Original Article

Safety monitoring of precautionary third dose of COVID-19 vaccines in a district in Northern India

Tirthankar Deb[1], Saurav Misra[2], Manmeet Kaur[2], Neelam Verma[3], Jayant Kumar Kairi[2], Nitika Sindhu[2]

[1]Department of Pharmacology and Coordinator, ADR Monitoring Centre, Kalpana Chawla Govt. Medical College and Hospital, Karnal, Haryana, India, [2]Department of Pharmacology, Kalpana Chawla Govt. Medical College and Hospital, Karnal, Haryana, India, [3]Deputy Civil Surgeon (Immunization), Karnal, Haryana, India

Abstract

Background: The World Health Organization (WHO) declared Coronavirus disease-19 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) a pandemic on March 11, 2020. On 16th January 2021, India began its vaccination programme using two COVID-19 vaccines (Covishield and Covaxin). Precautionary dose (booster shots) was administered to health and front-line workers in the beginning and then to all eligible populations. **Material and Methods:** This was a descriptive observational study conducted in the COVID-19 vaccination centres of Karnal district and the ADR monitoring centre, KCGMC, Karnal. During the visits to vaccination centres, all beneficiaries of the precautionary third dose of COVID-19 vaccines as well as healthcare workers were sensitized to report in case of any adverse event following vaccination as part of the policy of the vaccination programme run by the government and Pharmacovigilance Programme of India. The data were collected in suspected adverse drug reaction (ADR) reporting form version 1.4, and causality assessment was done as per the WHO–UMC scale. The data were analysed as simple proportions and percentages. **Results:** The booster dose was administered to 72,853 individuals, while the 1st dose and 2nd dose were given to 13,30,042 and 10,73,050, respectively. Only three ADRs were reported with the booster dose in 34 vaccination centres in the Karnal district. These three ADRs were classified as unlikely on causality assessment and hence not included in the analysis. **Conclusion:** The booster dose administered for the prevention of COVID-19 has been found to be reasonably safe. The population who received COVID-19 booster doses was significantly less than the populations who received the first and second doses, which suggests a low acceptance rate.

Keywords: COVID-19, Pharmacovigilance Programme of India (PvPI), precautionary dose (booster shots)

Introduction

Global public health has been seriously threatened by the Coronavirus disease 2019 (COVID-19) pandemic caused by the novel coronavirus SARS-CoV-2.[1] The World Health Organization (WHO) declared COVID-19 a pandemic on March 11, 2020.[2] Huge challenges for humanity have been brought about by this pandemic. The COVID-19 vaccine programme, one of the most effective vaccination campaigns in human history, is unquestionably one of them.[3] On 16th January 2021, India started its vaccination programme using two COVID-19 vaccines (Covishield - Oxford–AstraZeneca vaccine produced under license by Serum Institute of India and Covaxin, a vaccine created locally by Bharat Biotech).[4] Initially, precautionary dose (booster shots) was given to only health and front-line workers, as well as people over 60 years with co-morbidities or other health concerns, and then it was administered to all above 18 years of age.[5] As of March 2023,

Address for correspondence: Dr. Saurav Misra, Department of Pharmacology, Kalpana Chawla Govt. Medical College and Hospital, Karnal, Haryana, India.
E-mail: saurav181087@gmail.com

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65% of the world population is fully vaccinated with the second dose of COVID-19 vaccines, of which only 31% population are prevented by the booster dose. In India, 69% population are fully vaccinated with the second dose of COVID-19 vaccines, of which only 16% population are prevented by the booster dose.[6] COVID-19 vaccines have demonstrated excellent effectiveness against both the primary (original) strain and variants of concern (VOC).[7-9] Data indicates declining immunity following COVID-19 vaccinations; however, the long-term efficacy of COVID-19 vaccines is yet unknown. In fact, it has been noted that antibody titres decrease with time.[10] Scientists, public health organisations, and governments began debating the administration of a booster dose of vaccine—that is, a dose above that recommended by the original vaccine protocol. For the majority of COVID-19 vaccines, data on the safety and immunogenicity of a booster dose have been validated, indicating boosting antibody and neutralising responses. Regarding efficiency, a number of studies have found that booster dosages can help prevent COVID-19 infection and reduce severity, hospitalisation, and mortality.[10-13] Moreover, post-vaccination adverse events have been documented, ranging from minor problems to death.[14,15] There has been a rising number of novel variations found globally. Misinformation is a factor that affects vaccination acceptance and demand on a number of levels, including time and place, perceptions of the dangers and diseases, culture, religion, and other factors.[16] The primary healthcare system played a crucial role in responding to the COVID-19 outbreak as it was the first point of contact for undifferentiated cases in every country. Various functions assigned to general practices, such as screening, education, and home quarantine monitoring, were essential worldwide. By using integrated and coordinated healthcare delivery systems, primary care physicians had triage patients to specialized hospitals for proper care, reducing hospital overcrowding.[17] Primary care physicians have been instrumental in vaccinating patients, especially in remote areas, as they are highly trusted members of the community. The majority of individuals consider their primary care physicians to be the most effective messenger when it comes to vaccines. In addition, around 50% of unvaccinated individuals have expressed their willingness to receive the COVID-19 vaccine if it were made available to them during their routine annual primary care physician visit. Therefore, primary care physicians also played a significant role in reducing vaccine hesitancy by influencing vaccine-related decision-making and increasing vaccine uptake among the general population.[18] Access to a family physician has been shown to improve patient satisfaction, hospitalization rates, clinical outcomes, and equity, making family doctors uniquely positioned to respond to the pandemic.[19]

To the best of our knowledge, no study evaluating the safety profile of an additional (booster) dosage of COVID-19 vaccinations has been published in India. Though most COVID-19 vaccines have demonstrated great performance and safety profiles in clinical research and vaccination programmes, the safety profile of the booster (precaution) dosage needs to be investigated. As there is inadequate data to predict patterns of adverse drug reactions (ADRs) after receiving an additional dosage of COVID-19 vaccines, the current study was conducted to investigate the safety profile of the additional dose in an eligible population.

Materials and Methods

This was a prospective, descriptive, observational study conducted in the COVID-19 vaccination centres of Karnal district and the ADR monitoring centre, KCGMC, Karnal for the period of 12 months (Jan 2022–Dec 2022). As per Government of India guidelines, a precautionary 3rd dose was given to eligible population above 18 years of age, which includes health and frontline workers, as well as people over 60 years with co-morbidities or other health concerns, and healthy adults were included consecutively. This study was conducted after obtaining permission from the institutional human ethics committee (IEC). All the vaccination centres were covered for sensitization of healthcare workers on ADR reporting following immunization as part of the policy of vaccination programme run by the government and Pharmacovigilance Programme of India (PvPI). Posters promoting reporting of ADRs with ADR monitoring centre contact information were put up at the vaccination centres. In case of ADRs voluntarily reported by beneficiaries to the vaccination centres or ADR monitoring centres, data were collected from in Suspected Adverse Drug Reaction Reporting form and Case Notification form as prescribed by the PvPI. All the minor and serious adverse events following immunization (AEFIs) were reported in the forms. The Case Notification form was used only for Serious AEFI. Causality assessment of suspected ADRs was done using the WHO–UMC Causality Assessment Scale. Patients' demographic details such as age and gender along with treatment details were collected from the ADR reporting form. Details of the first and second doses of the vaccine, gap with the booster dose, and co-morbidities were also recorded. ADR reports with causality as certain/probable/possible were considered for further analysis. The collected data were anonymized and linked through a unique ID number for retrieval and authenticity. All data were stored confidentially with limited access only to study investigators. Statistical analysis was done using Microsoft Excel.

Results

The booster dose was administered to 72,853 individuals, while the 1st dose and 2nd doses were given to 13,30,042 and 10,73,050 individuals, respectively. Category-wise COVID-19 vaccination coverage status in the Karnal district is shown in Table 1. Three reports of suspected ADRs were received, but on causality assessment, these were found to be 'unlikely' and hence not included for further analysis.

In our study, three reports of suspected ADRs were received. The full description of the three cases is as follows:

Case 1

A 43-year-old male, a known case of type 2 diabetes mellitus since 3 years, was on tab metformin 1000 mg. As his HbA_1c was

Table 1: Category-wise COVID-19 vaccination coverage status in Karnal district

Category	Beneficiaries Vaccinated with 2nd Dose	Beneficiaries Vaccinated with Precautionary Dose	% vaccinated with Precautionary Dose
Health-care Worker (HCW)	12,440	4134	33.23
Front-line Worker (FLW)	13,398	2575	19.21
18–44 Years General	595,048	27,715	5
45–59 Years General	218,809	14,797	7
>60 Years General	154,870	23,636	15.26
Total	994,565	72,857	7.32

not under the target range, he was started on tab glimepiride 2 mg a day before taking a booster dose. He took both the drugs and skipped breakfast and came to the vaccination centre for a COVID-19 booster dose. He presented with fatigue, palpitation, and sweating after getting the vaccine.

Case 2

A 71-year-old male came to the vaccination centre after travelling 17 km to take the booster shot. He came empty stomach and was also dehydrated. After getting the booster vaccine, he presented with fatigue.

Case 3

A 25-year-old male patient who had a fever for the last 2 days came to the vaccination centre to take a Covaxin booster dose. He presented with malaise after taking the vaccine.

On causality assessment of the above cases, these were categorised as 'unlikely' and hence not included for further analysis. Hence, no ADR was ascertained following the precautionary third dose of COVID-19 vaccines in our study.

Discussion

The available data have shown that the COVID-19 vaccines are effective against it, albeit for a short time. Studies have demonstrated that the effectiveness of vaccine protection against symptomatic disease gradually diminishes over time, necessitating the administration of a COVID-19 booster dose, with the protection against symptomatic COVID-19 disease significantly increasing after the booster dose.[20] The present study is interesting due to the heterogeneity of participation from age groups and the involvement of HCWs working with COVID-19 patients. The goal of this study is to provide guidance for the COVID-19 immunisation campaign to public health experts and national health authorities. Regarding the eligible population, nearly every country eventually included HCWs, and in the majority of situations, the booster dosage was made available from the start of the campaign. There are several factors that might influence this choice, including the fact that HCWs are exposed to a higher infection risk as well as the need to safeguard patients as the ability to prevent infection from vaccinated people who are ill also seems to decline with time.[10] The clinical features of the patients were still another important factor in selecting the booster dose. Nearly all countries have taken into account patients affected by illnesses that suggest a higher vulnerability to COVID-19 or a higher likelihood of disastrous evolution. People with co-morbid conditions, such as heart disease, lung disease, diabetes, and immunosuppressed patients are more likely to develop COVID-19 severe illness.[10] This is one of the first studies that discuss the safety of the third dose of the COVID-19 vaccine given to eligible populations. We discovered that a third dose or booster dose was well tolerated and no serious adverse effects were detected. However, three reports of suspected ADRs were received, which on causality assessment were found to be 'unlikely' as per the WHO–UMC scale.

In a study done by Menni C *et al.*,[21] which was a longitudinal, prospective, community-based study (ZOE COVID Study) to assess the effectiveness of three COVID-19 vaccines ChAdOx1 nCov19 (Oxford-AstraZeneca), BNT162b2 (Pfizer-BioNtech), and mRNA1273 (Moderna) in 3,17,011 participants, the most common systemic symptom was fatigue (n = 31,881; 10.1%), and the most common local symptom was tenderness (n = 1,87,767; 59.2%).[21] In our study, only three ADRs were reported: fatigue (n = 2) and malaise (n = 1). This difference can be because of the different types of vaccine administered in Menni C *et al.*'s study as compared to ours. In Menni C *et al.*, three vaccines were used, namely Covishield (viral vector vaccine), Pfizer-BioNTech, and Moderna COVID-19 (mRNA vaccines). These vaccines contain mRNA encoding the spike protein from the original (ancestral) strain of SARS-CoV-2, which produces COVID-19 as well as from the B.1.1.529 (Omicron) variants BA.4 and BA.5. In addition, age at vaccination and the time interval between the primary vaccination and administration of the booster dose can also account for the increase in ADRs in this study.

Comparing our results to other studies in which short-term side-effects of BioNTech (BNT162b2) in individuals aged 18–70 years were evaluated, fewer overall adverse reactions (40%, n = 208) were reported.[22] More side effects were reported in a younger population in some studies.[23,24] Pain redness at the injection site (88.9%), fatigue (43.8%), body pain (37.8%), fever (21.9%), and headache (15.9%) were the most frequently reported side effects, consistent with other studies.[25-29] These ADRs are very vague and could be due to other factors (co-morbidities and environmental factors). In our study, a COVID-19 booster dose was given for mainly two vaccines. The Covaxin vaccine is an inactivated vaccine, which is produced from whole-virion inactivated vero cells. As microorganisms in

inactivated vaccines cannot multiply, they are unlikely to reverse and result in harmful effects. They still include a dead virus that can train the immune system to build a defence against an infection even if it can no longer infect people. Historically, inactivated vaccines have been used for many years. More than 300 million doses of inactivated vaccines have been produced using the same process, all of which have a proven safety record. These vaccines include those for illnesses such as seasonal influenza, polio, pertussis, rabies, and Japanese encephalitis. It is the tried-and-true platform for vaccine technology, and it is the industry standard.[30]

COV-BOOST was a large multi-centre, randomised, controlled, phase 2 trial conducted in the UK on the third dose booster vaccination against seven different COVID-19 vaccines. Participants were aged older than 30 years and were at least 70 days post two doses of ChAd or at least 84 days post two doses of BNT primary COVID-19 immunisation course. Similar to our study findings, fatigue and pain were the most common adverse events, experienced more in people aged 30–69 years than those aged 70 years or older. No serious ADRs were found in this study too.[31] In another study conducted in the USA by Hause AM to monitor the safety of bivalent COVID-19 mRNA vaccine booster doses among persons aged ≥12 years, the researchers came to the conclusion that ADRs observed following a bivalent booster dosage resemble those reported following a monovalent booster and are less frequent and less severe than health effects related to COVID-19 disease.[32]

Despite our best efforts, we could not find any study conducted on Covishield and Covaxin in India or outside, but there were studies that were conducted on other COVID-19 vaccines. Dick *et al.* studied the association between booster doses of Pfizer-BioNTech and Moderna vaccines against SARS-CoV-2 during pregnancy and obstetrical outcomes. The study was a retrospective cohort study that compared women who received the booster vaccine dose during pregnancy with women who were not vaccinated and with those who only received two vaccination doses. The study found no differences among the triple-vaccinated, twice-vaccinated, and unvaccinated groups with regards to preterm birth and the incidence of small for gestational age neonates. However, women in the triple-vaccinated group had higher rates of postpartum haemorrhage (9.5% vs 3.21%; $P < 0.001$) and gestational diabetes mellitus (12.2% vs 8.3%; $P = 0.02$) and were less likely to have hypertensive disorders of pregnancy (0% vs 1.4%; $P = 0.041$) than the unvaccinated group.[33] In another study, Fadlyana E *et al.* evaluated the efficacy and safety of three potential booster vaccines (ChAdOx1-S, BNT162b2, and CoronaVac) given as full-dose homologous boosters or full-dose or half-dose heterologous boosters to CoronaVac-primed individuals. All booster groups achieved 100% seropositivity after 28 days of the booster dose, and very few local adverse events were reported. However, systemic adverse events were reported in the full-dose and half-dose ChAdOx1-S, full-dose and half-dose BNT162b2, and CoronaVac groups after 28 days of the booster dose. In all booster groups, the majority of the adverse events were mild. The study reported three serious adverse events.[34] Yechezkel M *et al.* conducted a clinical trial to evaluate the safety profile of the second BNT162b2 mRNA COVID-19 booster vaccine by using data from a retrospective cohort and a prospective cohort. The study had two cohorts: retrospective and prospective. The retrospective cohort had 94,169 and 17,814 participants who received the first and second booster doses, respectively. The second booster did not cause any of the 25 adverse events investigated. The prospective cohort had 1785 and 699 participants who received the first and second booster doses, respectively. There were no significant differences in heart rate and self-reported reactions between the first and second booster. However, the mean heart rate increased significantly during the first 3 days following the second booster, peaking on day 2. Mean heart rate values returned to baseline levels by day 6, with a decrease of 0.055 bpm (−0.56 to 0.45) compared to baseline.[35] All these studies assure safety for those eligible for a COVID-19 booster dose. It can help increase the number of high-risk individuals opting for the vaccine to prevent severe outcomes.

Strengths of our study

The sample size of our population was large; we covered 34 vaccination centres across Karnal district. No Indian studies have been published till now that discuss the adverse reactions of the COVID-19 vaccine booster doses, especially post-marketing vaccine follow-up.

Limitation of our study

The observed ADRs were based on the patient's self-reported data, which might result in misclassification, information bias, or missed data. This was a cross-sectional study, which means that we cannot provide information about changes in COVID-19 booster dose perception over time. Another limitation of our study was that we did not classify the healthcare workers based on their nature of work.

Conclusion

The current study demonstrates that the administration of the COVID-19 booster dose has an overall good safety profile. Adverse effects following booster doses were comparable to those following the second dosage. The incremental benefit of a booster dose of vaccine must be carefully balanced against the financial and opportunity costs of such programmes. The scope, size, and longevity of humoral and cell-mediated immune responses to variations require more study.[30] More evidence is also required to fill in other evidence gaps, such as those relating to the length of vaccine effectiveness of inactivated, subunit, viral vectored, and mRNA vaccines. These studies will be helpful to the general public, domestic immunisation partners, healthcare professionals, and governmental organisations. They could use this to make informed judgements about vaccination campaigns.

Ethical approval

Yes, From the Institutional Ethics Committee, KCGMC, Karnal.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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