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Seroprevalence for norovirus genogroups GII and GIV in captive non-human primates

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Abstract

Noroviruses (NoVs) are a major cause of epidemic gastroenteritis in children and adults. Several pieces of evidence suggest that viruses genetically and antigenically closely related to human NoVs might infect animals, raising public health concerns about potential cross-species transmission. The natural susceptibility of non-human primates (NPHs) to human NoV infections has already been reported, but a limited amount of data is currently available. In order to start filling this gap, we screened a total of 86 serum samples of seven different species of NPHs housed at the Zoological Garden (Bioparco) of Rome (Italy), collected between 2001 and 2017, using an enzyme-linked immunosorbent assay (ELISA) based on virus-like particles (VLPs) of human GII.4 and GIV.1 NoVs. Antibodies specific for both genotypes were detected with an overall prevalence of 32.6%. In detail, IgG antibodies against GII.4 NoVs were found in 18 Japanese macaques (29.0%, 18/62), a mandrill (10.0%, 1/10), a white-crowned mangabey (16.6%, 1/6) and in an orangutan (33.3%, 1/3). Twelve macaques (19.3%, 12/62), five mandrills (50.0%, 5/10), two chimpanzees (100%, 2/2) and a white-crowned mangabey (16.6%, 1/6) showed antibodies for GIV.1 NoVs. The findings of this study confirm the natural susceptibility of captive NHPs to GII NoV infections. In addition, IgG antibodies against GIV.1 were detected, suggesting that NHPs are exposed to GIV NoVs or to antigenically related NoV strains.

KEYWORDS
genotypes GII.4 and GIV.1, IgG antibodies, non-human primates, noroviruses

1 | INTRODUCTION

Noroviruses (NoVs) are a leading cause of sporadic cases and outbreaks of acute gastroenteritis across all age groups (Patel et al., 2008). NoVs are ubiquitous, associated with 18% of diarrhoeal disease worldwide and are estimated to cause 212,000 deaths annually worldwide (Lopman, Steele, Kirkwood, & Parashar, 2016).

NoVs are small non-enveloped viruses classified into the genus *Norovirus*, family *Caliciviridae*. The icosahedral capsid surrounds a 7.7-kb positive-sense single-stranded RNA genome organized into three open reading frames (ORFs). ORF1 encodes a large polyprotein that is cleaved into many non-structural proteins. ORF2 encodes a major capsid protein (VP1) while ORF3 a small basic protein (VP2) (Green, 2013). Based on the full-length VP1 amino acid sequence, NoVs have been divided into seven genogroups (G) and at least 40 genotypes (Vinjé, 2015). Viruses belonging to GI, GII and GIV can infect humans, with GII.4 strains being the most prevalent worldwide (Green, 2013).

NoV infections have also been documented in non-human primates (NHPs) (Bok et al., 2011; Farkas, Cross et al., 2010; Farkas, Dufour, Jiang, & Sestak, 2010; Farkas, 2016; He et al., 2017; Rockx,

Bogers, Heeney, Van Amerongen, & Koopmans, 2005; Sestak et al., 2012; Subekti et al., 2002; Wyatt et al., 1978). Experimental inoculation of different species of NHPs has demonstrated their susceptibility to NoVs, with active seroconversion and faecal shedding of NoV, although mainly in the absence of clinical disease (Bok et al., 2011; Rockx et al., 2005; Sestak et al., 2012; Subekti et al., 2002; Wyatt et al., 1978). Natural NoV infection in NHPs has been reported only occasionally so far. Using baculovirus-expressed VP1 of the human GI.1, GII.4 and GII.7 NoVs, IgG-specific antibodies were first detected in three Old World monkey species (mangabeys, pigtail and rhesus macaques) and in chimpanzees housed at the Yerkes National Primate Research Center (US) with rates ranging from 63.0% to 92.0% (Jiang, McClure, Fankhauser, Monroe, & Glass, 2004). A high prevalence (51.0%–61.0%) of antibodies against GI.1 and GII.5 has also been reported in a serological survey performed on a colony of rhesus macaques of the Tulane National Primate Research Center (US) (Farkas, Cross et al., 2010). Direct evidence for natural NoV infections for GI, GII and GIV NoVs has been obtained by molecular screening of 500 faecal samples from rhesus macaques with an overall prevalence of 8.2% (Farkas, Dufour et al., 2010; Farkas, 2016). More recently, GII sequences genetically close (99% nucleotide identity) to the novel NoV GII.P17_GII.17 variant Kawasaki 2014 have been detected in 32.0% of stool samples collected from rhesus monkeys living in a breeding facility in Yunnan Province, China (He et al., 2017). The variant Kawasaki 2014 emerged in several countries in Asia during winter season 2014–2015, replacing the GII.4/Sydney 2012 variant (Matsushima et al., 2015). The presence of human NoVs in NHPs raises concerns about the existence of unknown NoV reservoirs in animals with a potential for zoonotic transmission. In this study, to further investigate NoV epidemiology in NHPs, we screened a historical collection of sera obtained from seven different NHP species housed at the Zoological Garden (Bioparco) of Rome, Italy, by using an enzyme-linked immunosorbent assay (ELISA) based on virus-like particles (VLPs) generated from human NoVs of genotype GII.4 and GIV.1.

Impact

- Noroviruses (NoVs) have been identified as the most common cause of viral gastroenteritis in humans. In this study, the susceptibility to human GII and GIV NoV infections was serologically investigated in non-human primates (NHPs).
- By using an ELISA assay based on virus-like particles (VLPs) of human GII.4 and GIV.1 NoVs, specific IgG antibodies were detected in macaques, mandrills, white-crowned mangabeys, orangutans and chimpanzees with an overall seroprevalence of 32.6%.
- These findings indicate that not only GII, but also GIV strains circulate among NHPs populations. Further investigations are needed to establish firmly the possible transmission of NoVs from monkeys to humans and vice versa

2 | MATERIAL AND METHODS

2.1 | Serum sample collection

A total of 86 serum samples of NHPs born in captivity were collected in the 17-year time frame spanning 2001 to 2017. The sera were obtained from 62 Japanese macaques (*Macaca fuscata*), 10 mandrills (*Mandrillus sphinx*), 6 white-crowned mangabeys (*Cercocebus atys lunulatus*), 3 bornean orangutans (*Pongo pygmaeus*), 2 gorillas (*Gorilla gorilla*), 2 chimpanzees (*Pan troglodytes*) and 1 hamadryas baboon (*Papio hamadryas*) (Table 1). Most of the animals investigated (75/86) were adults (6–20 years old), while only 6 were older than 20 years and 5 younger than 3 years. None of the animals were specifically bled for this study, but only for regular health checks.

2.2 | Production of virus-like particles (VLPs)

The recombinant baculoviruses carrying the genes for the viral capsid proteins of the human NoVs, Hu/NoV/GII.4/MD14512/1987/US and Hu/NoV/GIV.1/SaintCloud/624/1998/US, were obtained as previously described (Bok et al., 2009; Di Martino et al., 2014, 2017). For large-scale production of VLPs, 100 ml of *Spodoptera frugiperda* (*Sf9*) cell (1×10^6 cell/ml) suspension culture was infected with the recombinant baculovirus at a multiplicity of infection of three plaque forming units/cell. After separation from the cell debris at 48 hr post-infection (PI), the culture medium was concentrated by ultracentrifugation through a 17% sucrose cushion in TEN-buffer (100 mM NaCl; 50 mM Tris-HCl, pH 7.5; 1 mM EDTA) and purified on a discontinuous 20%–60% (wt/vol) sucrose gradient.

TABLE 1 Seroprevalence of IgG antibody against norovirus GII.4 and GIV.1 in non-human primate serum specimens

NoV virus-like particles	Serum dilution				
	1:100 (%)	1:200 (%)	1:400 (%)	1:800 (%)	Total (%)
GII.4	5/86 (5.8)	3/86 (3.5)	0/86 (0)	0/86 (0)	8/86 (9.3)
GIV.1	7/86 (8.1)	0/86 (0)	0/86 (0)	0/86 (0)	7/86 (8.1)
GII.4 + GIV.1	5/86 (5.8)	4 (4.7)	2 (2.3)	2 (2.3)	13 (15.1)
	7/86 (8.1)	1 (1.2)	3 (3.5)	2 (2.3)	

Note. GII, genogroup II; GIV, genogroup IV; NoV, norovirus.

2.3 | Agar gel immunodiffusion (AGID)

The reactivity between the simian IgG antibodies of the seven NHP species and the anti-human IgG antibodies was assessed by agar gel immunodiffusion (AGID) test. Agar solution consisted of 0.8% Difco™ agar granulated (Becton Dickson, Sparks, Maryland, USA) in Tris buffer 0.2 M and NaCl 0.85%, pH 7.2. Tests were carried out in Petri dishes using a punch of six wells of 6 mm in diameter and 4 mm apart and incubated for 72 hr in a humid chamber at room temperature. Human anti-IgG (Sigma-Aldrich, Milan, Italy) diluted at 1:5,000 was added in the central well, while 70 µl of human serum diluted 1:100 was used as positive control and 70 µl of dog serum (1:100) as negative control. For each NHP species, 70 µl of serum diluted at 1:100 and 1:200 was assessed.

2.4 | Antibody-detection ELISA

For the development of the antibody-detection ELISA, the supernatant of mock-infected *Sf9* cells, NoV GII.4 and GIV.1 VLPs (final concentration of 1 µg/ml) were coated onto 96 well EIA plates (Costar, Italy) at 100 µl per well in carbonate–bicarbonate buffer (0.05 M, pH 9.6), as previously described (Di Martino et al., 2014). The protein concentration of VLP preparations was determined by measuring the optical density at 280 nm (OD_{280}) and visually by running aliquots containing bovine serum albumin (BSA) (Promega Corporation, Milan, Italy) standards on sodium dodecyl sulphate–10% polyacrylamide gel electrophoresis. The plates were incubated at 4°C overnight. The wells were washed five times with 0.1% Tween–phosphate-buffered saline (PBS-T) and then blocked with 300 µl of Superblock (Invitrogen, Ltd, Milan, Italy) at room temperature for 5 min. After washing five times with PBS-T, each NHPs serum sample (100 µl) diluted 1:100 in Superblock (Invitrogen, Ltd, Milan, Italy) was added to the antigen-coated wells and the plates were incubated at 37°C for 1 hr. After incubation with horseradish peroxidase-conjugated goat anti-human IgG (Sigma-Aldrich, Milan, Italy) at 1:5,000 dilution for 30 min at 37°C, the reaction was developed with the addition of 2,20-azino-di-(3-ethylbenzthiazoline-6-sulphonate) (ABTS) (Invitrogen, Ltd, Milan, Italy) substrate and the incubation at room temperature for 12 min. Absorbance was measured at 405 nm using a multiskan automatic plate reader (Thermo Labsystems, Finland). The cut-off point of the ELISA (OD_{405} ≥ 0.5) was established as the mean of the OD_{405} readings of 25 NHP serum samples negative in western blotting for GII.4 and GIV.1 VLPs plus 2 standard deviations. For each tested sample, a positive/negative ratio (OD_{405} of VLPs/OD_{405} of mock-infected cells) ≥2.0 was used to evaluate the background binding. All samples that had OD_{405} values ≥0.5 at the initial dilution of 1:100 were considered positive and titrated in 2-fold dilutions. Mean ELISA antibody titres were calculated and expressed as the reciprocal of the highest serum dilution that had positive absorbance (OD_{405} ≥ 0.5) for GII.4 and/or GIV.1 antigens.

2.5 | Statistical analysis

Statistical analysis was performed using GraphPad Prism Software (https://www.graphpad.com/scientific-software/prism/). Pearson's rank correlation test and paired sample *t* test were applied to assess the correlation between the two NoV-VLPs serum titres. Fisher's exact test was used to determine the difference in seroprevalence rates among the seven NHPs species and the difference among the age groups. A p value of <0.05 was considered statistically significant.

3 | RESULTS

A total of 86 serum samples collected from seven NHPs species housed at the Zoological Garden of Rome (Italy) were screened for the presence of antibodies against human GII.4 and GIV.1 NoVs.

Firstly, to ascertain the cross-reactivity between the simian IgG antibodies and the anti-human IgG antibodies, AGID test was performed for each NHP species investigated. The results obtained demonstrated that the serum of each monkey species was reactive either at dilution of 1:100 or 1:200 (Figure 1). When the samples were analysed by using the recombinant ELISA, out of 86 NHP serum samples tested at the initial dilution of 1:100, 32.6% (28/86) reacted with at least one NoV antigen. In detail, 8 (9.3%) sera reacted only with GII.4, 7 (8.1%) only with GIV.1 and a total of 13 (15.1%) reacted with both GII.4 and GIV.1 VLPs. When all the positive sera were rescreened by endpoint titration, 5 (5.8%) samples reacted with the GII.4 antigen at dilution of 1:100 and 3 (3.5%) at 1:200. Seven (8.1%) samples reacted with GIV.1 VLPs at

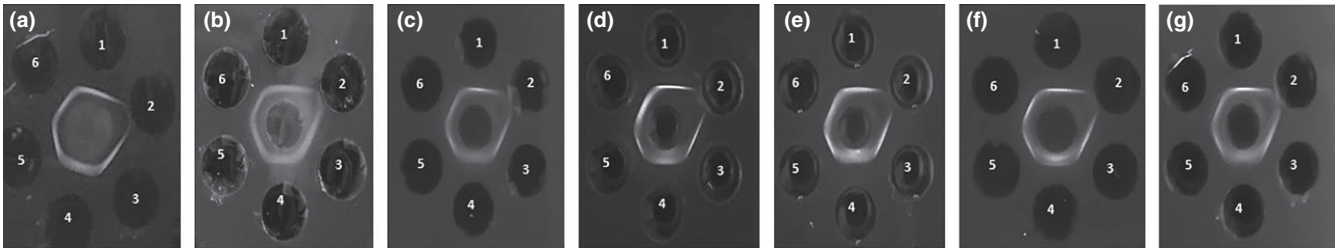

FIGURE 1 Agar gel immunodiffusion of each NHP species IgG antibodies and the anti-human IgG antibodies (central well). Peripheral wells contain a human serum as positive control (wells 1, 3, 5), a dog serum as negative control (well 2) and a NHP serum diluted 1:100 (well 4) and 1:200 (well 6). The precipitation lines (arrows) indicate the cross-reactivity between NHP IgG and anti-human IgG. (a) Japanese macaques; (b) white-crowned mangabey; (c) mandrill; (d) gorilla; (e) bornean orangutan; (f) chimpanzee; (g) hamadryas baboon

dilution of 1:100. Of 13 sera positive against both the antigens, eight sera (6.9%) reacted either with GII.4 or GIV.1 at the final dilution of 1:100 (4.6%, 4/86), 1:400 (2.3%, 2/86) and 1:800 (2.3%, 2/86), respectively. Three samples (3.5%) reacted at a dilution of 1:200 with GII.4 and at 1:100 with GIV.1, one serum at a dilution of 1:200 with GII.4 and 1:400 with GIV.1 and an additional serum sample reacted at a dilution of 1:100 with GII.4 and 1:200 with GIV.1 (Table 1). Analyses performed by Pearson's rank and *t* test revealed a high correlation between the levels of antibodies to GII.4 and GIV.1 antigens ($p < 0.0001$; $r = 0.907$).

Among the seven NHP species investigated in this study, IgG antibodies against GII.4 NoVs were found in Japanese macaques (29.0%, 18/62), white-crowned mangabey (16.6%, 1/6), orangutan (33.3%, 1/3) and mandrill (10.0%, 1/10). Twelve macaques (19.3%, 12/62), 5 mandrills (50.0%, 5/10), 2 chimpanzees (100%, 2/2) and a white-crowned mangabey (16.6%, 1/6) showed positivity for NoV GIV.1 VLPs. IgG antibodies against the two NoV antigens were not detected in gorillas and hamadryads (Table 2). Considering the seropositivity by year of sample collection (Figure 2), the overall prevalence ranged from 15.0% (3/20) in 2001, to 37.5% (3/8) in 2002, to 14.3% (1/7) in 2004, to 66.6% (2/3) in 2005, to 80.0% (4/5) in 2006, to 50.0% (1/2) in 2007 and 2008, respectively, and to 40.0% (2/5) in 2009. A high seroprevalence (44.0%, 11/25) was observed in the sera collected only from macaques in 2010. Of these, 4 animals were positive for GII.4, 1 only for GIV.1 and 6 either for GII.4 or GIV.1. None of the animals assessed in 2003 (3) and during 2011–2017 (6) were positive for IgG antibodies against the two NoV antigens.

4 | DISCUSSION

ELISAs based on VLPs have successfully been used to gather information on the epidemiology of NoVs in humans and animals (Di Martino et al., 2014, 2017). In this study, using baculovirus-generated VLPs based on human GII.4 and GIV.1 NoVs, IgG-specific antibodies were detected in Japanese macaques, mandrills, chimpanzees, white-crowned mangabey and orangutan. These findings confirm that captive NHPs are susceptible to infections by GII NoVs. In addition, this is the first study investigating the seroprevalence of anti-GIV.1 antibodies in monkeys. Human NoV GIV.1 (Alphatron-like) has been identified only sporadically in human patients (Ao, Yu, Li, Jin, & Duan, 2014; La Rosa, Pourshaban, Iaconelli, & Muscillo, 2008; Muscillo et al., 2013), although epidemiological studies based on the analysis of sewage and wastewater in Japan and Italy have revealed, unexpectedly, prevalence rates as high as 21.4% and 21.8%, respectively (Kitajima, Haramoto, Phanuwan, Katayama, & Ohgaki, 2009; Muscillo et al., 2013). A study conducted on an age-stratified collection of human serum samples (Di Martino et al., 2014) has revealed a seroprevalence for GIV.1 of 22.0%, thus suggesting that these NoVs are more common in human populations than previously believed. Susceptibility of NHPs to GIV NoV infections was also suspected in a molecular survey in macaques (Farkas, 2016). By using a quantitative RT-PCR, the RNA of GIV NoVs was detected in 0.6% (3/500) macaque faecal samples, although sequence information for the GIV-positive samples was not obtained (Farkas, 2016).

In our analysis, IgG antibodies against GII.4 and GIV.1 NoVs were found, respectively, in 24.4% (21/86) and 23.2% (20/86) of the sera assessed, suggesting frequent exposure of NHPs to these viruses. For thirteen positive samples, reactivity against both GII.4 and GIV.1 was revealed with titres ranging from 1:100 to 1:800. Previous evidence demonstrated that GI (GI.1, GI.2, GI.3) and GII (GII.4, GII.6, GII.12) VLPs are antigenically unrelated to GIV.1 and GIV.2 NoVs (Caddy et al., 2015; Di Martino et al., 2014), while cross-reactivity has been observed between GII.4 and GVI.2 genotypes (Di Martino et al., 2017), as well as between GIV.1 and GIV.2 (Di Martino et al., 2014). Accordingly, it could be argued that the dual reactivity for GII.4 and GIV.1 antigens found in 13 NHP sera was the result of a coinfection with GII.4 and GIV.1 NoVs or sequential infections over time. Otherwise, we cannot rule out the possibility that monkeys

TABLE 2 NHP species assessed for the presence of IgG antibodies against NoV GII.4 and GIV.1

NHPs tested	Positive GII.4 IgG	Negative GII.4 IgG	Positive GIV.1 IgG	Negative GIV.1 IgG	Total
Macaca fuscata (Japanese macaque)	18 (29.0%)	44 (70.9%)	12 (19.3%)	50 (80.6%)	62
Mandrillus sphinx (Mandrill)	1 (10.0%)	9 (90.0%)	5 (50.0%)	5 (50.0%)	10
Cercocebus atys lunulatus (White-crowned mangabey)	1 (16.6%)	5 (83.3%)	1 (16.6%)	5 (16.6%)	6
Pongo pygmaeus (Bornean orangutan)	1 (33.3%)	2 (66.6%)	0 (0.0%)	3 (100%)	3
Gorilla gorilla (Gorilla)	0 (0.0%)	2 (100%)	0 (0.0%)	2 (100%)	2
Pan troglodytes (Chimpanzee)	0 (0.0%)	2 (100%)	2 (100.0%)	0 (0.0%)	2
Papio hamadryas (Hamadryas baboon)	0 (0.0%)	1 (100%)	0 (0.0%)	1 (100%)	1

Note. GII, genogroup II; GIV, genogroup IV; NHP, non-human primate; NoV, norovirus.

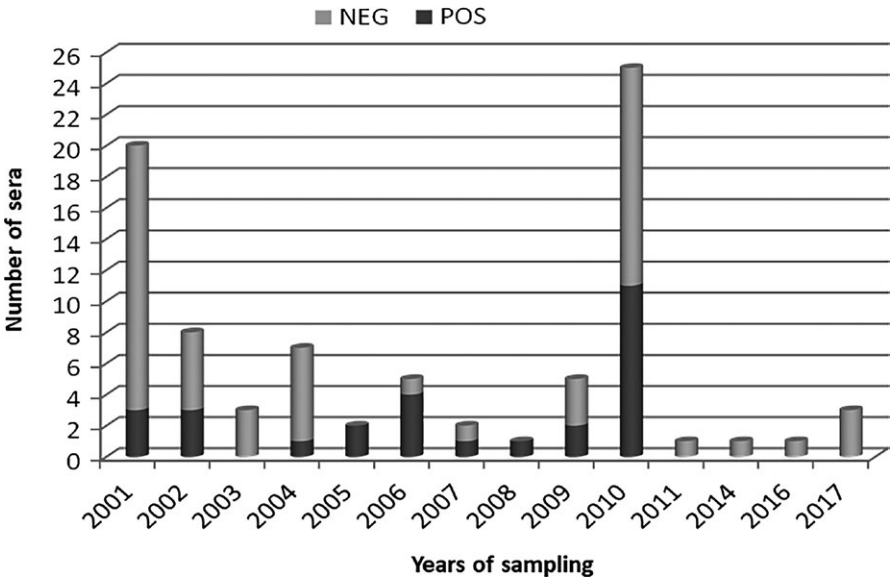

FIGURE 2 Seropositivity against NoVs in NHPs in the 17-year time frame spanning 2001 to 2017

were infected with genetically diverse NoVs, sharing conserved epitopes with GII.4 and GIV.1 NoVs. Several cross-reactive monoclonal antibodies (MAbs) able to block the interaction of VLPs with ABH histo-blood group antigens (HBGAs) have been characterized (Li, Zhou, Tian, Li, & Zhou, 2010; Parker, Kitamoto, Tanaka, Hutson, & Estes, 2005; Parra et al., 2013). A MAb binding to an epitope spanning amino acid residues 55–60 in the shell domain of the VP1 protein was shown to be reactive against VLPs from GI, GII, GIII and GV strains (Li et al., 2010). Also, a broadly cross-reactive Mab (TV20) reacting with VLPs of GI, GII, GIV and GV NoVs has been mapped to residues 52–56 (Parra et al., 2013).

With the exception of gorillas and hamadryads, all the species investigated in the present study resulted positive for at least one of the antigens tested, with the highest seropositivity in macaques (29.0%, 18/62) for GII.4 and mandrills (50.0%, 5/10) for GIV.1 VLPs. Also, high seroprevalences were found in orangutan for GII.4 (33.3%, 1/3) and chimpanzees for GIV.1 (100%, 2/2), although the number of sera for these two NHPs species was low. These findings demonstrate that, in addition to macaques, chimpanzees and mangabeys, mandrills and orangutans are also susceptible to NoV infections (Bok et al., 2011; Farkas, Cross et al., 2010; Farkas, Dufour et al., 2010; Farkas, 2016; He et al., 2017; Jiang et al., 2004; Rockx et al., 2005; Subekti et al., 2002; Wyatt et al., 1978). Furthermore, the serological data collected herein demonstrate that NoVs have circulated among NHPs housed at the Zoological Garden of Rome at least since 2001. The high seropositivity (44.0%) against both GII.4 and GIV.1 VLPs detected in 2010 only within the community of macaques allows us to speculate on the possible presence of a cluster of infection, a finding that is consistent with contamination from a common source. The lack of IgG detection in the period 2011–2017 may suggest the absence of circulation of NoVs in the analysed setting, or it could be related to the low number of sera (6/86) collected during this time span. Finally, we cannot rule out the circulation of strains unrelated antigenically to the NoV antigens used in our assay.

In conclusion, our findings demonstrate that not only GII, but also GIV strains circulate widely among NHPs populations. Whether and to which extent transmission of NoVs from monkeys to humans and vice versa occurs under natural and captive conditions should be assessed, to understand the ecology and evolution of human NoVs and track the origin of novel NoV strains.

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CONFLICT OF INTEREST

All authors declare that there are no financial or other relationships that might lead to a conflict of interest. All authors have seen and approved the manuscript and have contributed significantly to the work.

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