

■ Research Article

## ENG: comparative evaluation of side effects and the factors affecting vaccine preferences of healthcare workers within the booster COVID-19 vaccination in Turkey

*TR: Türkiye'de güçlendirici COVID-19 aşılması kapsamında sağlık çalışanlarının aşı yan etkilerinin ve aşı tercihini etkileyen faktörlerin karşılaştırmalı değerlendirilmesi*

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### ABSTRACT

**Aim:** The study's primary aim is to evaluate the frequency and distribution of 3rd dose vaccines' side effects, especially for the rare heterologous vaccine scheme. The secondary objective is to determine the factors affecting the booster COVID-19 vaccination preferences of HCWs.

**Material and Methods:** This single-center, retrospective descriptive study was conducted on 1058 HCWs, through an online survey. In this study, 3rd dose COVID-19 vaccine preferences, the affecting factors, and the side effects were questioned and analyzed.

**Results:** 87% of the participants (n=921) had the 3rd booster COVID-19 vaccine. Of those vaccinated, 82.4% (n=759) had Pfizer/BioNTech, and 17.6% (n=162) had CoronaVac/Sinovac. The most common factors that affect the 3rd dose vaccine choice are physicians'/HCWs' recommendations (53.4%; n=492), scientific publications (42.7%; n=393), and recommendations of the Ministry of Health (41.6 %, n=383). 83% (n=630) of 759 who were vaccinated with Pfizer/BioNTech developed post-vaccine side effects, while 59% (n=96) of 162 HCWs who were vaccinated with CoronaVac/Sinovac developed (p<0.001). The most common side effect observed was muscle-joint pain (49.2%), and it occurred most frequently in the first 48 hours after vaccination (36%). The most commonly reported side effects in the 2-7 days and 7-28 days post-vaccination were muscle-joint pain (11.6%) and fatigue (1.6%), respectively. It was observed that fatigue, headache, muscle-joint pain, local reaction at the injection site, fever, and lymphadenopathy side effects were more common in those who administered the Pfizer/BioNTech vaccine.

**Conclusion:** Although it is associated with developing more frequent side effects, mRNA vaccines are preferred by HCWs. Physician/HCWs recommendations and scientific publications were found to be the most valuable sources on the decision of vaccine preference.

**Keywords:** Coronavac/Sinovac, healthcare worker, Pfizer/BioNTech, side effects, vaccine preferences

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## ÖZ

**Amaç:** Çalışmanın birincil amacı, özellikle nadir görülen heterolog aşı şeması için 3. doz aşılardan yan etkilerinin sıklığını ve dağılımını değerlendirmektir. İkincil amaç ise sağlık çalışanlarının rapel COVID-19 aşılama tercihlerini etkileyen faktörlerin belirlenmesidir.

**Gereç ve Yöntemler:** Bu tek merkezli, retrospektif tanımlayıcı çalışma, çevrimiçi anket aracılığıyla, 1058 sağlık çalışanı ile yürütülmüştür. Bu çalışmada 3. doz COVID-19 aşısı tercihleri, tercihi etkileyen faktörler ve 3. COVID-19 aşısı ile gelişen yan etkiler sorgulanmış analiz edilmiştir.

**Bulgular:** Katılımcıların %87'si (n=921) 3. rapel COVID-19 aşısı oldu. Bunların %82,4'ü (n=759) Pfizer/BioNTech ve %17,6'sı (n=162) CoronaVac/Sinovac ile aşılandı. 3. doz aşı seçimini etkileyen en yaygın faktörler hekim/sağlık çalışanlarının önerileri (%53,4; n=492), bilimsel yayınlar (%42,7; n=393) ve Sağlık Bakanlığı tavsiyeleridir (%41,6; n=383). Pfizer/BioNTech ile aşılanan 759 kişiden %83'ünde (n=630), CoronaVac/Sinovac ile aşılanan 162 sağlık çalışanının %59'unda (n=96) aşı sonrası yan etki gelişti (p<0.001). En sık görülen yan etki kas-eklem ağrısı (%49,2) olup, en sık aşılardan sonraki ilk 48 saatte (%36) ortaya çıktı. Aşılardan sonraki 2-7. gün ve 7-28. gün en sık bildirilen yan etkiler sırasıyla kas-eklem ağrısı (%11,6) ve yorgunluk (%1,6). Pfizer/BioNTech aşısı yaptıranlarda CoronaVac/Sinovac aşısı yaptıranlara göre yorgunluk, baş ağrısı, kas-eklem ağrısı, enjeksiyon yerinde lokal reaksiyon, ateş ve lenfadenopati yan etkileri daha sık görüldü.

**Sonuç:** Sonuçta, daha sık yan etki gelişimi ile ilişkili olmakla birlikte, mRNA aşısı sağlık çalışanları tarafından daha fazla tercih edilmektedir. Aşı olma kararı ve aşı tercihleri konusunda en değerli kaynakların doktor/sağlık çalışanı tavsiyeleri ve bilimsel yayınlar olduğu görülmüştür.

**Anahtar kelimeler:** aşı tercihleri, Coronavac/Sinovac, Pfizer/BioNTech, sağlık çalışanı, yan etkiler

## Introduction

The pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has posed an extraordinary threat and burden of disease to global public health. Although the COVID-19 public health emergency ended on May 11, 2023, the pandemic is still ongoing, and most tools, like vaccines, treatments, and testing, remain available [1]. Vaccination against SARS-CoV-2 is still a key measure to prevent infection, serious illness, hospitalization, and death.

As of July 2023, WHO has validated 15 vaccines for COVID-19 emergency use listing (EUL). Seven vaccines are recombinant, three are inactivated, and five are mRNA vaccines [2]. Inactivated virus vaccines use a weakened form of the virus so it does not cause disease but generates an immune response. RNA and DNA vaccines are cutting-edge approaches that use genetically engineered RNA or DNA to create a protein that safely prompts an immune response [3]. The CDC recommends primary series vaccination for three monovalent COVID-19 vaccines (Moderna, Novavax, and Pfizer-BioNTech). People ages six months and older who previously received only monovalent doses are recommended to receive 1 or 2 bivalent mRNA doses, depending on age and vaccine product [4].

COVID-19 vaccination in Turkey started with the CoronaVac/Sinovac vaccine on January 14, 2021, after the "Emergency Use Approval" of the Turkish Medicines and Medical Devices Agency

[5], the Pfizer-BioNTech vaccine became available in April 2021 [6]. When the studies showed that the antibody response 90 days after two doses of vaccination with inactivated vero cell vaccine decreased significantly, the third vaccine dose became necessary [7]. The third vaccine dose was implemented for people over 50 and healthcare workers (HCWs) in July 2021, and people were freed to choose their vaccine[8].

In this study, we aimed to investigate the factors affecting the 3rd dose of COVID-19 vaccine preferences of HCWs, and the comparative side effects of the COVID-19 vaccines available in our country.

## Material and Methods

### Study Design and ethical statement

This single-center, retrospective descriptive study was conducted on HCWs who had previously received two doses of the CoronaVac/Sinovac vaccine and agreed to participate. The study was approved by the Gazi University Clinical Studies Ethical Committee (Decision number: 116 and date:17.02.2021). The study was conducted in accordance with the Declaration of Helsinki Principles ([www.wma.net/e/policy/b3.htm](http://www.wma.net/e/policy/b3.htm)) All participants provided informed consent.

### Study population and definitions

In this study, 3rd dose COVID-19 vaccine preferences, the factors affecting these preferences, and the side effects that

developed up to the 28th day after the third dose of COVID-19 vaccination were questioned and analyzed. The questionnaire forms were distributed online to 1058 HCWs

In the study, HCWs were defined and grouped according to the definitions determined by the WHO in 2006 [9]. The vaccine-related adverse events evaluated in the study were selected from the US Vaccine Adverse Event Reporting System (VAERS) Table of Reportable Events and a recent report from a European consortium on vaccine surveillance (ADVANCE project) [10]. In addition, side effects frequently reported during phase studies of the Coronovac and Pfizer/BioNTech vaccines were evaluated [11, 12]. In the study, 'Known vaccine side effect after vaccination or anything thought to be due to the vaccine' is described as a vaccine-related adverse event.

Serious adverse event report - These reports meet the definition of "serious" specified by the Code of Federal Regulations because one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization, permanent disability, congenital anomaly, or congenital disability [10].

Non-serious adverse event report - These reports do not meet the regulatory definition of a serious adverse event report [10].

Possible side effects after getting a COVID-19 vaccine to be defined as local reactions (pain, redness, swelling), systemic reactions (tiredness, headache, muscle pain, chills, fever, nausea, and others), by CDC (Centers for Disease Control and Prevention) [13].

### Statistical analysis

All data were analyzed by IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, N.Y., USA) and summarized with tables and graphs. Shapiro-Wilk test, histogram, and Q-Q plot were used to determine the normality distribution of the data. Categorical variables were expressed with numbers and percentiles. Continuous variables are defined as mean, standard deviation, median, and interquartile range.  $p < 0.005$  was accepted as statistically significant.

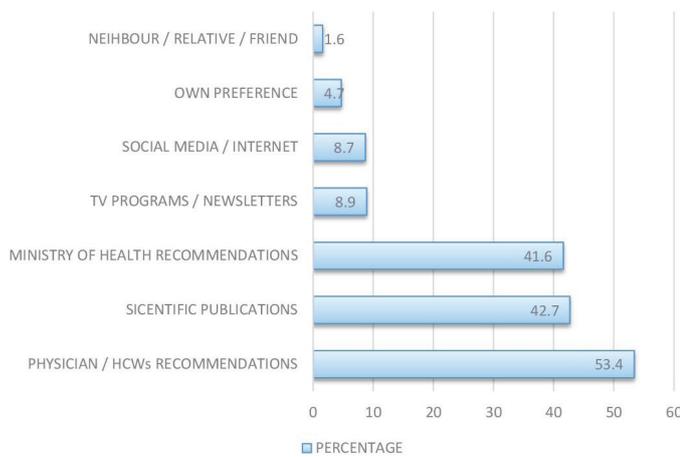
### Results

1058 HCWs participated in the online survey. 87% of the participants (n=921) had the third dose of the COVID-19 vaccine. The descriptive characteristics of HCWs who received the 3rd dose of the COVID-19 vaccine are shown in Table 1.

Of those vaccinated, 82.4% (n=759) had Pfizer/BioNTech, and 17.6% (n=162) had CoronaVac/Sinovac vaccine. Of those who received the Pfizer/BioNTech vaccine as the third dose, 77.3% (n=587) have had any vaccine in the last ten years. Of those who had the CoronaVac/Sinovac vaccine, 79.6% (n=129) have

had any vaccine in the previous ten years. 3.6% (n=27) of those who received the Pfizer/BioNTech vaccine as the 3rd dose of the COVID-19 vaccine, 2.5% (n=4) of those who received the CoronaVac/Sinovac vaccine had a previous allergic reaction to any vaccine. 17.4% (n=132) of those who received the Pfizer/BioNTech vaccine as the 3rd dose COVID-19 vaccine and 18.5% (n=30) of those who received the CoronaVac/Sinovac vaccine had a history of food/drug/cosmetics allergy. 44.1% (n=335) of those who received the Pfizer/BioNTech vaccine as the 3rd dose of the COVID-19 vaccine and 40.1% (n=65) of those who received the CoronaVac/Sinovac vaccine had a COVID-19 infection history. The most common sources HCWs use to decide on the choice of the 3rd dose vaccine are summarized in Figure-1.

<b>Table 1.</b> The descriptive characteristics of HCWs who received the 3rd dose of the COVID-19 vaccine (n=921)	
Age, median(IQR 25-75)	40 (33-46)
Gender, n (%)	
Male	363 (39,4)
Female	558 (60,6)
Occupational distribution of HCWs, n(%)	
Physician	126 (13,7)
Nurse	234 (25,4)
Technical personnel	89 (9,7)
Secretary	53 (5,8)
Cleaning staff member	83 (9)
Patient transport staff	94 (10,2)
Security	89 (9,7)
Others	153 (16,6)
Comorbid diseases, n(%)	
Hypertension	74(8)
Diabetes mellitus	60 (6,5)
Cardiovascular disease	36 (3,9)
Chronic lung disease	34 (3,7)
Chronic kidney disease	1 (0,1)
Malignancy	10 (1,1)
Hypothyroidism	63 (6,8)
Others	77 (8,4)
Smoking,n(%)	300 (32,6)
Previously known food, drug cosmetic allergy, n(%)	162 (17,6)
Vaccine allergy other than the COVID-19 vaccine, n(%)	31 (3,4)
Being vaccinated except COVID-19 vaccine in the last 10 years, n(%)	716 (77,7)
Have a relative who has been vaccinated except COVID-19 vaccine in the last ten years, n(%)	533(57,9)
Have COVID-19 history, n(%)	400 (43,4)
Have a relative who have COVID-19 history, n(%)	711 (77,2)
Any relative who has died due to COVID-19, n(%)	173 (18,8)
Any child going to kindergarten/school in the house you live in, n(%)	465 (50,5)
Any people over the age of 65 in your home, n(%)	145 (15,7)
Using public transport,n(%)	550 (59,7)



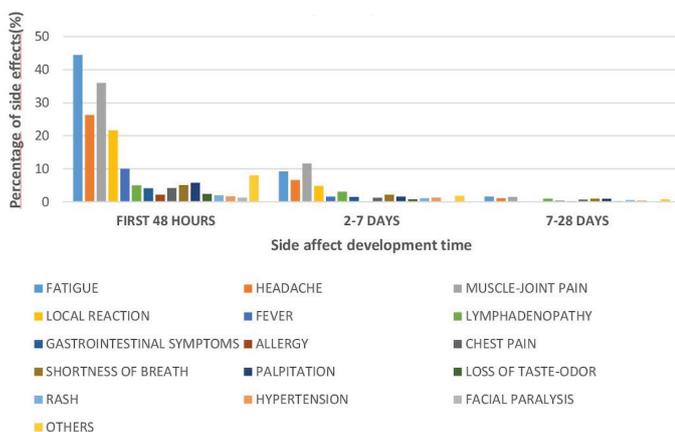
**Figure 1.** The most common sources HCWs use to decide on the choice of the 3rd dose vaccine

A comparative evaluation of sources affecting the preferences for 3rd dose of the COVID-19 vaccine in HCWs was summarized in Table 2.

**Table 2.** Comparative evaluation of sources that are affecting the preferences of 3rd dose COVID-19 vaccine in HCWs

	Pfizer/ BioNTech (n=759)	CoronaVac/ Sinovac (n=162)
Physician / HCWs recommendation, n(%)	433(57)	60(37)
Scientific publications, n(%)	336(44)	57(35)
Ministry of Health recommendation, n(%)	307(40)	76(46)
TV programs/newsletters, n (%)	77(10)	5(3)
Social media/internet, n(%)	75(9,8)	5(3)
Own preference, n(%)	22(2,8)	21(12)
Neighbor / relative / friend, n(%)	11(1,4)	4(2,4)

Local and systemic side effects that developed after the third dose of COVID-19 vaccines are summarized in Figure 2 in terms of the development time.



**Figure 2.** Distribution of side effects after 3rd dose of COVID-19 vaccine according to duration of side effect development, n=921

In the first 48 hours after vaccination, the most common side effect was fatigue (n=410, 44.5%); in the 2-7 day period, the most common side effect was muscle-joint pain (n=107, 11.6%); in the 7-28 day period the most common side effect was also reported as fatigue (n=15, 1.6%). The most common side effect observed after the 3rd dose of the COVID-19 vaccine was muscle-joint pain (n=453, 49.2%), and it occurred most frequently in the first 48 hours after vaccination. (suppl table 1)

Side effects were observed at any time after vaccination in 83% (n=630) of 759 HCWs who received the 3rd dose vaccine from Pfizer/BioNTech and 59% (n=96) of 162 HCWs who received CoronaVac/Sinovac (p< 0.001). (suppl table 2 and 3)

Comparative evaluation of post-vaccine side effects according to the preferred 3rd dose COVID-19 vaccine being Pfizer/ BioNTech or CoronaVac/Sinovac is summarized in Table 3.

**Table 3.** Comparative evaluation of post-vaccine side effects according to the preferred 3rd dose COVID-19 vaccine being Pfizer/BioNTech or CoronaVac/Sinovac (n=759, n= 162)

	Pfizer/BioN- Tech, n (%)	CoronaVac/ Sinovac, n (%)	p value
Fatigue	449 (59,2)	61 (37,7)	< 0,001
Headache	272 (35,8)	41 (25,3)	0,010
Muscle-joint pain	411 (54,1)	42 (25,9)	<0,001
Local reaction	219 (28,9)	25 (15,4)	<0,001
Fever	100 (13,2)	8 (4,9)	0,002
Lymphadenopathy	78 (10,3)	6 (3,7)	0,006
Vomiting, diarrhea	46 (6,1)	9 (5,6)	1
Allergy	17 (2,2)	6 (3,7)	0,27
Loss of taste-odor	25 (3,3)	6 (3,7)	0,81
Facial paralysis	10 (1,3)	4 (2,5)	0,28
Rash	25 (3,3)	8 (4,9)	0,34
Hypertension	23 (3)	9 (5,6)	0,15
Chest pain	47 (6,2)	9 (5,6)	0,85
Shortness of breath	68 (9)	8 (4,9)	0,11
Palpitation	63 (8,3)	14 (8,6)	0,87
Others	78 (10,3)	20 (12,3)	0,48

## Discussion

In our study, most HCWs received the 3rd dose of the COVID-19 vaccine, and the preferred one is mostly the Pfizer/BioNTech vaccine. The factors affecting vaccine choice were mostly physicians' recommendations and scientific publications. It was determined that the advice of the Ministry of Health was the situation that most influenced the preference of those who chose the Coronavac vaccine for the 3rd dose of the COVID-19 vaccine. It was observed that fatigue, headache, muscle-joint pain, local reaction at the injection site, fever, and

lymphadenopathy side effects were more common in those who received the Pfizer/BioNTech vaccine compared to those who received the CoronaVac/Sinovac vaccine.

When the studies conducted worldwide are evaluated, COVID-19 booster dose vaccination is preferred by 55-92% of healthcare professionals [14-16]. Similarly, in our study, 87% of the participants (n=921) had the third dose of the COVID-19 vaccine. Of those vaccinated, 82.4% (n=759) had Pfizer/BioNTech, and 17.6% (n=162) had CoronaVac/Sinovac.

The recommendations of physicians/healthcare professionals and scientific publications are the most valuable resources for getting vaccinated [17]. In a study conducted by Alhasan K. et al., it was observed that participants preferred social media (50.5%), hospital announcements (36.0%), and scientific journals (30.5%) as sources of information in their booster vaccine decision [18]. Our study found that the factors affecting booster vaccine decisions were mostly physicians' recommendations, scientific publications, and Ministry of Health recommendations. Physicians' recommendations mainly affected the Pfizer/BioNTech choice, and Ministry of Health advice mostly acted the CoronaVac/Sinovac choice as a 3rd booster dose.

Vaccine resources may be unevenly distributed worldwide, so there may be delays in vaccine supply. Using heterogeneous booster doses for COVID-19 has been an alternative strategy [19]. When the 3rd dose vaccination was started for HCWs, there was no vaccine in our country except CoronaVac/Sinovac and Pfizer/BioNTech. Vaccine preferences are not interfered with; everyone chooses different vaccines according to the source they received information from. Thus, various side-effect profiles emerged in heterologously vaccinated populations.

Various local and systemic side effects have been reported in many studies on COVID-19 vaccines. In a meta-analysis of 23 studies compared with the homologous booster group, there was a higher risk of fever, myalgia, and fatigue within seven days after boosting and a higher risk of malaise or fatigue within 28 days after boosting in the heterologous vaccination group [19]. In our study, those who received the Pfizer/BioNTech vaccine after two doses of the CoronaVac/Sinovac vaccine were an example of a heterologous booster vaccination. And fatigue, headache, muscle-joint pain, local reaction at the injection site, fever, and lymphadenopathy were observed more frequently after heterologous vaccination than homologous vaccination.

A systematic review and meta-analysis of randomized controlled trials examining the safety of SARS-CoV-2 vaccines

found that inactivated COVID-19 vaccine candidates had the lowest reported adverse effects [20]. A meta-analysis evaluating 49 placebo-controlled clinical trials found that inactivated vaccines had the most safety profile when COVID-19 vaccine types were compared regarding systemic side effects. mRNA vaccines had the worst safety profile [21]. The low risks of adverse events from inactivated vaccines are because inactivated vaccines do not replicate in the recipient [22]. In our study, the post-vaccine side effects of those who received the Pfizer/BioNTech vaccine, which is an mRNA vaccine, developed at a higher rate than those who received the CoronaVac/Sinovac vaccine, which is an inactivated vaccine (83% and 59% respectively,  $p < 0.001$ ).

According to a meta-analysis, injection site pain was the most common local symptom, and fatigue was the most common side effect in people receiving the mRNA vaccine (29-85% of participants [23]). In a single-blind randomized study conducted in Brazil, 1,205 people who received booster vaccination after two doses of the CoronaVac/Sinovac vaccine were evaluated. Pfizer/BioNTech vaccine was given to 333 people, CoronaVac/Sinovac to 281 people, and recombinant adenoviral vector vaccines to the rest. The most common side effects were pain at the injection site, headache, and myalgia [24].

In a study involving 428 HCWs who received the Pfizer/BioNTech as a 3rd dose vaccine after two doses of CoronaVac/Sinovac vaccine in Turkey, the most common side effects were fatigue (58,6%), muscle-joint pain (51,1%) and headache (40,7%), respectively [25]. Our study found the most common side effects in the same order. In patients who received the Pfizer/BioNTech as a 3rd dose vaccine (n=759), side effects were found to be fatigue (59,1%), muscle joint pain (54,1%), and headache (35,8%), respectively.

If we handle another side effect in our survey results, post-vaccine lymphadenopathy was found in 84 people (9,1%). Of these, 78 had received the Pfizer/BioNTech vaccine. A review of 10 studies pooled the incidence of clinically detectable axillary lymphadenopathy after COVID-19 vaccination was 91/22,532 (0,4%) [26]. In another review that included 15 studies, the incidence of lymphadenopathy was found to vary between 14.5% and 53% [27].

In our study, post-vaccine side effects were observed most frequently in the first 48 hours. The most commonly reported side effects in the 2-7 days and 7-28 days post-vaccination were muscle-joint pain (11.6%) and fatigue (1.6%), respectively. Although rare, serious adverse events may occur in the late

post-vaccine period. Between 10 and 23 December 2020, 1,893,360 people received the first dose of the Pfizer-BioNTech Covid-19 vaccine, and 21 people developed severe allergic reactions, including anaphylaxis, accounting for 11.1 cases per million. However, no deaths from anaphylaxis have been reported [28]. Based on an analysis of 40 case reports [29], the epidemiology and clinical picture of myocarditis related to the COVID-19 vaccine were presented in another study. Most cases were seen in males with 90% predominance, which were seen in the age group of 29.13 years old (mean, SD of 14.39 years). In 65% of cases, patients took the BNT162b2 vaccine; 30% of cases were reported with the mRNA-1273 vaccine, and 5% of cases with JNJ-78436735. Of all the cases, 80% are reported after the second dose of the vaccine with either Moderna or Pfizer. In our study, anaphylaxis or myocarditis did not occur in any of the HCWs who received the Pfizer/BioNtech vaccine for the first time. Post-vaccine adverse event monitoring should not be limited to the first 48 hours.

## Conclusion

According to our study, although the safety profile of inactivated COVID-19 vaccines is better, mRNA vaccines are preferred when considering efficacy. It has been determined that the recommendations of physicians/healthcare professionals and scientific publications are the most valuable resources for getting vaccinated. Post-vaccine adverse event monitoring should continue for a long time.

## Author contributions

1. Creating the concept and design of the study: Yeşim Yıldız, H. Selçuk Özger, and Esin Şenol. 2. Data collection: Yeşim Yıldız, H. Miraç Mavi, Fidan Sultanova, Merve Büyükkörük. 3. Analysis of data and expression of findings: Merve Büyükkörük, Yeşim Yıldız, H. Selçuk Özger, H. Miraç Mavi. 4. Drafting of the article: Yeşim Yıldız and H. Miraç Mavi, review of the scientific content by H. Selçuk Özger and Esin Şenol. 4. Approval of the final ready-to-print manuscript: all authors.

## Conflict of interest

No person/organization financially supports the work, and the authors have no conflict of interest.

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