



Review

The Rise of New Coronavirus Infection (COVID-19): A Recent Update and Potential Therapeutic Candidates

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Abstract

The recent catastrophic outbreak of a novel coronavirus (COVID-19), currently renamed as COVID-19; recalled us the earlier memories created by the Severe Acute Respiratory Syndrome Human coronavirus (SARS-CoV) from nearly two decades ago. With the new advancements in earlier detection techniques for infections and better treatments; now we are better supported to deal this recent infestation of 2B coronavirus.

Keywords: Coronavirus, emerging viruses, MERS-CoV, novel CoV, pneumonia, SARS-CoV, Wuhan, 2019-nCoV

Cite This Article: Mali SN, Pratap AP, Thorat BR. The Rise of New Coronavirus Infection (COVID-19): A Recent Update and Potential Therapeutic Candidates. EJMO 2020;4(1):35–41.

The Chinese city of Wuhan, is found to be the origin of the life threatening viral outbreak of Novel Coronavirus (2019-nCoV) i.e COVID-19.^[1,2] According to the World Health Organization (WHO) situation report (41st), updated on 1 March, 2020 there have been globally 87137 confirmed cases of Novel Coronavirus (2019-nCoV).^[3] Out of 79 968 confirmed cases from China, 2873 deaths were already occurred. It has been found significantly centered around Hubei Province. There have been report for 7169 confirmed and 104 death cases of 2019-nCoV involving 58 countries, on 1 March, 2020.^[3] On January 7, 2020, at around 9 o'clock, the virus was officially identified and named by the WHO as 2019-nCoV.^[3-5] Many rapid virological, clinical, and epidemiological research responses have been carried out on 31 December 2019; as an emergency response for pneumonia cases of unknown etiology found in Wuhan.^[6] The Centers for Disease Control and Prevention (CDC)

in the United States announced the 1st 2019-nCoV case on January 21, 2020. Researchers at the German Centre for Infection Research at the Charité university hospital in Berlin developed a laboratory assay on January 16th, 2020. This outbreak is rapidly escalating with the increase in number of contagion events. Tests required for detection of SARS-CoV (2002) and MERS-CoV (2012) were used for earlier detection of 2019-nCoV.^[7] This coronavirus (2019-nCoV) has thought to be having the same lineage from those causing the SARS-CoV.^[8] Initially, it has been found that the cluster was having exposure of seafood market, where wild animals were served at a restaurant and off course that was thought to be a point-source zoonotic route.^[7-9] There has been large number of literature reports on coronavirus including recent one.^[10-65]

This member coronavirus (2019-nCoV) is belonging to Betacoronaviruses like SARS-CoV (the Severe Acute Respira-

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Submitted Date: March 02, 2020 **Accepted Date:** March 29, 2020 **Available Online Date:** March 30, 2020

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tory Syndrome Human coronavirus) and MERS –CoV (the Middle-East Respiratory Syndrome Human coronavirus).^[9-15,53] These coronaviruses are belonging to a large family of singlestrand, positive-sense RNA enveloped, viruses having ~26–32 kb genome.^[6,25] These viruses usually reported for mild infestations mostly influenza like manifestations, excluding those (like SARS-CoV, MERS-CoV and 2019-nCoV) may be having association with severe complications like acute respiratory distress syndrome and death.^[11-15] Although there has been limited evidence, current outbreak depicted the fact of reduction of time lapse for emergence of highly infectious coronavirus. SARS-CoV was found to be causative agent for the severe acute respiratory syndrome occurred in Guangdong Province, China (in 2002 and 2003).^[16-20] In 2012, there has been reports for MERS-CoV causing Middle East respiratory syndrome coronavirus infections. Mortality rates were found to be 10% for SARS-CoV and 37% for MERS-CoV. These viruses are reported for moderate-to-high mutation rate having average substitution rate: ~10–4 substitutions per year per site as compared to rest single-stranded RNA viruses. Zhu et al.^[6] have reported the identification and characterization of 2019-nCoV. Till date, there has been report for 7 Human coronaviruses (HCoVs); which includes 229E and NL63 strains of HCoVs (Alphacoronaviruses), while OC43, HKU1, SARS, MERS, and newly added 2019-nCoV (Betacoronaviruses).

There has been large literature suggesting the role of climatic changes on living organism, including viruses. These recent changes forces viruses to adapt to changing environment, which also includes natural adaption, which finally leads to emergence of new adapted viral species.^[16-23]

Mode of Transmission and Prevention

It has been found that those visited a local fish and wild animal market in Wuhan in November, 2019 were thought to develop current infection.^[20-23] The possible mode of transmission of this infection is thought to be animal to human transmission. There have been several evidences, reporting the animal to human and inter-human transmission of the virus. In order to reduce the general risk of transmission of acute respiratory infections following basic principles could be useful as suggested by WHO:^[24]

- We should avoid contacts with 2019-nCoV patients.
- We should wash our hands regularly.
- Try to avoid unprotected animal contacts.
- Proper cough etiquette should be followed.
- There should be proper diagnosis facilities in hospitals for enhancement of the standard infection prevention.

Therapeutic Options for the 2019-New Coronavirus

Current treatment includes the use of Intensive care and ventilation for complications including the severe pneumonia. There has been no testing done so far for ensuring effectiveness of broad spectrum antivirals against newly emerged 2019nCoV. A latest article by Ralph et al., 2020 explains human-to-human transmission, travel-related cases, and vaccine readiness in regards with a 2019-nCoV infection.^[63] This article explains how marketed drugs such as metformin, glitazones, fibrates, sartans, and atorvastatin could be repurposed to treat or prevent the Acute respiratory distress syndrome (ARDS).^[55,60,61] Lu et al., 2020 beautifully explains the general methods, which could be used to discover the potential antiviral treatment of human pathogen coronavirus.^[54] These 3 methods includes screening/usage of existing broad-spectrum antiviral drugs, screening of a chemical library/databases, and redevelopment of new drugs based on the genome and biophysical understanding of virus.^[54,55] By taking considerations of current guidelines^[56] IFN- alpha (5 million U bid inh) and lopinavir/ritonavir (400 mg/100 mg bid po) are recommended as antiviral therapy. A recent published correspondence reported in Lancet, gives idea on how BenevolentAI uses artificial intelligence to Identify potential candidate against the 2019-nCoV infection. This study identifies Baricitinib for treatment of the 2019-nCoV. Zumla et al., 2020 explains the role of Interleukin 17 blockade in treatment of 2019-nCoV patients with high plasma concentration of interleukin 17.^[59] One study also suggests an attractive target for live-attenuated vaccines as the envelope protein (E).^[63] Their research analysis also suggested the role of the S protein for vaccine development.^[63] A recent in-vitro activity study^[58] elaborated as letter to editor by Wang et al., 2020 explains the in-vitro blockade of the 2019-nCoV infection at low-micromolar concentration by remdesivir (EC50 = 0.77 μM; CC50 >100 μM; SI >129.87) and chloroquine (EC50 = 1.13 μM; CC50 >100 μM, SI >88.50). They found to show high SI. This study was conducted for checking the antiviral efficiency of approved drugs including ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine, remdesivir (GS-5734); an adenosine analogue and favipiravir (T-705). The in-vitro results suggest potentials of chloroquine and remdesivir against the 2019-nCoV infection.^[58] It is important to note that the efficacy and safety of these drugs against the 2019-nCoV need to be assured and confirmed by clinical studies. A pre-print by Lei et al., 2020 explains potent neutralization of 2019 novel coronavirus by recombinant ACE2-Ig. The researcher aimed to develop a new recombinant protein by connecting the ex-

tracellular domain of human ACE2 to the Fc region of the human immunoglobulin IgG1. This study suggested that their fusion proteins exhibited reactivity against coronavirus and these may have potential for diagnosis, prophylaxis, and treatment of 2019-nCoV.^[57] A report by Clercq et al., 2020 also suggested the use of a guanine analogue, Favipiravir (T-705), for effective inhibition of RNA-dependent RNA polymerase of RNA viruses^[64,65] including 2019-nCoV (EC50=61.88 μM in Vero E6 cells).^[58] Zumla et al., 2016 describes Galidesivir (BCX4430), an adenosine analogue, as antiviral.^[55] It has also been reported that disulfiram could also inhibit the papain-like protease of MERS and SARS in cell cultures. One article also explains binding ability of Griffithsin to oligosaccharides on the surface of various viral glycoproteins. A recent study also explains inhibition of 2019-nCoV (EC50=2.12 μM in Vero E6 cells) by antidiarrhoeal Nitazoxanide.^[58] The HIV anti-retroviral agents Lopinavir and Ritonavir are currently being used to treat patients of 2019-nCoV in China Figure 1. It has been also evidenced for non-effectiveness of HIV anti-retroviral agents against SARS, as demonstrated by review of SARS.

Current Findings Related to Mode of Transmissions

In one of the study, Xu et al., 2020^[26] suggested the interaction of human ACE2 molecules with the RBD domain of CoV S-protein despite of its difference in sequence with SARS-CoV S-protein. They reported that this infection may cause significant risk of human transmission via the S protein–ACE2 binding pathway. Paraskevis et al., 2020^[27] explained how the full-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of

emergence as a result of a recent recombination event. Literature suggests that, we don't have specific coronavirus antivirals or vaccines, which proved efficacy in humans exist. Another research reported by Lu et al.,^[43] 2020 reports for close relations (88% identical) with bat-SL-CoVZC45 and bat-SL-CoVZXC21 (both were bat derived and collected from Zhoushan, China in 2018. This study also reports that 2019-nCoV is distant from earlier reported coronaviruses like SARS-CoV and MERS-CoV with percentages of 79% and 50% respectively. 2019-nCoV has same receptor binding domain as SARS-CoV, as it was depicted from homology modelling.^[43] A study on family cluster analysis by Chan et al., 2020^[44] explains the person-to-person transmission of pneumonia linked with 2019-nCoV. Another correspondence published by John, 2020.^[45] represents views for 2019-nCoV as from origins of MERS-CoV. A rapid communication by Riou et al., 2020^[53] describes a pattern of early human-to-human transmission of 2019-nCoV. Their studies estimated that basic reproduction number ($R_0 \sim 2.2$) indicating infectiveness of 2019-nCoV via human to human transmission. In one report, Benvenuto et al., 2020^[28] explained the role of mutations of surface proteins including the spike protein S, and of nucleocapsid N protein. Authors reported that the possible mutations in these two proteins could lead important characteristics of 2019-nCoV, which were a high stability than the bat-like SARS and a low pathogenicity than SARS coronavirus. These key characteristics may explain the zoonotic transmission and less mortality than SARS.

Current Findings-Still a Long Way Ahead

A study published in The Lancet, by Chaolin Huang^[1] and colleagues reported clinical features of the first 41 patients confirmed to be infected with 2019-nCoV by Jan 2, 2020. This study indicated the severity of 2019-nCoV infestation. A preprint by Hoffmann et al., 2020^[51] depicts the fact of the use of the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells by the 2019-nCoV. A study also suggests the use of TMPRSS2 inhibitor, which might become treatment option in future.^[51] One of the reports in the Lancet journal by Elfiky, 2020^[29] suggested the potential role of approved Sofosbuvir and Ribavirin (antipolymerase drugs) for targeting newly emerged Wuhan HCoV Figure 1. Author, utilised the Sequence analysis, modelling and docking in order to build a Wuhan 2019-nCoV RNA dependent RNA polymerase (RdRp) model. The results of the study depicted the effectiveness of Sofosbuvir, IDX-184 and Ribavirin as potential drugs against 2019-nCoV infection. A correspondence published by Richardson et al., 2020^[46] expressed the role of Baricitinib in treating respiratory diseases as-

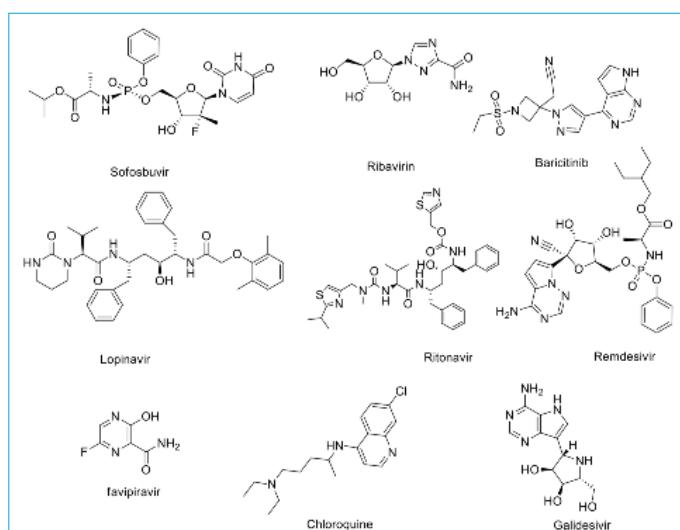


Figure 1. Available therapeutic candidates, which may have potential towards the novel corona virus (2019-nCoV).

sociated with 2019-nCoV. Study conducted by Tang et al., 2020^[30] suggested that intensive contact tracing followed by quarantine and isolation, can effectively reduce the transmission risk for 2019-nCoV. Majumder and Mandl, 2020^[2] reported their model which suggested that basic reproduction number associated with the outbreak may range from 2.0 to 3.1. Their research depicted the possible epidemic potential of a novel coronavirus. An article by Heymann, 2020^[47] explains role of free data sharing in order to provide real-time guidance regarding the current outbreak of 2019-nCoV. A modelling study conducted by Wu et al., 2020,^[41] published in Lancet clearly estimates the pathogenicity and spread of 2019-nCoV calculated as of January 25, 2020 for domestic as well as international potentials. One study conducted by Chen et al., 2020 on 99 cases of 2019-nCoV, for clarifying the epidemiological and clinical characteristics of 2019-nCoV pneumonia, reported 51% of patients suffering from chronic diseases.^[42] A bibliometric analysis published by Bonilla-Aldana et al., 2020^[48] explains metrics research findings till date regarding the coronaviruses. This letter, also bring to our knowledge that whether we have investigated enough regarding the coronaviruses? One more letter, explains data-driven correlational association of domestic passengers from Wuhan and confirmed cases of the 2019-novel CoV in various cities.^[49] They found that 10 fold increase in Wuhan train passengers is linked with increments in imported cases of 2019-novel CoV. An editorial published in journal of Travel Medicine and Infectious Disease explains severity and advice for travellers regarding 2019-novel CoV.^[50] Zhou, Peng, et al., 2020^[10] also reported the 75 to 80% similarity with viral genomes with SARS-CoV or bat coronaviruses. It has been also reported by Perlman, 2020; that 2019-nCoV grows better in primary human airway epithelial cells than in standard tissue-culture cells, as opposite to SARS-CoV.^[39] It has been also noted that 2019-nCoV appears to use same cellular receptor, which would be associated with SARS-CoV (human angiotensin-converting enzyme 2 [hACE2]).^[39] Corman and colleagues, 2020 explained the use of real-time RT-PCR for detection of the 2019 nCoV.^[40]

Homology modelling of the Papain-Like Protease PLpro

A study reported by Stoermer, 2020 demonstrated the homology models of the Papain-Like Protease PLpro from Coronavirus 2019-nCoV. Their work suggest that papain-like protease encoded by the 2019-nCoV is quite homologous to bat and SARS coronaviral PLpro. Their molecular dynamics analysis suggests that zinc is required for structural integrity of the protease.^[62]

A probable Mechanism of 2019-nCoV Infection: Cell Pyroptosis

A study reported^[1] in Jan 2020 depicted the involvement of lymphopenia (63%) compared to the leucopenia (25%). Typical symptoms of 2019-nCoV infection reported to include fever, lymphopenia, cough, myalgia or fatigue, haemoptysis, acute cardiac injury, pneumonia, etc. Out of reported symptoms some were observed to be non-specific. Also there were presence higher levels of IL-1beta and other inflammatory cytokines (IL-7, IL-8, IL-9, IL-10, MCP-1, TNF-alpha, IFN-gamma etc.) in plasma. From the above conclusions, a study conducted by Yang, 2020^[31] reported hypothesis of the cell pyroptosis as potential pathogenic mechanism of 2019-nCoV Infection. Research reported that cell pyroptosis is a novel inflammatory form of programmed cell death. There has been large number of studies for cell pyroptosis are reported in literature.^[31-38]

In consideration of current scenario regarding 2019-nCoV Infection, molecular diagnostic assays and phylogenetic analysis might play important role in rapid and accurate identification of new microorganisms. In order to rapid isolation, identification and treatment of 2019-nCoV cases, we have to entail higher end molecular diagnostic techniques aimed at detecting new viral strands in animal reservoirs resulting in prompt diagnosis and patient isolation.

Conclusion

There are several major gaps in our current knowledge of the origin, epidemiology, duration of human transmission, and clinical spectrum of disease, which could be fulfilled by more studies.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – S.N.M., B.T.; Design – A.P.P., S.N.M., B.T.; Supervision – A.P.P., S.N.M., B.T.; Data collection &/or processing – A.P.P., S.N.M., B.T.; Analysis and/or interpretation – A.P.P., S.N.M., B.T.; Literature search – A.P.P., S.N.M., B.T.; Writing – A.P.P., S.N.M., B.T.; Critical review – A.P.P., S.N.M., B.T.

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