Exploring the genetics, ecology of SARS-CoV-2 and climatic factors as possible control strategies against COVID-19

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SUMMARY

The world has been thrown into pandemonium due to the recent Coronavirus Disease 19 (COVID-19) pandemic. Early available clinical data have indicated that geriatric persons cum those with comorbidity such as cardiovascular, metabolic and immunological disorders suffered severe form of COVID-19. All countries and territories of the world are currently exploring available strategies to control the pandemic with the hope to significantly minimize its morbidity and mortality rate. This present study critically reviewed available and latest research progress on the genetics and ecology of SARS-CoV-2, as well as the influence of climatic factors on the spread of COVID-19, and thus, discussed how these concepts could be harnessed for COVID-19 control and further scientific advancements in resolving the pandemic.

Keywords: COVID-19, genomics, SARS-CoV-2, control measures.

INTRODUCTION

The world is currently battling with and trying to survive yet another pandemic that threatens human health security. Scientific experiences gained during the 2003 SARS-CoV and recent advances in throughput molecular biology can be harnessed in defeating SARS-CoV-2 transmission and overcoming the ongoing pandemic [1]. Understanding the genetics, ecology and mode of transmission of the SARS-CoV-2 could offer more preventive and control measures against the spread of COVID-19.

First, it is worthy to note that a single SARS-CoV-2 infected individual has the ability to infect approximately three uninfected persons [2, 3]. This occurs through the nano-particles of respiratory droplets which can spread, contaminate surfaces and hands where they remain stable for hours [2,

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3]. The hands now become a mechanical vector. Thus, a potential site to terminate and prevent it from invading the body. However, if the virus is not eliminated at this stage, it can move towards its predilection site (*i.e.* cells of the lungs) where it uses its spikes to dock and attach angiotensin-converting enzyme-2 (ACE-2) as receptors to gain access into epithelial cells of the respiratory tract. At this stage, SARS-CoV-2 compromises innate lung immunity [1]. It then takes advantage of these cells as replication site. The virus regenerates and sheds by disassembling itself and utilizing the machinery of the alveoli cells, precisely Golgi apparatus, to reproduce and repackage itself [1].

The SARS-CoV-2 exists in such a way that as it replicates and disrupts the protective function of the ACE-2 receptor which induces the process of fibrosis (scarring). It has been shown that patients with fatalities associated with SARS-CoV-2 present with a characteristic ground glass effect in their lungs and this sequela impedes efficient oxygenation. As the body tries to compensate for this deficiency, it gradually results to Severe Acute Respiratory Syndrome (SARS), where it becomes impossible for the respiratory system to make available oxygen to the rest of the body (hypoxia) [3]. This ultimately results in multiple organ failure. Based on available clinical data, those susceptible to contracting severe form of SARS-CoV-2 infection include the elderly (>65 years) population, persons with underlying disease conditions (cardiovascular, metabolic, respiratory and immunological disorders), and individuals with blood group A [1-4].

Clinical syndromes associated with SARS-CoV-2 include severe hypertension, cardiac failure and hypokalemia. Laboratory findings of COVID-19 patients have revealed significant lymphocytopenia (especially natural killer cells and T-cells), hypoalbuminemia and anemia. Whereas C-reactive protein, erythrocyte sedimentation rate, lactate dehydrogenase, D-dimer, neutrophils, alanine aminotransferase, aspartate aminotransferase, cardiac biomarkers and procalcitonin were elevated [5].

In order to accurately define suspicious cases of COVID-19, there is need to understand the hallmark of SARS-CoV-2-associated symptoms which include dry cough, fever, myalgia/arthralgia, headache, and gastrointestinal disturbance (in some instances) [6-8].

As at the 2:50PM GMT+1, 3rd April 2020, there were a total of 1039,922 confirmed cases in more than 180 countries and territories with 55170 deaths (5.3 % case fatality rate) and 222,240 recovered persons had been reported by "Worldometer" [10]. Currently, the active COVID-19 cases stand at 388,274 of which 19,659 (5%) of patients are in critical conditions, while 724097 (95%) of patients are in mild conditions.

Currently, there are no definitive antivirals and vaccines, however there are ongoing evaluations of candidate antiviral therapies and vaccines. These include strategies that target blocking SARS-CoV-2 from docking on the ACE-2 receptor; blocking the replication machinery of the virus; blocking the attack and packing of SARS-CoV-2 into alveoli cells; and killing the factory (infected cells) of the virus itself, by using activated natural killer and killer T cells [1, 9].

This present study critically reviewed available and latest research progress of the genetics and ecology of SARS-CoV-2 as well as the influence of climatic factors on the spread of COVID-19, and thus, discussed how these concepts could be harnessed for COVID-19 control and further scientific advancements in resolving the pandemic.

MOLECULAR ORGANIZATION AND GENETICS OF SARS-CoV-2

The genomic sequences of the first SARS-CoV-2 isolate from the person with COVID-19-associated pneumonia in Wuhan revealed a genome size of 29.9 Kilobases (kb) [12]. The virus has single stranded RNA with positive polarity [13]. The genome of the first Wuhan SARS-CoV-2 had 89% nucleotide homology with bat SARS-CoV and 82% with that of human SARS-CoV. For this similarity level with other SARS-CoVs, the new virus was officially referred to SARS-CoV-2 by the World Health Organization (WHO) and CoV study group of the International Committee on Taxonomy of Viruses on 30th January 2020 [14].

The open reading frames (ORFs) of coronaviruses slightly vary across members of the *coronaviridae* family [15]. About 67% of SARS-CoV-2 RNA are mainly located within the 1st ORF and translates the pp1a and pp1ab polyproteins. These encodes sixteen non-structural proteins (NSP). The remaining ORFs code structural and accessory proteins. The remaining part of the genome encodes

nucleocapsid (N) protein, spike (S) glycoprotein, matrix (M) protein, and small envelope (E) protein [16].

It has been reported that the small envelope and nucleocapsid proteins and certain accessory proteins arrests the initial innate immune response during SARS-CoV-2 replication. Worthy of note is the study of Angeletti et al. that reported a mutation in NSP2 and NSP3 of SARS-CoV-2. These essentially play significant roles in the infectiousness and differentiation mechanism of SARS-COV-2 [17].

In another study by Zhang et al., it was revealed that several forms of SARS-CoV-2 mutations exited in COVID-19 patients in China. In addition, virulence mechanisms of CoVs, and by extension SARS-CoV-2 have links to the activities of their non-structural and structural proteins. Among the structural elements of CoVs, the S glycoprotein is key in the pathogenesis of SARS-CoV-2 [18]. This protein has 2 subunits (S1 and S2). The homotrimer structures of S glycoprotein compose of spikes on the SARS-CoV-2 surface, which facilitates attachment to host receptors. On the S2 subunit of SARS-CoV-2 lies the fusion peptide, a transmembrane domain, and cytoplasmic domain which is highly conserved and could be harnessed as novel target for antiviral agents [19].

At the genomic level, SARS-CoV and SARS-CoV-2 have six regions of differences which include; RD1, RD2, RD3, RD4, RD5, and RD6. RD1 to RD3 are partial coding sequence of the orf lab genes, RD4 and RD5 coded for the partial sequence of S gene, while RD6 forms part of the orf7b and orf8 genes coding sequence. Due to the high homology (≥95%) between proteins of SARS-CoV-2 and SARS-CoV, it is believed that there is evolutionary similarity between these two viruses which could provide insight into engineering a candidate vaccine [13, 20, 21].

SARS-CoV-2 pathogenicity and virulence mechanism is believed to be linked to the non-structural and structural proteins by blocking host innate immune response and by facilitating viral assembly and release respectively [19]. Non-structural protein 3 (NSP3) is the largest protein in CoV genome and it contains multiple domain functions needed for replication of coronavirus [21]. According to a recent study, pathogenesis in SARS-CoV-2 is believed to be majorly mediated by mutation in NSP2 and NSP3. Apart from the envelope protein, there were 42 mutations in all the major structural and non-structural proteins of SARS-CoV-2. Mutations were also observed in nucleocapsid protein, ORF1ab polyprotein, matrix protein and spike surface glycoprotein [22]. These however raised the question whether mutations contribute to host tropism, changing antigenicity and rapid global spread [22]. In a recent study, it was observed that COVID-19 has mutated in different patients, leading to division into 6 genotypes [18].

Thus, scientists need to closely monitor the genome of SARS-CoV-2 in order to determine its virulence and possible future mutant strains.

SARS-CoV LIGAND AND ASSOCIATED RECEPTOR

The ACE-2 is a special receptor protein found on the surface of biological membrane of the cells of the heart, lungs, arteries, intestine and the renal tissues [23]. This receptor has been studied to show that asides its usefulness in the regulation of blood pressure, the evolving SARS-CoV-2 and other coronaviruses have also found it useful as a gate way into the human cell with consequential deleterious effect [23]. The virus outer surface is hydrophilic with a lipophilic side on the inside which is why it could be destroyed by detergents [24].

The SARS-CoV-2 invasion into human cells is facilitated by the trans-membrane spike glycoprotein that forms homotrimers distended from the viral external [25]. The S protein contains two functional variants accountable for binding to the human cell receptor (S_1 variant) and fusion of the viral and cellular membranes (S_2 variant). For many CoVs, S is hewed at the border between the S_1 and S_2 variants which remain non-covalently bound in the prefusion conformation [25]. The distal S_1 variant comprises the receptor-binding domains and contributes to stabilization of the prefusion state of the membrane-anchored S_2 variant that comprises the fusion apparatus [25]. For all the coronaviruses, S is further sliced by host proteases at the S_2 site located just upstream of the fusion peptide [25]. This cleavage has been proposed to trigger the protein for membrane fusion through extensive irreversible conformational changes. As a result, CoV entry into susceptible cells is a composite process that entails a concentrated action of receptor-binding

and proteolytic processing of the S protein to promote virus-cell fusion [25].
Different coronaviruses apply dissimilar domains within the S_1 variant to identify a variety of attachment and entry receptors, contingent on the viral specie. Widespread human coronaviruses OC43 and HKU1 attach through the S domain A (S^A) to 5-N-acetyl-9-O-acetyl-sialosides found on glycoproteins and glycolipids at the human cell surface to aid entry into vulnerable cells. SARS-CoV and several SARS-related coronaviruses (SARS-CoV-2) interact directly with ACE-2 through S^B to enter target cells [26].
As the coronavirus S glycoprotein is surface-exposed and mediate entry into human cells, it is the main target of neutralizing antibodies upon infection and the focus of therapeutic and vaccine design. S trimmers are extensively decorated with N-linked glycans that are vital for appropriate folding and to have accessibility to host proteases and neutralizing immunological markers [27].
The amazing structural resemblance and sequence retention among the S glycoproteins of both SARS-CoV and SARS-CoV-2 unequivocally attests to the huge relationship shared by the two species and recognize the human angiotensin-converting enzyme 2 receptor through which humans are invaded. The S protein fits perfectly on the ACE-2 receptor molecule which informs that breakthroughs in combatting the present pandemic is largely dependent on the absolute understanding of the workings of the spike protein and the ACE-2 receptor on the cells of the lower respiratory tract, acting as a docking site. It is assumed that the virus enters the host cell by cellular mediated endocytosis [27].

ECOLOGY AND VECTORS OF SARS-CoV-2

Previously, six CoVs have been identified as human-susceptible virus. Of these, 4 are considered low pathogenic CoVs and cause mild respiratory tract illnesses similar to those of rhinoviruses [12]. The other 2; SARS-CoV and MERS-CoV are highly pathogenic and potentially fatal. SARS-CoV-2 is the seventh discovered member of the family CoVs. Based on virus genome sequencing results and evolutionary analysis, bat has been suspected as reservoir host of the virus. So, SARS-CoV-2 might be transmitted from bats via yet to be confirmed intermediate hosts to infect humans. However, it has been suggested that possible intermediate hosts for SARS-CoV-2 include bamboo rats, pangolins and snakes. These animals might have contracted the virus through saliva, feces and urine of bats [28]. Emerging viruses of the late 21st century use animals as one of the key steps in their emergence process through zoonotic chain of transmission [28]. Indeed, an insight into better control of the spread of SARS-CoV-2 could be achieved through identifying the animal sources of these viruses.

TRANSMISSION MECHANISMS FOR SARS-CoV-2

An elaborate report from China had demonstrated that human-to-human transmission is the major means of acquiring SARS-CoV-2 [29].
Essentially, the primary source of SARS-CoV-2 infection is patients with COVID-19-pneumonia [12]. Earlier researches have confirmed respiratory droplets as means of contracting SARS-CoV-2. However, it has also been demonstrated to be transmitted through aerial droplets and direct intimate contact [28]. Worthy of note is the public health significance of asymptomatic SARS-CoV-2 infected persons in the transmission process [30]. Asymptomatic persons can transmit the pathogen within 14 days after being infected [30]. Another study suggested the possibility of fecal-oral transmission of SARS-CoV-2 [31]. However, food borne acquisition of SARS-CoV-2 from contaminated foods has not been elucidated. Mother-to-child transmission has also been suspected but more studies need to confirm vertical acquisition of SARS-CoV-2 [32]. Of particular importance is the recent findings that indicated aerosol as possible modes of SARS-CoV-2 transmission. The study further elucidated that SARS-CoV-2 can remain infectious in aerosols for 5-8 hours and 5-7 days on fomite surfaces [2]. The WHO suspects the possibility of aerosol transmission based on the report of van Doremalen et al. [2].

SPECIALIZED LABORATORY INVESTIGATIONS FOR SARS CoV-2

There is need for highly sensitive and specific laboratory protocols for COVID-19 diagnostics. The laboratory assays are essential for case detection,

contacts of case tracing, animal reservoir studies, and for infection control measures.

First, the use of viral culture for establishing acute diagnosis is not practical as it takes at least three days for SARS-CoV-2 to cause obvious cytopathic effects in selected cell lines, such as VeroE6 cells. Moreover, isolation of SARS-CoV-2 requires biosafety level-3 facilities which are not available in most healthcare facilities. Serum antibody and antigen detection tests have not yet been validated, and there may be cross-reactivity with SARS-CoV which shares a high degree (~80%) of nucleotide homology with SARS-CoV-2. Because of these limitations, reverse transcription-polymerase chain reaction (RT-PCR) remains the most useful laboratory diagnostic test for COVID-19 worldwide [33].

The availability of the complete genome of SARS-CoV-2 early in the epidemic facilitated the development of specific primers and standardized laboratory protocols for SARS-CoV-2. The protocol of real-time RT-PCR assays which target any of the RdRP, envelope (E), and nucleocapsid (N) genes of SARS-CoV-2 are now available for use [33]. One important thing to consider during test selection is possibility of false positive and negative results due to contaminations, poor and inadequate sampling.

The adoption and use of RNSa dependant Reverse Polymerase (RdRP) based RT-PCR assays has begun in many laboratories worldwide [33]. Initially, SARS-CoV-2 can be identified within the period of 1-2 days in the upper respiratory tract samples before the onset of symptom [34]. There can be persistence of the virus in moderate cases for 7-12 days and even up to 14 days in severe cases [34]. From day 5 after onset, viral RNA has been identified in the stool of about 30% of patients and up to 4-5 weeks in moderate cases. Verification of the significance of fecal viral shedding for transmission still has to be performed [34]. Among COVID-19 patients in Singapore, it was reported that there is a prolonged viral shedding from nasopharyngeal aspirates up to at least 24 days after symptom onset [35]. A recovery convalescent patient shows a long-standing viral shedding with high sputum viral load according to the report from a German study [36]. There can be persistence of viral RNA in body fluids over long periods of time which doesn't necessarily indicate that the person is still infectious [37]. Using viral culture for isolation of viruses is needed to show the virus infectivity [37]. Two asymptomatic cases show infectious virus according to the study by Hoehl et al. [37]. Clearance of SARS-CoV-2 is recommended after at least two (2) upper respiratory tract samples collected at >24-hour intervals are confirmed negative [38]. After the resolution of symptoms in symptomatic patients, at least seven days after onset or more than three days without fever, there should be collections of samples [38]. For persons with asymptomatic SARS-CoV-2 infection, minimum of 14 days is required to be observed after the initial positive test before taken the test to document the virus clearance [38]. The serology tests to record IgG antibody specific to SARS-CoV-2 will be of importance if validated and standardized as indicated in Italy [38]. It is important to use RT-PCR targeting two different genes at different occasions, *e.g.* E-gene and RdRP, for confirmation and discharging patients as negative.

POSSIBLE INFLUENCE OF CERTAIN CLIMATIC FACTORS ON SARS CoV-2 TRANSMISSION

It is a known fact that weather, environmental and climatic conditions greatly affect the emergence and transmission of infectious diseases, including those caused by respiratory tract viruses. Scientists have identified certain factors that contribute to this phenomenon. For some viruses, there are evidence for which climatic factors are most important for their transmission, whereas, for others no extrapolation has been made [39].

In the winter, the outdoor air is colder, and the air is dryer usually both indoors and out. For instance, influenza has been consistently studied in controlled laboratory experiment and has been shown that absolute humidity strongly affects its transmission, with drier conditions being more favorable that humid (moist) in its transmission [39]. Subsequently, this finding correlated with epidemiological patterns of flu epidemic. This suggests that similar mechanisms may be at work for other respiratory viruses. However, there is paucity of specific studies that demonstrated the role of humidity on CoVs transmission. Of note are studies that demonstrated favorable transmission of flu tropics in tropical and subtropical countries [40]. Thus, it is logical to assert that dry cold air in tem-

perate countries disadvantage transmission of flu. However, for CoVs, the significance of this factor is yet to be determined. Another important factor in the winter is that humans spend more time indoors than outdoor. This usually comes with less ventilation and less personal space, probably due to the density of households.

Of particular interest, schools are considered locus of much infectious disease transmission. For instance, higher transmission of respiratory viral infections has been reported during school terms [41]. Indeed, the significance of school terms and holidays are enormous in infection control such measles, flu and chickenpox. However, this is unknown for the SARS-CoV-2. Schools are places were large number of pupils or students converge. This tends to increase chances of rise in classrooms humidity and encourages incubation of pathogens.

The incidence of certain respiratory viruses greatly varied disproportionately across age groups. For instance, few children have been identified as cases of COVID-19 [41]. This may mean children are less susceptible to SARS-CoV-2 infections [42]. In other terms, it may mean that they get milder symptoms when infected, even though infected children are contagious [42]. Hence, concentrating asymptomatic infected children increases the risks of others getting infected. Understanding this is key if scientists and policy makers want to know whether school closures can help control COVID-19 spread, as well as to anticipate how much does school vacation may help reduce the spread of SARS-CoV-2.

Immunologically, it is possible that the immune system of a healthy person to be essentially worse in winter than summer [43]. One report has focused on the impact of melatonin on immune effects and how its module by sunrays. These has been shown to largely depend on seasonally, where more immune function existed during the summer [44]. In another study, it was demonstrated that the levels of vitamin D modulate our immune system in a positive fashion [45]. This vitamin depends on ultraviolet light exposure, which is higher in the summer season than winter.

In fact, this is best evidence for the relevance of vitamin D supplementation to boost immune function as a way to reduce the incidence of acute respiratory viral infection [46]. This is a promising area for more studies on COVID-19 recovery and cure. Although, regardless of seasonal variability, it is expected that viral epidemics rise exponentially, level off, and decline over time. Nonetheless, climatic changes and seasonality could have great impact in the transmission of SARS-CoV-2 infection and the COVID-19 pandemic.

URGENT INTERVENTIONAL RESEARCH NEEDS

Considering the impact of the ongoing COVID-19 pandemic on global economy and health security, scarcity of medical and diagnostic equipment (such as test kits), it is necessary for scientists to delve into fabrication, production and standardization of SARS-CoV-2 rapid diagnostic tests strips and enzyme immunoassay kits (antigen-based ELISA), as adjunctive to the currently available protocols (especially in developing countries).

Bio-informatics analysis and computational biology of SARS-CoV-2 isolates are key. These will help determine the previous structural protein events and possible future mutation using specialized software. Sero-surveys and molecular testing of suspected animals (*e.g.*, bats and snakes) to detect and identify possible reservoir and intermediate hosts of SARS CoV-2. This will largely assist in rationalizing comprehensive control measures through adoption of one health approach. Scientists across all regions should participate in ongoing anti-viral drug evaluations and vaccine clinical trials. This will provide better data on the universal safety and effectiveness of these biological products. Finally, it is necessary to consider comprehensive biophysical evaluations of environmental temperature, humidity, UV, aerosols in the maintenance and transmission of SARS-CoV-2.

CONCLUSION

As the COVID-19 continues to expand, it is crucial for countries and states to expand availability of standardized testing protocols, strictly impose the principle of social distancing, observe regular personal and environmental hygiene. All persons coming from a different nation should strictly be tested and undergo either supervised self-isolation or quarantine. Severely infected persons should be provided with adequate medical assistance.

In consideration of the epidemiological events during the great flu pandemic, it is expected that

SARS-CoV-2 will face low immune attack (high susceptibility), thus transmits and expand swiftly, regardless of seasonality. It is expected that season changes, coordinated laboratory testing and isolation/quarantine and school closures may help in controlling the COVID-19 pandemic, but are unlikely to halt the SARS-CoV-2 transmission. Therefore, there is an urgent need for more effective policies which can serve as adjunctive measures to augment the currently available control measures in order to exponentially minimize the spread of SARS-CoV-2.

Conflict of Interest
None declared.

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