Journal Of Harmonized Research (JOHR)

Journal Of Harmonized Research in Medical & Health Sci.
7(1), 2020, 01-06

ISSN 2395 – 6046

Review Article

# COVID-19 AN EMERGING EPIDEMIC: A REVIEW

**Om Prakash Agrawal[*1], CK Tyagi[2], Deenanath Jhade[3]**

[1]School of Pharmacy, Madhyanchal Professional University, Ratibad, Bhopal-466001
[2]College of Pharmacy, Sri Satya Sai University of Technology & Medical Sciences, Sehore-466001
[3]St. Wilfred's Institute of Pharmacy, Panvel, Navi Mumbai (M.H.) - 410206

**Abstract:** A novel coronavirus disease (COVID-19), triggered by infection with SARS-CoV-2, has flounced across 31 provinces in China and over 195 countries worldwide. The transition from first symptoms to acute respiratory distress syndrome (ARDS) is extremely probable to be due to unrestrained cytokine release. There is a crucial need to classify safe and active drugs for action. Chloroquine (CQ) exhibitions an inhibitory effect. However, the clinical use of CQ can cause severe side effects. Moreover, hydroxyl-chloroquine (HCQ) also exhibits an antiviral effect highly similar to that of CQ, inhibiting the cytokine storm by suppressing T-cell activation. Coronavirus vaccine will be carry after clinical trials ahead in markets.

**Key-words:** Conora Virus, Chloroquine, Vaccine, Hydroxychloroquine.

**Introduction:** Coronavirus disease (COVID-19) is an infectious disease caused by a novel discovered first case in Wuhan, China, in December 2019. Numerous people infected with the COVID-19 virus will experience mild to moderate respiratory illness and recover without requiring special treatment. Elderly and those with underlying medical problems like cardiovascular disease, diabetes, chronic respiratory disease, and cancer are more likely to develop serious illness[1-4].

**For Correspondence:**
om11agra85@gmail.com
Received on: March 2020
Accepted after revision: March 2020
DOI: 10.30876/JOHR.7.1.2020.01-06

The best way to prevent and slow down transmission is be well informed about the COVID-19 virus, the disease it causes and how it spreads. Protect yourself and others from infection by washing your hands or using an alcohol based rub frequently and not touching your face[5].

The COVID-19 virus spreads primarily through droplets of saliva or discharge from the nose when an infected person coughs or sneezes, so it's important that you also practice respiratory etiquette (for example, by coughing into a flexed elbow). At this time, there are no specific vaccines or treatments for COVID-19.

However, there are many ongoing clinical trials evaluating potential treatments[6].

The COVID-19 virus affects different people in different ways. COVID-19 is a respiratory disease and most infected people will develop mild to moderate symptoms and recover without requiring special treatment. People who have underlying medical conditions and those over 60 years old have a higher risk of developing severe disease and deathz[7].

Statistically, **coronavirus** COVID-19 is affecting **196 countries and territories** around the world, confirmed case 392440 with casualty 17159 while recovered 103,396 case **(Last updated: March 24, 2020, 12:35 GMT)**[8-9].

**Chloroquine and hydroxychloroquine Fight against COVID-19:** Chloroquine is a quinine analogue medication used to prevent and to treat malaria in areas where malaria is known to be sensitive to its effects. Certain types of malaria, resistant strains, and complicated cases typically require different or additional medication. So, Chloroquine and Hydroxy-chloroquine have been available as weapons to fight against COVID-19. Repositioning of drugs for use as antiviral treatments is a critical need. It is commonly very badly perceived by virologists, as we experienced when reporting the effectiveness of azithromycin for Zika virus. A response has come from China to the respiratory disease caused by the new coronavirus (SARS-CoV-2) that emerged in December 2019 in this country. Indeed, following the very recent publication of results showing the *in vitro* activity of chloroquine against SARS-CoV-2, data have been reported on the efficacy of this drug in patients with SARS-CoV-2-related pneumonia (named COVID-19) at different levels of severity [10-11.]

Indeed, following the *in vitro* results, 20 clinical studies were launched in several Chinese hospitals. The first results obtained from more than 100 patients showed the superiority of chloroquine compared with treatment of the control group in terms of reduction of exacerbation of pneumonia, duration of symptoms and delay of viral clearance, all in the absence of severe side effects[12-13]. This has led in China to include chloroquine in the recommendations regarding the prevention and treatment of COVID-19 pneumonia[14].

**Coronavirus vaccine:** The current threat of avian- influenza to the human population, the potential for the reemergence of severe acute respiratory syndrome (SARS)-associated coronavirus, and the identification of multiple novel respiratory viruses underline the necessity for the development of therapeutic and preventive strategies to combat viral infection. Vaccine development is a key component in the prevention of widespread viral infection and in the reduction of morbidity and mortality associated with many viral infections. In this part, coronavirus vaccine, especially SARS-CoV vaccines are mainly discussed[15].

Coronavirus vaccines can be inactivated coronavirus, live attenuated coronavirus, or S protein-based. Besides, there are still vectored vaccines, DNA vaccines, and combination vaccines against coronaviruses. Vaccines targeting several animal CoVs have been developed, and some have been demonstrated to be efficacious in preventing viral infection. However, a phenomenon of enhanced disease following vaccination has been observed in cats upon infection with feline infectious peritonitis virus following previous infection, vaccination, or passive transfer of antibody. The phenomenon is not fully understood but is believed to be a result of enhanced uptake and spread of the virus through binding of virus-antibody immune complexes to Fc receptors on the surfaces of macrophages; low-titer (subneutralizing) antibodies directed against the S protein are mainly responsible. Although antibody enhancement appears to be limited to feline infectious peritonitis virus among CoVs, similar concerns have been raised with regard to SARS-CoV. Previously infected mice and hamsters are protected from subsequent infection with SARS-CoV in the absence of enhanced disease, and vaccine studies and

passive immunoprophylaxis performed with mice and hamsters suggest that previous exposure and the presence of NAbs provide protection[16].

**Inactivated Coronavirus Vaccine:** The immunogenicity and efficacy of inactivated SARS-CoV vaccines have been established in experimental animals, and one such vaccine is being evaluated in a clinical trial. However, the development of inactivated vaccines requires the propagation of high titers of infectious virus, which in the case of SARS-CoV requires biosafety level 3-enhanced precautions and is a safety concern for production. Additionally, incomplete inactivation of the vaccine virus presents a potential public health threat. Production workers are at risk for infection during handling of concentrated live SARS-CoV, incomplete virus inactivation may cause SARS outbreaks among the vaccinated populations, and some viral proteins may induce harmful immune or inflammatory responses, even causing SARS-like diseases[17].

**Novel coronavirus related information:** MERS-CoV NEWMERS-CoV infection Novel Coronavirus 2012 (NCoV) Corona virus Human corona virus Corona virus symptoms Novel coronavirus infection New SARS-like Virus Coronavirus treatment SARS corona virus Spike protein Nucleo capsid Coronavirus replication Coronavirus hku1HCoV-EMC

**Live Attenuated Coronavirus Vaccine:** To date, live attenuated vaccines for SARS-CoV have not been evaluated. However, systems have been developed to generate cDNAs encoding the genomes of CoVs, including SARS-CoV. The panel of cDNAs spanning the entire CoV genome can be systematically and directionally assembled by in vitro ligation into a genome-length cDNA from which recombinant virus can be rescued. This system has been used for genetic analysis of SARS-CoV protein functions and will enable researchers to engineer specific attenuating mutations or modifications into the genome of the virus to develop live attenuated vaccines. While live attenuated vaccines targeting respiratory viruses, including influenza viruses and adenoviruses, have been approved for use in humans, the observation that infectious virus is shed in the feces of SARS-CoV-infected individuals raises concerns that a live attenuated SARS-CoV vaccine strain may also be shed in feces, with potential to spread to unvaccinated individuals. Another concern is the risk of recombination of a live attenuated vaccine virus with wild-type CoV; however, there may be ways to engineer the genome of the vaccine virus to minimize this risk.

**S-Protein-based Coronavirus Vaccine:** The roles of S protein in receptor binding and membrane fusion indicate that vaccines based on the S protein could induce antibodies to block virus binding and fusion or neutralize virus infection. Among all structural proteins of SARS-CoV, S protein is the main antigenic component that is responsible for inducing host immune responses, neutralizing antibodies and/or protective immunity against virus infection. S protein has therefore been selected as an important target for vaccine and anti-viral development.

Although full-length S protein-based SARS vaccines can induce neutralizing antibody responses against SARS-CoV infection, they may also induce harmful immune responses that cause liver damage of the vaccinated animals or enhanced infection after challenge with homologous SARS-CoV, raising concerns about the safety and ultimate protective efficacy of vaccines that contain the full-length SARS-CoV S protein.

**Vectored Vaccines against Coronavirus:** Several groups have reported preclinical evaluation of vaccines utilizing other viruses as vectors for SARS-CoV proteins, including a chimeric parainfluenza virus, MVA, rabies virus, vesicular stomatitis virus (VSV), and adenovirus. Chimeric bovine/human parainfluenza virus 3 (BHPIV3), a live attenuated parainfluenza virus vaccine candidate, was utilized as a vector for the

SARS-CoV structural proteins including S, N, matrix (M), and envelope (E), alone or in combination. Studies with vectored vaccines further demonstrate that induction of S protein-specific NAbs is sufficient to confer protection.

**DNA Vaccines against Coronavirus:** DNA vaccines have demonstrated strong induction of immune responses to viral pathogens in animal models, specifically in mice; however, clinical data on DNA vaccines in human subjects are limited. DNA vaccines encoding the S, N, M, and E proteins of SARS-CoV have been evaluated in mice. Vaccination with S-, M-, and N-encoding DNA vaccines induced both humoral and cellular immune responses, with some variation in the relative levels of induction.

**Combination Vaccines against Coronavirus**

Combination vaccines have also been evaluated for their ability to augment immune responses to SARS-CoV. Administration of two doses of a DNA vaccine encoding the S protein, followed by immunization with inactivated whole virus, was shown to be more immunogenic in mice than either vaccine type alone. The combination vaccine induced both high humoral and cell-mediated immune responses. High NAb titers were also observed in mice vaccinated with a combination of S DNA vaccines and S peptide generated in Escherichia coli. Combination vaccines may enhance the efficacy of DNA vaccine candidates.

The SARS-CoV vaccine strategies reported to date demonstrate that S protein-specific NAbs alone are sufficient to provide protection against viral challenge. While SARS-CoV has not yet reemerged, its unknown reservoir leaves open the possibility that it, or a related virus, will again infect the human population. The development of vaccines targeting this virus will help, in the event of its reemergence, to potentially stop its spread before it wreaks the social and economic havoc caused by the previous outbreak. Furthermore, lessons learned from the generation of these vaccines may aid in the development of future vaccines against known and newly identified coronaviruses**.**

**Pharmacological treatments with potential clinical benefit: Remdesivir (GS-5734):** Remdesivir is an investigational monophosphoramidate prodrug of an adenosine analog that was developed by Gilead Sciences, Inc. in response to the Ebola outbreak in West Africa from 2014-2016. In its active triphosphate nucleoside form, remdesivir binds to RNA-dependent RNA polymerase and acts as an RNA-chain terminator. It displays potent in vitro activity against SARS-CoV-2 with an $EC_{50}$ at 48 hours of 0.77 µM in Vero E6 cells. 3 Similar activities have been demonstrated against other zoonotic coronaviruses with EC50 values of 0.07 µM demonstrated for both SARS-CoV-1 and MERS-CoV. Remdesivir is highly selective for viral polymerases and is therefore expected to have a low propensity to cause human toxicity. Accordingly, Sheahan and colleagues demonstrated a wide therapeutic index for remdesivir in a human airway epithelial cell model.6 The drug also displays a high genetic barrier to resistance in coronaviruses and has a long intracellular half-life that allows for once daily dosing. The dose under investigation for treatment of COVID-19 is 200mg intravenously (IV) on day 1 followed by 100mg IV daily for up to 10 days, infused over 30-60 minutes.

**Lopinavir/ritonavir:** Lopinavir is a human immunodeficiency virus 1 (HIV-1) protease inhibitor administered in fixed-dose combination with ritonavir (LPV/r), a potent CYP3A4 inhibitor that "boosts" lopinavir concentrations. Lopinavir appears to block the main protease of SARS-CoV-1, inhibiting viral replication. In 2003, Chu and colleagues evaluated a series of antivirals for in vitro activity against SARS-CoV-1. They reported lopinavir at 4 mg/mL and ribavirin at 50 mg/mL inhibited SARS-CoV-1 after 48 hours of incubation and that the agents were synergistic when used together. de Wilde and colleagues later described the antiviral activity of lopinavir

against SARS-CoV-1 and demonstrated an EC50 17.1 ± 1 in Vero E6 cells which is near the upper range of LPV plasma concentrations previously measured in patients with HIV infected patients. 24,25 Sheahan and colleagues evaluated the in vitro efficacy of LPV/r in combination with interferon beta (INFb) against MERS-CoV and found the addition of LPV/r did not significantly enhance antiviral activity of INFb alone (EC50 =160 IU/mL vs 175 IU/mL, respectively).5 They also described the EC50 of LPV/r (8.5 µM) and LPV alone (11.6 µM), suggesting similar activity to that described for SARS CoV-1. Despite in vitro activity against MERS-CoV, therapeutic doses of LPV/r + INFb in mice models failed to reduce virus titer and exacerbated lung disease. This is notable as this was the same study where remdesivir demonstrated both more potent in vitro activity as well as in vivo efficacy. However, the in vivo animal data for MERS-CoV appears equivocal given a nonhuman primate model demonstrated improved clinical and pathological features following LPV/r treatment. A randomized controlled trial of LPV/r and recombinant interferon-β1b versus placebo is currently enrolling for patients with MERS-CoV, which might help clarify the apparent discrepancy between in vitro and animal models.

**Nitazoxanide:** Nitazoxanide has demonstrated potent in vitro activity against SARS CoV-2, with an $EC_{50}$ at 48 hours of 2.12 µM in Vero E6 cells. This potent activity is consistent with $EC_{50}$ values for nitazoxanide and its active metabolite, tizoxanide, against MERS-CoV in LLC-$MK_2$ cells where $EC_{50}$ values of 0.92 and 0.83 µM have been demonstrated, respectively. Nitazoxanide displays broad spectrum in vitro antiviral activity against influenza, respiratory syncytial virus, parainfluenza, rotavirus, and norovirus amongst others in addition to coronaviruses. This broad spectrum antiviral activity is believed to be due to the fact that the mechanism of action is based on interference with host regulated pathways involved in viral replication rather than virus-specific pathways.

**Conclusion: I**n this review, we encapsulate all the potential interferences for COVID-19 infection as per previous treatments of SARS and MERS. We have found that the general actions are identical significant to enhance host immune reply against RNA viral infection. The immune response has often been shown to be weakened by inadequate nutrition in many model systems as well as in human studies. However, the nutritional status of the host, until recently, has not been considered as a contributing factor to the emergence of viral infectious diseases. Therefore, we propose to verify the nutritional status of COVID-19 infected patients before the administration of general treatments. In addition, we also found coronavirus-specific treatments and antiviral treatments were very useful for the treatment of SARS and MERS. They should also be considered as potential treatments for COVID-19 infection. The other compounds should also be chosen as alternative options for the treatment as well as new drug designs.

**References**

1. Hemila, H. Vitamin C and SARS coronavirus. J. Antimicrob. Chemother. 52, 1049-1050, doi:10.1093/jac/dkh002 (2003).
2. Atherton, J. G., Kratzing, C. C. & Fisher, A. The effect of ascorbic acid on infection chick-embryo ciliated tracheal organ cultures by coronavirus. Arch Virol 56, 195-199, doi: 10.1007/bf01317848 (1978).
3. Field, C. J., Johnson, I. R. & Schley, P. D. Nutrients and their role in host resistance to infection. J Leukoc Biol 71, 16-32 (2002).
4. Hemila, H. Vitamin C intake and susceptibility to pneumonia. Pediatr Infect Dis J 16, 836-837, doi:10.1097/00006454-199709000-00003 (1997).
5. Tangpricha, V., Pearce, E. N., Chen, T. C. & Holick, M. F. Vitamin D insufficiency among free-living healthy young adults. Am J Med 112, 659-662,

doi:10.1016/s0002-9343(02)01091-4 (2002).
6. Holick, M. F. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 80, 1678S-1688S, doi:10.1093/ajcn/80.6.1678S (2004).
7. Nonnecke, B. J. *et al.* Acute phase response elicited by experimental bovine diarrhea virus (BVDV) infection is associated with decreased vitamin D and E status of vitamin-replete preruminant calves. J Dairy Sci 97, 5566-5579, doi:10.3168/jds.2014-8293 (2014).
8. Galmes, S., Serra, F. & Palou, A. Vitamin E Metabolic Effects and Genetic Variants: A Challenge for Precision Nutrition in Obesity and Associated Disturbances. Nutrients 10, doi:10.3390/nu10121919 (2018).
9. Beck, M. A. *et al.* Vitamin E deficiency intensifies the myocardial injury of coxsackievirus B3 infection of mice. J Nutr 124, 345-358, doi:10.1093/jn/124.3.345 (1994).
10. Beck, M. A. Increased virulence of coxsackievirus B3 in mice due to vitamin E or selenium deficiency. J Nutr 127, 966S-970S, doi:10.1093/jn/127.5.966S (1997).
11. Cai, C. *et al.* Macrophage-Derived Extracellular Vesicles Induce Long-Lasting Immunity Against Hepatitis C Virus Which Is Blunted by Polyunsaturated Fatty Acids. Front Immunol 9, 723, doi:10.3389/fimmu.2018.00723 (2018).
12. Begin, M. E., Manku, M. S. & Horrobin, D. F. Plasma fatty acid levels in patients with acquired immune deficiency syndrome and in controls. Prostaglandins Leukot Essent Fatty Acids 37, 135-137, doi:10.1016/0952-3278(89)90110-5 (1989).
13. Morita, M. *et al.* The lipid mediator protectin D1 inhibits influenza virus replication and improves severe influenza. Cell 153, 112-125, doi:10.1016/j.cell.2013.02.027 (2013).
14. Leu, G. Z., Lin, T. Y. & Hsu, J. T. Anti-HCV activities of selective polyunsaturated fatty acids. Biochem Biophys Res Commun 318, 275-280, doi:10.1016/j.bbrc.2004.04.019 (2004).
15. Rayman, M. P. Selenium and human health. Lancet 379, 1256-1268, doi:10.1016/S0140-6736(11)61452-9 (2012).
16. Beck, M. A. & Matthews, C. C. Micronutrients and host resistance to viral infection. Proc Nutr Soc 59, 581-585, doi: 10.1017/s0029665100000823 (2000).
17. Harthill, M. Review: micronutrient selenium deficiency influences evolution of some viral infectious diseases. Biol Trace Elem Res 143, 1325-1336, doi:10.1007/s12011-011-8977-1 (2011).
18. Beck, M. A. *et al.* Selenium deficiency increases the pathology of an influenza virus infection. FASEB J 15, 1481-1483 (2001).
19. Beck, M. A., Shi, Q., Morris, V. C. & Levander, O. A. Rapid genomic evolution of a non-virulent coxsackievirus B3 in selenium-deficient mice results in selection of identical virulent isolates. Nat Med 1, 433-436, doi: 10.1038/nm0595-433 (1995).
20. Ma, X., Bi, S., Wang, Y., Chi, X. & Hu, S. Combined adjuvant effect of ginseng stem-leaf saponins and selenium on immune responses to a live bivalent vaccine of Newcastle disease virus and infectious bronchitis virus in chickens. Poult Sci 98, 3548-3556, doi:10.3382/ps/pez207 (2019).