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RESEARCH ARTICLE

Retrospective observational survey of adverse events following immunization comparing tolerability of covishield and covaxin vaccines in the real world

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A R T I C L E I N F O

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A B S T R A C T

The COVID-19 vaccination drive is on a boost in India. On 16-January-2021 India has successfully driven the biggest vaccination drive for 300 million priority groups against the coronavirus disease (COVID-19) and rolled out the world's largest vaccination drive to vaccinate around. People were confused about which vaccination to choose and many were unaware of how these two vaccines differ from one other, while the government was working hard to build confidence and encourage people to come forward to take the made-in-India Covid-19 vaccine (COVAXIN and COVISHIELD). However, the result of the first phase and second phase vaccination drive clearly shows that both the Indian vaccines are effective and safe. Since, both the Indian vaccines have received Emergency Use Authorization (EUA) by Drugs Controller General of India (DCGI) in India, the regulatory agency and the manufacturers are keeping a close watch and monitoring on the Adverse event reported following immunization (AEFI) and to allow quick identification and action of any new safety information. A retrospective observational survey was conducted on 75 fully vaccinated volunteers. The data was collected and analyzed. The percentage of The AEFI experienced with COVISHIELD vs COVAXIN during 1st does was 92.45 % vs 77.27 % and with 2nd dose 86.79 % vs 72.72 % respectively. However, no SAE was reported during the survey and almost 20 % of subjects were aware of the AEFI reporting but because of negligence, didn't report. Fever was the most common AEFI experienced in both vaccines. Only 6.66 % of volunteers got an infection with COVID-19 post-vaccination.

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Introduction

At the beginning of New Year January 2021 India's drug regulatory agency, Central Drugs Standard Control Organisation (CDSCO) decided to approve the newly developed COVID-19 vaccines, which were undergoing clinical trials. The regulatory agency issued a restricted emergency approval for COVAXIN, besides COVISHIELD (Made in India vaccine and developed by the Oxford–AstraZeneca) (Sharma *et al*., 2021). On 16 Jan 2021, India began the world's largest vaccination program for COVID-19, targeting an initial group of 300 million people and have successfully driven the world's biggest Covid-19 vaccination drive (WHO News, January 16, 2021).

The excitement was noticeable as the first batches of the vaccines reached all of India's 3,006 sites by 16 Jan 2021, where around 100 persons at each site were scheduled to be vaccinated on an inaugural day.

To boost the confidence in public, the Govt. officials such as Ministers, CMs, PM, and healthcare workers took the vaccine jabs. During phase one and phase two vaccination drive many people were in a state of confusion and dilemma since there were 2 vaccines for COVID-19 in India so far.

"COVAXIN vs COVISHIELD"

As the results of phase one and two vaccination drive clearly show that both the vaccines are effective enough (against different variants of the COVID-19 virus detected in India so far) and safe. However, both vaccines are different from each other in various factors.

Manufactures

Both the vaccines are developed by different companies.

COVAXIN is developed by Hyderabad-based Company Bharat Biotech International Ltd. in collaboration with the Indian Council of Medical Research (ICMR) and the National Institute of Virology (NIV). Whereas COVISHIELD is the vaccine candidate from Pune-based Serum Institute of India**,** and it is equivalent (but not the same) to vaccine developed by the Oxford University and AstraZeneca (SII, 2021; Bharat Biotech, 2021).

Vaccine Type

COVAXIN is developed using "Whole-Virion Inactivated Vero Cell-derived platform technology". As the study says the inactivated vaccines do not replicate and are therefore not likely to revert and cause pathological effects. These type of vaccines contains the dead virus and they are incapable of infecting people but still able to instruct the immune system to mount a defensive reaction against an infection. This technology is the well-established, and time-tested platform in the world of vaccine technology (COVAXIN, Bharat Biotech, 2021). COVISHIELD is developed by "Viral Vector Platform Technology" and it's a different technology. Recombinant, replication-deficient chimpanzee adenovirus vector which is carrying the SARS-CoV-2 Spike (S) glycoprotein. Produced in genetically modified human embryonic kidney (HEK) 293 cells. This genetically modified virus is not capable of infecting the beneficiary but can very well instruct the immune system to prepare a mechanism against such viruses (SII, 2021).

Dose and dosing Intervals

COVAXIN is a 2-dose vaccination regimen given 28 days apart (COVAXIN, Bharat Biotech, 2021) whereas the COVISHIELD vaccination course consists of two different doses of 0.5 mL each. The 2nd dose should be administered between 28 days to 42 days after the 1st dose. However, there is data available that suggests the administration of the 2nd dose up to 84 days (12 weeks) or more, has a better efficacy rate as presented in Table 1 (SII, 2021).

Vaccine efficacy reported in Clinical trials

In an ongoing trial in India, COVAXIN has been shown to generate immunity following 2 doses given with an interval of 28 days. As per the company the phase 3 trial has been conducted on 25800 participants. COVAXIN showed about 81% interim efficacy in preventing COVID-19 in those without prior infection, after the completion of the vaccination regimen. (BB, Phase 3 Results, 2021). As per the recent study published, the COVISHIELD**'s** vaccine efficacy reached 82.4 %, after a 2nd dose in those with a dosing interval of 12 weeks or more (95 % confidence interval 62.7 % to 91.7 %) and if the two doses were given less than 6 weeks interval the efficacy was reduced to only 54.9 %. (Wise J, 2021). The data has been presented in Table 1

Table 1: Summing up the differences between COVISHIELD and COVAXIN

	COVISHIELD	COVAXIN
Doses Interval	12-16 weeks	4-6 weeks
Clinical Efficacy	Efficacy rate 82.4%	Interim efficacy 81%
Targeted Population	People above 18 years of age can opt for this vaccine	This vaccine can be injected into people above 18 years of age
Storage condition	2-8° Centigrade	2-8° Centigrade
Regulatory approval	DCGI granted approval for emergency restricted use	DCGI allowed COVAXIN for restricted use in emergency situations

Safety

As per the interim analysis and a preliminary review of the clinical trial's safety data which showed that for COVAXIN the severe, serious, and medically important adverse events occurred at very low numbers and it was balanced between both, the vaccine and placebo groups. (BB, Phase 3 Results, 2021).

Commonly reported adverse events during the clinical trial were –

- Swelling and pain at the injection site
- Headache
- Fever
- Nausea
- Body ache
- Rashes
- Vomiting (COVAXIN, Bharat Biotech, 2021).

COVISHIELD was also safe and well-tolerated during the clinical trial studies (Phase II and Phase III) conducted in different countries (United Kingdom, Brazil, and South Africa). Phase-II/III clinical trial on 1600 participants within India has already started (Clinical Trial Registry of India, 2021).

Overall, the incidence of solicited reactions reported with COVISHIELD included -

Injection site reactions such as pain, itch, swelling, tenderness, redness, warmth

The systemic reactions include

- Fever
- Chills
- Fatigue
- Malaise
- Headache
- Arthralgia
- Myalgia (SII, 2021).

The Risk-benefit ratio of both vaccines was maintained.

Bleeding and clotting events following COVID vaccination

As per the recent report submitted by The National AEFI Committee to the Union Health Ministry about the Bleeding and clotting events following COVID vaccination minuscule in India, more than 2300 cases were reported through the COWIN Platform and only 700 Adverse events were reported to be severe (MoHFW, 2021).

The AEFI Committee has done a deep review of all these reports, of which only 26 cases were reported to be potential thromboembolic events following the administration of the Covishield vaccine. Hence, the data shows a very minuscule but definitive risk of thromboembolic events.

Whereas there were no potential thromboembolic events reported following administration of the Covaxin vaccine. (MoHFW, 2021).

Role of vaccine-vigilance during COVID vaccination drive

In this Challenging period of COVID-19, our country is fighting a battle against the virus by manufacturing a huge number of COVID-19 vaccines, driving the largest vaccination drive, and at the same time maintaining social distancing. It is a very difficult task to be handled. At the same time, the vaccine which is approved for restricted use in an emergency needs to be monitored continuously to collect the data. Millions of people are daily getting their COVID-19 Jab. Many of them may have experienced an adverse event or serious adverse event but it is very important to report that and it will help the agency to reduce the risks associated with vaccines.

In India, we have AEFI Program. The Immunization Division of MoHFW (Ministry of Health & Family Welfare) has taken few steps to strengthen the national AEFI surveillance system for COVID-19 vaccinations. They have National AEFI Committee which closely monitors the Non-Serious/ Serious adverse events reported with the COVID-19 vaccine. The causality assessment is done by a Special Group of Experienced Physicians and Health care workers. The data gets published on the portal of MoHFW on monthly basis for public interests. Not always all the reported cases have a causal relationship with the drug, hence the Causality assessment and identifying the right safety information is very important (AEFI Guidelines MoHFW, 2021). Despite Govt. awareness campaign at vaccination centers in India for AEFI Reporting, AEFI cases are still underreported. People need to understand the importance of AEFI Cases.

The order in which the vaccines got approved in India are presented in Table 2.

Table 2: Vaccines on order in India

Vaccine	Status	Approval	Deployment
Covishield	In use	01 January 2021	16 January 2021
Covaxin	In use	03 January 2021	16 January 2021
Sputnik V	In use	12 April 2021	14 May 2021
Moderna	Approved	29 June 2021	Not yet
J & J	Approved	7 Aug 2021	Not yet
ZyCoV-D	Approved	20 August 2021	Not yet
Corbevax	Phase III trials	Awaiting	Not yet
Covovax	Phase III trials	Awaiting	Not yet

Overall vaccine distribution and administration (by brand) in India

As per the data published on the COWIN Plat from (Co-Win Statistics, 2021).

- 303.34 Million Doses of COVISHIED
- 42.49 Million Doses of COVAXIN
- 0.109 Million Doses of SPUTNIK V

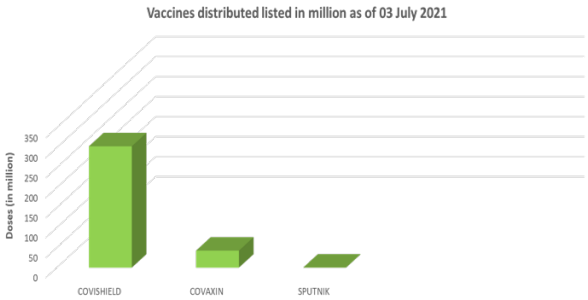

Fig 1: Vaccine Distribution in India

Retrospective observational cohort survey on AEFI

A survey has been done in a rural area in a group of people vaccinated with both the dose of COVID-19 vaccine. The motive behind the survey was to analyze the adverse event experienced after the vaccination and to see the awareness of the adverse event reporting in public of a rural area.

Subjects and methods

The retrospective survey was conducted at Jaitpur Primary Healthcare Centre (Pali, Rajasthan), covering a random group of 75 subjects, who have taken both doses of the COVID-19 vaccine. All the volunteers who were more than 18 years of age residing in nearby villages respective to the hospital and willing to participate in the survey were included. The data collected was analyzed. The data was collected using a pre-tested, semi-structured identification sheet questionnaire. The data included age, gender, number of volunteers with comorbid Conditions, vaccine administered (By Brand name), Adverse event experienced after 1st dose, Adverse event experienced after 2nd dose, COVID Infection post-vaccination, Aware of AE reporting, and Any Adverse event reported through COWIN or another platform. During this survey, informed verbal consent was taken from the survey volunteers. Assurance was given that the confidentiality regarding their information will be maintained strictly.

Table 3: Survey results

Variable	Subjects (%)
Age Group	**Subjects**
18-44	50 (66.66 %)
45-60	15 (20 %)
>60	10 (13.33 %)
Gender	
Female	27 (36 %)
Male	48 (64 %)
Number of Subjects with Comorbid Conditions	
Yes	47 (62.66 %)
No	28 (37.33 %)
Vaccine	
COVISHIELD	49 (65.33 %)
COVAXIN	26 (34.66 %)
Number of Subjects Experienced Adverse Event After 1st dose	
Yes	67 (89.33 %)
No	8 (10.66 %)
Most Common Adverse event Experienced After 1st dose	
Fever	57 (76 %)
Weakness, Body ache	49 (65 %)
Swelling and pain at the site	38 (50.66 %)
of injection	16 (21.33 %)
Headache	6 (8 %)
Nausea	
Number of Subjects Experienced Adverse Event After 2nd dose	
Yes	66 (88 %)
No	9 (12 %)
COVID Infection post Vaccination	
Yes	5 (6.66 %)
No	70 (93.33 %)
Adverse event reported through COWIN or other Platform	
Yes	4 (5.33 %)
No	71 (94.66 %)
Aware about AE reporting	
Yes	19 (25.33 %)
No	56 (74.66 %)
Aware about AE reporting but still not reported	15 (20 %)
Most Common Adverse event Experienced After 2nd dose	
Fever	23 (30.66 %)
Weakness, Body ache	23 (30.66 %)
Swelling and pain at the site	27 (36 %)
of injection	19 (25.33 %)
Headache	9 (12 %)
Nausea	
Vaccine Specific AEFI experienced	
After 1st dose	
COVISHIELD	49 (92.45 %)
COVAXIN	17 (77.27 %)
After 2nd dose	
COVISHIELD	46 (86.79 %)
COVAXIN	16 (72.72 %)

Discussion

It was observed from the Table 3, that among 75 subjects the 56(74.66%) subjects were not aware of adverse event reporting. 20% of subjects have experienced adverse events with the COVID-19 vaccine, also they were aware of the AE reporting but still didn't reported any adverse event. In this survey, it was observed that out of 75 subjects 67 (89.33%) of subjects have experienced adverse events after the first dose of the COVID-19 vaccine whereas 66 (88 %) subjects have experienced at least a single adverse event after their second dose of COVID-19 vaccine. The data percentage of the vaccine administered COVISHIELD Vs COVAXIN was 65.33% and 34.66% respectively as given in Fig 2.

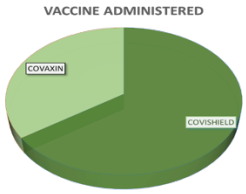

Fig 2: Vaccine Administered to Survey Group

Fever was a most common adverse event, which was experienced by 76% of subjects after the 1st dose but it has reduced to 30.66% in the 2nd dose of the COVID-19 vaccine. Weakness and Body ache was the second commonest adverse event, which was experienced by 65% of subjects after the 1st dose and 30.66% after the second dose COVID-19 vaccine. Almost 50.66% of subjects have experienced Swelling and pain at the site of injection during 1st dose and 36% after the second dose. We can see in the Table 3, that the data of adverse events experienced during the 2nd dose was less compared to the 1st dose of the COVID-19 vaccine. Some of the subjects have also experienced Headache (21.33%) and Nausea (8%) at a first dose and a second dose Headache (25.33%) and Nausea (12%). The data has been presented in Fig 3.

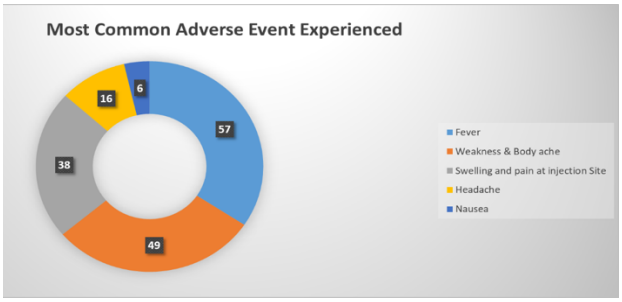

Fig 3: Adverse event Experienced Following Immunization by the survey group

No SAEs (Serious Adverse Event) had been reported during this survey.

It was observed that only 5(6.66%) subjects have been tested positive post-vaccination with very mild symptoms.

In this survey, it was observed that only 4(5.33%) have reported experienced adverse events through COWIN or another platform so far. It was also seen that 92.45% and 86.79% of subjects have experienced AEFI with COVISHIELD's 1st dose and 2nd dose respectively whereas with COVAXIN's 1st dose 77.27% and with 2nd dose only 72.72% of subjects have experienced AEFI. The Band specific AEFI experienced with COVISHIELD for 1st dose was 92.45% and 2nd dose 86.79%, whereas for COVAXIN's 1st dose was 77.27% and with 72.72% respectively. (**Table 3**).

As per the report of MoHFW, Only 26 cases were reported to be potential thromboembolic events following the administration of the COVISHIELD vaccine with a reporting rate of 0.61 cases/ million dose. Whereas there were no potential thromboembolic events reported following administration of the COVAXIN vaccine.

Conclusions

Vaccination for COVID-19 is very crucial and necessary as vaccination has proved to prevent the disease or decrease severity and prevent mortality due to COVID-19. Both the vaccines are equally effective in terms of the prevention of the COVID-19 disease or decreasing the severity of the COVID-19 Infection and also it is very safe to use. As per a report of the AEFI committee, the reported potential thromboembolic events were very less reporting rate (0.61 cases/ million dose) compared to UK's which was 4 cases/million, and Germany's 10 events/a million doses.

Although adverse events due to vaccines were reported during the survey none of them were serious and the events were in line with product information, hence it can be said that the Risk-Benefit ratio of both the vaccines was maintained. Many other vaccines are also in the pipelines, which will be marketed soon once they complete the clinical trials and get regulatory approval. Vaccine-vigilance will play a very crucial role in the future. The very important factor which was revealed by this survey, that the prevalence of adverse event reporting was very less (5.33%) and despite knowing the fact that experienced adverse event needs to be reported, still 20% of subjects haven't reported their adverse events. Awareness regarding adverse event reporting not only for vaccines but also for drugs needs to be created. The spontaneous reporting of AEFI, the contribution of HCP's in identifying the AEFI, and bringing it into the notice could improve the circumstances in health care outcomes and settings.

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Conflict of interest

None of the authors had any conflict of interest that could affect the performance of the work or the interpretation of the data.

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