2) of beneficiaries reported 4 AEs.

Out of the total 306 AEFIs, 287 AEFIs were expected as per the fact sheets. Out of the AEFIs specified in the fact sheet, 278 AEFIs were reported with the first dose of COVISHIELD™ and nine with the second dose of COVISHIELD™. A detailed description of reported AEFIs is presented in Figure 1.

Most of the AEFIs [63.41% (n=182)] were observed at the SOC of "general disorders and administration site conditions" and the least affected SOC was "blood and lymphatic system disorders" (n=1). The details of the SOC implicated in AEFIs are presented in Table 2.

After the causality assessment, out of 306 AEFIs to COVISHIELD™ vaccine, 94.22% (n=288) of events were categorized to have "consistent causal association with immunization," which included 227 (78.98%) events of "vaccine product-related reaction" and 61 (15.24%) events of "immunization anxiety-related reaction."

An estimated 96.42% of the AEFIs were mild, three events were moderate, and one event was severe. More than half of the study population (57.99%) sought medical attention due to AEs, and among them, the majority (91.66%, n=143) had telephonic contact with the doctor and the rest (8.44%, n=16) visited the health center. None of the events fulfilled the criteria to become a serious event. Data on medical attention were collected, while the AEFI was reported spontaneously, and all of them voluntarily decided to obtain medical attention for their AEFIs. All the study population recovered from their AEs without any sequelae.

Table 2: System organ classification of adverse events

System organ classification	COVISHIELD™	
	1st dose	2nd dose
Blood and lymphatic system disorders	1	–
Cardiac disorders	1	–
Eye disorders	2	–
Gastrointestinal disorders	14	–
General disorders and administration site conditions	182	9
Psychiatric disorders	2	–
Skin and subcutaneous tissue disorders	5	–
Nervous system disorders	28	–
Musculoskeletal and connective tissue disorders	42	–
Respiratory, thoracic, and mediastinal disorders	1	–
Total	278	9

DISCUSSION

Both the vaccines introduced in India had undergone the multistage testing process, including phase III clinical trials that involved thousands of subjects to ensure the safety of the vaccines.[9] A total of 184Cr doses of COVID-19 vaccines were administered in India through more than 52,000 vaccination sites. AEFI reported on COWIN portal consisted of 0.005% of total doses administered.[10] A total of 602,990 individual case safety reports of AEs to COVID-19 vaccines were recorded by VigiFlow of the Uppsala Monitoring Centre (the WHO collaborating center for international drug monitoring).[11] Europe reported the majority of the AEFIs to the global database, contributing to 73% of the total reports followed by 17% from America and 6% from Asia.[12,13]

Most of the AEFI were observed in the age group of 18–45 years, and an incidence of AEFI occurrence in this

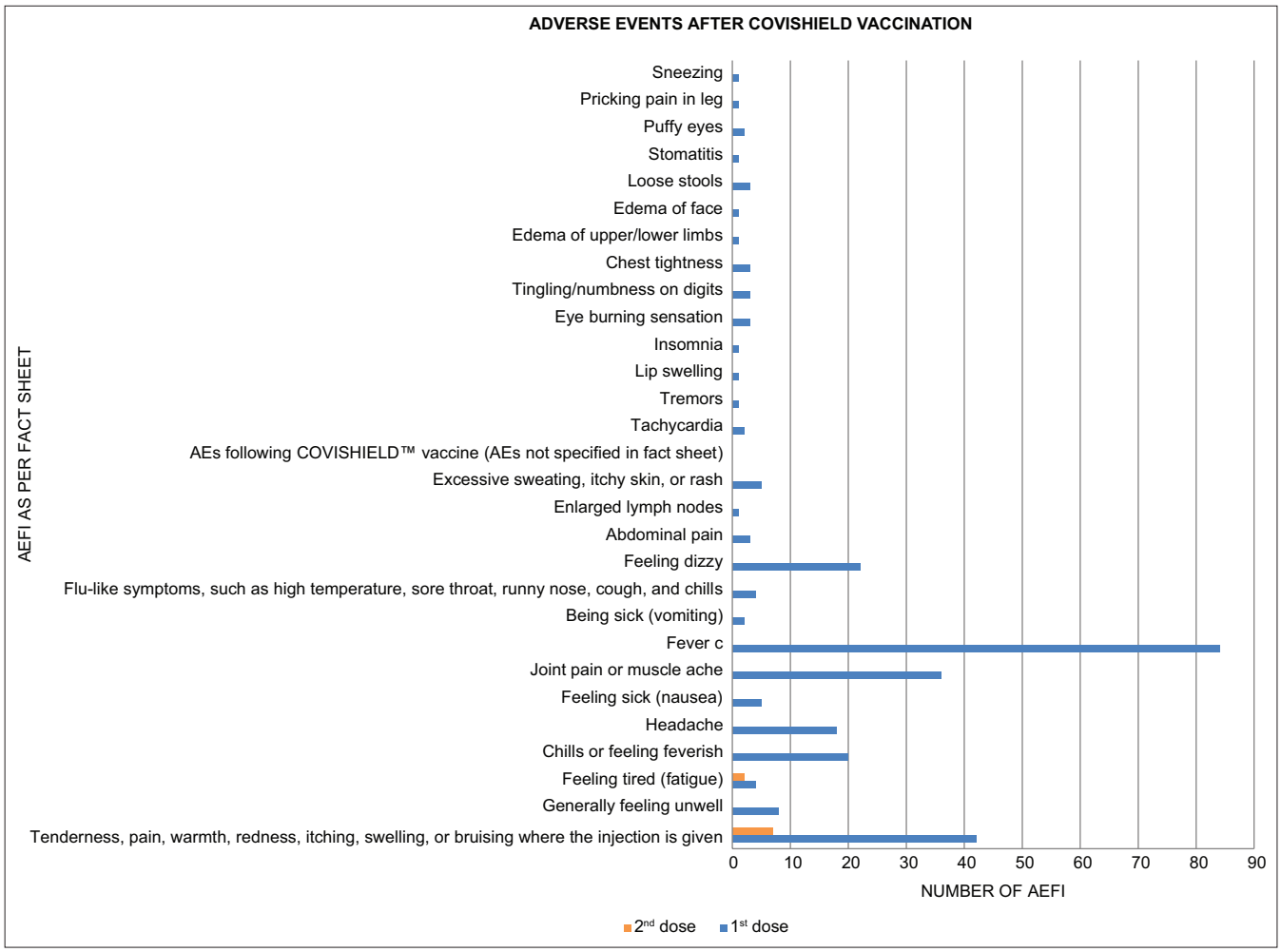

Figure 1: Distribution of adverse events as per the fact sheet. [c]Feverish is a self-reported feeling of feverishness, whereas fever is an objective fever measurement (mild: 100.4–101.2°F, moderate: 101.3–102.2°F, severe: more than 102.2°F

age group was5.67%. We also observed 40% of events following COVID-19 vaccines, in line with that reported in VigiAccess for the age group of 18–44 years.[14,15] This might be due to the fact that the subjects who received vaccination were health care workers and frontline workers who majorly belonged to this age group. In total, 73.60% of females developed AEFIs in this study comparable to 73% of females globally.[16]

We observed an incidence rate of 5.45% of AEFIs among the study population, whereas the national incidence rate reported was 0.005%.[10] Incidence rate of 3.48% was reported by Basavaraja et al., in their study.[17] This difference in the incidence rate might be due to the fact that most vaccinators across the country give more preference to vaccinate their beneficiaries and educate them about mild or moderate AEFIs. Still, there is need to educate people about expected AEs and also the under reporting should be addressed.

Furthermore, we observed that the incidence rate of COVISHIELD is higher when compared with Covaxin from available literature. This can be due to the different population in which vaccine was introduced. Covieshield was initially introduced to healthcare and frontline workers who were working in the hospital set up, and the beneficiaries were aware of the reporting system of AEs and had taken initiatives to contact the study team, whereas Covaxin was introduced to citizens who were not aware of the importance of AEFI reporting. The incidence rate of AEFIs reported within 30 min was 0.66%.

We observed AEFIs, which were not seen in the clinical trials of both COVISHIELD™ and COVAXIN™, and similar events were seen in the VigiAccess. A very less number of the study population with comorbidities developed AEFIs, which shows that the vaccine is safe for beneficiaries with any kind of comorbidities. The SOC implicated majorly in the AEFIs was "general disorders and administration site conditions," and the same is observed in the global database. We observed less number of events with the SOC of "blood and lymphatic system disorders" and observed a total of 25,160 events in this SOC in the VigiAccess. However,

we have not reported any event of blood clots, a majorly discussed rare event globally.[18] Another majorly involved SOC observed in VigiAccess was musculoskeletal and connective tissue disorders (n=209779), and 14.63% of the events were categorized under this SOC in the present study.[19]

In all, 94.22% of events, following COVISHIELD, were categorized as having a consistent causal association with immunization, out of which 306 (93.79%) events following COVISHIELD™ were classified as vaccine product-related reactions. A total of 6.23% of events following COVISHIELD™ were categorized under "indeterminate" as the temporal relationship was consistent, but there was insufficient definitive evidence for vaccine causing events. These events may be potential signals as these were not present in the fact sheets as well. A total of 13 events were categorized as coincidental as those were caused by something other than the vaccine product, immunization error, or immunization anxiety. In the new causality assessment scale, only reactions that have evidence in published peer-reviewed literature that this vaccine might cause the event if administered correctly are classified as a vaccine product-related reactions. Reactions observed for the first time during post-marketing surveillance were not considered as "consistent with a causal association with vaccine." All new serious AEs are labeled as coincidental events "inconsistent with causal association" or "unclassifiable," and the association with the vaccine is not acknowledged. This mandates the conduct of systematic post-marketing surveillance studies.[19]

Limitation of the study

The study followed a spontaneous reporting method, collecting the data from all beneficiaries who had comorbidities and did not develop AEFIs was difficult. In the urban health center, only COVISHIELD vaccine was given as per District guideline. Hence, direct comparison between COVAXIN and COVISHIELD was not possible in the same population.

CONCLUSION

This study observed a higher incidence rate of AEFIs than the country's overall incidence rate. None of the events reported were severe or serious, which reiterates that the vaccines used in India are safe and the events will last without any kind of sequelae. Studies of this nature reinforce the need for vigilant monitoring and reporting of AEFIs especially for newly introduced vaccines, as to identify potential signals.

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REFERENCES

1. Adverse Events Following Immunization (AEFI). Available from: https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/health-professionals-info/aefi [Last accessed on 2022 Mar 30].
2. Kumar VM, Pandi-Perumal SR, Trakht I and Thyagarajan SP. Strategy for COVID-19 vaccination in India: The country with the second highest population and number of cases. NPJ Vaccines 2021;6:60.
   https://doi.org/10.1038/s41541-021-00327-2
3. Safety and Efficacy of COVID-19 Vaccines. Available from: https://pib.gov.in/pib.gov.in/Pressreleaseshare.aspx?PRID=1703442 [Last accessed on 2022 Mar 30].
4. Available from: https://covid19vaccineog111chapter16.pdf. [Last accessed on 2022 Mar 30].
5. COVID-19 Vaccine Introduction Toolkit. Available from: https://www.who.int/tools/covid-19-vaccine-introduction-toolkit [Last accessed on 2022 Mar 30].
6. Available from: https://www.liberalisedpricingandaccelerated nationalcovid19vaccinationstrategy2042021.pdf [Last accessed on 2022 Mar 30].
7. Revised AEFI Guidelines Execute Summary.Available form: https://main.mohfw.gov.in/sites/default/files/Revised%20AEFI%20Guidelines%20Execute%20Summary.pdf. [Last accessed on 2022 Mar 30].
8. World Health Organization. Causality Assessment of an Adverse Event Following Immunization (AEFI): User Manual for the Revised WHO Classification. 2nd ed. Geneva: World Health Organization; 2018. Available from: https://apps.who.int/iris/handle/10665/259959 [Last accessed on 2022 Mar 30].
   https://doi.org/10.12688/f1000research.13694.1
9. Sharma O, Sultan AA, Ding H and Triggle CR. A review of the progress and challenges of developing a vaccine for COVID-19. Front Immunol. 2020;11:585354.
10. CoWIN Dashboard. Available from: https://dashboard.cowin.gov.in [Last accessed on 2022 Apr 05].
11. UMC Uppsala Monitoring Centre. Available from: https://who-umc.org/pv-products/vaccine-surveillance-in-vigiflow [Last accessed on 2022 Apr 05].
12. Lei J, Balakrishnan MR, Gidudu JF and Zuber PL. Use of a new global indicator for vaccine safety surveillance and trends in adverse events following immunization reporting 2000-2015. Vaccine. 2018;36(12):1577-1582.
    https://doi.org/10.1016/j.vaccine.2018.02.012
13. Department of Health Annual Report: Surveillance of Adverse Events Following Immunisation in Australia, 2015. Available from: https://www1.health.gov.au/internet/main/publishing.nsf/Content/cdi4103-l [Last accessed on 2022 Apr 05].
14. Fridman A, Gershon R, Gneezy A. COVID-19 and vaccine hesitancy: A longitudinal study. PLoS One. 2021;16(4):e0250123.
    https://doi.org/10.1371/journal.pone.0250123
15. VigiAccess. Available from: http://www.vigiaccess.org [Last accessed on 2022 Apr 05].

16. Adverse Events Following the First Dose of Covishield (ChAdOx1 nCoV-19) Vaccination among Health Workers in Selected Districts of Central and Western Nepal: A Cross-sectional Study. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0260638 [Last accessed on 2022 Apr 05].

https://doi.org/10.1371/journal.pone.0260638

17. Basavaraja CK, Sebastian J, Ravi MD and John SB. Adverse events following COVID-19 vaccination: first 90 days of experience from a tertiary care teaching hospital in South India. Ther Adv Vaccines Immunother. 2021;9:25151355211055830.

https://doi.org/10.1177/25151355211055833

18. COVID Vaccines and Blood Clots: What Researchers Know so Far. Available from: https://www.nature.com/articles/d41586-021-02291-2 [Last accessed on 2022 Apr 05].

https://doi.org/10.1038/d41586-021-02291-2

19. Chandler RE. Modernising vaccine surveillance systems to improve detection of rare or poorly defined adverse events. BMJ. 2019;365:l2268.

https://doi.org/10.1136/bmj.l2268

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SPP- Acquisition, analysis, or interpretation of data for the work; **SSC-** Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **ADK-** Drafting the work or revising it critically for important intellectual content; **VSP-** Analysis of data. Final approval of the version to be published

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