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RESEARCH ARTICLE

# Silenced Solutions: The Importance of COVID-19 Therapeutics and the Fight Against Suppression

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ABSTRACT

COVID-19 disease is caused by the *Betacoronavirus*, SARS-CoV-2. This virus gave rise to 676 million confirmed cases with 6.9 million deaths worldwide by early 2023. After first appearing in Wuhan, China in late 2019, the virus has mutated into seven successive major forms with progressive increases in infectivity: Alpha, Beta, Delta, Omicron, and Omicron variants BA.4, BA.5, and XBB.1.5. Liposomal mRNA vaccines have been developed against SARS-CoV-2. Many of these received Emergency Use Authorization, and all have been highly promoted by civil authorities and the media. On the other hand, therapeutics against COVID-19 have been developed, but some of these have been severely suppressed, even by reliance on retracted papers. Our laboratory found that chlorpheniramine maleate, an over-the-counter antihistamine, was active against the *Coronavirus* through drug-database searches, molecular modeling, and a preliminary retrospective clinical-study. The manuscript that described this work was rejected by several journal editors without peer review, thus providing further direct evidence for suppression of small-molecule therapeutics. Epidemiologic study of death statistics in the VAERS database showed that 19,710 people lost their lives after COVID-19 vaccination; mortality from all other common vaccines does not sum to even 20% of this staggering value. The vaccine has also been responsible for significant morbidity. A consensus has begun to develop among physicians and scientists that COVID-19 disease and vaccination both result in chronic symptoms in many people, now called "Long COVID" or "Long-hauler's syndrome". Thus, vaccination does not appear to be a reasonable approach to combat COVID-19 disease. In view of this, development, testing, and approval or repurposing of therapeutics is imperative, especially as we observe recent increases in mortality due to COVID-19 Omicron XBB.1.5. Chlorpheniramine maleate, an over-the-counter medication, is uniquely positioned to serve as a broad-spectrum antiviral against SARS-CoV-2 and other viruses in this post-pandemic age.

**Introduction**

COVID-19 viral disease began late in 2019 in Wuhan, China and soon spread to the rest of the world. By April 15, 2020, 206,682 persons were infected in the United States and millions worldwide during that week. This global pandemic ultimately resulted in over 676 million confirmed cases with nearly 6.9 million deaths worldwide by March, 2023[1]. The etiologic agent is the *Betacoronavirus*, SARS-CoV-2[2-8], as shown Figure 1. The original Wuhan strain quickly mutated into the Alpha variant (B.1.1.7) during late 2020[9] and remained quite virulent through early 2021, but it weakened as the Beta variant (B.1.351) emerged midway through 2021. At this point, some believed that the pandemic was over, but the rise of the Delta strain (B.1.617.2) late in 2021 showed that this hope was not to be realized. Delta was considerably more infectious than previous strains, and the virus infected many more people; unfortunately, it also proved to be quite virulent. The Omicron variant (B.1.1.529) displaced Delta in early 2022; this most-recent mutation was exceptionally infectious, but fortunately, was much less pathogenic. Omicron subvariants emerged, and waves of Omicron BA.2/BA.4, BA.5, and XBB.1.5 swept through the world in the first quarter of 2022, mid 2022, and early 2023, respectively. Most considered the pandemic to be over at this point, and that the endemic phase of COVID-19 had begun[10].

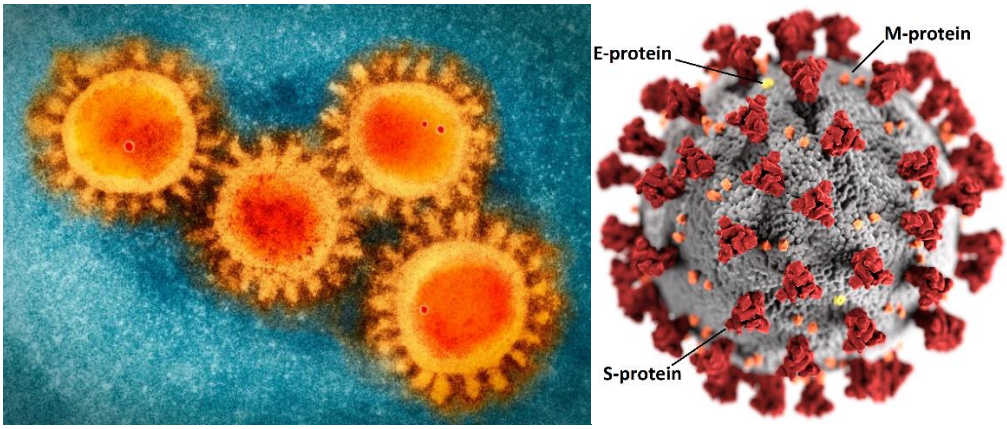


**Figure 1**. SARS-CoV-2, a *Betacoronavirus*, the etiologic agent of COVID-19. **Left.** False-colored transmission electron-microscope image; dark orange shows the nucleocapsid RNA on the interior of the virus. (Scripps Research, https://www.scripps.edu/news-and-events/press-room/2020/20200317-andersen-covid-19-coronavirus.html), **Right.** Computer-graphics image of SARS-CoV-2 with surface proteins identified. (US Centers for Disease Control and the present investigation)

Vaccines were developed in the fight against COVID-19. Many employed a new mRNA-based strategy[11-14] in which the sequence of the SARS-CoV-2 S-protein (spike protein) was encoded in RNA. The RNA molecule was then encapsulated in a lipid nanoparticle, and this preparation was used as an intramuscular vaccine. Various pharmaceutical manufacturers employed different lipids in their formulations and included higher or lower doses of RNA in their vaccines[15-16]. Other candidates were subunit vaccines, and still others used *Adenovirus* vectors[13]. Among these, mRNA vaccines were the most commonly administered globally throughout the pandemic. Ultimately, 50 vaccines were approved worldwide from 242 candidates that were investigated in 821 trials[17]. Vaccines were highly lauded and promoted by governments and health authorities worldwide[18,19]. At the same time, many adverse events were identified with these vaccines, including death[19,20].

Early in the COVID-19 pandemic, various investigators identified small-molecule and antibody therapeutics that showed apparent activity against SARS-CoV-2. These included camostat mesylate, arbidol, chloroquine, hydroxychloroquine, anakinra, lopinavir, darunavir, ribavirin, remdesivir, favipiravir, tocilizumab, sarilumab, siltuximab, bamlanivimab, etesevimab, clazakizumab, canakinumab, and canakinumab[9,21,22]. Later therapeutics included ASC09F, ruxolitinib, baloxavir, molnupiravir, ritonavir, nirmatrelvir, dexamethasone, methylprednisolone, ivermectin, azithromycin, camrelizumab, convalescent plasma,

shuanghuanglian, xuebijing, and tanreqing[23,24]. Hydroxychloroquine received the most scrutiny among these and was examined in 382 clinical trials with 512,586 patients[25]; it was also a most controversial drug. Studies showed that it both treated COVID-19 effectively and promoted death in COVID-19 patients; the well-known RECOVERY study[26] concluded "No clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19." Yet, meta-analysis of clinical work on hydroxychloroquine[25] showed that this drug was effective in all phases of COVID-19 but was most useful at early stages of the disease. Heavy pressure from political, academic, and media sources effectively banned use of this quinolone drug in the treatment of COVID-19[27]. Clinical studies on the other small-molecule drugs showed that ivermectin was very effective, and molnupiravir and remdesivir were reasonably able to treat COVID-19[25]. Ivermectin ($22 US per patient) received significant suppression from political, academic, and media sources, but remdesivir ($136,430 US per patient) was highly promoted.

Recently proposed drugs to treat COVID-19 include glycyrrhizin, quercetin, paxlovid, and chlorpheniramine maleate. Glycyrrhizin, a component of licorice, has been shown to be functional as a broad-spectrum antiviral[28]. Quercetin ($188 US per patient) is an anti-oxidant found in many fruits and vegetables that has been shown to be active against COVID-19[29]; it also has been shown to be a zinc ionophore[30]. Paxlovid (nirmatrelvir-ritonavir; $46,111 US per patient) was developed by Pfizer pharmaceuticals as a combination drug that interferes with SARS-CoV-2 replication by inhibition of the main viral protease (mPro)[31]; it is now widely used but shows only modest activity against COVID-19 somewhat like remdesivir in therapeutic profile[25]. My laboratory showed that the over-the-counter (OTC) antihistamine, chlorpheniramine maleate ($4 US per patient), resembled the structure and properties of hydroxychloroquine by DrugBank database structure-searches and by molecular modeling with energy minimization[32]. Furthermore, we conducted a small retrospective clinical study which showed that no participant who took chlorpheniramine entered the hospital or died from COVID-19[32]. Participants also believed that chlorpheniramine had helped them recover better and faster. This perspective article discusses the above points in further detail with new and updated information.

**Progression and Current State of the COVID-19 Pandemic**

The progression of the COVID-19 pandemic through February 2023 in the United States[33] is shown in Figure 2. The original Wuhan strain mutated into seven major variants: Alpha, Beta, Delta, Omicron, Omicron BA.2/Omicron BA.4, Omicron BA.5, and Omicron XBB.1.5 (a recombinant of BA.2.10.1 and BA.2.75). Each subsequent variant was more infectious than earlier strains, which provided the means for successor C*oronaviruses* to supplant and eliminate earlier strains. The Alpha strain was responsible for the greatest mortality during the pandemic, but the original Wuhan virus caused the greatest Case Fatality Rate (CFR). The CFR decreased progressively through SARS-CoV-2 variants until Omicron. However, from the original Omicron strain through XBB.1.5 and the present, the CFR began to rise; it reached a value just below that of the Delta strain by early 2023.

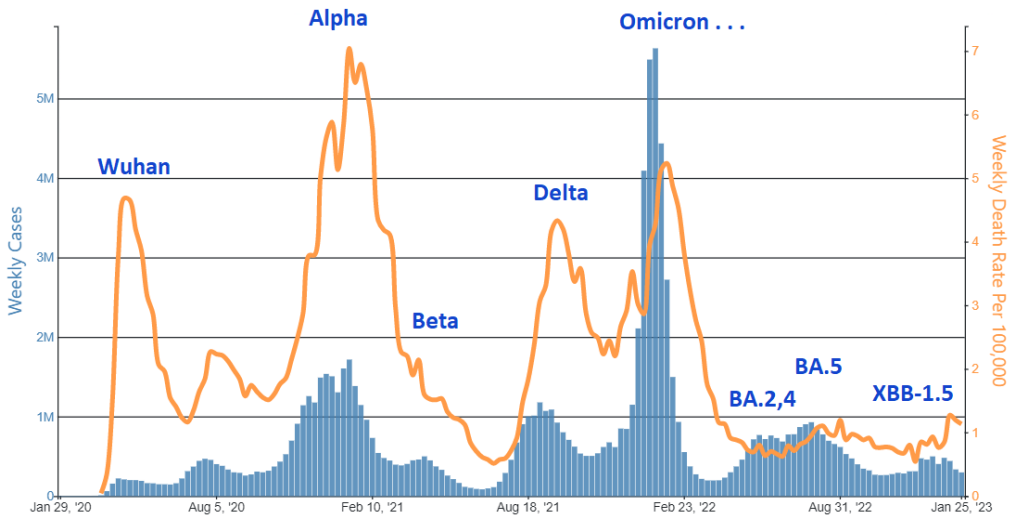


**Figure 2**. Progression of the COVID-19 pandemic in the United States of America. Total weekly confirmed cases are indicated by the left y-axis and are shown as blue bars in the figure. Weekly deaths due to COVID-19 per 100,000 population are shown by the right y-axis as a smoothed orange-line in the figure. Various strains of SARS-CoV-2 are indicated above the times of their maximum incidence and mortality. Data from the US Centers for Disease Control (CDC) and from the present investigation.

The course of the COVID-19 pandemic worldwide is shown in Figure 3[1]. Total cases and deaths reflect information in the introduction. World cases (red bars, right) parallel those shown in Figure 2, but the Beta wave was much larger, and the original Omicron wave shows two peaks instead of one. World deaths (white bars, right) also parallel those in Figure 2, but the original Wuhan strain was more significant, more deaths occurred during the Beta phase, and a significant Omicron XBB.1.5 spike in deaths was seen early in 2023. The lattermost observation is equivalent to the Omicron mortality rise reported above for the United States.

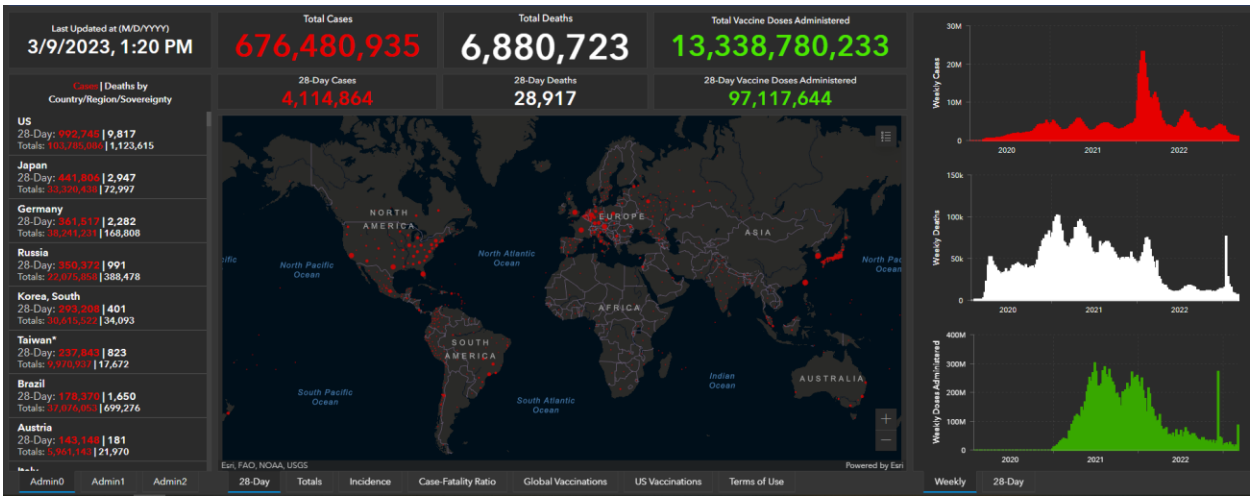


**Figure 3**. Progression of the COVID-19 pandemic throughout the world. Cases and mortality are shown numerically by country on the left and in summary on the top. Incidence by country is shown graphically in the center. Weekly cases (red bars), weekly deaths (white bars), and weekly vaccine doses (green bars) are shown on the right. Data from the Johns Hopkins Coronavirus Resource.

**Vaccine Woes and Therapeutic Vindication**

Liposomal mRNA vaccines based on the SARS-CoV-2 spike protein were developed in early 2020, and the first human trials were begun by Moderna Therapeutics in Seattle, WA[34]. At the same time, the University of Minnesota began a clinical trial of the FDA-approved antimalarial drug, hydroxychloroquine, repurposed against COVID-19. Subsequently, more vaccines were developed, tested, and some received EUA; these were widely promoted as safe and effective. In contrast, work on the therapeutic, hydroxychloroquine, was denounced and suppressed. In May and June of 2020, the prestigious journals, the *New England Journal of Medicine*[35] and *Lancet*[36], respectively, published large clinical studies which showed that COVID-19 patients died at significantly higher rates if they had been treated with hydroxychloroquine. Even though both studies were subsequently retracted, public discourse ramped up against hydroxychloroquine and other promising therapeutics against COVID-19. In contrast, COVID-19 vaccines were promoted throughout the pandemic, and these continue to be recommended as safe and effective today, especially the bivalent vaccine updated with the Omicron spike-protein sequence[37].

Despite the enormous, worldwide push for vaccination, evidence has accumulated which shows that COVID-19 vaccines are the most dangerous ever approved. The author's study of the CDC VAERS database[38] revealed that 19,710 people died after vaccination for COVID-19 by early 2023. In comparison, mortality from all other common vaccines in the same period represents less than 20% of the distressing level of mortality caused by COVID-19 vaccines. A single death in previous vaccine trials was sufficient to disapprove a candidate vaccine; on this basis, COVID-19 vaccines should be pulled from the market. However, mortality is not the only problem with these vaccines. Significant morbidity has been experienced in coagulation disorders that include thrombosis; pericarditis, myocarditis, and other forms of cardiac injury; respiratory distress syndrome; colitis and enteritis; and many others pathologies[20,39].

Long COVID[40,41], also known as Post COVID, Chronic COVID, Post-acute COVID, and Long-hauler's Syndrome, was first recognized by the World Health Organization (WHO) on October 6, 2021[34]. All cases of COVID-19 likely became Long COVID, and it appears that vaccine injury also leads to Long COVID[42]. Dr. Pierre Kory, a critical-care physician, describes "Post COVID-Vaccination Syndrome"[43] that includes long-term fatigue, muscle weakness, tachycardia, short-term-memory loss, tinnitus, joint pain, and many other maladies. However, patients usually present with normal blood-work, electroencephalograms, MRI scans, and echocardiograms. He believes that most symptoms of this syndrome are based on inflammatory processes due to the spike protein.

Another problem with COVID-19 vaccines is a lack of efficacy. Pfizer and Moderna vaccines showed ~95% effectiveness early in the pandemic. Now, however, vaccines are far less effective, and neutralizing antibodies wane within a few months after vaccination[44]. Thus, COVID-19 vaccines now have insufficient efficacy and cause unacceptable levels of morbidity and mortality. Therefore, EUA for all COVID-19 vaccines should be suspended immediately for the sake of public health.

Like hydroxychloroquine, work from the author's laboratory on chlorpheniramine maleate (completed in July 2020) was highly suppressed. Many journal editors rejected the manuscript on this work, though it finally received peer review in *Cureus* and was published in early 2022[32]. Our database studies in Drug Bank followed by energy minimization and structure alignment showed that chlorpheniramine should be active against COVID-19. A retrospective clinical study[32,45] revealed that no participant died or was hospitalized if they used chlorpheniramine. Furthermore, they recovered about 50% faster and believed that chlorpheniramine had helped them an average of 66% in updated results. The author used this OTC drug periodically through the pandemic and never contracted the *Coronavirus*, though he had been exposed to COVID-19 directly on numerous occasions throughout the pandemic. Prophylactic use of chlorpheniramine maleate was also effective. One case, in this connection, is notable in which "Person A" traveled in a small car for four hours with a friend who had an active case of COVID-19. Person A had taken chlorpheniramine preventively and did not contract the virus. On the other hand, seven family members at their destination were exposed to the infected friend and, soon thereafter, all became ill with COVID-19, one requiring hospitalization.

Chlorpheniramine maleate was also studied in tissue culture of human Vero 76 cells challenged with SARS-CoV-2[46]. Westover *et al.* found that chlorpheniramine caused a 99.7% decrease of virus in these cells. This shows that not only can chlorpheniramine interfere with the entry of SARS-CoV-2 into the cell via the ACE-2 receptor, but it is also virucidal. These investigators currently study a chlorpheniramine nasal spray they hope will serve to curb COVID-19 infection.

Other research groups showed that chlorpheniramine maleate was active against the *Influenza* virus[47] and the EBOLA virus[48]. OTC pharmaceutical manufacturers reformulated most cold and flu products late in the pandemic to include chlorpheniramine maleate. For example, Actifed™ traditionally contained the antihistamine, triprolidine, and pseudophedrine, but generic successors were reformulated late in the pandemic to include chlorpheniramine maleate with pseudophedrine. These findings, in concert with those above, suggest that chlorpheniramine serves as an accessible, broad-spectrum antiviral.

Many recent clinical studies with ivermectin have shown that it is highly effective to treat COVID-19 with a modest cost of $22 US per patient[25]. Public outcry against this drug sought to curb its use[49], but physicians, nonetheless, continued to prescribe this repurposed anthelmintic. Ivermectin also appears to be a viable approach to treat COVID-19.

## Conclusion

The COVID-19 pandemic has been with us since late 2019, and, over intervening years, the world has been ravaged by waves of SARS-CoV-2 and many major variants (Alpha, Beta, Delta, Omicron). Each successive strain exhibited greater infectivity, and the most recent Omicron recombinant subvariant, XBB.1.5, is not only the most infectious yet but also exhibits substantially increased mortality. COVID-19 vaccines were developed to combat this dangerous virus, but these are plagued with many dangerous morbidities, falling efficacy, Long COVID symptoms that may persist in patients for years, and troubling mortality. We have little choice other than to remove these from general use for the common good. Once highly suppressed, small-molecule therapeutics such as ivermectin, hydroxychloroquine with zinc, quercetin with zinc, glycyrrhizin, and chlorpheniramine maleate now stand as the best alternatives to vaccines and should be able to carry us through the endemic age of COVID-19 and other viruses. Chlorpheniramine maleate is the most accessible and affordable alternative among these.

## Author Contributions

The author, S.D.B., performed all work on this project and with this manuscript.

## Conflict of Interest Statement

There are no conflicts to declare.

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