Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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SHORT REPORT

Delta variant and black fungal invasion: A bidirectional assault might worsen the massive second/third stream of COVID-19 outbreak in South-Asia

M.S. Bari[a,1], M.J. Hossain[a,1,*], S. Akhter[a], T.B. Emran[b]

[a] *Department of Pharmacy, State University of Bangladesh, 77 Satmasjid Road, Dhanmondi, Dhaka 1205, Bangladesh*
[b] *Department of Pharmacy, BGC Trust University Bangladesh, Chittagong 4381, Bangladesh*

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Summary
Background. — Here, we have shortly reported the recent updates on the disastrous progressions of the deadly delta variant and a virulent coinfection or post-COVID-19 infection of black fungus in India and its neighbouring countries.
Methodology. — We searched by utilizing appropriate keywords in Google Scholar, PubMed and other scholarly databases alongside several national and international newspapers to collect the latest data regarding the targeted topic.
Results. — Recently, the delta variant is wreaking havoc in India, UK, and other countries around the globe and has also exhibited successful infections in around 20 to 55% of the people who have already recovered from COVID-19 originating from the different strains. Besides, a significant catch is the prevalence of 85.5% and 64.11% of Mucormycosis infections being co-morbid with COVID-19 and diabetes, respectively in South-Asian regions.
Conclusions. — To avert the emergence of an epidemic amid the pandemic, prompt actions from concerned authorities are warranted. Proper education on black fungus infection and associated risks from the COVID-19 and diabetes, adequate public awareness, and sufficient healthcare assistance to battle such fungal infections effectively should be ensured as quickly as possible.

* Corresponding author.
E-mail addresses: jamal.du.p48@gmail.com, jamalhossain@sub.edu.bd (M.J. Hossain).
[1] These authors contributed equally to this work.

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Background

The world is currently fighting against the third wave of the ongoing coronavirus disease 2019 (COVID-19) pandemic and facing several unprecedented challenges such as viral mutations or coinfections like fungal invasions that are worsening the already devastating situation. In this brief-report, we intended to highlight the deadly strain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral infection and black fungal invasion which are conjointly worsening the current massive second/third wave of COVID-19 outbreak in the South-Asian countries.

Methods

Data collection and search strategy

Several popular scholarly databases such as Google, Google Scholar, PubMed, Embase, ScienceDirect, and other academic databases, alongside several websites of national and international newspapers, were utilized for searching to collect the latest data regarding the infections, mortality, and transmissibility of the aggressive and double mutant delta variant of SARS-CoV-2. Besides, we have also accumulated the newest information available to report on the surprising invasion of the black fungus with COVID-19 in India and its bordering countries. We searched by using the key terms like: ''coronavirus disease 2019'', ''COVID-19'', ''SARS-CoV-2'', ''delta variant'', ''delta variant plus'', ''Indian variant'', ''UK variant'', ''black fungus'', ''Mucormycosis'', ''Bangladesh'', ''India'', ''Pakistan'', ''Nepal'', ''South-Asian countries'', and so on, to collect the relevant and appropriate articles.

Results

Delta variant and delta variant plus

India, the second largest population globally, is currently facing the brunt of the second wave of the COVID-19 pandemic with tremendous rates of both infection and mortality. While throughout February 2021, India seemed to have contained the devastating impacts of the pandemic, both incidence and mortality suffered sharp rises in number from early April, which have been associated with the community transmission of the Indian variants of the SARS-CoV-2 virus (B.1.617.2), also known as the delta variant or UK variant. The variant has been called ''double mutant'' as it evolved through mutations in two separate sequences of the spike protein, namely E484K and L452R, both of which are located essentially on the antibody-recognizable site of the virus that might be responsible for reinfections with a breakthrough 16% confirmed cases of COVID-19 vaccinated health workers [1,2]. India has first traced this virulent variant in October 2020, and upon its emergence, the contagiosity and mortality incidence has surged excessively. The World Health Organization (WHO) has already recognized this exceptional transmissibility of this variant and declared it as a variant of global concern, which has already pervaded more than 60 countries [2].

Epidemiological modelling study has demonstrated that the transmission rate of the delta variant is at an enhanced extent of 1.1 to 1.4 times compared to the other variant circulating across the largest country of South-Asia (India). Besides, the delta variant also demonstrated successful infections in around 20 to 55% of the people who have already recovered from COVID-19 originating from the other strains [3]. In addition to its enhanced transmissibility, the variant has also been characterized with superior infectivity as it illustrates the increased, more efficient cellular entry of virus and intracellular replication of the viral genome. Above all, the delta variant has already been confirmed to be resistant against vaccine-generated immunity in the case of most of the existing vaccines. The effectiveness of the vaccines from Oxford-AstraZeneca and Pfizer-BioNTech was demonstrated to be curtailed by around 6.2 times and 2.9 times, respectively, by the delta variant compared to that against the alpha variant [3]. However, while the delta variant is challenging the healthcare sector on every front possible, yet another mutation in its genome has culminated in developing the called K417N ''Delta Plus'' variant (B.1.617.2.1 or AY.1), also originating India. Although the implication of this strain on the overall progression of the pandemic is still unclear, scientists have expressed their concerns over a number of possible traits of the strain, including superior transmissibility, enhanced receptor binding at alveoli, and improved resistance against antibody-mediated immunological responses. Particularly, the experts of various public health organizations fear a massive third wave of infection in India due to the impact of the delta plus variant. And, as neighbouring countries, most of the South-Asian territories have also been a new cause of concern by this more powerful and infectious novel strain. Consequently, responsible authorities worldwide are on constant alert over the transmission of this variant on a community scale [4].

Black fungus invasion

A rare but life-threatening angio-invasive Mucormycosis or black fungus infection caused by fungi Mucorales genera commonly found in our surrounding environments (for instance, soils, plants, manure, and rotting fruits, and so on), has recently grown a buzzword globally, mainly in South-Asian countries. Though the exact epidemiological data of this infection is unknown, the prevalence of this black fungus infection in India is eighty (80) times higher than in developed countries [5]. Due to this fungal infection, the mortality rate might be up to 96% depending on the severity of the invasion and underlying patients' health situations [6].

The most severe/third phase of COVID-19 is presented in the form of hyper-inflammation, also known as the cytokine storm syndrome, which is primarily manifested by an abundant outburst of pro-inflammatory cytokines. Based on the experiences from earlier coronavirus epidemics including SARS and MERS, healthcare professionals around the world have utilized immunosuppressive agents for the mitigation of hyper-inflammatory conditions and the use of such anti-inflammatory agents in the management of COVID-19 have been further justified through multiple synchronous clinical trials [7,8]. However, apart from the beneficial consequences, immunosuppression in COVID-19 has also been

deemed dangerous as it exposes the patients' physiology against pathogenic agents leading to secondary infections, especially stemming from bacterial and fungal invasions [9].

This subsequent contagion caused by black fungal infection, has threatened the whole of India and affected patients who are still recovering from COVID-19. Although such infection can rarely invade healthy and immunocompetent persons, the use of immunosuppressive agents or any pathological condition leading to immunodeficiency can augment the susceptibility of the human physiological system towards such fungal incursion, and its outcome can be as drastic as death [10]. Eventually, the exhaustion of human immunity in COVID-19 together with the use of immunosuppressive agents for its management and the prevalence of prior long-term conditions (e.g., diabetes) have facilitated Mucormycetes to overpower the body's defence and induce black fungus infection in patients recovering from COVID-19. Physiologically, the invasion invades vascular lamina that might result in inflammation, infarction, and necrosis. Subsequently, the incursion and progressive necrosis cause severe damage at several anatomical positions based on the extremity of the fungal exposure [11]. This infection can affect the neck and head, central nervous system, gastrointestinal and respiratory tract, and other body areas. Besides, the black fungus can transmit to the patients' eyes, likely to cause blindness or the brain, occurring headaches or seizures [12].

As of July 20, 2021, India counted 45,432 confirmed cases and 4252 deaths of black fungal infections, and this predominance is unprecedently higher than the global rate. Among the cumulative infections, around 85% and 65% were comorbid with COVID-19 and diabetes [13]. In many areas of India, post-COVID patients have been forced to re-visit to hospital with Mucormycosis infection, and some are losing one or both of their eyes under surgery as the only way to prevent further illness. To emphasize the extent of danger and severity and to alert the general population accordingly, black fungus infection has been declared as an epidemic in four states by May 20, 2021, and other states followed suit by necessity [2,14].

Impact of delta variant and black fungus in India's neighbouring countries

India is the largest in South-Asia, and the seventh-largest country in the world, and the country shares its borderline with nine countries, Bangladesh, Pakistan, Nepal, Bhutan, China, Myanmar, Sri Lanka, Maldives, and Afghanistan. Among the closely associated neighbours of India, Nepal is noteworthy as it maintains an almost invisible border with India with well-connected trade routes and transportation services. In an almost identical fashion as India, Nepal also experienced a similar rise in COVID-19 infection cases in early April, which climbed as high as 9000 cases per day by mid-May [15]. Such outrage from the SARS-CoV-2 in Nepal was soon attributed to the extraordinary transmissibility of its delta variant. Among the 47 swab samples collected from randomly selected COVID-19 patients from early June to mid-July 2021, 100% were identified as delta variants through genomic sequencing. Moreover, three of these samples were further traced to delta plus lineage, indicating increasing transmission of the newer variant [16]. However, apart from the concerns regarding rising infection rates and death tolls, the Nepalese population is also being burdened with growing cases of black fungus infection. Around two dozen cases of black fungus infection, along with at least three confirmed fatality from the disease so far, have instigated Nepalese healthcare professionals to remain vigilant to avoid the emergence of an epidemic like that prevalent in its neighbour country India [15,16].

Similar trends of infection by both the SARS-CoV-2 and Mucormycetes have also taken hold in Pakistan, another major country from South-East Asia. The COVID-19 condition in Pakistan, both in terms of daily infection rates and deaths, took a sharply negative turn in late March 2021 and flared through April and May while dissipating throughout June. Besides, the prevalence of the delta variant was only confirmed on May 28 [17], indicated the lack of any significant influence of the variant on the overall COVID-19 situation in Pakistan. However, as of July 27, 2021, Pakistan Observer reported that according to National Command and Operation Centre (NCOC), more than 70% of new COVID-19 cases have resulted from the deadly delta strain, although experts claimed this prevalence is around 92% [18]. Meanwhile, amidst the severe third wave of the pandemic, fungal infections are also reported frequently across Pakistan. Aggravated cases of both Mucormycosis and pulmonary aspergillosis (a pulmonary disease caused by Aspergillus) are being diagnosed in both COVID-19 patients and people recovering from COVID-19, especially in the presence of diabetes or prolonged hospital admittance. Public health concerns over the fungal manifestations are gradually becoming prominent as several fatalities have already been reported due to the black fungus infection, especially in Karachi, and the overall mortality rate has remained above 50% [19].

Geographically Bangladesh is surrounded by Indian territories on three sides and maintains extensive transport routes and economic connections with India through multiple land ports. Thus, Bangladesh stood already at a greater risk of being affected by the delta variant [20,21]. Bangladeshi authorities also implemented cautionary measures early on, as air travels between the two countries were suspended on April 14, 2021 and traveling through land borders was seized completely from April 26, 2021. However, for the sustenance of the already-devastated economy from the first wave, a complete shutdown of trade and commerce with India was not a viable option and was still allowed through land ports [22]. Consequently, the first case of contamination by the Indian variant in Bangladesh was reported on May 8. Moreover, by June 4, community transmission of the variant was evident as 80% of the sample genomes being sequenced in the country turned out to be of delta variant [23]. The terrible consequence of the second wave of COVID-19 in India with its sharp attacking delta variant has been perceived in the border areas of Bangladesh virulently, especially in the districts of Satkhira, Khulna, Jessore, Rajshahi, Dinajpur, Jaipurhat, Champai Nawabganj, and so on. As both incident rate and death toll have been rising rapidly, the government of Bangladesh has declared strict lockdown (from June 28, 2021) for the third time since March 2020 in the fight against the forthcoming massive third wave of COVID-19 in Bangladesh [24]. While Bangladeshi

healthcare professionals struggle to balance the increased number of patients and limited medical facilities available to them, the possibility of a black fungus epidemic is also emerging on the horizon [25,26]. Cases of black fungus infection are being reported sporadically across the country [27]. However, the actual situation is still incomprehensible as most of the population is unfamiliar with black fungus infection and its risk in immunosuppressed COVID-19 patients. Thus, they fail to recognize the symptoms of such conditions and eventually report them appropriately to the concerned authorities.

Moreover, the heavy environmental pollution that has been persistent in the South-Asian countries like Bangladesh over the past decades can serve as a rich source of Mucormycetes. Furthermore, the region's backward and comparatively under-educated population has been practicing irrational drug use for a long time, which has become especially noticeable during the pandemic [28]. Consequently, excessive and unreasonable intake of immunosuppressive agents can lead to unprecedented immunosuppression in them. The accumulated manifestations of all these underlying factors have the potential to culminate into a major healthcare concern and impose a heavy burden on the already crippled medical system of these vulnerable South-Asian countries, including Bangladesh [29].

Conclusion and actionable measures

The emerging catastrophic situation due to a dual attack by delta variant and black fungal invasion continues to drive a worsening of COVID-19 pandemic in South-Asian countries that has already persuaded the prime concern of the world public health leaders. Another most substantial venture is the lack of adequate vaccines for mass people. Though India executed vaccine diplomacy with its neighbouring nations except for Pakistan, the domestic upsurge of the COVID-19 crisis has rushed to renege on the promised vaccine supply to the COVAX facility [30].

Since India already serves as a well-defined scenario of ''epidemic stemming from pandemic/pandemic to the epidemic'', the borderline countries should learn from their neighbour and implement necessary action plans stringently and immediately. Strict adherence to doctor-provided prescription for immunosuppressive agents along with proper and careful isolation while using them must be encouraged and ensured among patients. In addition, any public gatherings, including tourist spots, must be strictly prohibited for an unspecified period. The authorities or government of each country should ensure more hospital beds, ICU facilities with ventilators, and sufficient oxygen supply to tackle the potential upcoming surge of COVID-19 in the South-Asian countries. Finally, enough vaccine production or collection must be ascertained diplomatically or administratively, along with being strict to implement public health guidelines for a successful fight against COVID-19.

Human and animal rights

The authors declare that the work described has not involved experimentation on humans or animals.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s) and/or volunteers.

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Author contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

Disclosure of interest

The authors declare that they have no competing interest.

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