COVID-19: Reviewing Risk Factors and Breaking Transmission

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ABSTRACT SARS-CoV-2, a member of the *Betacoronavirus* genera and causative agent of COVID-19 will go down in history as one of the most successful pathogens in recent times. COVID-19 was declared a pandemic on 11th of March 2020, and it is disturbing that only vaccines are available hitherto despite it being around for more than a year. Traditional virology attempts to explain events via host-pathogen interactions, yet it does not take into account of the multifarious factors that may alter odds for disease development. In line with this paucity, a literature review was performed to identify risk factors for developing severe COVID-19 from behavioural, demographical, environmental, genetic and physiological perspectives. Risk factors for disease are discussed by focusing on the receptors of SARS-CoV-2 which would be ACE2 and TMPRSS2 in addition to elaborating on multiple phenomena. An elaborate discourse is also performed to identify steps that can be taken to stymie or ideally break the chain of COVID-19 transmission in addition to discussing on what one should do after being confirmed or suspected as being COVID-19 positive.

KEYWORDS: Anti-vaxxers and COVID-19, COVID-19 risk factors, Factors affecting ACE2, Factors affecting TMPRSS2, Stopping COVID-19 transmission.
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Review Article

INTRODUCTION

Pandemics are defined as large-scale outbreaks of infectious diseases that can greatly increase morbidity and mortality over a wide geographic area and cause significant economic, political and social disruption (Madhav *et al*., 2017). COVID-19 was declared a pandemic on 11th of March 2020 by the World Health Organization (WHO) Director General during a media briefing (WHO, 2020a). An incertitude that needs to be cleared early on would be the difference between the terminologies "COVID-19" and "SARS-CoV-2", as many individuals use them interchangeably. The former is the name given for the disease and it is derived as follows; '**CO**' stands for corona, '**VI**' stands for virus, '**D**' stands for disease and '**19**' refers to the year 2019, hence the name **COVID-19**. The latter is the name of the virus causing the disease and it was derived from **S**evere **a**cute **r**espiratory **s**yndrome **co**rona**v**irus **2** (**SARS-CoV-2**). Interestingly, this is the first pandemic caused by a coronavirus, although an epidemic was caused by severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 affecting 26 countries (WHO, 2020b), while Middle East respiratory syndrome coronavirus (MERS-CoV) that occurred primarily in the Arabian Peninsula demonstrated the potential to be an epidemic (Memish, 2014).

COVID-19 has caused multifarious deleterious effects to all levels of society and it is unlikely that the issue would be ameliorated in the near future. The scientific community has recognized the threat posed by SARS-CoV-2 and much effort has been placed in evaluating the potential for drug repurposing, identifying novel drug targets and developing vaccines. Concurrently, clinical phenotypes present in patients have also been reported with great detail to identify optimal therapeutic interventions. However, there is a gap in literature as risk factors that predispose individuals to infection and development of disease has not been explored. In line with this paucity, the current review attempts to provide a detailed discussion pertaining select risk factors that render individuals susceptible to infection and disease development. Similarly, a discourse is performed to

describe some strategies that can limit or ideally break COVID-19 transmission and a discussion is also done to evaluate what one should do upon being confirmed as a COVID-19 patient.

ORIGINS OF SARS-CoV-2

Three theories have been proposed to explain the origins of SARS-CoV-2; (1) Natural selection in an animal host before zoonotic transfer, (2) Natural selection in humans before zoonotic transfer, and (3) Lab-made. In (1), it was suggested that SARS-CoV-2 could have originated from *Rhinolophus affinis* bat or *Manis javanica* (Malayan pangolins) as SARS-CoV-like coronaviruses which are very similar to the virus have been detected in these animals (Andersen *et al*., 2020; Zhang *et al*., 2020c; Zhou *et al*., 2020b). In (2), it has been postulated that a progenitor of SARS-CoV-2 may have infected humans and spread extensively without being detected (Andersen *et al*., 2020). Extensive undetected human-to-human spread would have aided the virus to acquire receptor binding domains (RBDs) with high affinity towards human angiotensin converting enzyme 2 (ACE2) and gradually acquire polybasic cleavage sites. Idea (2) is supported by the previous spillover of MERS-CoV from camel populations into humans which followed a similar trajectory (Dudas *et al*., 2018).

Theory (3) is a contentious one as there are proponents and opponents to the stance. Opponents state that a lab origin for SARS-CoV-2 is not possible because acquisition of polybasic cleavage site is only possible via prolonged passage in *in vitro* and/or *in vivo* systems as observed in influenza viruses (Ito *et al*., 2001). Similarly, presence of O-linked glycans in SARS-CoV-2 is indicative of immune system involvement, which is unlikely to be present in a laboratory setting (Bagdonaite & Wandall, 2018). Another argument against an inadvertent laboratory release scenario is the absence of prior literature reporting work performed on a progenitor virus.

Proponents of the lab origin theory state that SARS-CoV-2 was likely the result of an accidental or deliberate leak from a laboratory (BBC News, 2020a; Gartland, 2020; TheWeek, 2020). Initially, thoughts on the subject were primarily based on suspicion rather than concrete facts but recently, two reports provided an array of facts to support the notion (Yan *et al*., 2020a; Yan *et al*., 2020b). Multiple arguments were presented in the aforementioned manuscripts and some highlights are as follows; (a) SARS-CoV-2 was likely created by using ZC45 or ZXC21 bat coronaviruses as the backbone, (b) The Spike protein, particularly the RBM was manipulated and proof would be the presence of unique restriction enzyme digestion sites at either end of the RBM and (c) The introduction and insertion of an unusual furin cleavage site at the S1/S2 junction of the Spike protein. The peer review process has since debunked the claims made (Koyama *et al*., 2020).

ANATOMICAL AND GENOMIC DESCRIPTION OF SARS-CoV-2

Coronaviruses are named as such due to spike glycoproteins on the viral envelope which confers them a crown-like appearance (Abdelrahman *et al*., 2020). Morphologically, virions of coronaviruses have a spherical appearance that is pleomorphic and their size ranges from 80 to 220 nm. The envelopes have large, widely spaced club-sized peplomers while the nucleocapsid is tubular with a helical symmetry (Burrell *et al*., 2017). SARS-CoV-2 is no exception as the virions are spherical with some polymorphism which confers them the appearance of a solar corona (Zhu *et al*., 2020). The particles are sized between 60-140 nm.

Taxonomically, coronaviruses belong to the subfamily *Coronavirinae* that is placed in the family *Coronaviridae* and the order *Nidovirales* (Cui *et al*., 2019). The aforementioned subfamily can be subdivided further into four genera which would be *Alphacoronavirus*, *Betacoronavirus*,

Deltacoronavirus and *Gammacoronavirus*, in which the former two only infect mammals while the latter two predominantly infect birds yet may also infect mammals (Woo *et al*., 2012; Cui *et al*., 2019). *Betacoronavirus* has four subgroups A, B, C, and D (Woo *et al*., 2010). SARS-CoV-2 belongs to subgroup B alongside SARS-CoV.

Coronaviruses have a positive single-stranded RNA genome about 26-32 kilobases (kb) in size, which is the largest known genome for RNA viruses (Su *et al*., 2016). SARS-CoV-2 genome size varies between 29.8 kb to 29.9 kb (Khailany *et al*., 2020). The genome of SARS-CoV-2 is that of a typical coronavirus and possesses at least ten open reading frames (ORFs). The first ORFs (ORF1a/b) which comprise about two-thirds of viral RNA are translated into two large polyproteins (Li *et al*., 2020b). These polyproteins undergo processing by virally encoded proteinases which lead to production of 16 non-structural proteins (nsp1-nsp16) that are well conserved among coronaviruses (Li *et al*., 2020b; Naqvi *et al*., 2020). Remaining one-third of viral RNA encodes for the four main structural proteins which are envelope (E), membrane (M), nucleocapsid (N) and spike (S) proteins (Li *et al*., 2020b).

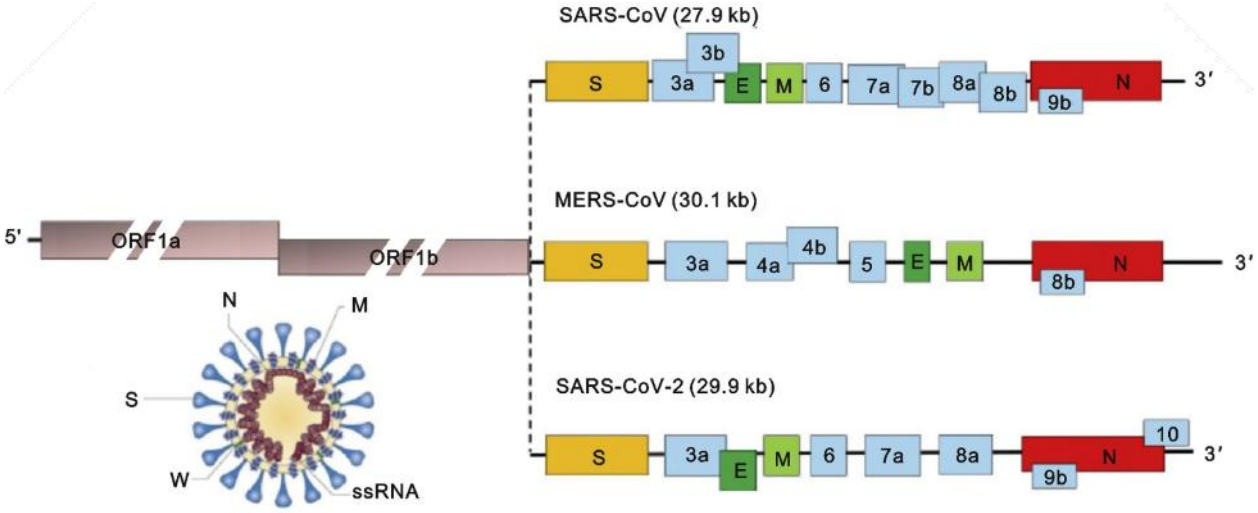

Figure 1. An overview of the genomes of SARS-CoV, MERS-CoV and SARS-CoV-2 (Li *et al*., 2020b).

DETECTION OF SARS-CoV-2

Detection of COVID-19 patients is imperative as it permits identification of individuals that are actively spreading SARS-CoV-2 besides identifying presymptomatic and asymptomatic individuals. COVID-19 tests available hitherto can be divided into two major groups which would be those based on nucleic acid amplification tests (NAATs) and antibody detection. Latest additions to the detection arsenal would be the breath test which detects SARS-CoV-2 in under a minute and the paper-based test that uses clustered regularly interspaced short palindromic repeats (CRISPR) (BBC News, 2020b; The Australian Jewish News, 2020). In NAATs, the main technique employed is real time reverse transcription polymerase chain reaction (rRT-PCR). The technique is considered a 'gold standard' for diagnosis and has the benefits of rapidity, adequate sensitivity and specificity. However, it has the issue of being unable to discriminate between infectious viral particles and viral debris present after clearance of infection. Other NAATs are also available and I refer the reader to (Mathuria *et al*., 2020), for a detailed review on the subject.

Serologic techniques function by detecting the presence of IgM and/or IgG which are both antibodies produced through the course of an illness. The technique provides valuable information pertaining one's exposure to SARS-CoV-2. In COVID-19, IgM and IgG antibodies against the virus are detectable 5 and 14 days respectively after symptom onset (Guo *et al*., 2020a). Serologic tests are

prone to generating false negatives because presymptomatic patients would not have antibodies against SARS-CoV-2. Along the same lines, symptomatic patients have higher IgG levels against SARS-CoV-2 in comparison with asymptomatic patients and decrease in neutralizing serum antibodies is higher in asymptomatic patients compared to symptomatic patients (Long *et al*., 2020a). The lower IgG levels and decrease in neutralizing serum antibodies can be a problem for serological testing as these patients may turn up as false negatives if the tests do not have adequate sensitivity. False positives are a possibility with serological techniques as cross-reactivity occurs with SARS-CoV (Guo *et al*., 2020a), in addition to potentially occurring with other coronaviruses such as MERS-CoV 229E, HKU1, NL63 and OC43 (Rashid *et al*., 2020).

RISK FACTORS

An important point that should be noted by the reader would be that susceptibility to infection and susceptibility to disease are independent (Flint *et al*., 2015). Indeed, just because an individual is more susceptible to infection, does not mean that they would suffer a more serious illness. In this article, risk factors for disease shall be discussed. The European Patient's Academy (EUPATI) categorizes risk factors into five major groups which are behavioural, demographic, environmental, genetic and physiological (EUPATI, 2015). Susceptibility to disease shall refer to any factors that affect detection of COVID-19 and/or alter severity of COVID-19 post-infection. Susceptibility to disease shall also refer to factors that modulate two key players in infection Angiotensin Converting Enzyme 2 (ACE2) and Transmembrane Protease Serine 2 (TMPRSS2) as they are the bona fide receptors for infection by SARS-CoV-2 at the time of writing (Astuti & Ysrafil, 2020; Hoffmann *et al*., 2020; Zhou *et al*., 2020b). These definitions form the cornerstone of this manuscript but some modifications may be performed to ensure a thorough discussion and alterations made shall be explicitly mentioned.

Figure 2: An overview of select risk factors for infection by SARS-CoV-2 and development of severe COVID-19.

GENETIC RISK FACTORS

Virology traditionally focuses on understanding host-pathogen interactions that occur besides understanding a virus' life cycle to discern possible outcomes of disease. However, it should be understood that genetic variation of hosts would also play equally important roles in explaining dissimilitude of clinical course and disease outcomes. This subsection shall deliberate upon the aforementioned context besides discussing genetic variants that may be present for the genes. In this subsection, risk factors for disease shall refer to genes that influence COVID-19 progression or severity in any manner.

Angiotensin Converting Enzyme 1 (ACE1) and Angiotensin Converting Enzyme 2 (ACE2)

Prior to delving into this area, a brief description is necessary pertaining the relationship between ACE1 and ACE2 as they have a "yin-yang" relationship and lacking understanding about this could be an issue later on. Graphical pathways explaining the concept elegantly can be found here (Gemmati *et al*., 2020), but the simplified key idea would be that elevated expression of Angiotensin II (Ang II) leads to deleterious effects as it acts on the AT1-receptor to promote fibrosis, inflammation and vasoconstriction (Gemmati *et al*., 2020). ACE1 promotes conversion of Angiotensin I (Ang I) to Ang II while ACE2 converts Ang II to Ang 1-7, which upon complexation with MAS-receptor antagonizes the biological effects due to Ang II (Gemmati *et al*., 2020).

Angiotensin converting enzyme 1 (ACE1) is known by many other names and is encoded by the *ACE* gene located on chromosome 17 (17q23.3) (Mattei *et al*., 1989). The *ACE* gene possesses either an insertion (I) or deletion (D) of a 287-base pair Alu repeat sequence in intron 16, hence leading to three genotypes, II, ID and DD (Rieder *et al*., 1999). COVID-19 cases and prevalence of the *D* allele correlated negatively in a significant manner (Delanghe *et al*., 2020a; Delanghe *et al*., 2020b), and as per the authors, the *D* allele is associated with lower levels of ACE2 expression. A different research group reported that the II genotype is associated with lower risk of severe disease among individuals regardless of the population albeit at varying degrees (Yamamoto *et al*., 2020). At normal physiological conditions, ACE1 and ACE2 would be at balance but upon infection by SARS-CoV-2, ACE2 would undergo downregulation hence leading to decreased degradation of Ang II (Pal & Bhansali, 2020). Considering that ACE1 promotes Ang II production and that in COVID-19, ACE2 is not able to counteract the effects due to ACE1, genotypes correlated with higher levels of ACE1 expression would be a risk factor for developing severe COVID-19.

Discussing *ACE1* genotypes associated with increased risk of severe COVID-19, the *I* allele would be a protective factor as prior literature has indicated this avenue (Rigat *et al*., 1990), and the idea aligns well with that of a different research group (Yamamoto *et al*., 2020). Considering that the *I* allele is associated with lower levels of ACE1, even post-infection the levels of ACE1 would still be lower in these patients when compared to those possessing the *D* allele that are known to express higher levels of ACE (Rigat *et al*., 1990), hence serving as a potential explanation on why the *I* allele is protective. The *D* allele has been suggestively associated with lower levels of ACE2 expression (Delanghe *et al*., 2020b), but hitherto no such relationship has been reported. Considering the gaps present, it would be useful if *in vitro* and/or *in vivo* investigations are performed to assess the impact of I/D polymorphism on ACE1 and ACE2 levels.

ACE2 has received much attention during the COVID-19 pandemic due to its status as a functional receptor that permits entry of SARS-CoV-2 (Zhou *et al*., 2020b). A study identified several missense variants of ACE2 that causes destabilization of interactions between the receptor and S protein of SARS-CoV-2. (Benetti *et al*., 2020). A different investigation reported expression quantitative trait loci (eQTL) variants associated with high ACE2 expression (Cao *et al*., 2020). A recent work still in preprint, identified a missense variant, K26R which promotes high affinity binding between ACE2 and SARS-CoV-2 (Al-Mulla *et al*., 2020). Another investigation probed into the same area and reported that alleles rs73635825 (S19P) and rs143936283 (E329G) may offer some resistance against infection (Hussain *et al*., 2020b). A different study highlighted protective (p.Asp355Asn, p.Glu37Lys and p.Gly352Val) and predisposing (p.Gly326Glu) missense variants (MacGowan & Barton, 2020).

The literature surrounding ACE2 and genetics certainly looks like a mass of discordance, but this is not the case because variation in results obtained can be explained via two avenues. The first one

would be expression levels of ACE2, as any allele or mutation associated with higher levels of ACE2 can be described as a risk factor for severe COVID-19 as more ACE2 would also equal towards increased odds of successful viral entry thus resulting in higher viral loads. Similarly, alleles or mutations that reduce ACE2 expression can be described as protective. The second avenue would be alleles or mutations that affect interactions between ACE2 and SARS-CoV-2 as mutations that result in higher affinity or stability can be considered as risk factors for severe COVID-19. Likewise, alleles or mutations that result in bindings that are less stable or of lower affinity can be described as being protective. However, it is possible that individuals expressing higher ACE2 levels would be at elevated risk for severe COVID-19 as degradation of ACE2 due to SARS-CoV-2 invasion would cause imbalances between ACE1 and ACE2 at a higher degree.

Human Leukocyte Antigen (HLA)

The human major histocompatibility complex (MHC) is encoded by a set of genes that are about 3,600 kilobases in length located on the short arm of chromosome 6 (6p21) (Choo, 2007). The region has three classes; Class I which has the *HLA-A, HLA-B* and *HLA-C* genes, Class II which has a series of subregions, each containing *A* and *B* genes encoding α and β chains respectively and Class III which does not encode HLA molecules but instead has genes for components of the complement system, 21-hydroxylase, tumour necrosis factors (TNFs) and others (Choo, 2007). It has been reported that *HLA-A*01, HLA-A*02:01, HLA-A*03, HLA-A*25, HLA-A*25:01, HLA-B*07, HLA-B*08, HLA-B*15:01, HLA-B*38, HLA-B*44, HLA-B*46:01, HLA-B*51, HLA-C*01, HLA-C*01:02, HLA-C*03, HLA-C*05* and *HLA-E*01:01* predispose one towards infection by SARS-CoV-2 and developing severe COVID-19 while *HLA-A*02:02, HLA-A*02:06, HLA-A*11:01, HLA-B*14, HLA-B*15:03, HLA-B*18, HLA-B*49, HLA-B*54:01* and *HLA-C*01:02* are protective (Correale *et al*., 2020; Habel *et al*., 2020; Nguyen *et al*., 2020a; Saadati *et al*., 2020; Sakuraba *et al*., 2020; Toyoshima *et al*., 2020; Vietzen *et al*., 2021). Similar observations have been made within the context of MERS-CoV and SARS-CoV as well (Lin *et al*., 2003; Ng *et al*., 2004; Chen *et al*., 2006; Hajeer *et al*., 2016).

A Spanish study suggested that COVID-19 severity and HLA-I viral peptide binding affinity have an inverse relationship (Iturrieta-Zuazo *et al*., 2020). It is likely that individuals possessing high-risk variants may be unable to present adequate amounts of immunodominant virus derived epitopes hence leading to reduction in rapidity of immune response (Correale *et al*., 2020). Indeed, low binding affinity between proteins encoded by the *HLA* alleles and SARS-CoV-2 epitopes could be leading to extensive viral proliferation prior to detection by the immune system, thus resulting in severe COVID-19. The same Spanish study identified individuals homozygous for loci A and C were more likely to belong in the severe COVID-19 group (Iturrieta-Zuazo *et al*., 2020). HLA homozygosity has been associated with poorer disease resistance, peptide presentation and lymphocyte proliferation in response to an antigen (Ovsyannikova *et al*., 2013; Arora *et al*., 2020). Extrapolating from Human Immunodeficiency Virus-1 (HIV-1), it is possible that SARS-CoV-2 may be encoding virulence factors that affect proteins encoded by particular HLA alleles (Tokarev & Guatelli, 2011). Deducing from data on other RNA viruses, particular HLA molecules may intrinsically possess more cross-reactive cytotoxic T-lymphocyte (CTL) repertoires that better control viral loads during the acute phase of infection in addition to priming innate immunity to respond against SARS-CoV-2 by functioning as a ligand for natural killer (NK) cells (Crux & Elahi, 2017). Considering the effects of HLA variation in altering COVID-19 outcomes, it is recommended that HLA typing should be included alongside SARS-CoV-2 testing to identify individuals that may be at a higher risk for severe COVID-19.

Transmembrane Protease, Serine 2 (TMPRSS2)

TMPRSS2 is encoded by the *TMPRSS2* gene located on chromosome 21 (21q22.3) (Paoloni-Giacobino *et al*., 1997). Several studies in preprint have identified mutations which increase expression levels of TMPRSS2 (Russo *et al*., 2020b; Santos *et al*., 2020), and considering its importance in the infection cycle of SARS-CoV-2 (Astuti & Ysrafil, 2020), these mutations are risk factors for severe COVID-19 and similar findings have been reported in influenza (Cheng *et al*., 2015). A different study reported that rs12329760 and its mutant V160M may be protective against viral entry, as the protein encoded by these mutants possess decreased stability (Vishnubhotla *et al*., 2020). Another investigation identified 21 SNPs that affect TMPRSS2 function but rs75603675 (creates a *de novo* proteolytic site), rs875393 (creates a donor site, silencer and broken enhancer motifs) and rs12627374 (affects a wide spectrum of miRNAs) are of particular interest due to their *sui generis* effects (Paniri *et al*., 2020). A recent work highlighted two synonymous variants, rs61735794 and rs61735792 which were detected at statistically different frequencies in groups with and without COVID-19 (Torre-Fuentes *et al*., 2020). The role played by these variants is not well known because synonymous variants are usually not pathogenic but as mentioned by the authors, the proteins encoded by them may facilitate SARS-CoV-2 in some way via smaller modifications (Torre-Fuentes *et al*., 2020). A different investigation revealed that eQTL variant, rs35074065 was associated with elevated expression of TMPRSS2 but decreased expression of IFN-α/β-inducible gene, *MX1* splicing isoform (Russo *et al*., 2020b). Noteworthily, *MX1* expression increases in response to SARS-CoV-2, thus a reduced baseline expression of MX1 may contribute to severe COVID-19 among individuals with the rs35074065 variant (Bizzotto *et al*., 2020).

PHYSIOLOGICAL RISK FACTORS

The state of 'normal physiology' is hard to define at an organism level as each system of the human body appears to have its own definition of 'normal', but a common theme between all of them would be that normal physiological conditions are free of disease. As such, any state which promotes or causes deviation from the 'normal' state can be described as an abnormal physiological condition. In this subsection, risk factor for disease shall be defined as factors that may alter detection and/or progression of disease in any manner post-infection. Risk factor for disease shall also refer to factors that may alter ACE2 and/or TMPRSS2 in organs other than the respiratory system, which may promote further infection during viraemia of SARS-CoV-2 (Chan *et al*., 2020a; Huang *et al*., 2020a).

Cardiovascular diseases

COVID-19 patients have been reported to experience multiple forms of cardiovascular injuries such as acute coronary syndrome, arrythmia, coagulation abnormalities, myocardial injury, myocarditis, heart failure, sudden cardiac arrest and thrombosis (Nishiga *et al*., 2020). Multiple studies concerning COVID-19 patients identified some form of cardiovascular disease (CVD) as a comorbidity (Guan *et al*., 2020; Wang *et al*., 2020a; Zhou *et al*., 2020a), and a 10.5% mortality rate has been reported within this group (Feng *et al*., 2020). A meta-analysis illustrated that the proportion of patients with CVD in COVID-19, SARS and MERS patients were 4.5%, 2.1% and 20.9% respectively (Yang *et al*., 2020a). The complete range of mechanisms that cause cardiovascular complications remain to be discovered but current literature indicates that coronary manifestations may be due to adverse effects of various therapies, altered myocardial demand-supply ratio, direct myocardial injury, electrolyte imbalances, plaque rupture and coronary thrombosis, severe hypoxia and systemic inflammation (Bansal, 2020; Tan & Aboulhosn, 2020). It is difficult to say that COVID-19 is causing the observed cardiovascular manifestations but it is highly likely that among patients with

underlying coronary issues, SARS-CoV-2 infection may function as the precipitating factor leading to severe COVID-19.

The heart may experience infection during viraemia of SARS-CoV-2 as ACE2 and TMPRSS2 respectively are expressed in cardiomyocytes (ACE2=6.6%, TMPRSS2=0.8%), cardiovascular progenitor cells (ACE2=12.5%, TMPRSS2=0.4%) and smooth muscle cells of the heart (ACE2=10.38%, TMPRSS2=0.16%) (Qi *et al*., 2020; Zou *et al*., 2020). Of interest, individuals with failing hearts (Chen *et al*., 2020), myocardial infarct (Burrell *et al*., 2005), and obstructive hypertrophic cardiomyopathy (Bos *et al*., 2020), have elevated expression of ACE2 mRNA and protein hence indicating increased risk for severe COVID-19 but the postulate for increased risk of severe COVID-19 needs future work(s) to assess alterations of TMPRSS2 in these conditions. Hitherto, the exact reason for increased ACE2 in these conditions is unknown but it has been suggested to be a pathoresponsive counter-regulatory mechanism (Burrell *et al*., 2005; Bos *et al*., 2020).

Chronic obstructive pulmonary disease (COPD)

Chronic obstructive pulmonary disease (COPD) is associated with significantly higher expression of ACE2 and TMPRSS2 and interestingly the expression is higher among overweight COPD patients (Higham & Singh, 2020; Leung *et al*., 2020a; Sharif-Askari *et al*., 2020), which indicates that COPD patients may be at higher risk for infection by SARS-CoV-2. Pooled prevalence of COPD patients that experienced COVID-19 was only 2% but the mortality rate within this group was 60%, indicating that COPD patients have a proclivity to develop severe COVID-19 (Alqahtani *et al*., 2020). COPD patients are more likely to develop complications such as acute renal failure, acute respiratory distress syndrome (ARDS), coinfections and septic shock in addition to experiencing more symptoms such as diarrhoea, fatigue, shortness of breath and unconsciousness (Wu *et al*., 2020a). Viruses are well known exacerbators of COPD (Wedzicha, 2004), hence in COVID-19, pulmonary manifestations among COPD patients may be a combination of damage caused by COPD and SARS-CoV-2. The culprits for increased disease severity among COPD COVID-19 patients could also be immune and airway epithelial cells (Sajjan, 2013; Bhat *et al*., 2015). Airway epithelial cells in COPD patients possess defective innate immunity, compromised cellular junctions, lower mucociliary clearance and experience recurrent bacterial infections which collectively lead to enhanced viral binding and persistence besides causing reduced viral clearance. COPD patients also have blunted innate and adaptive immunity in the lung microenvironment and systemically which renders them incapable of mounting a rapid and strong immune response.

Diabetes

Multiple studies have reported pancreatic involvement mainly in the form of acute pancreatitis throughout the clinical course of patients infected with SARS-CoV-2, particularly among those with severe COVID-19 (Hadi *et al*., 2020; Liu *et al*., 2020a; Wang *et al*., 2020b), hence it is of interest to know if diabetics are at higher risk for severe COVID-19 due to increased infection by SARS-CoV-2. At the time of writing there is an absence of studies reporting alteration of ACE2 and TMPRSS2 in the lungs due to Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM). However, the stance needs clarification as a prior investigation reported increased circulating ACE2 among those with T1DM (Soro-Paavonen *et al*., 2012), hence it is not known if this may be the case for ACE2 in the lungs and if the findings would be similar among T2DM patients. Interestingly, elevated blood sugar alone causes increased expression and activity of ACE2 in multiple organs other than the lungs (Lavrentyev *et al*., 2007; Coelho *et al*., 2010; Härdtner *et al*., 2013), hence it is possible that diabetics regardless of type may be more vulnerable to severe COVID-19. Diabetes occurrence requires pancreatic involvement and a pooled analysis identified that less than 1% of acinar, ductal, endothelial and stellate cells coexpressed ACE2 and TMPRSS2 (Coate *et al*., 2020). Apical surface of

ductal epithelial cells coexpressed the aforementioned proteins yet spatial distinction was observed hence indicating that odds of SARS-CoV-2 infection in the pancreas may be low (Coate *et al*., 2020).

A large body of literature describes diabetes as a risk factor for severe COVID-19 (Guo *et al*., 2020b; Huang *et al*., 2020b; Kumar *et al*., 2020a; Li, *et al*., 2020a; Roncon *et al*., 2020; Singh *et al*., 2020; Targher *et al*., 2020; Wargny *et al*., 2020). This is unsurprising as similar accounts were reported with MERS and SARS (Booth *et al*., 2003; Matsuyama *et al*., 2016). The exact mechanism(s) behind worse outcomes for diabetic COVID-19 patients is/are not known but chronic low-grade inflammation, impaired innate and adaptive immunity, elevated production of adhesion molecules that mediate tissue inflammation, increased production of glycosylation end products, lung injury, macro- and microvascular complications and oxidative stress are all possible mediators (Rahman *et al*., 2007; Hussain *et al*., 2020a; Zhou *et al*., 2020c).

Hypertension

Within the framework of COVID-19, multiple studies associate hypertension (HT) with worse outcomes (Almeida-Pititto *et al*., 2020; Barrera *et al*., 2020; Parveen *et al*., 2020; Pranata *et al*., 2020), hence indicating that it may be a risk factor for severe COVID-19. Similar findings were reported for MERS (Matsuyama *et al*., 2016), yet HT may not be contributing to worse outcomes as a large number of individuals that developed severe COVID-19 were rather elderly (≥60 years old). It is noteworthy that the older population is plagued with other comorbidities discussed above and they are more likely to have underlying vascular endothelial dysfunction and/or organ damage which may be confounders for the elevated severe COVID-19 risk observed in HT patients (Kario *et al*., 2020). Enhanced viral infection would also be unable to explain worse outcomes among HT patients as it does not cause alterations in systemic ACE2 and/or TMPRSS2 levels. Interestingly, the culprits may be multifarious as aberrant cytokine signalling, dysregulated innate immunity, immunosenescence and aberrant activation of cytotoxic T lymphocytes, increased Ang II, lymphocyte dysregulation, lymphocyte loss and vascular remodelling have all been reported to promote proinflammatory states among hypertensive patients (Singh *et al*., 2014; Kreutz *et al*., 2020; Zhang *et al*., 2020a). Among COVID-19 patients, the pre-existing proinflammatory state may render them susceptible to the infamous 'cytokine storm'.

BEHAVIOURAL RISK FACTORS

Alcohol Consumption

Alcohol consumption has been associated with increased risk of contracting COVID-19 (Testino, 2020), and alcohol consumption is likely a risk factor for severe COVID-19. Findings from a meta-analysis using data from clinical studies over the past 30 years, lucidly illustrated that alcohol consumption caused a 1.8-fold increased risk for community acquired pneumonia (CAP) (Simou *et al*., 2018). A prior study identified that alcohol significantly inhibited the production of type I interferons (IFNs), IFN-α and IFN-β which resulted in enhanced production of hepatitis C virus (HCV) within infected cells (Ye *et al*., 2010). Similar findings have been reported as acute and prolonged alcohol treatment attenuated Toll like receptors (TLRs), TLR4- and TLR8-induced production of IFN-β (Pang *et al*., 2011). A study pending peer review has demonstrated that SARS-CoV-2 encodes ORF3b, a virulence factor that is a potent type I IFN antagonist (Konno *et al*., 2020). The antagonistic effect against type I IFN may explain the 'cytokine storm' phenomenon observed in patients, and considering that alcohol consumption contributes to blunted innate immunity, it can be described as a risk factor for disease. Negative ramifications of alcohol consumption also extend onto adaptive immunity as aberrant immunoglobulin profiles, impaired antigen presentation,

impaired T-cell activation and a predominantly Th2 response are observed among alcoholics (Szabo & Saha, 2015).

Smoking

A prior study reported that smoking contributed to significantly increased protein expression levels of ACE2 in the airway epithelia of smokers and interestingly this phenomenon was also observed in the cells of former smokers albeit at a lower level as they were between those of never-smokers and current smokers (Leung *et al*., 2020a). Cigarette smoke contains multiple components that cause deleterious effects but within the context of COVID-19, nicotine is of particular interest as an *in vitro* study illustrated that nicotine acts upon the Alpha7-nicotinic Acetylcholine Receptor (α7-nAChR) and subsequently induces ACE2 expression (Russo *et al*., 2020a), thus suggesting higher odds of severe COVID-19 due to increased viral attachment. Primary human non-smoker airway basal stem cells (ABSCs) which experienced short term cigarette smoke (CS) exposure consistently had two- to three-fold increased viral loads in comparison to unexposed ones (Purkayastha *et al*., 2020). The elevated viral loads were ascribed to downregulation of interferon-induced protein with tetratricopeptide repeats (IFIT) *IFIT1, IFIT2, IFIT3* and interferon-induced protein 44-like (*IFI44L*) which play a role in the interferon-based response to SARS-CoV-2. Note worthily, smoking also blunts both the innate and adaptive arms of the immune system (Qiu *et al*., 2017).

Besides negatively impacting immunity, CS extract has been reported to adversely affect cell-cell contacts and cell-matrix contacts in primary bronchial epithelial cells (PBECs) and human bronchial epithelial 16 HBE cells (Heijink *et al*., 2012). CS extract also reduced restoration of epithelial cell-cell contacts during the repair process and attenuated barrier function of PBECs upon wounding which was suggested to facilitate transport of viruses and bacteria (Heijink *et al*., 2012). This is unsurprising as CS exposure has been noted to predispose one towards acute lung injury (ALI), promote lung endothelial cell activation, and promote apoptosis of lung endothelial cells which collectively function as a precipitating factor for occurrence of ARDS (Lu *et al*., 2018). SARS-CoV-2 inhibited the repair process of both control and CS exposed ABSCs, but in cells exposed to CS, genes involved in metabolism and wound healing were downregulated hence suggesting a higher likelihood of severe COVID-19 among patients with a history of smoking (Purkayastha *et al*., 2020).

A preliminary meta-analysis based on Chinese patients indicated that active smoking was not significantly associated with a heightened risk of disease progression towards severe COVID-19 (Lippi & Henry, 2020), but a systematic review of literature arrived at a different conclusion stating that smoking was most likely associated with adverse outcomes of COVID-19 (Vardavas & Nikitara, 2020). Current literature does not possess information pertaining effects of second- and third-hand smoke on the incidence or severity of COVID-19. Based on previous literature which illustrates the negative effects of second- and third-hand smoke (Shang *et al*., 2011; Naeem, 2015; Jacob 3rd *et al*., 2017), it likely causes enhanced infection, diminishes the immune response and increases likelihood for severe COVID-19 as well.

Social Behaviour

Currently, there are no studies which exclusively explore the transmission dynamics of coronaviruses as a function of social behaviour hence extrapolation from existing findings would be performed to conduct an adequate discussion. Prior studies have modelled the importance of social behaviour on transmission of influenza (Kucharski *et al*., 2014), parvovirus (Melegaro *et al*., 2011), and varicella (Melegaro *et al*., 2011). A commonality between these studies would be that they reported close contacts are the primary conduits for pathogen transmission. This is unsurprising, as close contacts would generally encompass individuals that one would meet often and possibly for

extended periods of time hence resulting in an increase of opportunities present for pathogen spread. More than 50% of physical contacts occur at home (23%), work (21%) or school (14%) (Mossong *et al*., 2008). 16% of physical contacts occur during leisure activities which is pretty close to the reported contacts at school (Mossong *et al*., 2008). Somewhat similar trends were reported in a modelling study which reported that 41.6%, 28.4%, 26.7% and 3.3% of 2009 H1N1 influenza transmission occurred in households, general community, schools and workplaces respectively (Ajelli *et al*., 2014). Households are responsible for a large number of transmissions that occur but the risk is inversely proportional to the household size (Cauchemez *et al*., 2011). In households, the highest transmission occurs among children of different ages likely due to sibling relationship (LeGresley *et al*.,2011). High transmission rates are also observed among adults in households, likely between spouses (LeGresley *et al*., 2011). Interestingly, temporal variation was observed as highest number of transmissions occurred during the morning at schools, during the evening in the general community and during the night at households (Ajelli *et al*., 2014). A separate peak of transmission was observed during the early morning, and this likely corresponds to contacts which occur during the commute from home to work/school and vice versa (Ajelli *et al*., 2014).

Influenza A infection is heavily driven by interactions between children with their peers and parents (Kucharski *et al*. 2014). Different studies simulating transmission of respiratory diseases identified similar findings hence it is unsurprising that children also experience the greatest number of infections (Wallinga *et al*.,2006; Johnstone-Robertson *et al*., 2011). Children demonstrate assortative mixing behaviour, usually among those with the same age as them hence they drive the spread of infections for diseases spread by droplets and close contacts such as COVID-19 (Wallinga *et al*., 2006; Mossong *et al*., 2008; LeGresley *et al*., 2011). Despite assortative mixing, children also frequently come into contact with individuals aged 30-50 years or younger whom are likely their parents, hence a fair dispersal of infection occurs across all age groups (Mossong *et al*., 2008; Kucharski *et al*., 2014). Interestingly, adults also illustrate assortative mixing hence parent-child transmission occurrence is also a possible driving force for pandemics (Wallinga *et al*., 2006; Mossong *et al*., 2008; LeGresley *et al*., 2011).

A review of literature identified that the estimated mean R_0 for COVID-19 is around 3.28 which was higher than the WHO estimate of R_0, 1.95 (Liu *et al*., 2020c). The rather high R_0 value is indicative of high transmissibility potential hence social behaviour considerably increases the risk of an individual to be exposed to SARS-CoV-2 and develop COVID-19. In the same vein, social behaviour becomes a modifiable risk factor towards others because the act of a single person can put many others in danger. The risk is compounded by the fact that infectiousness of individuals infected by SARS-CoV-2 begins 2.3 days before symptom onset and peaks at 0.7 days before symptom onset which consequently results in pre-symptomatic transmission (He *et al*., 2020). In the case of influenza, a large proportion of assortative mixing occurs among school children and adults when they are healthy (Kerckhove *et al*., 2013). However, when these individuals experience illness, alterations occur in their social behaviour whereby they have fewer encounters with other individuals (Kerckhove *et al*., 2013). This leads to reduction in transmission opportunities thus leading to lower R_0 values, and this is likely the case in COVID-19 as well if individuals are unwell enough to moderate their social behaviour. In both influenza and COVID-19, asymptomatic cases are a norm as it has been identified that about 33% and 16% of cases fit in this category (Carrat *et al*., 2008; He *et al*., 2021). Asymptomatic COVID-19 cases are 42% less infectious than symptomatic cases (Byambasuren *et al*., 2020), but this should not be taken with a sigh of relief, rather it should reinforce the stance that preventive measures are imperative (Refer to "Methods to Stop Transmission").

DEMOGRAPHICAL RISK FACTORS

Age

Older age is associated with an increased risk for mortality due to COVID-19 (Bialek *et al*., 2020; Li, *et al*., 2020d; Richardson *et al*., 2020; Zangrillo *et al*., 2020; Zhou *et al*., 2020a), which indirectly also reflects increased risk for a more severe form of the disease. Most studies report an increased risk of mortality for patients ≥60 years old while some report it for ≥65 years old but regardless of criteria, the data illustrates that senescence is indeed associated with a higher mortality risk. There are detailed reviews discussing the relationship between increased age and decline in immune function (Montecino-Rodriguez *et al*., 2013; Simon *et al*., 2015). Summarizing the content in them would reveal that causes for immunological decline would be accumulation of inflammatory mediators in tissues, impaired B cell functionality, decreased migration of naïve B and T cells from primary to secondary lymphoid organs, reduction in growth hormone (GH) and insulin-like growth factor-1 (IGF-1) that stimulate thymopoiesis, reduced capability to establish immunological memory in response to *de novo* antigens, decreased functionality of senescent neutrophils and macrophages and also decreased capacity to produce lymphocytes due to increased myeloid potential of hematopoietic stem cells (HSCs).

ACE2 expression in nasal epithelium is age-dependent and younger children have lower levels of ACE2 compared to adults (Bunyavanich *et al*., 2020). A different study reported that children have lower ACE2 and TMPRSS2 expression in bronchial and nasal cells compared to adults (Sharif-Askari *et al*., 2020). However, these findings may not be applicable for the older population as senescence is associated with a dramatic reduction of lung ACE2 expression (Xie *et al*., 2006). Considering the negative association between aging and ACE2 expression levels, the older population should actually be protected from the disease but the growing body of evidence has illustrated that this is not necessarily the case. It is likely that reduction of ACE2 may decrease the odds for infection by SARS-CoV-2 but it predisposes the elderly towards the development of severe COVID-19. ACE2 confers protection against lung injury (Imai *et al*., 2005), and consequently a reduction in the amount of ACE2 would also probably translate into decreased protective effects from the protein.

Ethnicity

Enhanced susceptibility to severe COVID-19 due to ethnicity is likely governed predominantly by genetic variations present in different groups. Indeed, mutations in ACE2 and TMPRSS2 gene sequences can be associated with outcomes of COVID-19 under two premises; (1) functional mutations which alter the virus' cellular accessibility, and (2) mutations which confer quantitative modifications of gene expression which subsequently alters the number of binding and internalization sites present for the virus (Santos *et al*., 2020). A study which evaluated the effect of host genetics pertaining viral entry genes, identified that different populations exhibit varying levels of susceptibility to experience severe COVID-19 (Ortiz-Fernández & Sawalha, 2020). Africans were genetically associated with lower ACE2 and TMPRSS2 expression levels hence indicating lower susceptibility to severe COVID-19. South Asian and East Asian populations were associated with higher ACE2 and TMPRSS2 levels which indicate higher susceptibility to severe COVID-19. Similar findings were reported for East Asians as rs182366225 and rs2097723 polymorphisms which potentially increase ACE2 expression were more frequent in this group, particularly among the Chinese and Vietnamese populations (Khayat *et al*., 2021).

African populations possess higher rates of ACE2 polymorphisms rs147311723, rs142017934, and rs4646140 (Khayat *et al*., 2021). Polymorphism rs142017934 is *sui generis* to this population and may enhance ACE2 expression yet the same population has a higher allele frequency of the

polymorphism rs5934250 which reduces ACE2 expression in certain tissues (Khayat *et al*., 2021). Considering such variations, it is suggested that more studies should be performed to identify allele frequencies of protective and deleterious alleles of ACE2 and TMPRSS2 in varying populations. For instance, ACE2 rs2285666 polymorphism present in Indians has been negatively correlated with COVID-19 occurrence and case fatality rates (Srivastava *et al*., 2020). On the other hand, indigenous Amazon populations possess ACE2 polymorphisms rs2285666 and rs35803318 with higher frequencies and these have been associated with elevated ACE2 expression in various tissues (Khayat *et al*., 2021). The Amazonian population is a particularly vulnerable one as it experiences less exposure to viral infections and as observed during the 1918-19 pandemic, remote or isolated populations experienced high mortality as they had insufficient prior immunity (Mathews *et al*., 2009).

A number of authors have recognized that individuals of colour and of ethnic minorities are at increased risk of death from COVID-19 (Aldridge *et al*., 2020; Raifman & Raifman, 2020), thus indicating that genetics may not be the only factor predisposing these individuals towards infection and subsequent development of severe COVID-19. Indeed, it has been identified that Black, Asian and Minority Ethnics (BAME) communities are predisposed to certain non-communicable diseases and are subject to adverse healthcare disparities than their white counterparts (Abuelgasim *et al*., 2020). Similarly, the reason for the observed discrepancy may be vitamin D deficiency as a prior study did report that 42.2% of South Asians and 12.5% of Black African-Caribbeans had severe vitamin D deficiency (Patel *et al*., 2013). On a different note, the observed difference may also be a reflection of the socioeconomic differences that are present in which BAME could be experiencing educational and linguistic obstacles in adopting preventive measures, limited access to healthcare and poor living conditions (Abuelgasim *et al*., 2020).

Occupation

Healthcare personnel (HCP) are at higher risk to be infected by SARS-CoV-2 in comparison with general members of the public (Choi *et al*., 2020b; Koh, 2020). Indeed, the prevalence of COVID-19 was 2747 cases for every 100 000 front-line HCP in comparison with 242 cases for every 100 000 individuals in the general community (Nguyen *et al*., 2020b). The risk for contracting COVID-19 was increased in all healthcare settings for HCP but it was highest for those working in inpatient settings and nursing homes (Nguyen *et al*., 2020b). The reasons for increased risk of COVID-19 among HCP are inadequate personal protection, exposure to large numbers of infected patients, shortage of personal protective equipment (PPE), inadequate training for infection prevention and control (IPC), and aerosolization of viruses due to aerosol generating procedures (AGPs) (Herron *et al*., 2020; Wang *et al*., 2020c).

A study based on United States of America (USA) workers identified that about 10% of the population was employed in occupations where disease or infection exposure occurs at least once a week (Baker *et al*., 2020). As expected, HCP were the ones experiencing highest exposure but other occupational sectors such as community and social services, construction and extraction, education, office and administrative support, and protective services were also having high proportions of exposed workers. Similar findings were reported in a different study as work-related COVID-19 cases were identified among HCP, cleaning and domestic workers, drivers and transport workers, public safety workers, and services and sales workers (Lan *et al*., 2020). Interestingly, the occupations at risk demonstrated a temporal variation (Lan *et al*., 2020). Earlier on during the outbreak, cases were predominantly among construction labourers, drivers, religious professionals, and services and sales workers. However, during later phases of the outbreak, cases were mainly among cleaning and domestic workers, drivers, HCP, police officers and religious professionals.

The aforementioned temporal shift is indeed concerning because only 43.2% of cases among non-HCP could be traced back to the source of infection (Lan *et al*., 2020). This is way lower in comparison to HCP whereby 95% of cases had a clear and traceable contact history. Considering the lack of traceability among non-HCP, it is highly likely that extensive viral dissemination may occur in the community as the pandemic progresses. An intriguing finding was that long-term unemployed individuals were 1.84 times more likely to be hospitalized due to COVID-19 compared to employed individuals (Dragano *et al*., 2020). Short-term unemployed individuals and special benefit recipients were also 1.18 times and 1.31 times more likely to be hospitalized due to COVID-19. Increased prevalence of underlying health conditions among socioeconomically disadvantaged groups was postulated as an explanation for the observations (Dragano *et al*., 2020).

ENVIRONMENTAL RISK FACTORS

Temperature

Multiple reports illustrate that temperature can accelerate or decelerate spread of the pandemic (Auler *et al*., 2020; Demongeot *et al*.,2020; Ferretti *et al*., 2020; Liu *et al*., 2020b; Ma *et al*., 2020; Menebo, 2020; Prata *et al*., 2020; Şahin, 2020; Shi *et al*., 2020b; Tosepu *et al*., 2020; Wu *et al*., 2020b; Xie & Zhu, 2020). Dissimilitude in results demonstrated geographical variation but it does not completely explain the outcome as in China, both higher and lower temperatures have been associated with increased risk for infection (Ma *et al*., 2020; Shi *et al*., 2020b; Wu *et al*., 2020b; Xie & Zhu, 2020). The variance observed may be explained as follows. Higher temperatures could be promoting individuals to 'break' lockdown rules and go out in nations that are generally colder. In warmer nations however, cooler weather which is usually accompanied by rain may cause individuals to stay indoors. In this sense, weather may not be the direct risk factor, rather it would be changes in human activity that occur with ambient temperature, as a weak positive relationship has been observed between warmer ambient temperatures and increased prosocial behaviour (Lynott *et al*., 2017). A different study reported a negative association between increased ambient temperature and prosocial behaviour (Belkin & Kouchaki, 2017), but as aforementioned the variance in social behaviour likely depends on how the local population responds to alterations in temperature. Another way to explain the variance would be the studies themselves that were performed with different participants and models.

Multiple studies have assessed the stability of SARS-CoV-2 at temperatures ranging from 4 °C up until 40 °C and the common theme would be that elevated temperatures are associated with reductions in viral stability (Biryukov *et al*., 2020; Chan *et al*. 2020c; Kratzel *et al*., 2020; Riddell *et al*., 2020). Interestingly, strong reductions in infectivity are only observed during the initial drying process afterwards which, the virus remains infectious in the dried state for several days regardless of alterations in ambient temperature (Kratzel *et al*., 2020). Surface type also plays a role as viral stability is lower on non-porous surfaces compared to porous ones (Riddell *et al*., 2020). Exploring temperature as a risk factor for disease suggests that lower temperatures may be associated with increased severity of COVID-19. Previous work investigating the effect of temperature on growth of rhinoviruses on mouse airway epithelial cells revealed that viral growth was more pronounced at lower temperatures due to diminished response of innate antiviral immunity (Foxman *et al*., 2015). The study identified that the interferon (IFN) response to rhinovirus mediated by RIG-I-like receptors and IRN-αβR-dependent signalling were less robust at 33 °C compared to 37 °C which contributed to more vigorous viral replication. Similarly, it has been suggested that lower temperatures contribute to decreased blood supply which in turn cause decreased delivery of immune cells to the nasal mucosa (Sun *et al*., 2020).

Wind Speed and Direction

Studies performed to investigate the effect of wind speed as a risk factor for infection are rather unsuccessful at addressing the confusion as there are those that report positive and negative correlations and even absence of correlation between wind speed and the number of COVID-19 cases (Ahmadi *et al*., 2020; Bashir *et al*., 2020; Gupta *et al*., 2020; Menebo, 2020; Rosario *et al*., 2020; Şahin, 2020). The idea behind wind speed as a risk factor for infection is that air movement would aid in transmitting particulate matter that may have SARS-CoV-2 on them. Therefore, the variance observed may be due to direction of the wind rather than the wind speed. Hypothetically, if the wind were to blow towards a place with high population density, regardless of the wind speed case numbers would experience an increase. However, if the wind were to blow in a direction that would cause air movement towards places that have limited or no people at all, the rise in case numbers would be rather low or nil as the number of individuals that come into contact with contaminated particulate matter would be small or non-existent. This avenue has been explored before in the context of COVID-19 via wind rose analysis (Rendana, 2020). Similar findings were reported for influenza viruses and porcine epidemic diarrhoea virus as well (Jonges *et al*., 2015; Beam *et al*., 2016). Another explanation, would be that the wind may be diluting particle matter containing SARS-CoV-2 hence decreasing the occurrence of new cases in addition to potentially exposing the viruses to more solar radiation that may inactivate the viruses.

Animals, Arachnids and Insects

A significant body of literature indicates that cats, dogs, ferrets, fruit bats, gorillas, hamsters, lions, macaques, minks, monkeys, rabbits, raccoon dogs, tigers and tree shrews are susceptible to infection by SARS-CoV-2 (Barrs *et al*., 2020; BBC News, 2020c; Chan *et al*., 2020b; Daly, 2020a; Daly, 2020b; Freuling *et al*., 2020; Hartman *et al*., 2020; Munster *et al*., 2020; Oreshkova *et al*., 2020; Schlottau *et al*., 2020; Shi *et al*. 2020a; Xu *et al*., 2020; Zhao *et al*., 2020; Mykytyn *et al*., 2021). A study which employed a two-step homology search between human ACE2 sequences and ACE2 sequences of wildlife and domestic animal species identified a plethora of organisms that were deemed susceptible (Kumar *et al*., 2020b). Noteworthily, some of the species deemed susceptible by the *in silico* study have been corroborated by *in vivo* studies as well (Kumar *et al*., 2020b). Chickens, ducks, pigs and turkeys are not susceptible to infection by SARS-CoV-2 (Berhane *et al*., 2020; Schlottau *et al*., 2020; Shi *et al*., 2020a). Interestingly, susceptibility to the virus does not match phylogenetic relationships or ACE2 sequence similarities across species (Alexander *et al*., 2020).

As multiple species demonstrate susceptibility to infection, the risk of experiencing COVID-19 would be heightened in areas with large numbers of these animals because they can function as viral reservoirs and/or intermediate hosts. Recombination events between RaTG13-like CoV and Pan_SL-CoV_GD-like viruses led to the acquisition of the SARS-CoV-2 receptor binding motif (RBM) that is highly efficient in binding to human ACE2 (Li *et al*., 2020c). SARS-CoV was also identified to possess a recombination history with at least three different groups of bat coronaviruses (Li *et al*., 2020c). Considering the propensity for coronaviruses to recombine, dissemination among multiple animal species may lead to the emergence of novel variants with broader host tropism, heightened infectivity or heightened virulence due to recombination with other coronaviruses that may perhaps even be unknown to science. Nonetheless, these possibilities can be easily prevented/minimized by following preventive measures among humans (Refer to 'Methods to Stop Transmission') and ensuring that pets of COVID-19 patients are kept indoors to prevent animal-to-animal transmission (Kiros *et al*., 2020).

Cockroaches and houseflies may be able to function as mechanical vectors to transmit SARS-CoV-2 (Dehghani & Kassiri, 2020). Indeed, both of these insects are well known for consumption of a

variety of animal and human waste materials hence indicating that they may be able to carry pathogens to new areas or surfaces. The stance is corroborated to a certain extent by findings from a study which probed the potential of SARS-CoV carriage by cockroaches in which one uncertain positive result was obtained via nested RT-PCR out of 15 assays (Dehghani & Kassiri, 2020). Similarly, *Musca domestica* (houseflies) have been identified to mechanically transmit turkey coronavirus (Calibeo-Hayes *et al*., 2003). A discussion of arachnids and insects would not be complete without a discourse on mosquitoes and ticks that are notorious for disseminating arboviruses (Alatoom & Payne, 2009; Rames, 2020). Current findings suggest that mosquitoes, at least from the genus of *Aedes, Anopheles* and *Culex* would be unsuitable for transmission of SARS-CoV-2 as studies have identified that the virus is unable to propagate within them and their cell lines (Huang *et al*., 2020c; Xia *et al*., 2020a). Moving on to arachnids, corona-virus like agents tentatively termed as Runde virus have been isolated from *Ixodes uriae (I. uriae)* on seabirds in Runde, Norway (Traavik *et al*., 1977), and it is convenient to assume that SARS-CoV-2 could be transmitted via ticks. The preconceived notion would be erroneous as hitherto, there is no evidence for it yet the avenue should not be ignored completely and as such further work to evaluate the capability of ticks to transmit SARS-CoV-2 is warranted.

METHODS TO STOP TRANSMISSION

Measures to stymie transmission of SARS-CoV-2 are largely dependent on the actions of individuals. One should aim to increase hygiene levels as coronaviruses survive on various types of materials and remain infectious for varying periods of time ranging from 2 hours up until 9 days (Kampf *et al*., 2020). The survival of these viruses is inversely proportional to temperature and at 4 °C their survival exceeds 28 days (Kampf *et al*., 2020). Considering their survival on multiple surfaces, it is recommended that disinfection should be performed often. As per the WHO's guidelines, for non-healthcare settings initial cleaning should be performed with soap and water or a detergent to remove organic matter and subsequently surfaces should be disinfected with sodium hypochlorite (bleach) at a concentration of 0.1% or alternately alcohol at concentrations between 70-90% (WHO, 2020c). Similarly, fomite-based transmission is possible for SARS-CoV-2, hence hand hygiene should be increased. The Centers for Disease Control and Prevention (CDC) recommends that hand washing should be done with soap and water for at least 20 seconds after being in a public place, blowing your nose, coughing or sneezing and in the event soap and water are not available a hand sanitizer containing at least 60% alcohol should be utilized and rubbed until the hands feel dry (CDC, 2020a).

The usage of face masks such as medical masks, cloth masks and respirators like N95 are *sui generis* as they are non-pharmacological public health interventions that can play pivotal roles in impeding spread of disease. Surgical mask usage is effective in decreasing virus presence in respiratory droplets or aerosols (Leung *et al*., 2020b). Similarly, usage of surgical masks and N95 respirators has an inverse relationship with risk of clinical respiratory illness (Seto *et al*., 2003; Long *et al*., 2020b). The prior statements may promote one to easily dismiss cloth masks as they are useless but this is not the case as hybrid cloth masks (masks with a combination of different fabrics) have been identified to exceed 80% efficiency and 90% efficiency in filtering our particles in the <300 nm and >300 nm range respectively (Konda *et al*., 2020). However, when it comes to cloth masks there are a few guidelines that need to be followed in terms of design to maximize efficiency and these would be using higher thread counts, tight weaves, low porosity materials and combining layers of different materials to ensure both mechanical and electrostatic filtering (Konda *et al*., 2020). In line with this, Universal Face Mask Usage (UFMU) should be widely promoted as it is a double-pronged strategy that protects healthy people from becoming ill in addition to preventing virus transmission

from infected individuals that are asymptomatic, presymptomatic or mildly symptomatic (MacIntyre & Hasanain, 2020).

Social distancing is another commonly employed approach. Different nations are recommending different minimum distances and it varies from 1 m recommended by the WHO up until 2 m recommended by Ireland, New Zealand and UK (Williams, 2020). The variation in recommendations is interesting as all of them claim that their advice is based on scientific evidence. The rationale for social distancing, as the name suggests would be to avoid close contact with individuals that may expel droplets containing infectious SARS-CoV-2 virions but there is the possibility that social distancing may have limited efficacy in real life settings as evidence suggests that the virus may travel up to 4 m via aerosols (Guo *et al*., 2020c). The exact recommended distance is a subject that is best left to experts in their particular nations but a general guideline would be that the public should be given a reference point of sorts to visualize what exactly the recommended distance looks like (Ie: Length of a single bed, length of a small car, three large steps) as this would aid their understanding besides potentially increasing compliance.

In tandem with social distancing, the traditional handshake should be avoided. A previous study reported that the handshake transfers significantly higher numbers of bacteria in comparison to the high five and fist bump (Mela & Whitworth, 2014). Unsurprisingly, increased durations of contact transferred more bacteria regardless of the greeting type but interestingly increased grip strength also increased the transfer of bacteria (Mela & Whitworth, 2014). The study only measured transfer of *Escherichia coli* (*E. coli*) but as the author suggested, similar results can be expected for other pathogens such as Influenza viruses and even SARS-CoV-2. Therefore, avoiding the handshake seems like a pretty good idea at this point and the thought is shared by Dr. Anthony Fauci whom said that not shaking hands would dramatically decrease the spread of coronaviruses and influenza (PTI, 2020). Some alternatives such as the bow, elbow bump, foot stomp, Vulcan and the iconic Namaste have been suggested (Gollom, 2020). Similarly, handshake-free zones (HFZs) have also been recommended but granted the prevalence and popularity of the handshake in society the feasibility of this measure is questionable (Gollom, 2020).

Members of the public need to be responsible and report themselves to local healthcare facilities if they have symptoms of COVID-19 as this not only enables them to receive proper treatment but they can be quarantined away from the general population to curb SARS-CoV-2 transmission. People should perform self-quarantine for at least 14 days if they have mild symptoms or if they are suspected to have been in contact with COVID-19 patients. The reason for the 14-day quarantine would be because most patients develop symptoms within the time period with the median incubation duration being 5.1 days but extended quarantine periods may be necessary in extreme cases (Lauer *et al*., 2020). Individuals should also cooperate with local authorities and provide any relevant information as required because it would aid in tracing new clusters of infection, which if left unchecked may cause a spike in the number of COVID-19 cases.

All the methods described above would be incredibly effective if SARS-CoV-2 transmission occurred only by fomites and droplets but airborne transmission has been projected as the main route of transmission (Zhang *et al*., 2020b). Indeed, SARS-CoV-2 RNA was detected via rRT-PCR at distances of up to 56 m from wards harbouring COVID-19 patients but subsequent analysis of infectivity yielded negative results (Nissen *et al*., 2020). Despite absence of infectivity, it is noteworthy that patients in the said study were in later phases of COVID-19 hence it is possible that the RNA may have been from viral particles inactivated by antibodies. A similar study corroborated and reinforced the stance of airborne transmission as not only was viral RNA detected in air samples

but infectious SARS-CoV-2 virions were also isolated (Santarpia *et al*., 2020). Airborne transmission likely occurs even in the outdoors as presence of SARS-CoV-2 RNA on particulate matter (PM) has been reported (Setti *et al*., 2020). The risk posed by particulate matter for infection by SARS-CoV-2 can be described as being inversely correlated with the diameter of the particle and it has been described as the 'diameter-related effect' (Jiang *et al*., 2020), in which smaller particles such as $PM_{2.5}$ may be more likely to penetrate deeper into the alveolar region containing type II alveolar cells that possess high concentrations of ACE2 (Zou *et al*., 2020).

Transmission by air is particularly troublesome indoors as a lot of homes and buildings employ mechanical ventilation or heating, ventilating and air conditioning (HVAC) systems. These systems primarily aim to control indoor air quality hence the odds of infected individuals sharing SARS-CoV-2 laden air with susceptible people is high (Morawska *et al*., 2020). SARS-CoV-2 demonstrated stability in the form of airborne particles with a half-life of 1.1 to 1.2 hours (Doremalen *et al*., 2020). Interventions to decrease odds of infection via airborne transmission would be increasing ventilation rates, avoiding air recirculation, and employing air cleaning and disinfection services (Morawska *et al*., 2020). Some methods available to inactivate airborne viruses includes usage of heated air, non-thermal plasma, microwave irradiation, far-ultraviolet C (far-UVC) irradiation, low concentrations of ozone (O_3) gas and low concentrations of chlorine dioxide (ClO_2) gas (Wu & Yao, 2014; Ogata *et al*., 2016; Xia *et al*., 2019; Buonanno *et al*., 2020; Dubuis *et al*., 2020; Xia *et al*., 2020b; Yu *et al*., 2020).

Since the pandemic's herald, multiple vaccines have been designed ranging from live inactivated vaccines up until mRNA vaccines (Kaur & Gupta, 2020). Each vaccine type has its own set of pros and cons (Kaur & Gupta, 2020), but they all function to alter COVID-19 in some manner and it is envisaged by many that vaccinations would signal the pandemic's end. Sterilizing immunity at its highest efficiency, precludes pathogen replication in a host thus preventing infection (Lavine *et al*., 2021), but this is not a common phenomenon among vaccines currently available against COVID-19. The reason for absence of sterilizing immunity among SARS-CoV-2 vaccine candidates is not well known but it may be due to the intramuscular administration method which fails to mimic a protective response generated in response to a natural infection (Kim *et al*., 2020).

Sterilizing immunity is a desirable goal for SARS-CoV-2 vaccines but such an ideal is not a necessity to confer meaningful clinical benefits. In the current scenario, the primary issue is not infection by SARS-CoV-2, rather it is occurrence of COVID-19. Vaccinations which decrease disease severity are sufficient as these would greatly aid in preventing healthcare systems from being overwhelmed that may lead to increased case-fatality rates (Bedford *et al*., 2020). For example, rotavirus vaccines which aim to reduce disease severity demonstrated an overall reduction of hospitalizations by 69% for all ages combined (Baker *et al*., 2019). Of interest, vaccine efficacy was 95% among children aged <5 years, which is the high-risk group for rotavirus hospitalization (Annarita *et al*., 2010; Baker *et al*., 2019). Similar findings were observed for influenza vaccinations as a single administration was sufficient to provide infection-permissive immunity as identified by lower lung viral titres and protection against virus-induced inflammation and pathology (Choi *et al*., 2020a).

Despite availability of vaccines, other mitigating measures discussed above should still be implemented due to a few reasons; (1) Time is required for an effective immunological response to occur, (2) Not everyone has access to the vaccine, and (3) As not everyone has equal access, there will be multiple groups in society that would be susceptible to infection by SARS-CoV-2 and developing COVID-19. Vaccinated individuals may asymptomatically transfer the virus to susceptible individuals (Bleier *et al*., 2020). However, severity of COVID-19 among susceptible

individuals would be decreased as the viral dose obtained by them from vaccinated individuals would be lower (Bailey *et al*., 2020). SARS-CoV-2 antibody-resistant variants have been detected at low frequencies among currently circulating viral populations (Weisblum *et al*., 2020). However, sera from vaccinated individuals indicate that this avenue is of low concern as virus neutralization is only reduced and not completely obviated (Williams & Burgers, 2021). Hence, it has been suggested that a higher proportion of the population should be vaccinated to reduce the number of susceptible individuals thus decreasing the opportunities for SARS-CoV-2 to disseminate and mutate further (Williams & Burgers, 2021).

A novel issue that has arisen in recent times and precipitated as of late would be emergence of anti-vaxxers, whom are individuals that strongly believe that vaccines are very harmful (Smith & Reiss, 2020). Six major themes form the bulk of the ethos for anti-vaxxers; (1) Civil Liberties, (2) "Everyone is an Expert", (3) "Science won't save us (nature is better)", (4) "Skew the Science", (5) "They are lying to you", and (6) "They are out to harm you" (Smith & Reiss, 2020). Anti-vaxxers commonly correlate vaccinations to autism, blame vaccines for containing toxins and exaggerate reports of side effects that vaccines may have, such as the increased occurrence of narcolepsy among individuals that received H1N1 vaccines during the 2009 pandemic (Sarkanen *et al*., 2018; Hoffman *et al*., 2019; Boodoosingh *et al*,. 2020). Social media represents the major area in which misinformation pertaining vaccines spreads (Burki, 2020; Johnson *et al*., 2020). Addressing anti-vaxxers is imperative as they are major impediments on the road to herd immunity via vaccination for COVID-19. Similarly, it is possible that in the long term they may end up forming the bulk of population thus outweighing pro-vaccination movements and leading to devastating consequences that would stretch beyond COVID-19, such as that observed with the emergence of anti-maskers as well (Boodoosingh *et al*., 2020). The responsibility of handling anti-vaxxers falls in the hands of educators, mass media, healthcare professionals, regulatory authorities, researchers and religious scholars (Khan *et al*. 2020). Collectively, they shall function to decrease or ideally eliminate misinformation, educate the public about vaccines on multiple areas and debunk religion-based arguments which claim vaccination to be 'un-Christian' and 'un-Islamic' (and presumably other religions) (Boodoosingh *et al*., 2020; Khan *et al*., 2020; Ashton, 2021).

MEASURES TO TAKE IF YOU ARE INFECTED

In this subsection, recommendations provided by the CDC shall be used to conduct a brief discussion on steps that should be taken if one is infected by SARS-CoV-2 (CDC, 2020b). Once one has been confirmed or suspected to have been infected by SARS-CoV-2, the individual should aim to isolate or quarantine him-/herself at home. During the time period of isolation/quarantine which would be about 14 days, contact should be avoided with people as much as possible (CDC, 2020b). If contact is necessary, social distancing should be practiced and masks should be worn at all times. In the event the individual requires groceries, food products or other items, these should be preferably bought online or help should be sought from a family member, friend or anyone else to procure the items. The items should be left outside the doorstep of the residence and the ill individual should take them after the other person has left. These steps collectively decrease the odds of others to be exposed to SARS-CoV-2 that would be expelled by the ill person.

After being exposed to SARS-CoV-2, it is likely that an individual would develop COVID-19. Throughout the duration of quarantine, one should stay in touch with their local physician and update them about one's condition every now and then. However, if emergency warning signs such as breathing difficulties, bluish lips or face, inability to wake or stay awake, new confusion and persistent pain or pressure in the chest appear, emergency medical attention should be sought

(CDC, 2020c), as the aforementioned symptoms indicate lack of oxygen in the body. During the time period of COVID-19, it is recommended to have a diet which is balanced and nourishing as it would aid the body to recover from disease. Indian herbs (Pitchiah *et* al., 2020; Vellingiri *et al*., 2020), Traditional Chinese Medicine (TCM) (Yang *et al*., 2020b), and herbs from diverse geographic locations (Islam *et al*., 2020), have been suggested as potential therapeutics against SARS-CoV-2. The idea sounds attractive but there are concerns surrounding it as these supplements have been viewed as a modifiable risk factor (Young & Zampella, 2020).

It is understandable that not everyone would have an entire residence to themselves and in this case, one should stay in the same room as much as possible. If contact needs to be made with others, masks should be worn at all times. Nevertheless, mask wearing can be avoided if one has breathing issues but, in this scenario, coughs and sneezes should be covered in some other way to prevent dispersion of virus laden droplets. The individual should clean and disinfect 'high touch' areas as per the guidelines discussed in the previous section. Hand hygiene should also be elevated by the ill to minimize or ideally prevent fomite-based transmission. The CDC recommends that hand washing should be done with soap and water for at least 20 seconds after being in a public place, blowing your nose, coughing or sneezing and in the event soap and water are not available a hand sanitizer containing at least 60% alcohol should be utilized and rubbed until the hands feel dry (CDC, 2020a).

The ill individual should refrain from sharing items such as bedding, cups, dishes, drinking glasses, eating utensils or towels with other people in a household to prevent SARS-CoV-2 transmission (CDC, 2020b). The person should wash the aforementioned items thoroughly after using them with soap and water to inactivate the virus. All the cleaning and disinfecting agents discussed in this section are effective against coronaviruses as they work by disrupting the lipid bilayer membrane of coronaviruses which confers them protection from the external environment (Adedokun *et al*., 2020).

CONCLUSION

The current review has provided a comprehensive overview of select risk factors for developing severe COVID-19. Risk factor for severe COVID-19 was defined as factors that affect detection of COVID-19 and/or alter severity in any manner. It was also defined as factors that modulate ACE2 and/or TMPRSS2 in any manner. Discussions were performed from the viewpoints of behavioural, demographic, environmental, genetic and physiological risk factors. Collectively, it would be rather evident that a multitude of variables affect the clinical outcome of a patient.

Nevertheless, identifying the factors can be deemed imperative as these would be points that the global community should cooperate to address and bring the pandemic under control. A discourse was performed on steps that can be performed to break transmission in addition to considering steps that should be taken by one upon being confirmed or suspected as a COVID-19 patient. On a positive light, it is envisaged that COVID-19 should serve as a wakeup call to us that novel pathogens with pandemic potential are always around the corner and it is likely just a matter of time before they find their way into society, yet with adequate collaboration at multiple levels, mankind may just be able to triumph in the evolutionary race between us and pathogens.

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