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A RECENT REVIEW ON ETIOLOGY AND MANAGEMENT OF COVID-19 PANDEMIC

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ABSTRACT

Coronavirus disease 2019(COVID-19) is a global, ongoing pandemic since its initial detection in Wuhan, China, in December 2019. Currently, 178,701,170 confirmed cases all across the world with 3,877,316 deaths itself speak of its significant spread and deadly impacts on the human race. The absence of specific drugs defined treatment protocol, and time-tested vaccine to treat or prevent COVID-19 has accelerated drug repurposing efforts. SAR-CoV-2 vaccines are in the development process. A cocktail of existing antiviral medications like experimental antiviral remdesivir, antimalarials hydroxychloroquine/chloroquine, and a combination of HIV drugs Kaletra (lopinavir and ritonavir) and other combinations including interferon beta-1a are being tested in clinical trials. A comprehensive investigation on SARS-CoV-2, mode of transmission, and the promising molecules with their mode of action and status in clinical trials is highlighted in the article.

Keywords: Coronavirus, COVID-19, SARSE-CoV-2, Drugs, Vaccines.

I. INTRODUCTION

Throughout history, there have been several pandemic diseases; the more notable and recent ones caused by viruses include the influenza pandemic (Spanish flu) in 1918 and another by the influenza virus H1N1 in 2009. There have been incidences of SARS-CoV (member of the Beta-coronavirus subgroup) in Guangdong province of China (2003) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in Saudi Arabian nationals (2012). Similar to SARS-coronavirus, patients infected with MERS-coronavirus suffered pneumonia, followed by ARDS and renal failure. The COVID-19 outbreak by the new coronavirus strain was recognized as a pandemic by the World Health Organization (WHO) on March 11, 2020, after, a cluster of cases of pneumonia reported in Wuhan, China in December 2019, confirmed to be associated with a novel coronavirus, nCoV, later named as SARS-CoV-2.

The novel coronavirus is a previously unidentified strain of coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the World Health Organization (WHO). It is an enveloped, positive-sense, single-stranded RNA β-coronavirus which targets cells through the viral structural spike (S) protein that binds to the angiotensin-converting enzyme 2 (ACE2). Upon receptor binding, the virus particle uses host cell receptors and endosomes to enter cells. It is primarily spread between humans through small droplets from the nose or mouth when an infected person coughs or sneezes. Hence what sets it apart from the rest of RNA viruses is its high infection rate which has been facilitated by extensive globalization activities.

II. EPIDEMIOLOGY

178,701,170 confirmed cases of COVID-19, including 3,877,316 deaths globally were reported by World Health Organization (WHO) on 23rd June 2021. As of 21st June 2021, a total of 2,414,347,324 vaccine doses have been administered.

Table 1: Country wise data of confirmed cases and deaths [1]

Country	Confirmed Cases	Deaths	Vaccine doses administered
United States of America	33230655	597037	317983185
India	29977861	389302	261740273

Brazil	17966831	502586	78583450
Russian Federation	5350919	130347	32831196
The United Kingdom	4640511	127981	71672208
France	5650315	109879	41912459
Italy	4253460	127291	42952982
Spain	3764651	80689	31493943
Germany	3722782	90472	62132301
Colombia	3968405	100582	13167044

III. SARS-COV-2 VIRUS DESCRIPTION

Coronaviruses belong to the genus Coronavirus, Coronaviridae family in the Nidovirales order. Coronavirus gets its name from the crown-like spikes on the outer surface of the virus. These are minute in size (65 -125nm in diameter) and contain a single-stranded RNA as genetic material, sizes ranging from 26 to 32kbs in length [2].

SARS-CoV-2, causative pathogen of COVID-19 is identified as the seventh type of coronavirus to infect humans [3]. Other coronaviruses are known to cause human disease, including severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) with a high mortality rate [4]. According to the genome characteristics, coronavirus is classified into four genera: α-CoV, β-CoV, γ-CoV, and δ-CoV. Deep sequencing indicated that the novel coronavirus identified from COVID-19 patients' lower respiratory tract samples belongs to the -CoV family, which has crown-like features under electron microscopy.. They have enveloped viruses with a single-strand, positive-sense RNA genome, which is the largest known genome for an RNA virus [5].

All coronaviruses have the same genomic organisation and expression pattern, with 16 nonstructural proteins encoded by two huge overlapping reading frames (ORF1a/b), followed by ORFs for four key structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) [6]. Spike protein plays an essential role in binding to receptors and is critical for determining host tropism and transmission capacity [7]. It is functionally divided into the S1 domain and S2 domain, responsible for receptor binding and cell membrane fusion respectively [8].

Phylogenetic analysis of the evolution history showed that SARS-CoV-2 shared a closer sequence homology toward the genomes of SARS-CoV than to that of MERS-CoV [9]. SARS-CoV-2 is highly similar to a bat coronavirus RaTG13 (the strain of Rhinolophus affinis bat), with an overall genome sequence identity of 96.2% [10], indicating that bat, which was discovered to be the natural reservoir host of various SARS-related coronaviruses [11], may also be the original host of SARS-CoV-2. The intermediate host in the process of transmission remains uncertain.

However, the alarming fact about SARs COV-2, what makes it more fatal than its SARS-COV is the structure of the SARS-CoV-2 spike protein revealed in cryogenic electron microscopy (Cryo-EM), it has 10 to 20-fold higher binding affinity to human angiotensin-converting enzyme 2 (ACE2) than SARS-CoV does [12].

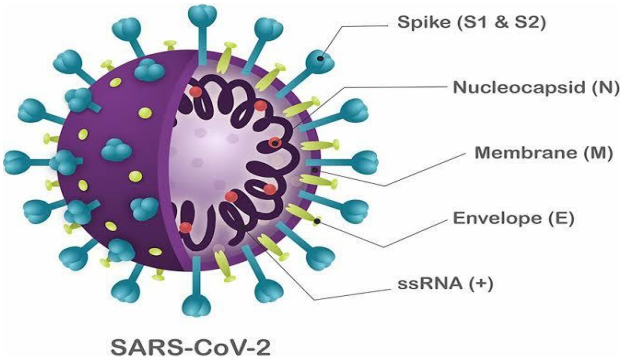

Figure -1: Schematic Diagram Of Sars-Cov-2 Structure

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IV. VIRAL PATHOGENICITY

All coronaviruses contain specific genes in the open reading frame (ORF1) downstream regions that write proteins for viral replication, nucleocapsid, and spikes formation [13]. The conjugated protein spikes on the outer surface of coronaviruses help within the attachment and entry of the virus to host cells. The receptor-binding domain (RBD) that is loosely connected among viruses helps the virus to infect multiple hosts [14,15]. Other coronaviruses largely acknowledge aminopeptidases or carbohydrates as a key receptor that helps within the entry to the human cells whereas SARS-CoV and MERS-CoV acknowledge exopeptidase [16]. The mechanism of entry of a coronavirus depends upon cellular proteases that embrace, human airway trypsin-like enzyme (HAT), cathepsins, and transmembrane enzyme amino acid two (TMPRSS2) that facilitate to separate the spike protein and establish more penetration changes [17,18]. SARS-coronavirus need angiotensin-converting catalyst two (ACE2) of the host cell as a key receptor [14,16].

The virus begins its life cycle once the S protein binds to the cellular receptor ACE2. Once receptor binding occurs, conformation amendment within the S protein happens that facilitates viral envelope fusion with the cell wall through the endosomal pathway. Then SARS-CoV-2 releases polymer into the host cell. Genomic polymer is translated into virus replicase polyproteins pp1a and 1ab (these area units the multifunctional proteins concerned within the transcription and replication of viral RNAs) that area unit then cleaved into little products by viral proteinases. The enzyme produces a series of subgenomic mRNAs by discontinuous transcription that finally translated them into relevant viral proteins. viral proteins and genomic polymer area unit later on assembled into virions within the Endoplasmic reticulum and Golgi then transported via vesicles and free out of the cell. The entire mechanism of pathogenicity of SARS-COV-2, from attachment to replication is well mentioned in figure [19].

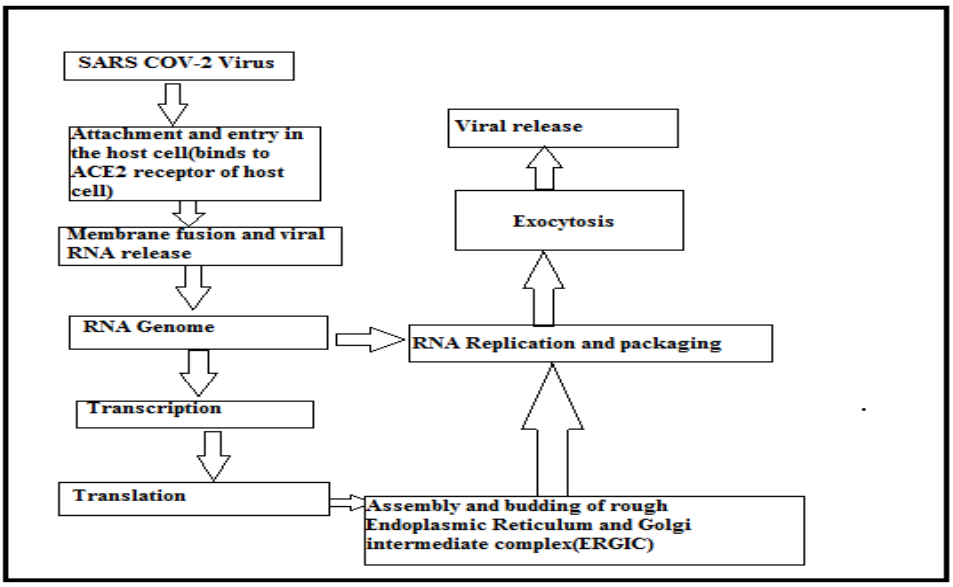

Figure 2: Schematic diagram of LIFE CYCLE OF SARS-COV-2 IN HOST CELLS. ACE2, angiotensin-converting enzyme 2; ERGIC, ER–Golgi Intermediate complex

V. TRANSMISSION OF SARS-COV-2

Several new SARS-CoV-2 cases in association with the Huanan market in Wuhan [20] recommended an animal host may be known as a supply of virus transmission. Bats are probably the host for their antecedent SARS-CoV to that they're identical with. Bat coronavirus RaTG13 may be a SARS-like beta-coronavirus that infects the horseshoe bat Rhinolophus affinis and is that the nearest acknowledged relative of SARS-CoV-2 [21, 22]. Though RaTG13 is more or less ninety-six similar to SARS-CoV-2, indicating that it cannot effectively bind to human ACE2 [22]. Besides, whereas there's no animal CoV quite about to SARS-CoV-2, the vary of the CoVs is greatly undersampled in bats and different animals [23,24]. Within the S1–S2 junction of the CoV mutations (two spike protein junction), insertions and removal of nucleotides occur [23].

A standard evolutionary cycle can result in a polybasic cleavage location. so as for the precursor virus to get the polybase site of cleavage and therefore the spike protein mutations necessary for the human binding of ACE2, it will possibly need an animal host with a large population density (for natural selection to occur effectively) and an ACE2 gene close to that present in human [25]. The SARS-CoV-2 ascendant has most likely jumped to humans, gaining the mentioned genomic options by evolving throughout unrecognized human-to-human transmission. Such diversifications allowed the pandemic of the sickness once it's been noninheritable. It was suspected that direct contact with host animals or consumption of untamed animals could also be the most route of SARS-CoV-2 transmission. The infection is primarily thought to transmit from human to human among people close (about half a dozen feet) with one another through direct contact and droplets. Such droplets could fall or be indrawn by a cough or sternutation onto the mouths or throats of close folks. Moreover, it's been rumored that folks are acknowledged to be a lot of infectious once they are most (sickest) symptomatic. Besides, a person could get SARS-CoV-2 by contacting a surface or entity contaminated with the virus by rubbing ears, nose, and perhaps eyes when direct contact. The SARS-CoV-2 virus in a number of the infected populations 'community spread' seems to be current quickly and sustainably among people [26].

WHO ARE AT RISK?

The individuals who are more susceptible to severe disease:

1. Elderly patients (>65years of age)
2. People with underlying diseases.

Underlying health conditions that increase susceptibility [25,26]:

1. Arterial Hypertension
2. COPD (Chronic Obstructive Pulmonary Disease)
3. Type 2 Diabetes
4. Cardiovascular disease
5. Cerebrovascular disease

SYMPTOMS:

Table 2: Commonly observed signs and symptoms in COVID 19 infection [31]

Disease	Common symptoms	Uncommon symptoms	Symptoms in severe disease
Covid-19	Fever	Headache	Difficulty in walking
	Dry cough	Loss of smell	Confusion
	Fatigue	Nasal congestion	Bluish face or lips
		Sore throat	Coughing up blood
		Coughing up sputum	Persistent chest pain
		Shortness in breath	Kidney failure
		Pain in muscle or joints	
		Chills	High fever
		Nausea and vomiting	
		Diarrhea	

The common symptoms associated with COVID-19 are fever, dry cough, shortness of breath, fatigue which are similar to those of SARS and MERS. A small proportion of patients had hemoptysis, and several cases were found relatively asymptomatic [27].The uncommon symptoms associated with this disease are headache, loss of smell, loss of taste, nasal congestion, sore throat, coughing up sputum, pain in muscles or joints, diarrhea, chills, nausea, and vomiting [28]. In severe cases of the disease, the clinical manifestations are difficulty walking, confusion, bluish face or lips, coughing up blood, persistent chest pain, decreased level of WBC, kidney failure, high fever [29]. COVID-19 patients may have normal or lower white blood cell counts, lymphopenia, or

thrombocytopenia, with the increased C-reactive protein level. People who have a fever and upper respiratory tract symptoms with leukopenia or lymphopenia should be suspected of the disease, especially for patients with travel history to foreign countries or endemic areas or close exposure records [30,31].

DIAGNOSTIC TESTING:

Laboratory confirmed COVID-19 patients had positive results on real-time polymerase enzyme chain reaction (RT-PCR) of the nasal and pharyngeal swab, sputum, blood, feces, and excretion specimens [32]. The detection of SARS-CoV-2 specific immunoglobulin M and immunoglobulin G antibodies also can be used for diagnosis. COVID-19 infection could be determined with one amongst the next criteria: positive specific immunoglobulin M, the transformation of specific immunoglobulin G from negative to positive, a 4-fold increase [33] in immunoglobulin G titer throughout recovery amount compared with the results of the acute part. Though antibody detection was easy, rapid, and cheap, it's still not widely used because of inherent limitations, as an example, false-negativity resulted from the existence of window amount, noncomparable sensitivity and specificity with RT-PCR, absence of exclusion criteria creating it a diagnosis tool solely [34]

Table 3: SARS-Cov-2 USA FDA EUA Commercialized Diagnostic Tests [35-41]

TEST NAME	COMPANY	TEST TYPE	RESULT TIME(hr)	APPROVAL
ID NOW COVID-19	Abbott	Isothermal amplification	<1	US FDA EUA
Abbot RealTime SARS-CoV-2 EUA Test	Abbott	PCR	4-6	US FDA EUA
ANDi SARS-Cov-2 RT-qPCR Detection Kit	3D Medicines	PCR	4-6	US FDA EUA
Atila iAMP COVID-2019 Detection Kit	Atila Biosystems, Inc	Isothermal amplification	1	US FDA EUA
BioFire COVID-19 test	Biofire Defense, LLC	PCR	<1	US FDA EUA
Xpert Xpress SARS-CoV-2	Cepheid	PCR	<1	US FDA EUA
Simplexa COVID-19 Direct RT-PCR Kit	DiaSorin	PCR	1	US FDA EUA
ePlex SARS-Cov-2 Test	GenMark Diagnostics	PCR	2	US FDA EUA
Panther Fusion SARS-CoV-2 assay	Hologic	PCR	3	US FDA EUA
ARIES SARS-CoV-2 assay	Luminex Corp	PCR	2	US FDA EUA
New Cornavirus RT-PCR test	Perkin Elmer	PCR	4-6	US FDA EUA
Quest SARS-CoV-2 RT-PCR	Quest	PCR	96-120	US FDA EUA
QIAstat-Dx Respiratory Panel 2019-nCoV	QIAGEN GmbH	PCR	1	US FDA EUA
Lyra SARS-CoV-2 Assay	Quidel	PCR	4-6	US FDA EUA
Cobas SARS-Cov-2	Roche	PCR	3-8	US FDA

				EUA
TaqPath COVID-19 Combo Kit	Thermo Fisher Scientific	PCR	4	US FDA EUA

VI. TREATMENT

Treatment is essentially supportive and symptomatic. Steps for identification and sorting of patients with serious acute disease, guidelines for laboratory identification, early confirmatory medical aid and observation, management of septic shock and respiratory failure, and ways of treatment for pregnant patients square measure being self-addressed in World Health Organization pointers dated twenty-eighth January 2020 [42-43].

The treatment portfolio included broad-spectrum antibiotics, interferons-α nebulization, and anti-viral drugs to reduce the viral load but the only remdesivir showed promising viral impact [44]. Remdesivir alone and in combination with chloroquine or β-interferon significantly blocked the SARS-CoV-2 replication and patients were found to recover clinically [12]. Moderate results were exhibited by Favipiravir, Nitazoxanide, Ribavirin, Baricitinib, Penciclovir, Ritonavir, and Arbidol when tested against infection in vitro clinical isolates and patients. Several alternative formulations have additionally been tested against COVID-19 infections in humans and mice like combos of antibiotic or antiviral medication with the normal Chinese medicines [45]. The convalescent plasma therapy was additionally tested by doctors in Shanghai China and the USA yet during which plasma was isolated from clinically treated COVID-19 patients and injected within the infected patients and they showed positive results with fast recovery [46]. A list of drugs and vaccines for the management of COVID-19 undergoing various phases in clinical trials are being documented below.

Table 4: Drugs used in COVID-19 disease [45-49]

DRUG	TARGET	STAGE
Danoprevir+Ritonavir	HepC/HIV Protease inhibitors	Phase IV
Actemra(Tocilizumab)	IL-6 inhibitor	Phase III
Lenzilumab	Anti- granulocyte-macrophage colony stimulating factor	Phase III
CD24Fc	IL-6 inhibitor	Phase III
Prezcobix(darunavir and cobicistat)	HIV Protease inhibitor+CYP3A inhibitor	Phase III
Colchicine	Tubulin disruption	Phase III
Kevzara(Sarilumab)	IL-6 inhibitor	Phase II/III
Chloroquine/Hydroxychloroquine	ACE-2 inhibitor	Phase II/III
Avigan(Favipiravir)	RNA Polymerase inhibitor	Phase II/III
Avastin(Bevacizumab)	VEGF inhibitor	Phase II/III
Remdesivir	Adenosine analogue	Phase II
Leronlimab	CCR_5 antagonist	Phase II IND field
Aviptadil	IL-6 inhibitor	Phase II
SNG001	Interferon β-1a	Phase II
Gilenya(Fingolimod)	Sphingosine-1-phosphate receptor modulator	Phase II
Airuika(Camrelizumab)	HepC/HIV Protease inhibitors	Phase IV

Table 5: Authorized/approved vaccines and vaccines under clinical trial [50-53]

Candidate	Primary developers/Sponsor	Mechanism	Trial phase
Comirnaty (BNT162b2)	Pfizer, BioNTech; Fosun Pharma	mRNA-based vaccine	Approved
Moderna COVID-19 Vaccine (mRNA-1273)	Moderna, BARDA, NIAID	mRNA-based vaccine	Approved
CoronaVac	Sinovac	Inactivated vaccine (formalin with alum adjuvant)	Approved
COVID-19 Vaccine AstraZeneca (AZD1222)	BARDA, OWS	Adenovirus vaccine	Approved
Sputnik V	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Non-replicating viral vector	Approved
BBIBP-CorV	Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	Inactivated vaccine	Approved
EpiVacCorona	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology	Peptide vaccine	Approved
Covaxin	Bharat Biotech, ICMR	Inactivated vaccine	Approved
NVX-CoV2373	Novavax	Nanoparticle vaccine	Phase 3
Bacillus Calmette-Guerin (BCG) vaccine	University of Melbourne and Murdoch Children's Research Institute; Radboud University Medical Center; Faustman Lab at Massachusetts General Hospital	Live-attenuated vaccine	Phase 2/3
CVnCoV	CureVac	mRNA-based vaccine	Phase 2b/3
ZyCoV-D	Zydus Cadila	DNA vaccine (plasmid)	Phase 3
GX-19	Genexine	DNA vaccine	Phase ½
INO-4800	Inovio Pharmaceuticals	DNA vaccine (plasmid)	Phase 2/3
HDT-301	University of Washington; National Institutes of Health Rocky Mountain Laboratories; HDT Bio Corp; Gennova Biopharmaceuticals	RNA vaccine	Phase ½
AdimrSC-2f	Adimmune	Protein subunit vaccine	Phase 1

bacTRL-Spike	Symvivo	Monovalent oral vaccine (bifidobacteria)	Phase 1
COVAX-19	Vaxine Pty Ltd.	Monovalent recombinant protein vaccine	Phase 2
DelNS1-nCoV-RBD LAIV	Xiamen University, Beijing Wantai Biological Pharmacy	Replicating viral vector	Phase ½
GRAd-COV2	ReiThera; Leukocare; Univercells	Adenovirus-based vaccine	Phase 2/3
SCB-2019	GlaxoSmithKline, Sanofi, Clover Biopharmaceuticals, Dynavax and Xiamen Innovax; CEPI	Protein subunit vaccine	Phase 2/3
UB-612	COVAXX	Multitope peptide-based vaccine	Phase 2/3
VXA-CoV2-1	Vaxart	Recombinant vaccine (adenovirus type 5 vector)	Phase 1
AAVCOVID	Massachusetts Eye and Ear; Massachusetts General Hospital; University of Pennsylvania	Gene-based vaccine	Pre-clinical
AdCOVID	Altimmune	Intranasal vaccine	Phase 1
ChAd-SARS-CoV-2-S	Washington University School of Medicine in St. Louis	Adenovirus-based vaccine	Preclinical
LineaDNA	Takis Biotech	DNA vaccine	Pre-clinical
MRT5500	Sanofi, Translate Bio	Recombinant vaccine	Phase ½
PittCoVacc	UPMC/University of Pittsburgh School of Medicine	Recombinant protein subunit vaccine (delivered through microneedle array)	Pre-clinical
T-COVIDTM	Altimmune	Intranasal vaccine	Pre-clinical

VII. PREVENTION

Since at this time of writing this article, there are no approved treatments for this infection, prevention is crucial [54]. Many properties of this virus create interference tough particularly, non-specific options of the illness, the infectivity even before onset [55] of symptoms within the time period, transmission from symptomless individuals, long time period, response for membrane surfaces like the mucous membrane, prolonged period of the illness [56] and transmission even once clinical recovery. Caregivers ought to be asked to wear a surgical mask once within the same area as patient and use hand hygiene each 15–20 min [57]. The best risk in COVID-19 is transmission to tending staff. It's necessary to guard tending staff to make

sure continuity of care and to stop transmission of infection to different patients. Patients ought to be placed in separate rooms or cohorted along. Negative pressure rooms are not typically required [58]. The rooms and surfaces and instrumentation ought to bear regular remotion ideally with bleach. Tending staff ought to be supplied [59] with N95 respirators and protecting suits and spectacles. Transmission mechanism precautions ought to be taken throughout aerosol generating procedures like cannulisation, suction and tracheostomies. All contacts together with tending staff ought to be monitored for development of symptoms of COVID-19 [60].

World Health Organization (WHO) recommends to avoid 3Cs. 3Cs include crowded places (many people are nearby), Close-contact settings (especially where people have close range conversations) and confined and enclosed spaces (places having poor ventilation). The risk is higher in places where these 3 factors overlap. Even as restrictions are lifted due consideration should be given while avoiding the 3Cs [61].

VIII. CONCLUSION

Until now, various promising clinical treatments or prevention strategies are being developed for an efficient therapeutic strategy against human coronaviruses. We are extremely anxious to escape this terrible pandemic with the best care steps imaginable. We can take vitamin-C, vitamin-D and zinc containing supplements for boosting immunity. At present many efficient vaccines available for common man. After vaccination also, we should follow the followings to reduce the risk of infection like social distancing, use of face masks, stay at home, no travelling, no, public transport, work from home, hands to be washed properly, avoid touching nose, eyes, face, cough or sneeze on bent elbow and maintain proper hygiene.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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