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Health Disparities on COVID-19: The Need of a Holistic Model That Must Recognize the Biology Perspective

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Opinion Article

As the global coronavirus disease 2019 (COVID-19) pandemic has taken hold across the world, millions of lives have been impacted or slashed by this newly emerged virus [1]. As epidemiological information emerged, a glaring gap in terms of morbidity and mortality become apparent. Although information on race is still limited, it become evident that minorities are more likely to be hospitalized and also exhibited higher mortality rates [2].

When scientists and health authorities were asked why minorities were more susceptible, many are rushing to provide reasons based on social and structural determinants of health. The list includes discrimination, under-use of preventive measures, inequalities in education and health care [3,4]. They mostly resort on other pandemics, yet as the foundations to fight this pandemic are built, information needs to be based on strict science. Health disparity figures in which only structural and sociodemographic disparities are blamed can perpetuate harmful myths and delay appropriate responses.

To uncover new insights into this problem, we need to highlight that the processes driving an infectious disease includes an interplay between viral replication and the host immune system [5]. So even if social and structural determinants of health are less than optimal, the immune response is critical in preventing infection in those exposed to the virus, and to stop the growth of the invading pathogen. Within this concept there are individuals with standard immune responses that will effectively control the pathogen as most of the population [6]. The elite controllers are a different group who have a more effective immune response that successfully hold in line the pathogen, and the initial inflammatory upsurge [7]. They can also have a limited availability of susceptible target cells/receptors. Notably, disparities on the expression of the ACE2 which is the human cell receptor of SARS-CoV-2, have been reported by gender, race, smoking, and pollution [8]. There are others with an exaggerated immune response who could in theory either resolve the infection in a shorter period of time, or can complicate the course of the disease due to their excessive inflammatory response. In some cases, their heighten response is due to priming by stressors, prior exposure to the pathogen or chronic use of alcohol. Finally, we have those with poor immune responses, mostly due to underlying conditions that compromised immune system [9].

More sophisticated models of within-host viral dynamics even characterized the roles of the innate immune response, and when secondary infections are common, such as in the case of HIV, the adaptive immune response is also included. In the case of COVID-19, the excessive release of cytokines that is known as cytokine storm seems to play a protagonist role [10-12]. Cytokine storm syndrome has been previously described in conjunction with other viral infections such as SARS coronavirus (SARS-CoV), MERS coronavirus (MERS-CoV), influenza and dengue [13]. Reflecting innate immune activation, levels of pro-inflammatory cytokines, such as TNF, IL-1β, IL-6, IL-8, G-CSF and GM-CSF have significantly higher in COVID-19 infected subjects when compared to healthy individuals [14]. Some of them were particularly higher in severe cases as compared to

those with mild cases (e.g., IL1B, IL1RA, IL7, IL8, IL9, IL10, IFNγ, IP10, and MCP1 [15].

Unfortunately, scientists assessing cytokines in patients with COVID-19 have not analysed cytokine levels by age, gender, and race, although it is well known that cytokines are affected by these factors [16]. For example, analyses of older individuals have described age-related increases in certain proinflammatory cytokines, so relevant that IL-6 has been labelled a "cytokine for gerontologists" [18]. An observation that is also valid for tumour necrosis factor (TNF)-α. tackling the complex drivers of health disparities requires to ensure that relevant confounders and contextually appropriate controls are included when conducting this kind of analyses [19].

Though studies analysing racial or ethnic differences run the risk of undervaluing the diversity that exists among persons within groups, this risk needs to be weighed against the fact that differences in immune parameters, particularly those linked to the inflammatory response have been identified within subgroups (defined by ethnicity, geography, or genetic backgrounds).

Of relevance to this disease, differences in biomarkers of inflammation have been documented [20]. Although in the past, the argument against the existence of immune differences was the sample size of the studies, the limited representation of some groups or the lack of controls, differences have now been documented in multiple cross-sectional and prospective national cohort studies with large samples [21-23]. For instance, in the National Social Life, Health and Aging Project the mean C-reactive protein (CRP) level was three times higher among African Americans than among Caucasians (0.63 vs 0.20 mg/L). In the Multi-Ethnic Study of Atherosclerosis (MESA) study, African Americans had higher mean levels of IL-6 across categorical gradients of education and income. In the Coronary Artery Risk Development in Young Adults (CARDIA) study, Black men and women independently had higher mean levels of both CRP and IL-6 than their Caucasian counterparts. Several adipokines, high-sensitivity CRP, and cytokines such as tumour necrosis factor (TNF)-α, and interleukin-6 (IL-6) were elevated in Hispanics/Latinos with and at risk of type 2 diabetes [24].

More genetic dissimilarities have been noted on IL-1, IL-18, IL-6, IL-10 in African Americans, as compared to Whites [25]. We have previously described differences on circulating levels of pro-inflammatory cytokines IL-6, and IL-17 among African Americans and Hispanics, as compared to Caucasians [26]. Findings are in line with the racial variation in the rates of diseases with inflammation and/or chronic infection such as autoimmune diseases, infectious diseases such as tuberculosis, septicaemia, and HIV/AIDs, and some types of cancers (colorectal, liver, lung, prostate, and stomach) [27,28].

In addition, taking advantage of technological advances many COVID-19 studies have analysed single nucleotide polymorphisms (SNPs) [29,30]. Analyses of the relationships between race and allele frequencies of 70 cytokines and cytokine receptors, SNPs demonstrated that allelic frequencies for 52 out of the 70 SNPs meeting criteria for analysis differed significantly by race [31]. Of the 32 pro-inflammatory and 20 anti-inflammatory SNPs for which the allele frequencies varied significantly by race, variant allele frequency differences between Caucasians and African Americans ranged between 6%–37% and 7%–53% for pro-inflammatory SNPs and anti-inflammatory SNPs, respectively. Although it needs to be recognized that some studies have not found differences in circulating levels or in the SNPs by race and ethnicity [32]. The general consensus is that disparities in inflammatory cytokines do exist and may increase their risk for worse disease outcomes [33]. In addition, myelopoiesis is regulated by a number of cytokines and chemokines, and by regulating immune cells and platelets they can further change the course of infection or inflammation [34]. COVID-19 is characterized by a depletion in total white blood cell (WBC) and neutrophil counts [35]. Notably, African Americans normally have lower numbers of these first responders whose job is either to phagocyte the pathogen or release inflammatory products to destroy the pathogen. Differences in the expression of these consistent findings point to a more general pattern of immune response in different racial/ethnic groups [36,37].

Even if these genetic polymorphisms account for only a fraction of the differences, we posit that race is more than just a social construct. Rather, sociodemographic conditions are latent factors that can influence stress and have stronger negative impacts on minorities compared to Whites. Stress is one of the most powerful modifiers of immune response, and when combined with other factors such as pathogens, obesity and drug use it can lead to exaggerated or prolonged inflammatory responses. In addition, cytokine changes associated with stress seem to systemically sensitize the host, so that later challenges promote dysfunctional stress responses. This is known as epigenetic changes and can explain, at least in part, the link between the socio-structural factors divide and biology, and highlight the need of a more holistic approach to address these problems [38-40] (Figure 1).

Although scientists have raised concerns that a biological explanation can inadvertently feed structural racism in this mist of a societal and public health crisis. Health disparity figures in which only structural and sociodemographic inequalities are blamed can perpetuate harmful myths and delay appropriate responses. Equally faulty is to consider these factors as isolated phenomena without interactions between each other. Recognizing those at risk will permit to transform medicine, perhaps we stop the one size fits all approach and rather see this as an opportunity to personalized and provide special care for those in more need. Holistic models such as the one in figure 1 will aid to design

theory-based interventions and prioritize those at risk to effectively reduce health disparities during this pandemic or in new waives of the disease.

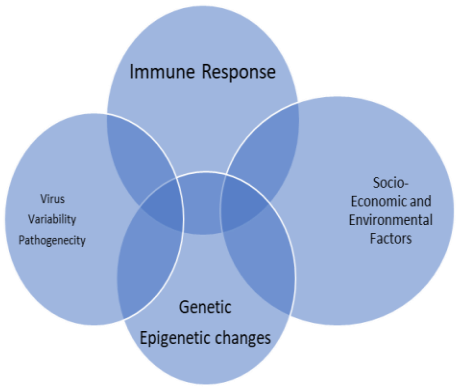

Figure 1: *Holistic Model to aid the design theory-based interventions.*

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