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## Short Communication

Favorable outcome without corticosteroids during post-artesunate delayed hemolysis with positive direct antiglobulin test in severe imported *Plasmodium falciparum* malaria, France

Olivier Paccoud<sup>1</sup>, Xavier Chamillard<sup>2</sup>, Eric Kendjo<sup>3</sup>, Isabelle Vinatier<sup>2</sup>, Laure Surgers<sup>4,5</sup>, Denis Magne<sup>6</sup>, Benjamin Wyplosz<sup>7</sup>, Adéla Angoulvant<sup>8</sup>, Olivier Bouchaud<sup>9,16</sup>, Arezki Izri<sup>10</sup>, Sophie Matheron<sup>11</sup>, Sandrine Houzé<sup>12,13</sup>, Marc Thellier<sup>3,14</sup>, Alioune P. Ndour<sup>15</sup>, Pierre Buffet<sup>15</sup>, Eric Caumes<sup>1,4,16</sup>, Stéphane Jauréguiberry<sup>3,7,16,17,\*</sup>, on behalf of the French National Reference Center for Imported Malaria Study Group<sup>18</sup>

<sup>1</sup> Sorbonne Université, Assistance Publique des Hôpitaux de Paris (AP-HP), Service des Maladies Infectieuses et Tropicales, Hôpital de la Pitié-Salpêtrière, Paris, France

<sup>2</sup> Etablissement Français du Sang (EFS) Ile-de-France, Laboratoire de Biologie Médicale de l'EFS Ile-de-France, Paris, France

<sup>3</sup> Centre National de Référence du Paludisme (NRC-M), Paris, France

<sup>4</sup> Sorbonne Université, INSERM, Institut Pierre Louis d'Épidémiologie et de Santé Publique, Paris, France

<sup>5</sup> Sorbonne Université, Assistance Publique des Hôpitaux de Paris (AP-HP), Hôpital Saint-Antoine, Service des Maladies Infectieuses et Tropicales, Paris, France

<sup>6</sup> Sorbonne Université, Assistance Publique des Hôpitaux de Paris (AP-HP), Laboratoire de Mycologie et Parasitologie, Hôpital Saint-Antoine, Paris, France

<sup>7</sup> Université de Paris Saclay, Assistance Publique des Hôpitaux de Paris (AP-HP), Service des Maladies Infectieuses et Tropicales, Hôpital de Bicêtre, Le Kremlin Bicêtre, France

<sup>8</sup> Université de Paris Saclay, Assistance Publique des Hôpitaux de Paris (AP-HP), Laboratoire de Mycologie et Parasitologie, Hôpital de Bicêtre, Le Kremlin Bicêtre, France

<sup>9</sup> Université Sorbonne Paris Nord, Assistance Publique des Hôpitaux de Paris (AP-HP), Service des Maladies Infectieuses et Tropicales, Hôpital Avicenne, Bobigny, France

<sup>10</sup> Université Sorbonne Paris Nord, Assistance Publique des Hôpitaux de Paris (AP-HP), Laboratoire de Mycologie et Parasitologie, Hôpital Avicenne, Bobigny, France

<sup>11</sup> Université de Paris, Assistance Publique des Hôpitaux de Paris (AP-HP), Service des Maladies Infectieuses et Tropicales, Hôpital Bichat Claude Bernard, Paris, France

<sup>12</sup> Université de Paris, IRD, MERIT, Paris, France

<sup>13</sup> Université de Paris, Assistance Publique des Hôpitaux de Paris (AP-HP), Laboratoire de Mycologie et Parasitologie, Hôpital Bichat Claude Bernard, Paris, France

<sup>14</sup> Sorbonne Université, Assistance Publique des Hôpitaux de Paris (AP-HP), Laboratoire de Mycologie et Parasitologie, Hôpital de la Pitié-Salpêtrière, Paris, France

<sup>15</sup> Université de Paris, INSERM, Biologie Intégrée du Globule Rouge, Laboratoire d'excellence GR-Ex, France

<sup>16</sup> Société Française de Médecine des Voyages

<sup>17</sup> Université de Paris Saclay, INSERM, Centre de Recherche en Épidémiologie et Santé des Populations, Villejuif, France

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## ABSTRACT

**Objectives:** Positive direct antiglobulin tests (DATs) have been reported in cases of post-artesunate delayed hemolysis (PADH), but the causal role of auto-immune hemolysis remains unclear. We aimed to analyze a cohort of patients with PADH and DAT during severe malaria.

**Methods:** We describe PADH and DAT results in a 7-year multi-center retrospective cohort of patients receiving artesunate for severe imported malaria.

**Results:** Of 337 patients treated with artesunate, 46 (13.6%) had at least one DAT result within 30 days of treatment initiation, and 25/46 (54.3%) had at least one positive DAT. Among 40 patients with available data, 17 (42.5%) experienced PADH. Patient characteristics were similar for patients with a positive or negative DAT, and DAT positivity was not associated with PADH occurrence ( $P = 0.36$ ). Among patients, 5/13 (38.5%) with a positive DAT after day 7 experienced PADH, compared to 10/13 (76.9%) of those with

\* Corresponding author: Tel.: +33145217420, Fax: +33145217423

E-mail address: [stephane.jaureguiberry@aphp.fr](mailto:stephane.jaureguiberry@aphp.fr) (S. Jauréguiberry).

a negative DAT after day 7 ( $P = 0.11$ ). Overall, 41% of patients required blood transfusions, and outcome was favorable without corticosteroids, even in cases of PADH.

**Conclusions:** DAT does not appear to be a marker of PADH, but rather an indirect marker of an immune-mediated mechanism. DAT positivity should not lead to the administration of systemic corticosteroids during PADH.

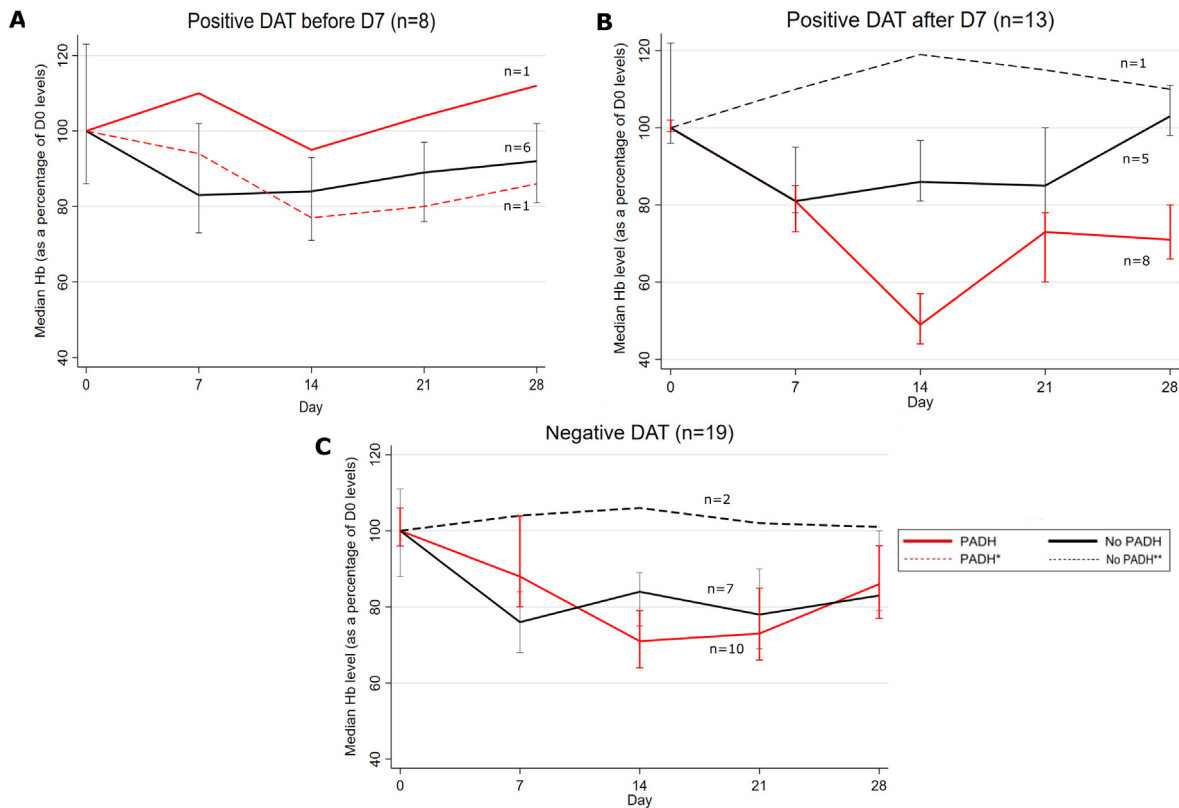
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**Introduction**

Post-artesunate delayed hemolysis (PADH) is a common nonrecurring adverse effect of artesunate during severe *Plasmodium falciparum* malaria, which occurs after the first week of treatment in an estimated 10–30% of cases in nonimmune travelers [1,2]. Reports of positive direct antiglobulin tests (DAT) in patients experiencing PADH suggest an immune-driven process [1,3]. In a systematic review, 44% of patients with PADH had a positive DAT [4]. Most previous reports focused only on patients experiencing PADH and not on other patients with severe malaria. Levels of positivity, antibody specificity, and delay between artesunate and DAT were often lacking [2,3]. Ring-stage parasites killed by artesunate are removed from erythrocytes in the spleen microcirculation through

a process called ‘pitting’. These pitted (once-infected erythrocytes) are spared from destruction and remain in circulation but with a decreased lifespan compared to uninfected erythrocytes [5]. It has been postulated that PADH results from the synchronous hemolysis of once-infected erythrocytes 7–28 days after the acute phase of infection [5]. The potential participating role of autoimmunity in the pathogenesis of hemolytic anemia during PADH remains debated. A positive DAT indicates that hemolysis is likely immune-mediated but is not pathognomonic of autoimmune hemolytic anemia and can also simply reflect nonspecific coating of red blood cells by immunoglobulins and/or complement. Herein, we describe parameters of hemolysis and DAT results in patients treated with artesunate, with the aim of determining whether DAT positivity could be involved in PADH pathophysiology.



**Figure 1.** Kinetics of hemoglobin levels from D0 to D28 in a cohort of patients with severe imported *Plasmodium falciparum* malaria, according to occurrence of PADH and timing of DAT results. (a) Positive DAT before D7 and PADH and no PADH pattern. (b) Positive DAT after D7 and PADH and no PADH pattern. (c) Negative DAT all the time and PADH and no PADH pattern. DAT, direct antiglobulin tests; PADH, post-artesunate delayed hemolysis.

Note:

\* & \*\*: Patients with two DAT results available during follow-up.

\*: Patient who experienced PADH, with a positive DAT before D7 and a negative DAT after D7 (A).

\*\* On panel B: one patient who did not experience PADH, with a negative DAT before D7 and a positive DAT after D7.

\*\* On panel C: two patients who did not experience PADH, with two negative DATs from D0–D28.

**Table 1**  
Patient characteristics according to occurrence of PADH, and according to DAT results.

Patient characteristics	Patients with available data	According to occurrence of PADH			According to DAT results		
		PADH (n = 17)	No PADH (n = 23)	P	DAT + (n = 21)	DAT– (n = 19)	P
Sex	40			0.23 <sup>b</sup>			0.35 <sup>b</sup>
Male		7 (41.2)	13 (56.5)		11 (52.3)	9 (47.4)	
Female		10 (58.8)	10 (43.5)		10 (47.7)	10 (52.6)	
Age (years)	40	45 (36–49)	43 (32–56)	0.76 <sup>c</sup>	43 (33–49)	45 (38–55)	0.32 <sup>c</sup>
Place of birth	40			0.75			0.577
Sub Saharan Africa		11 (64.7)	16 (69.6)		15 (71.4)	12 (63.2)	
France		6 (35.3)	7 (30.4)		6 (28.6)	7 (36.8)	
Presumed immune status <sup>d</sup>	40			0.27			1
Nonimmune		6 (35.3)	4 (17.4)		5 (23.8)	5 (26.3)	
partially immune or semi-immune		11 (58.9)	19 (69.6)		16 (76.2)	14 (73.7)	
Number of severity criteria (French severity criteria for imported malaria – Text S1)	40			0.24			0.18
1 among the list		1 (5.9)	6 (26)		6 (28.6)	1 (5.3)	
2 among the list		6 (35.2)	5 (21.7)		5 (23.8)	6 (31.6)	
≥3 among the list		10 (58.8)	12 (52.2)		10 (47.6)	12 (63.1)	
Delay between symptom onset and presentation	40	4.5 (0.8)	4.8 (0.5)	0.7	3.5 (3–7.5)	4 (3–5)	0.38
Number of artesunate doses	40	4.9 (0.2)	5.3 (0.4)	0.61	5 (4–6.5)	5 (4–5)	0.8
Parasitemia at D0	38	11.4 (5.6–20)	6 (1–9)	0.046	6.2 (0.88–13)	9 (5.5–19.2)	0.18
Hb level at D0 (g/dL, reference range: 13–17g/dL)	40	12.4 (12–13.9)	11.2 (8.1–12.4)	0.021	11.6 (9.4–12.4)	12.4 (11.5–13.9)	0.11
Hb level at D7	40	10.8 (9.6–11.5)	9 (7.5–10.1)	0.01	9.2 (7.6–10.5)	10.2 (8.7–11.6)	0.09
Hb level at D14	39	9 (6.7–9.8)	9.4 (7.7–10.6)	0.69	8.9 (7.05–9.85)	9.3 (7.9–10.5)	0.26
Hb level at D21	36	9.3 (8.4–10.6)	8.8 (7.8–10.6)	0.65	9 (7.8–10.4)	9.3 (8.4–10.8)	0.42
Hb level at D28	35	10.6 (9–11.1)	10.2 (9.5–11.5)	0.8	10.2 (8.9–11.3)	10.3 (9.6–11.2)	0.75
Hb nadir	40	8.2 (6.9–9.8)	7.6 (7–9.7)	0.8	7.3 (6.5–9.2)	8.8 (7.5–10.2)	0.07
Reticulocyte counts at D0 (G/L, reference range: 50–100G/L)	38	30 (13–54)	35 (20–80)	0.36	40 (29–80)	33 (19–60)	0.17
Reticulocyte counts at D7	37	64 (24.5–104)	91 (75–186)	0.07	90 (69–151)	74.5 (32–132)	0.33
Reticulocyte counts at D14	37	195.5 (114–236)	140.5 (109–222)	0.5	165 (110–248)	154 (108–233)	0.82
Reticulocyte counts at D21	36	151 (129–222)	121 (101–182)	0.09	133.5 (85–207)	155 (129–228)	0.24
Reticulocyte counts at D28	34	126 (114–200)	119 (89–171)	0.22	114 (70–139)	128 (114–200)	0.12
LDH levels at D0 (U/L, reference range 125–245U/L)	38	771 (706–926)	979 (648–1320)	0.23	1080 (648–1507)	808 (712–978)	0.29
LDH levels at D7	38	714 (621–799)	812 (659–1230)	0.2	814 (673–1166)	707 (642–793)	0.25
LDH levels at D14	37	1326 (1055–1761)	731 (545–1082)	0.009	985 (646–1461)	1126 (734–1346)	0.7
LDH levels at D21	36	960 (783–1360)	630 (534–892)	0.06	589 (378–1098)	765 (627–1045)	0.19
LDH levels at D28	35	613 (559–734)	457 (350–672)	0.19	449 (293–882)	613 (559–728)	0.18
LDH zenith	40	1326 (946–1855)	1030 (673–2064)	0.29	1110 (673–2067)	1243 (845–1596)	0.7
Packed blood transfusion before D7	40	9 (53)	10 (43.5)	0.74			
On or after D7		1 (11.1)	10 (100)				
Positive DAT		8 (88.9)	0 (0)				
IgG pattern ( <sup>a</sup> )	40	7 (41.2)	14 (60.9)	0.36			
IgG pattern (> <sup>a</sup> )		3/7	11/14				
IgG and C3d pattern		1/7	2/14				
C3d pattern		2/7	1/14				
Positive DAT before D7 <sup>a</sup>	40	2/8 (25)	0/6 (0)	0.44			
IgG pattern		2/2 (100)	0				
C3d or IgG and C3d pattern		0	0				
Positive DAT after D7 <sup>a</sup>	40	5/15 (33.3)	8/11 (72.7)	0.11			
IgG pattern		2/5 (40)	7/8 (87.5)				
C3d or IgG and C3d pattern		3/5 (60)	1/8 (12.5)				
G6PD/PK deficiency	10	0/6	2/4				
Iron deficiency	35	2/15	2/20				
Vitamin B9/B12 deficiency	22	0/6	1/16				
Chronic renal failure	40	0/17	3/23				
Potential confounding factor associated with DAT positivity	40				6 (28.6)	2 (10.6)	0.26
HIV					3 (14.3)	2 (10.6)	
Other <sup>e</sup>					3 (14.3)	0 (0)	
Biological markers associated with DAT positivity	12				10 (47.6)	6 (31.6)	0.54
Polyclonal hypergammaglobulinemia					6 (28.6)	3 (15.8)	
Positive antinuclear antibody test					7 (33.3)	3 (15.8)	

DAT, direct antiglobulin test; G6PD, glucose-6-phosphate dehydrogenase; Hb, hemoglobin; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; PADH, post-artesunate delayed hemolysis; PK, pyruvate kinase.

<sup>a</sup> 14 patients had DAT tests performed before D7, and 26 had tests performed after D7.

<sup>b</sup> Fischer's exact test.

<sup>c</sup> Mann-Whitney test.

<sup>d</sup> Presumed immune status: partially immune for adult immigrants from a malaria-endemic region and living in Europe; semi-immune for adult immigrants who had been living in a malaria-endemic region for at least 2 years at time of diagnosis; nonimmune for European natives who had never lived in a malaria-endemic region.

<sup>e</sup> Hodgkin's lymphoma (n = 1), auto-immune thyroiditis (n = 1), idiopathic thrombocytopenic purpura

## Materials and methods

In this multicenter observational study, we evaluated DAT results prescribed by clinicians during the follow-up of patients receiving artesunate for severe imported *P. falciparum* malaria (2017 French criteria, Supplementary Text 1). We screened all adults ( $\geq 18$  years) receiving  $\geq 3$  doses of artesunate with at least one DAT result within 30 days of treatment initiation in five teaching hospitals from May 1, 2011, to October 1, 2018. We analyzed demographic characteristics, clinical presentation, severity criteria, and parameters of anemia and hemolysis (routinely collected at day (D) 0, D3 (+/-1), D7 (+/-2), D14 (+/-3), D21 (+/-3), and D28 (+/-3) of treatment initiation), treatment, and outcome. Case definitions and statistical methods are available in Supplementary Text 2.

## Results

Of 337 patients fulfilling cohort selection criteria, 225 had sufficient follow-up data, among whom 41/225 (18.2%) experienced PADH. We included 46 patients with at least one DAT during follow-up (Supplementary Table 1). There were no significant differences in median age, region of birth, and median baseline parasitemia between our 46 patients and the 291 other patients from the cohort (data not shown). Fifty-three DATs were performed in 46 patients, a median of 10 days (range: 1–30) after treatment initiation (Table 1), 27/53 (50.9%) of which were positive. The majority of positive tests had an immunoglobulin (Ig)G pattern (22/27, 81.4%). Indirect antiglobulin tests were negative in 6/6 patients. Forty patients had sufficient follow-up data to analyze kinetics of PADH, including 21 with a positive DAT. When combining DAT results before and after D7, we found no differences in characteristics of patients with a positive or a negative DAT. Among 17 patients experiencing PADH, the mean decrease in hemoglobin levels during PADH was 3.9g/dL (range: 1.2–8 g/dL). We found no association between a positive DAT and experiencing PADH ( $P = 0.36$ ). Of six patients with a severe PADH (hemoglobin nadir  $<7$ g/dL), four (67%) had a positive DAT and two (33%) had a negative DAT. Among 17 patients with PADH, 4/7 (57.1%) with a positive DAT had severe PADH, compared to 2/10 (20%) with a negative DAT ( $P = 0.12$ ). The hemoglobin nadir of patients with PADH and a positive DAT was lower than that of patients with PADH and a negative DAT (7.9g/dL vs 9g/dL,  $P = 0.06$ ). Kinetics of hemoglobin levels according to onset of PADH were similar when considering DAT performed before or after D7 (Figure 1). Twenty-six patients had a DAT result after D7, including 13 with a positive test. Fifteen of these experienced PADH. In total, 5/13 (38.5%) patients with a positive DAT experienced PADH, compared to 10/13 (76.9%) of those with a negative DAT ( $P = 0.11$ ). DAT with a Human Complement C3d protein (C3d) or IgG and C3d pattern were only found after D7, and 3/4 of those patients experienced PADH. No patients with PADH received systemic corticosteroids, versus one patient without PADH for post-malaria neurological syndrome *sensu lato*.

## Discussion

We found no association between having a positive DAT result, regardless of its timing, and experiencing PADH. DAT was positive in half of tested patients and was most often positive with an IgG pattern and low positivity levels.

Previously, DAT results were only reported from a subset of patients experiencing PADH, and not from other patients with severe imported malaria [3,4]. We found no differences in clinical and biological presentations between patients with a positive or a negative DAT. We also found no association between having a positive DAT and experiencing PADH.

Previous studies have shown that patients with PADH and a positive DAT were more likely to be prescribed corticosteroids [4], and resolution of PADH was reported after corticosteroid treatment [3]. In our cohort, the outcome of PADH was favorable in all cases, despite none of the patients receiving systemic corticosteroids, including patients with PADH and a positive DAT. These results argue against the systematic use of systemic corticosteroids for mild PADH, even in cases of DAT positivity [4,5]. However, it remains possible that corticosteroids may be beneficial in cases of severe PADH with strongly positive DAT results, arguing for severe associated autoimmune hemolysis.

Our study does not completely exclude the possibility of an auto-antibody's participation in PADH pathophysiology, as previously discussed [3,6,7]. Indeed, in a study of post-treatment hemolysis following oral artemisinin combination therapy in 75 patients, those with PADH were more frequently positive for anti-erythrocyte antibody screening at D14 than patients without PADH (57% vs 28%) [6]. There has been interest in the role of auto-antibodies directed against phosphatidylserine components of the erythrocytic membrane in the pathophysiology of malarial anemia and PADH [7]. DAT positivity could be a reflection of the immune-driven clearance of infected/uninfected erythrocytes during the immune response to *P. falciparum*, regardless of treatment options and severity of malaria [8]. Indeed, DAT positivity was extensively reported before artesunate during the acute phase of malaria in up to 50% of children from endemic areas [9]. Some patterns of DAT positivity, such as when the DAT is positive for complement, may be associated with an immune-driven event, as evidenced by the 3/4 patients in our study with a C3d or IgG/C3d pattern experiencing PADH [3]. While DAT positivity may not be associated with the occurrence of PADH, it may be associated with a more severe PADH event, possibly as a marker of more pronounced immune-driven erythrocyte clearance during PADH.

This study presents some limitations. The limited number of patients means that comparisons between groups were likely underpowered, especially for subgroup analyses. A more longitudinal evaluation of DAT results during acute and convalescence phases of malaria would have helped with the interpretation of DAT results.

In conclusion, our study shows that DAT is positive in approximately half of tested cases in severe imported malaria, regardless of the occurrence of PADH. PADH is generally a self-limiting event, and DAT positivity during PADH should not systematically lead to the administration of systemic corticoids.

## Declarations of competing interest

The authors have no competing interests to declare.

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## Ethical approval

Data collection and storage by the NRC-M were approved by the French National Commission for Data Protection and Liberties (declaration number 1223103). The study was conducted in accordance with French law on noninterventive clinical research, which requires the nonobjection of patients but not their written consent, according to articles L1221-1.1 and L1211-2 of the French Public Health Code.

## Author contributions

Study concept and design: OP and SJ. Statistical and data analysis: OP and SJ. Writing the original draft: OP and SJ. Project man-

agement: SJ. Data acquisition: OP, XC, EK, KN, IV, MK CB, LS, BW, AA, OB, AI, SM, SH, MT, EC, and SJ. Review of the final manuscript: XC, EK, KN, IV, MK, CB, LS, BW, AA, OB, AI, SM, SH, MT, AN, PB, EC, and SJ.

## Note

Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines were followed.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.ijid.2023.10.018](https://doi.org/10.1016/j.ijid.2023.10.018).

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