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Review Article

COVID-19: global pandemic with divergent waves: an exigent public health concern worldwide with special context to Indian scenario

Shehna Sharaf[1], Faisal Moossa Athikkavil[2], Shiny Deena Varghese[1], Sreelekshmi Sreekumar[1], Reshmi Ramakrishnan[1], Jeslin Varghese[1], Lakshmi Sree Dharan Pillai[1]*, Saikant Regidi[1], Abi Santosh Aprem[1]

[1]Corporate Research and Development Centre, HLL Lifecare Ltd., Government of India Enterprise, Akkulam, Thiruvananthapuram, Kerala, India
[2]Department of Biotechnology, University of Calicut, Kerala, India

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***Correspondence:**
Dr. Lakshmi Sree Dharan Pillai,
E-mail: lakshmideependran08@gmail.com

ABSTRACT

The review discusses, how the COVID-19 virus evolved to the present form, genome organization and genetic variation of SARS- CoV-2 prevalent globally with special emphasis on Indian strains, a comparison of the first vs. second wave in terms of infectivity and transmission patterns. The population impacted, importance of surveillance, study of genetic variants of COVID-19 virus, development of diagnostics developed in First and second waves of infection and preventive measures like physical means, vaccine administration and treatment strategies using different classes of anti-viral, anti-inflammatory, antibiotic and corticosteroid drugs. The study used the detailed and qualitative online research. The literature studies were conducted to explore the havoc of the COVID-19 Pandemic from the very beginning era to current and future repercussions in worldwide with special context to India. The idea of our work is to be on a high alert and vigilant in the constant studying of the varying characteristics of the pandemic and to produce resources and be able to modify treatment methodologies quickly, if needed, and disseminate our work to the scientific world and community as soon as possible for coordinating a global action to cut off the inevitable future waves of this pandemic. Securing vaccine is the most concern, along with the strategies that could be forward to strengthen the health care system. This paper gives insight by warning the third wave, unless taken utmost care by each individual, national as well international organization could be catastrophic to the entire World.

Keywords: Transmission, Mutant viral strains, SARS-CoV-2, Anti-viral, Anti-inflammatory

INTRODUCTION

Pandemics are never a new term as it was there earlier and will exist in the future too if not looked upon. From the onset of the 21st century, we have witnessed several emanations and outbreaks of multiple zoonotic pandemics and infectious diseases which are caused by bacteria, viruses, and several other organisms that are transferred from animals to human beings.[1,2]

Since 2000 we have been troubled with three pandemics, namely severe acute respiratory syndrome (SARS) in 2003, H1N1 swine flu in 2009 and, now novel coronavirus-COVID-19.[3,4] SARS-CoV-2 also known as covid19 virus is a zoonotic pathogenic viral disease of bat origin as it could be the possible primary reservoir, however intermediate root of origin and further transfer to humans was in doubt or unknown.[5,6]

SARS-CoV-2 pandemic emanation to the present

The onset of SARS-CoV-2 (novel coronavirus) started on December, 2019 as zoonotic transmission from in Wuhan, China, which is also considered as the epicenter for the

virus outbreak.[7] This new pandemic was named as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, Covid19) as it shared around ~ 89% homology with a category of SARS-like Coronaviruses of bats in China (genus Beta coronavirus).[8,9] The First sequence to be shared of Covid19 on the National Center for Biotechnology Information (NCBI-GenBank) was with the accession id NC_045512.2 (NCBI Curated and Updated). The virus induced a series of symptoms in which the prime immediate mortality factors were septic shock, multiple organ dysfunction and, ARDS (acute respiratory distress syndrome).[10] Subsequently, the highly contagious transmission between humans was also a key factor in declaring this viral disease as a global pandemic (WHO). Epidemiological reports suggest the most affected ones are elderly and the mortality rate is higher as compared to children.[11,12] Approximately around 200 countries and territories are under this viral attack and as of May 14th, 2021, after the first and second wave, around 160 million cases along with 3.33 million deaths have been reported worldwide and are subjected to increase further rapidly as stated by the centre for systems science and engineering (CSSE) at John Hopkins University.[13,14]

First wave vs. second wave: how different?

In India the initial cases were reported from Kerala state, among the passengers who returned back from Wuhan, China on the 30th January & 3rd February 2020.[15] Further, two more cases were reported between the Indian returnees from Italy and Dubai and the cases began to increase slowly. On 18th June 2020, India reported 11,000 cases and the following two months, it added on about an average of new 35,000 plus cases every day. The first wave of the covid19 virus spike was seen in 2020 September which decreased gradually. Nearly after six months the coronavirus cases in India started to climb in early March 2021, marking the onset of the pandemic covid19's second wave within the country. During the second wave, India confirmed about 22,000 on March 10th 2021 with an average of 18,000 cases per day and in the next 30 days, the daily average rose sharply over 3,90,000 cases creating havoc in the country. Experts state that the second wave's faster spreading nature accounts for such a steep increase of cases across the country. Presently India overtook all the other countries, and emerged as one of the worst hit nation of the second wave of coronavirus.[16] Several countries have observed a two-wave pattern in the COVID-19 pandemic cases.[17] The data reports suggests that the characteristics nature and the way virus attacks do vary between the two waves and there is also a slight variation in the age group and severity of the illness.[18,19] The most common indications were mentioned in (Figure 1, Table 1).[20,21] Furthermore, early reports states that the asymptomatic cases are higher in the second wave the genetic double mutant variant has more transmissibility rate.[22]

The prime victims of this pandemic still continue to be the older population as they are the most vulnerable ones. However, a slight increase has been seen in younger age people getting infected with the coronavirus. The percentage of the affected cases are depicted in the (Table

Table 1: Covid-19: first wave vs. second wave.

Profile	First wave	Second wave
Mortality	Older people >50 years of age	Under 45 years of age
Number of positive cases	Older people >50 years of age	Under 45 years+ children
Average age of Patients	Mainly 50+	Mainly 49+
Infection among 30-45 years of age	21%	21%
Infection under 30 years of age	31%	32%
Hospitalization Requirement age 0-19	4.2%	5.8%
Hospitalization Requirement age 20 -39	23.7%	25.5%

Genome organization - novel coronavirus

SARS-CoV-2, a single stranded positive sense RNA virus of 26 to 32 kb with 6 to 14 open reading frames, use its spike protein to bind with ACE 2 which is primed by the host serine transmembrane protease TMPRSS2 cleave the viral proteins that helps to engage and bring the virus into the cell through receptor mediated endocytosis by cathepsin L which cause rapid infection which can lead to exacerbated immune responses based on the level of immune mediators and hence the complication varies in individuals and hence the transmission of the virus which leads to the mutant variants.[23-27]

Global mutant variants

Like all viruses, SARS-CoV-2 rack up mutations at a slower rate that leads to the changes in the genetic code over time as it replicates with an inherent repair mechanism due to higher genomic nucleotide substitution and recombination rates. As per the SARS-CoV-2 Interagency Group (SIG), Centers for Disease Control and Prevention, three set of variants being monitored based on the global impact as variants of interest, concern and high consequence.[28,29]

Variants in play in India

As per the recent studies new specific variant B.1.617, found in Vidarbha region of Maharashtra, detected with double mutations, E484Q and L452R similar to the

lineage B.1.1.7 from United Kingdom and B.1.351 from South Africa in key areas make the spike protein more infectious which could be able to escape the immune system.[30]

Table 2: Genetic variants correspond with specified lineage, spike protein substitutions with the name of the strain and country first detected.

Name (lineage)	Spike Protein Substitutions	Name (next strain)	First detected
B.1.526	(L5F*), T95I, D253G, (S477N*), (E484K*), D614G, (A701V*)	20C/ S:484K	United States (New York) – November 2020
B.1.526.1	D80G, Δ144, F157S, L452R, D614G, (T791I*), (T859N*), D950H	20C	United States(New York) –October 2020
B.1.525	A67V, Δ69/70, Δ144, E484K, D614G, Q677H, F888L	20A/ S:484K	United Kingdom/Nigeria– December2020
P.2	E484K, (F565L*), D614G,V1176F	20J	Brazil - April2020
B.1.617	L452R,E484Q, D614G	20A	India -February2021
B.1.617.1	(T95I), G142D, E154K, L452R, E484Q, D614G,P681R,Q1071H	20A/ S:154K	India -December 2020
B.1.617.2	T19R, (G142D), Δ156, Δ157, R158G, L452R, T478K, D614G, P681R, D950N	20A/ S:478K	India -December 2020
B.1.617.3	T19R, G142D, L452R, E484Q, D614G, P681R, D950N	20A	India -October2020
B.1.1.7	Δ69/70, Δ144, (E484K*), (S494P*), N501Y, A570D, D614G, P681H, T716I, S982A, D1118H(K1191N*)	20I/ 501Y.V1	United Kingdom-December 2020
P.1	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I	20J/501Y.V3	Japan/ Brazil- January 2021
B.1.351	D80A, D215G, Δ241/242/243, K417N, E484K, N501Y, D614G, A701V	20H/501.V2	South Africa-October 2020 and later in United Kingdom January 2021
B.1.427	L452R, D614G	20C/S:452R	United States-(California)-February 2021
B.1.429	S13I, W152C, L452R, D614G	20C/S:452R	United States-(California)-February 2021

Other variant with fast-transmission emerged in the United Kingdom, called B 1.1.7 that has been found to be present in large numbers in northern India, could also be a possible impact for the quick rise in cases (Table 3-5).

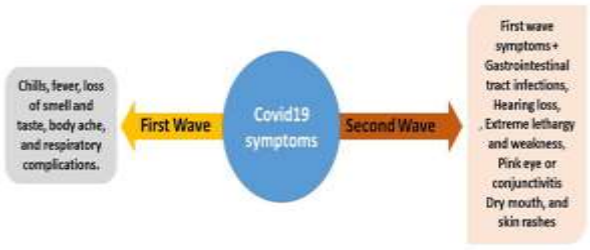

Figure 1: COVID-19 Symptoms, first wave vs. second wave.

Importance of surveillance and study of genetic variants of COVID-19 virus

The genomic epidemiology is also a developing field in the mitigation and control of the SARS-CoV-2 outbreak. Thousands of changes in the genome have already been reported with a potential to increase transmission among public. India has submitted more than 60,000 SARS-CoV-2 viral genomes via many labs in the country.[34] The presence of novel coronavirus genetic variants among patients may also make an impact on the performance of diagnostic tests. Some false results will occur even when very accurate SARS-CoV-2 tests are being used. This novel coronavirus mutations and its impact on testing has been strictly tracked by the FDA throughout. The molecular surveillance based on real-time viral genomic data is really important for a timely management of the pandemic.

Development of diagnostics

As per WHO guidelines, validated RT-PCR assay should target at least two regions of SARS- CoV-2 viral genome. Most of the kit manufactures used viral gene targets nucleocapsid (N), envelope (E), spike (S), and RNA dependent RNA polymerase (RdRP) genes in the RT-PCR test kits which are highly sensitive and specific. Hence, globally Nucleic acid amplification tests (NAAT) based RT-PCR technique is currently a gold standard test used for routine confirmation of cases of COVID-19.

Preventive strategies

Self-awareness of preventive measures including adoption of a healthy lifestyle and diet, physical exercise, optimal metabolic control, vitamin D intake is very important to prevent spread of disease. The management of COVID-19 include improving hygiene level, identification infected persons and proper isolation, lockdown and wearing Masks.[35]

Table 3: Most prevalent SARS-CoV-2 mutations in India: summary of the top 61 non-synonymous Indian variants of SARS-CoV-2 (arranged by prevalence) listing the genomic mutation and the corresponding amino acid change in the associated viral protein.

Variant	Protein_position	Protein_mutation	Prevalence	Percentage
A23403G	S:614	D614G	4430	82.29
C14408T	ORF1b:314	P314L	4375	81.12
G28881A	N:203	R203K	2096	38.87
G28883C	N:204	G204R	2086	38.68
G28882A	N:203	R203K	2086	38.68
G25563T	ORF3a:57	Q57H	1256	23.29
C5700A	ORF1a:1812	A1812D	1209	22.42
C28854T	N:194	S194L	1096	20.32
G11083T	ORF1a:3606	L3606F	761	14.11
C13730T	ORF1b:88	A88V	655	12.15
C28311T	N:13	P13L	650	12.05
C6312A	ORF1a:2016	T2016K	593	11
C8917T	ORF1a:2884	F2884F	447	8.29
C6573T	ORF1a:2103	S2103F	301	5.58
G9389A	ORF1a:3042	D3042N	300	5.56
C25528T	ORF3a:46	L46F	295	5.47
T1947C	ORF1a:561	V561A	234	4.34
C9693T	ORF1a:3143	A3143V	215	3.99
C3267T	ORF1a:1001	T1001I	192	3.56
G26173T	ORF3a:261	E261*	190	3.52
C21034T	ORF1b:2523	L2523F	187	3.47
G28183T	ORF8:97	S97I	187	3.47
T28277C	N:2	S2P	163	3.02
C1218T	ORF1a:318	S318L	121	2.24

Vaccines

Vaccination helps to prevent infection or to reduce disease severity, shedding of virus meanwhile controlling transmission and disease outbreak.[36] Vaccines such as Moderna's mRNA-1273, Astra Zeneca's AZD1222, Johnson and Johnson's Ad26.COV2.S and Pfizer/BioNTech's Comirnaty are authorized vaccines and recommended for prevention of COVID-19 virus infection.[37]

Vaccines reduce mortality and taking vaccine is more cost effective than treatment. Inovio pharmaceuticals company has developed a DNA vaccine named INO-4800 to prevent COVID-19 infection which induces T cell activation by delivering DNA plasmids that express S protein of coronavirus.[38] One of the mRNA vaccine Moderna (vaccine mRNA-1273) is a lipid nanoparticle-encapsulated, nucleoside-modified vaccine that encode S-glycoprotein stabilized in its prefusion conformation.

Oxford AstraZeneca COVID19 vaccine, sold with other names such as Covishield and Vaxzevria, is developed by Oxford university and AstraZeneca. It is an adenovirus vector vaccine achieving humoral responses against spike glycoprotein receptor binding domain of COVID-19 virus by day 28 as well as T-cell responses.

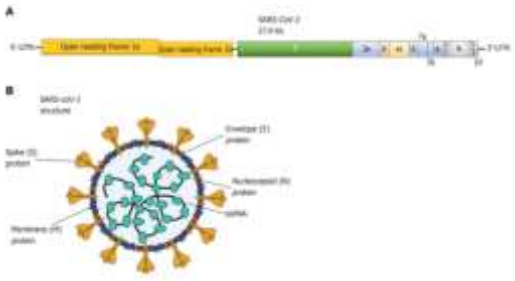

Figure 2: A) Representation of the genomic organization of SARS-CoV-2; B) Diagram of the structural features of SARS-CoV-2.

The vaccine consist of an mRNA drug material that is incorporated into lipid nanoparticles (LNPs) which contains three commercially available lipids such as cholesterol, DSPC and polyethylene glycol PEG 2000 DMG (dimyristoyl glycerol) and SM-102.

Wuhan institute of biological products and institute of medical biology, Chinese academy of medical sciences are prime developers of inactivated virus vaccines. Protein subunit vaccines are full length recombinant coronavirus glycoprotein nanoparticle vaccine adjuvant with Matrix M ™ adjuvant. As a simplified vaccine delivery method, dissolvable microneedle patches are to be considered as a possible ticket for future pandemic coronavirus infections.

Treatment options of 1st And 2nd wave

The patients with early disease benefit more when treated with antiviral agents, hence timing of the treatment is very crucial.

Table 4: Most prevalent SARS-CoV-2 mutations in India: summary of the top 61 non-synonymous Indian variants of SARS-CoV-2 (arranged by prevalence) listing the genomic mutation and the corresponding amino acid change in the associated viral protein.

Variant	Protein_position	Protein_mutation	Prevalence	Percentage
G21724T	S:54	L54F	115	2.13
G28878A	N:202	S202N	104	1.93
A4372G	ORF1a:1369	G1369G	103	1.91
T28144C	ORF8:84	L84S	103	1.91
G29474T	N:401	D401Y	93	1.72
A21551T	ORF1b:2695	N2695L	87	1.61
A21550C	ORF1b:2695	N2695L	87	1.61
C10815T	ORF1a:3517	S3517F	84	1.56
C6310A	ORF1a:2015	S2015R	80	1.48
A2292C	ORF1a:676	Q676P	74	1.37
C18568T	ORF1b:1701	L1701F	73	1.35
C16726T	ORF1b:1087	H1087Y	71	1.32
C21575T	S:5	L5F	70	1.3
G23593T	S:677	Q677H	70	1.3
G11417T	ORF1a:3718	V3718F	67	1.24
G1820A	ORF1a:519	G519S	63	1.17
C20384T	ORF1b:2306	A2306V	61	1.13
G3871T	ORF1a:1202	K1202N	60	1.11
C19862T	ORF1b:2132	A2132V	58	1.08
G8371T	ORF1a:2702	Q2702H	58	1.08
C26447T	E:68	S68F	58	1.08
T25556G	ORF3a:55	V55G	58	1.08
G21974T	S:138	D138Y	56	1.04
C23604A	S:681	P681H	53	0.98

The patients with severe and late disease may benefit from anti-inflammatory drugs also.[39,40] Several traditional medicines could also be used for treatment of COVID-19 and studies were conducted in elucidating the medicinal value of herbal medicines as well the molecular targets for the new developing drugs as in (Figure 3, Table 6).

Drugs and vaccines in trial

Anti-Covid oral drugs-2-DG developed by Govt. of India found the efficacy of the 2-DG drug against SARS –CoV-2 based on the preliminary experiments inside the lab and DCGI authorized to direct the phase II clinical trials. The trials exhibited significant signs of recovery in patients. Following the effective phase-II trials in the middle of 2020, the 2-DG undergo phase-IIa/phase-IIb trials, at hospitals conducted on 110 patients and received approval for Phase-III trials by DCGI in November 2020. Molnupiravir is an experimental oral antiviral originally developed to treat influenza can be used against SARS-COV-2 by inhibition of RNA-dependent-RNA polymerase. The Phase III clinical trials was started on May 2021 by Yashoda hospital in tie up with Natco pharma who received DCGI approval for oral administration for patients with mild and moderate symptoms.

Nasal spray vaccine shows promise in animal trials and clinical trial by Bharat biotech

Based on the reports from Lancaster university in England and Texas Biomedical Research Institute in San Antonio, a nasal spray vaccine showed strong effect against SARS-CoV2 on animals tested with two doses with reduced inflammation and lung damage by the production of antibodies and T cell responses. The Bharat biotech is aiming the first intranasal vaccine in India and had signed an agreement in association with virologics, at the Washington university school of medicine in St. Louis, US.

Table 5: Most prevalent SARS-CoV-2 mutations in India: summary of the top 61 non-synonymous Indian variants of SARS-CoV-2 (arranged by prevalence) listing the genomic mutation and the corresponding amino acid change in the associated viral protein.

Variant	Protein_position	Protein_mutation	Prevalence	Percentage
G28899T	N:209	R209I	53	0.98
G28209C	ORF8:106	E106Q	52	0.96
C26060T	ORF3a:223	T223I	52	0.96
T8022G	ORF1a:2586	V2586G	52	0.96
G28221T	ORF8:110	E110*	47	0.87
C11195T	ORF1a:3644	L3644F	47	0.87
C19154T	ORF1b:1896	T1896I	46	0.85
C6027T	ORF1a:1921	P1921L	44	0.82
T22882G	S:440	N440K	43	0.8
C22227T	S:222	A222V	5	0.09
G23012A	S:484	E484K	3	0.06
A23063T	S:501	N501Y	2	0.04
G22992A	S:477	S477N	1	0.02

Table 6: Drugs used for the treatment of COVID-19.

Drug	Company	Initial target	Mode of action	Mode of administration
Antiviral drugs				
Remdesivir	Gilead	Ebola	Nucleotide analogue	intravenous
Chloroquine/hydroxyl-chloroquine (aralen/plaquenil)	Sanofi	Malaria	Heme polymerase inhibitor	Oral
Favipiravir (avigan)	Fujifilm	Influenza	RNA polymerase inhibitor	Oral
Umifenovir (arbidol)	Pharmstandard	Influenza	Inhibits membrane fusion (entry)	Oral
Camostat	Ono Pharmaceutical	Experimental	Protease inhibitor	Oral
Ribavirin	Bausch Health	Hepatitis C	Lower respiratory tract infection due to RSV	Inhalation
Lopinavir-ritonavir	Abbott	HIV	Inhibits 3CLpro	Oral
Anti-inflammatory drugs				
Interferon alfa-2b		Hepatitis C	Immune modulator	Sub-cutaneous
Tocilizumab (Actemra)	Roche	Rheumatoid arthritis	IL-6R Ab	intravenous
Sarilumab (Kevzara)	Sanofi	Rheumatoid arthritis	IL-6R Ab	intravenous
Baricitinib (Olumiant)	Eli Lilly	Rheumatoid arthritis	Inhibition of JAK	Oral

Three waves of the COVID-19 pandemic

We have already experienced high death toll and severe after effect of the COVID-19 even after clinically cured.[41]

The first wave has affected the most vulnerable sections of the population: the old, sick and the immune-compromised. The second wave started when the epidemic has spread into the general population, who do not have protective antibodies against the pathogen. The second wave affected those who suffer in the medium-

terms due to measures taken to limit the spread of COVID-19, includes those with delayed presenting to health care due to fear, progressive diseases and it includes those who delay presenting to healthcare facilities for fear of COVID-19 infection and those missed the regular screening. Whereas, the third wave is expected to be on the next generation and it is clear that the third wave of this Covid19 virus is inevitable as when this wave will come and for how long could not be predicted. The second and the possible third waves of the infection is usually due to the strains that under gone mutation which have the capability to escape immunity offered.[42,43]

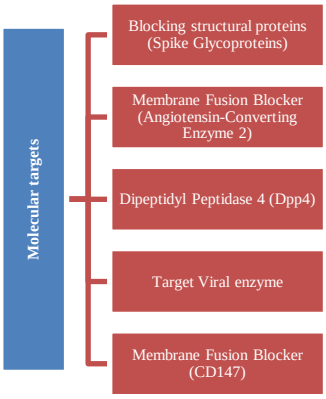

Figure 3: Molecular targets for new developing drugs against SARS-CoV-2.

Possibilities of the third wave and repercussions

Being prepared for the third COVID-19 wave hitting us is crucial. While securing vaccine is the most concern, along with the strategies that could be forward to strengthen the health care system. Experts opined that the third wave of COVID-19 will hit children in a big way and it is time for both the central and state governments to chalk out strategies. The third wave, when it hits developing countries like Africa, Asia and South America, could be the deadliest yet. Govt. of India explained that a third wave depends on how effectively all the guidelines are followed and implemented. The strategies to control the possibility of third wave of COVID-19 pandemic include screening, containment or suppression and mitigation by improving overall health; by early detection, and by improving quality of life, treatment as well recovery. The foremost primary prevention strategy is vaccination, to be taken against any infectious diseases which have been one of the greatest successes in medicine.

CONCLUSION

The point of our work is to be on a high alert and vigilant in the constant studying of the varying characteristics of the pandemic and be able to modify treatment methodologies quickly, if needed, and disseminate our work to the scientific world and community as soon as possible for coordinating a global action to cut off the inevitable future waves of this pandemic.

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