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The epidemiology, evolution, transmission, and therapeutics of COVID-19 Outbreak: an update on the status

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Abstracts:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an etiologic agent of the respiratory disease in humans that is known as coronavirus disease 2019 (COVID19). The first outbreak of the disease was initially documented in Wuhan, Hubei Province, China in late December 2019 where people had experienced SARS pneumonia-like symptoms with unknown etiology. Since then it has been observed that COVID-19 positive patients have been showing mild to severe upper respiratory illness symptoms. The type of virus is known to make its transfer from animals to humans and for the concerned virus; researchers have claimed its origin from bat coronavirus at whole-genome level with a 96 % sequence identity. The COVID-19 virus is very contagious and communicable in nature and has been spread throughout the globe since its first outbreak in China. On March 9, 2020, WHO declared it as a Pandemic, and within a month it was already reported to have shown its presence in 213 countries and territories or areas. As of April 29, 2020, this novel virus infected 3,218,183 people and caused 228,029 mortalities worldwide with a variable mortality rate from 3-13 % across the planet and also varied by age and gender. Diagnosis of the disease is a key component in understanding and controlling the spread of the virus and several techniques have been devised including RT-PCR, ELISA, and sequencing-based approaches. To cure COVID-19 patients as of now we do not have proven to be a safe and effective treatment. Therapeutic options currently under investigation in various parts of the world. However, there are various effective therapeutic targets to repurpose the present antiviral therapy for developing potential interventions against SARS-CoV-2. Boosting the immune system can also help to prevent and spread of COVID-19 using various medication and exercises. In this review, our goal to summarize and discussed the present scientific advancements to fight against this novel pandemic.

Keywords: COVID-19, Evolution of SARS-CoV-2, replication, emerging disease 2019 and diagnostic tools

Introduction:

The first report of Severe Acute Respiratory Syndrome like pneumonia with unknown etiology was observed in late December 2019 in Wuhan, China [1-3]. International Committee on Taxonomy of Viruses (ICTV) named the agent responsible as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Later a number of cases of the same have surged and WHO named this new disease as coronavirus disease 2019 [4]. The onset of the initial animal to human transfer has been traced back to the wet market in Wuhan and shortly after that human to human transmission was observed [5]. The researchers have traced its emergence to pangolins, and more precisely to Bat (*Chiroptera*) with 96 % of the genome matched. The category of virus is known to make an inter species transfer to finally find a way to attach to a host cell receptor in humans. SARS-CoV-2 is the 7th coronavirus known to us that has made an infectious transfer from animals to humans [5]. Previously, documented coronaviruses i.e. severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) were some that have made similar transfers to humans and then spread within the same species.

SARS-CoV-2 is a newly emerged member of a Coronaviridae with a genome size of ~30,000 bases. The size of its virion is roughly 70-90 nm in diameter [6]. Coronaviruses are made up of four different structural proteins; spike (S), envelope (E), membrane (M), and nucleocapsid (N) and 16 non structural proteins [7]. The previously known coronaviruses are large, positive-sense

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and single-stranded RNA (+ssRNA) viruses that are classified into 4 different genera which are alpha coronavirus, beta coronavirus, gamma coronavirus and delta coronavirus. Among these alpha and beta coronavirus are known to infect humans. In fections of these viruses can be fatal in some severe cases. SARS-CoV, MERS-CoV, and SARS-CoV-2 can cause severe upper respiratory illness in humans while 4 other known coronaviruses HCoV 229E, NL63, OC43, and HKU associate with mild symptoms in human [8-11] which globally account for 10-30 % of upper respiratory tract infections specifically in adults. Coronaviruses have different ecological niches with a wide diversity documented in bats [12-17]. Thus, having a higher probability of SARS-CoV-2 evolving from Bat. Further we are addressing following questions:

A. What are the different modes of transmission of SARS-CoV-2?

B. How the SARS-CoV-2 originate and what its apparent replication mechanism?

C. What are the current effective diagnostic tools and therapeutic options are available to control and cure the COVID-19?

Transmission:

Transmission of SARS-CoV-2 occurs through different modes; primarily through respiratory droplets of infected person when exhaled, sneezed, or cough, viral particles come out in air with coronavirus droplets. Respiratory droplets emissions are classified into “large” and “small” droplets. Compared to small droplets, lLarge droplets quickly settle down than it evaporate into air, contaminating the nearest environment of the infected person. [18]. Van et al. [19]

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documented that this novel virus can survive up to 3 hours in air at 65% relative humidity. Other modes of SARS-CoV-2 spreading is through persons if comes in contact with the infected person or with objects which are already used by infected person or he/she is already comes in contact with virus contaminated surfaces and objects like doors knobs, water-tap, bathroom, utensils, groceries stuffs, currency, clothes, papers, *etc*. As it is known that SARS-CoV-2 can survive on plastic and stainless steel up to 72 hours, on copper less than 4 hour, on card board less than 24 hours therefore to prevent the virus spreading, avoid the contact with these materials for at least four day or unless it is properly sanitize [19]. The warm climate could be a barrier of transmission of the COVID-19 probably due to the quick loss of humidity in air and it might lead to death of Coronavirus. There is no direct evidence but as per the disease confirmed case indicating that may be good for those countries which have higher temperature like India, Pakistan, Sri Lanka, Australia, Africa, Sri Lanka *etc* because the number of cases are lower in these countries as of April 16, 2020. There are "n" number of possible modes of transmission could be from fruit market, vegetable market, groceries stores, grains market *etc* because we do not know if some people are asymptomatic or have very mild symptoms which are very hard to predict about the COVID-19. As of the current death and worsening of the symptoms suggest that those who are aged or might have some other associated disease such as asthma, diabetes, heart patients or genetics of person etc.

Pathogenicity:

Virus get entry into the host cells possibly via fusion of spike protein with membrane or through the interaction of spike RBD with either human ACE2 receptor or Glucose Regulated Protein 78

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(GRP78) receptor present on the type II alveolar cells (AT2) [20-25]. However, SARS-CoV2 does not use other receptors that SARS-CoV uses for entry into cells. Once virion gets into the respiratory system, it gets a chance to interact with lung type II alveolar cells receptor ACE2 and is followed by its priming by TMPRSS2. Because lung AT2 cells strongly co-express ACE2 and TMPRSS2 receptors [22, 24] which is the primary root for SARS-CoV-2 entry into host cells. Hamming et al [26] reported the ACE2 abundantly expressed on the type-2 alveolar (AT-2) epithelial cells and small intestine, which is most susceptible for infection of COVID-19. SARS-CoV2 human infection proceeds through stage I to III. In stage I, patients will experience asymptomatic or mild symptoms of dry cough, diarrhea and headache. Whereas stage II, the patient feels shortness of breath with pneumonia-like symptoms, and at stage III, chronic inflammatory response occurs *i.e.* high blood pressure, heart problems or chronic respiratory conditions, cardiac failure [27].

The higher expression level of ACE2 is possibly associated with a higher rate of mortality in the older age group or with people who have heart disease due to COVID-19 patients. Increased ACE2 expression at protein and transcriptional level has been observed in patients with heart disease therefore such patients were considered as more vulnerable to virus infection and may have severe effect of COVID-19. Therefore, mortalities observed in China with COVID-19 could be linked to myocardial injury in patients [27-28]. Pericytes that have ACE2 expression could be linked to the target of cardiac cells for SARS-CoV-2 entry. Pericytes damage linked with virus infection which may further be associated with the capillary cells, endothelial cell malfunction leads to microvascular dysfunction [29]. Acute respiratory illness noticed in some of COVID-19 patients, like it was noticed with SARS-CoV and MERS-CoV infected individual with signature of the pulmonary ground glass alteration on imaging [30].

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Higher level of different cytokines; proinflammatory (IL-2), inflammatory (IFN-γ), and anti-inflammatory (IL-6, IL-10) observed in the peripheral blood of critical cases compared to the mild cases of COVID-19 [31]. However, the exact role of these cytokins is unknown in the aspect of COVID-19. Different rates of mortality (3-13 %) was observed in different countries which could be governed by different factors, such as immunological cross protection via some earlier infection, presence of specific miRNA, hygiene, pollution or climate effect,, type of population like percentage of old age group, culture, density, etc.

Genome and replication:

Coronaviruses are large, enveloped, (+)ssRNA that belong to Coronavirdiae, order Nidovirales. The previously known coronaviruses are classified into 4 different genera which are alpha coronavirus, beta coronavirus, gamma coronavirus and delta coronavirus Among these alpha and beta coronavirus are known to infect humans [32-33]. The first genome of SARS-CoV-2 was discovered from the samples collected from bronchoalveolar lavage fluid from a patient from Wuhan, China [34]. SARS-CoV-2 genome is +ssRNA, ~30 000bp long with 5′-cap and 3′-poly-A tail belonging to Coronaviridae family. The sequence of genes (5′ to 3′) in the viral genome map is open reading frame 1a, (ORF1a), ORF1b, spike (S), envelope (E), membrane (M) and nucleocapsid (N) [34]. SARS-CoV2 enters into the airway primary epithelial cells using ACE2 receptors. Once it have in the cells it directly use its RNA genome as a template to synthesize polyprotein 1a/1ab that encodes 16 non structural protein 1-16 (nsp1-16) to established replication transcription complex in the double membrane vesicle [35] and after wards ssRNA genome synthesized through replication transcription complex in discontinuous

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manner. Roughly two-third of the entire genomes size covers the first open reading frames 1a/1b ORFs (ORF1a/b), that encode 16 non-structural proteins. Other ⅓ of the virus genome towards the 3' end encodes spike, membrane, envelope, and nucleocapsid proteins [34].

Evolution of SARS-CoV-2:

The evolution of SARS-CoV-2 based on its phylogenetic and taxonomic nature has been speculated from family of coronaviruses in host organisms with higher resemblance to SARS-CoV as suggested by Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses [36] SARS-CoV-2 whole genomic sequence share 96 % similarity with Bat coronavirus (BatCoV RaTG13) source from *Rhinolophus affinis* from Yunnan Province in China, indicating that SARS-CoV-2 has a very high probability of having its origin from bats [37]. Primary genomic sequencing obtained from 5 different infected people with SARS-CoV-2 in China exhibited a 100 percent of sequence similarity. However, SARS-CoV 2 shares 96 % and 91.02 % genomic sequence similarity with BatCoV RaTG13 and Pangolin-CoV respectively [38].

Malayan pangolins (*Manis javanica)* coronavirus (Pangolin-CoV) shows 91.02% and 90.55% identity at the whole genome with SARS-CoV-2 and BatRaTG13 respectively [39]. Zhang et al. [39] study indicates that Pangolin-CoV is the common ancestor for Bat RaTG13 and human SARS-CoV-2. Amino acid sequence analysis suggests that the S1 protein sequence of Pangolin-CoV resembles more with SARS-CoV-2 as compared to Bat RaTG13. Interestingly 5 amino acid residues of Spike RBD that interact with human Angiotensin-converting enzyme 2

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(ACE2) are conserved between SARS-CoV-2 and pangolin-CoV, but are not identical with RaTG13 due to four amino acid mutations. The binding efficiency of Pangolin COV and SARS CoV-2 spike RBD with ACE2 resembles that indicating the possibility of it being an intermediate host. However, the difference in genetic sequence similarity of SARS-CoV-2 with other coronaviruses could be a recombination of different coronaviruses, maybe via infecting a common unknown host before coming in contact with humans. These developed chimeric viruses simultaneously that can interact with various cells of the host and infect. Though verification of this hypothesis warrants further studies. Concluded that there is any intermediate host for viruses to infect humans.

Diagnosis and Prevention:

Diagnosis is an important part of controlling a disease, especially a communicable one and has played its pivotal part in the containment of COVID-19. With proper diagnosis we can steer the tactful implementation of control measures to limit the spread primarily by identifying and isolating the affected individual. Proper diagnostic measures are very important as the symptoms shown by infected people are very wide and aren't a true prognosis or measure of the infection. Thus, validating the requirement of highly sensitive and specific laboratory diagnostic assessments. Almost four months after the initial cases the genomic and proteomic components of the pandemic have been discovered. However, the host response to the virus infection is yet to be explored [40]. Various approaches are being followed to understand the COVID-19 infection including a combination of computed tomography imaging, whole genome sequencing, and electron microscopy [41]. Moreover, ELISA based antibody and antigen detection tests are being

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194 developed as well. Although not yet been completely validated and still under research. This can
195 have a much precise outcome given genetic sequence similarity to the antibodies generated [42-
196 43]. The lack of diagnostic measures have paved the path to use RT-PCR as a gold standard
197 diagnostic measure and have shown reliable results worldwide [44]. Furthermore, RT-PCR
198 detection also previously exhibited high sensitivity and specificity for SARS-CoV and MERS-
199 CoV infection. Another commonly used nucleic acid based detection technology is high-
200 throughput sequencing of the entire viral genome, but it is an expensive and time consuming
201 detection method. To tackle these problems, CRISPR-based sensitive, rapid and potentially
202 portable diagnostic tests are in the development to facilitate rapid point-of-care testing and solves
203 worldwide testing shortages of COVID-19. [45]. In India, recently CRISPR-Cas9 technology
204 based paper-strip tool was developed and operates by converting the RNA into DNA then
205 amplification and finally utilizing the Cas9 complex to detect the genetic material of COVID-19.

206 The unavailability of clinically proven therapeutic agents is also a gigantic reason for
207 such a blanket spread of COVID-19. However, development of therapeutics and vaccines is
208 underway. There are various potential therapeutic targets to repurpose the present antiviral
209 therapy for developing effective interventions against this novel coronavirus. One of the
210 promising antiviral drugs against RNA viruses *in vitro* and *in vivo* is Remdesivir which is a
211 nucleoside analogue that blocks viral RNA synthesis [46]. Furthermore, potential clinical trials
212 have been reported to combat COVID-19 using the HIV drug combination of Lopinavir–
213 Ritonavir [47]. Additionally, other nucleoside analogues *i.e.* Favipiravir, Ribavirin and
214 Galidesivir are in the pipeline and may have potential clinical application against COVID-19
215 [48]. The National Medical Products Administration of China has approved an antiviral drug
216 'Favilavir' for the treatment for coronavirus [49].

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Favilavir has reportedly shown efficacy in 70 patients in a clinical study. Allowing other protease inhibitors such as but not limited to Lopinavir-Ritonavir that are previously approved for HIV treatment to be studied. The two protease inhibitors mentioned above works by blocking viral entry inside the cell and inhibiting viral particle maturation. This can be one of the effective therapy for management and treatment of COVID-19. Other FDA approved drugs including Chloroquine and Hydroxychloroquine are being tested in multiple studies as well. So far they have demonstrated an efficient inhibition of COVID-19 infection *in vitro* and in clinical studies [50]. Chloroquine phosphate has also been coined as a potential drug based on current clinical trial data. The mechanism of hydroxychloroquine consists of inhibition of the virion assembly in the endoplasmic reticulum and Golgi intermediate compartments. Followed by attenuating the expression of pro-inflammatory factors, receptors and phosphatidylinositol binding clathrin assembly protein (PICALM), which prevents endocytosis-mediated uptake of COVID-19 virus [51]. Azithromycin along with hydroxychloroquine also has been found to be efficient on SARS-CoV-2 infection treatment in Chinese COV-19 patients and found it reinforced with other drugs because it inhibits the super infection of bacteria [52].

The subsequent drugs can be designed in a way that inhibits or blocks S protein binding to ACE2 receptors. This can be an efficient way of attenuating or even completely ceasing the infection of the virus in COVID-19 patients [53]. As with the current understanding of COVID-19, the virus invades the host cells through an ACE2 receptor that is predominantly present in lungs epithelial cells. The other major target for drug development via high affinity can also be AP2-associated protein kinase 1 (AAK1) as some recent studies suggest [54]. Moreover, the kinase inhibitor including 'baricitinib' can also be a potential candidate that can be evaluated in the clinical trial settings for COVID-19 management [54]. Currently, the plasma/serum

immunoglobulin of patients recovered from COVID-19 can produce favorable results in COVID-19 patients especially the one who are in later stages of disease progression [55]. There are other potential therapies and as the science has grown so much we can also look at the current generation of monoclonal antibodies (mAb), this can play a mechanism of neutralizing the virus and hence reducing the symptoms of COVID-19. Also, by binding with the receptor-binding domain of virus can also be developed as a potential candidate therapeutics of COVID-19 infections [56]. We strongly believe and understand the importance of vaccination in the current scenario and if it spreads with current prediction vaccination would be utmost important and the best way to control the spread of disease. There have been various studies at different levels of development currently underway in almost every part of the globe a lot of them have been shown tested *in vivo* and shown promising results. The vaccination can be of different types and these include live-attenuated, inactivated, subunit, recombinant DNA and proteins vaccines [57]. The major disadvantage of any strategy or vaccine development is that it requires approximately 2 years to be available for use with many more years and a well crafted strategy for it to reach parts of the world. Being the need of the hour a lot of new pharmaceutical molecules including HIV drugs and stem cell therapies are in testing phases of clinical trials. Needless to mention the advent of modern technology has paved the path of other treatment opportunities like siRNA, tumor necrosis factor-alpha inhibitors, interferons, neutralizing antibodies, neuraminidase inhibitors, corticosteroids, pentoxifylline *etc*. Further evaluation of these mechanisms can elaborate their usage and how these can help in combating the current epidemic crisis [58].

We are still in a phase where we are unfolding the layers, evaluating and understanding the virus. The new development in the current knowledge may open an opportunity for many

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more therapeutic agents and targets to control the spread, manage and treat COVID-19. Needless to mention this requires extensive research both in discovery science and clinical study settings. The research community worldwide has come together and never before have we seen such a sharing of research findings and joining of hands to work against a common goal to eradicate this unwanted disease from our society. In the meantime when the research community is utilizing every second available on the clock the people awaiting have to be strong and follow self care and as a lot of scientists have suggested that boosting the immune system can play a pivotal role to prevent the spread of COVID-19 infection. These trying times have provided us with an opportunity to analyze and manage our lifestyle. This won't only help us with the current epidemic but in general with other epidemiological diseases as well. Some of us have the privilege to do workout routines, yoga, meditation, tai-chi, breathing exercise, aerobics and many more ways to stay healthy, calm, eliminate anxiety and also take care of mental health needless to mention as little of a task as getting proper sleep can be very essential and helpful to boost the immune system [59]. Also, we can always access the ancient treasure and utilise the wisdom from traditional systems of medicine like Ayurveda, herbal medicine, Chinese medicine etc. These could also help or maybe possess a preventive potential measure while we still await a tried and tested cure from modern medicine [60].

Conclusion:

The current available diagnostic technologies have enabled researchers to develop new realtime efficient COVID-19 diagnostics tools. Based on the current knowledge of Coronavirus pathogenesis and SARS-CoV-2 disease mechanisms known so far, newer tools could attainably

be developed to prevent, diagnose and treat people affected with COVID-19 and also to manage the disease in general. In conclusion, we would like to stress out again on the importance of diagnostics as a part of the important components to dealing with outbreaks in future. The proper management and availability of diagnostic tools can aid in curbing the spread of pathogens like coronavirus thus leading to a better survival rate. Some of the drugs may also have prophylactic and therapeutic effects against COVID-19 infection, exploring the mechanisms of these drugs and the keep on evaluating the effect of virus is absolutely necessary to explore and develop new preventative and therapeutic strategies.

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Declaration of Competing Interest

All authors have declared no conflicts of interest.

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Figure Legends

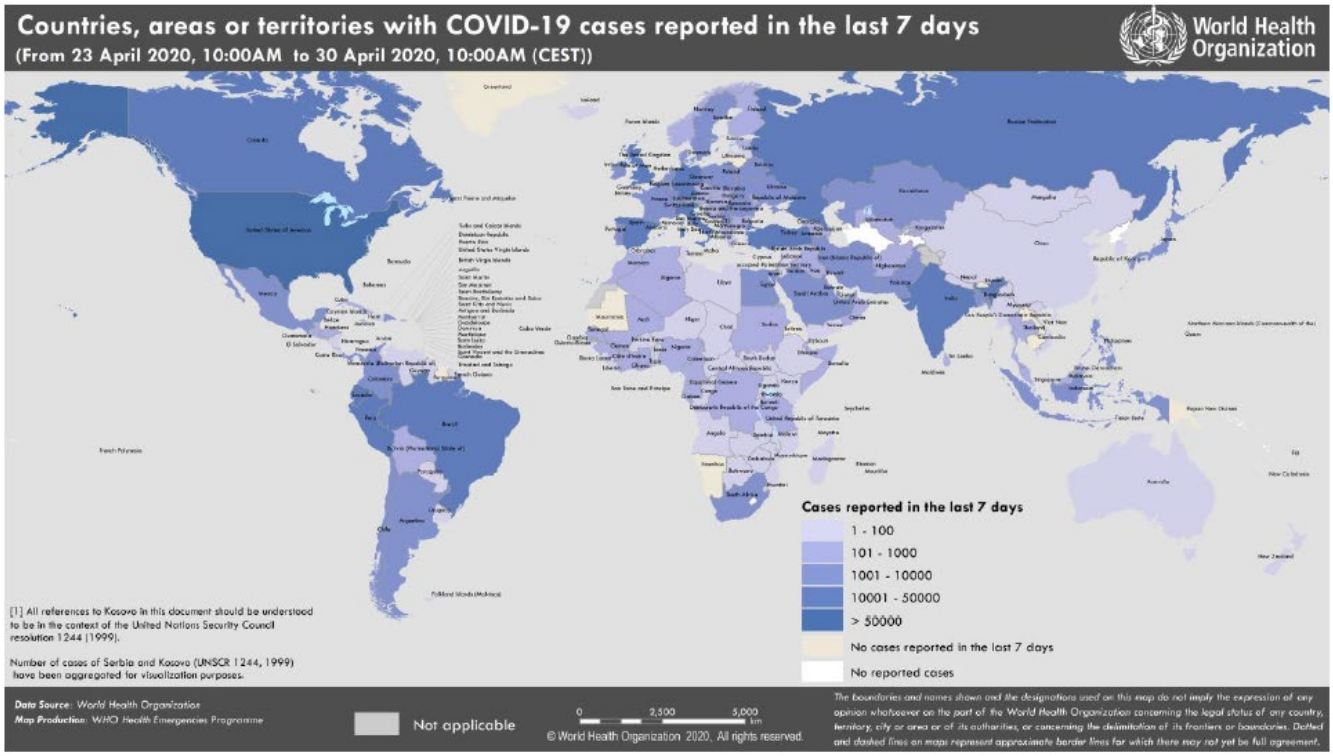
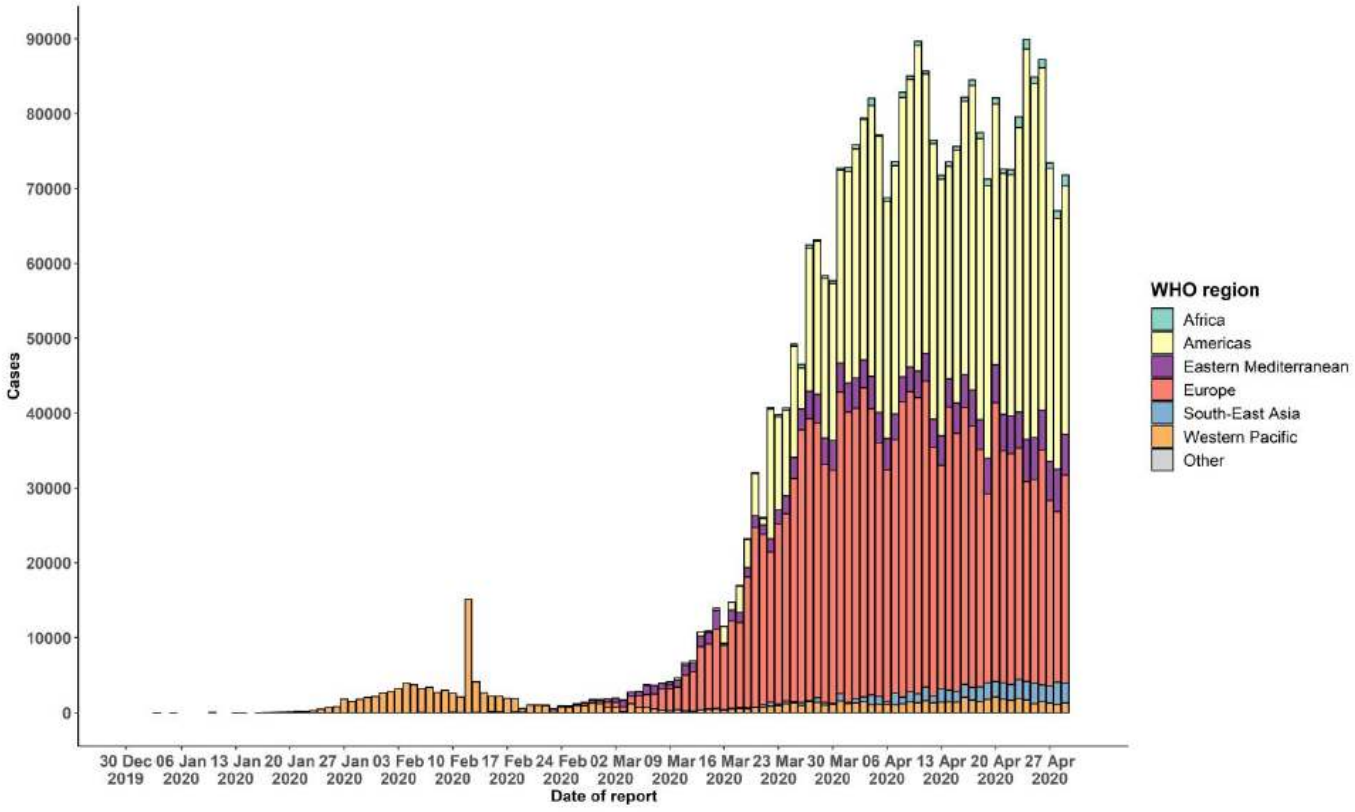


Figure 1: Represent the number of confirmed cases across countries, territories or areas as of 30 April 2020 (with permission this figure was adopted from WHO situation report 101 on the

500 COVID-19;https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-
501 reports).



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503 **Figure 2.** Represent the epidemic curve of confirmed COVID-19, by date of report and WHO
504 region through 30 April 2020 (with permission this figure was adopted from WHO situation
505 report 101 on the COVID-19; https://www.who.int/emergencies/diseases/novel-coronavirus-
506 2019/situation-reports

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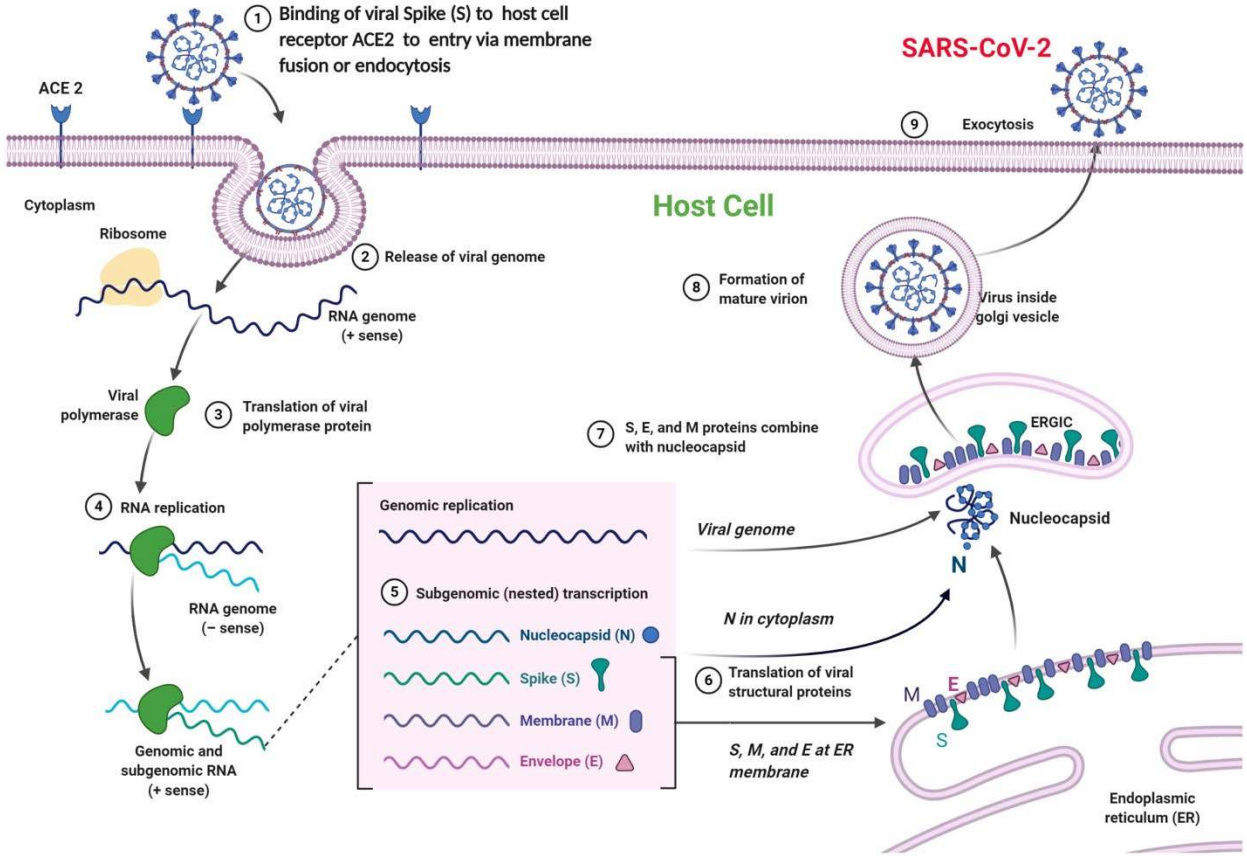

Figure 3: Represent the SARS-CoV2 entry in to the host cell through the binding of viral spike (s) protein with host cell receptor ACE2 receptor and its replication

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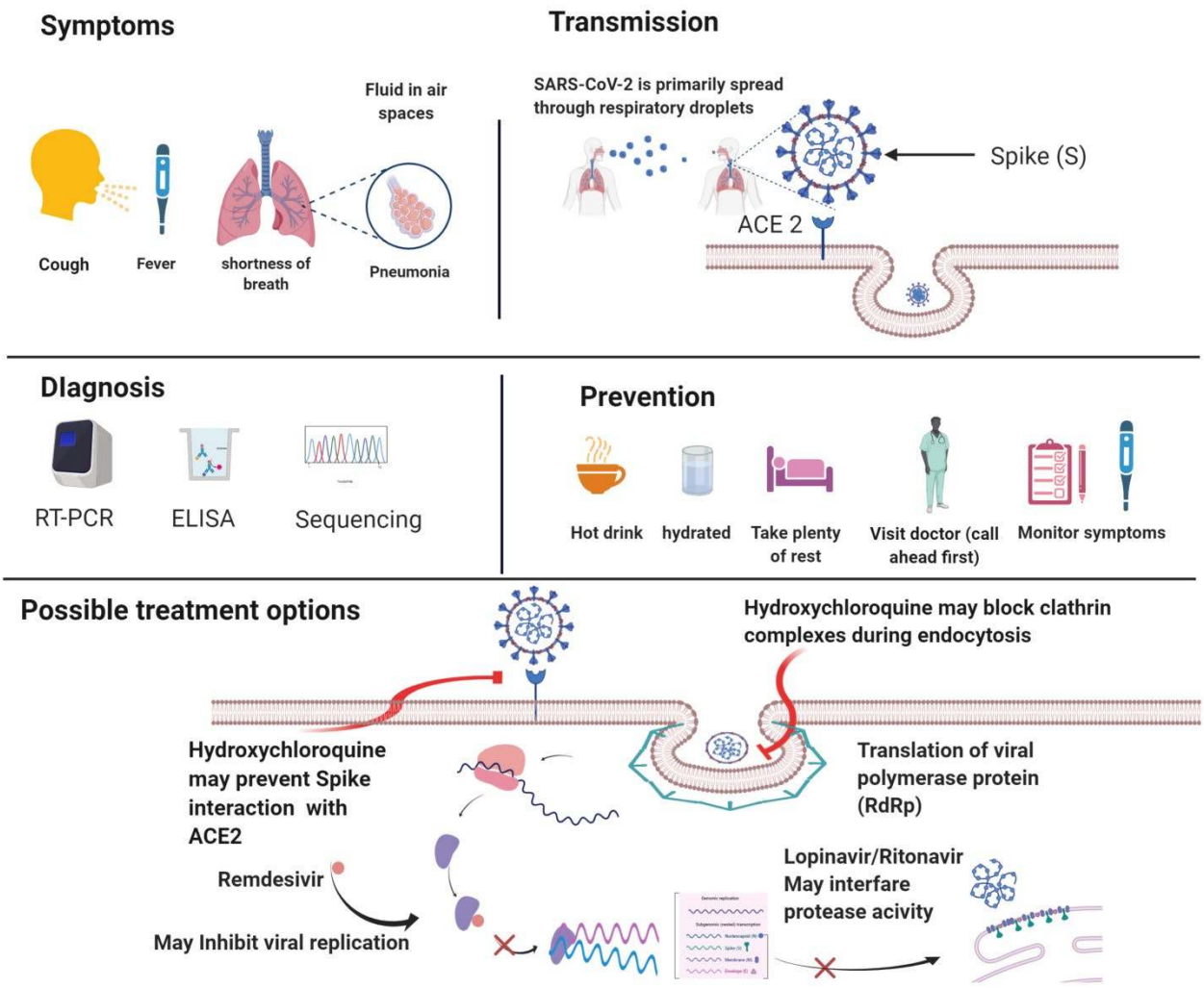

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515 **Graphical abstract:**

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