ORIGINAL RESEARCH ARTICLE

A sentinel surveillance of adverse events and breakthrough infections following COVID-19 precautionary dose among south Indian healthcare workers

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ABSTRACT

Background: Adverse events following immunization (AEFI) is defined as any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. Break-through infections are referred to as antigen or SARS-CoV-2 RNA positivity of respiratory specimens more than 14 days after receiving all recommended doses. **Aim:** The study was conducted to identify adverse events and break-through infections following the precautionary dose of the COVID-19 vaccine among healthcare workers. **Methodology:** The study was designed as a cohort event monitoring; all healthcare professionals who received COVID-19 precautionary dose from the study site were included in the study. The study population was actively followed for any adverse event following immunization (AEFI) through telephonic contact (within 30 days of post-vaccination). Reported adverse events were carefully scrutinized and evaluated by the AEFI investigation team of the study site. **Results:** Out of 1232 vaccine beneficiaries, a total of 359 (29.14%) individuals were reported with 385 AEFIs. Of which 138 (38.44%) individuals were laboratory-confirmed (RTPCR positive) breakthrough cases. Less severity and low morbidity were observed among all the breakthrough cases. According to the WHO's new causality assessment algorithm, 183 (47.53%) events were vaccine product-related and 202 (52.46%) were co-incidental events. **Conclusion:** There was a prevailing outbreak of COVID-19 infection in the study site, which resulted in many breakthrough infections soon after immunization. Initially, all breakthrough infections were misleading as vaccine-related events, where this study helped to break the concerns among the study population.

Keywords: adverse events following immunization (AEFI); breakthrough infection; causality assessment; COVID-19 vaccine; precautionary dose

1. Introduction

The advent of the COVID-19 epidemic from the city of Wuhan turns into a massive pandemic within a gap of a few months was an appalling experience. Thanks to the accelerated development and introduction of COVID-19 vaccines, today the massive pandemic turns into an endemic infection in many parts of the world. The high virulence of the organism (SARS-CoV-2) and the rapid evolvement of different variants (Alfa, Beta, Gamma, Epsilon, Delta, omicron, eta, zeta, theta)[1] still pose challenges to the development of herd immunity.

On 16 January 2021, India launched the world's largest vaccination campaign to vaccinate 1.38 billion of its population[2]. Today, India completed two years of the vaccination campaign and accounts 86% of its adult population has been fully inoculated with one of the licensed COVID-19 vaccines[3]. COVISHIELD was the most commonly used vaccine followed by COVAXIN[4]. The efficacy was found to be 93% and 50% respectively (after two doses) in the prevention of re-infection among the Indian population[5,6].

A high viral load, mutant strains, comorbidities, variants of concern (VOC) leading to vaccine escape and casual attitude of people towards COVID-appropriate behaviors are the various factors which influence breakthrough infections[7]. Vaccine breakthrough COVID-19 infections are defined as an individual testing positive for SARS-CoV-2 by RRT-PCR or rapid antigen test (RAT) any time after 14 days of receiving one dose of any of the licensed COVID-19 vaccines[8]. Initially very low rate of breakthrough cases was reported but many studies conducted in different parts of the world showed an incidence range of 0.04% to 13%[9]. According to the World Health Organization (WHO) Programme for International Drug Monitoring (PIDM) database; a total of 5130 vaccine breakthrough cases have been reported to date[10].

Periodic waning of neutralizing antibodies and evolvement of new mutated virus possessed significant need on additional dose of COVID-19 vaccines. The Omicron-driven third wave of the pandemic affected India from late December 2021 to March 2022. At the same time, the country kick-started the third dose of the COVID-19 vaccine for high-risk citizens (including healthcare workers)[11]. In this study, surveillances were conducted to identify different AEFIs following COVID-19 precautionary dose among the health care workers.

2. Materials and method

2.1. Study design

The study was designed as a cohort event monitoring and was conducted for a period of 6 months in the immunization centre of a tertiary care hospital in India. The enrolment period was from 12 January to 11 March, 2022, and the follow-up period was completed on 30 June 2022. The study site has 2200 health care workers (HCWs) employed in various departments and the study enrolled only those HCWs who received the precautionary dose during the study period. The study is conducted in a sentinel site recognized by WHO for AEFI monitoring and reporting.

2.2. Study procedure

Eligible study participants were enrolled after taking informed consent exclusively designed as per the requirements of the Indian Council of Medical Research guidelines for biomedical research on human subjects. The contact details of the study population who were willing to participate were collected during their vaccination (precautionary dose) time itself. The study excluded all those who were unwilling to participate and who were unavailable to contact during the follow-up period. The study population who were not responding after the enrollment and during the follow-up period was considered as dropouts from the study.

The vaccine safety surveillance was conducted by initiating two telephonic contacts that are: Surveillance I: 7 ± 2 days of post-vaccination and surveillance II: 30 ± 2 days of post-vaccination respectively. Each HCW enrolled in the study was interviewed for any adverse events following COVID-19 immunization. Collected information through the telephonic interview was documented in a suitably designed data collection form.

Information such as demographic details, medication history, breakthrough infection and other relevant background histories of each of the vaccine beneficiaries were collected during the surveillance period. In case of any adverse events (AE) reported, the study team used a suitably designed additional case report

form to collect the required data. The case report form had the provision to document demographic details, allergic status, past medical history, and AE details. The adverse events following immunization (AEFI) section of the case report form was developed based on WHO's AEFI core variables and had the provision to collect details of the vaccine, description of AEFI, date and time of the start of AEFI, date and time of stop of AEFI, duration of the AEFI, severity, seriousness, details of medical attention sought due to AEFI, management of AEFI, the outcome of the developed AEFI, details of the reporter, and a free text space for any additional information[12].

2.3. Assessment of AEFI

The causality assessment team of the study site performed the causality assessment of each reported AEFI. The team is composed of two senior professors of Paediatrics, a clinical pharmacist and a clinical pharmacologist who have interest and experience in the area of vaccine safety. Brighton Collaboration case definitions were used for the valid diagnosis of AEFIs. Causality assessment of AEFIs was performed using WHO's new causality assessment algorithm by checking the eligibility, using the checklist and algorithm. Finally, the AEFIs were categorized as per the causality assessment classification[13].

2.4. Statistical analysis

The data obtained were compiled and entered in Excel spreadsheet and analyzed using Statistical Package for the Social Sciences (SPSS) software version 16.0. The sample size was calculated as a minimum of 784 HCWs by using the below formula; while this study could able to enroll 1232 HCWs from the study site.

$$N = (Z\alpha + Z\beta)^2 (pq) \div e^2$$

where,

$Z\alpha$ is 95% level of significance,
$Z\beta$ is 80% power of the study,
p is the population and $q = p - 1$,
e is the error of margin.

3. Results

During the recruitment period (2 months), 1932 vaccine beneficiaries were identified as eligible study populations from the study site. In which a total of 63.77% ($n = 1232$) of the study population responded to the two phases of surveillance conducted at different time intervals. While a total of 36.23% ($n = 700$) of the study population [surveillance I: 233 dropouts and surveillance II: 467 dropouts] were unavailable or non-responders during the follow-up period and they were considered dropouts from the study. Among the 1232 responders, 60.47% ($n = 745$) of them were females and the remaining 39.53% ($n = 487$) were males. The majority of the responders belong to the age group of 20 to 30 years (56.65%). A detailed description of the study population is given in **Figure 1**.

The study reported a total of 385 AEFIs from 359 individuals during the surveillance period (conducted in two phases). The calculated incidence rate of AEs following the COVID-19 (precautionary dose) vaccination is 29.14% [total number of subjects who developed AEFIs (359)/total number of beneficiaries (1232) × 100] of which 138 AEFIs were identified as COVID-19 breakthrough infections with laboratory-confirmed COVID-19 test. The incidence of AEFI among the female population (41.63%) was found to be higher than in the male population (39.54%) in the study. **Table 1** provides a comparative demographic description between the study population who developed AEFI and those who don't report any AEFI.
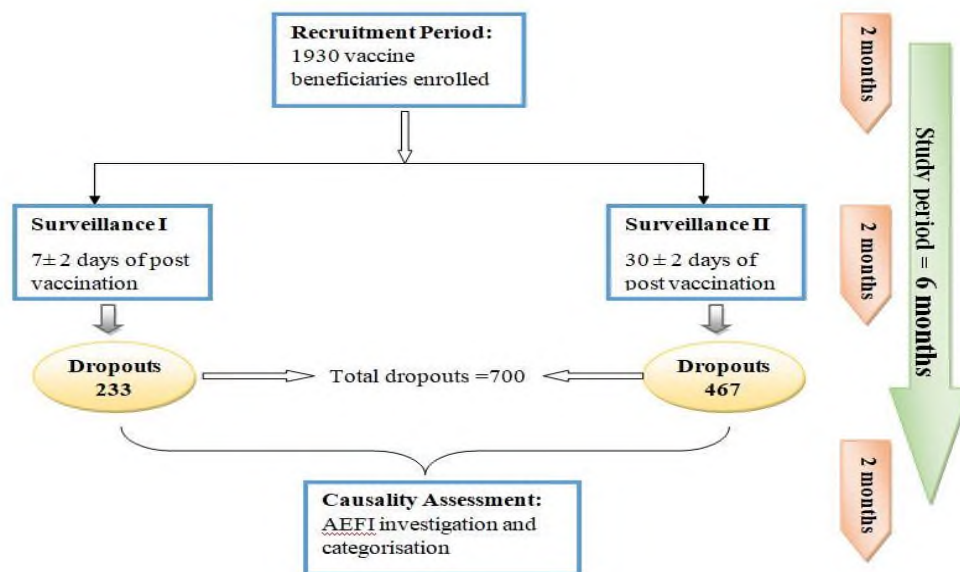
Figure 1. Consort diagram of the study.

Table 1. Demographic distribution of the study population.

Demographic characteristics		Study population developed AEFI (*n* = 359)	Study population without any AEFI (*n* = 875)	Total study population (*n* = 1232)
Gender	Male	139 (28.54%)	348 (71.46%)	487 (53.53%)
	Female	220 (29.53%)	525 (70.47%)	745 (60.47%)
Age in years	20 to 30 years	217 (31.10%)	481 (68.91%)	698 (56.65%)
	31 to 40 years	76 (29.34%)	183 (70.65%)	259 (21.02%)
	41 to 50 years	47 (24.35%)	146 (75.65%)	193 (15.66%)
	51 to 60 years	18 (25.00%)	54 (75.00%)	72 (5.84%)
	61 to 70 years	1 (11.11%)	8 (88.88%)	9 (0.73%)
	Above 70 years	0	1 (100%)	1 (0.08%)
Co morbidities	Hypertension	7 (25.92%)	20 (74.07%)	27 (2.19%)
	Diabetics	3 (42.85%)	4 (57.14%)	7 (0.56%)
	Hypothyroidism	1 (20.00%)	4 (80.00%)	5 (0.40%)
	Respiratory problems	2 (100%)	0	2 (0.16%)

* Incidence rate of each group is included in the bracket as percentage.

Among the 359 HCWs who developed AEFIs, 202 of them reported COVID-19-like symptoms in the post-vaccination days. 38.44% (*n* = 138) were identified as laboratory-confirmed COVID-19 breakthrough cases and another 56 HCWs didn't take any of the prescribed COVID-19 tests, though they had symptoms similar to COVID-19. The remaining seven of them had a negative RTPCR test during the same period though there were similar symptoms of COVID-19.

During the first phase of surveillance, a total of 238 AEFIs were reported from the study population. 75.63% (*n* = 180) of the events were associated with vaccine product-related reactions. Additionally, 56 HCWs had COVID-19-like symptoms, of which 52 of them were laboratory-confirmed breakthrough cases. Four of them were in home quarantine and didn't undergo any of the prescribed COVID-19 tests for confirmation.

The second phase of surveillance identified 146 HCWs with COVID-19-like symptoms (coincidental events) and one event categorized as indeterminate (categorized during causality assessment). While the

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coincidental events include 86 laboratory-confirmed breakthrough cases, 52 did not take any tests and seven of them were RTPCR negative but had symptoms. Detailed graphical representations of various reported events during the follow-up period were described in **Figures 2** and **3**.
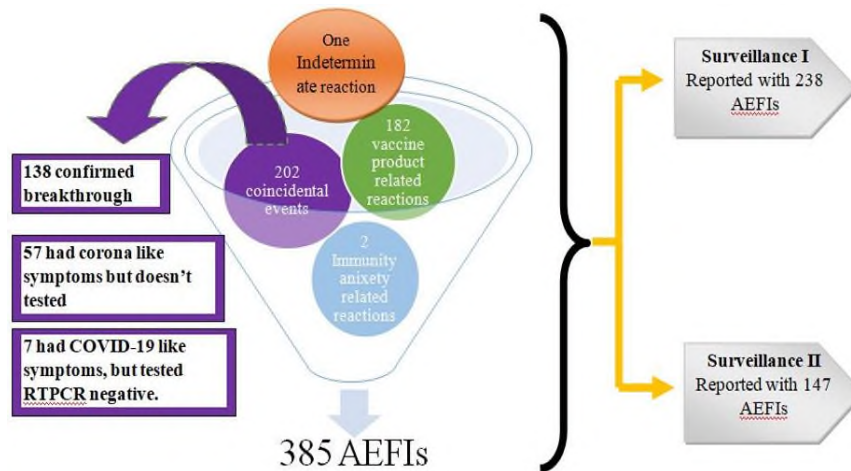

Figure 2. Summary of reported AEFIs during the surveillance period of the study.
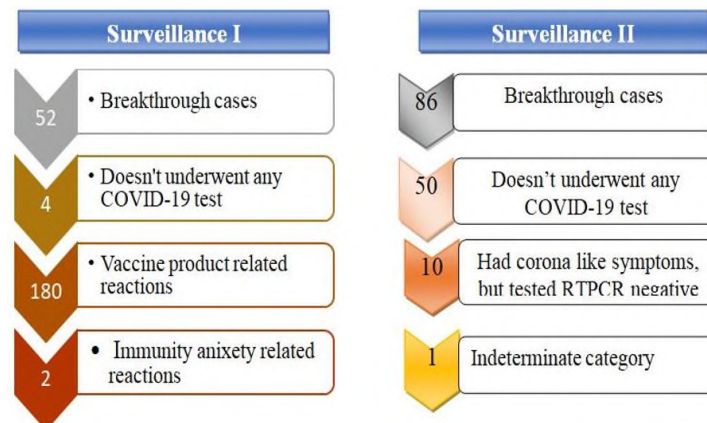

Figure 3. Various AEFIs reported during two phases of surveillance.

4. Causality assessment

In total, from two phases of surveillance 202 (52.55%) of healthcare workers were identified as having coincidental events during the study period. This includes 138 (68.66%) breakthrough cases, 57 (28.22%) cases without laboratory tests and 7 (3.48%) who had COVID-19-like symptoms but tested negative by RTPCR. The causality assessments of 64 unconfirmed cases were concluded as coincidental events by analyzing the background information collected during the surveillance period. Among these 64 coincidental events, 57.14% ($n = 36$) of them had a history of close exposure with the known primary contact and 15.90% ($n = 10$) developed COVID-19-like symptoms after 48 h of vaccination (no temporal relationship to the vaccine administration). 28.12% ($n = 18$) had both a history of exposure and development of symptoms beyond the window period (>48 h). The temporal relationship and causality assessment of 385 events during the study period is shown in **Figure 4**.

The remaining 184 events had a definite time temporal relationship with immunization and they were categorized as 180 (46.75%) vaccine product-related events, 2 (0.52%) immunization anxiety-related events and one (0.26%) indeterminate event respectively (according to causality assessment of AEFI algorithm developed by WHO).
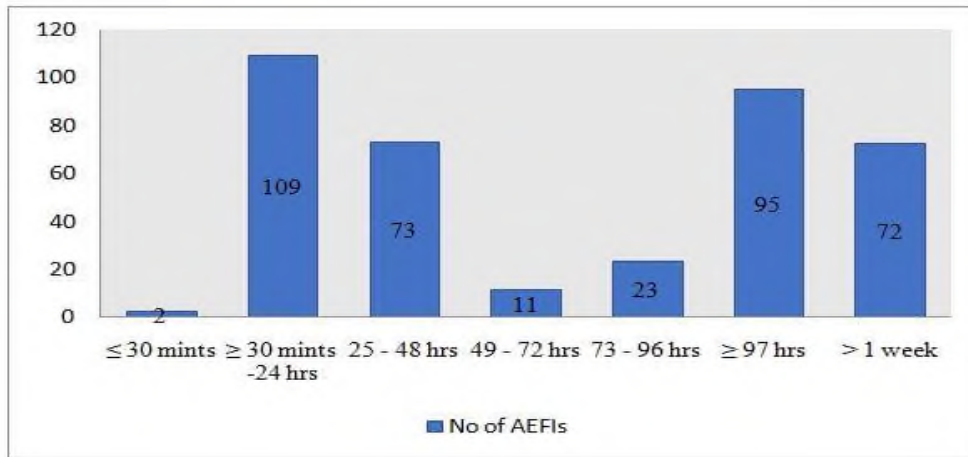
Figure 4. Time-temporal relationship of COVISHIELD™ precautionary dose and AEFI.

From the total number of AEFIs reported from the study population, 1.30% ($n = 6$) of them were hospitalized and they tested positive later (confirmed breakthrough cases). 7.80% ($n = 30$) of them reported severe symptoms of COVID-19 infection and 1.81% ($n = 7$) of them consulted the physician through telephone contact during the same time. 28.83% ($n = 111$) of the reported events were moderate and 54.81% ($n = 211$) of them had mild symptoms. Additionally, 4.15% ($n = 16$) of them remained as asymptomatic but tested positive in the subsequent RTPCR test done for other purposes (e.g., travel). Finally, 0.52% ($n = 2$) of the healthcare workers had long-term adverse events on post-vaccination and are still on treatment (autoimmune arthritis [diagnosed] & loss of appetite and persistent weight loss [under observation]). A description of each reported event from the study population is provided in **Table 2**.

Table 2. List of AEFI reported among the study population.

Sl.No	Category	Events
1	Vaccine product related reactions 162 people developed 180 events	Fever (30), body pain (18), pain at injection site (117), swelling at injection site (1), cough (1), cold (1), headache (9), myalgia (1), tiredness (2).
2	Immunization anxiety related reactions	Giddiness (1), irritability and headache (1).
3	Indeterminate	Autoimmune arthritis (1).
4	Coincidental events** 202 developed 358 events	Fever (123), body pain (73), cough (50), sore throat (2), cold (25), breathing difficulty (3), headache (14), fatigue (11), myalgia (30), tiredness (6), loose stools (1), tasteless (2), giddiness (1), asymptomatic, but tested positive (16), prolonged loss of appetite and persistent weight loss (1).

** All individuals developed COVID-19 like symptoms were calculated together as breakthrough cases.

The study identified more coincidental events (52.21%) than vaccine product-related reactions (46.75%).

5. Discussion

Healthcare workers are categorized as a high-risk population for COVID-19 infection especially when there is a continuous threat of mutated viruses. All healthcare professionals in the study site, who have completed 9 months after the second dose of COVID-19 vaccination, were eligible for the precautionary dose as per the country's regulation. The study site had a total of 2200 HCWs working in various departments. A total of 87.81% of the HCWs in the study site was vaccinated with their precautionary dose and was identified as eligible population to participate in the study. A small proportion of HCWs (12.05%, $n = 265$) didn't receive their precautionary dose because they were infected with COVID-19 (omicron driven 3rd wave). Consequently, the study was not able to include these healthcare workers during the entire recruitment period since they were in their ineligible period (precautionary vaccination only after 3 months

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after a recent COVID-19 infection). While three of the HCWs avoided their precautionary dose since they were in their gestational period (indicates vaccine hesitancy among pregnant population).

The study observed more incidences of AEFIs among the female population (29.53%, $n = 220$) compared to the males (28.54%, $n = 139$). The study site had more female HCWs as compared to male HCWs (859 males:1341 female HCWs). However, this study could enroll and represent 56.70% (487) of total male and 55.56% (745) of the total female HCWs employed in the study site. Various studies conducted in different parts of India reported an increased incidence of AEFIs among the female population[14–16]. Finally, this study could estimate more risk of 0.97 (relative risk) among female population for developing an AEFI as compared to male population. An increased incidence of AEFIs among COVISHIELD vaccine beneficiaries was observed in this study population, this is possibly because the number of COVISHIELD vaccine beneficiaries was far more than that of other vaccines.

Other risk factors for developing an AEFI in the study population were identified as age and co-morbidities status. HCWs belonging to the age group of 20 to 30 years had the highest incidence (31.10%) of AEFIs, followed by 30–40 age groups (29.34%). The co-morbid status of the study population did not factor in as a potential predictor for the severity of AEFIs (low co-morbidities encountered in the study population). A cross-sectional study conducted by Kaur et al.[17] among vaccinated healthcare professionals in India reported different factors such as age, gender, comorbid status and allergic conditions as possible predictors for AEFI occurrence.

Each reported event was carefully analyzed and categorized by the study causality assessment team at the study site. The majority of the AEFIs (61.82%) were reported during the first surveillance, while the remaining was identified in the second phase of surveillance (follow-up). The study could identify immediate (0.52%) as well as short-term events (most of the vaccine product-related events) in the first phase of surveillance. Long-term (0.52%) events and many coincidental events were reported in the second phase of surveillance.

During the causality assessment of the study, many of the healthcare professionals reported COVID-19-like symptoms and later this was confirmed by positive RTPCR test. All those who tested COVID-19 positive (laboratory confirmed) were considered COVID-19 breakthrough cases. Those who did not test but had COVID-19-like symptoms were categorized as suspected breakthrough cases because either they had primary contacts or had COVID-19-like symptoms after the time window. The study also came across HCWs who tested negative but had COVID-19-like symptoms and also had known primary contacts. Such events were considered coincidental based on their background history (primary contact or symptoms developed after 48 h).

The study observed a high incidence of breakthrough cases (35.84%) as compared to other similar studies[18–21]. This is mainly because the prevailing COVID-19 outbreak happened in the study site during the same period of immunization. The incubation period of COVID-19 infection is on average of 5–6 days and can be extended up to a maximum period of 14 days[22]. Similarly, antibody titer hike was observed within 7 to 14 days of post vaccination[23], indicates all the immediate breakthrough cases reported in the study site were serving the activation period of immunization. While the protection period of COVID-19 vaccines was accounted within an average of 6 to 8 months via pervious immunization or infections[24].

Here the study population received their previous vaccination (two doses, within a gap of one month: according to the prioritization criteria followed in the country[25]) 10 months before. However, several studies conducted in western countries point out an 80% to 50% decline in vaccine effectiveness over a period of 6 months[26–29].

Even though a high incidence of breakthrough infection was reported, the severity of the cases was less. There were no deaths and only six HCWs were admitted to the hospital with serious symptoms of COVID-

19. Of these, three of the HCWs had breathing difficulties and were admitted to the hospital for one week (no ICU admission was reported). Seven HCWs reported severe symptoms (high-grade fever and body pain, headache, cough, tiredness) which subsided via self-management. Others reported mild to moderate symptoms and some were asymptomatic ($n = 16$) throughout the study period. Overall, low severity implies the effectiveness of the COVID-19 vaccine. Similar reduction in severity, hospitalization and death associated with the infection is supported by contemporary studies[29,30].

Other than the coincidental events, vaccine product-related reactions accounted with 46.75% among the reported AEFIs, of which pain at the injection site (65%) was the most common event. All vaccine product-related reactions were mild or moderate events and subsided without taking any medication. Where two of the events was reported within 30 min to 1 h of post-immunization and categorized as an immunization anxiety-related event. One rare AEFI of autoimmune arthritis (diagnosed) was also identified in this study and was categorized as indeterminate. This event had temporal relationship but insufficient evidence was available to link the event with vaccination. Flaring up of autoimmune arthritis following COVID-19 vaccination was reported in previous studies[31–36], and can be a new vaccine-linked event. This rare event was identified during the second surveillance of the study and adequate follow-up was done by the study team but was unable to confirm a causal relationship and hence was classified under the 'indeterminate' category. It should be specially note that all these contemporary studies too reported the stimulation of autoimmune disorders in very short span of time (6–14 days) resembles a close match with the study.

6. Limitations and challenges

The study team faced challenges during the surveillance period, especially during the second phase of surveillance where many of the healthcare workers were unable to be contacted. Not much information could be gathered about long-term events due to the high dropout rate in the second phase of surveillance. Secondly, the causality assessment team found it difficult to differentiate real vaccine product-associated reactions as well as coincidental events that occurred due to the prevailing infection. Many times, symptoms reported were identical and causality assessment depended on laboratory confirmation to identify the breakthrough infections. Many subjects in the study population remained oligosymptomatic and were not willing to take a RTPCR test for confirmation. In this study recheck of HCWs with a negative RTPCR test was not able to reproduce. Finally, this study is limited to HCWs of a single study site, observations and rare events reported in this study are narrowed to only this study population.

7. Conclusion

Currently, the burden of breakthrough cases even after complete vaccination has increased all over the world. In this study, there was a prevailing outbreak of COVID-19 infection in the study site, which resulted in many breakthrough infections soon after immunization. All the events reported through this study are considered as adverse events following the precautionary dose of COVID-19 vaccine. While all breakthrough cases reported during the surveillance period was identified and classified as co-incidental according to WHO causality assessment algorithm.

Significantly, all breakthrough infections in the study site were blamed as vaccine-related events initially. This study helped to allay and resolve the safety concerns among the study population. Additionally, the study showed the impact of COVID-19 immunization, which resulted in low severity and hospitalization of healthcare workers during the outbreak. The study also demonstrated the need for active surveillance of vaccine beneficiaries, to track rare events and patterns of AEFIs. Even though COVID-19 vaccines completed for more than one year, many of the long-term adverse events are still unknown. We recommend a long-term follow-up for identifying new signals associated with the vaccine. Since the study site is a recognized WHO sentinel site for AEFI monitoring and reporting, such studies could widely address many

of the safety concerns and misconceptions regarding these newly developed COVID-19 vaccines. Also, potential signals especially delayed and rare AEFIs among different population characteristics need to be identified and investigate further.

Authors contributions

Conceptualization, MM; methodology, MM; formal analysis, JS; investigation, DJ, DV, SS and MSM; resources, DJ, DV, SS and MSM; data curation, DJ, DV, SS and MSM; writing—original draft preparation, MM; writing—review and editing, JS; supervision, JS and CKB; project administration, CKB. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

Ethics approval statement

This study was approved (Ref No: JSSMC/IEC/240921/01NCT/2021-22) by the Institutional Ethics Committee of JSS Medical College, Mysuru.

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