# Review: Improving Therapeutics for COVID-19 with Glutathione-boosting Treatments that Improve Immune Responses and Reduce the Severity of Viral Infections.

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**Abbreviations:**

ALA, Alpha Lipoic Acid;

COVID-19, Corona Virus Disease 2019;

IL, Interleukin;

INFγ, Interferon gamma;

GCL, glutamate-cysteine ligase;
GSH, reduced glutathione;
GSSG, oxidized glutathione/glutathione disulfide;
GSH-C4, N-butanoyl GSH derivative;
NAC, N-Acetyl Cysteine;
Nrf2, Nuclear factor erythroid 2-related factor 2 transcription factor;
NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells;
ROS, Reactive Oxygen Species;
SARS-CoV-1, Severe Acute Respiratory Syndrome-Corona Virus-1;
SARS-Cov-2, Severe Acute Respiratory Syndrome-Corona Virus-2;
TGF-β1, Transforming Growth Factor- Beta1;
Th, T helper;
T2DM, Type II Diabetes Mellites;

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## Abstract

Glutathione-boosting treatments have been shown to enhance immune responses and reduce the severity of influenza, coronavirus, HIV and other viral infections. Such viral infections markedly increase the production of Reactive Oxygen Species (ROS) and deplete cysteine and critical antioxidants, including reduced glutathione (GSH). These viruses use depletion of GSH to create an oxidized environment needed for viral replication/assembly and evading the host immune system. High levels of reduced glutathione in antigen presenting cells is critical for mounting an adaptive immune response to viral infections and for avoiding inflammatory cytokine responses. SARS CoV-1 up-regulates TGF-β1, which increases ROS, depletes glutathione and lowers substrate and enzyme needed for glutathione synthesis. Demographic groups with highest susceptibility to SARS-CoV-2 infection (e.g. the elderly; diabetics and African-Americans) have lower levels of Glutathione, lower amino acid substrate and/or critical enzyme needed to synthesize glutathione. Increased susceptibility of the elderly,

diabetics and African-Americans to SARS-CoV-2 may in part be due to a reduced ability to maintain high GSH and redox status during viral infection.
This paper reviews a substantial body of evidence that Glutathione-boosting supplements including N-Acetyl Cysteine (NAC), Alpha Lipoic Acid (ALA) and Liposomal Reduced Glutathione have beneficial effects in combating viral disruption of redox status and immune responses in animal models and in humans. Glutathione-boosting treatments improve immune responses, as well as reduce viral replication, inflammatory cytokines and/or severity of viral infections, including HIV and even Influenza in the elderly. The potential for glutathione-boosting supplements to reduce risks of severe COVID-19 induced cytokine storms and disease in susceptible populations is addressed. Clinical trials are needed to determine if the severity of COVID-19 is reduced from onset of symptoms by: combined oral treatment with up to 2400 mg/day NAC and 1200 mg/day ALA; or with NAC, ALA and 2000 mg/day oral Liposomal Reduced Glutathione; versus a placebo control.

**Keywords:** COVID-19, SARS-CoV-2, Glutathione, N-Acetyl Cysteine, Alpha Lipoic Acid; Liposomal Reduced Glutathione; Cytokine Storm; Improving Therapeutics for COVID-19; Glutathione-boosting Treatments; Reducing severity of viral infection

**Summary:** Viruses induce oxidative stress, deplete glutathione and subvert immune defenses. N-Acetylcysteine, Alpha Lipoic Acid and Liposomal Reduced Glutathione boost glutathione, enhance immunity, reduce severity of viral infections and need testing in COVID-19.

## REVIEW

**Glutathione is the most important antioxidant in the body, especially in the lung**. It is synthesized within cells as a three amino acid peptide consisting of glycine, cysteine and glutamic acid. Of these amino acids, cysteine is the most rate-limiting for the synthesis of glutathione. Glutathione occurs in the thiol reduced form (GSH) and the disulfide-oxidized form (GSSG) (Fraternale et al. 2017). GSH reacts with ROS and other oxidizing species before the latter can react with cellular proteins and nucleic acids,

reducing them while converting glutathione to the oxidized GSSG form. With the aid of Lipoic Acid, several critical antioxidant enzymes then convert the oxidized form back into the reduced form, regenerating GSH. The relative amount of each form, e.g. the GSH/GSSG ratio or cellular redox status is used as an indicator of cellular antioxidative capacity. GSH also plays critical roles in detoxification of toxic compounds and regulating the immune system.

**Influenza, Coronavirus and HIV infections markedly increase the production of ROS and deplete cellular antioxidant defense systems including decreasing glutathione and several critical antioxidant enzymes** (Khomich et al. 2018). Many viruses, including Influenza and Coronaviruses, also use the depletion of GSH and critical antioxidants to create an oxidized environment needed for viral replication/assembly and to evade the host immune system (Imai et al. 2008, Morris et al. 2013, Fraternale et al. 2017).
SARS CoV-1 protease up-regulates TGF-β1 by a pathway involving increased ROS/p38 MAPK/STAT3 (Li et al. 2016). This is important since ROS activates and induces TGF-β1, which depletes glutathione, inhibits many antioxidant enzymes, including the rate limiting enzyme in glutathione synthesis, glutamate-cysteine ligase (GCL) and increases protein and lipid peroxidation (Liu and Pravia 2010, Liu et al. 2012). TGF-β1 inhibition of GCL and depletion of GSH seems to be an early event in viral infection and the development of pulmonary fibrosis (Liu et al. 2012).

In essence, several viruses including influenza, coronavirus and HIV, use the depletion of GSH to create an oxidized cellular environment needed for viral replication~~,~~ and evading the host immune system. The studies below describe a novel approach that defends against viral attack and depletion of GSH by boosting GSH with nutritional and nutraceutical treatments that improve immune responses and reduce the severity of viral infections. Since this glutathione-boosting approach has shown promise with other viral infections, clinical trials are needed to determine the efficacy of these glutathione boosting strategies for treating COVID-19.

**Research shows that treatments that increase GSH, including the cysteine derivative N-acetyl cysteine (NAC) and bioavailable GSH preparations can reduce the severity of some influenza and coronavirus infections, and can synergize with antivirals for greater efficacy**. De Flora and colleagues showed in a randomized clinical trial that long-term treatment with NAC (1200 mg/day) markedly attenuated the severity of seasonal $H_1N_1$ Flu, especially in the elderly (De Flora et al. 1997). While NAC did not reduce the rate of infection, it improved cell-mediated immunity and greatly reduced the severity of influenza-like symptoms and length of bed rest. NAC also helps to break up mucous.
Another study showed that NAC alleviated cellular injury and the severity of Porcine Epidemic Diarrhea virus infections, a coronavirus that causes diarrhea in pigs (Wang et al. 2017).

**Cysteine is generally considered to be the rate-limiting amino acid for the synthesis of reduced glutathione, the most important antioxidant in the lung.** Low levels of glutathione can often be ameliorated with NAC and/or adequate dietary protein. NAC also acts directly as a free radical scavenger. Antioxidants in certain foods and especially Alpha Lipoic Acid (ALA) induce antioxidant enzymes and the glutathione biosynthetic enzyme, glutamate-cysteine ligase (GCL). Thus, combining NAC with antioxidants contained in darkly colored fruits and vegetables, (blueberries, pomegranate, broccoli, etc.), and with ALA proves even better at reducing oxidative stress and increasing glutathione in important tissues like the lung (McCarty and DiNicolantonio 2015). It is relevant to note that cysteine and glycine may also limit glutathione synthesis in the elderly, vegetarians and others on low protein diets (Sekhar et al. 2011, McCarty and DiNicolantonio 2015, McCarty et al. 2018).

Studies in mice show that protein malnutrition decreases immunity and increases susceptibility to influenza infection (Taylor et al. 2013). These and other studies show the importance of adequate nutrition in maintaining glutathione levels and fighting off viral infections (Minich and Brown 2019). Adherence to a Mediterranean diet has been associated with increased GSH/redox balance and decreased oxidative stress (Dai et

al. 2008, Bettermann et al. 2018). These finding emphasize why public policy should also consider nutrition during this COVID-19 pandemic, when many have been displaced from their jobs and sources of income to purchase or grow food.

NAC inhibits virus replication and expression of pro-inflammatory molecules in a human lung cell line following infection with highly pathogenic H5N1 influenza A virus (Geiler et al. 2010), suggesting that NAC may represent a potential treatment option for influenza pandemics.

NAC is considered to be a safe antidote for many different conditions that involve a deficiency of cysteine/glutathione (Atkuri et al. 2007). The beneficial effects of NAC involve both antioxidant and anti-inflammatory mechanisms, including restoring GSH and attenuating proinflammatory cytokines (Bemeur et al. 2010).

Nencioni and colleagues discuss viral redox signaling and antioxidants that could be used to target influenza infections (Nencioni et al. 2011). While some have suggested antioxidants as potential therapies for severe influenza, others have raised concerns as to the effectiveness of antioxidants like NAC for all strains of influenza, and if treatment is initiated after a viral challenge (Sgarbanti et al. 2014). Combining antioxidants with antiviral drugs synergistically reduced the lethal effects of influenza virus infections (Uchide and Toyoda 2011). Experiments in mice showed that NAC alone was only partially protective, while combined treatment with NAC and the antiviral, oseltamivir, was fully protective of lethal influenza infection (Garozzo et al. 2007). These studies suggest that agent(s) with antioxidant and antiviral activities could be effective treatments for patients with severe influenza-associated complications.

**Problem with increasing glutathione with cysteine formulations:** Cysteine is toxic at high concentrations and easily oxidizes to the less soluble cystine (Fraternale et al. 2017). Thus compounds that can be metabolized to cysteine are used as pro-drugs to increase levels of GSH. The simplest of these, NAC, is relatively inexpensive, approved for certain uses in humans and is available over the counter but has a limited bio-

availability. Other pro-glutathione compounds that can be metabolized to cysteine and are more bioavailable have been developed, including I-152, a Conjugate of N-acetyl-cysteine and mercaptoethylamine **(Crinelli et al. 2019)** but there is less known about their relative safety.

A clinical trial evaluating the effect of oral treatments on redox status in volunteers with metabolic syndrome found that low-dose NAC and sublingual GSH improved redox status, while orally ingested GSH did not (Schmitt et al. 2015). These and other data suggest that oral GSH has a relatively low bioavailability in humans. GSH-derivatives that can be absorbed by cells have also been developed, including a N-butanoyl GSH derivative, GSH-C4, that increased GSH levels, blocked viral replication and inhibited inflammation (Amatore et al. 2019). Even in old mice infected with influenza A, GSH-C4 was very effective at increasing GSH levels, blocking viral replication and inducing a predominant Th1 immune response (Amatore et al. 2019).

**Boosting Glutathione with Liposomal GSH:** Liposomal Reduced Glutathione (Liposomal GSH) formulations for delivering GSH have been developed that can be taken orally, are absorbed through the oral/stomach mucosa, pass through lymphatics into the blood stream (bypassing first pass metabolism) and are absorbed into cells, with relatively high bioavailability (Ly et al. 2015, Sinha et al. 2018). Oral supplementation with 500 to 1000 mg/day of liposomal GSH elevated blood, plasma and peripheral blood mononuclear cell glutathione levels and improved markers of immune function (Sinha et al. 2018).

The use of Liposomal GSH to boost GSH concentrations has the potential advantage of rapidly increasing cellular GSH regardless of whether cysteine, GCL or other glutathione biosynthetic enzymes are depressed. Since glutathione levels and GCL activity are decreased in diabetics and the elderly, and since several viruses, including Coronaviruses, appear to further deplete cysteine and GCL, oral Liposomal reduced glutathione may be a better candidate for restoring glutathione during SARS-COV-2 infection even in the midst of a cytokine storm.

**Cytokine Storm:** The symptoms of severe influenza are often attributable to an overly exuberant immune response that involves release of proinflammatory cytokines and chemokines triggered by the virus infection (Liu et al. 2016). Severe lung injury caused by SARS-CoV-1 depends on the viral activation of oxidative-stress, coupled to a proinflammatory host response by the innate immune system (Imai et al. 2008, Smits et al. 2011). These so called “cytokine storms” can also be seen with SARS-COV-2 and the resulting inflammation greatly contributes to the lethality of severe COVID-19 (George 2020).

Boosting GSH with long-term NAC promoted adaptive immune responses to Influenza H1N1 infection while decreasing inflammatory responses and the severity and duration of influenza symptoms (De Flora et al. 1997). For HIV, other glutathione-boosting drugs helped restore Th1/Th2 cytokine balance in a mouse AIDS model (Brundu et al. 2016). Treatment with Liposomal GSH during viral infections helped restore a balance of cytokines that promoted cell mediated immunity and reduced inflammation. Relative to healthy controls, HIV patients show decreased GSH, decreased Th1 cytokines including Interleukin (IL)-12, IL-2 and INFγ, and elevated free radicals and inflammatory cytokines, including IL-6, IL-10 and TGF-beta (Valdivia et al. 2017). In two different HIV clinical trials, oral Liposomal GSH boosted glutathione; increased Th1 cytokines including IL-12, and INFγ; lowered oxidative stress and inflammatory cytokines including IL-6 and IL-10; while improving the ability of peripheral blood mononuclear cells to kill Mycobacterium tuberculosis (M.tb.) (Ly et al. 2015, Valdivia et al. 2017).

The finding that liposomal reduced glutathione supplementation reduced elevated levels of inflammatory cytokines including IL-6 in HIV patients is very significant to the current pandemic since a study to be published (Tao Liu et al., Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China) noted that elevated IL-6 in Covid-19 patients was the clearest predictor for respiratory failure and need for mechanical ventilation.

**Glutathione and the immune response of Diabetics and African-Americans:** Data shows that SARS-CoV-2 infections are more severe in the elderly, Type II diabetics and African-Americans, all of which have lower glutathione levels (Sekhar et al. 2011, Sekhar et al. 2011, Morris et al. 2012, McCarty and DiNicolantonio 2015). Total and reduced GSH are lower in plasma and monocytes of Type II Diabetics (T2DM) than in healthy controls (Lagman et al. 2015). The lower glutathione levels in diabetics seems to be due to elevated TGF-beta decreasing Glutamine-Cysteine Ligase Catalytic Subunit, and therefore glutathione synthesis (Lagman et al. 2015). While T2DM are several times more susceptible to infectious diseases including M. tb, supplementation of their cultured monocytes with 10 mM NAC or 10 micromolar liposomal GSH improved immune responses and reduced survival of M. tb (Lagman et al. 2015).
In addition to lower glutathione levels (Morris et al. 2012), African-Americans show higher levels of oxidative stress and inflammatory markers, including IL-6, than Caucasians (Feairheller et al. 2011), both of which would be expected to increase risk for more severe COVID-19 infections.

**Glutathione and Immune response in the Elderly:** Levels of glutathione decrease in elderly humans (Sekhar et al. 2011, McCarty and DiNicolantonio 2015) and in elderly mice (Amatore et al. 2019). In addition to decreased glutathione, elderly humans also have reduced levels of two of its amino acids constituents, cysteine and glycine, than younger individuals (Sekhar et al. 2015). Similarly, old mice have much lower levels of glutathione and cysteine in lung and lymph nodes compared to young mice (Amatore et al. 2019).

While most studies have indicated that Cysteine is rate limiting for glutathione synthesis, supplementing elderly humans with NAC and glycine for 14 days increased the levels of cysteine, glycine, glutathione, and GSH/GSSG ratio, while decreasing oxidative stress (Sekhar et al. 2011). These studies suggest that glutathione deficiency in the elderly is, in part, due to decreased supply of precursor amino acids, and restoring adequate protein/amino acid intake helps restore glutathione levels (Sekhar et al. 2011, McCarty and DiNicolantonio 2015).

Maintaining high levels of glutathione is important since glutathione levels in antigen presenting cells determine whether a T helper1 (Th1) or Th2 cytokine response will predominate (Peterson et al. 1998). The reduced levels of glutathione in the elderly are thought to contribute to the decreased immune response (through the Th1 pathway), and the increased inflammatory response (through the Th2 pathway) (Fraternale et al. 2017). In essence, during aging glutathione levels decline and the immune system shows a deficiency in the Th1 immune response, which weakens host defenses against viral infection (Amatore et al. 2019).

Treatments that increase glutathione levels partially restore the immune responses of the elderly toward that of younger individuals. In aged influenza-infected mice, boosting glutathione with a GSH-C4-derivative inhibited viral replication and helped restore a Th1 predominant immune profile (Amatore et al. 2019). These results are similar to those found in a randomized human clinical trial with long term 1200 mg/day NAC. In this human clinical trial, NAC progressively improved cell mediated immunity and greatly decreased the severity of influenza like symptoms, especially in the elderly (De Flora et al. 1997). However, in severe influenza, antioxidants including NAC alone may not be sufficient to prevent cytokine storms (Liu et al., 2016). Combinations of antioxidants and immunomodulators either alone or in combination with antivirals may be needed to treat severe influenza.

The finding that SARS-CoV-1 upregulates TGF-β1 through ROS is important since SARS-CoV-2 likely shows a similar effect. Demographic groups with highest susceptibility to severe SARS-CoV-2 infections, including the elderly, diabetics and African-Americans, have lower levels of glutathione/GCL and are more susceptible to oxidative stress (Sekhar et al. 2011, Sekhar et al. 2011, Liu et al. 2012, Morris et al. 2012, McCarty and DiNicolantonio 2015). NAC and GSH have been used to treat fibrotic diseases and have greatest effects when initiated in early inflammatory stages (Liu and Pravia 2010).

While GSH levels have been rarely considered in COVID-19 patients, a small case study to be published measured levels of reduced Glutathione (GSH) levels and Reactive Oxygen Species (ROS) in four COVID-19 patients (Alexey Polonikov, Department of Biology, Kurst State Medical University, Russian Federation). Although the data are very limited, the two individuals with severe COVID-19 had lower GSH levels, higher ROS levels and much higher ROS/GSH ratio than the two patients with mild COVID-19. While confirmatory studies are needed, the limited data and literature review of Polonikov, as well as the current more extensive review, support the hypothesis that inability to maintain glutathione levels in the face of SARS-CoV-2 generated ROS as an important risk factor for severe COVID-19 infection.

These observations suggest that the increased susceptibility of the elderly, diabetics and African-Americans to COVID-19, is in part due to their reduced ability to maintain high GSH and redox status during viral infection. If so, boosting GSH should reduce the severity of COVID-19.

**Alpha Lipoic Acid or Lipoic Acid (ALA)** is a powerful over-the-counter antioxidant that upregulates several antioxidant enzymes, increases glutathione levels and the regeneration of reduced antioxidants, including reduced GSH (Suh et al. 2004). ALA induces a transcription factor, Nuclear factor erythroid 2-related factor 2 (Nrf2), that induces synthesis of several critical antioxidant enzymes, including glutamate-cysteine ligase (GCL), the rate limiting enzyme controlling glutathione synthesis (Suh et al. 2004). Nrf2 declines with age, resulting in lower GCL and lower GSH in the elderly. However, treatment with ALA induced Nrf2, GCL catalytic subunit/GCL activity and helped restore glutathione levels in old rats (Suh et al. 2004).

ALA helps recycle Glutathione, Vitamin C, Vitamin E and Co-enzyme Q10 from their oxidized state back to their reduced, active state (Rochette et al. 2015, Hagen 2019). ALA also scavenges reactive oxygen and nitrogen species, including those increased by viral infections. Because of these diverse actions, ALA is often considered a universal antioxidant. ALA also reduces inflammation by inhibiting the activation of NF-

KB (Rochette et al. 2015). ALA binds iron, thereby reducing chances for iron/copper mediated redox cycling of antioxidants, which can cause extensive oxidative damage (Valko et al. 2005). Typically, only very low levels of ALA are present in foods, and oral supplements of 600 to 1200 mg per day in split doses are required for beneficial health effects.

A randomized clinical trial to be published examined the effect of intravenously administered ALA 1200 mg/day on critically ill COVID-19 patients (Ming Zhong et al., Department of Critical Care Medicine, Zhongshan Hospital, Fudan University, Shanghai, China). The 30-day all-cause mortality in this study tended to be lower in the ALA treatment group (3/8, 37.5%) compared to that in the placebo control (7/9, 77.8%, P=0.09). Although sample sizes and statistical power were limited, the data suggest ALA warrants additional clinical trials in COVID-19 patients.

Oral ALA helped restore glutathione and lymphocyte function in HIV infected patients (Jariwalla et al. 2008). ALA showed beneficial effects in Influenza A infected cells, including reducing virus propagation, reducing nuclear translocation of NF-κB, reducing Caspase-3 and increasing Type 1 Interferons (Bai et al. 2012). Additionally ALA has been used to reduce oxidative stress, blood sugar and peripheral neuropathy in diabetics, (Rochette et al. 2015, Sarezky et al. 2016).

Nutraceuticals including NAC, ALA, selenium, zinc, Spirulina, and Yeast Beta-Glycan have also been proposed to boost immune responses and reduce inflammatory responses to viral infections, including influenza and COVID-19 (McCarty and DiNicolantonio 2020). Of note, selenium is an essential cofactor for glutathione peroxidases and influenza is more pathogenic in selenium-deficient mice (McCarty and DiNicolantonio 2020). Using a population-based biological selenium marker, regions of China with selenium deficiency showed higher death rates from COVID-19 infection, whereas regions with adequate selenium showed higher cure rates from the infection

(Zhang et al. 2020). These authors provide additional converging evidence supporting the need for further clinical research in this area.

**A Race:** Once a SARS-COV-2 infection has started, there is likely a race between the host synthesizing and replenishing glutathione needed to mount an effective immune response, versus the virus depleting glutathione, cysteine substrate and enzymes needed to synthesize glutathione, and thwarting an effective immune response. Combined treatment with NAC and ALA is likely to be more effective than either compound alone for restoring glutathione and reducing severity of viral infections. Combined treatment increases cysteine levels, glutathione biosynthetic enzymes, including GCL, as well as other antioxidant enzymes that help regenerate reduced GSH. Combined treatment with NAC and ALA should help shift the advantage toward restoring glutathione and immune defenses. The addition of Liposomal reduced Glutathione to NAC and ALA should be even more effective in counteracting COVID-19 to restore cellular GSH levels and immune function and reduce inflammation/cytokine storm. Efficacy of these treatments need to be tested in standard or adaptive clinical trials.

**Need for Clinical Trials of Glutathione-boosting nutraceuticals on COVID-19:** As described above for several viral diseases, boosting glutathione inhibits viral replication, and improves immune responses, while reducing oxidative stress, inflammatory responses and disease severity. However, we do not know about effects on COVID-19.

Randomized clinical trials are needed to determine if the severity of COVID-19 is reduced by combined oral treatment with up to 2400 mg/day NAC and 1200 mg/day ALA; or with combined NAC, ALA and 2000 mg/day oral Liposomal Reduced Glutathione; versus a placebo control.

While combined NAC, ALA and Liposomal Glutathione is likely most efficacious and may be needed for more severe COVID-19 cases, supplies of Liposomal Glutathione are likely more limiting. Thus, the combined NAC and ALA treatment should be included

since it may be sufficient to reduce severity of mild to moderate COVID-19 cases. Treatments should be administered on an empty stomach in divided doses through the day.
Inclusion of adequate diets including adequate protein is important, especially for the elderly. The efficacy of glutathione boosting treatments reducing the severity of COVID-19 is likely greater if initiated at the very beginning of viral infection/symptoms.

Ideally, clinical trials would include collecting patient samples for analysis of SARS-COV-2 viral loads, cytokines, chemokines, GSH/redox status and oxidative stress markers (Ho et al. 2013). In the midst of the SARS-COV-2 pandemic, collection and analysis of such samples may be difficult, thus flexible adaptive trials may need to be conducted as part of emergency clinical treatments.

Emerging data shows that the effects of SARS-COV-2 infections are highly variable between individual humans. It appears that some people show no symptoms for COVID-19, but shed virus, while others show moderate symptoms and still others show severe respiratory symptoms requiring hospitalization and causing death. We need to investigate the sources of this variability, including genetic, nutritional and environmental factors. Since GSH boosting treatments improve the balance of Th1/Th2 cytokines and improve immune responses during viral infections (Ly et al. 2015, Valdivia et al. 2017), immune responses of COVID-19 patients should also be analyzed to determine if the proposed treatments improve immune responses and the duration of immunity.

The identification of OTC therapeutics that reduce the severity of COVID-19 could potentially reduce the percentage of patients requiring hospitalization and ventilators. This could save lives and markedly reduce the pressure on hospitals and medical system, especially in regions and countries with less developed health care systems. The identification of OTC therapeutics that reduce the severity of COVID-19 would also reduce the risk of lifting “isolations-in-place” and enable a more rapid return to open societies and functioning economies.

**It is prudent to consult one's physician before taking any drug**. NAC, ALA and Liposomal Glutathione have highly favorable safety profiles and oral doses up to those discussed above have not been associated with serious adverse reactions (Ziegler 2004). However, several authors have indicated that NAC should not be taken by those on nitroglycerin or isosorbide, since these compounds interact to markedly lower blood pressure. Individuals with a thiamine (Vitamin B1) deficiency or with a risk of this deficiency, due to heavy drinking, should take a thiamine supplement along with ALA (Magnifico 2016). Most common side effects of NAC include, nausea, vomiting, or dizziness. At doses above 1200 mg ALA per day, some individuals have shown toxic effects including nausea, vomiting, abdominal pain, rash and vertigo. Substantially higher doses of NAC and ALA can be toxic.

## Conclusion

Scientific evidence is presented that several pathogenic viruses, including influenza and corona viruses, create an oxidized environment in host cells needed for viral replication/assembly and for evading the host immune system. These viruses accomplish this to a significant degree through generation of massive levels of ROS and depletion of GSH and associated antioxidant defense systems. GSH and ALA play critical roles in antioxidant defense systems needed to help defend against viral attack. GSH also plays important roles in redox signaling, and along with ALA can improve immune responses to viral infection while helping to avoid inflammatory cytokine and chemokine responses. Cysteine and glycine are reduced in the elderly and viruses also reduce levels of cysteine. Glutathione-boosting treatments, especially NAC, ALA and Liposomal GSH, have been scientifically shown to enhance immune responses and reduce the severity of influenza, HIV and corona virus infections. A randomized clinical trial conducted over 20 years ago showed that long-term NAC (1200 mg/day) markedly reduced the severity of Influenza A, especially in the elderly. Evidence is reviewed that GSH boosting treatments, alone or in combination, improve the balance of Th1/Th2 cytokines and improve immune responses to the above-mentioned viral infections in lung cell lines, in animal models and/or in humans. In essence, these data suggest that

nutritional/nutraceutical supplementation with NAC, ALA and Liposomal GSH boosts a healthy immune response to infections by the above viruses, strengthening a Th1 response without overstimulating an inflammatory Th2 response.

But what about COVID-19? Since groups with highest susceptibility to COVID-19, including the elderly, diabetics and African-Americans have decreased glutathione levels/synthetic capacity, the need for clinical trials of glutathione-boosting nutritional/nutraceutical supplements is evident. Clinical trials would help test this explanation for the high susceptibility of these groups to severe COVID-19. Information gained from clinical trials and additional experiments could potentially lead to an improved understanding of the factors controlling susceptibility to severe COVID-19, as well as nutritional and nutraceutical treatments that could be used to reduce the severity of this viral disease worldwide.

In conclusion, in the midst of this serious COVID-19 pandemic, the case is made that there is urgent need for well-designed clinical trials of glutathione-boosting treatments.

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