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Review Article **Open Access**

Invasive fungal infections and COVID-19: a review

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Abstract:

Invasive fungal diseases (IFDs) are major causes of morbidity and mortality among hospitalized patients all over the world with a global prevalence of 15%. Since the first case of COVID-19 was reported on February 27, 2020, in Nigeria, it had been discovered across all geopolitical zones in Nigeria. As the medical community confronts the ongoing COVID-19 pandemic, determining whether patients infected with SARS-CoV-2 develop fungal complications, especially invasive aspergillosis, is crucial. This review aimed to highlight the fungal co-infections that might be associated with SARS-CoV-2 infection, and modalities for their diagnosis, prevention, and management, with the view to reducing the high mortality associated with these infections.

Keywords: Fungal infections; opportunistic; candidiasis; mucormycosis; aspergillosis

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Infections fongiques invasives et COVID-19: une revue

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Résumé:

Les maladies fongiques invasives (MFI) sont des causes majeures de morbidité et de mortalité chez les patients hospitalisés partout dans le monde avec une prévalence mondiale de 15 %. Depuis que le premier cas de COVID-19 a été signalé le 27 février 2020 au Nigeria, il avait été découvert dans toutes les zones géopolitiques du Nigeria. Alors que la communauté médicale est confrontée à la pandémie de COVID-19 en cours, il est crucial de déterminer si les patients infectés par le SRAS-CoV-2 développent des complications fongiques, en particulier l'aspergillose invasive. Cette revue visait à mettre en évidence les co-infections fongiques qui pourraient être associées à l'infection par le SRAS-CoV-2, et les modalités de leur diagnostic, prévention et gestion, en vue de réduire la mortalité élevée associée à ces infections.

Mots-clés: Infections fongiques; opportuniste; candidose; mucormycose; aspergilloses

Introduction:

Invasive fungal diseases (IFDs) are major causes of morbidity and mortality among hospitalized patients all over the world, with a global prevalence of 15% (1). An outbreak of coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread globally to affect countries in all the continents of the world.

The first case of COVID-19 in Nigeria was reported on February 27, 2020 in Lagos after an Italian who came into the country from Italy two days earlier presented with signs and symptoms remarkable for the disease. Most patients infected with SARS-CoV-2 suffer a self-limited viral infection or no symptoms, but a significant minority have severe acute respiratory distress (ARDS) with other symptoms that necessitate hospitalization (2-5), and patients who recover from severe COVID-19 are also likely to face long-term sequelae.

One of the complications observed in COVID-19 cases is secondary infection. The immune system of the body becomes depleted when the burden of SARS-CoV-2 increases, leading to increase in the risk of fungal infection. Most immunocompetent patients who develop severe forms of COVID-19 have more than one underlying conditions such as chronic obstructive pulmonary disease, hypertension, diabetes or chronic kidney disease (6), but none of these predisposing factors generally are associated with increased risk for fungal infections. Some researchers have raised concerns on the occurrence of invasive fungal diseases among the hospitalized patients with COVID-19 and expr essed opinion that fungal co-infections associated with COVID-19 globally might be missed or misdiagnosed (7,8).

Several risk factors including ICU admission, corticosteroid therapy, intubation/mechanical ventilation, underlying respiratory disease, and cytokine storm, have been attributed with invasive fungal infections (IFIs) and high mortality among COVID-19 patients in the clinical setting (8). The most common fungi causing IFIs are the yeasts, *Candida* spp and *Cryptococcus* spp, with *Candida* spp being the most frequently encountered. The commonly isolated moulds are *Aspergillus* spp and *Fusarium* spp. Fungi pathogens especially *Aspergillus flavus*, *Candida glabrata* and *C. albicans* were recovered from respiratory sample cultures in one study (2), however, the role of *Candida* as a respiratory pathogen is doubtful even among critically ill patients and could be regarded as a colonizer. In a study, Yang et al., (9) found *A. flavus and A. fumigatus* from two of the seven patients with hospital-acquired pneumonia identified among 52 critically ill patients admitted to ICU in Wuhan, China. In another retrospective study conducted in Wuhan in two different hospitals concerning 85 deadly COVID-19 cases, 9 patients were reported to have positive fungal culture from sputum in 33.3% of cases, with 8 (9.4%), 3 (3.5%) and 2 (2.4%) patients receiving voriconazole, fluconazole and caspafungin (10) respectively. Interestingly, Antinori and coworkers (11), reported a high rate of candidaemia (6.9%) among 43 patients treated with tocilizumab, a recombinant humanized anti-human IL-6 receptor monoclonal antibody that has been suggested to be active against the cytokine storm described in patients with severe COVID-19.

Aspergillus co-infection has been increasingly reported in severe influenza pneumonia resulting in acute respiratory distress syndrome (ARDS) (12). Influenza virus causes alveolar epithelial and endothelial damage together with impaired mucociliary activity, while pathologic findings in COVID-19 pneumonia include pulmonary oedema, hyaline membrane formation, multinucleated syncytial cells with atypical enlarged type II pneumocytes (13). The diagnosis of invasive pulmonary aspergillosis (IPA) in ICU patients is considered difficult for several reasons and even if available algorithms are applied, they show variable and generally low performance with sensitivities ranging from 23 to 85% and specificities from 70 to 80% (14, 15). The diagnosis of IPA was made with a median of 5 days post-ICU admission and with an overall mortality of 67% in all patients hospitalized in the ICU. *Aspergillus fumigatus* was cultured in most cases from tracheal aspirate of bronchoalveolar lavage, and galactomannan antigen performed on serum was positive only in 23.1% of cases. Secondary or hospital-acquired infections have been reported in 5.1% to 38.9% among Chinese patients and in 4.8% to 27.4% of patients in the Western countries, but all the data appeared biased by the limited follow-up, especially for those patients hospitalized. Invasive aspergillosis is a well-described complication of severe influenza pneumonia (14, 15), but many intensivists seem to overlook this superinfection (6).

As the medical community confronts the ongoing COVID-19 pandemic, determining whether patients infected with SARS-CoV-2 develop fungal complications, especially invasive aspergillosis, is crucial. To provide effective treatment, COVID-19 patients with *Candida, Aspergillus* and other opportunistic fungal infections would require a comprehensive diagnostic work-up for early detection (7). This review is aimed at highlighting fungal co-infections that might be associated with COVID-19, and modalities for their diagnosis, prevention, and management, with the view to reducing the high mortality associated with these infections.

Methodology:

Online database searches for relevant publications were conducted on PubMed and Google Scholar. Six search strategies were used

to retrieve the publications with each of the fungal diseases associated with COVID-19 searched separately with the terms 'candidiasis', 'aspergillosis', 'mucormycosis', 'histoplasmosis', 'coccidiodomycosis', 'pneumocystis', and COVID -19. Two hundred and ten, 2430, 655, 685, 430, and 2300 articles were respectively retrieved for candidiasis, aspergillosis, mucormycosis, histoplasmosis, coccidiodomycosis, pneumocystis, and COVID-19 on Google scholar, and 159, 62, 60, 50, 8 and 4 articles on PubMed from 2020 to date. In all, 6961 articles (6712 from Google Scholar and 249 from PubMed) were retrieved.

Upon applying filter, 113 publications (82 from Google Scholar and 31 from PubMed) were assessed for relevance. The content of the relevant articles including the title, abstracts, and full texts were carefully reviewed by the authors. After eliminating duplicate articles (n=58), a total of 55 articles were deemed eligible. References of the eligible articles were scrutinized to find additional articles that might not have been included in the results of these search strategies. Five additional articles fell into this category, giving a total of 60 articles for the review as shown in Fig 1. The University Ethics Committee approval was not applicable in this review article.

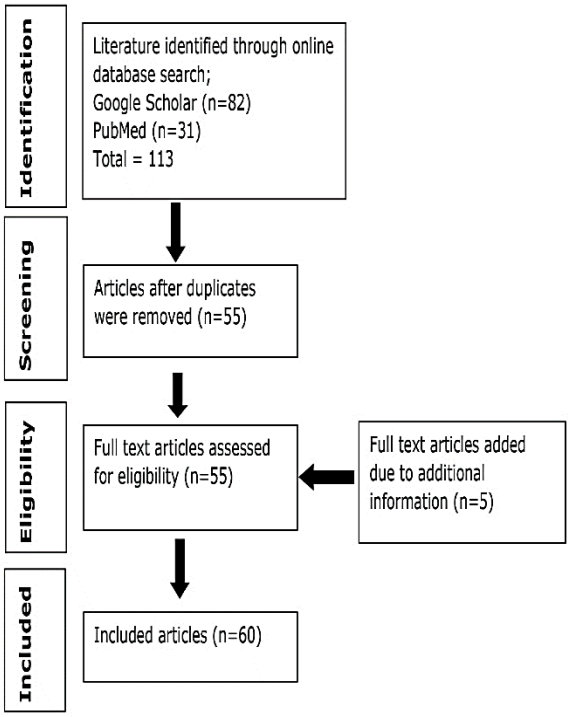

Fig 1: Process of selection of publications (PRISMA guide) for the review

Results and Discussion:

Clinical and laboratory data of fungal infections in COVID-19 patients

Candidiasis and COVID-19

Candida species especially *Candida albicans* are normal flora of human beings, and the main cause of invasive fungal infections, with a very high mortality rate. Candidemia and candidosis are increasingly being recognized as complications of severe COVID-19 (16), and the risk of invasive and mucocutaneous candidiasis in patients with severe COVID-19 cannot be over-emphasized. Some of these patients might have been treated with broad-spectrum antibacterial drugs, undergone parenteral nutrition and invasive examinations, or accompanied with prolonged neutropenia and other immune impairment factors (7).

In the face of the distinct immune hyperexcitability in COVID-19, outstanding defects in immune cells required for host immunity to *Candida* have not been reported (16). In one of the series of case studies reported early in the epidemic, it was observed that there was an increased risk for critically ill COVID-19 patients to develop *Candida* co-infection that increased the mortality rates. In another study, several putative cases of oropharyngeal candidiasis among hospitalised patients in intensive care units (ICU) were discovered (17). Oral manifestations especially candidiasis has been observed in many patients with coronavirus disease 2019 (COVID-19), however, it is not too clear if the manifestation is due primarily to COVID or secondary to concurrent systemic diseases (18). In Spain, four cases of candidaemia were reported among 88 co-infections and super-infections, while in a related study in Italy, 21 cases of candidaemia in patients with COVID-19 were reported, with a higher incidence of candidaemia in COVID-19 patients compared with cohort history in the hospital. (19,20) Some of these patients experienced lymphocytopenia, had cytokine storms, used corticosteroids and were intubated (8). Increased age was also reported to be significantly associated with fungal infections in COVID-19 patients (21).

Candidaemia can easily be diagnosed with available culture and non-culture diagnostic methods. These include mannan and anti-mannan IgG tests, *C. albicans* germ tube antibody (CAGTA), 1,3-β-D Glucan (BDG), MALDI-TOF and PCR-based assays (17,22,23) (Fig 2). *Candida albicans* is still the commonest *Candida* species followed by *C. glabrata, C. parapsilopsis, C. tropicalis,* and *C. krusei* (7). Patients with

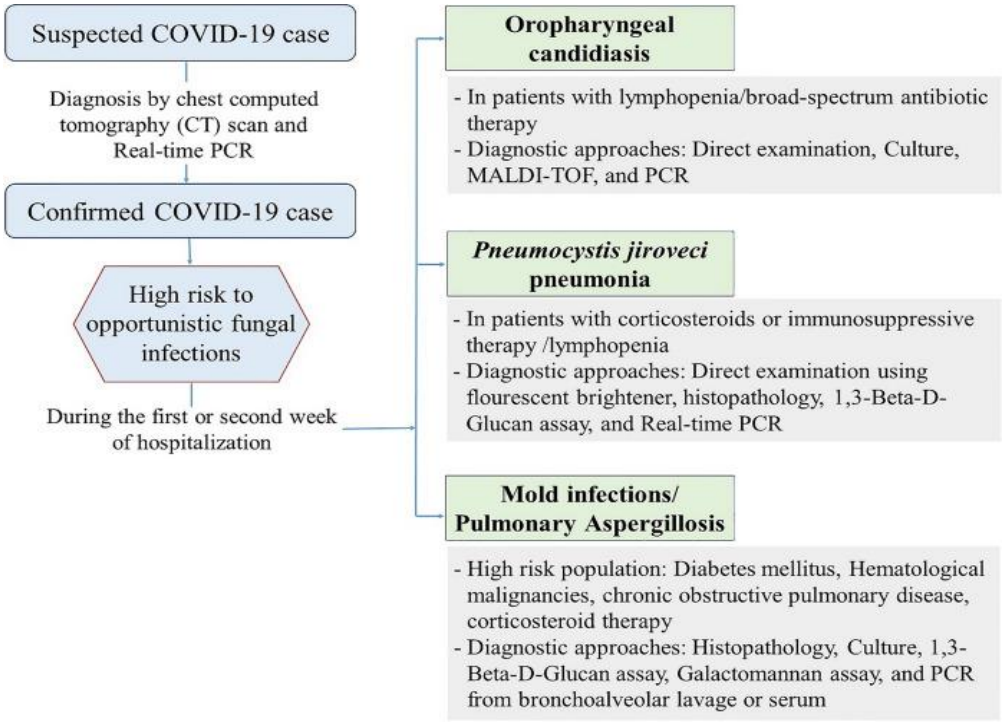

Fig 2: Clinical and diagnosis data of opportunistic fungal infections among COVID-19 patients
Adapted from Salehi et al., (17)

confirmed candidaemia can be treated with echinocandins (caspafungin, micafungin and anidulafungin), azoles (fluconazole, voriconazole, itraconazole), and amphotericin B and its liposomes. To improve the outcome of COVID-19 patients on admission in the hospital, early recognition of *Candida* infection and appropriate therapy should be instituted (24). There should be increased awareness as well as the routine screening of COVID-19 patients to reduce the diagnostic challenges of candidaemia (16).

Aspergillosis and COVID-19

In those with high risk factors, invasive aspergillosis could be an important cause of life-threatening infection among COVID-19 patients. The potential risk factors for the patients include glucocorticoid use, chronic obstructive pulmonary disease (COPD), prolonged neutropaenia, allogeneic haematopoietic stem cell transplant (allo-HSCT), solid organ transplant (SOT), inherited immunodeficiencies, haemopoietic malignancy (HM), cystic fibrosis (CF) and others (25, 26). At the initial stage of the pandemic fewer than 5% of patients with COVID-19 are treated in intensive care units (ICUs) due to respiratory failure. Recently, it has been observed that rates of invasive aspergillosis are high among patients with severe influenza admitted to the ICU (14, 27). Influenza pneumonia in critically ill patients can be complicated by invasive pulmonary aspergillosis (IPA) due to the viral destruction of bronchial mucosa, facilitating invasion of *Aspergillus* species, and that compromise the host defenses to *Aspergillus* (28,29). Influenza-associated aspergillosis can be diagnosed within an average of three days after ICU admission, with its associated high mortality (14). In a case-series of patients studied in New York, USA, an estimated 14-30% of hospitalized patients diagnosed with COVID-19 developed severe respiratory failure requiring intensive care (30). In another study conducted in Brazil, 5.4% of the patients with IFI were positive for different *Aspergillus* species such as *A. fumigatus, A. flavus, A. penicillioides* and *A. niger* (31).

The diagnosis of invasive aspergillosis (IA) in COVID-19 patients could be challenging because of lack of suitable specimen acquisition and consensus suitable methods. However, it requires a combination of microbiologic, histopathologic, and radiological evidence. Some of the invasive procedures such as lung biopsy or bronchoalveolar lavage (BAL) might be contraindicated in patients with severe respiratory failure and coagulation disorders (7,32). Most of these tests make use of bronchoalveolar lavage (BAL) and serum for the confirmation of acute invasive aspergillosis. The galactomannan index (GMI) and PCR-based assays can be used for the detection of *Aspergillus* in BAL, serum, and occasionally in sputum of COVID-19 patients (33,34). Definitive confirmation can be by ident-

ification of the characteristic acute angle branching septate hyphae of *Aspergillus* spp or histologic findings of the Grocott-Gomori's methenamine-silver stain (GMS) and Periodic Acid Schiff (PAS) stains of fixed tissues (7). However, due to the diagnostic challenges and lack of specificity in the classification of probable, putative, or possible COVID-19 associated pulmonary aspergillosis (CAPA), aspergillosis might be over diagnosed (35,36). COVID-19 patients with confirmed aspergillosis of any form can be treated with azoles (voriconazole, itraconazole, posaconazole and esaconazole), amphotericin B and its liposomes derivatives, and echinocandins such as micafungin and caspofungin (37,38).

Mucormycosis and COVID-19

Mucormycosis, an opportunistic infection caused by *Mucorales* has been responsible for increasing cases of devastating rhino-orbito-cerebral infection in susceptible COVID-19 patients (39). The predominant form of mucormycosis observed in COVID-19 patients was rhino-orbital, followed by pulmonary, gastrointestinal and rhino-cerebral (40). COVID-19 patients who also have premorbid conditions such as diabetes mellitus, hematological malignancies, prolonged neutropenia, and increased use of glucocorticoid are more likely to develop mucormycosis. COVID-19 induces microvascular thrombosis and endothelitis in the vascular beds. which may result in the infarction of the infected tissues that may compound the angioinvasive impact of mucormycosis (39,41). In a cross-sectional study conducted in Iran on biopsy-proven mucormycosis patients with confirmed COVID-19, the mean interval time between COVID-19 and development of mucormycosis was 7 days in patients with favourable risk factors compared with mean interval time of 8 and 11 days between diagnosis of COVID-19 and clinical presentations of oropharyngeal candidiasis and pulmonary aspergillosis respectively (42,43).

In another systematic review of cases reported worldwide and in India, Awadhesh Kumar Singh et al., (44) reported that cases of rhino-orbital mucormycosis were being encountered in more and more numbers amidst people with COVID 19, particularly in India. They reported on 101 cases, with 82 from India, and 19 from other parts of the world, and an overall mortality of 30.7%. The most frequent presenting features were involvement of nose and sinuses (88.9%) and rhino-orbital infection (56.7%). The co-morbidities were diabetes mellitus (80%), corticosteroid intake (76.3%), and diabetic ketoacidosis (14.9%). They concluded that COVID-19 in association with pre-existing diabetes mellitus and administration of corticosteroids combined to worsen the prognosis of COVID-19 patients and increased the probability of acquiring mucormycosis.

The diagnosis of mucormycosis can be suspected with the observation of non-septate or pauci-septate *Mucorales* hyphae on direct microscopy or florescent brighteners. This can be confirmed with the appearance of non-septate hyphae invading tissues after staining with GMS and HE stains (45). Definitive identification of the organisms can be done to species level by culture on supportive media giving characteristics whitish cottony colonies that changes to grayish black colonies with time. Other form of diagnosis include PCR and sequencing as well as Magnetic Resonance Imaging (MRI) (40). Management of COVID-19 patients with confirmed mucormycosis include complete surgical treatment and early administration of systemic antifungal therapy. The antifungal treatment includes amphotericin B lipid complex, liposomal amphotericin B and posaconazole as first line drugs in combination with isavuconazole. Posaconazole can be given as prophylaxis to those with high-risk factor and in graft versus-host disease (46).

Histoplasmosis and COVID-19

Histoplasmosis is caused by *Histoplasma capsulatum*, a dimorphic thermal fungus that mainly affects people who are immunocompromised such as HIV patients (47). It can present in the form of flu-like symptoms, or as different manifestations of disseminated histoplasmosis (DH). There is a paucity of information on the co-infection of COVID-19 with histoplasmosis. Predisposing factors to histoplasmosis co-infection with COVID-19 include advanced HIV infection with $CD4^+$ count of <200 cells/mm^3 and resident in endemic areas (48,49). Fernando et al., (49) reported a case of disseminated histoplasmosis in a 36 year old female in Argentina who developed COVID-19 during hospital care. The patient had advanced HIV infection as the predisposing factor to the development of histoplasmosis in the first place. She presented with papule-like lesions in the right malar region and in the proximal area of the nose and erythematous lesion with slight central ulceration in the central palate. Chest computed tomography (CT) also revealed a bilateral and diffuse micronodular interstitial pattern, compatible with miliary histoplasmosis. After being treated for histoplasmosis, the patient's initial fever subsided, but later developed a second bout of fever, with laboratory investigations helping the diagnosis of COVID 19 (49).

Recently, Cafardi et al., (50) reported

two cases of opportunistic fungal infections in patients with COVID-19. One of them was infected by *H. capsulatum,* whose diagnosis was made by complement fixation test for yeast phase and mycelial phase histoplasma antigens. The underlying factors were a history of hypertension and chronic obstructive pulmonary disease. The diagnosis in these cases were made possible through blood culture, serology (antigen detection in urine and serum) and histological staining methods like Giemsa, Wright, and Gomori-Grocott (GMS). Management of COVID-19 patients with histoplasmosis include administration of antifungal drugs such as amphotericin B deoxycholate and itraconazole (51).

Coccidiodomycosis and COVID-19

Coccidioidomycosis is a respiratory infection caused by inhalation of fungal spores of *Coccidioides* in dust (52). It is a soil-dwelling dimorphic fungus, which spores are found in hot and arid environments. A meta-analysis showed that coccidioidomycosis outbreaks frequently occur among workers in construction and agricultural sectors who were regularly exposed to dust (52). They also carried a higher risk factor for illness and death from viral respiratory infections including COVID-19 (52-55). The wide range of symptoms of coccidiodomycosis such as cough, fatigue, and breathlessness are also common among patients with COVID-19. These may cause diagnostic challenges especially in endemic areas. In two cases reported, a man and a woman, the main predisposing factor discovered was being residents in endemic areas (40). Other risk factors that are associated with co-infections of coccidioidomycosis and COVID-19 include older age, immunosuppression, DM and smoking (52). Early management of cases and assessment of the risk factors for severity as well as regular follow-up visits to monitor symptoms can be crucial to mitigating severe diseases. Prompt initiation of antifungal treatments reduces the chances of unnecessary use of antimicrobial drugs and resolves symptoms more effectively (52).

Pneumocystis and COVID-19

In COVID-19 patients who are critically ill with high level of lactate dehydrogenase (LDH) especially in those undergoing immunosuppressive or corticosteroid therapies, *Pneumocystis jirovecii* pneumonia (PJP) was suspected based on radiological signs (17). However, the researcher's observations were not supported by mycological, immunological, and molecular assays. Remarkably, lymphopenia was the main laboratory finding in 85% of critically ill patients with COVID-19 (17). Since lymphocytes play a decisive role in maintaining immune homeostasis and defensive response against microbial invasion throughout the body, it might be hypothesized that inadequate lymphocyte count may be a key factor contributing to secondary fungal infections such as PJP in COVID-19 patients (17).

Pathophysiological factors of invasive fungal infections in COVID-19

The following may contribute to super-infection by mycoses in patients with COVID 19; (i) during the process of respiratory infection by SARS CoV-2, there is severe damage to the lung parenchyma resulting in microthrombi formation in the vasculature, and hyaline membrane formation and infiltration of the interstitium by lymphocytes (56,57); (ii) there are immunologic abnormalities associated with SARS CoV-2 infection which include high levels of cytokines, that can lead to immunosuppression, a predisposing condition to IFI (7,8); (iii) the use of mechanical ventilation can predispose to development of opportunistic fungal infections (58); and (iv) the use of dexamethasone in treating COVID-19 patients who are on mechanical ventilation, which though has been shown to reduce mortality rate and length of hospital stay, may however lead to immunosuppression, predisposing these patients to super-infection by fungi such as *Aspergillus* and *Coccidoides* (58-60).

Diagnostic challenges of invasive fungal infections in developing countries

In developing countries, the diagnosis of fungi infections is based on direct or histopathological microscopy and fungal cultures. Molecular assays, antigen testings for galactomannan and 1,3-β-D-glucans, and other modern diagnostic assays for further differentiation of fungi are rarely available in these regions.

Conclusion:

There are great similarities between respiratory symptoms of COVID-19 and chronic pulmonary diseases caused by fungal infections. The presence of co-morbidities such as HIV infection, DM, corticosteroid administration increases the risk of mortality from COVID 19 and the possibility of super-infection with the invasive mycoses. It is recommended that all COVID-19 patients with co-morbidities as exemplified, who require respiratory support be routinely screened for pulmonary mycotic infections using sensitive laboratory methods. Employers and public health officials should mitigate exposure to dust, other risk factors and SARS-CoV-2 by promoting the use of face masks and social dist-

cing practices.

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