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# The Effectiveness of a Combination Therapy in Treating Severe Influenza: Hypothesis on The Efficacy of Hydroxychloroquine Combined with A Macrolide and Potentially Natural Therapies

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## Abstract

The influenza virus is the source of annual epidemics that pose significant public health challenges, leading to substantial morbidity and potentially high mortality, particularly among the elderly and individuals with risk factors. The severity of these impacts varies from year to year. Currently, the primary method of combating the influenza virus is vaccination, which has demonstrated variable effectiveness depending on the circulating serotype. Additionally, the pneumococcal vaccine plays a role in preventing bacterial superinfections, which can complicate cases of influenza.

It seems increasingly important to revisit the possibility of curative treatments. At present, oseltamivir is the main pharmacological options available. We hypothesize that hydroxychloroquine, in combination with macrolides and potentially natural therapies (e.g., Elderberry (*Sambucus nigra*)), could be beneficial due to their mechanisms of action. These drug therapies might significantly reduce the morbidity and mortality associated with influenza when administrated art the early phase of the disease. Further research and exploration of such integrated approaches are warranted to better address the public health burden of influenza.

**Keywords:** Influenza; macrolide; hydroxychloroquine; Elderberry; *Sambucus nigra;* alkalinization

## Introduction

The medical treatment for influenza is very limited in common practice. Typically, the flu vaccine remains the cornerstone of influenza prevention. The vaccine against pneumococcal infections is also of paramount importance, particularly for elderly individuals and those with risk factors, as bacterial complications of viral infections are common and sometimes severe. As the saying goes, "the aggression is viral, and the infection is bacterial," highlighting the need to take these infections seriously as well. A study published in Archives of Internal Medicine in 1999 demonstrated that pneumococcal vaccination alone was associated with a 27% reduction in hospitalizations for pneumonia and a 34% reduction in mortality among elderly individuals with chronic lung disease. Furthermore, the combination of influenza and pneumococcal vaccines provided additional benefits, with a 63% reduction in hospitalizations for pneumonia and an 81% reduction in mortality compared to no vaccination (1). The flu vaccine, while a key tool in combating influenza, has variable efficacy depending on how well it matches the circulating strains. While neutralizing antibodies may develop after vaccination, the possibility of facilitating antibodies cannot be entirely ruled out. These may lead to ADE (Antibody-Dependent Enhancement)

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phenomena, especially when the vaccine is not fully adapted to the circulating strain (2-5). This limitation highlights the need for a pharmaceutical treatment capable of both preventing and curing influenza.

A meta-analysis titled "Association between Vitamin D and Influenza: Meta-Analysis and Systematic Review" published in 2022 concluded that vitamin D supplementation significantly reduces the risk of influenza infections. The authors analyzed 10 randomized controlled trials involving a total of 4,859 participants and found that vitamin D supplementation was associated with a 22% reduction in the risk of influenza infection (RR = 0.78, 95% CI: 0.64–0.95). These findings suggest that vitamin D supplementation could be an effective strategy for influenza prevention (6). Elderberry (*Sambucus nigra*) has demonstrated notable antiviral properties against influenza viruses, operating through several molecular mechanisms. Numerous studies have shown that elderberry exhibits activity against the influenza virus by inhibiting hemagglutination and viral proliferation, as well as preventing the virus from adhering to receptor cells. Furthermore, elderberry is believed to stimulate the immune system by increasing the production of cytokines and antibodies. The flavonoids it contains, with their antioxidant properties, may also contribute to a beneficial effect against the influenza virus. There are also proteins in elderberry extracts that inhibit the action of ribosomes and, consequently, the translation of viral RNA into proteins (7-9). This aligns with the possible mechanism of action of macrolides discussed in this article.

These findings highlight the potential of elderberry's bioactive components to disrupt critical stages of the influenza virus's life cycle, supporting its role as a natural therapeutic agent for preventing and managing influenza infections. Hawkins et al. meta-analysis, involving 180 participants, assesses the effects of elderberry supplementation on upper respiratory symptoms, considering factors such as vaccination status and underlying pathology (10). The findings indicate a significant symptom reduction with a substantial effect size. These results suggest that elderberry could serve as an alternative to antibiotics for viral respiratory infections and a safer option than prescription drugs for the common cold and influenza. Oseltamivir and peramivir are antiviral medication used to treat and prevent influenza. It works as a neuraminidase inhibitor, targeting a key enzyme of the influenza virus (11). Neuraminidase facilitates the release of new viral particles from infected cells and promotes the spread of the virus within the body. By inhibiting this enzyme, Oseltamivir reduces viral replication, limits the infection of healthy cells, and alleviates flu symptoms. It is most effective when administered within 48 hours of symptom onset. Tamiflu has however shown very modest efficacy, provided that the medication is used very early.

Baloxavir acts on the cap-dependent endonuclease (CEN), a specific influenza virus enzyme contained within the acidic polymerase (PA) subunit of the viral RNA polymerase complex, thereby inhibiting the transcription of influenza virus genomes (12). Manuel et al. compared baloxavir and oseltamivir in children with influenza. Baloxavir significantly reduced the duration of fever compared to oseltamivir, but the time to resolution of influenza symptoms was nevertheless similar (13). The effectiveness of amantadine against the influenza virus somewhat parallels the action of hydroxychloroquine, although via a different pathway. Amantadine inhibits the M2 ion channel of the influenza virus, preventing the acidification required for the virus to enter the cell and replicate. This is somewhat similar to the effect of hydroxychloroquine, which alkalinizes the phagolysosome, though in a nonspecific manner (14). These specific-action antivirals, targeting a precise stage of the viral cycle, are indeed prone to resistance development. This resistance typically arises due to mutations in the viral genome, driven by the selective pressure exerted by the treatment. This highlights the need for cautious use, particularly by adhering to therapeutic indications, avoiding inappropriate prescriptions, and, if possible, considering combinations of antivirals to limit the risk of resistance (15). Due to the potential for mutations and resistance, as well as the moderate antiviral efficacy of each of these different drugs, it seems necessary to consider therapeutic combinations and to consider a non-specific anti-influenza virus treatment, which would not be subject to viral mutations.

## The hypothesis

Some studies have demonstrated the efficacy of hydroxychloroquine in the treatment of influenza infection. Hydroxychloroquine has the property of alkalinizing the intracellular environment, particularly the phagolysosome, which is the site of entry for enveloped viruses (16). Its action is therefore nonspecific. Hydroxychloroquine could be effective against many viruses, as some articles have already suggested. The efficacy has been suggested on the HIV virus, filoviruses, and coronaviruses (17-20). An article from the IHU in Marseille on more than 30,000 patients suggested that the treatment could be effective against SARS-CoV-2 (21). Numerous articles have also discussed the action of hydroxychloroquine on the influenza virus (22-26). Several studies have highlighted the efficacy of hydroxychloroquine against the influenza virus, though the majority have been conducted in vitro rather than in vivo. Notwithstanding, an animal model study has also demonstrated its effectiveness. In humans, research addressing infection prevention has failed to show significant efficacy. It seems plausible that hydroxychloroquine neither fully prevents infection nor eliminates symptoms, but instead serves primarily to mitigate severe forms of the disease—an aspect that

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remains unexplored. Moreover, as we shall see, exploring the potential synergy of hydroxychloroquine with other compounds could prove an intriguing avenue for future investigation (27, 28). Hydroxychloroquine is particularly interesting due to its nonspecific mechanism of action and the fact that influenza virus mutations are unlikely to induce resistance. Furthermore, due to its unique properties, which allow intracellular accumulation thousands of times greater than serum concentration, low doses of this medication could be sufficient.

By analogy with some studies conducted during the Covid-19 pandemic, notably those by the IHU Méditerranée, it might be interesting to combine it with a macrolide, specifically azithromycin. Macrolides with different ring structures exhibit diverse antiviral activities against influenza A virus. Macrolides are known for their ability to inhibit bacterial ribosomes, explaining their antibiotic effect. By reducing protein synthesis, macrolides could automatically decrease viral production through cellular machinery. The off-target effects of drugs correspond to their action on a target different from the one intentionally aimed at. This term describes unexpected effects, which can sometimes be negative but, in certain cases, also positive. It is therefore interesting to study the off-target effects of macrolides, which involve their antiviral activity through various mechanisms. Macrolide antibiotics exhibit strong affinity for bacterial prokaryotic ribosomes (70S) due to their low Kd values. Conversely, eukaryotic ribosomes (80S) differ significantly from bacterial ribosomes in their protein composition. These structural differences greatly reduce the affinity of macrolides for eukaryotic ribosomes, resulting in much higher Kd values. Consequently, the impact of macrolides on protein synthesis in human cells is diminished. However, off-target effects may occur, particularly at high doses, leading to impacts on protein synthesis. These off-target effects could explain certain adverse effects, although treatments are usually short (29).

However, as stated before, it seems that protein translation by eukaryotic cell ribosomes can also be affected, as highlighted by this Nature article studying the ribosome of a yeast that underwent a genetic mutation (30). This translation inhibition is context-dependent, varying by protein and very likely by the type of macrolide. Furthermore, some macrolides, such as rapamycin, influence the mTOR protein kinase, which regulates various biochemical activities, including stimulating ribosome function (31). The action on this particular protein kinase can thus inhibit protein formation by ribosomes, with applications already envisioned for cancer treatments. By inhibiting the translation of viral proteins, macrolides could significantly reduce viral replication. It thus seems important to study the activity of different macrolides on protein translation in mammals, particularly on viral proteins. In contrast to hydroxychloroquine, which likely does not require high doses due to its intracellular concentration properties, it might be worth administering higher doses of macrolides to enhance the inhibition of protein synthesis. Azithromycin (AZI) also effectively inhibits influenza A virus activity, particularly when the virus remains outside host cells during repeated cycles of propagation. A retrospective study assessed the effect of intravenous azithromycin in patients with influenza virus pneumonia and respiratory failure. The results showed a significant reduction in 30-day mortality in the severe group with azithromycin. In the moderate group, the duration of invasive mechanical ventilation was shorter. These results suggest beneficial effects of azithromycin in patients requiring mechanical ventilation or oxygen (32). Although AZI does not interfere with the binding interaction between viral hemagglutinin (HA) and the sialic acid (SA) receptor on host cells, it disrupts the internalization process mediated by endocytosis (33).

However, in certain cases, macrolides may affect viral attachment to the cell. For example, clarithromycin has been shown to decrease the expression of SAα2,6Gal, a key receptor for human influenza virus (34). Viral ribonucleoproteins (vRNPs) require an acidic environment within endosomes to undergo de-envelopment and be released into the cytoplasm, initiating viral replication. May we put forward that certain macrolide, such as clarithromycin, impair the formation of acidic endosomes by increasing the pH within endosomes in airway epithelial cells. This aligns with the mechanism of action of hydroxychloroquine, through alkalinization of the phagolysosome. Additionally, there is evidence suggesting that AZI may act directly on the virus itself, preventing its internalization into host cells. Finally, macrolides and hydroxychloroquine may exhibit more of an additive effect, creating a true synergy of antiviral action. This includes, on the one hand, a specific effect by targeting particular receptors, and on the other hand, a non-specific effect involving hydroxychloroquine, which acts by alkalinizing the phagolysosome. To summarize, it seems important to consider a multi-therapy approach instead of a monotherapy, as was traditionally the case for the treatment of influenza. Different drugs or natural therapies may have synergistic effects, and the use of multiple agents with different mechanisms of action reduces the likelihood of mutation and, consequently, resistance. Last but not least, Hydroxychloroquine and macrolides have anti-inflammatory effects through various mechanisms, particularly by modulating the functions of inflammatory cells such as neutrophils, lymphocytes, and macrophages, as well as acting on different cytokines. Hydroxychloroquine reduces the activation of T lymphocytes, which play an important role in the occurrence of inflammatory pulmonary complications. These effects could be beneficial in inflammatory diseases,

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pulmonary conditions such as influenza, or COVID-19, by reducing the likelihood of progression to an inflammatory phase characterized by a cytokine storm, often associated with significant morbidity and mortality (35-39).

## Testing the hypothesis

The combination of Hydroxychloroquine and macrolides could therefore represent an effective prevention or treatment strategy for influenza and deserves further study. The aim of the treatment is primarily to target the antiviral phase during the early stage of influenza. However, as mentioned, immunomodulatory and anti-inflammatory effects could also play a role in addressing the potential inflammatory phase of the disease (cytokine storm). The hypothesis could be tested on an animal model and/or in humans through a prospective randomized study. A control group would receive standard and routine care, while the treatment group could be administered low doses of hydroxychloroquine (200 mg per day) and 250 to 500 mg of azithromycin for just under a week. Much higher doses of macrolides could be administered in animal models to support the hypothesis that these antibiotics reduce viral protein synthesis and decrease the viral load. Elderberry (*Sambucus nigra*) extract could be added to this bi-therapy in a group of patients.

Evaluation would be based on viral load measurement (intermediate criteria), symptom severity (assessed by both a clinician and the patient), and complications requiring hospitalization. The hypothesis could be tested both preventively, in prophylaxis, particularly among individuals representing risk factors for severe influenza, and curatively, through early administration. Macrolides, such as azithromycin, in addition to its antiviral action, could also play a preventive role against bacterial superinfections, which are one of the main causes of influenza-related mortality. Hydroxychloroquine also has potential benefits by alkalinizing the phagolysosome, thereby enhancing the effectiveness of the antibiotic. The treatment and its evaluation could thus also be conducted on bacterial complications of influenza, which represent a significant cause of morbidity and mortality.

## Conclusion

The flu vaccine has several limitations, particularly due to mutations of the influenza virus that can reduce the vaccine's effectiveness and potentially lead to paradoxical phenomena such as ADE (Antibody-Dependent Enhancement). It is therefore crucial to have a safe and effective pharmaceutical treatment. The combination of macrolide antibiotics and hydroxychloroquine could be effective if administered early and have a synergistic effect against the influenza virus, while also reducing the risk of mutations that could undermine the effectiveness of the therapy. This combination works through multiple mechanisms of action, including specific effects on targeted pathways and a non-specific effect of hydroxychloroquine, which, by alkalinizing lysosomes, prevents the virus from entering the cells. This treatment could be complemented by natural therapies, such as elderberry (*Sambucus nigra*), to enhance its efficacy. Vitamin D supplementation should also be considered. Beyond its antiviral effects, these treatments have an interesting intrinsic anti-inflammatory effect, which may help prevent cytokine storm.

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