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Letter to the Editor

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Dear Editor,

The US Government reports that it is conducting historically unprecedented intensive monitoring of COVID-19 vaccine safety [1,2]. However, there are major shortcomings in the FDA's recent publication of its first "near real-time surveillance" study [3]. The analysis was not sensitive enough to detect safety signals for known adverse reactions: myocarditis was not detected for Moderna vaccine in all data sources, and only detected for Pfizer vaccine in two of three data sources. This raises serious concerns about whether the surveillance system is fit for its purpose.

Another major concern is the FDA's approach towards false positives. Safety surveillance systems should be optimized for high sensitivity, erring on the side of caution by ensuring true associations are not missed. A highly sensitive approach will result in some false positives, but those will be subjected to further study and quickly identified as spurious. In contrast, because fewer associations are identified at the surveillance stage, fewer associations will result in further study, and more true associations will be missed. The FDA's approach decreased the statistical significance threshold as part of its effort to "reduce type I [false positive] errors,". The consequence is an increase in false negative (type II) errors [4]. This problem with the FDA's approach raises a broader question: Has the FDA previously specified any standards for sensitivity and specificity in detection of specific adverse event types?

In addition, a test margin was selected "for each AESI based on expert guidance to avoid minimal risk increases that were unlikely to be clinically relevant." No details were provided for how and which experts determined the level of increased risk considered "minimal" or "unlikely to be clinical relevant." Given a vaccine administered to billions, we are concerned that even minimal risk increases would imply harm to thousands, or perhaps millions, of younger people, many of whom may be at low risk of serious complications from coronavirus infection.

The FDA's approach accomplished its stated aim, insofar as no potentially false positive association was detected despite more than 350 statistical tests. The only safety signals identified were for already established adverse events. Furthermore, considering that FDA's analysis did not identify multiple safety signals for myocarditis, FDA's priority of reducing false positives came at the cost of missing true positives. By redefining thresholds, the FDA was able to reduce the risk of false positives. But a consequence was a higher risk that some true positive AESIs were missed and remain unidentified false negatives.

Another shortcoming is that the decision not to pool data across the three data sources further increased the chances of missing true associations. Pooling data would increase power and we see no valid rationale not to do so. Many of the same authors previously pooled these same three data sources to investigate myocarditis risk from the vaccines [5,6].

Furthermore, the Immunization Information Systems (IIS) data were only incorporated into the analysis for seven states (Appendix A); excluding the 43 other states further increased false negative risk. The study acknowledged this limitation, but did not explain why critical information is absent for 43 states. An explanation should be provided.

To enable replication and independent analysis, FDA should share the data. Data pooling and sensitivity analyses are needed along with age-specific results to permit meaningful comparisons with other studies. Overall, FDA's screening study failed to identify known adverse reactions and is not sensitive enough to delineate overall COVID-19 vaccine safety. Its value was further diminished because results were not published in a timely fashion. True pharmacovigilance requires that safety signals be detected and reported without delay. But FDA's study was published 21 months after vaccine rollout began [3]. As no preprint or other public announcement of the results was made prior to publication, this cannot be realistically termed a "near real-time" surveillance system.

Data availability

No data was used for the research described in the article.

Declaration of Competing Interest

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