RESEARCH ARTICLE

The Safety of Covishield (ChAdOx1 nCoV-19) Vaccine after Three Doses Vaccination under Mass Vaccination Program of Government of India

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Abstract

Aims and objectives: In coronavirus disease-2019 (COVID-19) disease, there is no antiviral drugs, hence, Covishield vaccination is the best way of prevention. In India, after two doses of vaccination drive, there has been reports of adverse drug events (ADEs) but there has been creation of misinformation about the safety of the vaccine in some reports. Only few studies are available to monitor the ADEs after the third dose of COVID-19 vaccine. Therefore, this study was planned to establish the safety of Covishield vaccine after three doses.

Materials and methods: An observational, non-interventional, retrospective study based on surveillance was conducted to assess the safety of Covishield vaccine after three doses. The vaccine was given by Department of Immunization, Preventive and Social Medicine Department, Sri Guru Ram Das Hospital, Amritsar. Subjects were instructed to record solicited/unsolicited adverse reactions in the proforma provided to them in English/Hindi/Punjabi language and were instructed to record ADEs up to 42 days post-vaccination period.

Results: A total of 1,364, 1,340, and 1,296 subjects were given the first, second, and third doses of vaccine. The most common solicited ADEs after the third dose with duration was pain at injection site in 48.1% of subjects for 1 day, mild fever temperature ≤100.5°F for 2 days, malaise in 13.1%, injection site swelling in 7%, headache in 5%, myalgia in 4%, chills in 2.5%, rigors in 1.4% of the subjects for 1 day. Adverse drug events seen in subjects with comorbidities were 62.2% after the first dose, 26.2% after the second dose, and 11.4% after the third dose showing a significant reduction in ADEs after each dose.

Conclusion: Covishield vaccine is safe and effective after the third dose as compared with the second and first dose.

Keywords: Coronavirus disease-2019, Covishield, ChAdOx1 nCoV-19, Solicited, Unsolicited.

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Introduction

There were many reports of infection due to coronavirus disease-2019 (COVID-19) virus in Wuhan province, China in December of 2019. Many patients suddenly presented with pneumonia because of unknown etiology. The virus responsible for SARS virus-mediated infection was SARS-CoV-2 virus (COVID-19) that belonged to Zoonotic Coronaviruses (CoV) family called as Coronaviridae. The spread of COVID-19 infection is nosocomial, that is, from the one infected persons throat/nose to another person while coughing, sneezing, or even when speaking and then transmitting to another person via same route. Within few weeks of epidemic in China, COVID-19 infection was seen worldwide. On March 11, 2020, the COVID-19 infection was declared as global pandemic by WHO (world health organization) and gave the advisory to the world about upcoming disastor.[1] Corona virus disease presented with wide range of symptoms as asymptomatic, mild respiratory illness with complete recovery to severe respiratory illness with pneumonia and sepsis. It was realized later that the people with one or more comorbidities as advanced age, patients having one or more associated problems, such as having diabetes mellitus, cardiovascular disease, chronic respiratory illnesses, or cancer were at the higher risk of seriousness of COVID-19 infection and were having higher mortality in these subsets of patients. Thus, the best way to tackle the disease was to spread awareness in public about how the virus spreads, ways to prevent its spread, such as maintaining social distance, wearing masks, and practicing proper hand hygiene at that time. Many drugs were tried unsuccessfully for its treatment with little or no results. Multiple strategies were applied to stop the pandemic, such as tracking, tracing, testing, and then isolation of the infected patients. In many countries, even lockdown was implemented to slow transmission of the virus from person to person.[2] It was soon realized that only hope to slow or halt the spread of infection was by achieving heard immunity, for which safe effective vaccine need to be developed and the basis of this was success achieved in the past of vaccine's in controlling global pandemics of other infections. SARS-CoV2 of Coronavirdae family is the cause of COVID-19 infection. SARS-CoV2 is f RNA virus with high mutation rate due to genetic instability. This has posed a challenge to develop effective vaccines against such viruses. So many pharmaceutical companies in collaboration with government support developed Corona Virus vaccine in a very short notice.

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Till the end of December 2020, there were officially 150 projects for development of vaccine against COVID-19 virus worldwide.[3,4]

Vaccine in India

The first COVID vaccine in world was CoronaVac in China and it was developed by SinoVac Biotech Ltd. in laboratory of China's Central Military Commission. This vaccine was developed for Chinese Military and the medical staff in late August 2020, and this was followed by vaccine development by many other countries including India. The first vaccination program was done in Russia in December 2020 with Sputnik V vaccine and the development of this vaccine was done by Gamaleya Research Institute, a National Center of Epidemiology and Microbiology under Russian Ministry of Health, Russia. In India by May 2020, 30 different vaccines were in the development phase and some of them were in preclinical trials.[5] Various Indian Pharmaceutical houses with research facilities as Panacea Biotec, Bharat Biotech, Zydus Cadila, Serum Institute of India (SII), Dr Reddy's and many other players were trying hard to develop vaccine on the rapid scale. By the end of January 2021, Drug Controller General of India (DCGI) approved vaccination with the Oxford–AstraZeneca vaccine ("Covishield") on emergency ground to the people of India.[6] On the same grounds, DCGI allowed on emergency basis allowed interim use of BBV152 ("Covaxin"). This vaccine was developed by Bharat Biotech, India in collaboration with the Indian Council of Medical Research (ICMR) and National Institute of Virology (NIV).[7] Finally vaccination drive in India was initiated on 16 January, 2021 administrating the first dose of vaccine in 3006 centers.[8] The first priority of vaccination by MOH and Family welfare, Government of India was given to front line workers such as doctors/healthcare workers (HCWs), police, military/paramilitary personals, workers involved in sanitation, and disaster management volunteers dealing directly with the COVID patients. Covishield vaccine was manufactured by using pathogenic protein labeled as S protein from replication-deficient simian adenovirus vector ChAdOx1 of SARS-CoV-2, the strain causing infection in human cells. Covishield is the trademark of vaccine manufactured by Serum Institute of India Pvt. Ltd., Pune, India.[9] Another vaccine made in India was Covaxin, which was a trademark of Bharat Biotech, India. This vaccine was manufactured in collaboration with ICMR based on the technology of inactivated replication deficit virus. In the randomized control trials, an acceptable safety profile of Covaxin was well established in healthy subjects.[10] In the 2nd phase of vaccination, the coverage was further extended to the people. This phase covered all people > 60 years of age, people in the ages group 45–60 years with one or more comorbidities (such as diabetes, cardiac illness, and immunological diseases, etc.), and any leftover health care or frontline workers not received the earlier dose of vaccine in phase I. In April, 2021 the inclusion eligibility of the vaccination was enhanced and it covered all residents >45 years of age, irrespective of those having or not infection. In April 2020, DCGI to booster the vaccination against COVID-19 infection approved the use of Russia's Sputnik V vaccine for emergency use in India by choice of the person. Covishield vaccine showed an efficacy of 91.6% and was well tolerated in a phase III multicentric trial, conducted in September 2020, with the booster dose vaccination program.[11] In April 2021, the Government of India started the next phase of the vaccination program for COVID-19 pandemic to cover all the residents >18 years. On 20 August 2021, the Government of India permitted grant for emergency use of Zydus Cadila's vaccine ZyCoV-D. As per the report of August 2022, Indian bulletin more than 2.04 billion doses of first, second, and booster doses of COVID-19 vaccine has been given in Indian population[12] in 94% of the eligible population (>12 years) with at least one dose, and 86% (>18 years) with all the doses.[13] In the first phase, two vaccines as Covishield and Covaxin were approved by the Indian drug regulatory authorities for emergency use.[14] There has been extrapolation of the several adverse drug events (ADEs) reports with COVID-19 vaccines in media, social platforms (like Facebook, Twitter), newspapers etc. These reports were of mild-to-severe reactions, such as headache, fever, pain at injection site, neurological problems, systemic anaphylaxis, cardiovascular problems such as deep vein thrombosis, high incidences of myocardial infraction, etc.[15,16] This misinformation has created a panic among the general people about the safety of the vaccine. Moreover, the emergency development of the COVID-19 vaccines has been linked to lesser generation of data about the safety of the vaccine following immunization (AEFI). Thus, monitoring and reporting the AEFI to public following vaccination is the need of the time for ensuring the safe use of vaccine. The established safety of the vaccination can give confidence to people about the vaccination.

Materials and Methods

It was a retrospective, observational, surveillance based and was non-intervention carried out in the subjects willing for COVID-19 vaccination under the Universal Program of Immunization against COVID-19 infection. The purpose of the study was to assess the safety of Covishield vaccine in subjects volunteered for vaccination after three doses. There was no planning for the sample size and the study was based on participation of the subjects and spontaneous ADEs, reports following Covishield vaccination. The vaccine was provided by the Central Government of India and was delivered by the Department of Immunization, Preventive and Social Medicine (PSM) department at Sri Guru Ram Das (SGRD) Hospital, attached to teaching college and hospital (SGRDIMSAR), under Sri Guru Ram Das University of health sciences (SGRDUHS), Amritsar, Punjab, India. Only those subjects who themselves consented for Covishield vaccination were included in the study and were administered vaccine. The subjects were administered 0.5 mL of Covishield vaccine intramuscularly (IM), in 3 doses as per the guidelines of the Government of India under mass vaccination program. The vaccine was injected into the deltoid area of left arm, after sterilizing with alcohol. The standard operating procedures (SOPs) for mass vaccination program was followed. Post-vaccination, the subjects were observed for half an hour in a room nearby area for monitoring of any untoward event. The second dose was injected between 6–8 weeks after the first dose, and the third dose was given after 1 year of the first dose of Covishield vaccine. The subjects who were injected vaccine were advised to report any type of ADEs by personal interaction, telephonic calls, or via WhatsApp group created by pharmacovigilance cell, SGRDIMSAR, Amritsar, Punjab, India. A diary card was given to each subject with details of the contact person in the case of ADEs to improve the reporting. Subjects were instructed to record both solicited/unsolicited adverse reactions in the predesigned proforma that has been provided to them in any of the English/Hindi/Punjabi language after the Covishield vaccination up to 42 days post-vaccination period. The number of the subjects experiencing ADEs, SADEs, adverse drug reactions (ADRs) or SADRS in each category was managed, noted, and analyzed for final evaluation. The information received from the evaluation of quantitative data was expressed as percentage for

Table 1: Total number of subjects by age and gender after three doses

	First dose (N = 1,364)			*Second dose (N = 1,340)*			*Third dose (N = 1,296)*		
Age (Years)	*Males*	*Females*	*Total (%age)*	*Males*	*Females*	*Total (%age)*	*Males*	*Females*	*Total (%age)*
20–30	107	187	294 (21.5)	104	185	289 (21.5)	99	173	272 (20.9)
>30–40	142	123	265 (19.4)	139	120	259 (19.3)	132	114	246 (18.9)
>40–50	157	183	340 (24.9)	153	179	332 (24.7)	142	174	326 (25.1)
>50	196	269	465 (34.0)	194	266	460 (34.3)	187	255	452 (34.8)

final evaluation. The generation of the proforma was based on the observation of solicited and unsolicited reactions, and parameters were based on the literature from the Serum Institute of India (SII).[17] The solicited and unsolicited ADEs were noted in the proforma as fever, pain at the injection site, headache, malaise, tenderness, fatigue, myalgia, and chills and pain/swelling of the joints and nausea. The unsolicited ADRs as changes in liver function/kidney function tests, neurological deficits, moderate-to-severe fever, hematoma at injection site, itching all over body, generalized rash, etc. were noted in the study evaluation. The unsolicited ADEs were also reported to the national pharmacovigilance center (NPC) at PvPI (Pharmacovigilance Program of India), Central Drugs Standard Control Organization (CDSCO), Indian Pharmacopoeia Commission (IPC), Ghaziabad, UP, India. The information received from the proforma was reviewed by investigators and was transcribed for the final evaluation. The data obtained were presented in the form of Tables, and the number and percentages were drafted as per the terms in the Medical Dictionary for Regulatory Activities (MedDRA),[18] version 23.1, for each dose for comparative evaluation and interpretation.

Inclusion Criteria

The subjects having taken 2 doses of the Covishield of the vaccine at SGRDIMSAR, Amritsar were included in the study group to evaluate the safety of the vaccine after three dosages.

Exclusion Criteria

The subjects having immunocompromised status/taking any immunosuppressive drug during or before the observation period were excluded.

Study Objectives

The study was planned to assess the safety of vaccination by reporting solicited and unsolicited ADEs following three dosages of Covishield vaccination.

Rescue Medicine

The following rescue medicines were used as for pain as Tablet Paracetamol (PCM) 650 mg SOS with a gap of 4 hours between two tablets and maximum up to four tablets per day. For nausea or vomiting, the rescue medicines given was domperidone 10 mg Tablet SOS with a dose of maximum of 10 mg twice/day. Severe reactions were managed as per the guidelines of the standard treatment of the diseases as per the Standard Treatment Guidelines (Speciality/Superspeciality wise).[19]

Statistical Analysis

The tabulated results obtained were presented in the form of %age for final data evaluation, such as incidence, types, severity, and outcomes of ADEs. The descriptive findings of the study were helpful to analyze and interpret the data. The Data obtained were expressed as numbers and percentage using Microsoft Excel 2016 for analysis and overall evaluation.

Table 2: Total number of solicited ADEs after 1st dose (*N* = 1,078, 97.3%)

Averse drug event (ADE)	*Number of subjects*	*%age*	*Mean duration (days)*
Injection site pain	594	55.1	2
Injection site swelling	42	3.8	2
Fever grade (mild, T = ≤100.5°F)	201	18.6	1
Headache	38	3.5	1
Malaise	134	12.4	1
Chills	15	1.3	1
Rigors	12	1.1	1
Nausea	11	1	1
Vomiting	1	NS	1
Diarrhea	1	NS	1
Influenza-like symptoms	2	NS	1

NS, not significant; that is, %age <1 or zero value

Results

This study primarily focused on monitoring the various types of ADEs following COVID-19 vaccination at our center. In the present study, a total of 1,364, 1,340, and 1,296 subjects received first, second, and third dose of Covishield vaccine, respectively (Tables 1 and 2). The number of subjects not reporting for the second and third doses of the vaccination was 14 and 68. These subjects could not be contacted by telephone or by personal visits and also did not responded to telephonic calls. There was no report of AEFIs within 60 minutes of the first, second and third doses of Covishield vaccine. Subjects were allowed to do their routine activity after 60 minute of vaccination and were asked to report to the hospital in the case of any solicited/unsolicited adverse reactions requiring treatment.

Parameters after First Dose (Tables 3 and 4)

Age Grouping

The pattern of the age after each dose of the vaccine was same as with the first dose, and a total of 1,364 subjects with 602 (44.1%) males and 762 (55.9%) females, with male/female ratio of 0.79/1 were involved. The age group with dose was same as that with the first dose as >50 years in 465 (34.0%), >40–50 in 340 (24.9%) subjects, >20–30 years in 294 (21.5%), and age group > 30–40 years in 265 (19.4%) subjects.

Adverse Drug Events

A total number of ADEs in (solicited and unsolicited) in both sexes were 1,119 subjects with 1,078 (96.3%) were solicited and 41 (3.6%) were unsolicited. Out of 1,078 solicited ADEs, the most common with the order of frequency and duration include injection pain in

Table 3: Total number of unsolicited ADEs after 1st dose (*N* = 41, 3.6%)

Averse drug event (ADE)	*Number of subjects*	*%age*	*Mean duration (days)*
Fever grade (moderate/high, that is, T = ≥100.5°F)	19	45	2
Dizziness	13	31.7	2
Appetite decreased	06	14.6	2
Hematoma at injection site	Nil	NS	NS
Itching all over body	02	4.8	1
Generalized rash	Nil	NS	NS
Impaired liver function tests	01	NS	3
Impaired kidney function tests	Nil	NS	NS
Neurological dysfunction	Nil	NS	NS
Hyperhidrosis	Nil	NS	NS
Pain in abdomen	Nil	NS	NS
Bleeding	Nil	NS	NS
Lymph node enlargement	Nil	NS	NS

NS, not significant; that is, %age <1 or zero value

Table 4: Total number of solicited ADEs after 2nd dose (*N* = 559, 97.2%)

Averse drug event (ADE)	*Number of subjects*	*%age*	*Mean duration (days)*
Injection site pain	364	64.7	2
Injection site swelling	22	3.9	2
Fever grade (mild, T = ≤100.5°F)	52	9.3	2
Headache	18	3.2	1
Malaise	64	11.4	1
Myalgia	12	2.2	1
Chills	11	1.9	1
Rigors	7	1.2	1
Nausea	6	1	1
Vomiting	1	NS	1
Diarrhea	1	NS	1
Influenza-like symptoms	1	NS	1
Arthralgia	2	NS	1

NS, not significant; that is, %age <1 or zero value

594 (55.1%) for 2 days, Mild fever (body temperature ≤100.5°F) in 201 (18.6%) for ≤2 days, Malaise in 134 (12.4%) for 1 day, Injection site swelling in 42 (3.8%) for 1 day, headache in 38 (3.5%) for 1 day, Myalgia in 23 (2.1%) for 1 day, Chills in 15 (1.3%) for 1 day, Nausea in 11 (1%) for 1 day, Rigors in 12 (1%) for 1 day. The non-significant ADEs in 1,119 subjects with percentage <1 was as influenza-like illness, vomiting for 1 day, and single/multiple joint pains for 3 days (Table 2). Out of the 41 unsolicited ADEs (3.6%), the most common with duration include fever of high grade with temperature ≥100.6°F in 19 (45%) for 2 days, dizziness in 13 (31.7%) for 2 days, fall in appetite in 6 (14.6%) for 2 days, pruritus in 2 (4.8%), 1% subjects had non-significant ADEs as impaired liver function test (marginally raised ALT/APT) for 3 days. However, there was no episode of rash over the body, severe diarrhea, severe pain, local or systemic thrombosis, markedly impaired liver or kidney function test, cardiac diseases, CNS dysfunction, or lymph node enlargement (Table 3). It was also noted that out of 1,119 subjects, only 604 (53.9%) required Tablet paracetamol in the dose of 650 mg for high fever/intolerable pain with a mean duration of 1–2 days.

Table 5: Total number of unsolicited ADEs after 2nd dose (*N* = 16, 2.7%)

Averse drug event (ADE)	*Number of subjects*	*%age*	*Mean duration (days)*
Fever grade (moderate/high, that is, T = ≥100.5°F)	7	43.8	2
Dizziness	5	31.5	2
Appetite decreased	2	12.6	2
Hematoma at injection site	Nil	NA	NS
Itching all over body	1	6	1
Generalized rash	Nil	NA	NS
Impaired liver function tests	Nil	NA	NS
Impaired kidney function tests	Nil	NA	NS
Neurological dysfunction (facial palsy)	1	6	7
Hyperhidrosis	Nil	NA	NS
Pain in abdomen	Nil	NA	NS
Bleeding	Nil	NA	NS
Lymph node enlargement	Nil	NA	NS

NS, not significant; that is, %age <1 or zero value

Parameters after Second Dose (Tables 4 and 5)

Age

After second dose, it was observed that the total number of subjects given Covishield vaccine were 1,340. Out of 1,340 subjects, 590 (44.1%) were males and 759 (55.9%) were females with male/female ratio of M:F = 0.77/1. The subjects in age group were as >50 years: 460 (34.3%), 40–50 years: 332 (24.7%), 20–30: 289 (21.5%) and 30–40 years: 259 (19.3%) (Table 1).

Adverse Drug Events

The total number of ADEs observed were 575 in both males and female subjects. Out of all the ADEs, 559 (97.2%) were solicited and 16 (2.7%) were unsolicited events. Out of all solicited 559 ADEs, the most common event and duration include pain at injection site seen in 362 (64.7%) for 2 days, mild fever temperature ≤100.5°F seen in 52 (9.3%) for 2 days, malaise seen in 64 (11.4%) for 1 day, injection site swelling seen in 22 (3.9%) for 1 day, headache seen in 18 (3.2%) for 1 day, myalgia seen in 13 (2.3%) for 1 day, chills seen in 11 (1.9%) for 1 day, rigors seen in 7 (1.2%) for 1 day and nausea seen in 6 (1.0%) for 1 day. The non-significant ADEs with frequency and duration in <1% subjects include joint pains for 3 days, influenza-like illness and vomiting for 1 day duration. Similarly, out of 16 unsolicited ADEs, the most common ADEs with duration in subjects include high-grade fever (temperature ≥100.6°F) in 7 (43%) for 2 days, dizziness in 5 (31%) for 2 days, decrease in appetite in 2 (12%) for 2 days, itching all over body in 1 (6%) for 3 days. Out of 16 unsolicited ADEs, only 1 (6.2%) subject had facial palsy which remained for 7 days. However, there was no report of hematoma at injection site, impaired liver function/kidney functions or any neurological deficits or lymphadenopathy, abdominal pain. The unsolicited ADEs resolved spontaneously without any residual sequelae. Moreover, there was no case of serious ADEs leading to death, prolonged hospitalization, that is, >3 weeks or visit to emergency department of the hospital due to ADEs. The requirement of the rescue drugs was paracetamol 650 mg in 198 subjects out of 575 (34.4%) for 1–2 days indicated for fever/pain at injection site.

Parameters after Third Dose (Tables 6 and 7)

Age

The total number of subjects given Covishield vaccine was 1,296, and out of these subjects 560 (43.2%) were males and 716 (55.2%) were females. The male/female ratio after the third dose was (M:F = 0.78/1). The subjects in age group were as >50 years: 452 (34.87%), 40–50 years: 326 (25.15%), 20–30: 272 (20.9%), and 30–40 years: 114 (18.9%) (Table 1).

Table 6: Total number of solicited ADEs after 3rd dose (*N* = 137, 97.2%)

Averse drug event (ADE)	*Number of subjects*	*%age*	*Mean duration (days)*
Injection site pain	66	48.1	1
Injection site swelling	10	7	2
Fever grade (mild, T = ≤100.5°F)	23	16.7	1
Headache	8	5	1
Malaise	18	13.1	1
Myalgia	6	4	1
Chills	3	2.5	1
Rigors	2	1.4	1
Nausea	1	NA	NA
Vomiting	Nil	NA	NA
Diarrhea	Nil	NA	NA
Influenza-like symptoms	Nil	NA	NA
Arthralgia	Nil	NA	NA

NS, not significant; that is, %age <1 or zero value

Table 7: Total number of unsolicited ADEs after 3rd dose (*N* = 4, 2.7%)

Averse drug event (ADE)	*Number of subjects*	*%age*	*Mean duration (days)*
Fever grade (moderate/high, that is, T = ≥100.5°F)	3	75	1
Dizziness	1	25	1
Appetite decreased	Nil	NA	NS
Hematoma at injection site	Nil	NA	NS
Itching all over body	Nil	NA	NS
Generalized rash	Nil	NA	NS
Impaired liver function tests	Nil	NA	NS
Impaired kidney function tests	Nil	NA	NS
Neurological dysfunction (facial palsy)	Nil	NA	NS
Hyperhidrosis	Nil	NA	NS
Pain in abdomen	Nil	NA	NS
Bleeding	Nil	NA	NS
Lymph node enlargement	Nil	NA	NS

NS, not significant; that is, %age <1 or zero value

Adverse Drug Events

The total number of ADEs observed after third dose of Covishield vaccine was 141 in all the subjects. Out of all the ADEs, 137 (97.2%) were solicited while 4 (2.7%) were unsolicited ADEs. The most common solicited ADEs with duration seen in subjects were pain at injection site in 66 (48.1%) for 1 day, mild fever temperature ≤100.5°F: for 2 days, malaise in 18 (13.1%) for 1 day, injection site swelling in 10 (7%) for 1 day, headache in 8 (5%) for 1 day, myalgia in 6 (4%) for 1 day, chills in 3 (2.5%) for 1 day, rigors in 2 (1.4%) for 1 day. The non-significant ADEs reported were nausea for 1 day and there was no report of influenza-like illness, vomiting, arthralgia, diarrhea. Similarly, out of 4 unsolicited ADEs, the most common ADEs with duration include high-grade fever with temperature ≥100.6°F: 3 (75%) for 2 days, dizziness in 1 (25%) for 1 days. However, there was no report of decreased appetite, abdominal pain, hyperhidrosis, hematoma at injection site, pruritus, neurological deficits, impaired liver/kidney function test, body rash or lymphadenopathy (Table 5). The unsolicited ADEs resolved spontaneously without any sequelae. There were no serious ADEs leading to death, prolonged hospitalization, or visit to emergency department of the hospital due to ADE. The need for paracetamol 650 mg was seen in 3 out of 198 (1%) subjects for 1 day for the resolution of symptoms of fever/pain at injection site. There was no requirement of domperidone 10 mg in any of the subjects after third dose.

ADEs Seen in Subjects with Comorbidities after Each Dose (Table 8)

There were 61 subjects having ADEs with comorbidities, such as coronary artery diseases (CAD), heart failure, hypertension, diabetes mellitus, chronic kidney disease, chronic liver disease, chronic respiratory diseases, autoimmune illness like rheumatoid arthritis, etc. Out of the 61 subjects the percentage of ADEs was as 38 (62.2%) after the first dose, 16 (26.2%) after the second dose and 7 (11.4%) after the third dose. So from the data evaluation, it can be interpreted that there was a significant reduction in ADEs after each dose in subjects having comorbidities signifying the long-term safety of the vaccine.

Discussion

Ever since the idea of vaccine development was introduced, lots of concerns were raised about the safety and of the vaccine worldwide. The protection against severe disease and mortality due to COVID-19 infection can only be conferred by vaccination. Since, multiple doses of vaccine makes it very crucial to monitor post-vaccination adverse reactions so as to inform the public and policymakers of the safety and possible severe reactions of the vaccine. COVID-19 vaccination has fundamentally altered the course

Table 8: No of subjects having ADEs with comorbidities after each dosage (*N* = 61)

	After 1st dose		*After 2nd dose*		*ADEs after 3rd dose*	
Parameters	*With comorbidities*	*ADEs (%age)*	*With comorbidities*	*ADEs (%age)*	*With comorbidities*	*ADEs (%age)*
Males	08	17	07	05	05	01
Females	11	21	10	11	08	06
Total	19	38 (62.2)	17	16 (26.2)	14	7 (11.4)

of the COVID-19 pandemic. Several studies have demonstrated waning of immune responses and vaccine effectiveness of 2 doses within 6 months.[20,21] In many countries, additional third dose was given and this additional dose was associated with rapidly increased immune response and a superior immune response compared with the second dose.[22,23] In the present study, it was found that after the first dose of the Covishield vaccination, out of total 1,119 ADEs reported, 1,078 (96.3%) were solicited. The most common solicited ADEs with frequency and duration were pain at injection site (55.1%) for 2 days, mild fever (temperature ≤100.5°F) (18.6%). After the second dose, out of 574 ADEs reported, 559 (97.2%) ADEs were solicited and the most common ADEs in subjects were pain at the site of injection in 371 (64.7%) for 2 days, mild fever (temperature ≤100.5°F) in 53 subjects (9.3%) for 2 days. After the third dose, out of 141, the ADEs reported include 137 (97.2%) were solicited, the most common solicited ADEs with duration were pain at injection site in 67 (48.1%) for 1 day, mild fever temperature ≤100.5°F in 23 (16.7%) for 2 days. This indicated that the frequency of solicited ADEs decreased with each dose indicating the better safety and tolerability of the Covishield vaccine after each dosage. The unsolicited ADEs after first dose in 41 (3.6%) out of 1,119 subjects showed that the most common ADEs were high-grade fever with temperature ≥100.6°F seen in 19 (45%) subjects which remained for 2 days, followed by dizziness in 13 (31.7%) for 2 days. After the second dose, 16 unsolicited ADEs were observed out of 575 total ADEs; the most common ADEs with duration were as high-grade fever (Temperature ≥100.6°F) in 7 (43%) for 2 days, dizziness in 5 (31%) for 2 days. After third dose, only 4 unsolicited ADEs were reported out of total 137 ADEs reported and the most common ADEs with duration was high-grade fever with temperature ≥100.6°F: 3 (75%) for 2 days, dizziness 1 (25%) for 1 days. There was no report of decreased appetite, abdominal pain, hyperhidrosis, hematoma at injection site, pruritus, neurological deficits, impaired liver/kidney function test, body rash, or lymphadenopathy after the third dose. The above data indicating the frequency of unsolicited ADEs decreased with each dose. Indicating the additional doses of vaccine were better tolerated. After the first dose there were 38 subjects with comorbidities like diabetes mellitus, hypertension, heart failure, chronic kidney disease, chronic liver disease, chronic lung diseases, autoimmune disease such as rheumatoid arthritis and others. As persons with comorbidities were at higher risk of disease their ADEs were studied separately. For first, second and third doses of the vaccine 38, 34, and 28 subjects with comorbidities were enrolled. ADEs were reported in 62.2% after the first dose, 26.2% after the second dose and 11.4% after the third dose (Table 8). There was no episode of serious ADEs leading to mortality, prolonged hospitalization (>3 weeks), or any visit to emergency department of the hospital. This signifies that there was a significant reduction in ADEs in subjects having comorbidities signifying the safety of the vaccine in patients with comorbidities. In an interim analysis of safety of ChAdOx1 nCoV-19 vaccine,[24,25] the most common reported ADEs were tenderness at the site of injection (63.7%), pain at the site of injection (54.2%), tolerable headache (52.6%) and fatigue (53.1%) seen after the first dose. The majority of the ADEs were of mild-to-moderate in severity and the ADEs resolved spontaneously after few days of injection. According to the ADRs reports submitted by the Ministry of Health and Family Welfare (MOH), Government of India, the common ADRs included pain or swelling at the injection site followed by mild fever, irritability and headaches.[26] The UK Government information system reported ADRs following COVID-19 vaccination (known as Covishield in India) as fatigue, nausea, and joint pain.[27] In a study on 1,826 participants by Parida et al.,[28] 544 (29.8%) subjects reported AEFI and the percentage wise presentation in AEFI was pain at the injection site (14.6%), fever (9.7%), and myalgia (5.9%). It was also observed in the same study that AEFI incidence was higher following the first dose (38.1%) than after the second dose (26.4%). However, there was no serious/severe adverse events reported in the same study. Similarly, in another cross-sectional study,[29] it was observed that after two doses of COVID-19 vaccination, at DCH (Diploma in Child Health) in Mumbai, 49.68% of the subjects were in the age group of 45–60 years, followed by 34.70% were in >60 years age group. It was also observed that 88.71% had no AEFI after taking both the doses of vaccine with only 1.65% had mild, 9.63% had moderate AEFI. In an interim prospective, observational, safety analysis on 730 subjects with 7-day follow-up after the second dose of Covishield vaccination,[30] the percentage of AEFIs reported was 15.7%. The majority of AEFIs were mild-to-moderate and resolved spontaneously. Serious AEFIs, leading to hospitalization was noticed in 0.1% of the subjects and the cause of which could have been suspicion of immunization stress-related response (ISRR). Similar findings were observed in our study where we did not observe any serious side effects, hospitalization, or death following the first, second or third dose of the vaccination.

Limitations of Our Study

In the present study, we recorded only short-term ADEs (up to one year, that is, following three doses), but there can be possibility of long-term ADEs following vaccination like even after 1 year, so long-term follow-up studies are required to document long-term ADEs for developing a novel vaccination strategy against COVID-19 vaccination. Thus, in future, long-term studies (>1 year) are needed to establish the vaccine safety through post-vaccination period.

Conclusion

Thus, we conclude from our study that the number of AEFIs decreases after booster dose, that is, AEFIs are less with the third dose as compared with the second and first doses interpreting that all subjects should take the booster doses of Covishield vaccine as per the Government of India guidelines. However, the patients having comorbidities may have higher percentage of AEFIs, therefore need to be observed closely. Since, this study is based on the observation and their analysis after vaccination, and so it may not reflect the actual demographics in general population. So, more surveillance-based studies on safety of COVID-19 vaccination are required to validate our findings to extrapolate our study results.

Ethical Approval

This research paper is based on the observational and non-interventional analysis done in order to report the (%) percentage of ADEs of Covishield vaccine after three doses in subjects enrolled under mass vaccination program. The vaccination interval was decided as per the guidelines of Covishield vaccination program, Government of India. The standards of ethical research, such as confidentiality, informed consent, and risk *vs* benefits of the subjects were maintained in the present study as well.

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