

Adverse Events Related to SARS-Cov-2 Vaccination: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Vaccination has been adopted as a key public health strategy for combating the COVID-19 pandemic. The accelerated SARS-CoV-2 vaccines' development had limited time for extensive investigation of the adverse events. The study aimed to assess the average adverse events rates in published COVID-19 vaccination studies.

Subjects and Method: The study used systematic review and meta-analysis involving studies that reported adverse events following administration of any of the approved COVID-19 vaccines in humans. A highly specific search strategy was developed and implemented in PubMed. The core search string was "(COVID-19 OR COVID OR "coronavirus disease") AND vaccin* AND (side-effects OR "adverse events)". Titles and abstracts were screened, and full texts of potentially relevant articles were retrieved. Data extracted included general study background, adverse events and frequency of occurrence. Meta-analyses were conducted for adverse events reported by at least 5 studies. Meta-analysis of proportions was carried out using logit transformation with the generalized linear mixed model estimation method.

Results: A total of 108 adverse events were reported in 15 studies observing 735,515 participants from 10 countries. The highest pooled prevalence rates were pain at injection site (67.2%; 95% CI= 46.49 to 82.86; I²= 99.9%, 11 studies, 670,557 participants), weakness/fatigue (41.88%; 95% CI= 26.82 to 58.61, I²= 99.9%, 13 studies, 671,045 participants), muscle/joint pain (28.95%; 95% CI= 16.95 to 44.86, I²= 99.9%, 13 studies, 672,791 participants), and headache (27.78%; 95% CI= 17.59 to 40.95, I²= 99.9%, 14 studies, 672,883 participants). Four cases of death were reported by two papers enrolling 711 patients with cancer or multiple sclerosis, three due to comorbid disease progression and one case due to COVID-19. Forty-three cases of anaphylaxis were reported in three studies enrolling 68,218 participants.

Conclusion: The most prevalent adverse events among recipient of SARS-CoV-2 vaccines were local and general systemic reactions.

Keywords: COVID-19, SARS-CoV-2 vaccine, adverse events, meta-analysis, systematic review

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BACKGROUND

The novel coronavirus disease 2019 (COVID-19) is the fifth documented pandemic in history since the flu pandemic in 1918 (Liu et al., 2020). The virus was first reported in Wuhan, China and subsequently, it spread across the globe (Liu et al., 2020). As at April, 2022, half a billion cases have been recorded worldwide including over six million deaths (CDC, 2020; WHO, 2021a). The virus had killed 3,744,408 people worldwide as the date stated above (WHO, 2021a). Despite the reduction in COVID-19 related daily deaths by June 2020, the increasing number of cases have concerns about governments and decision making authorities' ability to reduce the spread and effect of the virus (Goumenou et al., 2020; Kostoff et al., 2020). At 19 months after the outbreak, there is no specific treatment agreed upon in the medical community for treatment of severe forms of COVID-19. However, some therapies seem to have produced some encouraging results (Arsene et al., 2020; Dehelean et al., 2020; Farsalinos et al., 2020; Nitulescu et al., 2020; Skalny et al., 2020; Stancioiu et al., 2020; Torequul et al., 2020).

Since the advent of COVID-19 pandemic, resources have been mobilised for novel research aimed at finding efficacious therapies, with some recorded successes. More importantly, pharmaceutical companies have been accelerated efforts at discovering and mass producing potent vaccines at the onset of the pandemic, the entire global community constituted a susceptible pool because of the novelty of the virus. As with other epidemic-prone infectious disease, the susceptibility would continue until herd immunity develops through vaccination or infection. Vaccine development has been at the forefront of efforts to contain the spread of SARS-CoV-2 (Ahammad and Lira, 2020; Vabret, 2020; Kifle, et al., 2021; Rahman et al., 2021).

Vaccine development is an important tool in reducing the spread of diseases globally (Lombard et al., 2007). Many public and private organizations have partnered to develop vaccine against respiratory virus and as at June 10, 2021, there were 185 vaccine candidates in the preclinical phase and 102 in the clinical phase (WHO, 2021b). Authorities in various countries across the globe had granted emergency approval for nine vaccines by early 2021 (Kaur et al., 2021). Safety data have been reported for 11 vaccines as preliminary reports or clinical trial publications (Ella et al., 2020; Folegatti et al., 2020; Jackson et al., 2020; Keech et al., 2020; Logunov et al., 2020; Mulligan et al., 2020; Polack et al., 2020; Sadoff et al., 2020; Xia et al., 2020, Xia et al., 2021; Zhu et al., 2020; Voysey et al., 2021; Zhang et al., 2021).

Based on the means by which vaccines can protect against COVID-19 infection, vaccines in use currently are mRNA (Pfizer and Moderna) and vector (Astrazeneca) vaccine structured (Vaccines and Related Biological Products Advisory Committee December 10, 2020 Meeting Announcement -12/10/2020-12/10/2020, 2021). Although, these vaccines are projected to offer significant protection against COVID-19, further studies are needed for safety concerns that may be beyond the local and systemic adverse reactions on patients (Halim, 2021).

Adverse events are medical occurrence temporally associated with the use of a medicinal product, but not necessarily causally related (Xu et al., 2018). All clinical trials have the potential to produce adverse events. An adverse event following immunization (AEFI), in accordance with "Definition and Application of Terms for Vaccine Pharmacovigilance", is described as any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage

of the vaccine. AEFIs can be related to the vaccine itself (product or quality defect-related reactions), to the vaccination process (error or stress related reactions) or can occur independently from vaccination (coincidental) (WHO, 2018).

The regulatory authorities such as the Food and Drug Administration (FDA) and European Medicines Agency (EMA) issued an Emergency Use Authorization (EUA) for several of the candidate vaccines by the end of 2020 (CDCMMWR, 2021; EMA, 2021). The EUA issue were mostly within a year of the onset of COVID-19 pandemic (WHO, 2021b). These accelerated vaccine development efforts had limited time for extensive investigation of the efficacy and adverse events of these candidate vaccines, as would normally be ideal (Calina et al., 2020). This warrants further investigations.

There is a need to assess the occurrence of adverse events from the administration of these vaccines given the emergency approval being granted without the completion of all phases of clinical trials (Kaur et al., 2021). To the best of our knowledge, no meta-analyses have assessed the average adverse event rates related to COVID-19 vaccination. Therefore, this study aimed to assess the average adverse events rates in published COVID-19 vaccination studies.

SUBJECTS AND METHOD

The study was registered in PROSPERO with ID CRD42021288781

1. Study Design

The study was a systematic review and meta-analysis.

2. Inclusion Criteria

In the PICO framework, the study population included adults receiving at least one dose of SARS-CoV-2 vaccine. The intervention was SARS-CoV-2 vaccine. No comparator was required because the systematic review was not a comparative effectiveness

study. The outcome included the wide range of adverse events that might be reported in any person who received the vaccine.

Study eligibility: This study included studies that reported adverse events following administration of any of the approved COVID-19 vaccines in humans. Studies must have included data sufficient for estimating the proportion of study population reporting an adverse event.

Search Strategy: This study developed and implemented a highly sensitive search strategy in PubMed. The core search string was “(COVID-19 OR COVID OR "coronavirus disease") AND vaccin* AND (side-effects OR "adverse events")”. The search was conducted on June 8, 2021

3. Exclusion Criteria

The systematic review excluded studies that were reported in languages other than English.

4. Operational Definition of Variables

Adverse events: These are medical occurrences that are temporally associated with the use of a medicinal product, but not necessarily causally related, including pain at injection site, weakness/fatigue, muscle/joint pain, swelling at injection site, and diarrhea (Xu et al., 2018).

5. Study Instruments

The study instruments designed and applied for the systematic review included the study eligibility screening form and the data extraction form. The screening form was used to assess the eligibility status of records in search outputs by reading through the titles and the abstracts. The data extraction form was used to collect data that were needed to meet the study objective.

Study screening: Three authors independently screened the titles and abstracts to select potentially relevant studies. One author harmonized and confirmed eligibility of the potentially relevant studies and discussed doubts with another independent

author. We retrieved the full texts of potentially eligible studies.

Data extraction: This study extracted data from included studies using a piloted data extraction form. Data extracted included general study background, e.g study design, sample size, country where the study was conducted, study population, data collection methods, duration of follow-up/observation, the mean/median age of study participants, and proportion of study participants that was male, name(s) of the vaccine (s), and proportion of participants that had been fully vaccinated. Also, we extracted data on the name of the adverse event, total number of participants observed for the event, and the frequency/percentage of the event.

6. Data Analysis

The measure of outcome used was prevalence (proportion) of an adverse event. In some studies, data were stratified by vaccine type/number of vaccine doses received, with data separated for different doses or vaccines. These data were included in meta-analysis as distinct, and labelled “Author, Year (a)” or “author, year (b)”, as appropriate.

In this systematic review, meta-analyses were conducted for adverse events reported by at least 5 studies. Meta-analysis of proportion was carried out using logit transformation with the generalized linear mixed model (GLMM) estimation method, and Hartung-Knapp adjustment for the random-effects model (Hartung and Knapp, 2001; Schwarzer et al., 2019).

Publication bias across the studies was evaluated using the funnel plot and Egger’s regression test. Data were analyzed in R version 4.1.3 (R Core Team, Vienna, Austria) using meta package (version 5.2-0).

RESULTS

A total of 814 titles and abstracts were screened from database search, 194 poten-

tially relevant records were identified, and 193 full-text reports were retrieved (Figure 1). Fifteen studies (735,515 participants) (Table 1) from 10 countries in Europe, Asia, North America, and the Middle East, were included in this systematic review (Figure 2). All of these studies were observational, and majority 12/15 (80%) were conducted among healthcare workers (Table 1).

The median number of participants across studies was 840 (IQR= 315 to 2413). A total of 108 adverse events were reported in 15 studies (Supplementary Materials). Data were synthesized quantitatively for 11 most widely reported adverse events (see Table 2).

Eleven studies contributed data to the prevalence of pain at injection site; the median number of participants observed across studies was 435 (IQR= 71 to 1,758); the pooled prevalence of pain at injection site was 67.21% (95%CI= 46.49 to 82.86; $I^2=99.9\%$) in Supplement (S1-1).

Thirteen studies contributed data to the prevalence of weakness/fatigue; the median number of participants observed across studies was 555 (IQR= 134 to 1,350); the pooled prevalence of weakness /fatigue was 41.88% (95% CI= 26.82 to 58.61; $I^2=99.9\%$) in Supplement (S1-2).

Thirteen studies contributed data to the prevalence of muscle/joint pain; the median number of participants observed across studies was 679 (IQR= 134 to 1,733); the pooled prevalence of muscle/joint pain was 28.95% (95% CI= 16.95 to 44.86; $I^2=99.9\%$) in Supplement (S1-3).

Fourteen studies contributed data to the prevalence of headache; the median number of participants observed across studies was 524 (IQR= 92 to 1,529); the pooled prevalence of headache was 27.78% (95% CI= 17.59 to 40.95; $I^2 = 99.9\%$) in Supplement (S1-4).

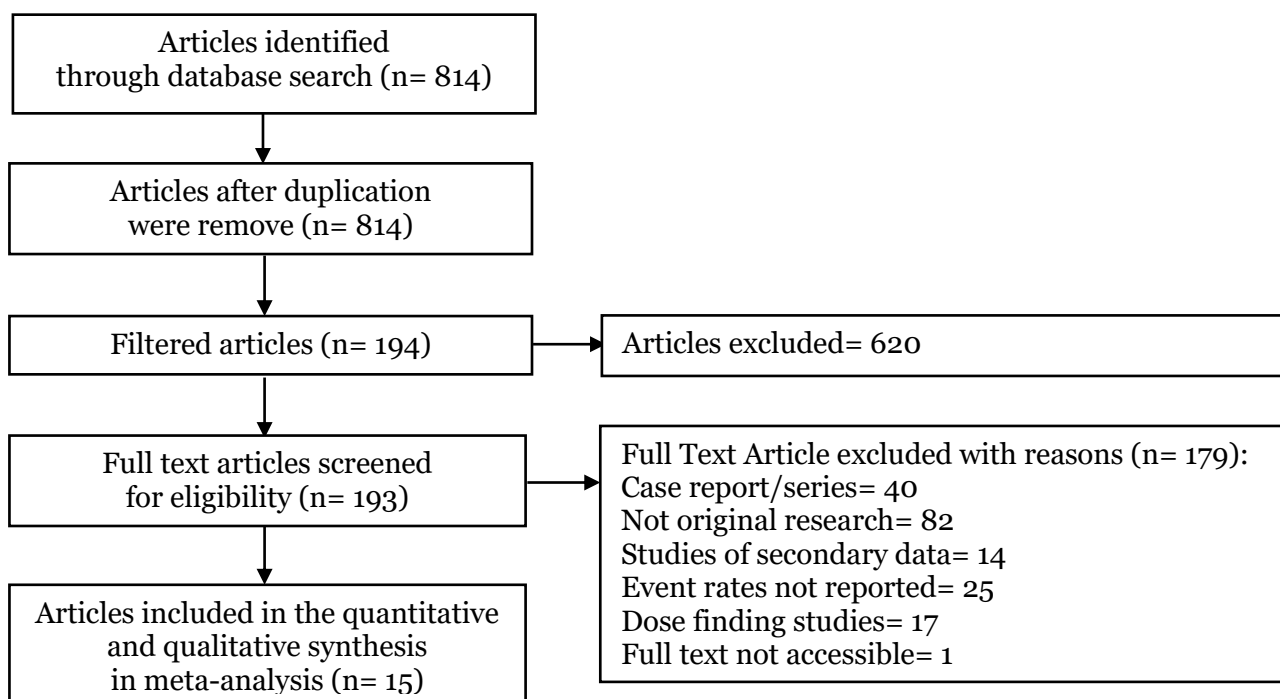


Figure 1. PRISMA Flowchart describing reference search and screening



Figure 2. Map of Study area

Table 1. Study characteristics of Adverse events related to SARS-CoV-2 vaccination (N= 735,515)

Study	Country	Study design	sample size*	Population	Intervention	Data stratification	Adverse events reported**
Sørvoll et al. (2021)	Norway	Cross-sectional	492	Healthcare workers	AstraZeneca	-	1,663
Abohelwa et al. (2021)	USA	Analytic cross-sectional	77	Healthcare workers	Pfizer-BioNTech	-	196

Study	Country	Study design	sample size*	Population	Intervention	Data stratification	Adverse events reported**
Achiron et al. (2021)	Israel	Prospective observational	574	Multiple sclerosis patients	Pfizer-BioNTech	Vaccine dose: first dose (a), second dose (b)	501
Song et al. (2021)	South Korea	Hospital-based surveillance	2,478	Healthcare workers	AstraZeneca	Vaccine type: AstraZeneca (a), Pfizer-BioNTech (b)	12,814
Gobbi et al. (2021)	Italy	Prospective observational	15	Healthcare workers	Pfizer-BioNTech	Vaccine dose: first dose (a), second dose (b)	38
Waissengrin et al. (2021)	Israel	Prospective observational	137	Cancer patients	Pfizer-BioNTech	Vaccine dose: first dose (a), second dose (b)	292
Blumenthal et al. (2021)	USA	Prospective observational	64,900	Healthcare workers	Pfizer-BioNTech, Moderna	Vaccine type: Pfizer-BioNTech (a), Moderna (b)	1,381
Riad et al. (2021)	Czech Republic	Cross-sectional	877	Healthcare workers	Pfizer-BioNTech	Number of doses received: one dose (a), two doses (b)	3,194
Bae et al. (2021)	South Korea	Prospective observational	5,866	Healthcare workers	AstraZeneca, Pfizer-BioNTech	Vaccine type: AstraZeneca (a), Pfizer-BioNTech (b)	47,949
Jeon et al. (2021)	South Korea	Retrospective observational	994	Healthcare workers	AstraZeneca	-	7,004
Menni et al. (2021)	UK	Prospective observational	655,590	General population (adults)	AstraZeneca, Pfizer-BioNTech	Vaccine type: Pfizer-BioNTech (a), AstraZeneca (b)	773,775
Nittner-Marszalska et al. (2021)	Poland	Cross-sectional	1,808	Healthcare workers	Pfizer-BioNTech	Number of doses received: one dose (a), two doses (b)	7,202
Djanas et al. (2021)	Indonesia	Cross-sectional	840	Healthcare workers	Sinovac	-	1,106
Geisen et al. (2021)	Germany	Cohort	64	Healthcare workers	Pfizer/Moderna	-	146
Kadali et al. (2021)	USA	Cross-sectional study	803	Healthcare workers	Pfizer-BioNTech	-	3,457

*Number of participants that received at least one dose of COVID-19 vaccine and were observed

**Aggregate data indicated that more than one adverse event was reported/observed per participant

Table 2: Results of meta-analysis of prevalence rates of adverse events following COVID-19 vaccination

Adverse event	N studies	N study participants observed	Median number of study participants observed (IQR)	Pooled prevalence (95% CI)	I ² (%)
Pain at injection site	11	670,557	435 (71 to 1,758)	67.21 (46.49 to 82.86)	99.9
Weakness/fatigue	13	671,045	555 (134 to 1,350)	41.88 (26.82 to 58.61)	99.9
Muscle/joint pain	13	672,791	679 (134 to 1,733)	28.95 (16.95 to 44.86)	99.9
Headache	14	672,883	524 (92 to 1,529)	27.78 (17.59 to 40.95)	99.9
Fever/chills	14	672,868	555 (134 to 1,707)	16.42 (8.39 to 29.64)	99.9
Swelling at injection site	10	668,759	829 (170 to 1,783)	11.26 (7.04 to 17.52)	99.8
Redness at injection site	9	670,300	917 (127 to 2,272)	7.49 (4.34 to 12.63)	99.8
Nausea and/or vomiting	8	670,962	994 (803 to 2,426)	6.39 (3.09 to 12.74)	99.9
Diarrhea	5	664,093	994 (822 to 157,95)	5.49 (2.05 to 13.92)	99.9
Tingling	6	11,795	803 (435 to 840)	2.38 (0.89 to 6.22)	98.5
Skin rashes	6	665,747	811 (170 to 4,799)	1.94 (0.88 to 4.21)	99.7

Four cases of death were reported by two papers. The first paper investigated safety of an mRNA COVID-19 vaccine in cancer patients (Waissengrin et al., 2021). The

paper reported three deaths among 170 patients, one of which was attributed to COVID-19; the other two deaths were attributed to cancer disease progression. The

three deaths were reported after the first dose of vaccine. A second study reported death in a man with long-standing multiple sclerosis (MS) and severe disability 21 days after being administered with the second dose of the mRNA COVID-19 vaccine (Achiron et al., 2021). The study enrolled 574 MS patients. Furthermore, 43 cases of anaphylaxis were reported in three studies with a total population of 68,218 (Blumenthal et al., 2021; Djanas et al., 2021; Song et al., 2021).

Table 3 shows the results of Egger’s regression test. For the pain at injection site

prevalence, the funnel plot suggested a symmetrical pattern in Supplement (S2-1), and this was supported by the result of the Egger’s regression test (intercept= 20.46; t= 2.01; p= 0.061).

Similar results were obtained for prevalence rates of weakness/ fatigue in Supplement (S2-2), muscle/joint pain, headache, fever/chills, nausea and/or vomiting, skin rashes, and diarrhea. However, swelling at injection site (p= 0.041), redness at injection site (p= 0.018) and tingling (p= 0.002) demonstrated significant publication bias.

Table 3. Egger’s regression test for publication bias

Adverse event	Number of studies	Intercept	t-value	p
Pain at injection site	11	20.46	2.01	0.061
Weakness/fatigue	13	16.95	1.60	0.128
Muscle/joint pain	13	20.30	1.92	0.072
Headache	14	9.68	0.98	0.339
Fever/chills	14	7.87	0.73	0.475
Swelling at injection site	10	13.87	2.30	0.041*
Redness at injection site	9	14.92	2.74	0.018*
Nausea and/or vomiting	8	8.04	0.83	0.425
Diarrhea	5	21.35	1.05	0.341
Tingling	6	-8.50	-4.99	0.002*
Skin rashes	6	10.53	1.42	0.195

*Statistically significant funnel plot asymmetry

DISCUSSION

This systematic review and meta-analysis included data on 735,515 participants across ten countries in 15 recent-published COVID-19 vaccination studies and evaluated the adverse events occurrence from the administered vaccines. Findings showed that of the 11 adverse events synthesised, pain at injection site (67.2%), weakness/fatigue (41.8%), muscle/joint pain (28.9%) and headache (27.7%) were the most prevalent adverse events reported in the primary studies. All pooled prevalence of adverse events showed considerable heterogeneity while estimates from studies for the adverse events swelling at injection site, redness at injection site,

and tingling showed significant funnel plot asymmetry indicating publication bias.

A major strength of the study is large sample size of participants in included studies. This gives the study a considerable precision to estimate the average prevalence of reported adverse events. More than three-quarter of the included studies enrolled health workers. Health workers were the first population group who were targeted for SARS-CoV-2 vaccination in most countries. It is reasonable to suspect the existence of a systematic difference in health-seeking behavior hence, adverse event reporting rate, between health workers and the general population.

Several months have elapsed since the date of execution of the time when the search was conducted for this study. More potentially relevant studies would have been conducted and were not included in this systematic review. There was gross heterogeneity in all of the pooled adverse events estimates. The statistical heterogeneity shown in the meta-analyses could be an extension of the clinical heterogeneity resulting from differences in the type of vaccines given, vaccine doses and possibly differences in time of outcome ascertainment. Therefore, the pooled estimates reported should be interpreted cautiously in this context. The heterogeneity was expected which justified the adoption of the random-effects model for the meta-analyses.

This systematic review included eligible studies indexed in PubMed. There are studies that may not have been indexed in PubMed. There is no reason to believe that these studies (if any) would differ systematically from those that we have included.

Our study analyzed adverse events reported including data also from population studies hence, focusing on real-world data. A systematic review compared the reactogenicity, immunogenicity and efficacy of SARS-CoV-2 vaccines between experimental and control groups and enrolled studies in phase I/II/III studies in human and non-human studies (McDonald et al., 2021). Another systematic review assessed adverse events in early phase clinical trials and enrolled clinical trials in phases I and II (Kaur et al., 2021). Other systematic reviews have either focused on pooling the risk of adverse events in clinical trials (Chen et al., 2021; McDonald et al., 2021), frequency of adverse events in the placebo arms of trials (Haas et al., 2022). Our study is the largest systematic review assessing adverse events in population-based studies.

A major implication of findings from this study is the comprehensive enumeration of adverse events reported from early studies on COVID-19 vaccination, demonstrating the average rate of occurrence of these adverse events. There has been reported hesitancy in taking the SARS-CoV-2 vaccination and misconceptions about the potential unintended effects from some of these vaccines have been reported (Zhuang et al., 2021). This is particularly rife because of the short duration of observation in studies which made many people to adopt a side-liner posture or delay their acceptance of the vaccines despite being administered free of charge.

In this study, only one death was ascribed to COVID-19 from the hundreds of thousand population enrolled and the case occurred in a patient with chronic co-morbidity. This implies a very safe short-term profile of these vaccines. The majority of the population may only experience injection site pain, general fatigue, headache and body aches. These are mild adverse events which would likely resolve with the use of analgesics and rest.

The systematic review focused on adverse events from observational studies. Methodological quality of studies was not assessed, the study not being a typical systematic review of interventions. Therefore, this study is similar to a study of real-world observational data which is well suited for meeting the study objective. The extent to which the methodological quality of studies may influence ascertainment and reporting of adverse events is not immediately clear.

The most prevalent adverse events among recipient of SARS-CoV-2 vaccines were local reactions such as pain at the site of injection and general systemic reactions such as fatigue, muscle/joint pain and headaches. Cases of mortality were extremely

rare and mostly related to co-morbidities. The study therefore, demonstrated the short to medium term safety profile of SARS-CoV-2 vaccination.

SUPPORTING INFORMATION

S1. Forest Plot showing pooled prevalence

[\(PDF\)](#)

S2. Funnel Plot of systematic review and meta-analysis

[\(PDF\)](#)

AUTHOR CONTRIBUTION

SB, BG, MMS, EAB, AF, OO, and ASA conceptualised the study. SB developed the search strategy and conducted the search. DTA, AA, and TO conducted screening and data extraction. SB and DTA conducted statistical analysis. SB, RFA, AF, ASA interpreted the results. All authors contributed to the writing of the manuscript and approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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