Assessment of worldwide COVID-19 transmission landscape for predicting its upcoming severity along with a clinical update for its prevention

Running title: Current trend of COVID-19 spread & its prevention

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Summary

The recent COVID-19 pandemic has created havoc across the globe. Although there are several controversies regarding its origin, the worldwide scientific fraternity currently indulges in developing various therapeutic strategies to combat this threat. Consequently, we aimed to provide a comprehensive evaluation of this pandemic's global transmission landscape to get an insight into its imminent fate on global populations. For this, we have analyzed the data on daily reported COVID-19 cases for 294 days since inception, i.e., from 31 December 2019 to 19 October 2020, in 210 countries across the five continents available in the ECDC database. Additionally, we have summarised an up-to-date list of currently available/under trial 23 drugs and vaccines to provide a consolidated reference to those who have a growing interest in knowing the status of related repurposed drugs and vaccines and to become acquainted with their mechanism of actions for preventing the pathogenesis of SARS-CoV-2 into the human host. We performed an extensive literature review to justify our findings and get the latest know-how on the COVID-19 pathogenesis. Our findings show that India is presently in the most critical condition, where the maximum COVID-19 cases (19.37%) reported globally in the last 14 days, which has turned into a major concern. So the government should give priority to deal with this pandemic. Besides, American and European countries are also in a risky position, as they harbor 33.31% and 34.52% of total COVID-19 cases in the last 14 days, respectively. The sudden spurt in the number of COVID-19 cases in Europe due to the beginning of extensive testing probably reflects the relaxation in policies for controlling this pandemic. Nevertheless, we should make predictions on how this virus would evolve further, which might help us design a 'magic compound' that can prevent any likely situation.

Keywords

SARS-CoV-2; COVID-19; global transmission landscape; anti-COVID-19 drugs and vaccines; COVID-19 in India

1. Introduction

Coronavirus is an RNA virus belonging to family *Coronaviridae* and subfamily *Coronavirinae*. This is the largest group of viruses belonging to the *Nidovirales* order, which are further classified into at least 25 species in four genera viz. α-coronavirus, β-coronavirus, γ-coronavirus, and δ-coronavirus (Masters & Perlman, 2013). Of them, α- and β-coronaviruses are found exclusively in mammals, whereas γ- and δ-coronaviruses primarily infect birds (Wertheim, Chu, Peiris, Kosakovsky Pond, & Poon, 2013). According to World Health Organization (WHO), Coronavirus family of viruses cause illness ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) (*https://www.who.int*). The name of this virus is due to the crown-like spikes emerging from its surface, which primarily cause enzootic infections, i.e. the infection remains within a particular species. However, in the last few decades, it has shown to be capable of infecting humans as well (Schoeman & Fielding, 2019). COVID-19 or the "Coronavirus-infected disease in 2019" is a coronavirus (CoV)-associated acute respiratory disease. This coronavirus provisionally named as "2019 novel coronavirus" or "2019-nCoV" by the WHO. The Coronaviridae Study Group (CSG) of the International Committee on Taxonomy of viruses has named this "2019-nCoV" as “severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)” (Gorbalenya et al., 2020).

2. SARS-CoV-2: from the historical perspective

Molecular clock analysis revealed that the ancestor for all CoVs dates back to 8100 BC, but the origin of SARS-CoV-2 falling under the β-coronavirus category is still debatable (Woo et al., 2012). Human CoVs first discovered in the 1960s, and at least seven CoV species are known to cause diseases in humans (**Table 1**). The viruses of 229E, OC43, NL63 and HKU1 only causes mild common cold symptoms, while the remaining three viruses, namely SARS-CoV, responsible for the outbreak of SARS in 2002-2003, the MERS inducing coronavirus (MERS-CoV) that emerged in 2012 and infected the camels, and SARS-CoV-2 that emerged in December 2019 in Wuhan of China (Zheng, 2020).

Initial phylogenetic analysis revealed the close relation of the viral genome sequences from environmental sources with the virus samples collected from the earliest infected patients from Huanan Seafood wholesale market of Wuhan (Gui et al., 2017). The first genome sequence of SARS-CoV-2 (WH-Human_1; Accession number: NC_045512) was released by China on 10 January, 2020 (*https://virological.org/t/novel-2019-coronavirus-genome/319*). Afterwards, this SARS-CoV-2 observed to be very closely similar to the Bat-CoV, RaTG13, with 96% whole genome similarity from *Rhinolophus affinis* bat from the Yunnan province of China (P. Zhou et al., 2020), and Pangolin-CoV with 91% whole genome similarity isolated from Malayan Pangolin – *Manis javanica* from Guangdong province of China (Zhang, Wu, & Zhang, 2020). However, this virus was divergent from SARS-CoV and MERS-CoV that caused epidemics in the past (Zhu et al., 2020), and the middle fragment of SARS-CoV-2 genome showed no significant similarity with any of the previously characterized coronaviruses (Paraskevis et al., 2020).

3. Genomic architecture of SARS-CoV-2 and its role in COVID-19 pathogenesis

SARS-CoV-2 is a new strain that was discovered on 31 December 2019, in Wuhan, China and not identified previously in human. The shape of this virus is spherical with a diameter of approximately 125 nm, as depicted in recent studies by cryo-electron tomography and cryo-electron microscopy (Wrapp et al., 2020). Like other coronaviruses, SARS-CoV-2 has four structural proteins known as the spike (S), envelope (E), membrane (M), nucleo-capsid (N) protein. However, this novel CoV is an enveloped, positively sensed, single-stranded RNA virus and the length of its RNA genome is almost 30kb, which is non-segmented, 5'-capped and 3'-polyadenylated (Kim et al., 2020). Comparative genome analysis of SARS-CoV-2 with other related CoVs illustrated that the genome of SARS-CoV-2 contains ORF1ab at the 5' end, occupying majority of the viral genome (**Figure 1A**). It encodes for the polyprotein pp1ab that consists of 15 non-structural proteins (NSPs) (**Figure 1B**), and **Table 2** mentions the functions of these NSPs. In contrast, the 3'-end of the genome encompassed by four structural proteins and eight accessory proteins

(Devendran, Kumar, & Chakraborty, 2020), and **Table 3** specifies the functions of these accessory proteins. Among the structural proteins, the E protein is small and essential in several aspects of the virus lifecycle, such as assembly, budding envelope formation, and pathogenesis; whereas the N protein holds the RNA genome, and E, M, S together create the viral envelope (Wu et al., 2020). Of them, the E and N proteins of SARS-CoV-2 are evolutionarily conserved, having 96.0% and 89.6% similarities with SARS-CoV, respectively (Y. Zhou et al., 2020). The S protein of SARS-CoV-2 is trimeric (Wrapp et al., 2020), comprising of two functional subunits, S1 and S2 (**Figure 1C**). S1 is responsible for binding to the host-cell receptor and S2 for the fusion of the viral and cellular membranes. The most crucial feature of SARS-CoV-2 is the polybasic cleavage site (RRAR) at the junction of S1 and S2, whereas the most viable part of CoV is the Receptor Binding Domain (RBD) in this protein (Andersen, Rambaut, Lipkin, Holmes, & Garry, 2020) (**Figure 1C**). Moreover, the S protein can be cleaved at two different sites, one located at the boundary of S1 and S2, the classical S1/S2 site (R685 P1 residue) and S2' site (R815 P1 residue) found upstream of the putative fusion peptide and within the S2 domain (Coutard et al., 2020). This second cleavage at the S2 domain is crucial for fusion activation of S protein with host cell membrane (Fehr & Perlman, 2015; Millet & Whittaker, 2015). The cleavage of S protein for the priming of the S glycoprotein depends upon host cellular proteases like human airway trypsin-like protease (HAT), cathepsins, transmembrane protease serine 2 (TMPRSS2), and furin, which facilitates the conformational changes of this protein (Millet & Whittaker, 2015). Consequently, the RBD comes to host ACE2 (Angiotensin-converting enzyme) receptor, thus, allowing the viral membrane to fuse with the host cell membrane (Wrapp et al., 2020). More importantly, the binding affinity of the SARS-CoV-2 S protein with the human ACE2 receptor is 10-20-fold higher than that of the SARS-CoV S protein (Baig, Khaleeq, Ali, & Syeda, 2020). Also, detailed research works reveal another evolutionary mutation, K403R, in S protein, which forms an adjacent RGD motif at the interaction surface (Yan, Sun, Bu, & Wan, 2020). After entering into the host-cell by endocytosis mechanism

(Ou et al., 2020)**,** the genomic material gets released, which is then utilized by the host translation machinery to produce the RNA dependent RNA polymerase (RdRp) that contains the viral NSPs like nsp12, nsp8 and nsp7 (Hillen et al., 2020). This RdRp further replicates the entire genome, from which all the structural proteins, accessory proteins and NSPs are produced. Some of these NSPs help in the degradation of host mRNA and inhibit the innate immune response of the host (**Table 2**). When subsequent processes generates all the viral protein machinery and the RNA genome, they are finally assembled into virions in the host ER and Golgi and released out of the cell by exocytosis (Shereen, Khan, Kazmi, Bashir, & Siddique, 2020).

4. Controversies over global pandemic

In the present context, we have assessed various theories regarding the origin of SARS-CoV-2. One theory says that the origin of this invisible pandemic is probably due to laboratory/industrial leakage, which also brings the concept of conspiracy theory. In contrast, another theory supports the origin of this virus is because of natural selection in humans following a zoonotic transmission. Some fascinating points have been raised by the senior investigative journalist of Epoch Times, Joshua Philipp, in his documentary entitled "Tracking down - The Origin of Wuhan Coronavirus" (*https://www.ntd.com/coronavirusfilm.html*) to support this conspiracy theory (Yang, 2020). Another vaccine researcher, Nikolai Petrovsky, has stated about SARS-CoV-2 to be "*not typical of a normal zoonotic infection*", as it unexpectedly showed up with the unconditional ability to infect human from the very first day of exposure. Also, the 'furin cleavage site' that allows the S protein to bind effectively to human ACE2 receptor does not match with other closely related coronaviruses (Birrell, 2020). Besides, there are various conspiracy theories linking COVID-19 with the upcoming 5G technology, which have also been argued very recently (Meese, Frith, & Wilken, 2020).

Meanwhile, the second theory proposes that the spillover of SARS-CoV-2 to humans probably has started at least in late November 2019, after gaining the genomic characteristics

including critical mutations in the RBD of S protein, polybasic cleavage site, and O-linked glycol residues (Andersen et al., 2020). These crucial substitutions can trigger the pandemic being undetected. In this regard, a professor from Perelman School of Medicine, Pennsylvania, also doubted "*There is no way anyone could design a virus that is this diabolical*" (Birrell, 2020). Currently, eminent scientists and experts are debating on this issue, and it is too early to reach a definite conclusion on its origin. Till now, there seems to be no direct evidence as such to disapprove the laboratory leakage that may be deliberate or inadvertent and the natural evolution concept. Therefore, more comprehensive research in future may enable us to reach an exclusive conclusion on this issue and rule out any whimsical theory.

5. The global transmission pattern of COVID-19

The ongoing SARS-CoV-2 outbreak has rapidly evolved and spread across 217 countries and territories around the world (*https://www.worldometers.info/coronavirus/*) (**Figure 2A** and **2B**). As of 19 October 2020, globally, there have been 40641433 confirmed cases of COVID-19, with 1122793 deaths (2.76% mortality) and 74.6% recovery rate (30348449/40641433). On that day, India possessed the highest rate of recovery, with 88.62% (6730617/7594736), and the USA faced the maximum death rate of 2.66% (225232/8458878).

To determine the route of transmission of COVID-19 across the globe, we retrieved data on the total number of daily reported COVID-19 cases for 294 days since inception, i.e. from 31 December 2019 to 19 October 2020, in 210 countries belonging to five continents from the database of European Centre for Disease Prevention and Control (ECDC) (*https://www.ecdc.europa.eu/en/publications-data/*). The **Supplementary Figure S1** portrays the continent wise overall distribution of COVID-19 cases. Our primary analysis shows that, globally, only six countries viz. USA, India, Brazil, Russia, Argentina, and Columbia, have accounted for 60.51% of the total reported COVID-19 cases as on 19 October 2020, and 51.50% of the total reported COVID-19 cases in the last 14 days, i.e. from 06 October 2020

189 to 19 October 2020 (**Table 4**). On calculating "*the cumulative number of COVID-19 cases*
190 *per 100000 people for the last 14 days*" within this period, we observed that on 25 March
191 2020, the initial cumulative number in Africa was 1. In contrast, the cumulative number for
192 other continents like America, Asia, Oceania and Europe were 4, 5, 7 and 46, respectively
193 (**Figure 2C** and **Supplementary Table S1**). Since the first report of infection was in China
194 (31 December 2019), Asia occupied the top position as on 01 March 2020 with a prominent
195 rise in cases (from 27 to 84664 cases in 62 days). In the case of Europe, the first report of
196 infection was on 25 January 2020 and a prominent rise in cases (from 3 to 2310 cases in 38
197 days) was observed on 02 March 2020. In Oceania, the first report of infection was on 25
198 January 2020 and a prominent rise in cases (from 1 to 161 cases in 49 days) was observed on
199 13 March 2020. For America, the first report of infection was on 14 January 2020 and a
200 prominent rise in cases (from 1 to 6305 cases in 64 days) was observed on 17 March 2020.
201 Finally, in Africa, the first report of infection was on 15 February 2020 and a prominent rise
202 in cases (from 1 to 2203 cases in 40 days) observed on 25 March 2020 (**Figure 2D** and
203 **Supplementary Table S2**).

204 Reports suggested that European countries have been hit considerably tougher than
205 other continents, and have transmitted the virus significantly more than other regions. At
206 least 93 countries across all five continents preceded the first COVID-19 cases that
207 accounted for more than half of the world's index cases having travelling history from and
208 within Europe. Italy alone reported index cases in at least 46 countries, in comparison to 27
209 countries associated with travel from China. We can ascertain the probable reason is due to
210 their delay in closing air-links. For example, Italy closed one terminal of Milan's main
211 airport on 16 March, whereas London's Heathrow and Paris's Charles De Gaulle airport were
212 left open as cases ascended. Therefore, in our analysis, we observed that 663542 new
213 positive COVID-19 cases have arisen in just 21 days (28 March 2020 to 17 April 2020)
214 (**Figure 2C**). However, most of the European nations initially failed to scale-up large-scale

testing as well, resulting in humongous spread due to travelling from there to the rest of the world (Penney, 2020).

Furthermore, travelling facilitated the spread of SARS-CoV-2 infection in Oceania, where the first case was reported in Australia on 25th January through a Chinese citizen who arrived from Guangzhou on 19th January (Hunt, 2020). The epicentre of the pandemic further moved to America, with the entry of nearly 430000 people in the US on direct flights from China, including thousands travelled directly from Wuhan after the disclosure of disease outbreak. In January, before the broad screening was in place, there were over 1300 direct passenger flights from China to the United States (Chatterjee, 2020). As on 30 March 2020, testing for COVID-19 carried out on 831000 Americans, and 98% of them were conducted after 14 March 2020, pointing the negligence in pandemic preparedness (Arnold, 2020; Lopez, 2020). Consequently, in our analysis, until 14 March 2020, we observed only 2874 positive cases in the USA. However, due to the increased number of testing, the number of positive cases reaches to 187223 in just the next 17 days, and 7050895 new COVID-19 positive cases were reported in the last 62 days (19 August 2020 to 19 October 2020). Lastly, in Africa, in particular, the spread of COVID-19 hit the political class first because of their frequent travel abroad, with hotspots emerged in South Africa, North Africa, and West Africa with spreading linked to factors like urban population density, the effectiveness of testing and reporting, and levels of international exposure (Infographic, 2020). In this context, we have noticed a much slower rate of spreading of COVID-19 as compared to other continents. Therefore, in 248 days (15 February 2020 to 19 October 2020), only 1647512 new COVID-19 cases (average no. cases per day: 138) have been reported (**Figure 2D**).

Additionally, we checked month-wise increment of the COVID-19 cases across the continents, which reveals that in September, globally, 21.12% cases were reported which is, in fact, the highest since inception, followed by August and July, having 19.85% and 17.61% of total reported cases across the world, respectively (**Table 5**). When we looked for continent wise distribution, we observed that in January and February, the maximum number

of cases (>98%) reported in Asia, due to the initial involvement of China and other neighbouring countries. In March, 60.53% of total reported cases were in Europe, because of the rapid outbreak in Italy, France and other neighbouring countries. However, from April to August, the American continent took the leading position in the total number of reported cases, as >47% cases reported in each of those months. In September, the Asian continent again came back to the leading position due to the sudden spurt in the total number of reported cases in India (**Figure 2E**). Lastly, in October, surprisingly, European continent overtook Asia (31.31%) by harbouring 32.05% of total globally recorded cases, whereas America is still in the topmost position with 33.86% of total cases (**Table 5**). This sudden surge in the number of COVID-19 reported cases probably attributed to the beginning of extensive testing in the European nations (Henley, Connolly, & Jones, 2020), which also reflect the relaxation in policies for controlling this pandemic (Maloletka, 2020). Nevertheless, India has become the second country with more than 7.5 million COVID-19 cases (18.81%) after the USA, where 20.32% of total COVID-19 cases have been reported as on 19 October 2020 (**Table 4**).

Apart from this, we also looked for the present COVID-19 situation among these 210 countries across the five continents (**Table 5**). Our analysis revealed that the nine countries in Oceania bearing the lowest number of cases (0.09%) are in better condition for COVID-19 situation with the minimum number of the cumulative cases (3151 cases) for the last 14 days. On the other hand, among the 55 countries in Africa bearing 4.10% of total cases, most of them are in a stable state, except for Morocco, South Africa, and Tunisia, where the cumulative number COVID-19 cases for the last 14 days were 40360, 22504 and 17089, respectively. In case of America that contained 47.06% of total cases, out of 49 countries, USA, Brazil and Argentina are in the alarming stage, where we observed the cumulative number COVID-19 cases for the last 14 days as 736750, 320055 and 191194, respectively. Next comes Europe bearing 17.75% of total cases, where among the 54 countries, France, UK, Russia, and Spain are in worrying position, where we found the cumulative number

COVID-19 cases for the last 14 days as 277864, 219431, 184333 and 123148, respectively. Lastly, in Asia that held 30.99% of total cases, among the 43 countries, India is on most dangerous position, where we noticed the cumulative number of COVID-19 cases as 926458, in the last 14 days, which is the highest worldwide. However, in other countries like Iran, Indonesia and Iraq, we saw the cumulative number of COVID-19 cases as 58608, 58369 and 47493, respectively, in the last 14 days.

6. The transmission pattern of COVID-19 in India

In India, to determine the course of COVID-19 spread, we have retrieved the data for the number of reported COVID-19 cases in the last 224 days, i.e. from 10 March 2020 to 19 October 2020, among 28 states and 07 union territories (UTs) belonging to six regions (Central: 2 states; East: 4 states; Northeast: 7 states; North: 6 states and 4 UTs; South: 5 states and 2 UTs; and West: 4 states and 1 UT), from the section "*COVID-19 India-Timeline an understanding across States and Union Territories*", generated by Indian Statistical Institute, Bangalore (*https://www.isibang.ac.in/~athreya/incovid19/logina/data/*) (**Supplementary Table S3**). In this regard, **Supplementary Figure S2** illustrates the region-wise overall distribution of COVID-19 cases in India. After comparing this data with the ECDC database, we speculated that the number of cases reported on 10 March 2020 probably included the infected persons since its first report on 30 January 2020. India reported its first COVID-19 case from Kerala, with a history of returning from Wuhan (Reid, 2020). By the 1st week of March 2020, the infection speeded to 22 persons having returned from Italy. At the end of March, various religious events held at Punjab and Delhi along with travel history from affected countries contributed to a sharp spike in positive cases across the nation (Wallen, 2020), but mainly in the North, South and West part of the country (**Figure 2F**). On impose of a nationwide lockdown for 21 days from 25 March 2020 and in later phases, had slowed the growth rate of the pandemic, but the impact of the past religious gatherings along with infringement of rules, and not following social distancing, led to the continuous increment in the case numbers during April and May (PIB Delhi, 2020). As a result, in June,

we observed the increasing trend of reported COVID-19 cases in the West and North India. From July to October, the South Indian region dominated the table with the highest number of cases (**Table 6**). However, we witnessed 60.76% of total COVID-19 cases in August (26.26%) and September (34.50%). We also perceived that among the total COVID-19 cases in India, South India comprised the maximum cases (37.59%) followed by West India (23.82%) and North India (18.82%). In contrast, Northeast India contained the lowest number of cases (3.73%).

7. Fight against COVID-19: an update on available drugs and vaccines

To combat the pandemic, various research laboratories and pharmaceutical companies have come up with some drugs and vaccines for the treatment and prevention of the disease, which are presently going through the different trial phases. These drugs and vaccines are being chosen and designed to prevent the sequential steps of the viral infections (**Figure 3**); the most common being the viral entry (Lurie, Saville, Hatchett, & Halton, 2020). In this regard, we have prepared an up-to-date list of currently available/under trial 23 drugs and vaccines from different resources such as *https://clinicaltrials.gov/*, *https://www.drugs.com/*, and *https://pubchem.ncbi.nlm.nih.gov/* (**Table 7**). In **Supplementary Table S4**, we have mentioned the detailed mechanism of action of these drugs and vaccines against COVID-19. Some of them are the repurposed drugs, i.e. the pre-existing drugs used to treat other bacterial or viral infections, which are also being tested for COVID-19 recently. However, potential nucleic acid-based and recombinant subunit-based vaccines are at present in the research and development stage.

8. Concluding remarks

Amid the global COVID-19 emergency, it is reasonable to wonder why the origin of the pandemic matters. Nevertheless, our analysis shows that presently, USA, India, Brazil, Argentina and some European countries are in grave condition, especially the European countries, as they collectively show 34.52% of total globally recorded COVID-19 cases,

followed by America (33.31%) and Asia (29.39%), in the last 14 days. In contrast, India alone harbours 25.96% of total recorded COVID-19 cases in the last three months and 19.37% of total recorded COVID-19 cases in the last 14 days across the globe. More importantly, in the southern and western part of India, where presently COVID-19 incidence is the most, respective authorities should give priority to deal with this pandemic. Another concern is that the novel mutations in the spike protein enable this SARS-CoV-2 to invade cross-species barrier. So, in future, if it evolves further, it may silently cause more significant casualty in quicker succession. Consequently, there is an urgent need for predicting the probable mutation patterns of this virus, based on which the drugs and vaccines would be designed in a broad spectrum to avert this kind of terrible situation to humankind.

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Conflict of interest

There is no conflict of interest.

Ethical statement

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is a review article with no original research data.

Author contributions

SK conceived the work and discussed the content with CS and SKG. AC, MK, AB, CS and SK performed initial data acquisition, primary data analysis and preliminary figure generation. UDG, SC, AB, IS, DD, DS, AG and RD supported initial data acquisition, primary data analysis and compilation. SK drafted the manuscript and finalized the illustrations. SK, CS and SKG reviewed and edited the final version of the manuscript. SK and CS supervised the work.

Data availability statement

The datasets supporting the conclusions of this article are included within the article and accompanying Supplementary Material file.

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501 # TABLES

502

503 **Table 1.** Recent discoveries of coronaviruses capable of infecting humans

Virus	Location	Group	Year	References
HCoV-229E	America	IV	1965	(Hamre & Procknow, 1966)
HCoV-OC43	America	IV	1967	(McIntosh, Dees, Becker, Kapikian, & Chanock, 1967)
SARS-CoV	China	IV	2003	(Drosten et al., 2003)
HCov-NL63*	Netherland	I	2004	(van der Hoek et al., 2004)
HCov-NL*	Netherland	I	2004	(Fouchier et al., 2004)
HCoV-NH*	New Haven CT	I	2005	(Esper, Weibel, Ferguson, Landry, & Kahn, 2005)
HCov-HKU1	Hong Kong	II	2005	(Woo et al., 2005)
MERS-CoV	Saudi Arabia	IV	2012	(Zumla, Hui, & Perlman, 2015)
SARS-CoV-2	Wuhan, China	IV	2019	(Andersen et al., 2020)

504 **Note.** This table has been adapted from (Kahn & McIntosh, 2005). The asterisk (*) marked viruses are closely related

505 **Table 2.** Functions of different NSPs encoded by ORF1ab (taken from (Fehr & Perlman, 2015))

Protein	Nucleotide position (no. of amino acids) [Accession no. NC_045512.2]	Function
nsp1	266-805bp (180)	Degrades cellular mRNA and blocks host-cell translation, for which the innate immune response in host is blocked.
nsp2	806-2719bp (638)	Unknown function, probably attaches to prohibit protein
nsp3	2720-8554bp (1945)	Large, multi-domain transmembrane protein, activities include: • Ubiquitin-like-1 (Ubl1) and Acidic (Ac) domain, interact with N protein • ADP-ribose-1'-phosphatase activity, promotes cytokine expression • PLPro (papain-like protease)/Deubiquitinase domain causes cleavage of viral polyprotein, whereby blocks the host innate immune response • Ubiquitin-like-2 (Ubl2), Nucleic Acid Binding (NAB), G2M, SARS-unique double-membrane vesicles (SUD), Y domain, unknown functions
nsp4	8555-10054bp (500)	Potential transmembrane scaffold protein, important for proper structure of double-membrane vesicles
nsp5	10055-10972bp (306)	Main protease (Mpro), cleavage of the viral polyprotein
nsp6	10973-11842bp (290)	Potential transmembrane scaffold protein
nsp7	11843-12091bp (83)	Forms hexadecameric complex with nsp8, possibly act as the processivity clamp for RNA dependent RNA polymerase (RdRp); may also act as primase
nsp8	12092-12685bp (198)	Forms hexadecameric complex with nsp7, probably act as the processivity clamp for RdRp
nsp9	12685-13024bp (113)	RNA binding protein
nsp10	13025-13441bp (139)	Acts as cofactor for nsp16 and nsp14, and form heterodimer with both; stimulates viral exoribonuclease and 2′-O-methyltransferase activities
nsp11	13442-13480bp (13)	----
nsp12	13442-13468,13468-16236bp (932)	RNA dependent RNA polymerase (RdRp)
nsp13	16237-18039bp (601)	RNA helicase, 5' triphosphatase
nsp14	18040-19620bp (527)	Acts as N7 methyltransferase that adds 5' cap to viral RNAs, and also acts as 3'→5' viral exonuclease that is important for proofreading of viral genome
nsp15	19621-20685bp (346)	Acts as viral endoribonuclease
nsp16	20659-21552bp (298)	Shows 2'-O-Methyltransferase activity; and shields viral RNA from the recognition of Melanoma Differentiation associated protein 5 (MDA5).

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507 **Table 3.** Functions of accessory proteins of SARS-CoV-2

Accessory protein name	Nucleotide position (no. of amino acid) [Accession no. NC_045512.2]	Incorporation into virions	Functions	Reference
ORF3a	25393-26220bp (275)	Yes	Up-regulates NF-κβ, JNK, IL-8, and RANTES; shows ion-channel activity; induces apoptosis and cell cycle arrest	(Narayanan, Huang, & Makino, 2008)
ORF6	27202-27387bp (61)	Yes	Type I IFN production and signalling inhibition.	
ORF7a	27394-27759bp (121)	Yes	Bone marrow matrix antigen 2 (BST2) can inhibit the release of newly assembled coronavirus from host-cell. SARSCoV ORF 7a directly binds to the BST2 and inhibits its activity by blocking the glycosylation of BST-2.	(Wu et al., 2020)
ORF7b	27756-27887bp (43)	Yes	Unknown function	
ORF8	27894-28259bp (121)	Unknown	Unknown function	
ORF10	29558-29674bp (38)	Unknown	Unknown function	----

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510 **Table 4.** Primary status of the notable COVID-19 affected countries as on 19 October 2020

Sl. No.	Continent	Country	1st report of COVID-19 cases	Duration of infection (Days)	Average no. cases per day	Total no. of cases as on 19 October 2020	% of total cases	No. of cases in the last 14 Days (%)
1	GLOBAL		31 December 2019	294	136527	40138973	100.00	4783195 (100.00)
2	AMERICA		14 January 2020	280	67469	18891298	47.06	1593093 (33.31)
3	ASIA		31 December 2019	294	42305	12437544	30.99	1405888 (29.39)
4	EUROPE		25 January 2020	269	26489	7125498	17.75	1651107 (34.52)
5	AFRICA		15 February 2020	248	6643	1647512	4.10	129956 (2.72)
6	OCEANIA		21 January 2020	269	138	37121	0.09	3151 (0.07)
7	AMERICA	USA	21 January 2020	273	29870	8154595	20.32	736750 (15.40)
8	ASIA	India	30 January 2020	264	28600	7550273	18.81	926458 (19.37)
9	AMERICA	Brazil	26 February 2020	237	22090	5235344	13.04	320055 (6.69)
10	EUROPE	Russia	01 February 2020	262	5341	1399334	3.49	184333 (3.85)
11	AMERICA	Argentina	04 March 2020	230	4303	989667	2.47	191194 (4.00)
12	AMERICA	Colombia	07 March 2020	227	4227	959572	2.39	104520 /(2.19)

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513 **Table 5.** Continent and month-wise status of worldwide COVID-19 cases up to 19 October 2020

CONTINENTS		AMERICA	ASIA	EUROPE	AFRICA	OCEANIA	Total no of cases: month-wise (%)
Continent wise distribution of 210 Countries		49	43	54	55	9	
No. of COVID-19 cases continent wise (%)	**DECEMBER**	---	27 (100.00)	---	---	---	**27 (0.00)**
	JANUARY	11 (0.11)	9766 (99.66)	15 (0.15)	---	7 (0.07)	**9799 (0.02)**
	FEBRUARY	86 (0.12)	73470 (98.33)	1139 (1.52)	3 (0.004)	19 (0.03)	**74717 (0.19)**
	MARCH	190000 (26.19)	85871 (11.84)	439104 (60.53)	5134 (0.71)	5298 (0.73)	**725407 (1.81)**
	APRIL	1113933 (47.60)	333821 (14.27)	857959 (36.66)	31598 (1.35)	2812 (0.12)	**2340123 (5.83)**
	MAY	1578660 (54.41)	592831 (20.43)	623643 (21.50)	105535 (3.64)	503 (0.02)	**2901172 (7.23)**
	JUNE	2396208 (56.36)	1119998 (26.34)	482669 (11.35)	251824 (5.92)	705 (0.02)	**4251404 (10.59)**
	JULY	4126614 (58.38)	1929948 (27.30)	486715 (6.89)	516291 (7.30)	8750 (0.12)	**7068318 (17.61)**
	AUGUST	4044723 (50.77)	2799266 (35.14)	774799 (9.73)	336450 (4.22)	11296 (0.14)	**7966534 (19.85)**
	SEPTEMBER	3299227 (38.93)	3512145 (41.44)	1431941 (16.90)	228136 (2.69)	3925 (0.05)	**8475374 (21.12)**
	OCTOBER	2141836 (33.86)	1980401 (31.31)	2027514 (32.05)	172541 (2.73)	3806 (0.06)	**6326098 (15.76)**
	TOTAL (%)	**18891298 (47.06)**	**1243754 4 (30.99)**	**7125498 (17.75)**	**1647512 (4.10)**	**37121 (0.09)**	**40138973 (100.00)**

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515 **Table 6.** Region and month-wise status of COVID-19 cases up to 19 October 2020 in India

REGIONS		SOUTH	WEST	NORTH	EAST	CENTRAL	NORTH EAST	Total no of cases: month-wise (%)
Region wise distribution of 35 Indian states		7	4	10	4	2	8	
No. of COVID-19 cases region-wise (%)	**MARCH**	521 (38.34)	294 (21.63)	443 (32.60)	44 (3.24)	55 (4.05)	2 (0.15)	**1359 (0.02)**
	APRIL	5150 (16.11)	13710 (42.88)	9058 (28.33)	1352 (4.23)	2643 (8.27)	58 (0.18)	**31971 (0.42)**
	MAY	25795 (18.00)	67579 (47.15)	33032 (23.05)	9752 (6.80)	5640 (3.94)	1524 (1.06)	**143322 (1.90)**
	JUNE	103236 (26.94)	121639 (31.74)	115153 (30.05)	25684 (6.70)	7793 (2.03)	9679 (2.53)	**383184 (5.08)**
	JULY	441254 (40.89)	275629 (25.54)	179445 (16.63)	119882 (11.11)	23598 (2.19)	39226 (3.64)	**1079034 (14.29)**
	AUGUST	822873 (41.51)	416191 (20.99)	327062 (16.50)	277475 (14.00)	52796 (2.66)	85978 (4.34)	**1982375 (26.26)**
	SEPTEMBER	882925 (33.90)	642738 (24.68)	532389 (20.44)	299080 (11.48)	144173 (5.54)	103213 (3.96)	**2604518 (34.50)**
	OCTOBER	556531 (42.02)	260935 (19.70)	224687 (16.96)	156846 (11.84)	83886 (6.33)	41625 (3.14)	**1324510 (17.54)**
	TOTAL (%)	**2838285 (37.59)**	**1798715 (23.82)**	**1421269 (18.82)**	**890115 (11.79)**	**320584 (4.25)**	**281305 (3.73)**	**7550273 (100.00)**

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519 **Table 7.** List of the drugs and vaccines developed to combat SARS-CoV-2

Sl. No.	Name	Manufacturer	Current status
POTENTIAL DRUGS			
1	Camostat Mesylate §	Ono pharmaceuticals (Japan) & AR Life sciences Pvt. Ltd. (India)	Phase 4
2	Nafamostat mesylate	Manus Aktteva BioPharma LLP (India)	Phase 2 & 3
3	Bromhexine along with Hydroxychloroquine	Zydus Cadila (India)	Phase 4- Recruiting
4	Chloroquine ¶	Sanofi S.A. (France)	Phase 2/3
5	Umifenovir	JSC Pharmstandard (Russia)	Phase 4 Recruitment Status – Enrolling by invitation
6	Ritonavir-Lopinavir	R-Pharm	Phase 2 Recruitment Status –Terminated
7	Remdesivir	Gilead Sciences (USA) Cipla & Glenmark Pharmaceuticals (Mumbai, India) Dr. Reddy's Laboratories (Hyderabad, India)	Phase 3 with ongoing Active Recruitments
8	Sofosbuvir (+Ledipasvir)	Gilead Sciences (USA) Natco Pharma (India)	Phase 3 Recruitment Status – Completed. Recruitment Status – Recruiting
9	Ribavirin	Genentech, Merck Sharp & Dome, Kadmon Pharmaceuticals, Aprazer (India)	Phase 2
10	Galidesivir	BioCryst Pharmaceuticals	Phase 1
11	Favipiravir (Favilavir)	Toyama Chemical – Fujifilm group (Japan)	Phase 3, not yet recruiting. Recruitment Status – Recruiting
12	Tocilizumab	Chugai Pharmaceuticals (Japan) Roche Pharma & Cipla (India)	Phase 2 with 332 participants enrolled and ongoing recruitments
13	Sariliumab +	Regeneron and Sanofi	Phase 2 Recruitment-Completed
14	NP-120 Ifenprodil	Sanofi, Algernon Pharmaceuticals	Phase 2 & 3
VACCINES			
15	mRNA-1273	ModernaTX (USA)	Phase 3 Recruiting
16	Fusogenix DNA vaccine	Entos Pharmaceuticals	Not Known
17	Ad5-nCoV	CanSino	Phase 2
18	INO-4800	Inovio	Phase 1
19	Sputnik V	Gamaleya Research Institute (Moscow)	Phase 3
20	AZD1222 (previous name-ChAdOx1 nCoV-19)	The University of Oxford, AstraZeneca, IQVIA, Serum Institute of India	Phase 3
21	Bacillus Calmette-Guerin (BCG)	University of Melbourne and Murdoch Children's Research Institute, Radboud University Medical Centre	Phase 3
22	Covaxin	Bharat Biotech & National Institute of Virology	Phase 2
23	NVX-CoV2373	Novavax	Phase 3

520 **Note. §** other brand name in different places - *https://www.drugs.com/international/camostat.html*; ¶ It has other
521 trade names, available at - *https://www.medindia.net/drug-price/chloroquine.htm*; + Sariliumab has different
522 treatments for different conditions of the patients, which are at different phase of trials -
523 *https://www.drugbank.ca/covid-19*.

FIGURE LEGENDS

Figure 1. Genomic organization of the SARS-CoV-2 virus. (A) An illustration of the complete RNA genome of the SARS-CoV-2 virus and its various components (10 ORFs). The numbers mentioned here are the nucleotide positions for each coding region within the genome. The region coding the ORF1a/ORF1ab enlarged to show its detailed structure and relative positions of respective NSPs. These NSPs are encoding a polyprotein, pp1ab, whose functions depicted in **(B)** that is adapted from *https://viralzone.expasy.org/764*. The primary structure of S protein and its domains, portrayed in **(C)**, is adapted from (Wrapp et al., 2020). **SS**, signal sequence; **NTD**, N-terminal domain; **RBD**, Receptor-binding domain; **SD1** and **SD2**, sub-domains 1 and 2; **S2′**, S2′ protease cleavage site; **FP**, fusion peptide; **HR1**, heptad repeat 1; **CH**, central helix; **CD**, connector domain; **HR2**, heptad repeat 2; **TM**, transmembrane domain; **CT**, cytoplasmic tail. Arrows denote protease cleavage sites. The numbers mentioned here are the respective amino acid positions, according to (Coutard et al., 2020).

Figure 2. Illustrations of worldwide transmission landscape of COVID-19 pandemic. COVID-19 cases timeline (per country over time) as of 14 January 2020 **(A)** and 19 October 2020 **(B)**. The portrayal of the cumulative rise in the number of COVID-19 cases per 100,000 people for the last 14 days **(C)**, and the total number of newly reported COVID-19 cases **(D)** across the five continents from 31 December 2019 to 19 October 2020. Besides, a depiction of the cumulative number of cases (by the number of days since 10,000 cases) in major COVID-19 affected countries (**E**), and a representation of the total number of newly reported COVID-19 cases across India's six regions from 10 March 2020 to 19 October 2020 (**F**). We generated parts A, B, and E from *https://www.worldometers.info/coronavirus/worldwide-graphs* and C, D, and F from MORPHEUS (*https://software.broadinstitute.org/morpheus/*).

Figure 3. Diagrammatic representation of the target sites of some anti-COVID-19 drugs.

SUPPLEMENTARY MATERIALS

SUPPLEMENTARY TABLES

Supplementary Table S1. Continent-wise cumulative number of COVID-19 cases per 100000 people for the last 14 days

Supplementary Table S2. Global day-wise distribution of COVID-19 cases from 31 December 2019 to 19 October 2020

Supplementary Table S3. Region-wide distribution of COVID-19 cases from 10 March 2020 to 19 October 2020 in India

Supplementary Table S4. An up-to-date list of 23 drugs and vaccines available to fight against COVID-19

SUPPLEMENTARY FIGURES

Supplementary Figure S1. Overall distribution of the total number of newly reported COVID-19 cases across the 210 countries belonging to five continents from 31 December 2019 to 19 October 2020

Supplementary Figure S2. Overall distribution of the total number of newly reported COVID-19 cases in India across the 28 states and 07 union territories belonging to six regions from 10 March 2020 to 19 October 2020