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Original

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Demographic, clinical and microbiological characteristics of the first 30 human monkeypox confirmed cases attended in a tertiary hospital in Madrid (Spain), during the May-June 2022 international outbreak

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ABSTRACT

The present outbreak of Human Monkeypox (HMPX) that has begun in May 2022 and has spread across all continents in less than two months has qualitative and quantitative characteristics that make it different from the pattern of human disease previously caused by this virus. It has spread with enormous ease, affects almost exclusively adults, behaves as a sexually transmitted disease and focuses on very specific groups and transmission conditions. The high incidence in the city of Madrid in males that have sex with males (MSM) has allowed us to observe and report the experience with the first 30 cases diagnosed in our institution. Patients presented with febrile symptoms, genital and paragenital skin lesions reminiscent of smallpox, but less extensive and severe. The disease may also cause proctitis, pharyngitis and perioral lesions. The PCR test for diagnostic confirmation has been shown to be very sensitive and effective, not only in skin lesions but also in blood and other fluids such as pharyngeal, rectal exudates and blood. A very high proportion of patients with HMPX also have other sexually transmitted diseases that must be actively detected in this context. The spontaneous evolution of our patients has been good and hospitalization has been practically unnecessary. Transmission to non-sexual cohabitants and health personnel has been nonexistent and the lesions have disappeared in less than 30 days without leaving sequelae and no need for specific antiviral treatment.

Keywords: Monkeypox, Human Monkeypox, Sexually transmitted infections , outbreak

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Características demográficas, clínicas y microbiológicas de los primeros 30 casos humanos confirmados de viruela del mono atendidos en un hospital terciario de Madrid (España), durante el brote internacional de mayo-junio de 2022

RESUMEN

El actual brote de la enfermedad por el virus de la viruela del mono humana (HMPX), que ha comenzado en mayo de 2022 y se ha extendido por todos los continentes en menos de dos meses, tiene unas características cualitativas y cuantitativas que lo diferencian del patrón de enfermedad humana causado anteriormente por este virus. Se ha extendido con enorme facilidad, afecta casi exclusivamente a adultos, se comporta como una enfermedad de transmisión sexual y se centra en grupos y condiciones de transmisión muy específicas. La alta incidencia en la ciudad de Madrid en varones que tienen sexo con varones (HSH) nos ha permitido observar y comunicar la experiencia con los primeros 30 casos diagnosticados en nuestra institución. Los pacientes se presentaron con síntomas febriles, lesiones cutáneas genitales y paragenitales que recuerdan a la viruela, pero menos extensas y graves. La enfermedad también puede causar proctitis, faringitis y lesiones periorales. La prueba PCR para la confirmación del diagnóstico ha demostrado ser muy sensible y eficaz, no sólo en las lesiones cutáneas sino también en la sangre y otros fluidos como los exudados faríngeos y rectales y la sangre. Una proporción muy elevada de pacientes con HMPX presentan también otras enfermedades de transmisión sexual que deben ser detectadas activamente en este contexto. La evolución espontánea de nuestros pacientes ha sido buena y la hospitalización ha sido prácticamente innecesaria. La transmisión a convivientes no sexuales y al personal sanitario ha sido inexistente y las lesiones han desaparecido en menos de 30 días sin dejar secuelas y sin necesidad de tratamiento antiviral específico.

Palabras clave: Virus de la viruela del mono, Viruela del mono humana, Enfermedades de transmisión sexual, Brotes

INTRODUCTION

Monkeypox is an Orthopoxvirus discovered in Cynolmolgus monkeys in Denmark [1]. It mainly affects rodents and monkeys and humans have traditionally been considered as occasional hosts [2]. Since the first human cases of Human Monkeypox (HMPX) were reported [3], this zoonosis has been largely confined to West and Central African countries, where it has been shown to affect animals and humans in the form of small outbreaks. Most of the documented endemic cases of this zoonosis have occurred in the Democratic Republic of Congo (DRC) [4], where HMPX has produced a disease presentation similar to that of eradicated smallpox [5], except for lesser severity and the almost constant presence of enlarged regional lymph nodes.

Outside Africa, the only historically reported cases of HMPX were a multi-state outbreak of 47 cases in the USA in 2003 linked to rodents imported from Ghana [6]. Since then, a trickle of imported cases has started to be reported in non-African countries from four non-endemic countries (Israel, Singapore, USA and UK) [7-13].

However, as of May 2022, a large international outbreak of HMPX has been declared in non-endemic countries as a result of human-to-human transmission. In just over a few months, the disease has spread to all continents with more than 77 000 cases in 109 different countries [14]. Monkeypox now affects patients with no history of travel to Africa or contact with African patients, and presents almost exclusively as a sexually transmitted disease in Men Who Have Sex with Men (MSM) [15].

Spain is one of the nations with the most reported patients in this outbreak (>7,400 cases) and the community of Madrid has the highest number of episodes in Spain (>2,500 cases) [16]. For this reason, we report our experience with the first 30 cases of HMPX diagnosed and followed up in a single hospital centre in Madrid.

METHODS

Our center is a 1,200-bed university and referral hospital serving a population of about 350,000 inhabitants in the city of Madrid (Spain). The Division of Clinical Microbiology and Infectious Diseases evaluated the suspected cases of HMPX that arrived at our center during the study period; between May 19 and June 7, 2022.

The diagnosis of HMPX was suspected in patients with mucocutaneous lesions suggestive of the disease but also in patients without mucocutaneous lesions who had unprotected sex and presented with other clinical manifestations including fever, enlarged lymph nodes, proctitis or pharyngitis. In all suspected cases, a blood sample and at least one mucocutaneous lesion (when present) were examined with a polymerase chain reaction (PCR) test against monkeypox virus (MPXV). After a DNA extraction protocol of the sample with EMAG®, we used BIO-RAD® C1000™ Thermal Cycler to run a commercial PCR test from Roche® (LightMix® Modular Monkeypox Virus) in which a 106 bp fragment of the J2L/J2R gene from the monkeypox virus is amplified with specific primers and detected with a HEX labeled hydrolysis probe.

Patients also had a systematic detection of human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV). In all cases a screening test for syphilis (treponemal test) was performed. In patients with suspected proctitis or pharyngitis we obtained, respectively, a rectal or pharyngeal exudate, to rule out both MPXV and other sexually transmitted diseases (*N. gonorrhoeae*, *C. trachomatis*, *M. genitalium* and herpes simplex virus).

A confirmed case was defined as a suspected case with a positive PCR for MPXV in one or more clinical samples.

As for follow-up, all confirmed positive patients were re-evaluated between days 3 and 5 after consulting for the first time, and at day +30. In this first reevaluation, we collected a series of clinical, epidemiological and microbiological variables using a modified checklist from the one proposed by the Ministry of Health of Spain for the HPMX case declaration. We paid special attention to the oro-ano-genital location of the mucocutaneous manifestations and the date of onset of the fever in relation to rash. A contact study was also carried out in symptomatic cohabitants and the usual sexual partner. At day+30 we evaluated the clinical course, the natural evolution of the mucocutaneous lesions and the occurrence of medical complications.

Ethical approval was obtained from the Investigation Ethics Committee of the Gregorio Marañón University and Referral Hospital on the 13th July 2022.

RESULTS

During the study period, 46 patients were considered suspicious and were asked for one or more MPXV PCR tests. Of these, 30 out of 46 (65%) were confirmed to be infected with MPXV. Of the patients who were negative, an alternative diagnosis was confirmed in our laboratory in 6 of the 16 HMPX-negative cases, and they were finally diagnosed with latent syphilis (1 patient), secondary syphilis (1 patient), VHS-1 primo-infection (1 patient), VHS-1 reactivation (1 patient), varicella (1 patient) and zoster (1 patient).

Demographical characteristics. Demographic characteristics of the patients are summarized in table 1. The mean age of our patients was 33 years and all of them were less than 50 years old. None of them had received the smallpox vaccine. There were no patients from or originating from African countries. Forty-three percent were Spanish Caucasians, 47% were Latin Americans and 10% were of other origin. None of these patients had a history of travel to Central Africa in the previous 3 months.

All of our patients with confirmed HMPX infection were men who have sex with men (MSM) with a history of unprotected sex in the 4 weeks prior to clinical onset. Comorbidi-

Table 1 **Demographical characteristics of the first 30 HMPX confirmed cases attended in a tertiary hospital in Madrid during the May-June 2022 international outbreak.**

Age, median (IQR)	32,73+/-6,33
Country of birth	
Spain	13/30 (43%)
Other European countries	1/30 (3%)
Latinamerican	14/30 (47%)
Syrian	2/30 (7%)
MSM	30/30 (100%)
Unprotected sex	30/30 (100%)
Trip to Central Africa	0/30 (0%)
Coinfections	
HIV infection	14/30 (47%)
Newly diagnosed HIV	0/14 (0%)
Known HIV infection	14/14 (100%)
HIV infection >200 CD4	14/14 (100%)
Patients HIV (-) on PrEP	8/16 (50%)
Syphilis	4/30 (13%)
Primary Syphilis	3/4 (75%)
Syphilis of unknown duration	1/4 (25%)
HBV	0/30 (0%)
HCV	1/30 (3%)
Smallpox vaccine	0 / 30 (0%)

Table 2 **Clinical characteristics of the first 30 HMPX confirmed cases attended in a tertiary hospital in Madrid during the May-June 2022 outbreak.**

Fever	23/30 (77%)
Before (mucocutaneous lesions)	6/23 (26%)
At the same time (of mucocutaneous lesion)	5/23 (22%)
After (mucocutaneous lesions)	12/23 (52%)
Lymph node enlargement	
Inguinal	18/30 (60%)
Cervical	10/30 (30%)
Axillary	3/30 (10%)
Mucocutaneous lesions:	29/30 (100%)
Primary lesions location:	
External genitalia: penis, scrotum and pubic area	16/30 (53%)
Perianal and intergluteal fold	10/30 (33%)
Perioral, oral and pharynx	10/30 (33%)
Extension to other parts of the body:	
Soles of the feet	6/30 (20%)
Palms of the hands	5/30 (17%)
Legs, feet and toes	16/30 (53%)
Arms, back of hands and fingers	14/30 (47%)
Chest	6/30 (20%)
Abdomen	4/30 (13%)
Back	14/30 (47%)
Asthenia	18/30 (60%)
Sore throat	8/30 (27%)
Myalgias	12/30 (40%)
Arthralgias	7/30 (23%)
Headache	16/30 (53%)

ties included previously known HIV infection in 47% of cases. There were no other known causes of immunosuppression in the patients included in the cohort. There was active syphilis in 4 of the 30 patients (13%), which was primary in 3 of them.

Clinical characteristics. Table 2 shows the main clinical manifestations of these cases. Subclinical manifestations were frequent. Fever was present at one time or another in 23/30 (77%) of the cases, either preceding the mucocutaneous lesions or during or after their appearance. A high proportion of patients (77%) had lymph node enlargement in the inguinal, cervical or axillary regions. The frequency of arthralgias, myalgias and asthenia was high.

Mucocutaneous manifestations were frequent in almost all cases. The location of the lesions was genital, paragenital or perianal in most of the patients (figure 1). Painless vesicles and pustules on the external genitalia (penis, scrotum) or in the pubic region were the cornerstone of mucocutaneous involvement, present in 16/30 patients (53%), together with inguinal lymphadenopathies in 18/30 patients (60%). In one third of the cases the lesions were oral, perioral or pharyngeal (figure 1). Outside these areas, lesions were found in other territories in more than 50% of the patients.

We observed that 9/30 (30%) of the patients reported symptoms compatible with proctitis (rectal bleeding, mucus production from the rectum, rectal pain, sensation of fullness in the rectum, diarrhea, etc.). Sometimes proctitis was accompanied by lesions in the perianal and intergluteal area (Figure 1), as well as inguinal lymphadenopathy.

Table 3 shows the 30 cases of this series individually. The incubation period could be calculated in those patients who, in addition to remembering the day of symptom onset, clearly reported the date of the unprotected sexual intercourse.

Microbiological Characteristics:

i) MPXV diagnosis confirmation. PCR in mucocutaneous lesions confirmed the diagnosis in 28/30 cases. No viral culture was performed and therefore viability of the detected

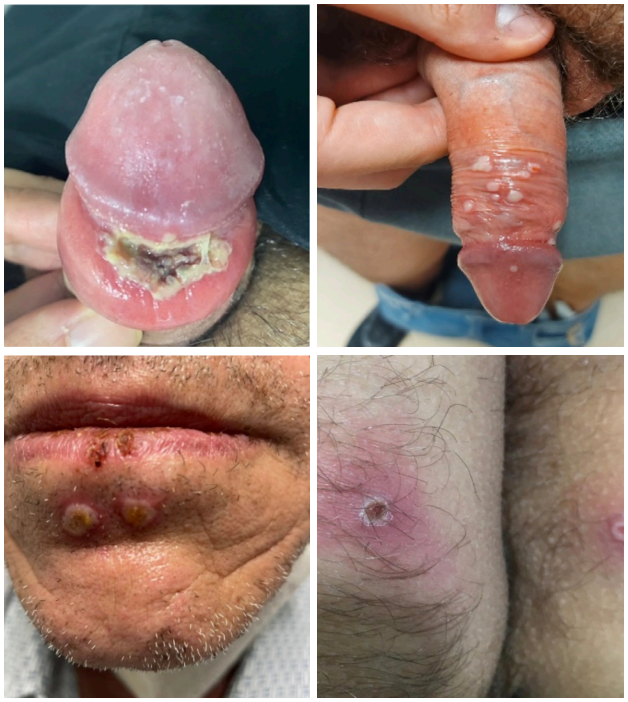

Figure 1 **A) Unique balanopreputial ulcer caused by Monkeypox; B) Multiple Monkeypox vesicles in the inner layer of foreskin; C) Monkeypox lesions in the perioral area after having oral sex; D) Monkeypox lesions in the intergluteal area in a patient with proctitis**

virus cannot be demonstrated. In the remaining 2 cases, blood PCR was positive and key to the diagnosis:

Case 16 was an HIV+ patient with fever and a very mild non-specific rash and no oro-ano-genital involvement who was studied because he was the sexual partner of a confirmed HMPX case. In this case, MPVX PCR in skin lesion was negative.

Case 27 was an HIV+ patient who presented with a sore throat and neck lymphadenopathy after oral sex. MPVX PCR in mucocutaneous lesion could not be practiced as there was no skin involvement.

Of the 28 cases confirmed positive by PCR in mucocutaneous specimens, 9 (32%) were negative by PCR in blood (figure 2). Patients with negative blood PCR did not have more extensive mucocutaneous involvement and appeared as early as the first day of symptoms (case 24) or as late as day 17 (case 5).

ii) Microbiological study of proctitis cases. Rectal exudate was obtained in 7 of the 9 patients with clinical proctitis. Of these 7 patients, MPVX-PCR was performed in 3, being positive in all of them. Results of the rest of the STDs are shown in Table 4.

Evolution and follow-up. In the first clinical reevaluation (+3-5 days), based on available microbiological results, many patients were treated for other STDs such as herpes, gonorrhea, chlamydia, *M. genitalium* or syphilis. There was only one symptomatic cohabitant, who was negative in the monkeypox study. However, three sexual partners tested positive.

One month after first medical consultation, apart from one patient hospitalized for drainage of an anal abscess, no hospitalizations were required, no other complications occurred and the patients evolved favorably while they were advised to stay at home for self-isolation with adequate pain management. We recorded no fatal outcomes. Specific antiviral treatment (tecovirimat) was not requested as, apart from being unavailable, all clinical cases progressed satisfactorily. No HMPX reinfections were detected and the skin lesions evolved favorably healing in 3-4 weeks after its appearance. The patients in whom the scabs disappeared did so without scarring.

DISCUSSION

Our study describes the clinical and epidemiological characteristics of a group of 30 patients with HMPX seen and followed consecutively in the same hospital and by the same group of researchers in Madrid in a very short period of time. All of them were men with high-risk sexual practices with other men (MSM) and in all of them MPXV infection was confirmed by PCR techniques. The infection was not limited to skin lesions and was a frequent cause of proctitis, pharyngitis and regional lymphadenopathy. The evolution was benign in all cases.

Our study provides an opportunity to analyze one of the first series of HMPX cases from the international outbreak that began in May 2022: The location of the primary lesions predominantly in the oro-ano-genital area strongly suggests that these areas play an important role in transmission of infection and were the most likely portal of viral entry. The main differential diagnosis of primary lesions in our setting was primary syphilis, genital herpes and genital zoster. Perioral lesions and oral sores, as well as sore throat without pharyngeal lesions, were probably caused by kissing or having unprotected oral sex with an HMPX-infected person. The appearance of vesicles and pustules on external genitalia or pubic region could be due to receiving oral sex or having unprotected insertive anal intercourse with an infected person. As for proctitis, in the majority of HMPX cases presenting with this syndrome, proctitis was the debut form of the disease and the main reason for clinical consultation. Secondary lesions of Monkeypox in extragenital areas appear in a scattered manner, sometimes confused with secondary syphilis, parvovirus B19 or adult varicella.

The presence of significant regional lymphadenopathy is a differential feature with episodes of classical smallpox. Diagnosis can be confirmed by PCR testing of lesions or by demonstration of MPXV in other body fluids or tissues, although in the appropriate epidemiologic setting the clinical picture is highly sugges-

Table 3 **Detailed demographical, clinical and microbiological information per case**

Confirmed cases	Sex/Age/Nationality	Incubation period	Primary lesions	Onset of fever in relation to the rash	Lymph node enlargement	PCR in blood
Case 1	cM/33/Brazilian	Unclear	O / EG	D+5	C / I	Negative (D+12)
Case 2	cM/29/Spanish	5	O	D+3	C	Positive (D+11) Ct 33
Case 3	cM/39/Spanish	Unclear	A	No fever	NO	Positive (D+6) Ct 39,2
Case 4	cM/33/Spanish	Unclear	EG	D+0	I	Positive (D+3) Ct 34
Case 5	cM/33/Spanish	Unclear	A	D+3	I	Negative (D+17)
Case 6	cM/31/Spanish	8	EG	D+2	I	Positive (D+7) Ct 37,6
Case 7	cM/32/Venezuelan	Unclear	EG	D+0	C / I	Negative (D+4)
Case 8	cM/46/Venezuelan	7	EG / A	No fever	NO	Positive (D+5) Ct 35
Case 9	cM/25/Venezuelan	10	EG	D+6	I	Positive (D+10) Ct 38
Case 10	cM/46/Venezuelan	10	EG	No fever	I	Positive (D+10) Ct 39,8
Case 11	cM//Venezuelan	Unclear	EG / A	D-2	I	Positive (D+7) Ct 34
Case 12	cM/29/Spanish	5	EG	D-3	I	Positive (D+6) Ct 35
Case 13	cM/29/Venezuelan	9	O / EG	D+3	C / I	Positive (D+4) Ct 35
Case 14	cM/26/Spanish	10	O	No fever	C	Negative (D+4)
Case 15	cM/27/Syrian	Unclear	O / EG	D+0	I	Negative (D+12)
Case 16	cM/30/Syrian	Unclear	NO	D-11	NO	Positive (D+15) Ct 36
Case 17	cM/36/Spanish	10	O	D+1	C	Positive (D+2) Ct 35,7
Case 18	cM/34/Ecuadorian	5	A	D-4	I	Negative (D+11)
Case 19	cM/41/Spanish	7	O / EG	D-1	C / I	Positive (D+1) Ct 36
Case 20	cM/40/Venezuelan	17	A	No fever	I	Positive (D+1) Ct 37
Case 21	cM/30/Venezuelan	5	EG	D+1	C / I	Positive (D+2) Ct 36
Case 22	cM/31/Venezuelan	11	EG	D+1	I	Negative (D+7)
Case 23	cM/22/Peruvian	3	O	D-1	NO	Positive (D+2) Ct 31
Case 24	cM/31/Spanish	Unclear	EG	No fever	NO	Negative (D+1)
Case 25	cM/32/Spanish	8	O	D+1	C	Positive (D+3) Ct 29
Case 26	cM/28/Honduran	Unclear	EG / A	D+1	I	Positive (D+7) Ct 29
Case 27	cM//Italian	2	NO	No fever	C	Positive (D+2) Ct 34
Case 28	cM/38/Spanish	9	A	A	NO	Positive (D+2) Ct 35
Case 29	cM/29/Cuban	2	A	D+0	NO	Negative (D+10)
Case 30	cM/37/Spanish	Unclear	A	D+1	I	Positive (D+5) Ct 36

cM, cis-male; O, Oral and Perioral; EG, External Genitalia; A, Perianal and Intergluteal fold; C, Cervical; I, Inguinal

tive of the disease. The PCR test on skin lesions proves to be very sensitive as has occurred in other series collected in our country that confirm that saliva, rectal exudate, semen, urine and blood itself, are frequently positive when obtained.

When specifically sought, a high percentage of our patients also had other sexually transmitted diseases, often undiagnosed, such as HIV infection, gonorrhea, Chlamydia infection and syphilis, corroborating data obtained in other centers in Spain and from outside Spain.

The present outbreak is peculiar in many aspects. In the quantitative side due to its dimension and rapid expansion and in the qualitative aspect due to the absence of an animal origin, its main affection in adults and its very scarce transmission outside sexual relations. The frequency of concomitant sexually transmitted diseases was very high and requires systematic screening in these patients. The evolution was benign and only one patient in our series required hospital admission for the treatment of a peri-rectal abscess.

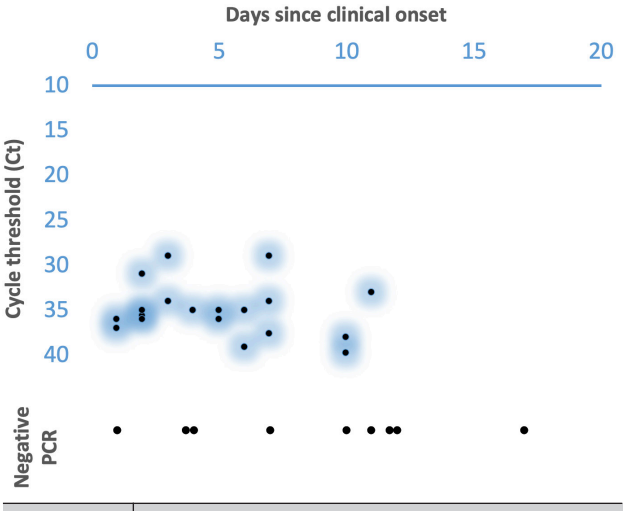

Figure 2 Results of the PCR in blood in the 28 HPMX confirmed cases by PCR in mucocutaneous lesions

Table 4 Microbiological study of rectal exudate in 9 HPMX confirmed patients with proctitis.

Number of case	Rectal swab				
	PCR HMPX	PCR TP	PCR NG	PCR CT	PCR HVS
3	NP	(-)	(-)	(-)	(-)
9	NP	NP	NP	NP	NP
11	(+)	(-)	(+)	(-)	(-)
13	NP	(-)	(-)	(-)	(-)
18	NP	NP	(-)	(-)	NP
20	NP	NP	(+)	(-)	NP
23	(+)	(-)	(-)	(-)	(-)
28	NP	NP	NP	NP	NP
30	(+)	(-)	(-)	(-)	(+)

PCR, polymerase chain reaction; HMPX, Human Monkeypox; TP, Treponema pallidum; NG, Neisseria gonorrhoeae; CT, Chlamydia trachomatis; HVS, Herpes simplex virus; (+), Positive, (-), Negative; NP, Non-practiced test

The situation of our patients did not require the use of Tecovirimat, which in any case was not available in our hospital during the first weeks of this outbreak. Something similar happened with vaccination of contacts of our patients. Imvanex type vaccines have not been available for widespread use in Spain until the second week of July 2022.

Our study has the limitation of having been collected in only one hospital but the data have been prospectively collected by a limited group of professionals with a very close follow-up of the patients.

After the experience gained with these first 30 cases, we believe it is important to rule out HMPX in any patient presenting with proctitis. In our opinion, a rectal swab should be taken for PCR of MPVX even if the patient does not appear to have mucocutaneous lesions at the time. Similarly, in patients with pharyngitis or sore throat without other clinical findings, patients should be explicitly asked whether they have recently had unprotected oral sex and, if so, consider monkeypox as a possible causative agent and take a pharyngeal swab for MPVX PCR. This may have an important implication for primary care, where we believe this infection is currently under-diagnosed.

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None to declare

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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