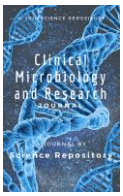

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Review Article

Analysis of an Epidemiological Anomaly of COVID-19: Transcultural and Immunological Psychiatry

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ABSTRACT

Evidence exists for an epidemiological trend of transmission concentrations of COVID-19 within migrant communities from tropical weather conditions. Minority groups are over-represented in hospitalisations and deaths from the virus, and it appears that the observed anomaly may be due to multifactorial causes. Underactive immune responses in cooler temperatures and diminished synthesis of vitamin D, both of which are associated with genetic factors among ethnic minority groups, could help to explain the higher incidence of COVID-19 among ethnic minority communities. Neither factor is specific to a migrant community but common to general populations. The overstatement of contributory genetic factors runs the risk of racial stigmatisation. If environmental factors are given their due importance, individuals belonging to ethnic minorities may try to adopt new ways to combat the pandemic, while overemphasising racial factors would only leave them helpless. The renewed interest of psychiatrists in immunology would support the emerging field of immunopsychiatry. COVID-19 is environmentally sensitive, and all medical specialities, including the mental health profession, should contribute their wisdom to defeating or making a truce with the viral phenomenon.

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Introduction

A higher infection rate of COVID-19 has been associated with immigrant communities from countries located in temperate climate zones. This finding has raised many questions about the vulnerability factors of ethnic minority members to COVID-19. Infection-related morbidity is recognised for those in the aged population and for patients with suppressed immunity. Environmental factors of immunity, rather than genetic factors, are considered to be responsible for the high incidence of complications among ethnic minorities. The finding that the first 10 doctors in the UK to die from COVID-19 were from ethnic minorities, along with observational data from the Intensive Care National Audit and Research Centre, showing that a third of COVID-19 patients admitted to critical care units are from an ethnic minority background that generated concerns about the link between ethnicity and COVID-19 in the UK [1, 2]. Subsequently, research on the first British patients to contract COVID-19 has shown that Black, Asian and minority ethnic (BAME) individuals are more prone to critical impacts than white British people.

Higher Incidence

Results from research conducted by the Intensive Care National Audit and Research Centre (ICNARC) showed that of nearly 2,000 patients with confirmed COVID-19, 35% were non-white British, though 13% of the UK's population are of BAME heritage [2]. Data drawn from 286 critical care units across the UK and collected until 3 April 2020 were included in the study. According to another study from the UCL Institute for Global Health, Bangladeshi, Pakistani, Indian, Black African, and Black Caribbean ethnic groups all had a substantially increased risk of death from COVID-19 in comparison with white British and white Irish groups. Also, Cook *et al.* pinpointed that of 119 NHS staff who died from COVID-19, 64 were from ethnic minority backgrounds [3].

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Aldridge *et al.* undertook the indirect standardisation of data (using the whole population of England as the reference) to produce ethnic-specific standardised mortality ratios (SMRs) adjusted for age and geographical region, and they found that the largest total number of deaths in minority ethnic groups were Indian (492 deaths) and Black Caribbean (460 deaths) groups [4]. Adjusting for the region, they found a lower risk of death for White Irish (SMR 0.52; 95% CIs 0.45-0.60) and White British ethnic groups (0.88; 95% CIs 0.86-0.0.89), but increased risk of death for Black African (3.24; 95% CIs 2.90-3.62), Black Caribbean (2.21; 95% CIs 2.02-2.41), Pakistani (3.29; 95% CIs 2.96-3.64), Bangladeshi (2.41; 95% CIs 1.98-2.91) and Indian (1.70; 95% CIs 1.56-1.85) minority ethnic groups [4].

The mortality rate of the UK's BAME population from the 2009 influenza A (H1N1) epidemic was nearly double that of the white British population. When other sociodemographic and health characteristics were controlled for, Pakistani and Bangladeshi populations were currently 1.8 times more likely to suffer COVID-19-related morbidity than white males of a similar age. Studies have also indicated that Black men and women are 4.2 and 4.3 times more likely to die from COVID-19, respectively, than their white counterparts. As suggested by Doherty *et al.*, other circumstances, such as socioeconomic disadvantages, do not completely explain this discrepancy, and there is other relevant information that needs to be uncovered [5].

Only first-generation migrants have been reported to have higher morbidity and mortality compared to second-generation migrants in the UK. This puts a question mark on the overrated genetic factors for the apparent anomaly of higher incidence of COVID-19 among ethnic minorities. Eight months is a short period to develop any form of genetic immunity or susceptibility to a new viral infection among the migrants that have arrived in Western countries. It takes a much longer period for any sort of genetic adaptation or mutation to occur among the migrated. About 20,000 to 25,000 genes have been estimated to be present in each individual, and about 1% of these genes are somewhat different. The human leukocyte antigen (HLA), also known as the major histocompatibility complex (MHC), is a cluster of gene complexes responsible for the regulation of the immune system. As a result, HLA is largely responsible for human health. How this will fit in with the observed anomaly is difficult to determine. General immune suppression due to varying factors appears to be the main reason for the higher COVID-19 incidence and severity among the BAME population.

Interest has also concentrated on the possibility of ethnic differences in the expression of angiotensin-converting enzyme 2 (the host receptor for SARS-CoV-2) and the risk of both acute kidney injury and cardiac complications because of a higher prevalence of cardiovascular risk factors in ethnic minority populations [6-8]. Protein residues in active domains of the essential genes related to viral susceptibility are highly protected among populations, and there is no evidence for ethnic group differences in ACE2, TMPRSS2 and genes associated with viral binding and endocytosis. The genetic determinant for the binding affinity between SARS-CoV-2 and ACE2 does not show a significant difference between populations [9]. Non-genetic factors may be more responsible for the disproportionate incidence of mortality and morbidity among the BAME community.

Non-Genetic Factors

There are several non-genetic factors involved in this anomaly. The elevated incidence and severity in minority groups may be linked to socioeconomic, cultural or lifestyle factors, genetic predisposition or pathophysiological differences in susceptibility or response to infection. Poverty is known to vary substantially by ethnic group and geographic region in England. Occupation is also likely to play an important role in terms of increased risk of infection, as BAME people are more likely to have occupations that involve greater social exposure and less ability to work from home. Black minorities form a disproportionately large percentage in the caring and leisure industries. Likewise, Pakistani and Bangladeshi groups are overrepresented in the sales and consumer service occupations. Equally, broader socioeconomic disparities may also add to ethnic differences in health. BAME groups are more likely to have a low income, be in zero-hour contracts and non-salaried jobs than white British groups. This may make it harder for them to comply with COVID prevention guidelines.

There are many susceptibility factors noted among the BAME community for higher infection rates. An increased risk of admission for acute respiratory tract infections, an increased prevalence of vitamin D deficiency, vaccination policies in their country of birth and immune effects, increased inflammatory burden and higher prevalence of cardiovascular risk factors such as insulin resistance and obesity than white populations have to be taken into account when analysing the high-risk factors of the BAME community to COVID-19 [10-12]. Some of these are also risk factors for increased disease severity in COVID-19.

Thermal Factors

Our human body is overly sensitive to temperature alterations. The commonly observed response to cold temperature is that the body will shiver because during shivering, the muscles are doing some mechanical work so as generate some heat to balance the body's temperature. There is evidence that certain immune cells work better in higher temperatures, as supported by the fact that fevers, which are products of the immune system, activate the immune system to defend us against invading pathogens. As a result, body temperature increases in an attempt to clear the infection. Therefore, we usually have a raised temperature during almost all acute infections. Immune responses that are temperature-dependent have been found to be associated with genetics.

The immune cells of BAME individuals are genetically wired to function better in hot weather and cannot function optimally in cold weather. As a result, their immune cells are not adapted to cold weather and so are slow in response to viral invaders. This helps to explain the improved immune response among white British individuals who were born and raised in colder climates and are adapted to lower temperatures compared to BAME persons. In cold weather, the immune cells of BAME individuals may become inactive. Though COVID-19 thrives equally well in hot and cold weather, the BAME population has immunity shortcomings for surviving colder months; this insight might prompt them to take special precautions in future cold seasons. BAME groups that have migrated to colder regions were born and raised in warmer regions prior to their migration, and their immune system has evolved to function at a higher temperature.

Immunosuppression has been found to be associated with low body temperatures. Also, the migration of ill cold-blooded animals to warmer areas has been observed. An elevated body temperature has long been known to be a defence mechanism against infection and inflammation. It has also been established that an increase in the body's temperature by 1°C results in a corresponding increase in immunity by 5-6 times. The proliferation and differentiation of CD8+ cytotoxic T-cells are enhanced by hyperthermia. The organizational structure of the membranes of T-cells is altered by elevated body temperature; this helps to facilitate the effects of temperatures in a micro-environment on cell functionality. Sub-thermoneutral laboratory housing temperature was shown to induce immunosuppression in mice when the mice were housed in a thermoneutral ambient temperature, and striking reductions in tumor formation, growth rate, and metastasis were observed [13].

Vitamin D

The higher incidence of COVID-19 in the BAME community could also be explained by other mitigating factors. Vitamin D receptors are found on almost all immune cells, and they connect to vitamin D networks in the immune system (Link 1). Apart from helping to balance immune function, both the innate and adaptive immune systems are regulated by vitamin D. Vitamin D reduces the production of pro-inflammatory cytokines associated with lung damage caused by acute viral respiratory infections, such as influenza and COVID-19 [7]. Because of higher melanin levels in their skin, which results in lower vitamin D absorption, BAME communities are prone to vitamin D deficiency. Consequently, prolonged exposure to sunlight is required to accrue the equivalent vitamin D quantity produced in a white person. This is further exacerbated in colder countries with little sunlight (e.g. the UK), where people also spend more time indoors without much opportunity to absorb vitamin D. Thus, a lack of vitamin D could be another explanatory factor for the high rates of COVID-19 in the BAME community.

Due to a large number of vitamin D receptors in the immune system, vitamin D is indicated to interact with it. Vitamin D deficiency is associated with immune dysregulation (Link 2). The various ways that vitamin D interacts with the immune system directly affect how the body defends against viruses. Vitamin D, for example, triggers the production of cathelicidin and other defensins, which are natural antivirals capable of viral invasion and replication. Vitamin D also increases the number of CD8+ T-cells, which play a critical role in clearing acute viral infections in the lungs (Link 3). Further, vitamin D suppresses pro-inflammatory cytokines and may also alleviate the cytokine storms occurring in the most severe COVID-19 cases (Link 4). This vitamin plays an essential role as well in glucose homeostasis, insulin sensitivity and the regulation of adipokines, such as leptin and inflammatory cytokines [14].

Evidence from randomized controlled trials suggests that regular vitamin D supplements may help protect against acute respiratory infections. Admittedly, the direct evidence of vitamin D's role in protecting against COVID-19 is still scant. A strong correlation between low vitamin D and severe COVID-19 infection has been found in one study from the United States and another from Asia. Low vitamin D levels of ICU patients before and during COVID-19 infections have been reported by some studies. Thus, it appears logical to hypothesise a link between the high COVID-19 infection rates in the UK and US BAME populations and their lower vitamin D levels (Link 5). Moreover, as it is not possible to gain a sufficient vitamin D supply through diet alone, exposure to sunlight is indispensable.

Social and Lifestyle Factors

There are other confounding environmental factors, including the likely large role of social determinants, which shape health and illness by ethnicity. The term 'lifestyle' factors may be cursory - indeed, lifestyle is a problematic term in the literature as it implies choice, a choice that may be unavailable for the most disenfranchised groups of the society. Ethnic inequalities are pervasive and unrelenting, and these inequalities manifest for particular ethnic groups in different localities in different ways. Inequality in housing and employment is severe for most ethnic minority groups, particularly in large urban areas that have been traditional settlement areas for ethnic minorities. Such a situation makes ethnic minorities highly vulnerable to the consequences of COVID-19 spread [15].

The spread of COVID-19 among the BAME community in the UK is disproportionately high compared to its spread in the countries of origin of these communities. A random analysis has demonstrated a higher incidence of viral infection among the migrated members of the family, while their family members still living in their countries of birth have no such higher incidence. Family studies have demonstrated that the rate at which BAME persons living in colder countries develop COVID-19 is faster but most of their family members living in their birth countries with a tropical climate are spared from infection. This observation is related to extrinsic factors like lifestyle and weather conditions rather than intrinsic genetic factors. The second-generation immigrant population is less affected, and mixed-race individuals, because of the diversity of immune cells, appear to be more resilient to the viral pandemic. An observation of this sort questions the genetic vulnerability to COVID-19. In cold environments, BAME individuals should take genetic vulnerability into consideration. Higher rates of cardiovascular disease, type-2 diabetes, and hypertension, which are linked to severe COVID-19 symptoms and complications, are also shown by this group.

Human immunity is generally fixed at an early age, as determined by bacterial flora, among other factors. Several trillion bacteria exist within our body, with the gut considered this bacterial colony's front yard. Of the 20,000 to 25,000 human genes, only about 3 million bacterial flora genes are the real immune cell trainers. Before humans evolved, the bacterial worlds were already in existence. When people migrated to Western countries from tropical regions, their bacteria had to adjust to the new lifestyle of their hosts. Some types of bacteria were replaced, and others may not have survived at all, leading to weakened immunity in their hosts.

Alongside these factors, many BAME individuals work in fields that carry a high risk of infection, such as healthcare, transport services and retail. In the UK, 40% of doctors, 20% of nurses and a large number of social care and unskilled migrant workers belong to BAME backgrounds. BAME community members tend to spend more time indoors clustered together, often in cramped accommodations, which increases the likelihood of person-to-person transmission, and this may

be another reason for the high incidence of these infections in ethnic minorities. A multigenerational family set-up is not helpful for social distancing in a pandemic, so this lifestyle could contribute to higher infection rates. Migrant communities tend to visit and keep in contact with their country of origin, which involves international air travel and thus increased infection risk.

Compromised Immunity

The high incidence of diabetes and coronary heart disease in the British Asian population has been well recognised, along with many other risk factors and comorbidities, including obesity, chronic obstructive pulmonary disease, chronic kidney disease and hypertension. These may partly account for this population's increased COVID-19-related mortality and warrant further exploration. Overnutrition and overstress are contributory factors to the development of type 2 diabetes. Admittedly, there are weaknesses in some of the data collection procedures and interpretations, which are theoretical speculations yet to be confirmed, modified, or falsified. Besides, COVID-19 seriously affects the aging people of the BAME community, as in the case of the general population, but they are more disadvantaged in terms of health care access.

Medically compromised individuals are also highly prone to catching this infection; this includes people who have had an organ transplant, those who have undergone certain types of cancer treatment and those who have a blood or bone-marrow cancer, such as leukemia (Table 1). The list of vulnerable individuals also includes people who have a severe lung condition, such as cystic fibrosis or severe asthma, people who have a health condition or are taking medicine that makes them more likely to get infections, and pregnant women with a serious heart condition. A US study also highlighted obesity as a serious risk factor for COVID-19 complications. Researchers from Glasgow University analysed data from 428,225 British people and observed that as body mass index (BMI) rose, so did their risk of having a severe case of the disease. Poor exercise and dietary habits make BAME people vulnerable to the epidemic of obesity.

Table 1: Compromised immunity.

a. Pre-existing respiratory conditions such as asthma, COPD, bronchiectasis, cystic fibrosis, taking daily inhaled steroid.
b. Individuals who had organ transplant.
c. Type 1 and Type 2 Diabetes Mellitus.
d. Heart Problems (Heart Failure, Angina, History of Heart Attack).
e. Chronic Kidney Disease (stage 3 and above).
f. Chronic Liver Disease including Hepatitis.
g. People with cancer who are undergoing active chemotherapy, people with lung cancer who are undergoing radical radiotherapy, people with cancers of the blood or bone marrow such as leukaemia, lymphoma or myeloma who are at any stage of treatment, people having immunotherapy or other continuing antibody treatments for cancer, people having other targeted cancer treatments which can affect the immune system, such as protein kinase inhibitors or PARP inhibitors, patients receiving radiotherapy or immunotherapy.
h. People who have had bone marrow or stem cell transplants in the last 6 months, or who are still taking immunosuppression drugs.
i. People with rare diseases that significantly increase the risk of infections (such as SCID, homozygous sickle cell).
j. Autoimmune disorders including on-going inflammatory bowel conditions (Crohn's, Ulcerative Colitis).
k. Pregnant women.
l. Older individuals with comorbid conditions.
m. Reduced Immune Response - AIDS/HIV, regular oral steroids.
n. Obesity.
o. Chronic alcohol abuse, heavy smoking.
p. Chronic Neurological Conditions (Parkinson's, Motor Neurone Disease, history of stroke (CVA), Multiple Sclerosis, Cerebral palsy).
q. Hypertension (on one or more anti-hypertensive medications.
r. Migrant population from tropical countries.

Because radiotherapy and chemotherapy are immunosuppressive, BAME individuals with cancer have a higher risk of contracting COVID-19. They also run the risk of nosocomial infection because of their frequent hospital visits for treatment and monitoring, as confirmed by a Wuhan study [16]. Patients with autoimmune disorders are also prone to develop cytokine storms and severe complications. In the absence of a good immune system, a person suffering from HIV infection runs a high risk of COVID-19 infection. Furthermore, people with weak immune systems could remain infectious for longer periods of time. The World Health Organization observed that those suffering from respiratory illnesses encounter an increased risk from COVID-19. These additional risks are applicable to BAME people just as they are relevant to the white British community.

COVID-19 has been more prevalent among elderly people of the BAME community. Statistical studies indicate that the severity of coronaviruses increases with age. People above the age of 70 are considered to be at risk for this viral infection, even though physiological age and numerical age are two different issues. In general, immunity declines as the years go by, unless special precautions are taken. Elderly BAME people with pre-existing medical conditions (i.e. asthma, diabetes, and heart disease) and those whose immunity has been compromised appear to be more vulnerable to becoming severely ill with this novel virus. Older patients and/or those with comorbidities may present with mild symptoms but have a high risk of deterioration [17]. Some immunologists postulate that aging itself is the outcome of immune decline. SARS-CoV-2 causes severe respiratory disease that mostly induces mild to moderate symptoms in younger individuals but causes devastating morbidity and

mortality in older BAME individuals. A key hallmark of severe disease is exuberant inflammation in the respiratory tract of patients [18]. As a consequence of weakened immunity, the lifespans of ethnic minority individuals are shorter in Western countries compared to the peer group in their country of origin.

Transcultural and Immunological Psychiatry

Ethno-psychiatry has different faces and has been dubbed as cross-cultural psychiatry, transcultural psychiatry, or cultural psychiatry. Immunological variations manifest differently in diverse cultures. As in the general population, amplification of psychiatric symptomatology has been observed among the ethnic minority group with existing psychiatric illness. These are insecure times for minority group individuals. Transcultural psychiatrists dealing with ethnic minority groups should become more cognisant of the immunological and environmental factors contributing to the higher incidence of COVID-19 among their clients. Such an awareness would help the ethnic minority community to be mindful of their own self-preserving immunity system. After analysing the negative psychological impacts of the COVID-19 pandemic on psychiatric patients, Hao *et al.* posit that studying the psychological impact on psychiatric patients during the COVID-19 pandemic has the potential to provide insight into how to develop a new immunopsychiatry service [19]. They also recommend more research to compare pro-inflammatory cytokines between psychiatric patients and healthy controls during the pandemic.

While the pandemic is going on, the time is ripe for the development of immunity-based psychiatry. The immunological aspects of COVID-19 and its manifestations in different ethnic minorities are of interest to immunopsychiatry. This fledgling field of research has great potential in the aetiological research of psychotic disorders for finding new treatment strategies [20]. The autoimmune aetiology of a subset of schizophrenia is gaining ground [21-25]. Psychotic symptoms are conjectured to be the outcome of autoimmune antibodies against the brain and later shaped by neurological and psychosocial factors. Metaphorically, immunity aberrations explain only the tectonic shift under the seawater of a tsunami formation. Nicholson *et al.* have hypothesised that anti-basal ganglia antibodies are responsible for obsessive-compulsive disorder in some adult individuals [26]. If such postulations are confirmed, anti-autoimmune antibodies or even anti-autoimmune antibody vaccination may become a future reality.

The cytokine storm that occurs due to COVID-19 is an autoimmune reaction, and the resulting neurotoxic effects exemplify how an autoimmune reaction could result in the formation of psychotic symptoms through the mediation of the brain. If subsets of psychotic disorders are the outcome of subtle autoimmune reactions, cytokine release syndrome that occurs in COVID-19 might offer an approximate conceptual model of the schizophrenic process and other psychotic disorders. These immunological abnormalities may have genetic contributions. It is now ever more documented that infection can trigger perturbation of the immune system, which could induce psychopathology. Also, psychiatric sequelae were observed after previous coronavirus outbreaks. With the triumph of immunopsychiatry, the deconstruction and reconstruction of psychiatric disorders and clinical practices could occur.

Conclusion

A higher rate of morbidity is recognised in cases of infections among some ethnic minorities, particularly in the aged populations and patients with suppressed immunity. The elevated incidence of complications among an ethnic minority also points to the environmental factors of immunity-it is a question of nurture rather than nature. A range of socioeconomic and geographical factors are involved in the higher infection rate among the BAME community, but the risks remain unexplained for some groups, and further analysis is warranted. Ultimately, it boils down to compromised immunity, and investigators should concentrate on immunological factors accounting for this anomaly. Too much focusing on ethnicity as a risk factor can be disadvantageous for the exceptionally large number of non-ethnic minority groups who also share deprived areas and overcrowded housing and have high-risk occupations.

No one can predict the outcome of this virus; it could become endemic in humans. Many viruses become less virulent over time in the process of 'attenuation'. It is also feared that COVID-19 could follow a similar trajectory to the deadly Spanish flu, which circulated through the globe in three waves. It started in March 1918 and mainly affected the elderly and frail during the First World War. The death spiked again from September to November when the virus had developed into a new strain. This time it hit young, healthy people, and death rates spiked again in the final wave among healthy 20- to 40-year-olds. It is envisaged that COVID-19 could go through a similar 'W curve' as the Spanish Flu, with three spikes, but modern advanced medical sciences could stop such an erratic sweep of the virus.

Historically, viruses eventually cause less serious illness through mutation. So, the current virus could mutate in such a way that it becomes more virulent, less transmissible, or could even disappear from microscopic attention. It is likely that global herd immunity must have occurred because of the fast transmission of the virus through modern trade routes and air travels, which did not exist during the time of the Spanish Flu. An effective and safe vaccine would drastically change the situation for the better. Harmonising immunity is the way forward to combat the onslaught of the viral pathogen, and BAME communities should become more observant of lifestyle changes and environmental factors.

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Conflicts of Interests

None.

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