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ACTIVE MONITORING OF EARLY SAFETY OF SPUTNIK V VACCINE IN BUENOS AIRES, ARGENTINA

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Abstract This study describes the incidence of early events supposedly attributable to vaccination or immunization (ESAVI) that occurred in healthcare workers who had been inoculated with the first component of the Sputnik V vaccine. Safety at 72 h post-immunization was analyzed based on a self-reported form. Between January 5 and January 20, 2021, in Buenos Aires, Argentina, a total of 707 healthcare workers (median age 35 yrs, female 67%) were vaccinated. The response rate was 96.6% (n: 683) and 487 (71.3%) participants reported at least one ESAVI. The incidence rate was 6.3 per 1000 person/hours. The total number of ESAVIs was 1434. A total of 469 local reactions were reported, 57% of the participants reported pain at the injection site, and 11% had redness and swelling. A total of 968 systemic reactions were informed, including new or worsened muscle pain, referred by 58% of the participants, fever referred by 40%, and diarrhea referred by 5%. Five percent (n: 34) had serious adverse events and one participant had to be hospitalized. The ESAVI rate was higher in females than males (66.4% versus 51.4%; HR 1.38; 95% CI 1.13-5.38) and in workers younger than 55 yrs old (63.0% versus 28.0%; HR 2.66; 95% CI 1.32-5.38). This study demonstrates high rates of early local and systemic reactions. However, serious events were rare. Studies on long-term safety, stratified by sex and age, are needed.

Key words: adverse effects, COVID-19 vaccines, public health surveillance

Resumen ***Monitoreo activo de la seguridad temprana de la vacunación con Sputnik V en Buenos Aires, Argentina.*** Este estudio describe la incidencia de eventos supuestamente atribuibles a vacunación o inmunización (ESAVI) en trabajadores de la salud después de la inmunización con el primer componente de la vacuna Sputnik V. La seguridad a las 72 horas de la inmunización se analizó en base a un auto-reporte. Entre el 5 y el 20 de enero de 2021, en Buenos Aires, Argentina, fueron vacunados 707 trabajadores de la salud (mediana de edad 35 años, 67% mujeres). La tasa de respuesta fue 96.6% (n: 683), y 487 participantes (71.3%) informaron al menos un ESAVI. Los ESAVI totales fueron 1434 y la incidencia fue 6.3 por 1000 personas/hora. Fueron informadas 469 reacciones locales: 57% de los participantes informaron dolor en el lugar de la inyección y 11% enrojecimiento e hinchazón. Entre las 968 reacciones sistémicas, el 58% de los participantes informaron dolor muscular nuevo o empeorado, 40% fiebre y 5% diarrea. El 5% (n: 34) presentó eventos adversos graves y un paciente tuvo que ser hospitalizado. La tasa de ESAVI fue mayor entre las mujeres (66.4% versus 51.4%; HR 1.38; IC 95% 1.13-5.38) y en el grupo de trabajadores menores de 55 años (63.0 versus 28.0; HR 2.66; IC 95% 1.32-5.38). Este estudio mostró altas tasas de reacciones tempranas locales y sistémicas; sin embargo, los eventos graves fueron raros. Son necesarios estudios sobre la seguridad a largo plazo, estratificados por sexo y edad.

Palabras clave: efectos colaterales y reacciones adversas relacionados con medicamentos, inmunoterapia activa, COVID-19, vigilancia sanitaria

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KEY POINTS
Evidence before this study

- The emergency management of the COVID-19 epidemic allows the administration of vaccines without having completed the phase 3 trials. Until February 2021, only ten countries have used the Sputnik V COVID-19 vaccine. Active and passive surveillance is essential for the notification of events supposedly attributable to vaccination and immunization.

Contribution

- This is the first study in evaluating the early safety of the Sputnik V COVID-19 vaccine under real conditions in Argentina. Among vaccinated healthcare workers, the early events supposedly attributable to the Sputnik V vaccine were fairly frequent but mostly mild.

The World Health Organization recommends vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to mitigate the coronavirus disease 2019 (COVID-19) pandemic. Effective and safe vaccines will reduce COVID-19 related rates of disease, hospitalization, and death in the short term and help to gradually restore normal activities in our country[1].

Sputnik V is a heterologous COVID-19 vaccine consisting of two immunogenic components that are applied in two doses separated by at least 21 days. The first component contains a recombinant adenovirus type 26 (rAd26) vector and the second contains a recombinant adenovirus type 5 (rAd5) vector. Both vectors carry the gene for the full-length SARS-CoV-2 spike glycoprotein (rAd26-S and rAd5-S)[2, 3].

On December 23, 2020, the Argentine National Administration of Drugs, Food and Medical Technology (ANMAT)[4] performed a confidential technical report on the Sputnik V vaccine; the (Argentine) National Ministry of Health authorized its use under the label of an "emergency authorization" within the framework of a national law specifically passed by the Argentine National Congress[4]. The Argentine National Ministry of Health[5] developed a strategic plan to reach the quality standards of safety and efficacy for the entire Argentine territory, being vaccination free, voluntary, performed in stages, and independent of a history of having suffered the disease[6].

For the surveillance of vaccine safety, the strategic plan prompts health effectors "to develop a specific plan for intensified passive and active surveillance of vaccine safety, which allows the continuous analysis of the notifications of events supposedly attributable to vaccination and immunization (ESAVI)"[6].

Faced with this epidemic emergency, which enables the administration of vaccines without having completed the phase 3 trials, it is essential to conduct safety research concurrent with the vaccination campaign. The Buenos Aires City´s Ministry of Health started, as a public policy, an active registry on surveillance of any vaccine applied to healthcare workers[7]. In this scenario of uncertainty, tools of information and communication technologies, like an ESAVI self-report form, are helpful to design collaborative epidemiological studies.

In Buenos Aires City, the vaccination campaign started on December 29, 2020, for healthcare workers from either public or private effectors, with an initial endowment of 24 000 Sputnik V vaccine schemes, granted by the National Ministry of Health in two batches.

The present study is a preliminary analysis of an ongoing multicenter study conducted in private health institutions in Buenos Aires City. The study is aimed to describe the incidence of ESAVI in healthcare workers after immunization with the first component of the Sputnik V vaccine. A previous version of this manuscript has been shared in medRxiv, a free online archive and distribution server for complete but unpublished manuscripts (preprints) in the medical, clinical, and related health sciences[8].

Materials and methods

A prospective cohort represented by healthcare workers immunized with the Sputnik V COVID-19 vaccine was carried out blinded. The surveillance period was 72 hours post-immunization. A self-report form was sent by email up to three times. Those workers who did not respond to the email were contacted by a nurse. Those reactions that were considered ESAVIs after medical evaluation were reported to the Argentine integrated health information system (SISA).

Quantitative data were expressed as mean and standard deviation or median and interquartile range (IQR) according to distribution. Qualitative data were expressed as absolute or relative frequencies.

The age categories were defined in 10-year groups, except for individuals between 18 and 30 years old who were grouped in one category. To allow external comparisons with other publications, we also defined a dichotomous classification in individuals $\leq$ 55 or > 55 years old.

The incidence rate of ESAVIs and 95% confidence intervals (95% CI) were estimated. The Kaplan-Meier estimator and plotter were performed by gender and age groups. Factors associated with the occurrence of ESAVI were evaluated using the Cox regression. The crude and adjusted Hazard Ratio (HR) were expressed with 95% CIs. A p level < 0.05 was considered statistically significant. The analysis was carried out with the R software version 4.0.3.

The protocol was approved by the Research Protocol Ethics Committee of the institution where the study was carried out under number 3876 and was registered in ClinicalTrials.gov Identifier: NCT04738435.

Results

A total of 707 healthcare workers received the first component of the Sputnik V COVID-19 vaccine in Buenos Aires, Argentina, between January 5 and January 20, 2021. Six hundred and eighty-three answered the self-report form, representing a 96.6% response rate. The median age was 35.0 years (IQR 30.5-42.0) and 67% were female. Thirty-four out of the 683 healthworkers

had previously had COVID-19 confirmed by real-time polymerase chain reaction. The test had been performed in case of symptoms or close contacts. Of these 34, the median time from COVID-19 positive test to vaccination date was 5.3 months (IQR 4.2-6.9), and none of them had active COVID-19 infection at the time of receiving the first vaccine component. In this institution, antibodies against SARS-CoV-2 are not routinely performed in healthcare workers. Table 1 shows the characteristic of vaccinated healthcare workers.

Four hundred and eighty-seven out of the 683 healthcare workers (71.3%) reported at least one ESAVI. The incidence rate was 6.3 per 1000 person/hour (95% CI 5.8-6.9). Regarding the clinical evolution of the ESAVI, 422 (86.6%) vaccinees had *restitutio ad integrum*, 25 (5.1%) needed medical assessment, and one was hospitalized due to an acute abdomen that resolved favorably without surgery. Three had COVID-19 diagnosed within 72 hours of vaccination. Local and systemic reactions are shown in Figure 1.

The cumulative incidence of ESAVI at 72 hours was 61.7% (95% CI 58.1-65.4); it was higher in women (66.4%; 95% CI 62.1-70.7) than in men (51.4%; 95% CI 44.9- 58.2). Figure 2 shows ESAVI cumulative incidence in males and females.

Regarding age groups, the incidence rate of ESAVI was higher in vaccinees aged up to 55 years than in those older than 55 years old, (72.8% n: 479 versus 32% n: 8). The cumulative incidence of ESAVI at 72 hours was 28.0% (95% CI 18.9-60.4) in people older than 55 years and 63.0% (95% CI 59.3-66.7) in those who were 55 years old or younger. Figure 3 shows ESAVI cumulative incidence in these age groups.

Both age and sex were factors associated with the incidence of ESAVI regardless of health condition before vaccination. Table 2 shows Cox regression analysis.

Discussion

In our study, the incidence of ESAVI with the Sputnik V vaccine among the 683 vaccinated healthcare workers (71.3%) was 17 times higher than the 4.7% disclosed in the "5th Surveillance Report on the Safety of Vaccines of the National Ministry of Health"[9] and similar to that reported in the interim analysis of the Sputnik V COVID-19 vaccine phase 3 trial (64.7%)[3]. Only one person (0.1%) required hospitalization in our study compared to 45 (0.3%) in the Sputnik V phase 3 study[3].

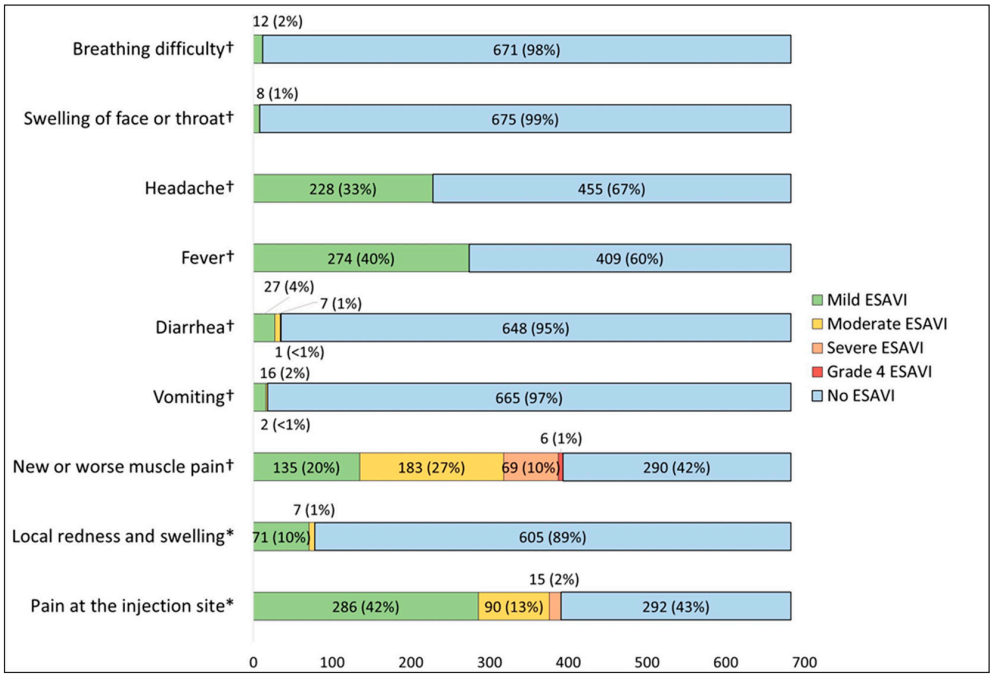
The incidence rates of pain at the injection site, fever, and headache in our study were within the range of values reported in previous Sputnik V vaccine studies[2]. However, we found muscular pain reported more than twice the rate reported in phase 1 and 2 of the Sputnik study (58% vs.

TABLE 1.– *Characteristic of the 683 vaccinated healthcare workers included in the study*

	n = 683	
	Number	%
Age, years		
18-30	171	25.0
31-40	307	44.9
41-50	140	20.5
51-60	60	8.8
61-70	4	0.6
71-80	1	0.1
Age category, years		
≤ 55	658	96.3
> 55	25	3.7
Sex		
Female	466	68.2
Male	217	31.8
Medical records		
Received any vaccination		
4 months before		
Yes	10	1.5
No	673	98.5
Any allergy		
Yes	36	5.3
No	647	94.7
Diabetes mellitus		
Yes	6	0.9
No	677	99.1
Hepatic disease		
Yes	4	0.6
No	679	99.4
Renal failure		
Yes	1	0.1
No	682	99.9
Corticosteroid treatment		
Yes	1	0.1
No	682	99.9
Autoimmune disease		
Yes	11	1.6
No	672	98.4
COVID-19		
Yes	34	5.0
No	649	95.0
Any other medical condition before vaccinationa		
Yes	33	4.8
No	650	95.2
Family history of reaction to vaccines		
Yes	6	0.9
No	677	99.1

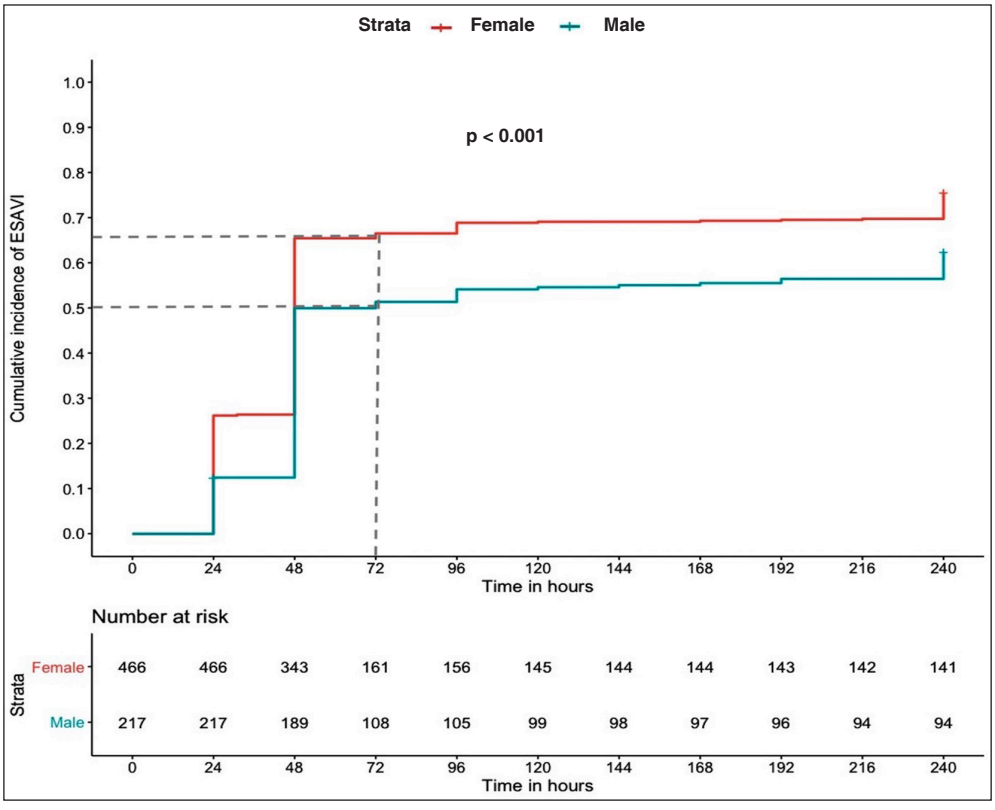
[a]*Any other medical condition as dyslipidemia, arterial hypertension, hypo or hyperthyroidism, asthma, gastrointestinal conditions such as dyspepsia, kidney stones and other nephropathies, dermatoses such as psoriasis, one person with thrombophilia, two with a history of lymphoma without active disease.*

Fig. 1.– Local and systemic reactions in healthcare workers after the administration of the first component of Sputnik V COVID-19 vaccine.



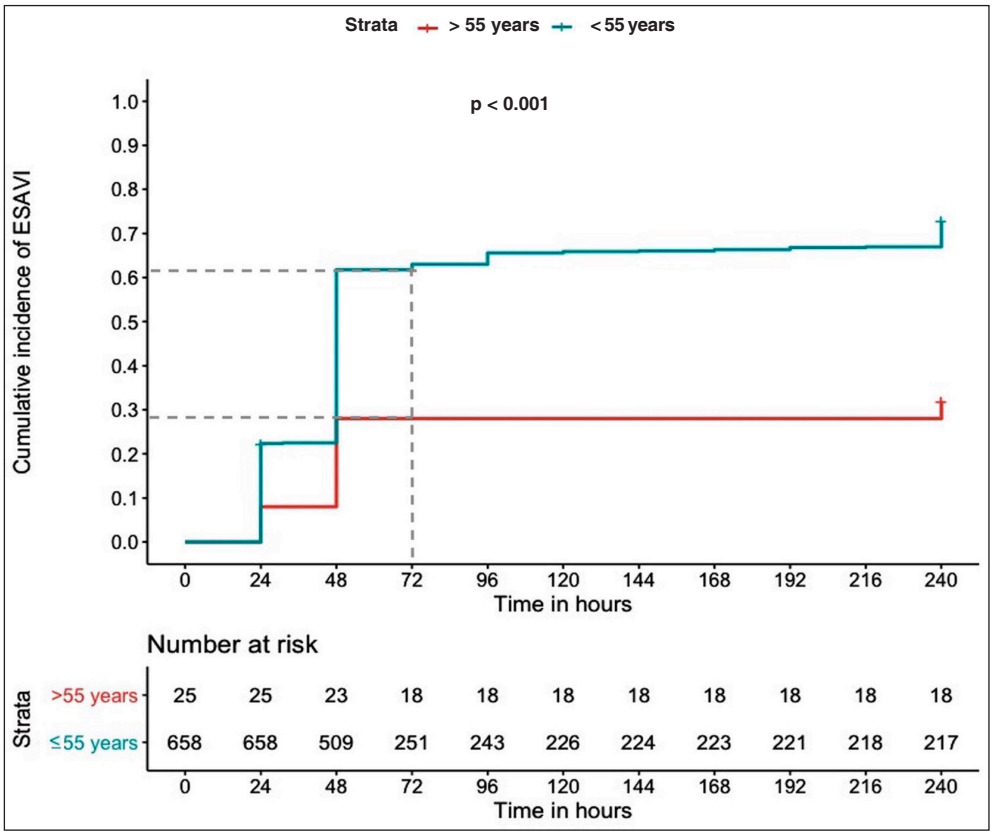
ESAVI: events supposedly attributable to vaccination and immunization ˚Local reactions, †Systemic reactions

Fig. 2.– Cumulative incidence of ESAVI in males and females after the administration of the first component of Sputnik V COVID-19 vaccine.



Dot lines show the cumulative incidence of ESAVI 72 hours after the administration of the first component of the Sputnik V COVID-19 vaccine. P value for Mantel-Cox compares incidence between males and females.
ESAVI: events supposedly attributable to vaccination and immunization

Fig. 3.– Cumulative incidence of ESAVI in healthcare workers by age group after the administration of the first component of Sputnik V COVID-19 vaccine.



Dot lines show the cumulative incidence of ESAVI 72 hours after the administration of the first component of the Sputnik V COVID-19 vaccine. P value for Mantel-Cox compares incidence between age groups.
ESAVI: events supposedly attributable to vaccination and immunization

TABLE 2.– *Factors associated with events supposedly attributable to vaccines in the 683 vaccinated healthcare workers included in the study*

Participant characteristic	Hazard Ratio (crude)	95% Confidence Interval	Hazard Ratio (adjusted)	95% Confidence Interval
Age category, yrs				
≤ 55	2.88	1.43-5.80	2.66	1.32-5.38
> 55	1			
Gender				
Female	1.41	1.15-1.72	1.38	1.13-5.38
Male	1			
Family history of reaction to vaccines				
Yes	0.82	0.30-2.19	0.88	0.33-2.37
No	1			
Any allergy before vaccination				
Yes	1.16	0.80-1.70	1.14	0.78-1.66
No	1			
Diabetes mellitus				
Yes	0.71	0.23-2.22	0.82	0.26-2.56
No	1			
Any other medical condition before vaccination				
Yes	1.22	0.82-1.81	1.22	0.82-1.82
No	1			

23% respectively); no data on muscular pain was reported in the interim analysis of phase 3 of this vaccine trial[3].

In our study, ESAVIs were more frequent in females. Similar to the study on the BNT162b2 mRNA COVID-19 vaccine (Pfizer)[10], we observed a lower incidence of ESAVIs in older people; adverse events among older than 55 years were 71% for Pfizer vaccine compared to 32% for Sputnik V in our study whereas in 55 years old and younger adverse events were 83% vs. 72.8%, respectively[9, 10]. In phase 3 interim analysis of the Sputnik V vaccine, the authors found higher levels of antibodies specific to the receptor-binding domain of SARS-CoV-2 glycoprotein S among the younger participants, compared to the older ones; however, they did not compare ESAVIs between age categories to relate the reactogenicity with the adaptive immune response to the vaccine[3]. We also found a higher incidence of ESAVIs among women compared to men (65% vs. 50%) but did not find a comparison of ESAVIs by gender in other studies.

To understand the frequency and kind of symptoms attributable to vaccination, it is important to analyze the reactogenicity[11, 12]. Reactogenicity refers to a subset of symptoms or reactions occurring shortly after vaccination, which are regarded as physical signs of the inflammatory response to the vaccine. These reactions usually are mild and self-limited and rarely have serious consequences. Reactogenicity may contribute to misperceptions (prejudices) against vaccination. A person could perceive a vaccine as excessively reactogenic and could reject additional doses, or a healthcare professional could advise against it. Reaching and maintaining a high vaccine coverage is critical to the success of vaccination programs and this kind of misperceptions jeopardize the endeavour[13].

On the other hand, a relation of reactogenicity with early innate and adaptive responses has been proposed but a predictive association between them has not been demonstrated; thus, no evidence has as yet been obtained of the known concept “no local pain, no gain in immunity”[14].

Recently, Sadoff et al published preliminary results of phases 1 and 2 of the Ad26.COV2.S vaccine (Janssen/Johnson & Johnson)[15]. This randomized clinical trial enrolled 805 healthy volunteers in two age cohorts to assess vaccine safety, reactogenicity and immunogenicity[14]. As we found in our investigation, they showed that the rate of adverse events decreased with the increase of age. Local and systemic reactions were generally resolved within 24 hours. Systemic reactions were largely responsive to antipyretic drugs. These authors found that the incidence of systemic adverse events among participants aged between 18 and 55 years was much lower after the second shot than after the first, regardless of having used the low or high dose, a finding that contrasts with observations made for messenger RNA-based vaccines, for which the second shot has been associated with increased reactogenicity[15].

It is worth mentioning that in the publication of the University of Oxford with the AstraZeneca vaccine, a subgroup inadvertently received half a dose in the first shot and a full dose in the second. During the follow-up, this subgroup had not only less reactogenicity but also higher immunogenicity[16, 17].

In our study, the response rate to the self-report form was very high, in part because an epidemiologist explained the ESAVI collection tool to the participants at the time of vaccination and a nurse reinforced the explanation by telephone. On the other hand, items questioned by the media, such as the origin of the vaccine or the delayed publication of the phase 3 trial results, could have prompted a greater report rate. The self-report form used in this study is being revised for validity and reliability.

Further research is needed to better understand the immune mechanisms involved in reactogenicity and epidemiological surveillance of long-term adverse events. Even though there is evidence that the immune response is lower in older adults and males[18, 19], understanding whether the efficacy of the vaccine is lower in people with low reactogenicity will be useful to define the vaccination scheme.

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Conflict of interests: None to declare.

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