Introduction and Data Analysis
COVID-19 emerged as a novel disease last year and the first confirmed case was reported on 17 Nov 2019 from the Wuhan district of China. The virus implicated was a zoonotic virus which was found to be a close relative of coronavirus RaTG13, found in bats. The similarity between their genetic sequences has been reported to be 96.2%. According to a study done by the University of Texas at El Paso in the US, the novel coronavirus could jump from animals to humans by mutating. It attained the ability to infect human beings by exchanging a gene fragment with another coronavirus that infects pangolins (a scaly mammal). Initially the virus was named as 2019-nCoV, but later it was renamed SARS-CoV-2 by the International Committee on Taxonomy of Viruses due to its significant similarity to SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus).

The virus spread so fast that the disease caused by it (Covid-19) affected humans in more than 180 countries across the world. According to Shrestha et al., an essential mechanism for faster transmission of Covid-19 has been globalization. It can be explained as interconnectedness of people from different countries across the globe through trade and travel which is due to rise in urbanization and the closer integration of the world economy. Along with the spread of COVID-19, it's mortality rate too was quite high. This health emergency, named Covid-19, was declared a global pandemic by WHO on 11th March, 2020. People infected with the virus showed symptoms of respiratory diseases like fever, cough, shortness of breath, tiredness and pneumonia-like disease etc. Besides, symptoms like loss of taste or smell, runny nose, headache, diarrhoea etc have also been reported in some patients. The severity of these symptoms has varied among patients, ranging from mild to severe. Factors like old age increase the risk of serious illness. Medical conditions like heart diseases, hypertension, cancer, diabetes mellitus, asthma, liver disease and others significantly increase mortality among patients with Covid-19. The disease itself could cause olfactory and gustatory dysfunctions, changes in ECG (mostly ST-T abnormalities) etc. The disease has also shown recurrence in some patients which may be due to limited protection by acquired immunity.

Since COVID-19 was a new disease, none of the nations could perceive the potential threat from it. Even though the virus seemed to have originated in China (an eastern country) and spread to different nations simultaneously, the Western world was the first to be severely affected by this outbreak. The map in Figure 1 clearly shows the West being affected much more than the East. Countries like USA, UK, Spain, Germany and France have seen higher death rates despite their strong health systems. Also, a disproportionate number of deaths were observed among healthcare workers from different ethnic minority backgrounds. On the other hand, both infectivity and mortality rates for the disease were substantially lower in the East (Table 1 and Figure 2). Data analysis shows that the
Eastern countries like China, South Korea and India have an infection rate of 0.0065, 0.17% and 0.8%, respectively. However, in France, UK, Spain and US, the percentage infection rate varies from 5.76 to 8.86. Figure 3 exhibits the total number of tests undertaken till 8th March ‘21 by some countries from East as well as West. Almost all the countries have used a combination of RT-PCR and antigen tests (www.ourworldindata.org). It may be argued that the countries in the East did not undertake sufficient tests for detecting SARS-CoV-2. But the COVID-19 death rate/million population substantiates data on %infection rate. This article puts forth some plausible reasons for the differences in susceptibility and severity of Covid-19 between the eastern and the western world.

**Plausible Reasons for Differences in Susceptibility and Severity of Covid-19 Between the Eastern and the Western World**

*Strict measures may have reduced virus evolution and spread in Eastern countries*

By Jan’20, SARS-CoV-2 had already reached countries around the world. None of the countries was prepared for this scale of spread of the novel virus. Due to inadequate information about

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**Table 1. Infection rate and death rate/million population in some countries of East and West.**

| COUNTRY     | POPULATION* | NO. OF INFECTED INDIVIDUALS* | INFECTION RATE (%) | NO. OF DEATHS FROM DISEASE* | DEATH RATE ACCORDING TO OVERALL POPULATION (PER MILLION) |
|-------------|-------------|-----------------------------|--------------------|-----------------------------|--------------------------------------------------------|
| China       | 1439323776  | 89912                       | 0.006              | 4636                        | 3.22                                                   |
| India       | 1380004385  | 11123619                    | 0.8                | 157275                      | 113.97                                                 |
| US          | 331002651   | 29314254                    | 8.86               | 527226                      | 1592.81                                                |
| UK          | 67886011    | 4182009                     | 6.16               | 122953                      | 1811.17                                                |
| Spain       | 46754778    | 3123700                     | 6.68               | 69609                       | 1488.81                                                |
| France      | 65273511    | 3760671                     | 5.76               | 86803                       | 1329.83                                                |
| South Korea | 51269185    | 90028                       | 0.17               | 1605                        | 31.30                                                  |

*Data as on 1st march, 2021; taken from https://www.worldometers.info/.*
this virus as well as the nature, transmission and management of Covid-19, most of the countries could not control it's spread. However, the epidemics in Western countries were ahead of the rest of the world by a few months and were severe too. As a result, most of the globally confirmed COVID-19 cases in 2020 were reported from United States, the UK, Spain, Italy, Germany, and France. Since most of these first world countries have curbed infectious/communicable diseases to a great extent, it is likely that their public health systems failed to identify the potential threat posed by the novel disease. They did not make testing widely available and did not impose physical distancing guidelines early in pandemic. In fact, UK did not impose lockdowns initially in an effort to generate herd immunity. Besides, Western countries could probably not implement strict measures to control the spread of corona virus or were late in putting them into force. Being a zoonotic virus, presence of many hosts at a given time may have led to faster evolution of the virus giving rise to a deadlier strain. This may have led to higher mortality rates in the West.

Taking their learnings from the western world, stricter interventions were imposed by Eastern countries which may have slowed down the evolution of the virus leading to a less deadly variant. Countries like South Korea, Singapore, Vietnam, Taiwan, Hong Kong and India recognized the threat well in advance and took strict measures to curb the spread of Covid-19. In South Korea, Covid cases peaked by Feb, 2020, but country presented the world with one of the most successful models of handling the pandemic. They implemented social distancing and lockdowns in areas with high transmission, extensive testing including drive-through screening tests,
contact tracing and putting their contacts in quarantine.\textsuperscript{14} Vietnam started with community-based programs by case identification, isolation, contact tracing, quarantining contacts, ensuring masks, etc. Hong Kong and Taiwan used similar proactive approaches. India, the second most populous country in the world, went for an early but a stringent lockdown to prepare the necessary health infrastructure (in terms of creating dedicated COVID hospitals, availability of PPE kits, ventilators, oximeters, medicines etc and to create and expand the testing capacity) to deal with Covid-19 and saved millions of lives in the process. These small but firm approaches saved the hospital systems in the East, which cater to much denser populations, from crumbling under pressure of Covid-19 cases and reduced mortality rates.\textsuperscript{15}

**Differences in national policy on BCG vaccination**

The differences with respect to the national policies regarding the Bacillus Calmette-Guérin (BCG) vaccination may have contributed to the differences in the mortality rates in the Eastern countries and the Western world. Countries such as the United States never had a universal BCG vaccination program in place. Map in Figure 4 represents the status of universal BCG vaccination programs worldwide.\textsuperscript{16} It is very clear from the map that most of the countries having high impact of Covid-19 either never had any BCG vaccination programme or discontinued it, most of these being European countries. On the other hand, the countries still using BCG vaccine suffered lesser impact from SARS-CoV-2. Covian et al,\textsuperscript{17} in a study analysed the immunization monitoring data of WHO for comparing the infection and mortality rates due to COVID-19 between countries with or without BCG vaccination in their national policy. They hypothesized that BCG might play a protective role in SARS-CoV-2 infected cases.

BCG vaccine provides immunity against *Mycobacterium tuberculosis* and is prepared from a weakened strain of *M. bovis*. It has been shown to increase the secretion of pro-inflammatory cytokines, specifically IL-1\(\beta\), TNF\(\alpha\) and IL-6 with a vital role in antiviral immunity (Figure 5).\textsuperscript{18, 20} The BCG priming has also been found to cause persistent chromatin conformational changes in the cells of innate and adaptive immunity.
that improve anti-mycobacterial, bacterial, fungal and viral immunity. The vaccine is thought to provide ‘trained immunity’ to create “memory” of a pathogen specifically in cells of innate immunity like macrophages. These cells have Pathogen Recognition Receptors (PRRs) that include Toll-like receptors (TLR), Nucleotide-binding oligomerization domain-like receptors (NLR), C-type lectin receptors (CLR), RIG-1 like receptors (RLR) on their surface. These receptors can detect a battery of pathogen associated molecular patterns (PAMPs) which are conserved molecular structures of pathogens like viral RNAs, bacterial lipopolysaccharide and flagellin etc. These PAMPs may be common across various pathogens. Both Mycobacterium and SARS-CoV-2 are causative agents of respiratory diseases and have also shown similarity in host interaction. It is quite possible that the 2 may be sharing a few PAMPs. That’s how the BCG vaccine may be providing non-specific protection from a wide spectrum of respiratory diseases reportedly reducing the number of cases and mortality to a certain extent.

Presence/absence of frequent exposure to infectious diseases

Lack of exposure to infectious diseases in childhood or throughout adult life could lead to more severe infections to the newly evolving pathogens and an inadequate, poor immune response by the body. The East happens to have dense populous countries with lesser surface areas leading to frequent
spread and transmission of communicable/infectious diseases here, whereas, they are almost absent in the West. However, this exposure to infectious diseases helps develop immunity to other viruses or pathogens in general and provides the ability to the body to put a stronger fight, even when they are absolutely foreign to the body. This happens due to cross reacting antigens. Indians have also been found to have more NK cells which can detect and kill pathogens and terminate diseases at early stages. In a recent study, data from 122 countries was analysed to find correlation between COVID-19/million population, health efficiency, water current score, % rural population, population living in slums and fraction of diarrhoeas. It was found that Covid-19 deaths are lower in countries which have a higher population exposed to a diverse range of microbes. As a result, their microbiome helps in digestion, protection against disease-causing bacteria, regulation of the immune system and production of vitamins. SARS-CoV-2 is a new virus, but perhaps populations of the Eastern countries have better immune responses than the Western ones owing to their exposures to similar diseases and pathogens and hence, reduced mortality rates.

**Mutations in virus genome**

RNA viruses are known to mutate quickly inside their hosts. Most of these mutations are single-letter changes in viruses isolated from different people. In case of SARS-CoV-2, a large number of single-letter (point) mutations have been recorded. It seems that in a bid to adapt to a geographical area, the virus has undergone mutations in the genome. In fact, the virus has been found to be still mutating. Of the more than 2000 mutations detected, the most prominent mutation isolated from samples in USA is D614G where Aspartic acid (D) at 614 position gets replaced by Glycine (G). This mutant was also isolated from Indian samples. Another mutant isolated from Indian samples is P314L. On Dec.15, 2020, a new variant of coronavirus (SARS-CoV-2 VOC 202012/01) has been reported to be identified in Britain. It has been found to be growing much faster in some parts of the country. South Africa (501Y.V2) and Brazil too have identified presence of new variants in their countries. It shows that virus is still mutating and evolving. That is why finding correlation between these mutants and their ability to infect more people is an important subject for investigation.

**Genetic differences in populations in East and West**

I) **ACE receptors:** Coronavirus infects by binding to Angiotensin-converting enzyme 2 (ACE2) receptors, now also known as SARS-CoV-2 receptors, found on the surfaces of cells in CVS, lungs, kidneys and the gut. The activation of ACE2 (MAS/G protein coupled receptors) is responsible for the reduction in acute injuries and inhibition of fibrogenesis of the lungs, thereby, offering protection to the cardiovascular and respiratory system along with the other organs. SARS-CoV-2 virus attacks and gets attached to these receptors through its S spike proteins and these proteins get primed by the serine protease TMPRSS2. This diminishes the expression of ACE2 receptors leading to severe lung damage. Moreover, the ill-effects of angiotensin like causing endothelial injury and thrombotic effects, etc. are not dampened due to hindrance in the work of ACE2 receptors by the virus, which normally do the work of counter-balancing the RAAS (Renin-Angiotensin-Aldosterone-System) axis. Therefore, the observed clinical spectrum of severe respiratory distress, myocardial injury, renal failure, and increased mortality due to SARS-CoV-2 infection results among the subjects with cardiovascular and metabolic diseases, which are more common in the Western population, being a more aged population. In addition to ACE2 receptors, there exists another type of ACE receptor, ACE1. There is presence of D (deletion) allele in them that leads to reduction of the expression of ACE2 genes. This means less infection due to lesser receptors but increased lung damage. Reportedly, Asians have a lower occurrence of the D allele as compared to the Europeans leading to more severe lung infections in them and hence, more deaths. Hence, the involvement of both types of ACE receptors along with some other contributory factors like lifestyle diseases and an aged population might be making the Western populations more susceptible to this novel disease.

II) **MHC:** MHC molecules are one of the essential cell-membrane receptors responsible for antigen recognition by the immune system. Two types of MHC molecules i.e., Class I and Class II present endogenous antigens to CD8+ T cells and exogenous antigens to CD4+ cells, respectively. Small fragments of processed antigens bind to the peptide-binding cleft of MHC molecules and are presented. MHC loci encoding these molecules are highly polymorphic resulting in tremendous diversity of these peptide-binding clefts. These, in turn, take care of all the pathogens existing in the environment. Since exposure and kind of pathogens vary from place to place, there exist geographical differences in MHC molecules of people belonging to different ethnic groups, countries, continents etc. A study on differences in HLA class I alleles in 5 major outbred groups living in USA suggested distinct evolutionary histories of HLA loci in the geographical regions. Another study reported presence of molecular signatures of demographic and selective events in this locus. Despite polymorphism, some of the class I alleles are poorly expressed and others are well expressed. The inadequately expressed class I alleles act as generalists to protect against a wide array of infectious agents, while highly expressed alleles can act as specialists.
to provide protection against new and dangerous pathogens. In fact, pathogen diversity leads to evolution of MHC alleles. The MHC locus is also of interest as there is extensive body of information linking certain HLA alleles to either susceptibility or protection to certain diseases. In case of viral diseases too, occurrence or severity of disease is being associated with presence of certain HLA types, e.g., HLA-A*2301 may increase the risk of seroconversion in human immunodeficiency virus 1 (HIV-1). HLA alleles like HLA-A*0207 and HLA-B*51 have been shown to be linked with increased secondary disease severity among ethnic Thais suffering from dengue. On the other hand, some alleles also impart protection against diseases. HLA DRB1*01 has been found to provide protection by inducing a selective T H cell response against a strongly immunogenic and highly conserved HIV-1 epitope. Similarly, occurrence of HLA-A*02, and HLA-Cw*15 haplotypes are protected epitope. In case of SARS-CoV, individuals with haplotypes HLA-B*07, HLA-B*46, HLA-DRB1*12, and HLA-Cw*08, have been found to be more susceptible to coronavirus infection, whereas HLA-DRB1*03, HLA-A*02, and HLA-Cw*15 haplotypes are protected from SARS-CoV infection. Similarly, occurrence of MERS-CoV infection has been linked to alleles HLA-DRB1*11 and HLA-DQB1*02.

There is likelihood that some HLA alleles of patients may play a role in regard to disease severity and clinical outcome of patients with COVID-19. Usually, MHC class I molecules are involved in antigen presentation of viruses. However, in some patients of Covid-19, MHC class II has also been found to present antigenic fragments to CD4 + T cells. de Sousa et al. tried to study as to how variants in the SARS-CoV-2 genome may change peptide binding to the most frequent MHC class I and -II alleles in Africa, Asia and Europe C4. They hypothesised that a single mutation in the wild type sequence of SARS-CoV-2 could influence the peptide binding of SARS-CoV-2 variants to MHC class II, but not to MHC class I alleles. Accordingly, MHC class II alleles may select for viral variants and subsequently shape the quality and quantity of cellular immune responses against SARS-CoV-2. In another study, Nguyen et al. found that HLA-B*4601 had the fewest predicted binding peptides for SARS-CoV-2, suggesting that individuals with this allele may be particularly vulnerable to COVID-19, as they were previously shown to be for SARS C5. Conversely, HLAB*15:03 showed the greatest capacity to present highly conserved SARS-CoV-2 peptides that are shared among common human coronaviruses, suggesting that it could enable cross-protective T-cell-based immunity. Both the studies recommended that HLA typing must be paired with COVID-19 testing.

**Conclusion**

In general, COVID-19 has been disastrous for the world, but more so for specific regions of the world than the others. In this article, various reasons have been explored to understand this difference. It is clear that a combination of reasons might be responsible for the different behaviour of the virus in different places. Hence, there is a need to carry systematic studies on these aspects. The data so obtained would help in predicting the clinical outcome of patients with Covid-19 and accordingly help in prioritizing the treatment modalities. It may also give an insight into the differences in the infectivity and mortality seen in the eastern and the western world.

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