Comparative Analysis of Susceptibility and Severity of COVID-19 in Countries from the Eastern and the Western World Till March ‘21

Microbiology Insights
Volume 14: 1–8
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DOI: 10.1177/11786361211041367
SAGE

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ABSTRACT: Majority of the world’s human population today is affected by Covid-19. The disease has not only exhibited differences in susceptibility among people of different countries, but also the mortality rate. In general, Western world has been reporting a greater number of infected cases than eastern countries. Even the mortality rates are quite high there. The aim of this study was to analyse the data available on the infectivity and mortality rates of Covid-19 in different countries till March’21 and then reviewed the literature to find reasons for the differences in susceptibility and severity in eastern and western countries. The reasons for the observed differences may be: (i) Eastern countries followed stricter modalities and got grace period to create better healthcare facilities to tackle COVID-19. This probably also slowed the transmission of virus and its evolution, (ii) Vaccination policies in the east may have provided some immunity due to cross reactivity, (iii) Frequent exposure to infections at young age in eastern countries might be helping in better immunity, (iv) Mutations in viral genome may be geography based and (v) Genetic differences in the immune system of the hosts with respect to ACE receptors and MHC may be playing an important role. In this article, an attempt has been made to put forth and discuss these plausible reasons along with suitable evidences. These findings may help in future research on the diagnosis, treatment and prevention of Covid-19.

KEYWORDS: SARS-CoV-2, Covid-19, pandemic, immunity, histocompatibility antigens, ACE-2 receptors, western world

RECEIVED: December 19, 2020. **ACCEPTED:** July 27, 2021.

TYPE: Review

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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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%.[1] 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).[2] 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).[3]

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,[4] 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.[5] 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.[5,6] The disease itself could cause olfactory and gustatory dysfunctions, changes in ECG (mostly ST-T abnormalities) etc.[7,8] The disease has also shown recurrence in some patients which may be due to limited protection by acquired immunity.[9]

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.[10] 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

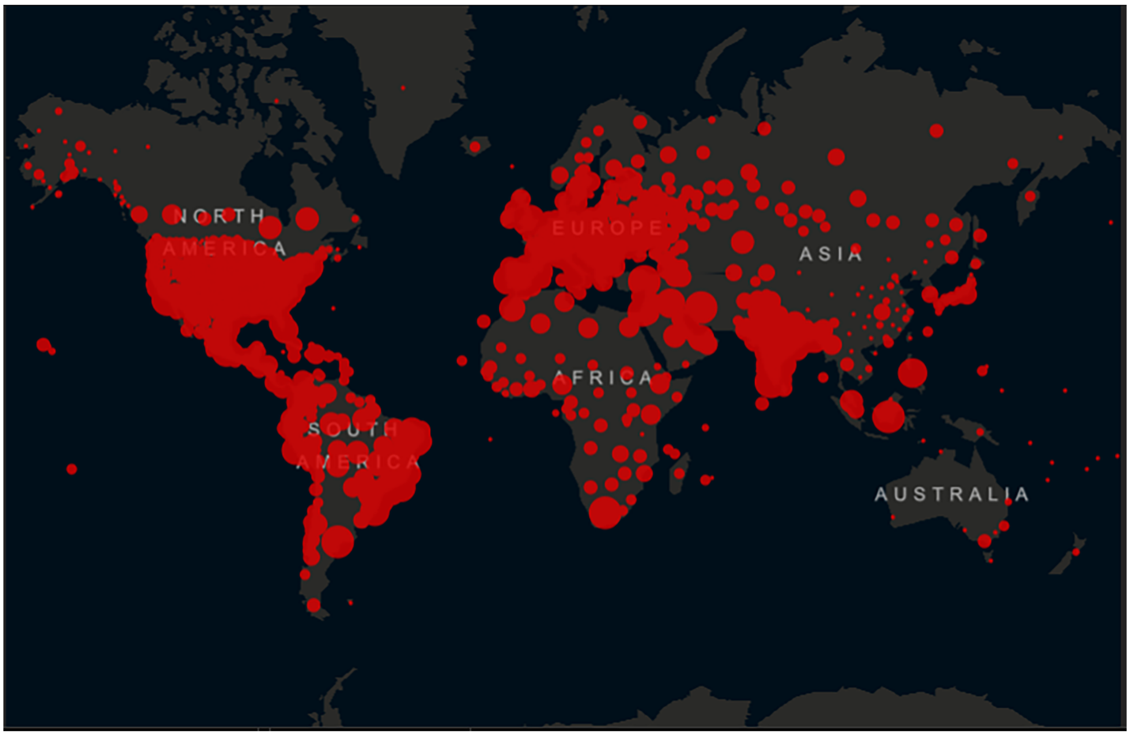

Figure 1. Map showing effect of Covid-19 on countries lying in various geographical zones.
Still of the COVID-19 Dashboard by CSSE at John Hopkins University; https://coronavirus.jhu.edu/map.html.

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	1 439 323 776	89 912	0.006	4636	3.22
India	1 380 004 385	11 123 619	0.8	157 275	113.97
US	331 002 651	29 314 254	8.86	527 226	1592.81
UK	67 886 011	4 182 009	6.16	122 953	1811.17
Spain	46 754 778	3 123 700	6.68	69 609	1488.81
France	65 273 511	3 760 671	5.76	86 803	1329.83
South Korea	51 269 185	90 028	0.17	1605	31.30

*Data as on 1st march, 2021; taken from https://www.worldometers.info/.

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

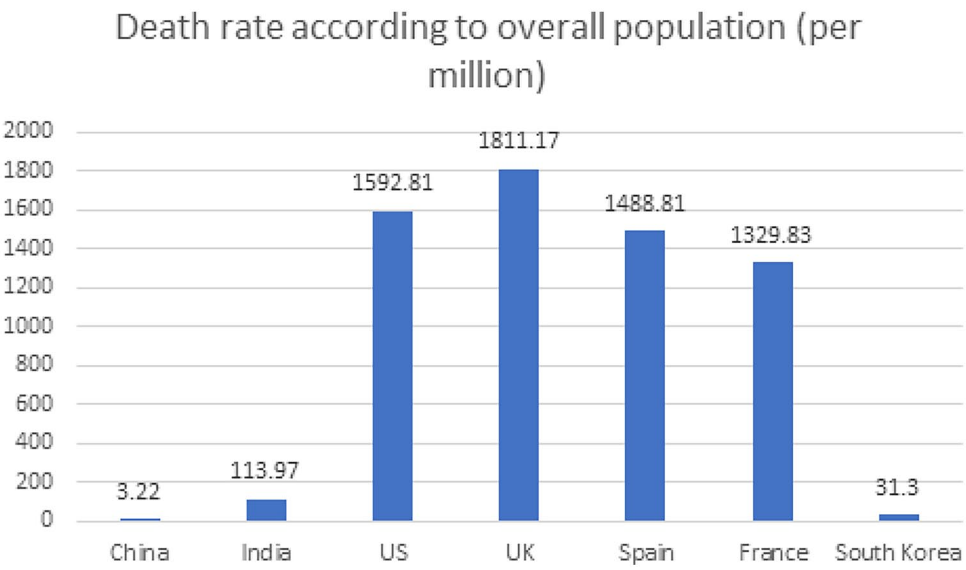

Figure 2. Bar chart showing death rate/million population due to COVID-19, in different countries.

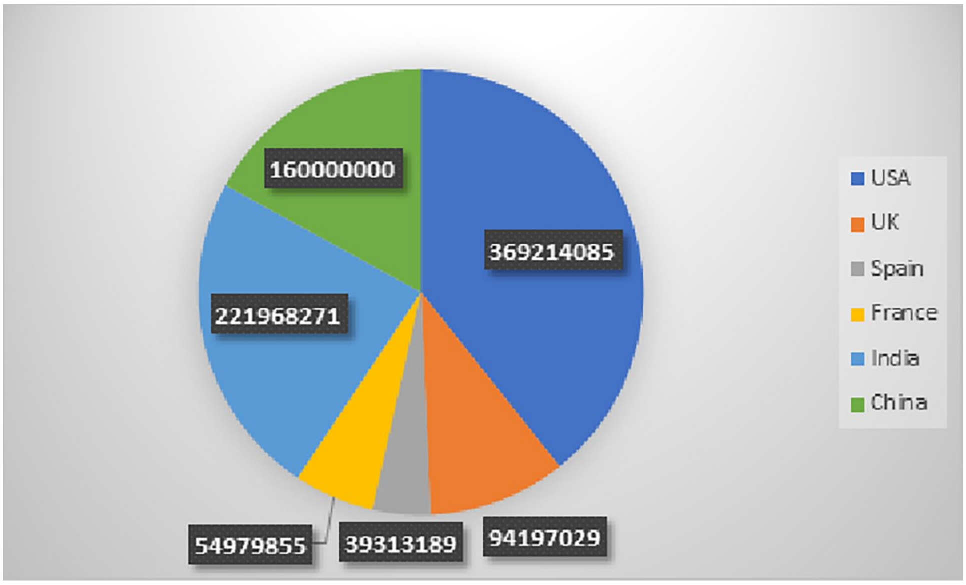

Figure 3. Pie chart representing the total no. of COVID-19 tests undertaken in different countries till 8th March, '21 (Information on testing in South Korea could not be found till 8th March '21); taken from https://www.statista.com/.

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.[11] 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.[12] In fact, UK did not impose lockdowns initially in an effort to generate herd immunity.[13] 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,

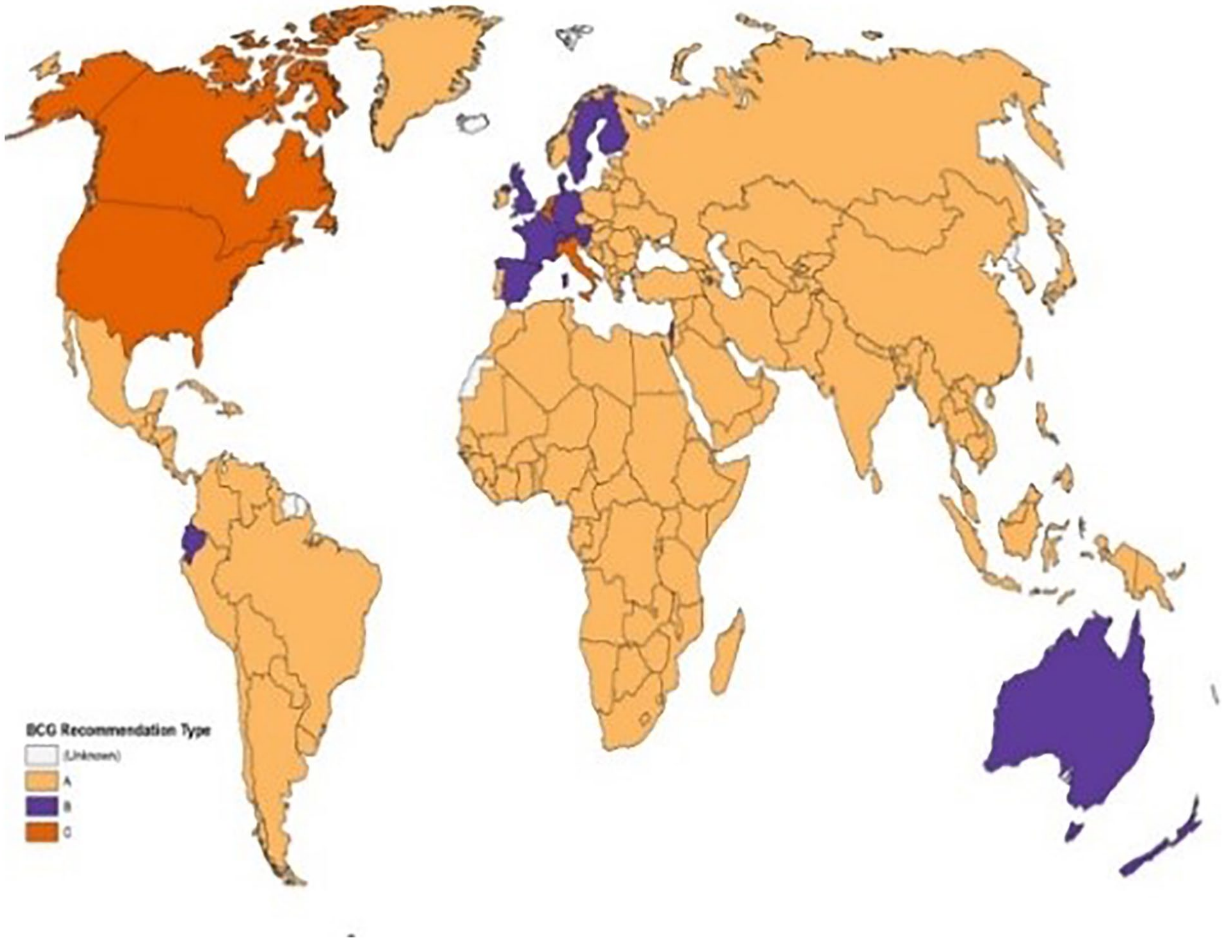

Figure 4. World map showing the status of BCG vaccination programme across the world. Reprinted from Zwerling.[16]
A (Yellow): The country currently has universal BCG vaccination program.
B (Violet): The country used to recommend BCG vaccination for everyone, but currently does not.
C (Orange): The country never had universal BCG vaccination programs.

contact tracing and putting their contacts in quarantine.[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, oxymeters, 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.[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.[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,[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-1β, TNFα and IL-6 with a vital role in antiviral immunity (Figure 5).[18-20] The BCG priming has also been found to cause persistent chromatin conformational changes in the cells of innate and adaptive immunity

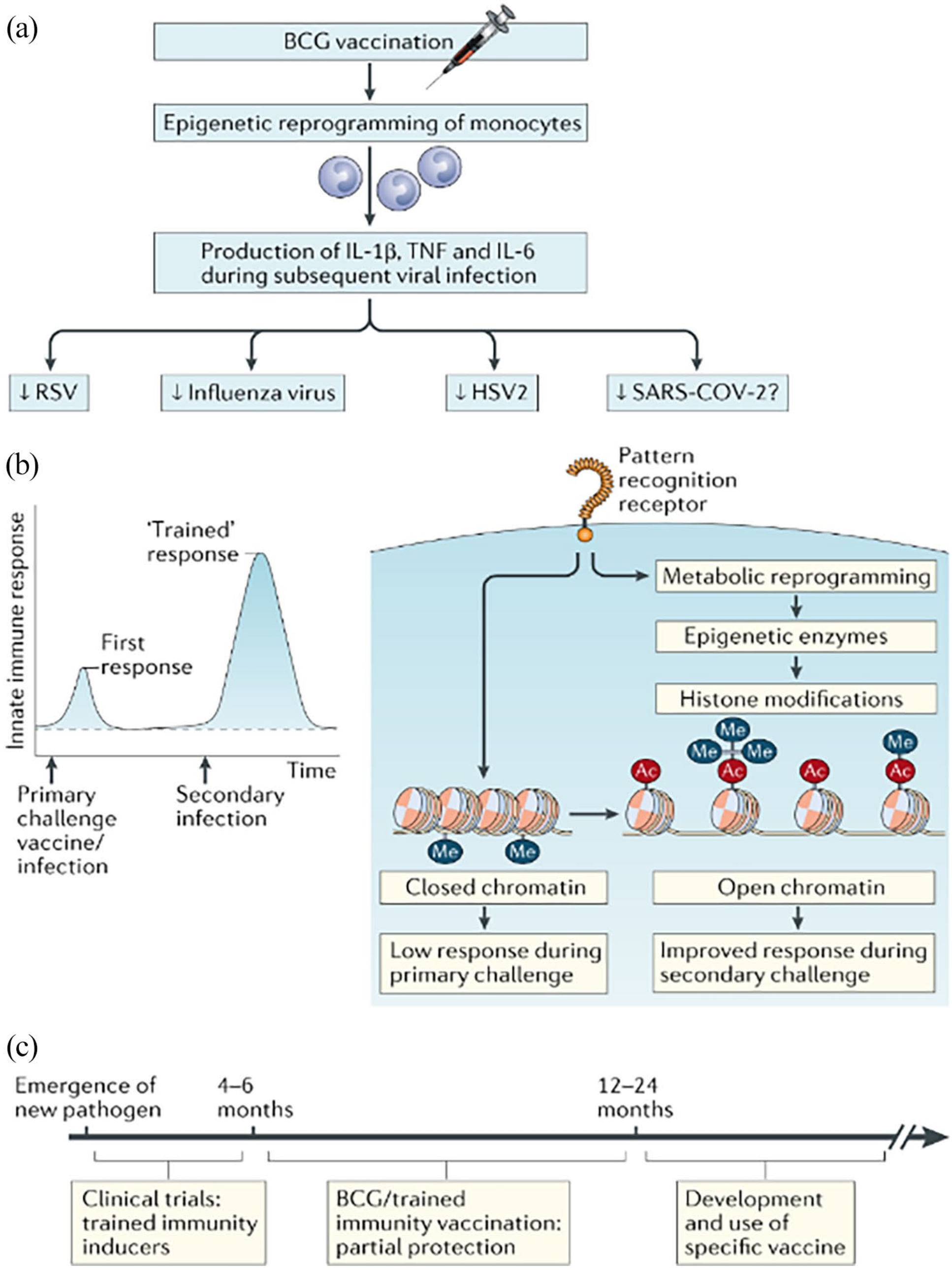

Figure 5. Role of BCG in generating immune response. Reprinted from O'Neil and Netea.[20]

that improve anti-mycobacterial, bacterial, fungal and viral immunity.[21] The vaccine is thought to provide 'trained immunity' to create "memory" of a pathogen specifically in cells of innate immunity like macrophages.[22] 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[23] and have also shown similarity in host interaction.[24] 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.[25]

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.[26] 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.[27] In a recent study, data from 122 countries was analysed to find coorelation between COVID-19/million population, health efficiency, water current score, % rural population, population living in slums and fraction of diarrohes.[28] 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.[29] 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.[1] 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.[30] 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.[30]

   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[27,30,31] 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.[32] Another study reported presence of molecular signatures of demographic and selective events in this locus.[33] 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.[34] In fact, pathogen diversity leads to evolution of MHC alleles.[35]

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).[36] 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.[37] On the other hand, some alleles also impart protection against diseases. HLA DRB1*01 has been found to provide protection by inducing a selective TH cell response against a strongly immunogenic and highly conserved HIV-1 epitope.[36] In case of SARS-CoV, individuals with haplotypes HLA-B* 07, HLA-B* 46, HLA-DRB1* 12,[38,39] and HLA-Cw* 08,[40] 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.[41] Similarly, occurrence of MERS-CoV infection has been linked to alleles HLA-DRB1* 11 and HLA-DQB1* 02.[42]

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[43] 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[44] 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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REFERENCES

1. Gordon DE, Jang GM, Bouhaddou M, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature*. 2020;583:459-468.
2. How coronavirus jumped from animals to humans decoded. The Economic Times, e-paper. 2020. Accessed February 20, 2021. https://m.economictimes.com/news/science/how-coronavirus-jumped-from-animals-to-humans-decoded/articleshow/76104187.cms
3. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020;395:565-574.
4. Shrestha N, Shad MY, Ulvi O, et al. The impact of COVID-19 on globalization. *One Health*. 2020;11:100180.
5. Coronavirus disease 2019 (COVID-19). Accessed February 22, 2021. https://www.mayoclinic.org/diseases-conditions/coronavirus/symptoms-causes/syc-20479963
6. Mehraeen E, Karimi A, Barzegary A, et al. Predictors of mortality in patients with COVID-19-a systematic review. *Eur J Integr Med*. 2020;40:101226-101226.
7. Mehraeen E, Behnezhad F, Salehi MA, Noori T, Harandi H, SeyedAlinaghi S. Olfactory and gustatory dysfunctions due to the coronavirus disease (COVID-19): a review of current evidence. *Eur Arch Otorhinolaryngol*. 2021;278:307-312.
8. Mehraeen E, Seyed Alinaghi SA, Nowroozi A, et al. A systematic review of ECG findings in patients with COVID-19. *Indian Heart J*. 2020;72:500-507.
9. SeyedAlinaghi S, Oliaei S, Kianzad S, et al. Reinfection risk of novel coronavirus (COVID-19): a systematic review of current evidence. *World J Virol*. 2020;9:79-90.
10. Khunti K, Singh AK, Pareek M, Hanif W. Is ethnicity linked to incidence or outcomes of covid-19? *BMJ*. 2020;369:m1548.
11. Li D, Lau C-S. Combatting COVID-19: east meets west. *Br J Gen Pract*. 2021;70:e442-e443.
12. Blumenthal D, Fowler EJ, Abrams M, Collins SR. Covid-19—implications for the health care system. *New Engl J Med*. 2020;383:1483-1488.
13. Lee A, Morling J. COVID19: the need for public health in a time of emergency. *Public Health*. 2020;182:188-189.
14. Dighe A, Cattarino L, Cuomo-Dannenburg G, et al. Response to COVID-19 in South Korea and implications for lifting stringent interventions. *BMC Med*. 2020;18:321.
15. Shokoohi M, Osooli M, Stranges S. COVID-19 Pandemic: what can the west learn from the east? *Int J Health Policy Manage*. 2020;9:439-438.
16. Zwerling A, Behr MA, Verma A, Brewer TF, Menzies D, Pai M. The BCG World Atlas: a database of global BCG vaccination policies and practices. *PLoS Med*. 2011;8:e1001012.
17. Covián C, Retamal-Díaz A, Bueno SM, Kalergis AM. Could BCG vaccination induce protective trained immunity for SARS-CoV-2? *Front Immunol*. 2020;11:970.
18. Miller A, Reandelar MJ, Fasciglione K, Roumenova V, Li Y, Otazu GH. Correlation between universal BCG vaccination policy and reduced mortality for COVID-19. Preprint. MedRxiv 2020.
19. Kleinnijenhuis J, Quintin J, Preijers F, et al. Bacille Calmette-Guerin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes. *Proc Natl Acad Sci U S A*. 2012;109:17537-17542.

20. O'Neill LA, Netea MG. BCG-induced trained immunity: can it offer protection against COVID-19? *Nat Rev Immunol*. 2020;20:335-337.
21. Hegarty PK, Kamat AM, Zafirakis H, Dinardo A. BCG vaccination may be protective against Covid-19. Accessed November 25, 2020. https://sostelemedicina.ucv.ve/covid19/manuales/La%20vacuna%20BCG%20puede%20proteger%20contra%20Covid-19.pdf.
22. Chinnaswamy S. SARS-CoV-2 infection in India bucks the trend: trained innate immunity? *Am J Hum Biol*. 2020;e23504:1-25.
23. Ahluwalia P, Ahluwalia M, Vaibhav K, et al. Infections of the lung: a predictive, preventive and personalized perspective through the lens of evolution, the emergence of SARS-CoV-2 and its pathogenesis. *EPMA J*. 2020;11:1-21.
24. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science*. 2020;367:1444-1448.
25. Sala G, Miyakawa T. Association of BCG vaccination policy with prevalence and mortality of COVID-19. Accessed November 30, 2020. https://covid-19.conacyt.mx/jspui/bitstream/1000/2623/1/1102214.pdf.
26. Yamamoto N, Bauer G. Apparent difference in fatalities between central Europe and East Asia due to SARS-COV-2 and COVID-19: four hypotheses for possible explanation. *Med Hypothesis*. 2020;144:110160.
27. Jain VK, Iyengar K, Vaish A, Vaishya R. Differential mortality in COVID-19 patients from India and western countries. *Diabetes Metab Syndr Clin Res Rev*. 2020;14:1037-1041.
28. Kumar P, Chander B. COVID 19 mortality: probable role of microbiome to explain disparity. *Med Hypothesis*. 2020;144:110209.
29. New Variant of coronavirus identified in Britain. Accessed February 21, 2020. https://health.economictimes.indiatimes.com/news/industry/new-variant-of-coronavirus-identified-in-britain/79731913.
30. Samavati L, Uhal BD. ACE2, much more than just a receptor for SARS-COV-2. *Front Cell Infect Microbiol*. 2020;10:317.
31. Delanghe JR, Speeckaert MM, De Buyzere ML. The Host's angiotensin-converting enzyme polymorphism may explain epidemiological findings in COVID-19 infections. *Clin Chim Acta*. 2020;505:192-193.
32. Cao K, Hollenbach J, Shi X, Shi W, Chopek M, Fernández-Viña MA. Analysis of the frequencies of HLA-A, B, and C alleles and haplotypes in the five major ethnic groups of the United States reveals high levels of diversity in these loci and contrasting distribution patterns in these populations. *Hum Immunol*. 2001;62:1009-1030.
33. Buhler S, Sanchez-Mazas A. HLA DNA sequence variation among human populations: molecular signatures of demographic and selective events. *PLoS One*. 2011;6:e14643.
34. Kaufman J. Generalists and specialists: a new view of how MHC class I molecules fight infectious pathogens. *Trends Immunol*. 2018;39:367-379.
35. Manczinger M, Boross G, Kemény L, et al. Pathogen diversity drives the evolution of generalist MHC-II alleles in human populations. *PLoS Biol*. 2019;17:e3000131.
36. MacDonald KS, Fowke KR, Kimani J, et al. Influence of HLA supertypes on susceptibility and resistance to human immunodeficiency virus type 1 infection. *J Infect Dis*. 2000;181:1581-1589.
37. Stephens HA, Klaythong R, Sirikong M, et al. HLA-A and -B allele associations with secondary dengue virus infections correlate with disease severity and the infecting viral serotype in ethnic Thais. *Tissue Antigens*. 2002;60:309-318.
38. Lin M, Tseng H-K, Trejaut JA, et al. Association of HLA class I with severe acute respiratory syndrome coronavirus infection. *BMC Med Genet*. 2003;4:9.
39. Keicho N, Itoyama S, Kashiwase K, et al. Association of human leukocyte antigen class II alleles with severe acute respiratory syndrome in the Vietnamese population. *Hum Immunol*. 2009;70:527-531.
40. Chen YM, Liang SY, Shih YP, et al. Epidemiological and genetic correlates of severe acute respiratory syndrome coronavirus infection in the hospital with the highest nosocomial infection rate in Taiwan in 2003. *J Clin Microbiol*. 2006;44:359-365.
41. Wang SF, Chen KH, Chen M, et al. Human-leukocyte antigen class I Cw 1502 and class II DR 0301 genotypes are associated with resistance to severe acute respiratory syndrome (SARS) infection. *Viral Immunol*. 2011;24:421-426.
42. Hajeer AH, Balkhy H, Johani S, Yousef MZ, Arabi Y. Association of human leukocyte antigen class II alleles with severe Middle East respiratory syndrome-coronavirus infection. *Ann Thorac Med*. 2016;11:211-213.
43. de Sousa E, Ligeiro D, Lérias JR, et al. Mortality in COVID-19 disease patients: correlating the association of major histocompatibility complex (MHC) with severe acute respiratory syndrome 2 (SARS-CoV-2) variants. *Internet J Infect Dis*. 2020;98:454-459.
44. Nguyen A, David JK, Maden SK, et al. Human leukocyte antigen susceptibility map for severe acute respiratory syndrome Coronavirus 2. *J Virol*. 2020;94:e00510-20.