Unveiling the connection: The impact of SARS-CoV-2 infections and COVID-19 vaccinations on Epstein-Barr virus reactivation

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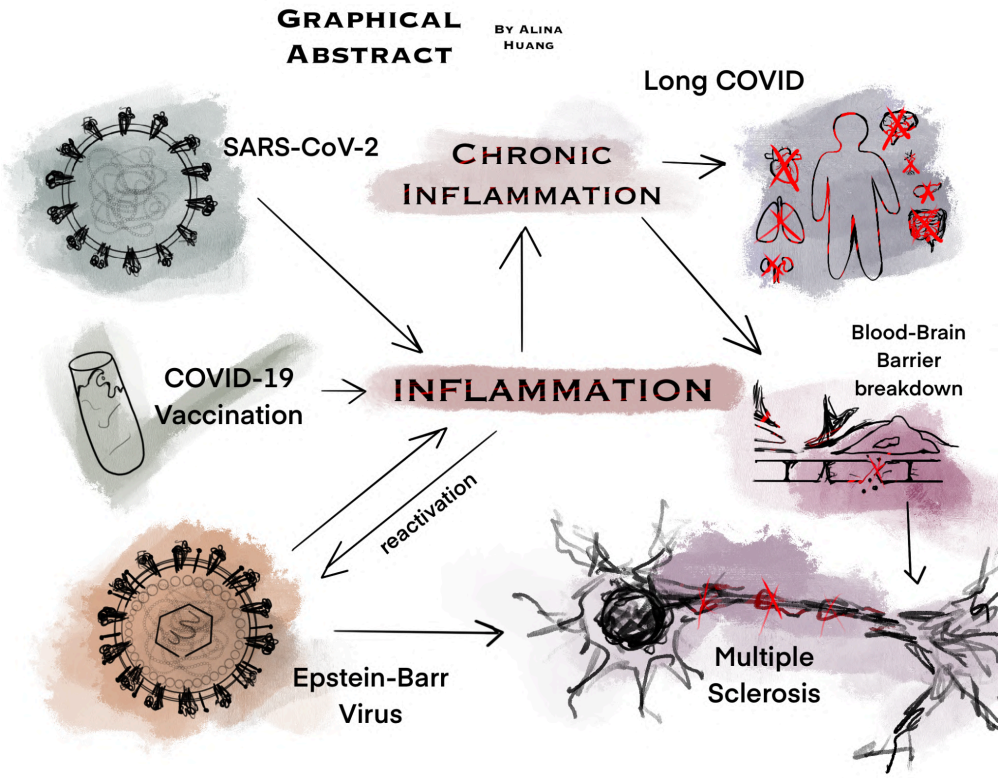


I. Abstract

Studies have suggested that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and/or COVID-19 vaccination can lead to the reactivation of Epstein-Barr virus (EBV), a common lymphotropic herpesvirus virus that spreads through saliva and is prevalent in young adults. In most cases, EBV infection results in cold-like symptoms, though recent research has found that EBV infection actually increases the likelihood of developing multiple sclerosis (MS), the most pervasive chronic debilitating neurodegenerative disease of the central nervous system (CNS), by thirty-fold. This paper discusses the research that supports the link between SARS-CoV-2 infection and COVID-19 vaccination and EBV reactivation. Evidence has shown that SARS-CoV-2 infection and/or COVID-19 vaccination is related to EBV reactivation. More than about 81.4% of the world's population has received at least one dose of the COVID-19 vaccine and more than 772 million people have gotten infected with SARS-CoV-2, making the possibility of the COVID-19 vaccine and COVID-19 being related to the reactivation of EBV a major concern [6]. Some studies have shown up to 82% of EBV co-infection in COVID-19 patients, and a meta-analysis reveals the incidence of EBV reactivation during COVID-19 pathogenicity to be 0.48. In another study of COVID-19 patients,

30.3% had long COVID, while 66.7% of the long COVID patients were positive for EBV reactivation, compared to 10% of the control group. In particular, we identify what connects these two viral infections. This topic has broad implications for understanding how exposure to the SARS-CoV-2 virus through infection or its components through COVID-19 vaccination can lead to the detrimental effects of EBV reactivation.

Keywords: COVID-19, coronavirus, SARS-CoV-2, COVID-19 vaccination, Epstein-Barr virus, multiple sclerosis

II. Introduction

COVID-19 is an infectious disease caused by a strain of coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It first emerged in 2019, with related deaths peaking in January 2021 and cases peaking in January and December 2022, then continuing to decrease until 2023 [1]. (Figure 1)

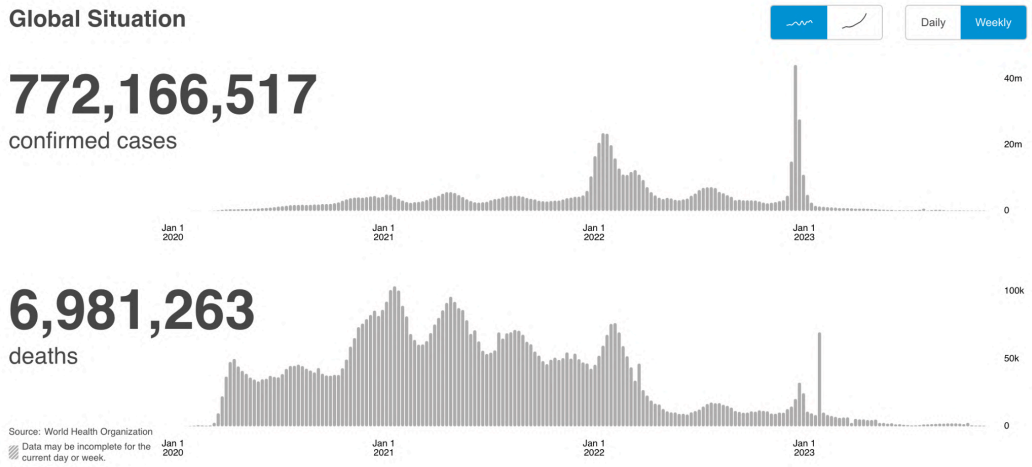
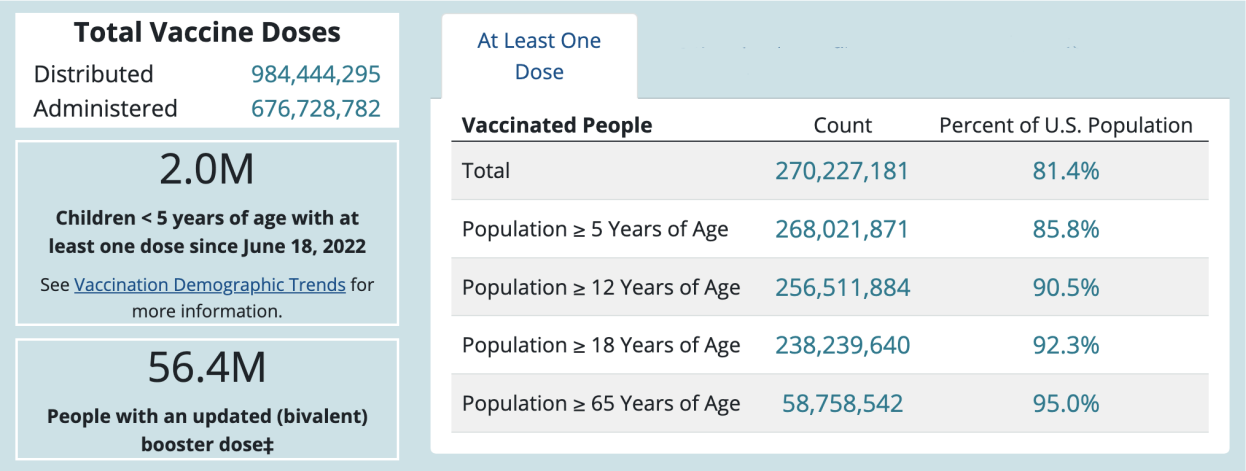


Figure 1: Global timeline of confirmed numbers COVID-19 cases and deaths.

According to the World Health Organization (WHO), there've been approximately 772.1 million confirmed cases of COVID-19, and 6.9 million deaths as of Nov. 2023. Data extracted and made available by WHO. https://covid19.who.int/ [1]

More than 81.4% of the world's population has received at least one dose of the COVID-19 vaccine, but there is still an ongoing debate on whether people should be vaccinated. (Figure 2)



Total Vaccine Doses

Distributed	984,444,295
Administered	676,728,782

2.0M

Children < 5 years of age with at least one dose since June 18, 2022

See Vaccination Demographic Trends for more information.

56.4M

People with an updated (bivalent) booster dose‡

At Least One Dose

Vaccinated People	Count	Percent of U.S. Population
Total	270,227,181	81.4%
Population ≥ 5 Years of Age	268,021,871	85.8%
Population ≥ 12 Years of Age	256,511,884	90.5%
Population ≥ 18 Years of Age	238,239,640	92.3%
Population ≥ 65 Years of Age	58,758,542	95.0%

About These Data | View Footnotes and Download Data

CDC | Data as of: May 10, 2023 6:00am ET. Posted: May 11, 2023

Figure 2: A timeline of the total COVID-19 vaccine doses administered as of May 2023.

This chart displays the total number of vaccine doses. About two million children younger than five have had at least one dose since June 2022, and there are around 56.4 million people with a booster dose. The population with the highest percentage of doses is that of people more or equal to 65 years of age.
Data extracted from the Centers for Disease Control (CDC).
https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-people-onedose-pop-total [2]

Contrary to the safety of the COVID-19 vaccine determined by the World Health Organization (WHO) and the CDC, recent studies have revealed links between Epstein-Barr virus (EBV) reactivation and COVID-19 vaccinations. Research suggests that EBV reactivation is related to the activation of cellular components of the cell-mediated immune response (CMI), such as B and T lymphocytes [3,4].

EBV is a member of the herpes virus family and the disease-causing agent of infectious mononucleosis, also known as the kissing disease or mono. Although EBV infection is mild, similar to a common cold, evidence has shown that EBV is linked to more serious illnesses because it can remain latent within the body after infection. This virus is a major risk factor in many autoimmune disorders, especially in MS, as highlighted by studies elucidating how EBV is a trigger and a “driver of disease activity” for this disorder [5]. Those who did not receive the COVID-19 vaccination and those that have been infected by SARS-CoV-2 before were not safe from this possible relation as well. The post-acute sequelae (PASC) of SARS-CoV-2 infection, also called “long COVID,” is a wide range of symptoms or conditions that persist in 10-20% of patients for weeks or months after the initial SARS-CoV-2 infection, and may have an impact on everyday functioning [1]. Cases of reactivation of EBV associated with SARS-CoV-2 infection and long COVID have been reported, but there is limited research determining how these infections are related [7].

Despite mounting evidence pointing to a link between the COVID-19 vaccination and/or SARS-CoV-2 infection and EBV reactivations, the relation between reactivation and SARS-CoV-2 infection or COVID-19 vaccination combined is unknown. The paper sets out to address this knowledge gap and discuss its further implications due to EBV’s connection to

increasing the likelihood of developing MS. Through discussion, this paper will find areas to focus on in future research and explicate the implications the findings have for the ever-present question: to vaccinate or not?

III. COVID-19 & long COVID

As of November 2023, there have been 772,166,517 globally confirmed cases of COVID-19, including 6,981,263 deaths, reported to WHO [1]. As COVID-19 is an ongoing, serious disease, it is important to understand its epidemiology. COVID-19 is primarily contracted from airborne transmission [8]. However, COVID-19 can live on surfaces for 2-3 days. If an infected surface was touched by someone who touched their face after, there is a rare chance of surface transmission [8]. When COVID-19 enters your body, it latches spike surface proteins to receptors on healthy cells through ACE2 receptors, especially in your lungs, and enters the respiratory tract [9]. ACE2 receptors found throughout the human body are mainly involved in counterbalancing the function of ACE, the angiotensin-converting enzyme able to cut/cleave proteins as part of the renin-angiotensin system, which regulates blood pressure and the balancing of fluids and salts in the human body. Throughout the body, the ACE2 receptors, which normally help regulate blood pressure, mark tissues vulnerable to infection by allowing viruses to enter the cells through it. Inside the cell, the virus takes control and replicates rapidly, invading other nearby cells. If the immune system doesn't get rid of and shed SARS-CoV-2 enough during this initial phase, the virus then turns to attack the lungs, where it can turn deadly [10–12]. If infected with SARS-CoV-2, reactions may vary from asymptomatic to life-threatening, appearing from within two to fourteen days of infection. Common symptoms include loss of taste or smell, fever, shortness of breath, congestion, body aches, fatigue, and diarrhea. COVID-19 lasts approximately six weeks, depending on the age and immune system of the individual. Major risk factors associated with complications from SARS-CoV-2 infection include older age (>65), chronic respiratory diseases, cardiovascular diseases, hypertension, diabetes, and obesity, and the most common complication is acute respiratory distress syndrome (ARDS) [13]. Over periods of time, mutations in SARS-CoV-2 have brought about infections of several variants of the virus, each with different abilities to affect both the vaccinated and unvaccinated populations [14].

Many people completely recover within days or weeks of infection with SARS-CoV-2; however, almost 16% of those adults infected never seem to recover fully, retaining lingering symptoms for weeks, months, or even years after their initial diagnosis that may worsen with physical activity [14,15]. Because it is a physiological condition that can affect multiple body systems, some with long COVID undergo increased risks of cardiovascular disorders, neurologic and mental health disorders, metabolic disorders, kidney disorders, and gastrointestinal disorders; additionally, some symptoms last for years or are expected to be lifelong. The substantial loss of health due to long COVID underscores the importance of understanding the health effects from the SARS-CoV-2 infection [17]. In those with long COVID, researchers have found T cell alterations: exhausted T cells, reduced CD4+ and CD8+ effector memory cell numbers, and increased amounts of autoantibodies [18]. Currently, studies find that there are likely multiple potential causes of long COVID, ranging from persisting amounts of SARS-CoV-2 in tissues, to autoimmunity or immune dysregulation, with possible reactivation of underlying pathogens like those of the Epstein–Barr virus (EBV).

IV. COVID-19 vaccination

The first COVID-19 vaccine was available to the public in 2020 [6], and currently, there are about four available COVID-19 vaccines for people around the world, namely the Moderna COVID-19 vaccine (bivalent), the Pfizer, Inc., and BioNTech COVID-19 vaccine (bivalent), the Novavax COVID-19 vaccine (adjuvanted), and the Janssen Pharmaceutical Companies of Johnson & Johnson [19]. As of October 2023, a total of 13,534,457,273 vaccine doses have been administered [1]. The bivalent COVID-19 vaccines broadly protect against COVID-19 with better protection against the circulating variants of the disease, and are available to anyone at least six months old; the adjuvanted vaccines help create a stronger immune response in people receiving it, and are available to those people age 12 and older (Nonovax). Both the Moderna and the Pfizer-BioNTech vaccines are messenger RNA (mRNA) vaccines, meaning they're made based on a vehicle that enables the delivery of a nucleic acid molecule encoding the antigen of interest into the human's target cell, and reportedly confer up to 95% protection from COVID-19 after a two-dose series [20,21]. With that, the cell is able to fabricate the target protein and express the antigen to elicit the immune response, which helps the immune system prevent the disease in time [21]. Novavax, a protein subunit (recombinant) vaccine, contains pieces (proteins) of the virus that causes COVID-19, called spike proteins, and an adjuvant that would help the immune system respond to that spike protein in the future; its design is similar in nature vaccines against the flu and shingles [22]. Finally, Janssen Pharmaceutical Companies of Johnson & Johnson's vaccine is a part of the family of viral vector vaccines, using a modified version of a vector virus to deliver instructions to cells. As of May 2023, this vaccine is no longer available for use in the US due to its expiration date. According to the NIH, "all vaccines may cause some side effects, which are normal signs that your body is making antibodies. These side effects go away in a few days. Many people have no side effects. Serious side effects that could cause long-term health problems are extremely unlikely after any vaccination, including COVID-19 vaccination. These rare side effects usually appear within six weeks of receiving a vaccine dose." [19] Although, in most cases, COVID-19 vaccination does not lead to serious side effects, more recent reports have suggested links between COVID-19 vaccination and EBV reactivation.

V. EBV & EBV reactivation

EBV, one of nine known human herpesviruses, infects more than 90% of people worldwide. It is the most common causative agent of Infectious Mononucleosis (or mono), a contagious disease characterized by swollen lymph glands, fever, sore throat, and extreme fatigue [23]. As a herpesvirus, EBV has both a productive/lytic and a non-productive/latent phase, with productive infection in the oral mucosal epithelium and long-term latent infection of naïve B lymphocytes, which produce antibodies that latch on and destroy invading viruses or bacteria. In rare cases, in addition to B cells and sometimes epithelial cells, EBV can also infect T cells and NK cells, though the mechanism of entry is unclear. EBV's latent infection quietly persists in B cells for the lifetime of the host in a non-pathogenic state invisible to the immune response, and reactivation occurs through regulated stages where numerous (immune) cell signaling pathways may trigger lytic cycle reactivation and infection, depending on the host cell type [5,24]. (Figure 3)

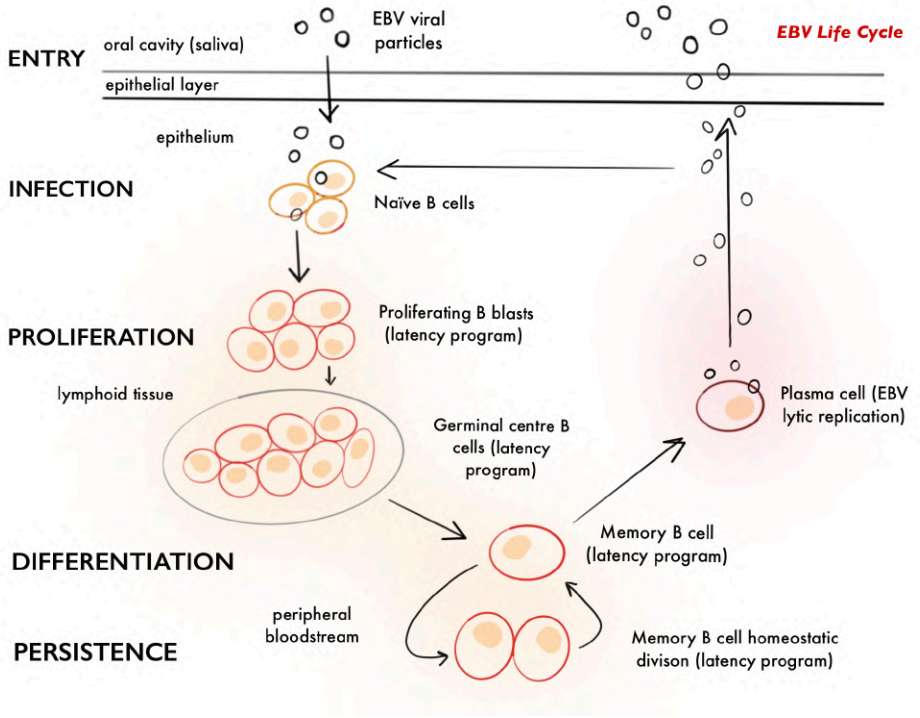


Figure 3: EBV life cycle and latency stages.

This graphic displays the five stages of the viral life cycle. The entry of EBV-infected cells into the peripheral bloodstream leads to the latency program, where many virtual gene expressions are downregulated. The resting memory cells where there is the quiescent virus are turned into sites of viral persistence as they aren't attacked by the immune system. Therefore, when SARS-CoV-2 infection triggers the lytic cycle of EBV, the infectious virus is released from those cells to infect the epithelial cells.
Made by data extracted from Molecules, made available by MDPI.
https://www.mdpi.com/1420-3049/24/5/997 [31]

EBV may also be reactivated by psychological stress, hormonal changes, infections, and other factors resulting in weakened cellular immunity. Reactivated EBV may occasionally cause sickness in those with weaker immune systems. In rare cases, EBV may lead to chronic active EBV infection (CAEBV), a serious condition where infection persists more than six months after initial mono diagnosis because the body's immune response cannot control the infection; CAEBV can lead to death [25]. Infection with EBV happens through the transfer of bodily fluids, especially saliva. Thus, people may get infected by kissing or sexual contact, through moist objects coated with infected saliva such as toothbrushes, cups, or children's toys, or through sharing food or drinks [27].

The Endoplasmic Reticulum (ER) is the compartment where transmembrane and secreted proteins transit to be matured and properly folded before routing to their final location. Therefore, function and homeostasis of the ER is crucial for cell fate. When ER is subjected to stress, a protein overload or any dysfunction, an adaptive response, called Unfolded Protein Response (UPR), is initiated to restore ER homeostasis. The XBP-1 transcription factor subsequently regulates the transcription of genes involved in ER homeostasis. XBP-1 is also

essential to the transition of mature B cells to antibody-secreting plasma cells; however, at the same time, it also may activate the latent EBV cells in the body with the sigma-1 receptor (S1R) [28,29]. Studies point to S1R as a modulator of multiple signaling pathways, and there it has effects on a wide range of cellular activities including calcium homeostasis, ion channel regulation, and responses to ER and oxidative stress [57]. The proposed general mechanism for S1R function is through protein-protein interactions [58], and in support of this, S1R has been reported to bind to at least 49 different proteins for generally diverse structures and functions. Experimental or bioinformatics studies have identified interactions between S1R and other functional proteins in the plasma membrane, ER, mitochondria, and even the cytosol. Approximately 40% of SARS-CoV-2-interacting proteins were associated with endomembrane compartments or vesicle trafficking pathways;, including S1R. Therefore, S1R ligands may provide antiviral activity against SARS-CoV-2 [59]. Such binding of S1R with viral proteins has shown to play a significant role in promoting viral replication cycle.

Therefore, these receptors are ideal targets for designing antiviral therapies to curb viral replication. And accordingly, S1R agonists such as fluvoxamine may prevent EBV reactivation, as it attenuates COVID-19 entry and may decrease COVID-19 replication and ER inflammation [30]. There are currently no vaccines available for EBV to the public due to it being a challenging target; however, there are evaluated antiviral drugs such as ganciclovir that inhibit EBV in vitro [31]. EBV changes along its life cycle and can cause tumors to develop, so incorporating entire sections of its viral proteins into vaccines is currently out of the question due to the possible increase of cancer risk [32]. However, the findings on S1R agonists represent the possibility of creating therapeutic drugs that limit EBV reactivation (and thus the increased possibility of MS) and long COVID symptoms. With the recent evidence on links between EBV, MS, and COVID-19, among other diseases, there are now three EBV vaccines in the making. Moderna's mRNA platform, which was used for COVID-19 vaccines, is being used for phase 1 clinical trials. The US National Institute of Allergy and Infectious Diseases is in an early-stage clinical trial for a possible vaccine, and Dr. Hank Balfour, professor of laboratory medicine, pathology, and pediatrics at the University of Minnesota, is also working on a vaccine for EBV [33].

VI. MS

MS is the most common chronic neurodegenerative autoimmune disease, affecting 2.8 million people worldwide. Although the exact etiology of MS remains unclear, it is considered a complex, multifactorial disease, with three main grouped factors involved in its pathogenesis: immune factors, environmental factors, and genetic associations 35. MS is identified by demyelinating lesions in the brain identified through magnetic resonance imaging (MRI) and characterized by the infiltration of autoreactive lymphocytes into the CNS as well as by chronic inflammation, demyelination, gliosis, and neuronal loss 36,37. This inflammation may cause the breakdown of the blood-brain barrier that shields us from bacteria that may be in the bloodstream, allowing the infiltration of lymphocytes into the CNS. Consequently, individuals with MS may have affected vision, sensations, pain and fatigue in muscles, nerves, and joints, bladder and bowel problems, and impaired motor function and cognitive and emotional functions 38,39. Currently, there are no widespread public vaccines for MS, but current research reveals a promising potential vaccine developed by researchers at the University of Chicago's Pritzker School of Molecular Engineering (PME). This uses a process much unlike the typical vaccine; instead of helping the immune system recognize a virus/bacteria as the enemy, it completely

reverses autoimmune diseases without shutting down the rest of the immune system by removing its memory of the molecule 40. Additionally, while currently there is no cure for MS, treatment found with ongoing clinical trials can reduce symptoms, prevent further relapses, and slow disease progression [41].

VII. The relation between EBV reactivation & MS

Usually, infection of EBV leads to asymptomatic or mild, cold-like symptoms and reactions; however, research has found that EBV is associated with a wide range of more serious illnesses, including around 200,000 cancers per year and auto-immune disorders, the most notable being MS. The risk of MS increases just about 32-fold with EBV infection, and even more with symptomatic to severe mono, as latent infection is a source of viral antigenic stimulation, and multiple EBV antigens are the target of cross-reactive autoantibodies found in MS [24,34]. Unfortunately, due to how widespread EBV is, causal links between MS and EBV are difficult to draw firmly; however, a 2023 study suggests that antibodies in our body deployed to fight EBV would mistakenly target a similar-looking protein in the CNS resembling alpha-crystallin B (CRYAB), which has a critical role in protecting our CNS from inflammation, namely the Epstein-Barr nuclear antigen 1 (EBNA1) [37]. This may be what causes the development of MS to increase by 32-fold, and it is not the first time EBV proteins resembled critical proteins in our body. Reports have also demonstrated the presence of EBV+ B cells in MS through demyelinated lesions (damaged areas in the brain and spinal cord caused by immune system attack, with the damaged myelin sheath protecting axons of nerve cells), suggesting that these cells infiltrate the brain through a damaged blood-brain barrier through activation of T cells, and that demyelination could be triggered by EBV infection [38]. This demyelination happens due to multiple zones of inflammation from T cell and macrophage infiltrations and oligodendrocyte death, and may interfere with the correct transmission of nerve impulses, leading to neuronal malfunction and communication issues between the brain and the rest of the body [39]. (Figure 4)

VIII. The relationship between COVID-19 vaccination, SARS-CoV-2 infection, long COVID, & EBV reactivation

A. How COVID-19 vaccination is related to EBV reactivation

Previous papers have analyzed the coinfection of COVID-19 and several herpesviruses, but COVID-19 vaccination side effects have not been thoroughly discussed yet. Several reports of reactivation of EBV after SARS-CoV-2 infection or COVID-19 vaccination prompt discussion on what exactly it is that causes this reactivation, and its aftereffects [4]. A 2021 case report describes reactivation of rapidly-growing EBV-positive posttransplant lymphoproliferative disorder, or PTLD, in a heart transplant 51-year-old male recipient after the COVID-19 vaccination (the Oxford/AstraZeneca ChAdOx1 nCoV-19 recombinant vaccine) [42,43]. PTLD results from uncontrolled B cell proliferation observed in some after solid organ or hematopoietic stem cell transplantation due to loss of active immune surveillance of EBV [42–44].

While this is based on one case, the possibility of EBV reactivation after COVID-19 vaccination supports the importance of assessing vaccine safety continuously, especially during the ongoing global vaccination for COVID-19, and the open communication of COVID-19

vaccination-associated adverse cases [36]. Some COVID-19 mRNA vaccines have been associated with an increased T helper type 1 (Th1)-cell response, which activates macrophages that help eliminate foreign substances from the body and may contribute to B lymphocyte tumorigenesis. For example, after the second dose of the Pfizer BioNTech COVID-19 (BNT162b2) vaccine, a 24-year-old man proved positive for EBV reactivation. This is the first case of EBV viral reactivation related to cutaneous effects in an immunocompetent vaccinated individual, and may be possibly due to the mRNA vaccines' association to increased T cell response, which likely increments inflammatory cytokines involved in a systemic inflammatory syndrome, causing an immune system imbalance [3]. A 2022 case reports a 57-year-old female patient with disseminated EBV infection and reactive lymphadenopathy (when lymph glands respond to infection by becoming swollen from the Pfizer-BioNTech vaccine [4], as EBV+ lymphocytes may exacerbate that inflammation). Similarly, a 2023 case where a 79-year-old male with a two-week history of fever after receiving the first dose of the Pfizer BioNTech mRNA COVID-19 vaccine, was revealed to contain EBV viremia. The EBV genome was localized in NK cells, therefore pointing to Epstein-Barr virus-associated lymphoproliferative disorders (EBV-LPD), an uncommon disease with persistent or recurrent inflammation alongside EBV infection of T or NK cells that is fatal if left untreated. From these cases, it is important to consider the possibility of EBV reactivation after COVID-19 vaccination to initiate targeted therapy early [60] . Additionally, a presentation of undiagnosed MS only a few days after receiving the COVID-19 vaccine suggests that the vaccine's causing an increased immune response may be associated with the triggering self-antigens of the immune system [45]. One week after receiving the first dose of the Pfizer BioNTech COVID-19 (BNT162b2) vaccine, a 32-year-old female with no past medical history of weakness in her body started receiving symptoms such as fever, gait instability, word slurring, and fine motor weakness in right hand, was later diagnosed for MS and being examined by MRI. The timing between COVID-19 vaccination and onset of MS favors the association between the triggering of MS after COVID-19 vaccination; however, more definitive data is needed to confirm. Whether the reactivation of EBV itself was directly involved with causing MS was not mentioned, as the study simply noted EBV as an environmental factor [45].

B. How SARS-CoV-2 infection is related to EBV reactivation

Similarly to the effects of COVID-19 vaccination, researchers found that infection/co-infection with SARS-CoV-2 reduced immune cell response, producing less spike-specific, lower functionality CD8+ T cells, especially if they weren't vaccinated, compared to vaccinated people who hadn't been infected [20,46]. SARS-CoV-2 infection tends to produce an immunosuppressive state with functionally impaired and decreased T lymphocytes (specifically CD4+ T cells, CD8+ T cells, and natural killer cells), exactly what can trigger EBV as it's an opportunistic virus. Studies have been conducted on herpesvirus reactivations in COVID-19 patients, as indicated in the table below. The results proved that in addition to an association between COVID-19 and EBV, it was found that infection with other viruses could do the same; however, for this paper we will mainly take into account the EBV reactivations. (Table 1)

Table 2. Selected studies of herpesviruses reactivations in severely ill COVID-19 patients.

Herpesvirus Reactivation and Study Reference	Total Patients and Clinical Characteristics of Study Group	Results	Conclusions/Comments
HSV-1 Luyt et al. [27]	Retrospective monocentric cohort study of 145 patients with severe COVID-19 pneumonia requiring invasive mechanical ventilation.	Among 145 COVID-19 patients, a total of 50% and 42% had HSV and CMV lung reactivations, respectively, compared to 63% and 28% HSV and CMV lung reactivations in a control group of 89 influenza patients.	HSV and CMV lung reactivations are frequent in COVID-19 patients subject to invasive mechanical ventilation; however, they are no more frequent than in controls with influenza. HSV and CMV reactivations were defined by a positive PCR test result in bronchoalveolar lavage fluid samples or whole blood samples.
HSV Meyer et al. [28]	Observational study using prospectively collected data, as well as HSV-1 blood and respiratory samples from 153 critically ill COVID-19 patients admitted to a regional intensive care unit (ICU) for at least 48 h, from February 2020 to February 2021.	Respiratory and blood samples were tested from 61/153 (39.9%) and 146/153 (95.4%) patients, respectively. On the basis of respiratory sample testing, HSV PCR was positive in 19/61 (31.1%) of patients, and on the basis of blood sample testing, HSV PCR was positive in 36/146 (24.7%) of patients.	Overall, 40/153 (26.1%) patients had an HSV PCR positive sample. HSV reactivation was defined as testing positive by HSV PCR. Day-60 mortality in the whole cohort was 39.9% higher in patients with HSV-1 reactivation (57.5% versus 33.6% in patients without HSV-1 reactivation, $p = 0.001$).
CMV Gatto et al. [32]	Observational study using prospectively collected data of all the patients with moderate to severe acute respiratory distress syndrome admitted to three COVID-19 ICUs at the University Hospital of Modena over the period from 22 February 2020 to 21 July 2021.	A total of 431 patients met the study's inclusion criteria. COVID-19 was confirmed by laboratory detection of SARS-CoV-2. CMV reactivation was evidenced in whole blood samples by CMV PCR with a cut-off of >62 IU/mL.	Blood CMV reactivation was detected in 88/431 (20.4%) patients, with a median onset of 17 days following ICU admission. Patients with CMV reactivation had prolonged hospital stays and a higher mortality rate than patients without reactivation. CMV reactivation was not independently associated with higher mortality.
CMV and HSV Weber et al. [35]	National German COVID-19 bio-sample and data banks were used to retrospectively analyse the CMV and HSV status of patients. Serum samples were collected from patients who experienced mild (n = 101), moderate (n = 130), or severe to critical (n = 80) COVID-19.	CMV seropositivity was 43.6% in cases of mild COVID-19, 72.3% in cases of moderate COVID-19, and 77.5% in cases of severe to critical COVID-19. HSV seropositivity was 71.3%, 93.8%, and 96.2%, respectively, in the same groups.	Patients aged <60 years with severe COVID-19 had a very high prevalence of CMV seropositivity. CMV seropositivity, unlike HSV, might be a strong biomarker for identifying patients <60 years with a higher risk of developing severe COVID-19, particularly in the absence of other co-morbidities.
EBV Chen et al. [39]	A retrospective, single-centre study from 9 January 2020 to 29 February 2020: a total of 188 hospitalised patients were recruited with PCR-confirmed SARS-CoV-2 infection.	EBV serology was available for 78 patients, and 11 failed to meet the study inclusion criteria. Of the remaining 67 patients, 37 (55.2%) had laboratory evidence of EBV reactivation. EBV viral load testing was not undertaken.	Patients with laboratory evidence of EBV reactivation had a 3.09-fold risk of having a fever symptom. C-reactive protein levels were significantly elevated in patients with EBV reactivation.
EBV Xie et al. [40]	Retrospective, single-centre, observational study of ICU admissions over the period from 31 January 2020 to 27 March 2020.	145 critically ill patients with SARS-CoV-2/PCR-confirmed COVID-19 were recruited into the study, and 128 met the study's inclusion criteria. EBV viral load testing (≥500 copies/mL) and serology were used as evidence of EBV reactivation.	Patients with EBV reactivation had higher (29.4%) day-14 and day-28 mortality rates compared to 7.8% and 10.9%, respectively, for patients without EBV reactivation. Patients with evidence of EBV reactivation showed more severe symptoms and received more immunosupportive treatment.
HHV-6 Lino et al. [42]	Retrospective, single-centre study of hospitalised patients with moderate to severe COVID-19	173 patients with suspected COVID-19 were recruited, of which 60 had a positive PCR test for SARS-CoV-2. Of these 60 confirmed cases, 13/60 (21.7%) were also had positive PCR tests for HHV-6.	HHV-6 reactivation did not impact general mortality.

Abbreviations: CMV = cytomegalovirus, EBV = Epstein–Barr virus, HHV-6 = human herpesvirus-6, HSV = herpes simplex virus, ICU = intensive care unit, PCR = polymerase chain reaction, VZV = varicella-zoster virus.

Table 1: Selected studies of herpesviruses reactivations in severely ill COVID-19 patients.

According to Chen et al., out of 188 hospitalized patients with SARS-CoV-2 infection, EBV serology was available for 78, and with 11 failing to meet the inclusion criteria, there were 67 remaining patients to be tested. 55.2%, or 37 patients, had evidence of EBV reactivation, and for this study EBV viral load was not tested. In Xie et al., out of 145 critically ill COVID-19 positive patients, 128 met the inclusion criteria. In this study, EBV viral load testing and serology were used to gauge EBV reactivation, and it was shown that those with reactivation had higher 14-day and 28-day mortality rates and worse symptoms than those without.
Overall, patients with evidence of EBV reactivation had higher mortality rates and more severe symptoms than those without EBV reactivation.
Data extracted from Vaccines, made available by MDPI.
https://www.mdpi.com/2076-393X/11/2/232#table_body_display_vaccines-11-00232-t002 [14]

Some studies have shown up to 82% of EBV co-infection in COVID-19 patients, though a meta-analysis of 11 studies with 993 COVID-19 patients on EBV reactivation during SARS-CoV-2 infection reveals the incidence of EBV reactivation during COVID-19 pathogenicity to be 0.48 [4,7]. (Figure 4)

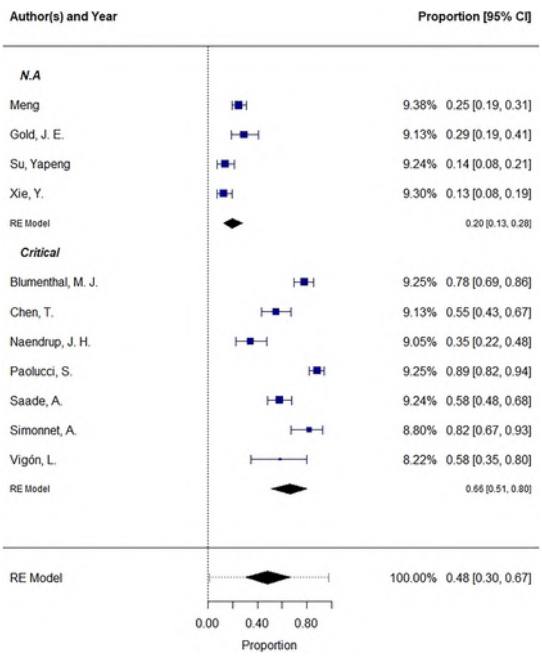


Figure 4: The pooled proportion of EBV reactivation cases among COVID-19 patients.

According to this model with data from multiple studies, approximately 48% of COVID-19 patients also had EBV reactivation.
Data extracted from the Journal of Medical Virology, made available by Wiley.
https://onlinelibrary.wiley.com/doi/10.1002/jmv.27823 [7]

From 2020-2021, a study conducted at Renmin Hospital of Wuhan University divided 67 COVID-19 patients (with onset time of within two weeks) into those with EBV coinfection and those with just SARS-CoV-2 infection and compared their characteristics. The study discovered a high incidence of EBV coinfection within COVID-19 patients, and EBV's potential reactivation was found to be associated with the severity of COVID-19. Patients with EBV coinfection with SARS-CoV-2 generally had initial symptoms as fever, dry cough, fatigue, myalgia (muscle aches/pain), and anorexia, and 55.2% tested positive for EBV viral capsid antigen (VCA) IgM antibody, which disappears around one to two weeks after the onset. Moreover, a SARS-CoV-2 infected dead patient's pathological report revealed an overactivation of T cells, meaning COVID-19 may cause severe immune injury in individuals [47]. Individuals infected with SARS-CoV-2 and EBV had higher mortality rates (over both a 28-day and a 14-day period) and more severe symptoms with notably less lymphocytes than the non-EBV individuals, as found by a study of patients admitted to the Wuhan No. 3 Hospital from 2020-2021. While this study was unable to prove causation, those with EBV had relatively severe symptoms, high mortality rates, lower lymphocytes, and high D-dimer levels (meaning the individual may have blood clotting problems) [48].

There have been more eccentric cases of EBV reactivation associated with COVID-19 infection. Sanchez et al. found EBV reactivation in a patient with a skin eruption, similar to an atypical pityriasis rosea (PR), associated with COVID-19. With several PR and PR-like eruptions reported as related to COVID-19 and HHV-6/7's pathogenetic role in PR well-known,

COVID-19 is suggested to play a role in triggering a chain viral reaction of HHV-6/7 and EBV reactivation and thus causing cutaneous PR to happen [49,50]. Furthermore, the first case of CAEBV exacerbated by COVID-19 coinfection was reported in 2021, in a 60-year-old Hispanic woman with a recent history of nausea, vomiting, fever, pancytopenia, anorexia, and altered mental status (fatigue, confusion, etc) over three different admissions to the hospital due to recurrence of these symptoms [51]. Previous admissions to the hospital provided treatment to diseases unrelated to CAEBV, and thus multiple times she was sent back without any CAEBV-related treatment. Her elevated titers (a test for the amount of antibodies in the blood to prove immunity to certain diseases) for EBV consistent with CAEBV increased again after decreasing some with treatment (valganciclovir for EBV suppression) due to co-infection with SARS-CoV-2, leading to rapid deterioration of health and eventually death eight days later. Because CAEBV cases are rare, this reflected the greater awareness of this condition's diagnostic/classification criteria so that antiviral therapy can be started early, with the goal of later bone marrow transplant [51].

C. How long COVID is related to EBV reactivation

Long COVID's relation to EBV reactivation has been studied as well. Infection with EBV and/or SARS-CoV-2 may lead to a number of long COVID symptoms, such as fatigue, depression, and insomnia [28]. Gold et al. recruited 68 COVID-19 patients to determine association between the occurrence of long COVID symptoms and the reactivation of EBV. (Figure 5) Based on positive titers for EBV VCA IgG (which means past infection with EBV), 30.3% of patients had long COVID, while 66.7% of long COVID patients were positive for EBV reactivation compared to 10% of the control group [61].

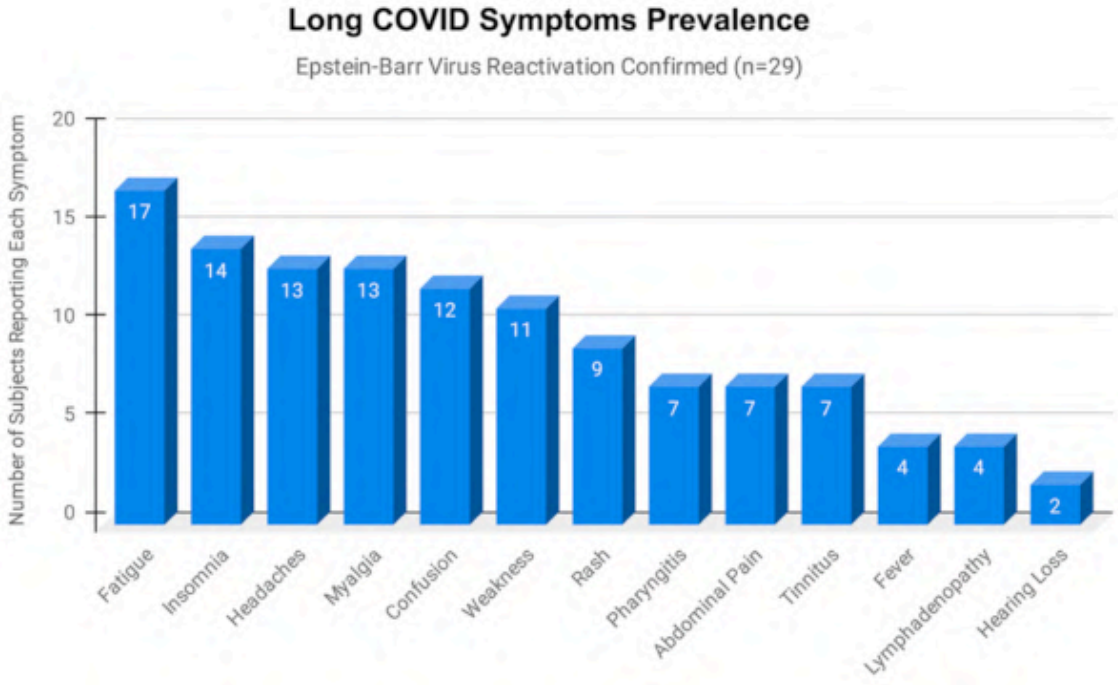


Figure 5: Data reported by 29 subjects positive for EBV reactivation on clinical manifestations of long COVID.

These subjects were from both long- and short-term COVID groups. The three most common long COVID symptoms from those who were EBV-positive were fatigue, insomnia, and headaches.
Data extracted from Pathogens, made available by PubMed Central.
https://pubmed.ncbi.nlm.nih.gov/34204243/ [61]

A second, similar ratio was found in a group of 18 patients 21 to 90 days positive for COVID-19; therefore, reactivation of EBV may be soon after or simultaneous with SARS-CoV-2 infection, and some long COVID symptoms may not be just because of COVID-19, but more directly be a result of COVID-19-induced EBV reactivation [51]. As a key characteristic of MS is chronic inflammation and EBV+ lymphocytes may exacerbate that inflammation in addition to SARS-CoV-2 infection eliciting a strong inflammatory response in infected and immune cells, continued inflammation after viral clearance and evidence of atypical cytokine activation (as EBV+ B cells can express cytokines that promote inflammation) in patients may contribute to long COVID. Accordingly, determining ways to minimize the mechanisms that cause inflammation may help relieve some symptoms for those infected with long COVID, MS, and EBV [52]. From a group of 294 adults with SARS-CoV-2 infection history, initial diagnosis of long COVID was associated with evidence of recent EBV reactivation but not with ongoing EBV viremia. Additionally, long COVID was observed in some but without evidence of EBV infection, pointing to the possibility that EBV reactivation isn't a prerequisite for long COVID symptoms [53].

IX. Discussion

COVID-19 and EBV are quite common viruses, with COVID-19 being common due to the pandemic in the past few years, and EBV simply because it is so easily transmitted and received (through saliva or bodily fluids) globally. However, what is not common is the leading to other diseases like MS and CAEBV from EBV and COVID-19. As it turns out, EBV, a virus previously recorded as almost harmless and often only causing cold-like symptoms , may lead to other serious diseases and even death in rare cases. And if a person had both COVID-19 and EBV, this may worsen resulting disease states. Those with both SARS-CoV-2 and EBV infection were found to have relatively more severe symptoms and higher mortality rates comparatively.

Emerging evidence suggests that COVID-19 vaccination and infection may lead to a series of health consequences, including EBV reactivation. COVID-19 vaccination and infection activates lymphocytes and promotes inflammation [1,20,45]. Furthermore, T cell responses—specifically, an up-regulated T cell response after COVID-19 vaccination, or a decreased T cell response due to over-activated T cell states from SARS-CoV-2 infection—can occur upon COVID-19 vaccination or infection [54]. Evidence suggests that these responses can promote EBV reaction. Interestingly, both SARS-CoV-2 infection and COVID-19 vaccination in this case seem to lead to immune system imbalance or injury that can lead to reactivation of EBV. The relations between these disease states seem causal, but with no concrete evidence of why or how, the only evidence being that these factors may contribute. Moreover, because of the link between COVID-19 vaccination and EBV, there should be greater awareness of CAEBV, a chronic and debilitating result of an EBV infection. And because the evidence of a link between EBV and MS is now strong enough that Thomas et al. states that EBV infection is likely a "prerequisite" for MS [55], consequently, the association between EBV and both SARS-CoV-2 infection and COVID-19 vaccination is an important field that must be studied in more depth.

Additionally, there is a need for better treatments for suppressing EBV symptoms and preventing EBV infection. Though usually, it is simply a harmless infection that is caught but usually stays latent, that in itself is dangerous, especially if other diseases such as COVID-19 or COVID-19 vaccinations may trigger it again, and due to the link between EBV infection and debilitating diseases such as MS. One promising therapy suggested from research data is S1R agonists that have been found to limit EBV reactivation and long COVID symptoms, though it has yet to be studied clinically. Another avenue for potential treatment includes antiviral drugs, such as ganciclovir which has been found to inhibit EBV in vitro and suppress EBV reactivation [31]. A study on effects of ganciclovir treatment in COVID-19 and EBV infected patients, displayed improved survival rates of 0.98 rather versus 0.88 for the non-treated patients [56], allowing for the possibility of future treatment of those with both EBV and SARS-CoV-2 infection.

In accordance with this evidence, the development of efficacious EBV vaccines is an urgent need. EBV is a challenging target, changing along its life cycle and possibly causing tumors to develop, so its viral proteins for vaccines is currently not done because of possible increased risk of cancer and MS, among other diseases [32]. But although EBV is not severe for most people and also hard to find a solution to, the piling amounts of evidence relating EBV to COVID-19, MS, long COVID, and CAEBV outweigh these reasons.

Long COVID, where previously infected individuals experience long-term effects from previous SARS-CoV-2 infection, was found not to occur simply because of COVID-19, but also can be a result of induced EBV reactivation, although EBV reactivation isn't a prerequisite for long COVID symptoms [5,16,53]. So while these symptoms may directly be caused by EBV reactivation, they can occur even without it. COVID-19 causes a strong inflammatory response in cells, and EBV+ lymphocytes may aggravate the inflammation; consequently, continued inflammation after infection and traces of atypical cytokine activation due to EBV+ B cells expressing cytokines that promote inflammation, may contribute to long COVID symptoms [52]. Hence, finding a treatment for these long COVID symptoms, which may range from mild to severe (heavily affecting the heart and lungs) due to the ongoing health problems, is, again, one that needs to be found as soon as possible, and may be assisted through reducing EBV reactivation rates.

X. Conclusion

With increasing widespread links between EBV and MS, and studies that suggest associations between EBV, COVID-19 vaccination, and SARS-CoV-2 infection, this field of study has proven itself in urgent need of further research. This paper reflects the importance of an understanding of possible factors that may influence a COVID-19 vaccination leading to further disease, such as the health history of patients with SARS-CoV-2 infection. Currently, there are several possible treatments aiming to relieve symptoms of individuals with EBV, MS, COVID-19, and long COVID, and vaccines aiming to prevent EBV are additionally being developed and evaluated. Although increasing evidence points to a relationship between EBV and COVID-19, currently none are strong enough to reach a definite answer; therefore, this link needs to be addressed in order to gain a better understanding of minimizing EBV reactivation and decreasing the likelihood of MS and long COVID symptoms.

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