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Decoding the paradox: Understanding Elevated Hospitalization and Reduced Mortality in SARS-CoV-2 Variants

Sunil J. Wimalawansa *

Endocrinology and Nutrition, Cardio Metabolic and Endocrine Institute, North Brunswick, New Jersey, USA.

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Abstract

Introduction and aim: SARS-CoV-2 outbreaks occur cyclically, aligning with winter when vitamin D levels are lowest, except after new variant outbreaks. Adequate vitamin D is crucial for robust immune function. Hypovitaminosis diminishes immune responses, increasing susceptibility to viral infections. The manuscript explores the discrepancy between increased SARS-CoV-2 hospitalizations and lower mortality.

Method: SARS-CoV-2 mutants, including Delta, BQ, and XBB Omicron lineages, developed immune evasion capabilities, reducing the effectiveness of COVID-19 vaccines and bivalent boosters. The failure of COVID-19 vaccines to prevent infections and spread to others, coupled with the immune evasion exhibited by mutant viruses, contributed to continued SARS-CoV-2 outbreaks. Interestingly, dominant new mutants, despite their increased transmissibility, have caused fewer deaths. This article scrutinizes the mentioned incongruity through an analysis of published data.

Results*:* Achieving herd immunity and eradicating SARS-CoV-2 has proven elusive due to ongoing mutagenesis and immune evasion, leading to recurrent viral outbreaks. The failure to approve repurposed early therapies for COVID-19 by regulators, as well as misinformation and weak strategies undertaken by leading health authorities, exacerbated the situation. Repurposed agents, including vitamin D and ivermectin, have demonstrated high efficacy against SARS-CoV-2 from the beginning, and remain unaffected by mutations. Despite their cost-effectiveness and widespread availability, regulatory approval for these generic agents in COVID-19 treatment is pending.

Conclusion: Regulators hesitated to approve cost-effective, repurposed generic agents primarily to safeguard the temporary approval status of COVID-19 vaccines and anti-viral agents under Emergency Use Authorization, which persists. This reluctance overlooked the opportunity to implement an integrated approach with repurposed agents alongside COVID-19 vaccines, potentially reducing hospitalizations and fatalities and preventing outbreaks; this led to the failure to eradicate SARS-CoV-2 and becoming endemic. It is imperative that regulators now reconsider approving affordable generics for SARS-CoV-2 to effectively control future viral outbreaks.

Non-technical Importance (Lay Abstract)

Adequate vitamin D levels significantly bolster the human immune system—deficiency compromises immune responses and increases susceptibility, particularly to viruses. While new SARS-CoV-2 mutations like Omicron are less severe, they are more infectious and adept at evading immunity from vaccines; thus, they offer a limited spectrum of protection and duration. Primary COVID-19 vaccines have reduced disease severity but have failed to prevent viral spread, contributing to outbreaks. Booster doses had little effect on the virus but caused immune paresis, thus increasing susceptibility to infections. Regulators should consider approving generic, repurposed agents like vitamin D and ivermectin as adjunct therapies to address this challenge and better prepare for future pandemics. Proactively

* Corresponding author: Sunil J. Wimalawansa

integrating vitamin D supplementation to fortify the immune system can mitigate vital outbreaks, alleviate hospital burdens, and reduce healthcare costs.

Keywords: 25(OH)D; 1,25(OH)2D; COVID-19; Outbreaks; Pandemic; Public health; Vitamin D; Virus

1. Introduction

Individuals aged 70 years and above, particularly those with comorbidities or immune suppression, are the most susceptible demographic to SARS-CoV-2 infection AND re-infections. Hospitalization due to original SARS-CoV-2 was infrequent among healthy adults under fifty, especially children; thus, they should not have prioritized receiving vaccines. While immunity following COVID-19 vaccination typically lasts around six to nine months, natural immunity persists for over 18 months [1-4].

Those recovered from SARS-CoV-2 infection develop robust protective immunity [5], enduring T-cell memory [6-8], and prolonged plasma cell-mediated immunity [9, 10]. Consequently, there is no rationale for them to receive COVID-19 vaccinations or booster doses [2]. Moreover, COVID-19 vaccines do not confer complete protection against SARS-CoV-2 infection or prevent transmission to others [11]. While SARS-CoV-2 Spike protein-mediated mRNA vaccination elicits humoral and cellular immunity, it critically lacks mucosal immunity [12]. Consequently, COVID-19 vaccines do not prevent infections or curb their spread to others.

Meanwhile, individuals with post-infection immunity who receive vaccinations unnecessarily heighten the risks of adverse effects, including antibody-dependent enhancement reactions [13-15]. However, compared to the original Wuhan SARS-CoV-2 virus, from 2021 onwards, dominant mutated viruses, such as the Delta and Omicron variants, exhibited increased infectivity (high R_0). They also displayed a rising trend of infecting younger individuals, some requiring hospitalization [16, 17]. Nevertheless, despite the heightened infectivity and symptomatic disease, fatalities remained significantly lower than the original SARS-CoV-2.

Notably, the reported statistics are influenced by factors unrelated to the SARS-CoV-2 virus. These include data collection, reporting, statistical errors, bias, and conflicts of interest. The widespread use of PCR and RAT screening tests and the availability of free testing kits since late 2020 contributed to the increased number of reported cases. These two methodologies, however, are only screening tests and not diagnostic. Additionally, reporting biases existed, with particular administrations exaggerating and others downplaying the reported infections and related deaths for financial and political reasons. The mentioned testing kits had notable false positives and negatives, compromising the accuracy of reported SARS-CoV-2 infection cases. Moreover, individuals with co-incidental positive tests have had deaths unrelated to SARS-CoV-2, inflating the reported COVID-19-related hospitalizations and fatalities.

2. Progress in managing COVID-19 during the pandemic

The initial two waves of SARS-CoV-2 in 2020 primarily impacted older individuals, particularly those with comorbidities residing in care facilities. A significant proportion of this demographic tends to exhibit severe vitamin D deficiency [18, 19], a crucial factor as immune cell activities largely hinge on adequate vitamin D levels [20, 21]. Consequently, individuals in this group have compromised immune systems [22, 23]. Regardless of age, individuals with comorbidities often experience hypovitaminosis D, leading to weakened immune systems and heightened susceptibility to infections. They face increased risks of developing complications and succumbing to viral illnesses such as SARS-CoV-2 [24, 25].

Since the inception of mRNA vaccines mainly related to the ACE-2 receptor binding domain (RBD), the rate of SARS-CoV-2 viral mutations has increased, especially among immune-compromised individuals [26]. These mutations have facilitated the emergence of dominant variants, such as the Omicron variants, characterized by increased viral transmission and rapid spread, denoted by higher R_0 numbers for SARS-CoV-2 viruses [27, 28].

The mutated viruses have demonstrated heightened infectivity among vulnerable individuals, including younger persons and those with compromised immune systems [26, 28]. The inability of COVID-19 vaccines to prevent the spread of SARS-CoV-2 [27] has contributed to increased virus transmission and subsequent outbreaks. Simulation approaches for assessing the COVID-19 pandemic have delved into vaccine logistics, SARS-CoV-2 variants, and spread rates [27, 29]. Figure 1 depicts the ongoing cases and outbreaks of SARS-CoV-2, accompanied by a significant reduction in deaths from infection.

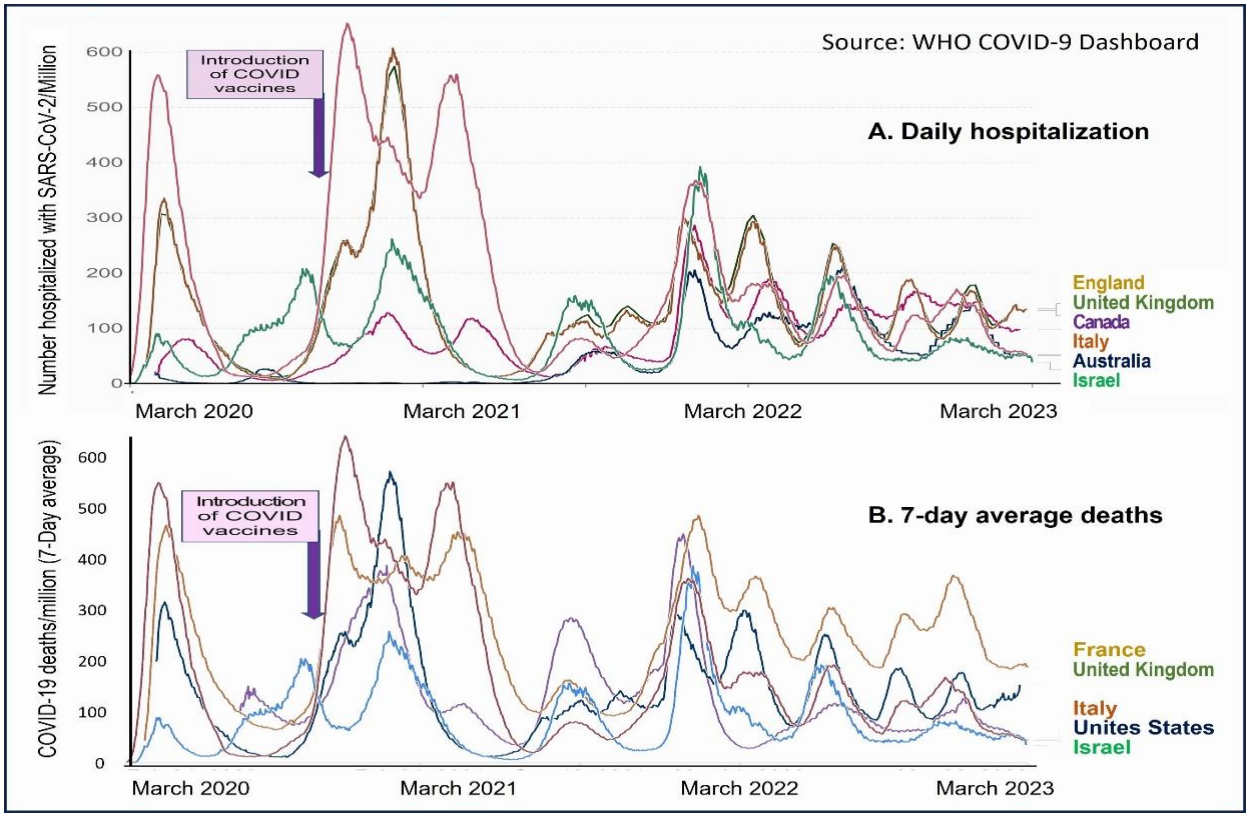

Figure 1 A). Daily new hospitalizations of individuals confirmed infected with SARS-CoV-2 per million population, and B) seven-day average deaths from COVID-19 per million population (Source: Our World in Data—WHO COVID Dashboard). The figure illustrates the sustained occurrence of significant outbreaks, primarily aligning with winter, and the gradual decline in incidents, regardless of the implementation of COVID-19 vaccines.

The key factor leading to complications is the host's inability to respond and control viral replication and spread due to a compromised immune system. Despite this, authorities and major health agencies prioritized infrastructure expansion—such as hospitals and intensive care units—and the establishment of quarantine centers for isolation. Without addressing the primary cause of vulnerability—having poor immune systems. The latter is primarily driven by vitamin D and other micronutrient deficiencies. Instead of taking steps to have robust immune systems, authorities primarily relied on vaccine-derived immunity to control the SARS-CoV-2 pandemic. Thus, public health guidance from leading health authorities entirely neglected in boosting immune systems, particularly in vulnerable individuals.

3. Importance of the robust immunity in the population

To date, health agencies have not taken the initiative to proactively encourage the public to enhance their immune systems for overall health and reduce infection vulnerability. Recommendations on daily safe sun exposure, micronutrient supplements like vitamin D, physical activity engagement, and mental well-being have been neglected [24, 25]. These measures could strengthen the population's immunity against complications and susceptibility to the virus [30-32].

Misguided governmental policies, such as lockdowns and restrictions, increased vitamin D deficiency, especially among indoor housebound residents, rendering them more susceptible to the virus and symptomatic disease [33, 34]. Intermittent lockdowns during the initial two years of the pandemic resulted in sedentariness, obesity, insulin resistance, and reduced sunlight exposure, contributing to a high prevalence of hypovitaminosis D. These factors heightened individuals' vulnerability to SARS-CoV-2 and complications [30, 35-37]. Excessive lockdowns and extended curfews were more detrimental to the public and the economy than the virus.

With additional mutations, Omicron variants, including BQ.1.1 and XBB1.5, impact lower and upper respiratory tracts, presenting distinct signs and symptoms compared to the original SARS-CoV-2. While these mutants lead to significantly more new infections and re-infections, they exhibit lower lethality [38]. Concurrently, the occurrence of Kawasaki-like disease and multisystem inflammatory syndrome (MIS) in infants and younger children saw a notable increase in 2021,

partly attributed to reduced outdoor activities and increased prevalence of hypovitaminosis D due to limited sun exposure. Severe hypovitaminosis D, with serum 25(OH)D concentrations less than 12 ng/mL, is frequent in children experiencing these severe complications [39-41].

4. Ongoing mutations of the SARS-CoV-2 virus

The Spike protein mutations in Delta and Omicron variants of SARS-CoV-2 have exhibited a heightened affinity for the ACE-2 receptor on human epithelial cells, enhancing their entry [42]. Individuals with low vitamin D levels (hypovitaminosis D) experience reduced neutralizing antibody titers from prior infection or vaccination [43]. Moreover, these individuals show lower responsiveness of neutralizing antibodies generated through vaccination, partly due to immune evasion [44, 45], particularly pronounced against bivalent vaccines, as seen with BQ and XBB subvariants [46].

The Omicron series is characterized by highly mutable single-stranded RNA genomes, leading to increased transmissibility and evasion from detection by COVID-19 vaccines, including bivalent vaccines [47]. Countries with higher vaccination rates experienced a higher incidence of viral mutations, particularly among those vaccinated, but also weakened immune systems due to severe vitamin D deficiency [43]. This has posed a significant public health threat, hindering the elimination of SARS-CoV-2 worldwide. The situation has further escalated with the notable reduction in the efficacy of bivalent vaccine boosters, amplifying the ability to spread SARS-CoV-2 variants [46, 47]. Despite three years of pandemic, health authorities, regulators, and administrations lack a contingency plan to address this dynamic situation.

Despite the vaccination of over 5.4 billion people [48], accounting for 74% of the world population [49], SARS-CoV-2 (variants) outbreaks persisted. The continuous mutagenesis, natural or otherwise, of the SARS-CoV-2 Omicron variants has led to the evasion of mutant recognitions by vaccine-derived antibodies, resulting in immune evasion [50]. This collective scenario has contributed to the breakdown of supply chains, economic collapse, and exacerbated challenges in manufacturing and distributing food and medicine. Notably, due to mutations, the contagiousness of associated outbreaks has increased, but their lethality has decreased. The immune evasion of COVID-19 vaccine-mediated neutralizing antibodies by Omicron variants has led to a rise in hospitalizations but a reduction in deaths [51] (Figure 2).

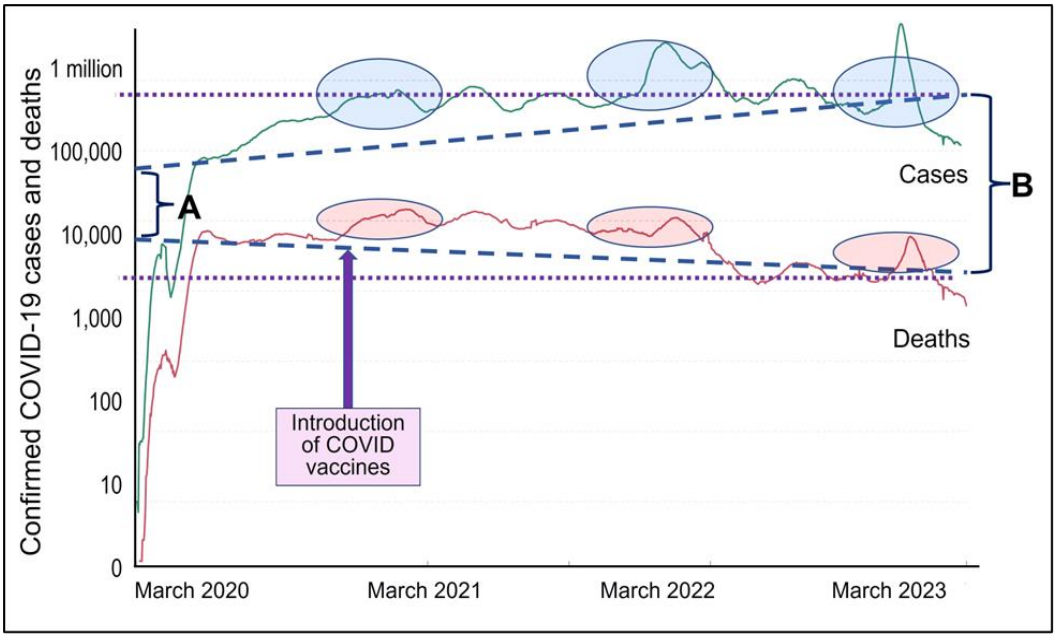

Figure 2 The chart depicts a seven-day rolling average of new confirmed SARS-CoV-2 cases and deaths worldwide over time. The blue dashed line highlights the increasing gap between SARS-CoV-2 infections (cases) and associated deaths over the X-axis time (linear) vs. the Y-axis (in the log). The blue oblong shape represents the winter-associated case incidences, while the red oblong shape corresponds to deaths reported during the same periods. The letters A in March 2020 showcase the difference in the number of reported cases, while B represents deaths in March 2023. The purple arrow indicates the introduction of COVID-19 vaccines. Data is sourced from Our World COVID data: John Hopkins University database and Our World COVID data.org/coronavirus (data from WHO COVID dashboard) [52]

Figure 2 illustrates the contrast between the rising number of cases and hospitalizations despite vaccination and a gradual decline in death rates (attributed to the milder nature of the mutants) from SARS-CoV-2 on a global scale. As denoted by letters A and B in Figure 1, at the initial stages of the pandemic, approximately 10% of deaths (one in ten—primarily impacting the elderly and individuals with multiple comorbidities, thus severe hypovitaminosis D) of hospitalized patients gradually decreased to less than 1% (fewer than one in 100 hospitalized patients). These variations might have been linked to disjointed efforts by leading health authorities and mismanagement by Western governments.

5. Pros and cons of mass vaccination and consequence of vitamin D deficiency

The Spike protein is an extremely toxic and highly immunogenic foreign protein, inducing high antibody titers, but only a fraction are neutralizing antibodies. Moreover, their protective effect is short-lived [53, 54], particularly in individuals with vitamin D deficiency. Many healthcare workers may not be aware of the significance of maintaining a therapeutic circulating 25(OH)D concentration above 50 ng/mL, which is crucial for a robust innate and adaptive immune system [55, 56]. Vitamin D deficiency heightens vulnerability, elevates the risk of hyperstimulation autoantibody formation, and diminishes the production of neutralizing antibodies.

Moreover, vitamin D deficiency leads to immune system dysregulation and heightened autoantibody formation, destroying normal healthy tissues. This associated hyper-inflammatory state may elevate the risk of Antibody-Dependent Enhancement (ADE) and cytokine storms. The toxicity of the Spike protein, whether from mRNA vaccines or SARS-CoV-2 infections, can instigate abnormalities in pulmonary and cardiovascular systems, along with generalized hyperinflammation and coagulation irregularities. Depending on vulnerability, these complications could range from mild to severe, including conditions such as myocarditis, thromboembolism, immunoparesis, central nervous system abnormalities, and fatalities [57].

6. Vitamin D deficiency increases the vulnerability to SARS-CoV-2

Several factors contribute to a higher prevalence of severe vitamin D deficiency among older adults, resulting in weaker immune systems [22]. Those with multiple comorbidities and/or hypovitaminosis in older individuals [58, 59] impair immune responses, making them more susceptible to infections, complications, and fatalities from viruses such as SARS-CoV-2 (Figure 1) [24, 25, 60]. In contrast, individuals with vitamin D sufficiency, 25(OH)D concentrations above 40 ng/mL, experience fewer adverse effects and complications from infection [36, 56, 61]. Maintaining therapeutic circulatory concentration necessitates a daily vitamin D intake between 5,000 to 8,000 IU (70 to 90 IU/kg body weight) for a non-obese adult [56, 61] or a weekly dose of 50,000 IU or once every ten days [36, 56] for healthy non-obese adults of ~70 kg; with a tolerable upper limit of 15,000 IU/day [62, 63].

Individuals who are obese or overweight and those with immune disorders like autoimmune diseases and cancer are more susceptible to viral infections [21, 64]. These individuals require higher amounts of vitamin D—two to four times more, based on their body weight—to achieve and sustain the target circulatory 25(OH)D concentrations [36, 60, 65]. Moreover, individuals with hypovitaminosis D due to factors such as immune-compromising disorders, gastrointestinal issues causing fat malabsorption, medications stimulating vitamin D catabolism (e.g., anti-retroviral or anti-epileptic therapies), and multiple comorbidities [66, 67], also need elevated doses of vitamin D beyond the standard recommendations to maintain their serum 25(OH)D concentrations [65, 68-71].

In the initial two waves of significant infectious outbreaks from the original SARS-CoV-2 in 2021, the groups with severe vitamin D deficiency, as mentioned above, were the most impacted and experienced higher mortality rates [60, 72]. However, the infection pattern changed in subsequent significant peaks caused by the Delta variant in 2021 and the Omicron variant in 2022, each lasting approximately six months. Notably, these major outbreaks self-stabilized, regardless of vaccination status. During the major outbreaks in 2022, there was a shift towards infecting younger populations [73-75], particularly those with vitamin D deficiency. These factors contribute to the dominant Omicron variants, increasing hospitalization but fewer deaths.

7. The currently recommended vitamin D doses are insufficient

Most governments widely recommend a daily intake of 800 IU (20 μg) of vitamin D, which is outdated and insufficient to confer non-skeletal benefits from vitamin D [76, 77], including controlling infections [56, 78]. In communities with more older people, routine vitamin D supplements would reduce the prevalence of severe vitamin D deficiency. It is not surprising to observe increased complications requiring hospitalization in individuals with hypovitaminosis D that strain healthcare systems, was during 2020. However, this is not necessarily the case with COVID-19 vaccinations. In

wealthy countries, such as the USA and the UK, a positive association was reported between higher vaccination rates and excess mortality from 2021 [79].

The prophylactic approach of using appropriate doses of vitamin D supplements and/or daily sun exposure proves beneficial for ethnic groups and communities with a high prevalence of vitamin D deficiency [36, 56]. The mentioned doses are effective in achieving therapeutic concentrations sufficient to combat infections. Without a loading dose, it may take several months for those who are vitamin D deficient to reach therapeutic levels [80]. The speed of repleting vitamin D to achieve the recommended therapeutic serum 25(OH)D concentrations is urgent for individuals infected or admitted to hospitals with symptomatology. Despite a higher loading dose [81], it takes approximately three days to elevate circulatory 25(OH)D levels needed to stimulate immune cells.

Elevating serum 25(OH)D concentrations in acutely ill patients, such as ICU patients, will take about a week [80]. This delay is attributed to the time it takes for vitamin D to be absorbed via the intestinal lymphatic system and undergo hepatic 25-hydroxylation to produce 25(OH)D, which is a rate-limiting step [82-84]. In acute situations, the optimal choice is to provide partially activated vitamin D, calcifediol [25(OH)D], using a dose of 0.014 mg/kg body weight [36, 56]. Calcifediol raises serum 25(OH)D concentration within 4 hours (8 hours in even those who are acutely ill) [56, 85] and enhances the immune system within a day [86-88], enabling it to combat infections [36].

8. How does vitamin D help immune cells?

Circulating vitamin D and 25(OH)D enter peripheral target cells, including immune cells, primarily through passive diffusion and endocytosis (when vitamin D is bound to VDBP) [89]. This process is vital for these cells to acquire adequate precursors (D3 and 25(OH)D) needed to generate intracellular calcitriol (36). Calcitriol is crucial for immune cells' autocrine and paracrine functions, which is key in ensuring robust immune functions [56].

In the context of vitamin D deficiency, Th1 regulatory lymphocytes cannot transition from a pro-inflammatory state (producing inflammatory cytokines) and Th17 (contributing to inflammation and autoantibodies) to Th2 and Treg species, respectively [90, 91]. This transformation is crucial for acquiring anti-inflammatory characteristics and promoting B-cell-mediated antibody formation [92, 93]. Additionally, Th2 cells detect complements, initiating an autocrine signaling system. This system involves the expression of VDR and 1-hydroxylase enzyme, facilitating the further generation of calcitriol and supporting autocrine and paracrine signaling in immune cells [92, 94].

Adequate circulating concentrations of vitamin D and 25(OH)D enable their entry into immune cells, increasing the expression of VDR and 1α-hydroxylase enzyme (CYP27B1) [95]. This leads to the generation of VDR and the formation of calcitriol-VDR-RXR complexes. These complexes migrate into the nucleus, interacting with vitamin D-responsive elements modulating gene transcription [96]. Hypovitaminosis disrupts immune cell functions and impairs autocrine and paracrine signaling, resulting in pathological outcomes. Figure 3 summarizes how vitamin D modulates the innate and adaptive immune systems.

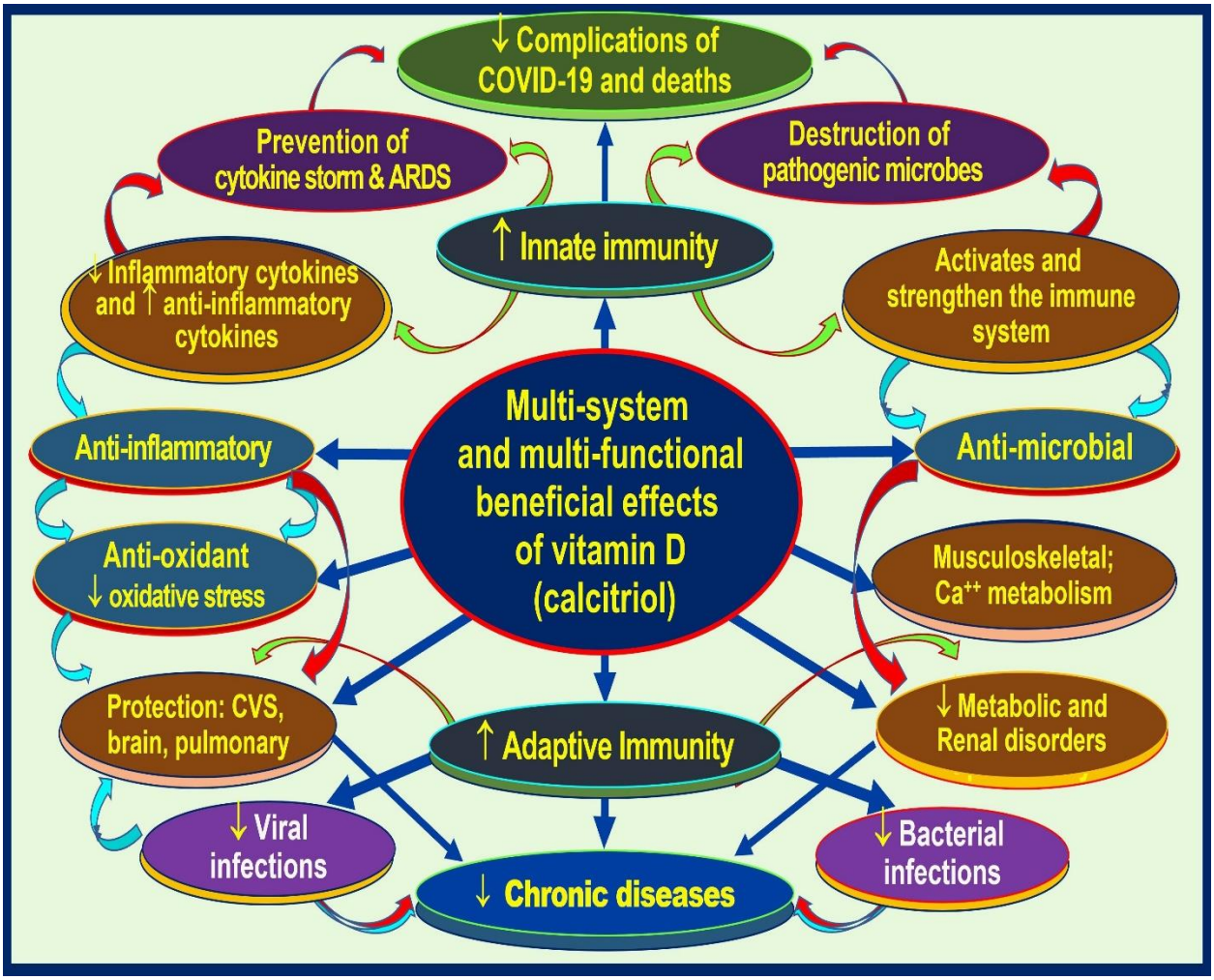

Figure 3 A schematic representation highlights the multi-organ-directed effects of vitamin D, with a particular emphasis on the innate and adaptive immune systems. The figure illustrates the interactions of these immune pathways with various organ systems, facilitating essential anti-microbial functions.

Vitamin D deficiency initiates a detrimental cycle, resulting in compromised immune responses against invading microbes and insufficient adaptive immune responses with reduced neutralizing antibody formation post-vaccination or infection [97, 98]. This deficiency also hampers memory cell functions, increases susceptibility to autoimmunity, and diminishes the cytotoxic effects of macrophages and other immune cells [98].

Moreover, the excessive generation of inflammatory cytokines triggers hyper-inflammatory responses, damaging healthy cells [99, 100]. This cascade may lead to autophagy, such as the destruction of pulmonary epithelium, causing pneumonia and fluid and virus leakage into soft tissues, resulting in hypoxia. A similar mechanism contributes to endothelial cell damage, causing coagulation abnormalities, thrombocytopenia, and micro-embolisms [101].

9. Mechanisms through which vitamin D controls inflammation

Vitamin D deficiency encourages a pro-inflammatory environment dominated by Th1 and Th17 cells [102]. The persistence of pro-inflammatory Th1 and Th17 lymphocytes during infections is primarily due to insufficient vitamin D and 25(OH)D in the bloodstream [91, 103]. Conversely, sufficient intracellular calcitriol availability transforms pro-inflammatory Th1 and Th17 cells into anti-inflammatory Th2 and Treg response cells [92, 94]. This transformation reduces the release of inflammatory cytokines and enhances the expression of anti-inflammatory cytokines, mitigating the risk of cytokine storms and ARDS [100, 103, 104].

The calcitriol-driven transition of Th1 cells into Th2 and Th17 to Treg cells initiates a shutdown program, allowing immune cells to shift from an inflammatory to an anti-inflammatory state and activate their autocrine and paracrine signaling mechanisms [91, 103]. This redirection transforms the pro-inflammatory milieu to an anti-inflammatory one

[105, 106], thereby diminishing generalized inflammation and boosting the expression of anti-inflammatory cytokines such as IFN-γ and IL-10 [91, 100, 103].

Older individuals and those with chronic diseases and comorbidities exhibit a higher prevalence of severe vitamin D deficiency [18, 19], resulting in a chronic inflammatory state and weakened immune systems [22, 100]. Hypovitaminosis increases the vulnerability of these individuals to contract and develop complications from viral infections like SARS-CoV-2, leading to a higher risk of mortality [24, 25, 60]. Figure 4 provides a schematic representation of the broader causes of vitamin D deficiency and its impacts on the innate and adaptive immune systems.

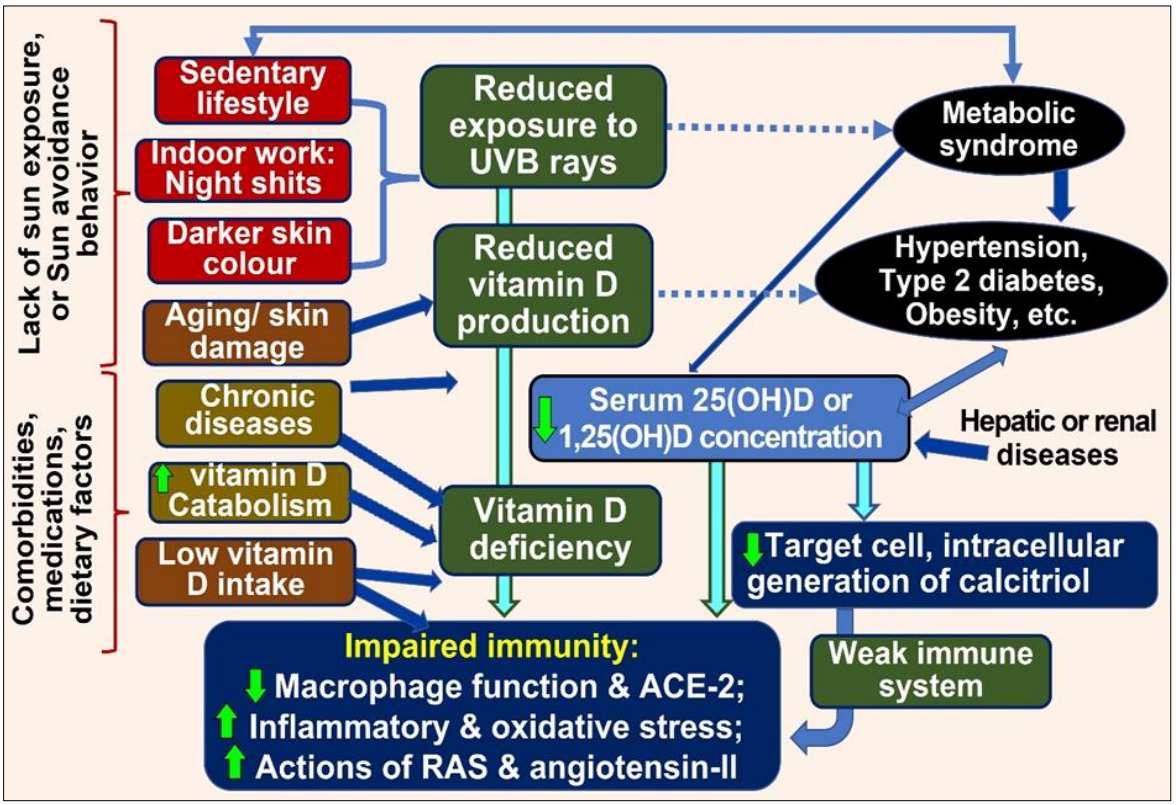

Figure 4 Causes and impacts of vitamin D deficiency on metabolic, cardiovascular, and immune systems

In addition to its non-genomic anti-viral effects [107, 108], the genomic actions of calcitriol enhance the transcription of several anti-microbial peptides, such as cathelicidin and defensin [109-111]. Vitamin D also stimulates immune cell chemotaxis [112, 113] and reduces the severity of COVID-19 [114]. Nevertheless, individual response variations occur due to epigenetic variances [21, 80]. Vitamin D improves the functions of Thαβ CD4+ T lymphocytes, suppresses T17 helper lymphocytes, and increases the expression of IL-10 and virus-specific IgG1 antibodies by activating T-cell-dependent B lymphocytes [56, 115].

The trend of immune evasion initiated with the Delta Plus variant and escalated with the Omicron variants [57], rendering the existing bivalent vaccines ineffective against the BA5 and XBB series [53, 116]. Additionally, contrary to previous assertions by vaccine companies, none of the current vaccines prevent SARS-CoV-2 transmission [17]. This crucial factor contributes to the global spread of dominant Omicron variants.

10. The failure to approve early therapies may have led to increased deaths

The failure of regulators to approve repurposed generic agents, despite extensive clinical research data for vitamin D and ivermectin, was an inexcusable error [117, 118]. Discouragement efforts by healthcare agencies, including the World Health Organization, CDC, NIH in the USA, and SCAN, NICE in the UK, were intensified and driven by politicians, Big Tech, and mainstream media. This led to a waste of resources, persistent SARS-CoV-2 outbreaks, increased hospitalizations, and escalated healthcare costs in most countries, including the USA, UK, Israel, and Australia.

Instead of promoting multiple boosters in wealthy countries with surplus COVID-19 vaccines, efforts should have been directed toward donating excess doses for primary vaccinations to developing nations that could not afford them.

Prioritizing single or two doses of primary vaccination for the entire population in these regions was more critical and effective in reducing hospitalizations and achieving herd immunity than providing multiple boosters to a fraction of the affluent, healthy population in industrialized countries.

Despite a rapid decline in antibody titers after a single vaccine dose, it initiates cellular immunity through lasting memory cells. This cellular response allows the body to swiftly counteract infections upon exposure to SARS-CoV-2 variants. Conversely, multiple COVID-vaccine booster doses result in immunoparesis and elevate the risks of adverse events like ADEs and autoimmunity [53], heightening susceptibility to SARS-CoV-2 infections and re-infection [57]. Individuals receiving these boosters may exhibit an exaggerated response to Spike proteins, akin to post-vaccination, leading to SAEs and potentially death upon infection with SARS-CoV-2 variants.

11. Policy errors and conflicts of interest of administrators

There is insufficient and unconvincing evidence to support the notion that COVID-19 vaccination provides substantial benefits for children and young adults, excluding those who are immune-suppressed [119]. The death rates among them were exceedingly low. Therefore, instead, these were subjected to unnecessary SAEs. The governmental strategy of promoting multiple booster doses of COVID-19 bivalent vaccines, lacking scientific justification, was a significant error.

New dominant SARS-CoV-2 variants exhibit increased infectivity with higher R_0 numbers than the original virus [16]. Like other coronavirus epidemics, natural SARS-CoV-2 viral outbreaks typically last less than six months, regardless of the provision of healthcare facilities or vaccination status. This pattern is evident in the outbreaks of the Alpha, Delta, and Omicron variants [53]. These infectious peaks naturally subside, regardless of healthcare interventions, including vaccination—reflecting the inherent natural history of these viruses.

Vaccination induces restricted immunity targeted at the Spike protein, lacking the generation of neutralizing antibodies against the core proteins of the virus. As a result, the protective antibodies have a shorter duration [120] compared to the broader immunity acquired through natural infection [54]. Besides, COVID-19 vaccines not only fall short in preventing viral transmission and new infections, but data indicate a rapid decline in post-vaccination immune responses, particularly in neutralizing SARS-CoV-2 variants [17]. Paradoxically, adverse effects persistently rise with additional booster doses.

12. Vaccination alone will not control the pandemic

Costly treatments like vaccines, anti-viral agents, and untested monoclonal antibodies received temporary approval through Emergency Use Authorization (EUA) [54]. While they appeared to decrease hospitalizations in 2021, the benefits were transitory [54], and there was no conclusive evidence of a reduction in death. Moreover, vaccination fails to prevent the spread of SARS-CoV-2 infections and does not contribute to achieving herd immunity, challenging assertions for vaccine passports and digital identities [17, 121].

Hence, the elimination of the COVID-19 pandemic through vaccination was not feasible. Because the new mutant viruses became milder, the health agencies proactively advocated repurposed agents as adjunct therapies for COVID-19, and the world had a second chance to achieve global herd immunity and eradicate SARS-CoV-2. This prospect relies on regulatory approval for healthcare workers to employ cost-effective early therapies for prevention and treatment. The mentioned rational strategy would alleviate the healthcare burden, save lives, and reduce costs substantially.

Even with primary vaccination and booster doses administered to over 70% of the adult population, countries heavily dependent on vaccines, including the USA, UK, Israel, Australia, etc., struggle to contain SARS-CoV-2 outbreaks. Figure 5 highlights the disparity, showing that high-income countries with substantial vaccination rates experience significantly higher SARS-CoV-2 outbreaks than low-income countries with markedly lower vaccination rates.

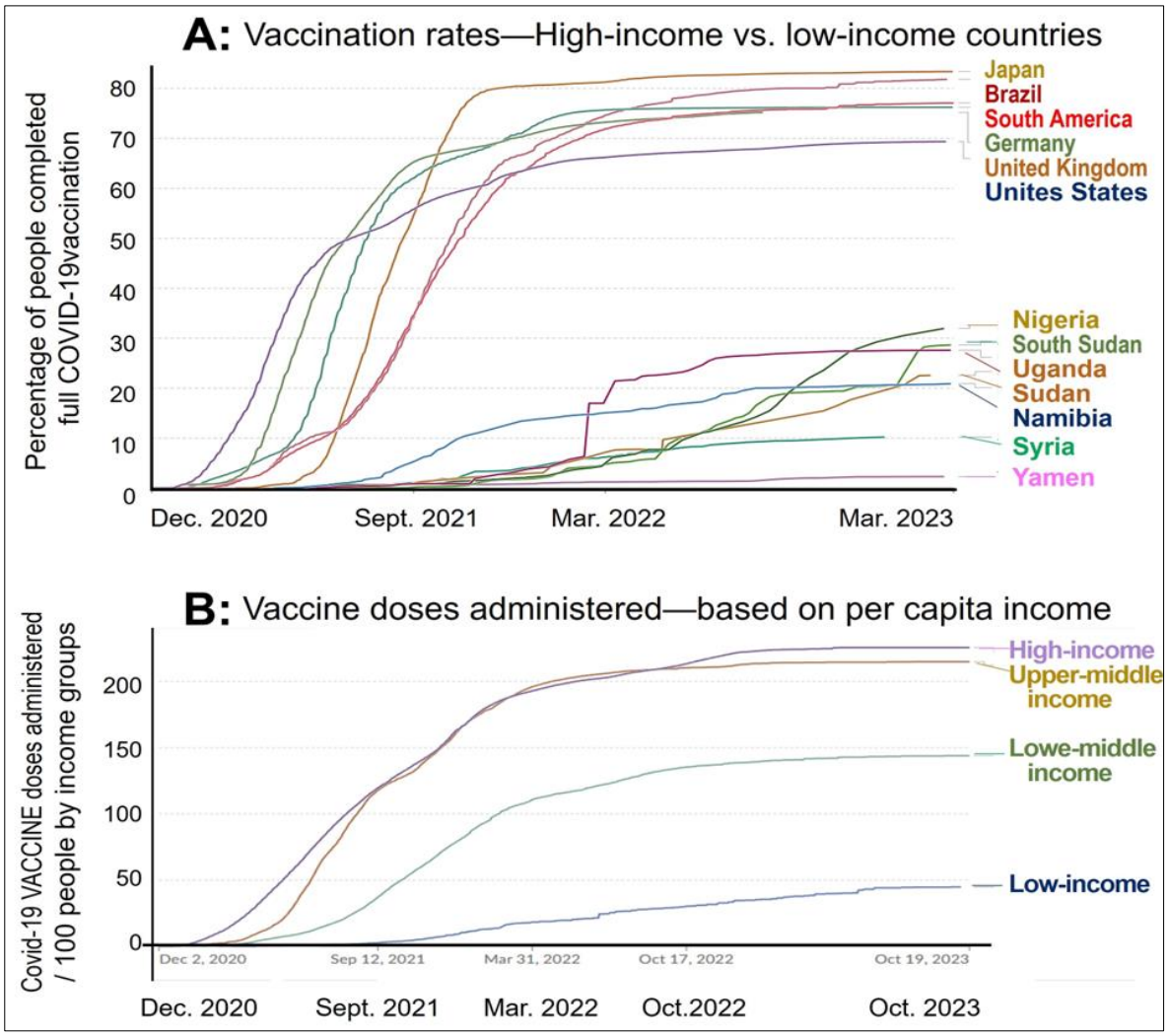

Figure 5: The figure provides examples of the disconnect between countries with primary series and booster doses exceeding 70%, as shown in Figure 1, still facing ongoing COVID-19 outbreaks. In contrast, low-income countries with lower vaccination rates experience minimal SARS-CoV-2 infections and virtually no deaths. Panel A illustrates two clusters of countries: one with high vaccination (above 70%) and another with low vaccination (below 15%) uptakes. Panel B depicts the number of doses of COVID-19 vaccine administered per 100 people in countries across four different income groups. High per capita income represents high vaccination rates, and low per capita income represents low vaccination rates (Data source: Our World in Data—WHO COVID Dashboard).

The evolution of the SARS-CoV-2 virus results in new dominant mutants that are more infectious but less lethal, regardless of the vaccination or available treatment in each country. This trend is illustrated in Figure 6, which shows daily deaths from SARS-CoV-2 standardized to millions of the population.

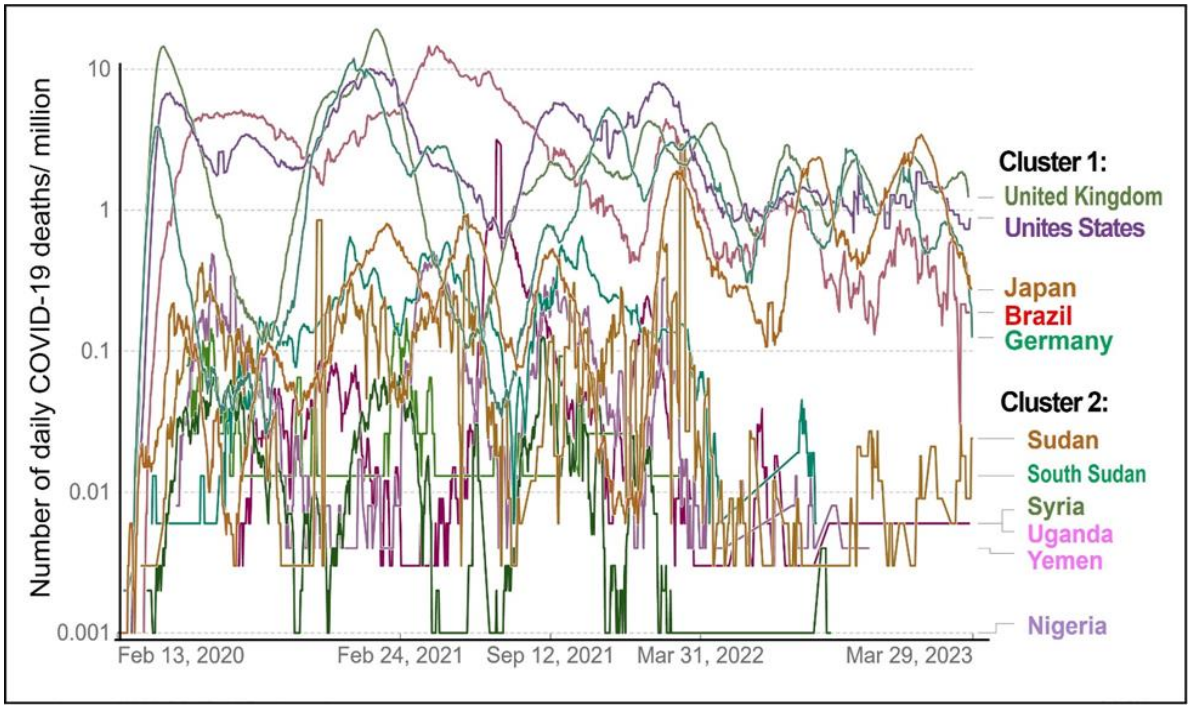

Figure 6 Demonstrates the daily deaths per million people in countries with high COVID-19 vaccination (high-income countries) in Cluster 1. It is compared with a few examples of low-income countries with low vaccination rates and significantly lower deaths

The surge in outbreaks with variants BQ and XBB subvariants is attributed to two critical reasons. Firstly, antibodies derived from Omicron-specific bivalent vaccines, used as boosters, fail to neutralize these viruses, leading to immune evasion [116]. Secondly, booster doses result in immune paresis, increasing the risk of infections and re-infections with mutant viruses in vaccine recipients [53, 120]. In contrast, vitamin D treatment has been shown to reduce hospitalization, length of stay, and mortality in individuals with COVID-19, even with comorbidities. Therefore, the prophylactic and proactive use of vitamin D should be a routine part of the COVID armamentarium [122].

13. Certain conditions made the situation worse

However, regulators' reluctance to approve over-the-counter, unpatented, economic medications and nutrients impeded progress in addressing these challenges. This situation has been further exacerbated by limiting access to primary data for independent scientists through coordinated efforts by regulators, organizations, and administrations. The lack of transparency and refusal to access primary data, combined with shortcuts in RCTs, suggest persisting statistical manipulations and data manipulation. Additionally, there is a promotion of patented medications, suppression of generic agents, and concealment of vaccine adverse effects. The dissemination of misinformation by mainstream media, big tech, and social media platforms has only worsened these challenges.

Children and individuals with natural immunity from prior COVID-19 infections do not benefit significantly from COVID-19 vaccines [123]. Complications from SARS-CoV-2 infections in children are rare compared to adults, and most children and young adults experiencing complications have severe vitamin D deficiency (i.e., serum 25(OH)D concentration less than 12 ng/mL) [39]. Therefore, rather than vaccination, the focus should have been on ensuring children have sufficient vitamin D levels. Extensive data sets confirm that the adverse effects of vaccines, especially in children and young males, far outweigh any minor benefits they might receive from COVID-19 vaccines. Thus, the vaccination of children is not justified [124] nor mandatory [125]; commercial and political interests drive such initiatives. The primary beneficiaries of mass vaccination propaganda are the vaccine companies, investors, and high-level administrators.

13.1 Vaccine conundrum

Vaccines are designed and intended to prevent infections and curb their spread. In the context of a viral epidemic or pandemic, logic dictates that vaccination should prioritize vulnerable groups, including the elderly and frontline workers such as police and healthcare professionals. This ethical approach becomes even more crucial when vaccine supplies are limited, as is often the case in developing countries. It raises ethical concerns when affluent nations

continue to administer multiple booster doses to their citizens while less than 15% of adults in developing countries have received even the primary vaccination.

The intensified vaccination campaign persisted even though vaccines do not prevent the transmission of SARS-CoV-2 to others [17] or guard against re-infection, partially bivalent COVID-19 vaccines [46, 47, 53, 116]. This push, accompanied by coercion, mandates, and ensuing political disputes, evolved into a substantial ethical and socioeconomic concern in 2021/22. Big Pharma and regulators collaborated with leading healthcare agencies and governments to prevent scientists' access to COVID-vaccine-related data and filtered and suppressed information from reaching the public to maintain the vaccine's EUA status. This censorship extended to silencing physicians and scientists, obstructing the dissemination of scientific knowledge, including data from alternative, highly cost-effective therapies such as vitamin D, ivermectin, and melatonin [126].

14. What does the world need now

The need for affordable, alternative, and cost-effective early-treatment strategies and therapies to combat COVID-19, independent of ongoing viral mutations, is paramount. Booster vaccine doses may elevate antibody levels, but these antibodies may not offer effective protection against new mutants, such as Omicron variants. Moreover, they pose higher risks of adverse effects. Despite widespread vaccination efforts, the incidence of SARS-CoV-2 infections and related deaths in 2021 exceeded expectations compared to 2020.

Hence, the world requires alternative approaches alongside or instead of vaccination. Experts attribute vaccine failures to factors such as human behavior, administrative errors, statistical anomalies, climate changes, emerging variants, and potential shortcomings of the vaccines—a combination of these factors. Notably, COVID-19 vaccines were granted EUA but lacked complete licensure, with unavailable long-term safety data. Although EUA was revoked after removing the emergency status in May 2023, signs indicate another COVID peak in 2023 due to its cyclical nature described above. The recent termination of EUA status should pave the way for using generic agents like vitamin D and ivermectin in the global prevention and treatment of SARS-CoV-2.

15. The need for investigating and approving generic agents in emergencies

If any affordable, unpatented agents were approved for COVID-19, it would automatically revoke the EUA approvals of all patented drugs for COVID-19, including vaccines, anti-viral agents, and monoclonal antibodies. While this presents a legal and administrative challenge, it's important to note that these treatments complement each other and can act synergistically. Therefore, another mechanism should be in place to allow regulators to approve repurposed generic agents in emergencies like COVID-19. This mechanism could involve updating regulatory frameworks to accommodate the approval of alternative treatments without automatically revoking the EUA approvals of existing patented drugs.

The current EUA legislation is outdated and needs amending to accommodate such changes for the benefit of the public. Without modifications to the EUA, similar catastrophes may be repeated in the future. The constraints of EUA and entrenched conflicts of interest among regulators have hindered the widespread use of highly economical and practical repurposed agents. Approving effective generic agents (or at least not preventing their use) could significantly reduce healthcare burdens, costs, COVID-19-related hospitalizations, and deaths. Therefore, urgent action is needed to update regulations and remove barriers to the approval and use of these agents.

16. Time to think correctly and act rationally

Countries with high percentages of vaccinated and boosted individuals (over 75% of adults in some countries and states) are witnessing increased spread of SARS-CoV-2 with Omicron variants [17]. This is attributed to the failure of vaccines to prevent viral transmission, increased vital mutations, booster-vaccine-mediated immune paresis, and the limited efficacy of bivalent boosters, as illustrated in Figure 6 [17].

Leaders must employ "common sense" and take immediate action to enhance the population's immunity, particularly among vulnerable individuals, through natural means such as safe sun exposure and vitamin D supplements. This was distinctly absent during the COVID-19 pandemic. Those measures mentioned above could have complemented vaccination efforts and provided additional protection for people against COVID-19 and its variants.

A key concern was neutralizing antibody production, which is only a small fraction of total antibody production. Even such antibodies target only the Spike protein and not the core proteins. In contrast, natural immunity derived from SARS-CoV-2 infection covers all virus components, producing a broader, longer-lasting immunity [127, 128].

Consequently, unlike vaccines, natural immunity and the immunity induced by vitamin D in conjunction with other micronutrients remain effective against all present and future mutated variants of SARS-CoV-2. This broader immune response provides more comprehensive protection against the virus and its variants [127].

17. Discussion

Governmental statistics indicated a significant reduction in hospitalizations (but not deaths) in early 2021 after introducing COVID-19 vaccines. However, towards the end of the year, the emergence of SARS-CoV-2 mutants, particularly the Delta and Omicron variants, exhibited immune evasion capabilities against original COVID-19 vaccines. The introduction of bivalent boosters made it worse.

Multiple mutations in the receptor binding domain of the Spike protein led to reduced antibody recognition, indicating immune evasions by mutant viruses. Consequently, vaccine effectiveness declined in late 2022 and became no different from a placebo. Mutant viruses, particularly the BQ and XBB lineages, gained increased transmissibility and dominance, although associated with fewer deaths. Besides, statistics from 2022 revealed that SARS-CoV-2 outbreaks were not correlated with vaccination status (i.e., percentage of people vaccinated) or booster uptake, with hospitalizations or deaths occurring in both vaccinated and unvaccinated individuals.

Scientific evidence suggests that genetic pressure from Spike-protein-derived mRNA vaccines contributed to the accelerated mutation rate in the immune recognition area of the Spike protein in SARS-CoV-2 mutants, such as Omicron B.A.5. The altered epitopes resulting from these mutations make mRNA vaccine-mediated neutralizing antibodies ineffective against the mutated viral components, leading to immune evasion by these viruses [53]. In contrast, information dating to early 2020 indicated that maintaining vitamin D adequacy and higher vitamin D supplements could substantially reduce hospitalizations, complications, and deaths associated with the SARS-CoV-2 virus [23, 129]. This suggests the potential effectiveness of vitamin D supplementation in mitigating the impact of COVID-19.

The first peer-reviewed article on SARS-CoV-2, emphasizing the advantages of high-dose vitamin D in COVID-19, was published on 28 February, 2020, in the European Journal of Biomedical and Pharmaceutical Sciences [23]. By the end of 2020, the literature on vitamin D and COVID-19 had grown to include over 100 publications, encompassing RCTs and extensive data analysis. Meanwhile, vitamin D sufficiency has been recognized as a protective factor against severe disease and death associated with viral infections [130]. This growing body of evidence underscores the potential benefits of vitamin D supplementation in mitigating the impact of COVID-19 [122, 131-133].

Before the pandemic, the biological plausibility and positive effects of vitamin D and calcifediol (intracellularly generated calcitriol within immune cells) were well-acknowledged [78, 92, 130, 134-139]. This affirmation aligns with the Bradford Hill criteria, providing a basis for establishing causality between vitamin D levels and complications or deaths associated with SARS-CoV-2 [140]. Despite this substantial evidence, the information has not been effectively utilized for the betterment of humanity. This highlights the need for greater transparency in RCTs and decision-making procedures [117, 118], as well as the recognition and implementation of vitamin D interventions to potentially mitigate the impact of COVID-19 and improve public health outcomes.

Despite high vaccination rates and multiple booster doses in individuals in industrialized countries, the continued spread and outbreaks of SARS-CoV-2 persist. Leaders in health agencies and governments must prioritize cost-effective approaches for the greater good of the public over power, ego, politics, and conflicts of interest. In this regard, it is crucial to retrospectively acknowledge the shortcomings of the COVID-19 management guidance and decision-making process. The failures of the WHO and the CDC to make proper, unconflicted statements highlighted the importance of maintaining transparency and integrity in future epidemics and pandemics benefiting the public.

Approving unpatented, cost-effective, preventative, repurposed, early treatment options for COVID-19 could have averted unnecessary hospitalizations and fatalities, preventing economic collapse and widespread devastation. Moving forward, there must be a concerted effort to learn from these lessons and prioritize recent evidence-based strategies prioritizing public health and well-being.

18. Conclusion

Due to various factors, including overreliance on COVID-19 vaccines, mutations leading to immune evasion, and shortcomings in vaccine technology and public policy, hindered the achievement of herd immunity and the eradication of the virus. Repurposed agents like vitamin D and ivermectin have maintained their effectiveness, even against mutations. Despite ample positive data and the availability of over-the-counter options, regulators hesitated to approve

or promote these drugs as adjunct therapies for COVID-19, favoring patented treatments. Approving repurposed agents alongside vaccines could have curbed outbreaks, reduced hospitalizations, and saved lives. Prioritizing evidence-based strategies, utilizing AI for data analysis, and integrating cost-effective preventative and treatment measures are crucial for effectively combating future epidemics and pandemics and safeguarding public health.

Compliance with ethical standards

Disclosure of conflict of interest

The author asserts the absence of any conflicts of interest, having neither received funding nor written assistance.

References

[1] Acharya, C.B., et al., Viral Load Among Vaccinated and Unvaccinated, Asymptomatic and Symptomatic Persons Infected With the SARS-CoV-2 Delta Variant. Open Forum Infect Dis, 2022. **9**(5): p. ofac135.

[2] Le Bert, N., et al., Highly functional virus-specific cellular immune response in asymptomatic SARS-CoV-2 infection. J Exp Med, 2021. **218**(5).

[3] . Kojima, N., N.K. Shrestha, and J.D. Klausner, A Systematic Review of the Protective Effect of Prior SARS-CoV-2 Infection on Repeat Infection. Eval Health Prof, 2021. **44**(4): p. 327-332.

[4] Shrestha, N.K., et al., Effectiveness of the coronavirus disease 2019 bivalent vaccine. Open Forum Infect Dis, 2023. **10**(6): p. ofad209.

[5] WHO. COVID-19 natural immunity: Scientific brief (May 2021). 2021 [cited 2022 Nev 4th, 2022]; Available from: https://apps.who.int/iris/bitstream/handle/10665/341241/WHO-2019-nCoV-Sci-Brief-Natural-immunity-2021.1-eng.pdf?sequence=3andisAllowed=y.

[6] Jung, J.H., et al., SARS-CoV-2-specific T cell memory is sustained in COVID-19 convalescent patients for 10 months with successful development of stem cell-like memory T cells. Nat Commun, 2021. **12**(1): p. 4043.

[7] Ansari, A., et al., Immune Memory in Mild COVID-19 Patients and Unexposed Donors Reveals Persistent T Cell Responses After SARS-CoV-2 Infection. Front Immunol, 2021. **12**: p. 636768.

[8] . Saade, C., et al., Live virus neutralization testing in convalescent patients and subjects vaccinated against 19A, 20B, 20I/501Y.V1 and 20H/501Y.V2 isolates of SARS-CoV-2. Emerg Microbes Infect, 2021. **10**(1): p. 1499-1502.

[9] Turner, J.S., et al., SARS-CoV-2 infection induces long-lived bone marrow plasma cells in humans. Nature, 2021. **595**(7867): p. 421-425.

[10] Dan, J.M., et al., Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science, 2021. **371**(6529).

[11] Swan, D.A., et al., COVID-19 vaccines that reduce symptoms but do not block infection need higher coverage and faster rollout to achieve population impact. Sci Rep, 2021. **11**(1): p. 15531.

[12] Tang, J., et al., Respiratory mucosal immunity against SARS-CoV-2 after mRNA vaccination. Sci Immunol, 2022. **7**(76): p. eadd4853.

[13] Sanchez-Zuno, G.A., et al., A review: Antibody-dependent enhancement in COVID-19: The not so friendly side of antibodies. Int J Immunopathol Pharmacol, 2021. **35**: p. 20587384211050199.

[14] Wan, Y., et al., Molecular Mechanism for Antibody-Dependent Enhancement of Coronavirus Entry. J Virol, 2020. **94**(5).

[15] Arvin, A.M., et al., A perspective on potential antibody-dependent enhancement of SARS-CoV-2. Nature, 2020. **584**(7821): p. 353-363.

[16] Liu, Y. and J. Rocklov, The reproductive number of the Delta variant of SARS-CoV-2 is far higher compared to the ancestral SARS-CoV-2 virus. J Travel Med, 2021. **28**(7).

[17] Singanayagam, A., et al., Community transmission and viral load kinetics of the SARS-CoV-2 delta (B.1.617.2) variant in vaccinated and unvaccinated individuals in the UK: a prospective, longitudinal, cohort study. Lancet Infect Dis, 2022. **22**(2): p. 183-195.

[18] Haq, A., et al., Clinical practice guidelines for vitamin D in the United Arab Emirates. J Steroid Biochem Mol Biol, 2018. **175**: p. 4-11.

[19] Wimalawansa, S.J., Extra-skeletal benefits, endocrine functions, and toxicity of vitamin D. J Endocrinol Diab, 2016. **3**(1): p. 1-5.

[20] Bui, L., et al., Vitamin D regulation of the immune system and its implications for COVID-19: A mini review. SAGE Open Med, 2021. **9**: p. 20503121211014073.

[21] Wimalawansa, S.J., Infections and autoimmunity-The immune system and vitamin D: A Systematic Review. Nutrients, 2023. **15**(17).

[22] Schwalfenberg, G.K., A review of the critical role of vitamin D in the functioning of the immune system and the clinical implications of vitamin D deficiency. Mol Nutr Food Res, 2011. **55**(1): p. 96-108.

[23] Wimalawansa, S.J., Global epidemic of coronavirus—COVID-19: What can we do to minimize risks? European J. Biomed and Pharma Sci., 2020. **7**(3): p. 432-438.

[24] Alguwaihes, A.M., et al., Severe vitamin D deficiency is not related to SARS-CoV-2 infection but may increase mortality risk in hospitalized adults: a retrospective case-control study in an Arab Gulf country. Aging Clin Exp Res, 2021. **33**(5): p. 1415-1422.

[25] Martin Gimenez, V.M., et al., Vitamin D deficiency in African Americans is associated with a high risk of severe disease and mortality by SARS-CoV-2. J Hum Hypertens, 2021. **35**(4): p. 378-380.

[26] Goes, L.R., et al., evidence of recurrent selection of mutations commonly found in SARS-CoV-2 variants of concern in viruses infecting immunocompromised patients. Front Microbiol, 2022. **13**: p. 946549.

[27] Sun, S., et al., SARS-CoV-2 Omicron variant: viral spread dynamics, disease burden, and vaccine effectiveness. Curr Med (Cham), 2022. **1**(1): p. 14.

[28] Khatri, R., et al., Intrinsic D614G and P681R/H mutations in SARS-CoV-2 VoCs Alpha, Delta, Omicron and viruses with D614G plus key signature mutations in spike protein alters fusogenicity and infectivity. Med Microbiol Immunol, 2023. **212**(1): p. 103-122.

[29] Erkayman, B., F. Ak, and S. Codur, A simulation approach for COVID-19 pandemic assessment based on vaccine logistics, SARS-CoV-2 variants, and spread rate. Simulation, 2023. **99**(2): p. 127-135.

[30] Carter, S.J., M.N. Baranauskas, and A.D. Fly, Considerations for Obesity, Vitamin D, and Physical Activity Amid the COVID-19 Pandemic. Obesity (Silver Spring), 2020. **28**(7): p. 1176-1177.

[31] Wimalawansa, S.J., Commonsense approaches to minimizing risks from COVID-19. Open J Pulm Respir Med, 2020. **2**: p. 28-37, https://doi.org/10.36811/ojprm.2020.110010

[32] Wimalawansa, S.J., Reducing risks from COVID-19: Cost-effective ways of strengthening individual's and the population immunity with vitamin D. J Endocrinol Sci, 2020. **2**(2): p. -13.

[33] Alrabadi, N., et al., The lockdown may contribute to the COVID-19 cases in developing countries, different perspectives on the curfew act, a report from Jordan. Ann Med Surg (Lond), 2021. **61**: p. 41-43.

[34] Majumdar, P., A. Biswas, and S. Sahu, COVID-19 pandemic and lockdown: cause of sleep disruption, depression, somatic pain, and increased screen exposure of office workers and students of India. Chronobiol Int, 2020. **37**(8): p. 1191-1200.

[35] Gornicka, M., et al., Dietary and Lifestyle Changes During COVID-19 and the Subsequent Lockdowns among Polish Adults: A Cross-Sectional Online Survey PLifeCOVID-19 Study. Nutrients, 2020. **12**(8).

[36] Wimalawansa, S., Overcoming infections including COVID-19, by maintaining circulating 25(OH)D concentrations above 50 ng/mL. Pathology and Lab. Medicine Int., 2022. **14** p. 37–60.

[37] Abdollahi, A., et al., The association between the level of serum 25(OH) vitamin D, obesity, and underlying diseases with the risk of developing COVID-19 infection: A case-control study of hospitalized patients in Tehran, Iran. J Med Virol, 2021. **93**(4): p. 2359-2364.

[38] Takahashi, K., et al., Duration of infectious virus shedding by SARS-CoV-2 Omicron variant-Iinfected vaccinees. Emerg Infect Dis, 2022. **28**(5): p. 998-1001.

[39] Smaha, J., et al., Patients with COVID-19 pneumonia with 25(OH)D levels lower than 12 ng/ml are at increased risk of death. Int J Infect Dis, 2022. **116**: p. 313-318.

[40] Panupattanapong, S. and E.B. Brooks, New spectrum of COVID-19 manifestations in children: Kawasaki-like syndrome and hyperinflammatory response. Cleve Clin J Med, 2020.

[41] Stagi, S., et al., Severe vitamin D deficiency in patients with Kawasaki disease: a potential role in the risk to develop heart vascular abnormalities? Clin Rheumatol, 2016. **35**(7): p. 1865-72.

[42] Arrindell, J., et al., Vimentin is an important ACE2 co-receptor for SARS-CoV-2 in epithelial cells. iScience, 2022. **25**(11): p. 105463.

[43] Shahini, E., et al., Can vitamin D status influence seroconversion to SARS-COV2 vaccines? Front Immunol, 2022. **13**: p. 1038316.

[44] Ahmadi, S., et al., Immune evasion of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2); molecular approaches. Mol Immunol, 2023. **156**: p. 10-19.

[45] Lind, M.L., et al., Use of whole genome sequencing to estimate the contribution of immune evasion and waning immunity on decreasing COVID-19 vaccine effectiveness. J Infect Dis, 2022.

[46] Wang, Q., et al., Alarming antibody evasion properties of rising SARS-CoV-2 BQ and XBB subvariants. Cell, 2023. **186**(2): p. 279-286 e8.

[47] Stati, G., et al., Concern about the effectiveness of mRNA vaccination technology and Its long-term safety: potential interference on miRNA machinery. Int J Mol Sci, 2023. **24**(2).

[48] Padma, T.V., COVID vaccines to reach poorest countries in 2023 - despite recent pledges. Nature, 2021. **595**(7867): p. 342-343.

[49] Holder, J. Tracking coronavirus vaccinations around the world. https://www.nytimes.com/interactive/2021/world/covid-vaccinations-tracker.html 2023 [cited Feb. 2nd, 2023; Available from: https://www.nytimes.com/interactive/2021/world/covid-vaccinations-tracker.html.

[50] Ao, D., et al., SARS-CoV-2 Omicron variant: Immune escape and vaccine development. MedComm (2020), 2022. **3**(1): p. e126.

[51] Kazancoglu, Y., et al., Impact of epidemic outbreaks (COVID-19) on global supply chains: A case of trade between Turkey and China. Socioecon Plann Sci, 2023. **85**: p. 101494.

[52] Anonymus. Our World COVID data: . 2023 [cited 2023 March 31st, 2023]; Available from: https://ourworldindata.org/grapher/.

[53] Patalon, T., et al., Waning effectiveness of the third dose of the BNT162b2 mRNA COVID-19 vaccine. Nat Commun, 2022. **13**(1): p. 3203.

[54] Kontopoulou, K., et al., Antibody titers after a third dose of the SARS-CoV-2 BNT162b2 vaccine in immunocompromised adults in Greece: Is a fourth dose necessary? J Med Virol, 2022. **94**(10): p. 5056-5060.

[55] Quraishi, S.A., et al., Prospective study of vitamin D status at initiation of care in critically ill surgical patients and risk of 90-day mortality. Crit Care Med, 2014. **42**(6): p. 1365-71.

[56] Wimalawansa, S.J., Rapidly Increasing Serum 25(OH)D Boosts the Immune System, against Infections-Sepsis and COVID-19. Nutrients, 2022. **14**(14).

[57] Guerin, P., et al., Structural Dynamics of the SARS-CoV-2 Spike Protein: A 2-Year Retrospective Analysis of SARS-CoV-2 Variants (from Alpha to Omicron) Reveals an Early Divergence between Conserved and Variable Epitopes. Molecules, 2022. **27**(12).

[58] Holick, M.F., The vitamin D epidemic and its health consequences. J Nutr, 2005. **135**(11): p. 2739S-48S.

[59] Wilkins, C.H., et al., Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults. Am J Geriatr Psychiatry, 2006. **14**(12): p. 1032-40.

[60] Shah, K., et al., Does vitamin D supplementation reduce COVID-19 severity?: a systematic review. QJM, 2022. **115**(10): p. 665-672.

[61] Wimalawansa, S., Overcoming infections including COVID-19, by maintaining circulating 25(OH)D concentrations above 50 ng/mL. Pathology and Lab. Medicine Int., 2022. **14**: p. 37–60.

[62] Holick, M.F., et al., Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab, 2011. **96**(7): p. 1911-30.

[63] Smith, L.M., J.C. Gallagher, and C. Suiter, Medium doses of daily vitamin D decrease falls and higher doses of daily vitamin D3 increase falls: A randomized clinical trial. J Steroid Biochem Mol Biol, 2017. **173**: p. 317-322.

[64] Wimalawansa, S.J., Controlling chronic diseases and acute infections with vitamin D sufficiency. Nutrients, 2023. **15**(16).

[65] Ekwaru, J.P., et al., The importance of body weight for the dose response relationship of oral vitamin D supplementation and serum 25-hydroxyvitamin D in healthy volunteers. PLoS One, 2014. **9**(11): p. e111265.

[66] Giusti, A., et al., Heterogeneity in serum 25-hydroxy-vitamin D response to cholecalciferol in elderly women with secondary hyperparathyroidism and vitamin D deficiency. J Am Geriatr Soc, 2010. **58**(8): p. 1489-95.

[67] Bacon, C.J., et al., High-dose oral vitamin D3 supplementation in the elderly. Osteoporos Int, 2009. **20**(8): p. 1407-15.

[68] Wimalawansa, S.J., Non-musculoskeletal benefits of vitamin D. J Steroid Biochem Mol Biol, 2018. **175**: p. 60-81.

[69] Wimalawansa, S.J., Vitamin D and cardiovascular diseases: Causality. J Steroid Biochem Mol Biol, 2018. **175**: p. 29-43.

[70] LeBlanc, E.S., et al., Baseline Characteristics of the Vitamin D and Type 2 Diabetes (D2d) Study: A Contemporary Prediabetes Cohort That Will Inform Diabetes Prevention Efforts. Diabetes Care, 2018. **41**(8): p. 1590-1599.

[71] Dawson-Hughes, B., J. Nelson, and A.G. Pittas, Intratrial exposure to vitamin D and new-onset diabetes among adults with prediabetes: A secondary analysis from the vitamin D and type 2 diabetes (D2d) study. Diabetes Care, 2021. **44**(5): p. e106.

[72] Wimalawansa, S.J., Polonowita, A. Boosting immunity with vitamin D for preventing complications and deaths from COVID-19. in COVID 19: Impact, mitigation, opportunities and building resilience "From adversity to serendipity," perspectives of global relevance based on research, experience and successes in combating COVID-19 in Sri Lanka. 2021. Colombo, Sri Lanka: National Science Foundation, Sri Lanka.

[73] Khemiri, H., et al., SARS-CoV-2 infection in pediatric population before and during the Delta (B.1.617.2) and Omicron (B.1.1.529) variants era. Virol J, 2022. **19**(1): p. 144.

[74] Mercier, J.C., et al., COVID-19 in children: SARS-CoV-2-related inflammatory multisystem syndrome mimicking Kawasaki disease. Bull Acad Natl Med, 2021. **205**(6): p. 579-586.

[75] Yu, H., et al., Characteristics of Kawasaki Disease Before and After the COVID-19 Pandemic in a Large Pediatric Heart Disease Center. Front Pediatr, 2022. **10**: p. 895408.

[76] Bivona, G., et al., Non-Skeletal Activities of Vitamin D: From Physiology to Brain Pathology. Medicina (Kaunas), 2019. **55**(7).

[77] Spedding, S., et al., Does vitamin D sufficiency equate to a single serum 25-hydroxyvitamin D level or are different levels required for non-skeletal diseases? Nutrients, 2013. **5**(12): p. 5127-39.

[78] Quraishi, S.A., et al., Association between preoperative 25-hydroxyvitamin D level and hospital-acquired infections following Roux-en-Y gastric bypass surgery. JAMA Surg, 2014. **149**(2): p. 112-8.

[79] Liu, J.Y., T.J. Chen, and M.C. Hou, Does COVID-19 vaccination cause excess deaths? J Chin Med Assoc, 2021. **84**(9): p. 811-812.

[80] Wimalawansa, S.J., Physiological basis for using vitamin D to improve health. Biomedicines, 2023. **11**(6).

[81] Wimalawansa, S.J. and R. Whittle, Vitamin D: A single initial dose is not bogus if followed by an appropriate maintenance intake. JBMR Plus, 2022. **6**(3): p. e10606.

[82] Heaney, R.P., et al., 25-Hydroxylation of vitamin D3: relation to circulating vitamin D3 under various input conditions. Am J Clin Nutr, 2008. **87**(6): p. 1738-42.

[83] Liberman, U.A., Disorders in Vitamin D Action, in Endotext, L.J. De Groot, et al., Editors. 2000: South Dartmouth (MA).

[84] Vieth, R., Vitamin D supplementation: cholecalciferol, calcifediol, and calcitriol. Eur J Clin Nutr, 2020. **74**(11): p. 1493-1497.

[85] Suñé Negre, J., Azpitarte, IO, Barrios, PDA, Hernández herrero, G, Calcifediol soft capsules, in *https://patents.google.com/patent/WO20161*. 2016, Assignee: WO 2016/124724 Al, 2016-08-11 Country: WO 2016: WWA.

[86] Perez-Castrillon, J.L., et al., Calcifediol is superior to cholecalciferol in improving vitamin D status in postmenopausal women: a randomized trial. J Bone Miner Res, 2021. **36**(10): p. 1967-1978.

[87] Quesada-Gomez, J.M., M. Entrenas-Castillo, and R. Bouillon, Vitamin D receptor stimulation to reduce acute respiratory distress syndrome (ARDS) in patients with coronavirus SARS-CoV-2 infections: Revised Ms SBMB 2020_166. J Steroid Biochem Mol Biol, 2020. **202**: p. 105719.

[88] Entrenas Castillo, M., et al., Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study. J Steroid Biochem Mol Biol, 2020. **203**: p. 105751.

[89] Rowling, M.J., et al., Megalin-mediated endocytosis of vitamin D binding protein correlates with 25-hydroxycholecalciferol actions in human mammary cells. J Nutr, 2006. **136**(11): p. 2754-9.

[90] Chau, A.S., et al., The Longitudinal Immune Response to Coronavirus Disease 2019: Chasing the Cytokine Storm. Arthritis Rheumatol, 2021. **73**(1): p. 23-35.

[91] Chauss, D., et al., Autocrine vitamin D signaling switches off pro-inflammatory programs of T(H)1 cells. Nat Immunol, 2022. **23**(1): p. 62-74.

[92] Chauss, D., et al., Autocrine vitamin D signaling switches off pro-inflammatory programs of TH1 cells. Nat Immunol, 2022. **23**(1): p. 62-74.

[93] McGregor, T.B., et al., The impact of COVID-19 on the Canadian Kidney Paired Donation program: an opportunity for universal implementation of kidney shipping. Can J Surg, 2020. **63**(5): p. E451-E453.

[94] McGregor, E., Kazemian M, Afzali, B, et al, An autocrine Vitamin D-driven Th1 shutdown program can be exploited for COVID-19 https://www.biorxiv.org/content/10.1101/2020.07.18.210161v1, 2020.

[95] Adams, J.S., et al., Regulation of the extrarenal CYP27B1-hydroxylase. J Steroid Biochem Mol Biol, 2014. **144 Pt A**: p. 22-7.

[96] Munteanu, C. and B. Schwartz, The relationship between nutrition and the immune system. Front Nutr, 2022. **9**: p. 1082500.

[97] Aranow, C., Vitamin D and the immune system. J Investig Med, 2011.

[98] Martens, P.J., et al., Vitamin D's Effect on Immune Function. Nutrients, 2020. **12**(5).

[99] Fassio, A., et al., Effects on Serum Inflammatory Cytokines of Cholecalciferol Supplementation in Healthy Subjects with Vitamin D Deficiency. Nutrients, 2022. **14**(22).

[100] Tan, Y., et al., Correlations of Inflammatory Cytokines in the Intestinal Mucosa, Serum Inflammation, Oxidative Stresses and Immune Changes with Vitamin Deficiency in Ulcerative Colitis Patients. Cell Mol Biol (Noisy-le-grand), 2022. **68**(7): p. 101-106.

[101] Zhang, J., P.A. McCullough, and K.M. Tecson, Vitamin D deficiency in association with endothelial dysfunction: Implications for patients with COVID-19. Rev Cardiovasc Med, 2020. **21**(3): p. 339-344.

[102] Roffe-Vazquez, D.N., et al., Correlation of vitamin D with inflammatory cytokines, atherosclerotic parameters, and lifestyle factors in the setting of heart failure: A 12-month follow-up study. Int J Mol Sci, 2019. **20**(22).

[103] Hurst, S.D., et al., New IL-17 family members promote Th1 or Th2 responses in the lung: in vivo function of the novel cytokine IL-25. J Immunol, 2002. **169**(1): p. 443-53.

[104] Pinheiro, M.M., A. Fabbri, and M. Infante, Cytokine storm modulation in COVID-19: a proposed role for vitamin D and DPP-4 inhibitor combination therapy (VIDPP-4i). Immunotherapy, 2021. **13**(9): p. 753-765.

[105] McGregor, R., et al., An autocrine Vitamin D-driven Th1 shutdown program can be exploited for COVID-19. bioRxiv, 2020.

[106] Tang, W.J., et al., Autocrine/paracrine action of vitamin D on FGF23 expression in cultured rat osteoblasts. Calcif Tissue Int, 2010. **86**(5): p. 404-10.

[107] Hii, C.S. and A. Ferrante, The non-genomic actions of vitamin D. Nutrients, 2016. **8**(3): p. 135.

[108] Cui, X., et al., Vitamin D and the brain: Genomic and non-genomic actions. Mol Cell Endocrinol, 2017. **453**: p. 131-143.

[109] Svensson, D., et al., Vitamin D-induced up-regulation of human keratinocyte cathelicidin anti-microbial peptide expression involves retinoid X receptor alpha. Cell Tissue Res, 2016. **366**(2): p. 353-362.

[110] Wimalawansa, S.J., Biology of vitamin D. J steroids Horm Sci, 2019. **10**(198(1)): p. 1-8.

[111] Jeng, L., et al., Alterations in vitamin D status and anti-microbial peptide levels in patients in the intensive care unit with sepsis. J Transl Med, 2009. **7**: p. 28.

[112] El-Shazly, A.E. and P.P. Lefebvre, Modulation of NK cell autocrine-induced eosinophil chemotaxis by interleukin-15 and vitamin D(3): a possible NK-eosinophil crosstalk via IL-8 in the pathophysiology of allergic rhinitis. Mediators Inflamm, 2011. **2011**: p. 373589.

[113] Bartels, L.E., et al., Human dendritic cell antigen presentation and chemotaxis are inhibited by intrinsic 25-hydroxy vitamin D activation. Int Immunopharmacol, 2010. **10**(8): p. 922-8.

[114] Ekemen Keles, Y., et al., Can Serum 25-Hydroxy Vitamin D Levels Predict the Severity of Multisystem Inflammatory Syndrome in Children and COVID-19? J Clin Res Pediatr Endocrinol, 2023. **15**(2): p. 190-198.

[115] Konijeti, G.G., et al., Vitamin D Supplementation Modulates T Cell-Mediated Immunity in Humans: Results from a Randomized Control Trial. J Clin Endocrinol Metab, 2016. **101**(2): p. 533-8.

[116] Wang, Q., et al., Alarming antibody evasion properties of rising SARS-CoV-2 BQ and XBB subvariants. Cell, 2022.

[117] Polonowita, A., Wimalawansa, SJ, Impact of Withholding Cost-Effective Early Treatments, Such as Vitamin D, on COVID-19: An Analysis Using an Innovative Logical Paradigm. Wold J. Adanced Pharma. Life Sci, 2023. **(in press)**.

[118] Polonowita, A., Wimalawansa SJ, Molecular quantum and logic process of consciousness—Vitamin D big-data in COVID-19—A case for incorporating machine learning in medicine. Euro. J. Biomedical Pharma. Sci, 2023. **10**(12): p. 1-17.

[119] Stein, M., et al., The Burden of COVID-19 in Children and Its Prevention by Vaccination: A Joint Statement of the Israeli Pediatric Association and the Israeli Society for Pediatric Infectious Diseases. Vaccines (Basel), 2022. **10**(1).

[120] van Ewijk, C.E., et al., COVID-19 outbreak in an elderly care home: Very low vaccine effectiveness and late impact of booster vaccination campaign. Vaccine, 2022. **40**(46): p. 6664-6669.

[121] Wee, L.E., et al., Nosocomial SARS-CoV-2 transmission in multi-bedded hospital cubicles over successive pandemic waves: Lower mortality but wider spread with Omicron despite enhanced infection-prevention measures. Infect Dis Health, 2023. **28**(2): p. 81-87.

[122] Gonen, M.S., et al., Rapid and effective vitamin D supplementation may present better clinical outcomes in COVID-19 (SARS-CoV-2) patients by altering serum INOS1, IL1B, IFNg, cathelicidin-LL37, and ICAM1. Nutrients, 2021. **13**(11).

[123] Kojima, N. and J.D. Klausner, Protective immunity after recovery from SARS-CoV-2 infection. Lancet Infect Dis, 2022. **22**(1): p. 12-14.

[124] Kraaijeveld, S.R., R. Gur-Arie, and E. Jamrozik, Against COVID-19 vaccination of healthy children. Bioethics, 2022. **36**(6): p. 687-698.

[125] Savulescu, J., J. Pugh, and D. Wilkinson, Balancing incentives and disincentives for vaccination in a pandemic. Nat Med, 2021. **27**(9): p. 1500-1503.

[126] Annonymus. Vitamin D for COVID-19: real-time analysis of all 300 studies: *https://c19early.org/d*. 2022 25 January, 2023]; Available from: https://c19vitamind.com/.

[127] Abou-Saleh, H., et al., Neutralizing antibodies against SARS-CoV-2 are higher but decline faster in mRNA vaccinees compared to individuals with natural infection. J Travel Med, 2022. **29**(8).

[128] Chen, J., et al., Decline in neutralising antibody responses, but sustained T-cell immunity, in COVID-19 patients at 7 months post-infection. Clin Transl Immunology, 2021. **10**(7): p. e1319.

[129] Wimalawansa, S.J., Controlling COVID-19 pandemic with cholecalciferol. World J Adv, Heathcare Res., 2020. **5**(1): p. 155-165.

[130] Kaufman, H.W., et al., SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels. PLoS One, 2020. **15**(9): p. e0239252.

[131] Greiller, C.L. and A.R. Martineau, Modulation of the immune response to respiratory viruses by vitamin D. Nutrients, 2015. **7**(6): p. 4240-70.

[132] Argano, C., et al., Protective Effect of Vitamin D Supplementation on COVID-19-Related Intensive Care Hospitalization and Mortality: Definitive Evidence from Meta-Analysis and Trial Sequential Analysis. Pharmaceuticals (Basel), 2023. **16**(1).

[133] Cicero, A.F.G., F. Fogacci, and C. Borghi, Vitamin D supplementation and COVID-19 outcomes: mounting evidence and fewer doubts. Nutrients, 2022. **14**(17).

[134] Hewison, M., Vitamin D and innate and adaptive immunity. Vitam Horm, 2011. **86**: p. 23-62.

[135] Davies, G., R.B. Mazess, and L.L. Benskin, Letter to the editor in response to the article: "Vitamin D concentrations and COVID-19 infection in UK biobank" (Hastie et al.). Diabetes Metab Syndr, 2021. **15**(2): p. 643-644.

[136] Hastie, C.E., J.P. Pell, and N. Sattar, Vitamin D and COVID-19 infection and mortality in UK Biobank. Eur J Nutr, 2020.

[137] Raisi-Estabragh, Z., et al., Greater risk of severe COVID-19 in Black, Asian and Minority Ethnic populations is not explained by cardiometabolic, socioeconomic or behavioural factors, or by 25(OH)-vitamin D status: study of 1326 cases from the UK Biobank. J Public Health (Oxf), 2020. **42**(3): p. 451-460.

[138] Walsh, J.B., et al., Title: Understanding a low vitamin D state in the context of COVID-19. Front Pharmacol, 2022. **13**: p. 835480.

[139] Werneke, U., F. Gaughran, and D.M. Taylor, Vitamin D in the time of the coronavirus (COVID-19) pandemic - a clinical review from a public health and public mental health perspective. Ther Adv Psychopharmacol, 2021. **11**: p. 20451253211027699.

[140] Hill, A.B., The Environment and Disease: Association or Causation? Proc R Soc Med, 1965. **58**(5): p. 295-300.