



# Invasive Fungal Infections in Dengue Recovered Patients: A New Phenomenon in the Covid-19 Era

Pawan Singhal<sup>1</sup> · Anshu Rawat<sup>1</sup> · Shivam Sharma<sup>1</sup> · Anjani Kumar Sharma<sup>1</sup> ·  
Kailash Singh Jat<sup>1</sup> · Shubham Agarwal<sup>1</sup> · Sunil Samdani<sup>1</sup> · Sunita Agarwal<sup>1</sup> ·  
Man Prakash Sharma<sup>1</sup> · Sudheer Bhandari<sup>2</sup>

Received: 14 February 2022 / Accepted: 25 August 2022  
© Association of Otolaryngologists of India 2022

**Abstract** Invasive fungal rhinosinusitis was seen to rise to epidemic levels after the 2nd wave of ongoing Covid pandemic, especially in tropical countries, maximally in India. A similar trend is being observed for cases who have recently recovered from dengue virus infection. Post dengue invasive fungal infection is a new presentation and any associations between it and Covid pandemic need to be studied in detail to help prepare for any complications. 3 patients presented to the out-patient department of E.N.T at a tertiary level teaching hospital in East India with complains similar to rhinosinusitis. These patients were then evaluated and diagnosed to be infected from Mucormycosis and Aspergillus fungal sinusitis after which they were managed with surgical debridement and systemic antifungal therapy. All had a recent history of recovery from Dengue virus infection and a possible association could be suspected. 3 patients presented with complains of pain over upper jaw with orbital swelling and loss of vision developing over a period of 24 days. Two of them had ulceration of hard palate. They were then subjected to Contrast MRI along with CT scan of

the Paranasal sinuses which depicted pansinus involvement with intracranial extension in two patients. These were then planned for diagnostic nasal endoscopies along with biopsies which turned out to be Invasive fungal sinusitis in the form of Aspergillosis and Mucormycosis. All the 3 patients had recent history of recovery from Dengue virus infection and did not have any other co-morbidities. Covid Associated Mucormycosis (CAM) is a well-known entity now but no reports of Dengue associated Invasive fungal sinusitis are yet reported. Whether this new phenomenon has anything to do with the interactions between dengue virus and coronavirus is not known at present and needs to be studied in detail so appropriate management protocols can be formulated.

**Keywords** COVID19 · Mucormycosis · Post dengue · New phenomenon

✉ Pawan Singhal  
drps.ent@gmail.com  
Anshu Rawat  
dranshurawat94@gmail.com  
Shivam Sharma  
shivam92@hotmail.com  
Anjani Kumar Sharma  
dranjaniisharma@gmail.com  
Kailash Singh Jat  
drkailashsms@gmail.com  
Shubham Agarwal  
drshubz.jpr@gmail.com  
Sunil Samdani  
sunilsamdhani@yahoo.com

Sunita Agarwal  
drsunitagarwal@gmail.com  
Man Prakash Sharma  
drmanprakash@yahoo.co.in  
Sudheer Bhandari  
drs\_bhandhari@yahoo.com

<sup>1</sup> Department of Otorhinolaryngology and Head Neck Surgery, S.M.S Medical College and Hospital, Jaipur, Rajasthan 302004, India

<sup>2</sup> Department of Internal Medicine, S.M.S Medical College and Hospital, Jaipur, Rajasthan 302004, India

## Introduction

WHO declared COVID 19 as a global pandemic on 11th March 2020 and has completed almost 2 years of human circulation now. After the initial case reports of acute respiratory distress syndrome (later proved to be caused by SARS CoV-2) on December 31, 2019 in the city of Wuhan, China, the outbreak spread significantly affecting all the countries around the world (1). Since then, all the continents across the globe have been facing the brunt of pandemic in terms of overwhelming health care systems, lack of health care workers and significant economic and psychological burden as well. Millions of people were infected and expired in the past two years owing to COVID 19 infection (2) (Table 1).

Coronavirus disease has a wide range of spectrum from being asymptomatic to severe pneumonia and about 5% of patients require ventilator support. Various studies and research papers have shown the pathophysiology of covid19 as: cytokine surge, markedly increased pro inflammatory CD4 and CD8 toxic granules, hyper coagulable state, altered iron metabolism and increased iron overload which result in hypoxia and multisystem failure [3, 4,]. All these factors lead to immune system dysfunction and are proposed to be the major causes of the emergence of acute invasive fungal infections of head and neck region in post covid patients (5).

In the pre covid era mucormycosis was a rare entity with an incidence of 0.0051.7 per million population. However, the Indian subcontinent has witnessed a marked rise in mucormycosis cases specially during the 2nd wave of covid 19 pandemic. The incidence of CAM was cited as 0.14/1000 diabetic patients which is 80 times higher than that reported in other parts of the world. This became a major public health burden in India (5, 6) and was declared as an epidemic. The possible etiological factors of CAM include Diabetes Mellitus (which in itself is a pandemic and an independent risk factor for mucormycosis) as the underlying disease in up to 5476% cases, and other factors like Diabetic ketoacidosis, cytokine storm and corticosteroid therapy to treat severe covid pneumonia cases (7). However, the true incidence and etiology of rhino-orbital mucormycosis in post covid patients is still unknown.

Such a high incidence of previously rare invasive fungal infection is a surprise thing in covid recovered patients, but what is more surprising is the emergence of mucormycosis cases in dengue recovered patients. This is because SARS CoV-2 being a novel infection, its exact pathophysiology and consequences are not completely understood at present, but dengue virus infection has been an endemic disease and a major public health concern throughout tropical and subtropical countries like India for many decades (8). Dengue virus is a single stranded RNA virus and has four serotypes from DEN 1 to DEN 4. All these serotypes are antigenically similar, yet they differ enough to elicit cross protection only

for a few months after infection from any one of them (9). To the best of our knowledge, invasive fungal infections were never seen as a complication in dengue recovered patients before the covid pandemic. Should we worry about this new phenomenon in the covid era?

## Case Series

Three patients of post dengue rhinoorbitocerebral mucormycosis presented in our tertiary care center, details of which are described below:

### Case 1.

A 43 years old female presented to us with complaints of left sided jaw pain, left periorbital swelling and loss of vision. On examination, the patient was conscious and oriented with negative perception of light in left eye and palatal erosion over left side of hard palate. There was gum abscess on the right side also (Fig. 1a). On the basis of clinical suspicion, the diagnosis of mucormycosis was made and injection liposomal Amphotericin B started at a dose of 5 mg/kg/day. Patient was not a known case of diabetes mellitus and no past history of covid infection or steroid use was present. However, she suffered from dengue 10–12 days before mucormycosis and was found to be hyperglycaemic at the time of admission to hospital. Contrast enhanced MRI with fat suppressed images of paranasal sinuses (PNS), orbit and brain was performed for further evaluation (Fig. 1b). Contrast enhanced CT scans were obtained to look for bony erosions of maxilla, orbit and skull base. Endoscopic biopsies were taken and sent for KOH mount, histopathological examination and fungal culture. Ophthalmological opinion was obtained. All routine investigations were done including complete blood counts, blood sugar, HbA1c, renal function tests, liver function tests, quantitative C reactive protein and d-dimer. Preanesthetic evaluation was done and patient planned for surgical debridement with left total maxillectomy, right infrastructural maxillectomy and left orbital clearance under general anaesthesia. Blood sugar was regularly monitored and controlled. Liposomal Amphotericin B injection (5 mg/kg/day) was continued for three weeks post-surgery. Then she was started on tab posaconazole 300 mg/day for six months. She was on monthly follow up for endoscopic crust removal for three months.

### Case 2.

This is a case of a 26 years old male student who suffered from moderately severe dengue. 5 days following recovery he developed a sudden onset of left eye proptosis, chemosis, loss of vision, headache and slurred speech (Fig. 2a). He was in a state of confusion and irritability at the time of

**Fig. 1** A shows right side gum abscess. B and C T2w MRI shows mucosal thickening in bilateral nasal cavity, maxillary, ethmoid, sphenoid and frontal sinuses. There is evidence of left orbital cellulitis with extension of inflammation up to the orbital apex resulting in left eye ball proptosis



presentation. There was no history of covid infection, diabetes mellitus or steroid use. Endoscopy revealed grossly necrosed left nasal mucosa and turbinates. Oral cavity examination was normal. Biopsy specimen sent for KOH mount, HPE and fungal culture. Inj. Liposomal Amphotericin B started at a dose of 5 mg/kg/day. Gadolinium enhanced MRI with fat suppressed images of PNS, orbit and brain showed hypointense mucosa in bilateral nasal cavity, left maxillary, ethmoid, sphenoid and frontal sinus, left orbital cellulitis and left temporal lobe abscess of 19×17×21mm size (Fig. 2b). Neurology and ophthalmology opinion obtained and tablet levetiracetam 500 mg was given twice daily along with injection mannitol 1.5 g/kg IV infusion. All routine blood investigations done similar to case 1. Transient hyperglycaemia was noted at the time of admission which was controlled. He was planned for bilateral sinonasal debridement with left orbital exenteration under GA. Post operative lip Amp B injection (5 mg/kg/day) continued for 4 weeks followed by tab posaconazole 300 mg daily for six months. Follow up was similar to case 1.

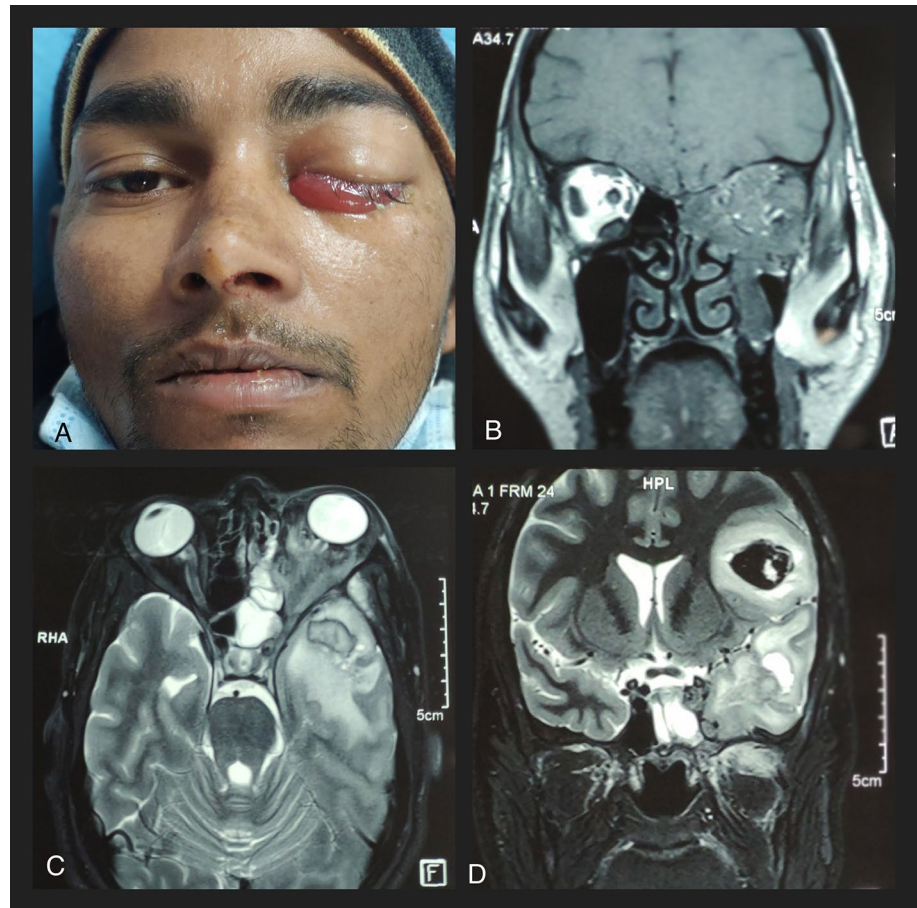
### Case 3.

A 61 years old male came to us with sudden onset bilateral periorbital edema (R>L) and vision loss in both eyes which developed 10 days after dengue infection (Fig. 3). There was no prior history of covid infection, diabetes mellitus or steroid use. Bilateral upper jaw ache, numbness and palatal erosion was present. Endoscopic biopsy, imaging and routine investigations were carried out similar to case 1 and 2. Liposomal Amphotericin B injection (5 mg/kg/day) started and continued for four weeks after surgery. Patient underwent bilateral sinonasal debridement with bilateral infrastructural maxillectomy and orbital clearance.

### Discussion

The fungi causing mucormycosis is ubiquitous in nature and is acquired mainly by inhalation of spores, less commonly via infected wounds and ingestion of spores. It is a highly fatal angioinvasive disease that causes tissue necrosis.

**Fig. 2** A Severe proptosis and chemosis of left eye. On B T1w C and D T2w MRI there is evidence of mucosal thickening in left ethmoid, sphenoid, maxillary sinuses and bilateral nasal cavities. Extension of inflammation also seen in left infratemporal space, involving the left retroantral fat pad and masticator space. There is associated cellulitis in left orbit intraconal, conal and extraconal post septal parts with involvement of extraocular muscles. Focal peripheral enhancing lesion in left temporal lobe measuring 19×17×21mm (AP x TD x CC) likely represents abscess formation (D)



**Fig. 3** Patient with gross periorbital swelling

Human infections are mainly caused by the species of genera *Rhizopus*, *Mucor* and *Rhizomucor* (10). The etiological agent in majority of the cases of CAM were *rhizopus* sp. And unspecified mucorales. *Aspergillus* and *candida* infections were also seen (11). This is contradictory to our study as in two cases *aspergillus* sp was identified predominantly on histopathological examination and fungal culture both.

According to the site of involvement, mucormycosis can be classified as rhino-orbito-cerebral, pulmonary, cutaneous and gastrointestinal forms. Rhino-orbito-cerebral invasion was most common among CAM patients followed by pulmonary and cutaneous mucormycosis (12, 13).

SARS-CoV-2 infection is found to be associated with impairment of beta cell function of pancreas. Due to this reason, previously euglycemic patients were found to develop hyperglycemia during the course of COVID 19. Hence, it may be concluded that, covid 19 infection may trigger development of diabetes mellitus with or without ketoacidosis which may persist weeks or months after recovery [14, 15]. This helps relating to the fact that although there was no history of covid infection in none of our patients yet transient hyperglycemia was noticed at the time of admission to the hospital.

On reviewing the literature for determining SARS-CoV-2 infection as an independent risk factor for development of mucormycosis, it is observed that covid 19 infection increases the synthesis of GRP78 protein, which is a specific receptor on host endothelium that facilitates fungal endocytosis [10, 16]. GRP78 being a stress related protein, is also enhanced with elevated blood glucose and ketone bodies. Furthermore, increase in *S. iron*, ferritin and heme in

**Table 1** shows the relevant details of the above mentioned three cases

	Case 1	Case 2	Case 3
Age/Gender	43 Y female	26 Y male	61 Y male
Signs and symptoms			
a. Paranasal sinuses	Left upper jaw pain	Left upper jaw pain	bilateral upper jaw pain
b. Eye	Left periorbital swelling and loss of vision	Left periorbital swelling and loss of vision	bilateral periorbital swelling and loss of vision
c. Palate	Erosion over hard palate and gingival abscess	Not involved	Erosion over hard palate
d. other		Dysarthria	
MRI findings:-			
a. PNS involvement	Bilateral all sinuses	Unilateral all sinuses	Bilateral all sinuses
b. Infratemporal fossa and soft tissue involvement	Present	Present	Present
c. Orbital cellulitis			
d. Palatal erosion			
e. Intracranial extension	Present (L > R) Erosion present	Present (L) No Left cavernous sinus	Present (R > L) Present Enhancing lesion in Right basifrontal lobe
HPE	No Aspergillus sp. and mucormycosis	No Aspergillus and mucormycosis	No Mucormycosis
History of covid infection	No	No	No
Past history of DM and steroid use	No	No	No
Dengue NS1 Ag test	Positive	Positive	Positive
Duration between symptoms of dengue and mucor	10–12 days	5–6 days	9–10 days
Treatment	Surgical debridement with left total and right infrastructure maxillectomy and orbital clearance followed by lip Amp B injections (5 mg/kg/day)	Endoscopic debridement with left orbital exenteration followed by lip Amp B injections (5 mg/kg/day). Anti epileptics and mannitol as suggested by neurosurgeons	Surgical debridement with infrastructure maxillectomy and orbital clearance followed by lip Amp B injections (5 mg/kg/day)

covid infection results in free radical injury and predisposes to endothelial damage which further add to thrombosis and angioinvasive property of mucorales [17–19]. Why India has the highest number of mucormycosis cases during covid pandemic requires in depth research.

The fungal infection associated with dengue in our cases is similar to that of post covid mucormycosis in terms of presentation, clinical signs and symptoms, MRI/CT findings and management. The notable difference between the two entities is seen in terms of sudden loss of vision in all cases as the first presenting symptom.

Recently, a few research papers have mentioned the interaction of dengue virus and SARS CoV 2 in terms of Antibody Dependent Enhancement and cross reactivity between antibodies against the two viruses. Both these viruses share some pathophysiological similarities such as capillary leakage, thrombocytopenia, coagulopathy and cytokine storm mediated by tumor necrosis factor (TNF), interleukin 6, interferon gamma and chemokines like macrophage

migration inhibitory factor (MIF) (20, 21, 22, 23). Further detailed studies are required to explain the interaction between dengue virus and SARS CoV 2 and whether this interaction plays any role in the emergence of invasive fungal infections as a post dengue sequelae.

## Conclusion

Invasive fungal infections like mucormycosis which were rarely seen in pre covid times are reported to occur in large numbers in 2nd wave of covid 19, maximally in India. Dengue is an endemic disease in tropical countries since many decades and mucormycosis is seen as a complication of dengue for the first time. Possibility of interaction between the two viruses and pathophysiology of SARS CoV 2 needs to be studied in detail. This will help in predicting the possible complications that can be encountered during pandemic as

no one is sure how long the virus is going to remain in the community.

**Author contribution** All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Dr. PS. The first draft of the manuscript was written by AR and SS and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Funding** This research did not receive any specific grant from funding agencies in the public, commercial, or not for profit sectors.

#### Declarations

**Conflict of interest** All the authors declare that they have no conflict of Interest.

**Consent informed** Consent was obtained from all individual participants included in the study. **Ethical approval.** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

#### References

- Cucinotta D, Vanelli M (2020) WHO Declares COVID-19 a Pandemic. *Acta Bio Medica Atenei Parmensis* 91(1):157
- Tsang HF, Chan LWC, Cho WCS, Yu ACS, Yim AKY, Chan AKC, Ng LPW, Wong YKE, Pei XM, Li MJW, Wong SC (2021) An update on COVID-19 pandemic: the epidemiology, pathogenesis, prevention and treatment strategies. *Expert Rev Anti Infect Ther* 19(7):877–888. <https://doi.org/10.1080/14787210.2021.1863146>
- Li G, Fan Y, Lai Y et al (2020) Coronavirus infections and immune responses. *J Med Virol* 92(4):424–432. <https://doi.org/10.1002/jmv.25685>
- Hosseini A, Hashemi V, Shomali N et al (2020) Innate and adaptive immune responses against coronavirus. *Biomed Pharmacother* 132:110859. <https://doi.org/10.1016/j.biopha.2020.110859>
- Al-Tawfiq JA, Alhumaid S, Alshukairi AN et al (2021) COVID-19 and mucormycosis superinfection: the perfect storm. *Infection* 49(5):833–853. <https://doi.org/10.1007/s15010-021-01670-1>
- Singh AK, Singh R, Joshi SR, Misra A (2021) Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. *Diabetes Metab Syndr* 15(4):102146. <https://doi.org/10.1016/j.dsx.2021.05.019>
- Prakash H, Chakrabarti A. Epidemiology of mucormycosis in India. *Microorganisms*. 2021; 9: 1–12 <https://doi.org/10.3390/microorganisms9030523>
- Ganeshkumar P, Murhekar MV, Poornima V, Saravanakumar V, Sukumaran K, Anandaselvasankar A, John D, Mehendale SM (2018) Dengue infection in India: a systematic review and meta-analysis. *PLoS negl trop dis* 12(7):e0006618
- Guzman MG, Harris E (2015) Dengue. *Lancet* 385(9966):453–465. [https://doi.org/10.1016/S0140-6736\(14\)60572-9](https://doi.org/10.1016/S0140-6736(14)60572-9)
- Petrikos G, Skiada A, Lortholary O, Roilides E, Walsh TJ, Kontoyiannis DP (2012) Epidemiology and clinical manifestations of mucormycosis. *Clin Infect Dis* 54(1):S23–34. <https://doi.org/10.1093/cid/cir866>
- Muthu V, Rudramurthy SM, Chakrabarti A, Agarwal R (2021) Epidemiology and pathophysiology of COVID-19-associated Mucormycosis: india versus the rest of the world. *Mycopathologia* 186(6):739–754. <https://doi.org/10.1007/s11046-021-00584-8>
- Jose A, Singh S, Roychoudhury A, Kholakiya Y, Arya S, Roychoudhury S (2021) Current understanding in the pathophysiology of SARS-CoV-2-associated rhino-orbito-cerebral mucormycosis: a comprehensive review. *J Maxillofac Oral Surg* 3:373–380
- Sen M, Honavar SG, Bansal R et al; members of the Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC) Study Group. Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India - Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC), Report 1. *Indian J Ophthalmol*. 2021 69(7): 1670-1692. doi: [https://doi.org/10.4103/ijo.IJO\\_1565\\_21](https://doi.org/10.4103/ijo.IJO_1565_21)
- Oriot P, Hermans MP. Euglycemic diabetic ketoacidosis in a patient with type 1 diabetes and SARS-CoV-2 pneumonia: case report and review of the literature. *Acta Clin Belg*. 2020;1–5. doi: <https://doi.org/10.1080/17843286.2020.1780390>
- Smith SM, Boppana A, Traupman JA et al (2021) Impaired glucose metabolism in patients with diabetes, prediabetes, and obesity is associated with severe COVID-19. *J Med Virol* 93(1):409–415. <https://doi.org/10.1002/jmv.26227>
- Moorthy A, Gaikwad R, Krishna S, Hegde R, Tripathi KK, Kale PG, Rao PS, Haldipur D, Bonanthaya K (2021) SARS-CoV-2, uncontrolled diabetes and corticosteroids—an unholy trinity in invasive fungal infections of the maxillofacial region? a retrospective, multi-centric analysis. *J Maxillofac Oral Surg* 3:418–425
- Gebremariam T, Lin L, Liu M et al (2016) Bicarbonate correction of ketoacidosis alters host-pathogen interactions and alleviates mucormycosis. *J Clin Invest* 126(6):2280–2294. <https://doi.org/10.1172/JCI82744>
- Colafrancesco S, Alessandri C, Conti F, Priori R (2020) COVID-19 gone bad: A new character in the spectrum of the hyperferritinemic syndrome? *Autoimmun Rev* 19(7):102573. <https://doi.org/10.1016/j.autrev.2020.102573>
- Perricone C, Bartoloni E, Bursi R et al (2020) COVID-19 as part of the hyperferritinemic syndromes: the role of iron depletion therapy. *Immunol Res* 68(4):213–224. <https://doi.org/10.1007/s12026-020-09145-5>
- Ulrich H, Pillat MM, Tárnok A (2020) Dengue fever, COVID-19 (SARS-CoV-2), and antibody-dependent enhancement (ADE): a perspective. *Cytom A* 97(7):662–667. <https://doi.org/10.1002/cyto.a.24047>
- Harapan H, Ryan M, Yohan B et al (2021) Covid-19 and dengue: Double punches for dengue-endemic countries in Asia. *Rev Med Virol* 31(2):e2161. <https://doi.org/10.1002/rmv.2161>
- Cardona-Ospina JA, Arteaga-Livias K, Villamil-Gómez WE et al (2021) Dengue and COVID-19, overlapping epidemics? an analysis from Colombia. *J Med Virol* 93(1):522–527. <https://doi.org/10.1002/jmv.26194>
- Masyeni S, Santoso MS, Widyaningsih PD et al (2021) Serological cross-reaction and coinfection of dengue and COVID-19 in Asia: experience from Indonesia. *Int J Infect Dis* 102:152–154. <https://doi.org/10.1016/j.ijid.2020.10.043>

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.