LM Critical Reasoning

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The right way to counter a poor Covaxin safety study

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The deafening silence around Covaxin's phase-3 trial final safety results must end

It took all of five days for the Indian Council of Medical Research (ICMR) to strongly criticise the poor design of the long-term safety study of Covaxin by researchers from the Banaras Hindu University, Varanasi. The study was published in the journal, *Drug Safety*. Bharat Biotech too pointed out the major limitations in the Covaxin study on May 16, 2024, three days after the paper was published.

Many gaps

The BHU study, which is based on one year follow-up, is of course riddled with major limitations. The study lacked a control arm and data on the background rates of observed adverse events, making it almost impossible to ascertain whether the adverse events observed were indeed caused by or associated with Covaxin. The study was carried out over the telephone and relied solely on participants' recall of adverse events 12 months after vaccination, thereby introducing recall bias.

Including a control arm is extremely important while studying vaccine safety. Only such a study can provide meaningful and reliable information about the adverse effects of a vaccine. Studying the safety of a vaccine in thousands of participants for periods lasting one to three years is vital. Clinical evaluation of every adverse event is also paramount to rule out causality. Finally, randomly assigning the participants either to an intervention arm or a control group is important to eliminate bias. A phase-3 randomised, controlled trial involving a large number of participants is thus ideal for studying vaccine safety.

Bharat Biotech and the ICMR had carried out such a phase-3 clinical trial that was randomised, placebo-controlled and double-blind, involving nearly 25,800 participants. The trial began in November 2020 and the interim results were first posted as a preprint on July 2, 2021. The interim results were based on data as of May 17, 2021 when 130 cases were reported in the trial. The safety data that was captured was only up to 56 days following vaccination.

A publication failure that is glaring

Three years after the interim data were posted as a preprint, Bharat Biotech and ICMR are yet to publish any long-term safety data of the Covaxin phase-3 trial. Given Bharat Biotech's excellent track record of publishing clinical trial results, including the animal and phase-1, phase-2 and interim phase-3 trial data of Covaxin, the failure to publish the long-term, final safety results of the phase-3 trial of Covaxin is perplexing. The failure to publish the trial safety data becomes all the more glaring as according to the information posted by the company in the clinical trial registry website, the duration of the phase-3 trial was only for one year. This would mean that both the ICMR and Bharat Biotech have been in possession of the phase-3 safety data but have failed to publish them even two and a half years after the trial came to an end. The lapse becomes all the more striking as Bharat Biotech had published six papers on Covaxin after the phase-3 interim results were published.

This failure is just one of many blinding shortcomings. On January 3, 2021, the drug regulator had granted emergency-use authorisation for Covaxin under "clinical trial mode", and the recipients were to be followed up for safety. In the second week of March 2021, the drug regulator removed the "clinical trial mode" tag. This was based on the first interim analysis of the vaccine when 43 COVID-19 cases were reported in the trial participants. According to Dr. V.K. Paul, Head of India's Vaccine Administration committee, more than 19 lakh people were administered Covaxin and 311 cases of "side-effects" were reported as on the day the drug regulator removed the "clinical trial mode" condition. Despite being in possession of these instances of adverse effects, no details of the vaccine safety have been published.

On the Covishield study

Finally, it is surprising that the ICMR did not criticise the BHU authors for a similar study carried out on people who were administered Covishield, and published in May 2023. In addition to the long-term Covishield safety study having similar limitations as the Covaxin study, the study found that people who received the vaccine after developing COVID-19 were two times at risk of persistent adverse events when compared to those who received the vaccine before COVID-19. Based on this, the authors went overboard to caution against mass vaccination of people with Covishield and instead advocated an individualised vaccination strategy as a "better alternative for public health safety". So did the ICMR react the way it did for the Covaxin study only because it was a co-developer of the vaccine and was involved in the clinical trials, and not because of the critical limitations of the study per se? While demanding that the journal retract the paper for its safety conclusions not based on evidence, the ICMR has failed to disclose its conflicts of interest, thus setting a bad example. Finally, the ICMR and Bharat Biotech owe it to the trial participants and the people who received the vaccine, and should publish the long-pending phase-3 vaccine safety data soon. That is the only right way to counter BHU's badly designed study findings. It should stop behaving like a bully by resorting to academic censorship (the ICMR had demanded that the journal Editor retract the paper).

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Question -1) According to the passage, what was the primary criticism of the BHU study on Covaxin?

A. It was not published in a reputed journal.
B. It included participants' recall of adverse events.
C. It was conducted over the telephone.
D. It lacked a control arm and had significant design limitations.

Question -2) What does the author imply about the publication of long-term safety data for Covaxin?

A. It was published promptly after the trial.
B. It has been delayed despite being available.
C. It was not collected during the trial.
D. It was not important for the safety assessment.

Question -3) What was the main difference in the ICMR's response to the BHU study on Covaxin and the similar study on Covishield?

A. ICMR criticized both studies equally.
B. ICMR praised the Covishield study but criticized the Covaxin study.
C. ICMR did not criticize the Covishield study but criticized the Covaxin study.
D. ICMR ignored both studies.

Question -4) What reasoning does the author provide for the importance of including a control arm in vaccine safety studies?

A. To reduce the cost of the study.
B. To introduce recall bias.
C. To provide meaningful and reliable information about adverse effects.
D. To increase the duration of the study.

Question -5) Based on the passage, which of the following is a consequence of the failure to publish the long-term safety data of Covaxin?

A. It undermines the credibility of Bharat Biotech.
B. It led to the immediate approval of the vaccine.
C. It caused a halt in the vaccination drive.
D. It increased the cost of the clinical trials.

Question -6) What action does the author suggest as a better approach to countering the BHU study's design limitations?

A. Criticizing the authors publicly.
B. Publishing the pending phase-3 safety data of Covaxin.
C. Ignoring the study's findings.
D. Conducting a new study with similar limitations.

Thank you for attempting!!!