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Review

Role of multiple factors likely contributing to severity-mortality of COVID-19

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ABSTRACT

COVID-19 stalled the world in 2020 and continues to be the greatest health crisis of this generation. While the apparent case fatality rates across fluctuates around ~2% globally, associated mortality/death rate (deaths per million population) varies distinctly across regions from the global average of ~600 per million population. Heterogeneous factors have been linked with COVID-19 associated mortalities and these include age, share of geriatric population, comorbidities, trained immunity and climatic conditions. Apart from direct or indirect role of endemic diseases, dietary factors and host immunity in regulating COVID-19 severity, human behaviour will inevitably control outcome of this pandemic. Comprehensive understanding of these factors will have a bearing on management of future health crises.

1. Background

As the COVID-19 pandemic swept across the globe starting from Wuhan in November 2019, it disproportionately affected North America and Europe in terms of high rates of hospitalization and mortality, while sparing several countries such as Taiwan and Cambodia that did early shutdown in December 2019 (Sheikh et al., 2020). The apparent case fatality rate (CFR which indicates ratio of total deaths to total diagnosed population) from COVID-19 in various WHO (World Health Organization) regions fluctuates around global average of ~2% (Table 1), recording highest for American and lowest for Western-pacific and Asian regions. For a particular time period, the case fatality rate (signifies severity of the disease) represents number of deaths within the diagnosed population while the mortality rate (signifies incidence of death) represents number of deaths by the total at-risk population. Thus, estimation of the true mortality rate will largely depend on the numerator while the population represents a stable denominator. However, estimation of true case fatality rate can be difficult due to its dependence on both numerator and an unstable denominator, which may lead to its gross under- or overestimation of number of laboratory testing performed. Thus, during an outbreak/pandemic situation, case fatality rates can represent poor indicators of assessing mortality risks. For SARS-CoV outbreak, the actual CFR (10%, calculated at the end) was significantly higher than reported at its beginning (3–5%) (Ghani et al., 2005). For COVID-19, CFR data in low income settings can greatly overestimate the true estimate of mortality risk due to limited diagnosis. However,

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Table 1
COVID-19 burden across various regions (as of September 1 2021).

Regions	COVID-19 Mortality rate (Deaths per million)	Case fatality rate (%)
Global	606.6	2.03
Africa	78.7	2.34
Americas	2117.3	2.45
South-East Asia	331.1	1.54
Europe	1386.8	1.91
Eastern Mediterranean	401.1	1.79
Western Pacific	48.5	1.35

Reported mortality and case fatality rate was sourced from WHO Coronavirus (COVID-19) Dashboard (covid19.who.int/). Case fatality rate is defined as percent ratio of total deaths to total diagnosed population. Mortality rate is defined as percent ratio of total deaths to total at-risk population.

population deaths are less likely to be grossly underestimated, thus signifying the mortality rate (number of deaths per million population) as more reliable measure of at-risk population from the disease. For COVID-19, while the CFR was observed to be globally similar, mortality rates presented significant differences across the regions (Table 1). The high mortality rate from COVID-19 in American and European regions has been attributed to higher rate of comorbidities (78% deaths had pre-existing chronic illness such as diabetes, hypertension and other serious diseases), higher population distribution of elderly aged 65–90 years, and a significant proportion of black people who have high rates of hospitalization and death likely driven by social determinants (Yancy, 2020; Sakurai et al., 2020; Williamson et al., 2020). This was also in accordance with WHO data showing highest life expectancy by birth in American, Western pacific and European regions (>77 years) compared to South east Asian, African and Eastern-Mediterranean regions (<71 years) for 2019 (WHO Data Life Expectancy). For the African region the lower mortality rate may be related to the low median age of the population (<20 years as per UN estimates for 2020) (Diop et al., 2020).

Since the onset of the pandemic, multiple population factors as gender, age, sex, race and non-pharmaceutical measures have been correlated with infection and mortality rate of COVID-19. The current review aims to enhance level of understanding of diverse factors which could be controlling vulnerability of populations towards COVID-19. While we also observe fast spreading of disease owing to emergence of variants of concern/interest (Singh et al., 2021a; Singh et al., 2021b; Kumar et al., 2021), knowledge of these factors could help in further management of the pandemic.

1.1. Behavioral factor

Human behaviour will be the center for mitigation of current pandemic and will overplay any other factors, which may or may not confer selective advantage against infection. Non pharmaceutical interventions as social distancing, isolation, and increased hygiene practice can effectively reduce the transmission of SARS-CoV-2. For instance in an early survey in UK (March 2020), physical distancing measures resulted in four-fold reduction in reproduction number from Ro ~ 2.6 (Jarvis et al., 2020). On the other hand, reduced adherence with social guidelines resulted in higher COVID-19 transmission in Brazil (Faria de Moura Villela et al., 2021). The second wave in India is another classical example, where non-compliance with appropriate COVID-19 behaviour has resulted in significant healthcare crisis at many levels (The, 2021).

1.2. Environmental factors

Based on several reports, it was clear that SARS-CoV-2 has a different trend for transmission (Sajadi et al., 2020). Temperature and humidity could play vital role in affecting the prevalence of a disease and transmissibility of pathogens (Mecenas et al., 2020). The climate changes along with socioeconomic and healthcare facilities play a pivotal role in shaping the seasonal patterns of climate sensitive infectious diseases and emergence of new infections in both tropical and non-tropical regions (Evengard and Sauerborn, 2009). In a recent report, regions in temperate zone, having mean temperature of 5–11 °C reported higher COVID-19 cases as compared to tropical African regions (Ghosh et al., 2020), indicating role of temperature in transmission of SARS-CoV-2. Nevertheless, Kumar et al. showed a non-linear pattern of transmission of SARS-CoV-2 with temperature, demonstrating lower range of temperatures as favourable factor for the spread of COVID-19 (Bherwani et al., 2020).

1.3. Diabetes prevalence, ACE2 polymorphism and dietary factors

A bidirectional relationship between COVID-19 and diabetes has been established where either condition can precipitate the other (The Lancet Diabetes E, 2020). Recent estimates (age: 20–79 years) on diabetes prevalence were reported to be highest among Western Pacific (11.4%, ~162 million number of people) followed by South-east Asian (11.3%, ~87 million people), North American and Caribbean (11.1%, ~47 million people) and European (6.3%, ~59 million people) regions (Saeedi et al., 2019). Interestingly, the territories with high COVID-19 burden and mortality rate (USA and Brazil) have 2.5–6.9 times less number of diabetic individuals than nations with largest diabetic population: India and China. The apparent inverse relationship between diabetes prevalence and COVID-19 mortality rate in different regions points towards the role of other hidden factors in mediating viral severity in population. The COVID-19 and diabetes nexus is postulated to be centred upon host angiotensin converting enzyme 2 (ACE2) receptor which is expressed in host metabolic organs, such as the pancreas and required by SARS-CoV-2 and related coronaviruses (SARS-CoV-1) to establish viral contact (Li et al., 2020). ACE2 polymorphism has been increasingly linked with COVID-19 susceptibility. A comprehensive genetic analysis from eighty-one thousand human genomes (general population) identified key mutations in ACE2, which are likely to be associated with pulmonary and cardiovascular injury (Hou et al., 2020). The African and American populations harboured M383T-D427Y mutations (allele frequencies, 0.003% and 0.01%) and P389H mutation (allele frequency of 0.015%), which cause slightly reduced affinity between spike protein of SARS-CoV-1 and ACE2 (Li et al., 2005). In another computational study, single K26R variant of ACE2 with highest frequency in European (0.503%) and American population (0.329%) compared to Asian and American (0.079–0.099%) population was shown to enhance binding with SARS-CoV-2 spike protein (Calcagnile et al., 2021). However, a recent survey of genetic variants in ACE2 showed high degree of conservation in viral interacting domains across all populations (Lee et al., 2020). The authors stressed on essential role of non-genetic, medical condition and environmental risk factors in governing susceptibility of different populations to SARS-CoV-2.

Studies on role of dietary factors in regulating ACE2 expression which further modulate viral severity studies are still in infancy, with current knowledge restricted to animal (mice) studies. Preliminary work in mouse/rat models showed direct role of dietary fat and fructose intake in downregulating ACE2 gene expression.(Bundalo et al., 2016; Gupte et al., 2008) Consequently, SARS-CoV-1 challenged ACE2 knocked out mouse/rat models displayed acute respiratory distress syndrome and lung injury while these symptoms improved upon treatment with recombinant ACE2 (Imai et al., 2005). Alternatively, human recombinant soluble ACE2 was shown to reduce SARS-CoV-2 infection in *in-vitro* cultures, engineered organoids and in a COVID-19 patient where ACE2 treatment reduced bilateral multifocal consolidations. (Zoufaly et al., 2020; Monteil et al., 2020) A recent community-based, cohort study of 6.9 million COVID-19 patients in UK concluded linear correlation between BMI (Body Mass Index) and intensive-care unit admissions (Gao et al., 2021). The study concluded that risk of severe COVID-19 and deaths increases at BMI > 23 kg/m^2. Mapping of nations

with highest (>0.1 million) cumulative COVID-19 related deaths(Max Roser et al., 2020; Dong et al., 2020) onto their daily caloric supply per person and percentage of obese persons (MRAH, 2013) places nations with highest mortality rate in an entirely distinct quadrant (Fig. 1). This quadrant pertains to >20% obese population (BMI > 25) with >3000 kcal daily caloric supply per person. Further inclusion of other tropical regions of Africa, South east Asia, Western pacific (which have recorded a low mortality rate) clustered along India to a separate quadrant with <15% of obese/overweight individuals and <3000 kcal daily caloric supply per person. The observations were consistent with study by Micha R. et al. on higher consumption of saturated and trans fats in North American and European regions compared to tropical nations (Micha et al., 2014). Alternatively, consumption of fructose in the form of high fructose corn syrups was also reported to be higher in North American and European nations compared to the rest of the world (Kmietowicz, 2012). It may be thus postulated that high dietary consumption of fats or fructose can affect ACE2 expression in humans and might explain variable COVID-19 associated mortalities across regions worldwide. Besides its role in regulating ACE2 expression, obesity/high BMI also impairs immune function, reduced lung function and difficult ventilation, which can increase risk of severe COVID-19 illness.

1.4. Heterologous immunogenic effects of unrelated vaccines

A growing body of evidence suggests that heterologous cell-mediated innate immunity (termed as "trained immunity") imparts beneficial non-specific protective effects against COVID-19 disease severity (Singh et al., 2020a). Many microbial stimuli including bacteria, viruses, fungal cells, and their components (LPS, β-glucan, chitin) are efficient inducers of memory response associated with trained immunity. Interestingly, many epidemiological studies in the past have shown that tropical regions have been more adversely affected by infectious diseases than temperate regions (Sattenspiel, 2000). Prior exposure with pathogens raises chances of inducing innate memory responses. SARS-CoV-2 has brought the concept of importance of innate immunity to the forefront and the role of trained immunity in conferring protections against unrelated infections (Singh et al., 2021c), or through "ACTIVATE" clinical trials for inducing trained memory responses in aged or high risk individuals (Giamarellos-Bourboulis et al., 2020). CD8 T cells recognize multiple regions of N proteins and induce multi-specific and long-lasting

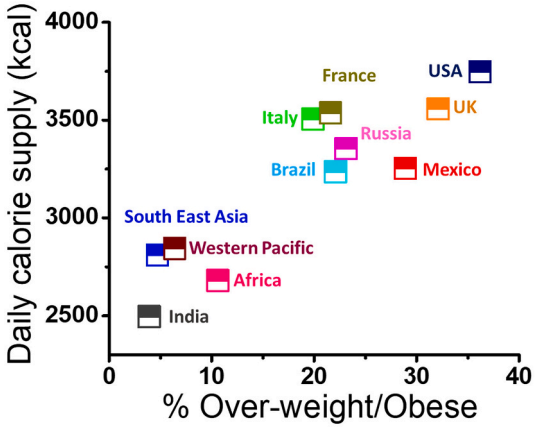

Fig. 1. Share of overweight or obese adults against daily calorie supply in various regions. Mapping of nations with highest COVID-19 related deaths onto map of share of obese/overweight adults *vs* daily supply of calories along the Western Pacific, African and South East Asian regions for 2016. Number of COVID-19 related deaths per million population recorded for Russia was ~730 and >1500 for USA, UK, Brazil, Italy, France and Mexico. Overweight or obese individuals were defined by body mass index of ≥than 25 and 30 respectively. Figure was created using published data (Bundalo et al., 2016; Max Roser et al., 2020; MRAH, 2013; MRAH, 2016).

immune responses. The memory T cells display cross-reactivity to SARS-CoV-2 for more than 15 years. CD4 T cells recognize spike protein and regulate the generation of memory B cells that target SARS-CoV-2 spike proteins (Pusnik et al., 2021). Memory B cells are long-lasting as compared to the antibodies and can provide durability in the immune response against SARS-CoV-2. Host directed therapies such as the use of umbilical cord-derived mesenchymal stem cells and anti-IL6 receptor antibodies have shown promising results on COVID-19 patients (Maeurer et al., 2021). Apart from the anti-viral approaches for specific treatment of COVID-19, scientists are also exploring broader interventions to support a healthy immune response through nutritional interventions that may regulate microbiota-mediated immunomodulatory effects. Hence, the role of immunonutrients to boost the immune system as part of the strategies to minimize the complications of SARS-CoV-2 infection is gaining global recognition (Ramalho et al., 2020). Some of the studies have shown that specific nutrients such as omega-3 fatty acid, vitamin C, Vitamin D, Zinc and selenium may help in improving the functioning of immune system, especially among aged people (Derbyshire and Delange, 2020). Recommended doses of Glutamine (25–35 g/day) and Arginine (25–35 g/day) can help in boosting the immune function. These immune-nutrients help in increasing the number of immune cells, regulate systemic or local inflammatory response and interact with gut microbiota to improve the overall functioning of the immune cells (Tang et al., 2021). Heyland et al. (2001) had reviewed whether immunonutrition can improve the clinical outcome of critically-ill patients and concluded that immunonutrition does not improve the mortality advantage but may decrease the complications associated with infectious disease (Heyland et al., 2001). Hence, the use of appropriate immunonutrients specific for improving the health status of COVID-19 patients is an open question that requires more methodological studies.

Recent studies also indicate that some of the unrelated vaccines including Bacille Calmette-Guérin (BCG), Measles Mumps and Rubella (MMR) and influenza vaccines may aid in reducing the severity of COVID-19 infection. BCG is a live attenuated vaccine for tuberculosis (TB) disease and MMR vaccine is trivalent live attenuated vaccine against Measles, Mumps and Rubella. Gold et al. showed in their study that IgG titres against mumps (in individuals vaccinated with MMR) likely mitigate severity of COVID-19 disease as observed in a cohort study of 70 patients clinically positive for SARS-CoV-2 and 10 clinically negative for COVID-19 despite COVID-19 exposure (Gold et al., 2020). Martin et al. also indicated probable protective effects of MMR vaccine against severity of COVID-19 disease (López-Martin et al., 2021). Another study demonstrated that clinically COVID-19 positive patients with prior vaccination with trivalent inactivated influenza virus show better clinical outcomes than clinically COVID-19 positive patients with no influenza vaccination, pointing towards beneficial non-specific effects of inactivated influenza vaccine in reducing severe effects of COVID-19 disease (Fink et al., 2020). A probable role of pneumococcal vaccine in protecting against severity of COVID-19 disease in an observational cohort study at Mayo clinic has been proposed (Root-Bernstein, 2020).

BCG, discovered nearly a century ago, has proven its efficacy in providing protection against wide repertoire of unrelated pathogens including viruses, especially those causing respiratory infections in children (Aaby et al., 2011; Stensballe et al., 2005; Biering-Sorensen et al., 2017). Vaccinating individuals with BCG for boosting the trained immunity to protect against COVID-19 has gained global attention (O'Neill and Netea, 2020). Countries, including India, where BCG is part of universal vaccination programme has shown relatively lesser severe impact of COVID-19 pandemic (Ehtesham et al., 2020), prior to the second wave, the severity of which had more to do with human behaviour. Cause-specific death rate/100,000 population was significantly lower in countries having BCG immunization policy (mostly in tropical regions (Nemes et al., 2018)), compared to those where a universal BCG vaccination policy did not exist (Ehtesham et al., 2020).

Another recent observational study indicated that exposure to Mycobacterium spp. (including BCG) is negatively correlated with COVID-19 disease and mortality in European countries (Singh et al., 2020a). Though the heterologous immunity conferred by BCG against SARS-CoV-2 infection is still debatable and uncertain, an interesting study recently revealed that BCG protects elderly against respiratory infections (interim results) (48), implying a role of BCG vaccination, though speculative, in circumventing COVID-19 spread. However, the beneficial effects of BCG vaccination against COVID-19 were not observed in Brazil. One of the contributing factors in this disparity could be lower median age of population in India (28.2 years) compared to Brazil (33.5 years) (population.un.org/). Another factor could be a single SARS-CoV-2 variant in Brazil since the beginning of the pandemic (Fig. S1) while for India, its temporal analysis showed co-dominance of multiple viral variants (Alam et al., 2021). While recognising the potential beneficial effects of BCG vaccination we agree with others who have urged that robust clinical trial evidence is needed before BCG vaccination can be recommended as an intervention to be applied on a wide scale for the prevention of COVID-19 morbidity and mortality (Nachega et al., 2021). In fact, scientists are proposing the concept of "heterologous vaccine boosting" which means a non-specific vaccine as a boost, second dose after the COVID-19 specific vaccine prime dose, especially when the second dose of COVID-19 vaccine is unavailable. (Hupert et al., 2021; Marin-Hernandez et al., 2021) This is right now only a hypothesis which warrants further investigations and trials.

2. Limitations

Though we have focused on several clinical and epidemiological studies for our interpretation and analysis, still there are limitations to this review. The factors linked to COVID-19 severity should be interpreted with caution as there are likely many confounding factors that have not been accounted for. For example, COVID-19 testing and hospitalization vary from place to place and time to time, that may impact the outcome of SARS-CoV-2 infection. Role of trained immunity in fighting against COVID-19 needs additional studies addressing the "cause-effect" phenomenon. We need data from various ongoing clinical trials (addressing effect of BCG on COVID-19 severity) to strengthen the correlation. A certain bias can also occur depending on the timing of our search and analysis as spatial and temporal variations impacted the spread of COVID-19 peaks. Dietary intake and lifestyle show variations from region to region, and even within a particular region/country, largely governed by socio-economic factors. The emergence of different variants of SARS-CoV-2 with higher binding affinity towards hACE2 along with immune escape ability(Singh et al., 2021a; Singh et al., 2021b) has been attributed to the increased COVID-19 positivity rate. These confounding variables need to be adjusted before assessing the actual mortality/morbidity rate of a given population.

3. Conclusions

The gradual spread of COVID-19 continues to impact and disrupt healthcare settings and the global economy in an unprecedented way. Genetic variations in SARS-CoV-2 have compounded its increased transmission and infectivity, as evident from global sweep of D614G variant in 2020 and N501Y variants in 2021 (Hui et al., 2021). However, multiple non-biological factors such as environment, socio-behavioral aspects, comorbidity *etc.* appear to contribute towards disparate COVID-19 associated mortality rate globally (Singh et al., 2020b). Additionally, endemic microbial infections, dietary factors and trained immunity substantially impacts COVID-19 disease burden. Given the rapid emergence of contagious mutants and an urgency to vaccinate all, non-specific vaccines have been proposed to be used to boost immunological response to COVID-19 specific vaccine.(Hupert et al., 2021; Marin-Hernandez et al., 2021) Taking clues from these non-genetic factors and past lessons from the HIV pandemic, SARS-CoV-1, MERS-CoV (Middle East Respiratory Syndrome) epidemics and other disease outbreaks, it is imperative to fully understand and utilize host-directed responses against infectious diseases. Comprehensive understanding of host-directed responses and population differences can be helpful in managing the current and future pandemics.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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