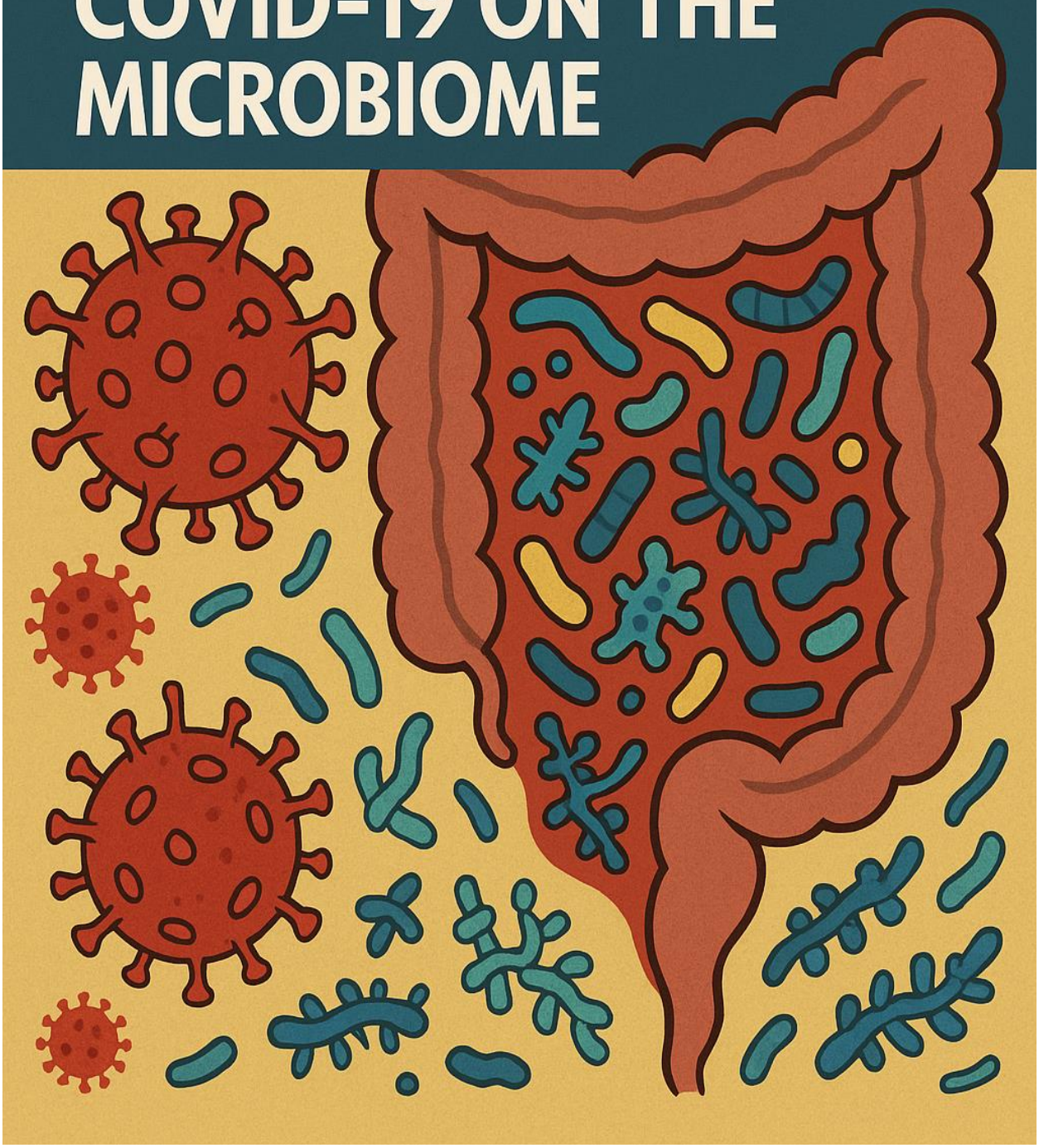
THE INFLUENCE OF COVID-19 ON THE MICROBIOME



Narrative Review

The influence of Covid-19 on the Microbiota.

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Forward

The aftermath of the COVID-19 pandemic, compounded by the widespread administration of the experimental vaccine, has left an indelible mark on modern medicine, contributing to an alarming rise in premature deaths from a multitude of complex and often unrecognized causes. As clinicians specializing in the treatment of traumatic brain injury (TBI) and its long-term sequelae, we have observed a distinct subpopulation of patients whose recovery trajectories diverge markedly from the expected course. Unlike the majority, who demonstrate steady neurological and cognitive improvements, this group exhibits erratic progress, characterized by alternating periods of symptomatic relief and exacerbation—without an immediately discernible cause.

It wasn't until we broadened our investigative lens to include the gut microbiome that the missing link began to emerge. Initially, many of these patients appeared to be gut-asymptomatic, showing no overt signs of gastrointestinal distress, such as nausea, bloating, diarrhea, constipation, or abnormal flatulence. Others, however, exhibited clear GI dysfunction, prompting us to delve deeper into the intricate gut-brain connection. What we uncovered was a profound disruption in microbial diversity and gut barrier integrity, influencing neuroinflammation, immune regulation, and systemic health—factors that may have been overlooked in post-COVID and post-vaccine evaluations.

This realization has propelled us to redefine our approach, recognizing that neurological recovery is inextricably linked to gut health. By addressing dysbiosis, intestinal permeability, and microbiome restoration, we are uncovering new pathways to healing, offering hope to those who have struggled to reclaim their cognitive and physical well-being in the wake of this unprecedented medical crisis.

Introduction

The ongoing global pandemic of coronavirus disease 2019 (COVID-19) is caused by the RNA virus severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), which primarily infects the respiratory tract. However, beyond pulmonary manifestations, gastrointestinal (GI) symptoms such as diarrhea, nausea, and vomiting have been reported in approximately 5%–33% of COVID-19 patients. Studies have detected SARS-CoV-2 RNA in stool samples and anal swabs, suggesting that the digestive tract serves as an extra-pulmonary site of infection.

The GI tract, as the largest immune organ in humans, plays a crucial role in host defense mechanisms against infections. Within it resides the gut microbiome—a diverse ecosystem of bacteria, fungi, viruses, and other microorganisms—which actively modulates host immunity. Emerging research has demonstrated that COVID-19 disrupts the gut microbiome, leading to significant alterations in microbial diversity and composition. Specifically, patients with COVID-19 exhibit a depletion of beneficial bacteria (e.g., *Faecalibacterium prausnitzii* and *Bifidobacterium spp.*) and an overgrowth of opportunistic pathogens (e.g., *Clostridium hathewayi* and *Bacteroides nordii*).

The interplay between SARS-CoV-2 infection and gut microbiome dysbiosis may contribute to disease severity, immune dysfunction, and persistent symptoms seen in long COVID. The presence of the virus in the gut alters microbial ecology, weakens immune defenses, and promotes gut barrier dysfunction, facilitating systemic inflammation. Additionally, microbial imbalances may hinder post-COVID-19

microbiome recovery, prolonging health complications.

This review examines the impact of COVID-19 on the human gut microbiome, detailing its effects on bacterial, fungal, and viral populations and their implications for immune responses and disease progression.

The Guardians of the Gut

Bifidobacterium spp.: The Cornerstone of Gut Health and Immunity

Bifidobacterium is a foundational genus of probiotic bacteria, celebrated for its indispensable role in maintaining gut homeostasis, fortifying immune defenses, and promoting overall well-being. These beneficial microbes are among the earliest colonizers of the human gut, shaping the microbial landscape from infancy and continuing to play a pivotal role in digestive health, metabolic function, and immune regulation throughout life.

A hallmark feature of *Bifidobacterium* is its ability to produce short-chain fatty acids (SCFAs), particularly acetate, which serves as both a metabolic fuel for intestinal epithelial cells and a powerful reinforcer of gut barrier integrity. By nourishing the mucosal lining and modulating gut permeability, *Bifidobacterium* acts as a first line of defense against harmful pathogens, preventing their colonization and reducing the risk of gastrointestinal infections, inflammation, and systemic immune dysregulation.

Beyond structural support, *Bifidobacterium* exerts profound immunomodulatory effects. It interacts closely with gut-associated lymphoid tissue (GALT), a key player in immune surveillance, to fine-tune immune responses. Through this interaction, *Bifidobacterium* helps balance pro-inflammatory and anti-inflammatory pathways, reducing excessive immune activation and lowering the risk of autoimmune disorders and chronic inflammatory diseases.

A decline in *Bifidobacterium* is strongly associated with gut dysbiosis, increased intestinal permeability ("leaky gut"), and heightened systemic inflammation, creating a cascade of metabolic and immune dysfunctions. Notably, studies have observed a significant depletion of *Bifidobacterium* in COVID-19 patients, which may contribute to worsened disease outcomes, prolonged inflammation, and reduced microbiome resilience post-infection.

Given its profound influence on gut, immune, and metabolic health, *Bifidobacterium* is widely recognized as a therapeutic target in probiotic interventions, with emerging research exploring its potential in enhancing antiviral immunity, restoring microbiome equilibrium, and mitigating the long-term effects of infections like COVID-19.

Akkermansia muciniphila: The Guardian of Gut Barrier Integrity

Akkermansia muciniphila is a keystone bacterium in gut health, renowned for its pivotal role in maintaining intestinal barrier integrity and metabolic balance. As a specialist in mucin degradation, *Akkermansia* thrives within the protective mucus layer lining the intestines, where it plays a dual role—nourishing the gut lining while reinforcing its defense mechanisms. By stimulating the production of mucin, this bacterium ensures a robust barrier against pathogens while fostering a symbiotic relationship with the host.

Beyond its structural benefits, *Akkermansia muciniphila* exerts profound metabolic and immunomodulatory effects. It enhances the secretion of glucagon-like peptide-1 (GLP-1), a crucial hormone that regulates insulin sensitivity, glucose metabolism, and appetite control, making it a powerful ally in the fight against metabolic disorders. Research has consistently shown that higher levels of *Akkermansia* are associated with lower inflammation, improved lipid metabolism, and reduced risk of obesity and type 2 diabetes—conditions that significantly elevate the severity of COVID-19 infections.

A decline in *Akkermansia muciniphila* has been observed in individuals with gut dysbiosis, chronic inflammation, and metabolic syndrome, leading to increased intestinal permeability ("leaky gut"), systemic inflammation, and heightened susceptibility to infections. Given its far-reaching influence on gut and immune health, *Akkermansia* is increasingly recognized as a therapeutic target for restoring microbiome

balance, with emerging research exploring its potential in probiotic supplementation and precision medicine strategies for COVID-19 recovery and metabolic health optimization.

Lactobacillus spp.: The Gut's Frontline Defenders

Lactobacillus species are among the most versatile and beneficial probiotic bacteria, renowned for their ability to fortify the gut microbiome, enhance immune function, and protect against pathogenic invasion. As powerful lactic acid producers, these microbes actively ferment carbohydrates into lactic acid, creating a mildly acidic gut environment that inhibits the growth of harmful bacteria, such as *Escherichia coli* and *Clostridium difficile*. This pH modulation is a key factor in maintaining microbial balance and preventing infections, particularly in individuals with compromised immunity.

Beyond their antimicrobial properties, *Lactobacillus* species play a critical role in mucosal immunity. They stimulate the production of secretory immunoglobulin A (sIgA), a key antibody that coats the intestinal lining, neutralizing pathogens before they can breach the gut barrier. Additionally, *Lactobacillus* reinforces tight junction integrity, preventing intestinal hyperpermeability ("leaky gut"), which is associated with chronic inflammation, autoimmune conditions, and systemic infections.

Certain strains, such as *Lactobacillus rhamnosus*, go a step further by producing bacteriocins, potent antimicrobial peptides that directly combat harmful microbes, further strengthening the gut's defenses. This ability to modulate immune responses and outcompete pathogens makes *Lactobacillus* an essential player in gastrointestinal and immune homeostasis.

Alarmingly, research has revealed that COVID-19 significantly depletes *Lactobacillus* populations, contributing to gut dysbiosis, increased inflammation, and weakened immune resilience. The loss of these beneficial bacteria may exacerbate prolonged inflammation, gut permeability issues, and post-viral immune dysfunction seen in long COVID.

Due to its profound influence on gut health, immunity, and inflammation control, *Lactobacillus* is increasingly recognized as a therapeutic target in probiotic strategies aimed at restoring microbial equilibrium, reducing systemic inflammation, and supporting recovery from infections like COVID-19.

Faecalibacterium prausnitzii: The Anti-Inflammatory Powerhouse of the Gut

Faecalibacterium prausnitzii is a cornerstone of gut health and immune regulation, widely regarded as one of the most beneficial and abundant commensal bacteria in the human microbiome. As a potent butyrate producer, this bacterium plays a pivotal role in gut barrier maintenance, immune modulation, and inflammation control.

Butyrate, the primary metabolic byproduct of *F. prausnitzii*, serves as an essential energy source for colonocytes, the epithelial cells lining the intestines. This nourishment of the gut lining enhances intestinal barrier integrity, reducing gut permeability ("leaky gut") and preventing the translocation of harmful microbial byproducts into the bloodstream—a key driver of chronic inflammation and systemic immune activation.

Beyond structural support, *F. prausnitzii* exerts profound anti-inflammatory effects by actively suppressing the production of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interferon-gamma (IFN-γ). At the same time, it promotes the release of anti-inflammatory cytokines such as interleukin-10 (IL-10), fostering immune balance and protecting against autoimmune and inflammatory disorders.

Studies have consistently shown that *F. prausnitzii* is significantly depleted in patients with inflammatory diseases, including Crohn's disease, ulcerative colitis, and metabolic syndrome. More recently, COVID-19 has been linked to a sharp decline in *F. prausnitzii*, contributing to intestinal dysbiosis, increased oxidative stress, and heightened inflammatory responses—factors that may worsen disease severity and hinder post-infection recovery.

Given its profound immunoregulatory and gut-protective properties, *F. prausnitzii* has emerged

as a therapeutic target in microbiome-based interventions, with probiotic and prebiotic strategies being explored to restore its populations, combat inflammation, and support recovery from immune-related conditions, including long COVID.

Roseburia spp.: The Butyrate-Producing Guardian of Gut and Immune Health

Roseburia is a keystone butyrate-producing bacterium that plays a fundamental role in maintaining gut integrity, immune balance, and systemic health. As a major producer of short-chain fatty acids (SCFAs), particularly butyrate, *Roseburia* contributes to intestinal barrier fortification, ensuring the gut lining remains resilient against pathogen invasion and inflammatory insults. Butyrate not only serves as a critical energy source for colonocytes, the cells lining the gut, but also reinforces tight junctions, reducing intestinal permeability ("leaky gut"), which is a known driver of chronic inflammation and immune dysregulation.

Beyond its role in gut homeostasis, *Roseburia* is a potent immune modulator, particularly in fostering immune tolerance. It actively promotes the differentiation of regulatory T cells (Tregs), which are essential for controlling excessive immune activation and preventing autoimmune responses. This ability to fine-tune the immune system is especially crucial in inflammatory conditions, as dysregulated immune responses can lead to widespread tissue damage and chronic disease progression.

Emerging research has revealed a significant depletion of *Roseburia* in COVID-19 patients, correlating with increased systemic inflammation, heightened gut permeability, and a greater susceptibility to gut-derived endotoxemia— a condition where bacterial toxins enter circulation and exacerbate immune dysfunction. Given its role in reducing inflammation, supporting gut-brain communication, and reinforcing immune defenses, *Roseburia* is increasingly recognized as a therapeutic target in microbiome restoration strategies aimed at mitigating post-viral complications and enhancing long-term recovery from infections such as COVID-19.

The Synergy of the Microbiome: A Unified Defense System for Gut, Immunity, and Brain Health

The human gut microbiome is not merely a collection of individual bacterial species but a highly coordinated ecosystem, where different microbes work in concert to maintain gut integrity, regulate immune responses, and protect brain function. This intricate synergy among key bacterial species—including Faecalibacterium prausnitzii, Bifidobacterium spp., Lactobacillus spp., Roseburia spp., and Akkermansia muciniphila—ensures that the gut functions as a fortified barrier, a metabolic powerhouse, and an immune-regulating hub. When this delicate balance is disrupted, the consequences extend far beyond the digestive system, contributing to chronic inflammation, autoimmune dysfunction, and neurodegenerative diseases.

Fortifying the Gut Barrier: The First Line of Defense

A healthy gut lining serves as the body's primary defense against harmful pathogens, toxins, and environmental stressors. This protective barrier relies heavily on the presence of butyrate-producing bacteria, such as *Faecalibacterium prausnitzii* and *Roseburia spp.*, which generate essential short-chain fatty acids (SCFAs), including butyrate, acetate, and propionate. These SCFAs play a crucial role in maintaining intestinal integrity by acting as a primary energy source for colonocytes, the cells that line the gut, thereby strengthening the structural foundation of the intestinal lining. Additionally, they enhance tight junction proteins, reducing the likelihood of increased gut permeability, commonly referred to as "leaky gut," which can allow endotoxins to enter the bloodstream and trigger systemic inflammation. By modulating immune responses, these SCFAs also help to suppress the production of pro-inflammatory cytokines such as TNF-α and IL-6, effectively lowering inflammation within the gut and throughout the body.

Beyond butyrate production, *Akkermansia muciniphila* plays a critical role in maintaining

the gut's protective mucus layer by facilitating mucin degradation and renewal. This process ensures that the intestinal lining remains robust and acts as a buffer against harmful bacterial infiltration while simultaneously creating a nutrient-rich environment that supports the growth of other beneficial microbes. Working synergistically, *Bifidobacterium spp.* contributes to this protective network by fermenting dietary fibers into SCFAs, which not only fuel colonocytes but also help sustain a balanced and diverse microbiota. Together, these microbial communities reinforce the gut barrier, reducing the risk of inflammation-driven diseases and fostering overall systemic health.

Enhancing the Immune System: Gut Microbes as Immune Regulators

The gut microbiome is intricately connected to the immune system, with nearly 70% of immune cells residing within the gut-associated lymphoid tissue (GALT). This microbial ecosystem plays a crucial role in maintaining immune homeostasis by regulating inflammation, defending against pathogens, and preventing immune overactivation. A balanced microbiome fosters an immune response that is neither too weak to fight infections nor too aggressive to trigger autoimmune reactions.

Among the key microbial players, *Roseburia spp.* and *Faecalibacterium prausnitzii* support immune tolerance by driving the differentiation of regulatory T cells (Tregs), which are essential for suppressing excessive immune activation and preventing autoimmune disorders. At the same time, *Lactobacillus spp.* enhances mucosal immunity by stimulating the production of secretory immunoglobulin A (sIgA), an antibody that coats the intestinal lining, neutralizing harmful pathogens and maintaining a protective barrier. Meanwhile, *Bifidobacterium spp.* and *Faecalibacterium prausnitzii* contribute to immune modulation by producing short-chain fatty acids (SCFAs), which help balance cytokine production. These beneficial bacteria reduce pro-inflammatory cytokines such as TNF-α while increasing levels of the anti-inflammatory cytokine IL-10, which helps prevent chronic systemic inflammation associated with autoimmune diseases, metabolic syndrome, and long COVID.

When the gut microbiome becomes imbalanced—whether due to COVID-19, antibiotic overuse, or a poor diet—the immune system can become dysregulated. This disruption may lead to a state of hyperactivation, increasing the risk of autoimmune disorders and chronic inflammation, or compromise immune function, making the body more susceptible to infections. By maintaining microbial diversity and supporting the symbiotic relationship between gut bacteria and the immune system, the microbiome serves as a critical regulator of immune resilience and overall health.

Protecting the Brain: The Gut-Brain Axis in Action

The gut microbiome is deeply intertwined with brain health, engaging in constant bidirectional communication through the gut-brain axis. This complex network of signaling pathways influences mood, cognition, and neurological resilience, making the gut microbiome a critical player in mental and cognitive well-being. When the microbiome is balanced, it supports neurotransmitter production, vagus nerve activity, and neuroinflammation control, all of which contribute to optimal brain function.

One of the key ways the gut impacts the brain is through neurotransmitter production. *Lactobacillus* and *Bifidobacterium* species synthesize essential neurotransmitters such as gamma-aminobutyric acid (GABA) and serotonin, both of which are critical for mood stability, stress resilience, and emotional regulation. With nearly 90% of the body's serotonin being produced in the gut, an imbalance in these microbial populations can lead to depression, anxiety, and cognitive impairment.

Another important mechanism is vagus nerve signaling, which serves as a direct communication highway between the gut and the brain. Short-chain fatty acids (SCFAs) produced by *Roseburia* and *Faecalibacterium* stimulate vagal nerve activity, which helps reduce neuroinflammation and support cognitive clarity. This interaction is vital in preventing neurodegenerative diseases and cognitive decline

by maintaining a balanced inflammatory response and promoting brain plasticity.

Additionally, the gut microbiome plays a pivotal role in controlling neuroinflammation, a key factor in conditions such as Alzheimer's disease, Parkinson's disease, and depression. By lowering systemic inflammation, beneficial gut bacteria help mitigate the harmful effects of chronic immune activation, which can contribute to blood-brain barrier dysfunction, oxidative stress, and neuronal damage.

When gut dysbiosis occurs—whether due to COVID-19, chronic stress, poor diet, or environmental toxins—it can disrupt serotonin production, weaken vagus nerve signaling, and increase systemic inflammation, all of which have been implicated in neurodegenerative diseases, brain fog, and anxiety disorders. Understanding and nurturing the gut-brain axis through microbiome restoration strategies offers a promising pathway to improving neurological health, mental clarity, and emotional well-being.

Conclusion: A Unified Microbial Network for Optimal Health

The synergy of the microbiome is what makes it such a powerful determinant of health. *Bifidobacterium*, *Lactobacillus*, *Roseburia*, *Faecalibacterium*, and *Akkermansia* function as a collaborative defense network, each playing a unique role in fortifying the gut, enhancing immunity, and protecting the brain. When in balance, this microbial ecosystem:

✅ Prevents systemic inflammation
✅ Strengthens gut barrier integrity
✅ Enhances immune tolerance and pathogen defense
✅ Supports cognitive health and mood regulation

Recognizing the profound influence of the gut microbiome on whole-body health highlights the necessity of nurturing it through diet, lifestyle, and targeted probiotic interventions—a strategy that may hold the key to resilient immunity, longevity, and neurological vitality in a post-pandemic world.

Addressing the Veteran Population

As of October 2021, over 95% of the 1.4 million active-duty U.S. military service members had received at least one dose of the COVID-19 vaccine (Military Health System 2024). Specifically, the U.S. Army reported that 98% of its active-duty soldiers were vaccinated, with 96% fully vaccinated by December 2021. (Army 2021)

However, it's important to note that these figures primarily reflect active-duty personnel, and comprehensive data for all branches, including reserves and the National Guard, are not uniformly detailed in the available sources. Additionally, the Department of Defense rescinded the COVID-19 vaccine mandate on January 10, 2023, allowing service members previously discharged for vaccine refusal to request reinstatement. (Army 2025) Therefore, vaccination rates may have changed post-mandate rescission.

The Bacteria of the Gut

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