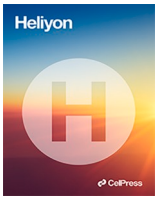
Heliyon 10 (2024) e34691

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Unlocking insights: Navigating COVID-19 challenges and Emulating future pandemic Resilience strategies with strengthening natural immunity

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A R T I C L E I N F O

Keywords:
25(OH)D
Immune system
Mutations
Omicron
SARS-CoV-2
Adjunt therapies
Vitamin D

A B S T R A C T

The original COVID-19 vaccines, developed against SARS-CoV-2, initially mitigated hospitalizations. Bivalent vaccine boosters were used widely during 2022–23, but the outbreaks persisted. Despite this, hospitalizations, mortality, and outbreaks involving dominant mutants like Alpha and Delta increased during winters when the population's vitamin D levels were at their lowest. Notably, 75 % of human immune cell/system functions, including post-vaccination adaptive immunity, rely on adequate circulatory vitamin D levels. Consequently, hypovitaminosis compromises innate and adaptive immune responses, heightening susceptibility to infections and complications. COVID-19 vaccines primarily target SARS-CoV-2 Spike proteins, thus offering only a limited protection through antibodies. mRNA vaccines, such as those for COVID-19, fail to generate secretory/mucosal immunity-like IgG responses, rendering them ineffective in halting viral spread. Additionally, mutations in the SARS-CoV-2 binding domain reduce immune recognition by vaccine-derived antibodies, leading to immune evasion by mutant viruses like Omicron variants. Meanwhile, the repeated administration of bivalent boosters intended to enhance efficacy resulted in the immunoparesis of recipients. As a result, relying solely on vaccines for outbreak prevention, it became less effective. Dominant variants exhibit increased affinity to angiotensin-converting enzyme receptor-2, enhancing infectivity but reducing virulence. Meanwhile, spike protein-related viral mutations do not impact the potency of widely available, repurposed early therapies, like vitamin D and ivermectin. With the re-emergence of COVID-19 and impending coronaviral pandemics, regulators and health organizations should proactively consider approval and strategic use of cost-effective adjunct therapies mentioned above to counter the loss of vaccine efficacy against emerging variants and novel coronaviruses and eliminate vaccine- and anti-viral agents-related serious adverse effects. Timely implementation of these strategies could reduce morbidity, mortality, and healthcare costs and provide a rational approach to address future epidemics and pandemics. This perspective critically reviews relevant literature, providing insights, justifications, and viewpoints into how the scientific community and health authorities can leverage this knowledge cost-effectively.

1. Introduction

The rapid development of messenger RNA (mRNA)-technology-based COVID-19 vaccines within six months in 2020 marked a

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https://doi.org/10.1016/j.heliyon.2024.e34691
Received 6 March 2024; Received in revised form 17 June 2024; Accepted 15 July 2024
Available online 17 July 2024

significant technological milestone during the COVID pandemic [1]. ten-billion-dollar grant from United States taxpayers facilitated its developments. Traditionally, vaccines aim to halt disease transmission. However, mRNA-based COVID-19 vaccines, while was effective in reducing hospitalizations, did not prevent the spread of SARS-CoV-2 [2,3]. Breakthrough infections in fully vaccinated individuals result in peak viral loads comparable to those in unvaccinated individuals, allowing both groups to continue transmitting SARS-CoV-2 to their contacts [2]. The Omicron variants, characterized by multiple mutations in the receptor binding domain, exhibit significant immunological differences from the original SARS-CoV-2 [4]. These variants demonstrate reduced lethality but with increased infectivity (high Ro) [5], and immune evasion against vaccine-derived antibodies.

Despite the three years of the declared pandemic [6], the potential for coronaviruses to mutate and evade immunity has been well-known for years [7]. Global health authorities, however, primarily advocated reliance on vaccines to control the COVID-19 pandemic outbreaks without offering broader strategies or recommending alternative adjunct early therapies for SARS-CoV-2 control and eradication [6,8]. The focus has been primarily on patented COVID-19 vaccines, antiviral agents, and monoclonal antibodies authorized under Emergency Use Authorization (EUA) [9].

In the USA and other countries, patented agents for COVID-19 received swift authorization from the Food and Drug Administration (FDA). Notably, one critical legal requirement for EUA approval and maintenance is the absence of alternative agents for disease prevention or treatment [9]. The approvals of COVID-19 vaccines and antiviral agents under EUA were expedited and released to the market without undergoing rigorous efficacy and longer-term adverse effect testing [9,10]. Despite the prompt approval of the patented COVID-19 vaccines, anti-viral agents, and monoclonal antibodies by regulators, a global urgency to identify and approve a genuinely compelling, cost-effective agent against SARS-CoV-2 failed to materialize [11–13].

The paper delves into aspects concerning COVID-19 outbreaks in industrialized countries and explores alternate options, specifically the potential use of vitamin D and ivermectin for future pandemic control. The author underscores concern (unlike traditional vaccines) regarding the predominant reliance on vaccines, pointing out their limitations in preventing infection and transmission. The potential use of globally available cost-effective repurposed agents, such as vitamin D and ivermectin, is evaluated. The manuscript also emphasizes the significance of recognizing natural immunity and advocates for considering alternative therapeutic approaches for the future.

A thorough search was conducted across various research databases using keywords related to COVID-19 vaccines, mRNA vaccines, complications, immune evasion, vaccine efficacy, alternative therapies, vitamin D, and ivermectin. Combining keywords narrowed the number of relevant manuscripts to a manageable quantity. The search encompassed databases such as PubMed, Medline, Web of Science, and EMBASE, focusing on clinical studies, randomized controlled clinical trials (RCTs), prospective clinical studies, as well as original and review articles, following a methodology similar to that employed for systematic or narrative reviews [14]. References were selected based on their relevance to the topic and incorporated into the manuscript after reviewing them.

1.1. Fundamentals of COVID vaccines

The mRNA and adenovirus vector-based COVID vaccines were designed based on the viral Spike protein sequences. mRNA-based immunizations utilize single-stranded mRNA to encode the desired antigen. The objective was to prompt the recipient's immune system to produce viral Spike proteins of SARS-CoV-2, comprising 1273 amino acids, to develop antibodies against the virus [15], despite Spike proteins are toxic to humans. In different vaccines, the modified Spike protein structures or selected portions of the viral sequences are not identical. As a result, the antigen expression and antibodies generated from mRNA and genetic adenovirus-vector vaccines differ [15].

COVID-19 vaccines were developed using different platforms, including live attenuated viruses, inactivated vaccines, and non-replicating viral vectors—RNA and DNA. mRNA vaccines were created using DNA templates encoding the Spike protein. These mRNA particles are encapsulated in a lipoprotein-based carrier to safeguard them from degradation and facilitate rapid cell entry [16]. mRNA molecules enter cells and undergo translation upon injection via the intramuscular route [17]. Once inside host cells, mRNA generates peptides with Spike protein sequences recognized by the body as foreign antigens, activating humoral responses and prompting B-cells to transform into memory cells. Viral antigens are presented on antigen-presenting cells, triggering immune responses. Upon secondary exposure to a Spike protein antigen, memory B cells activate protective mechanisms, including heightened synthesis of neutralizing antibodies [18].

The S1 subunit of the SARS-CoV-2 spike protein contains the receptor binding domain (RBD) along with the N-terminal domain, which is responsible for binding it to the angiotensin-converting enzyme-2 (ACE-2). The S2 subunit houses the fusion and transmembrane proteins, enabling viral attachment to the host cell and enter [19]. After the virus enters host cells, it undergoes uncoating and initiates the transcription and translation of mRNA, leading to viral assembly. The resulting exocytosis of viral particles from host cells into the bloodstream allows them to infect other cells.

Unlike vaccines developed through traditional approaches, the mRNA vaccines (i.e., Pfizer and Moderna) and adenovirus vector-based COVID-19 vaccine (J&J) did not incorporate core viral elements or the complete inactivated virus [20,21]. Immunity induced through traditional methods uses core components, which tend to have a broader spectrum and longer-lasting immune protection [22,23]. In contrast, the immunity triggered by the mRNA COVID-19 vaccine is narrow, targeting a part of the Spike protein sequence. Consequently, mRNA vaccines do not produce antibodies against co-components, like nucleocapsids and co-proteins [24,25].

Random mutations occur, affecting the binding domains of the SARS-CoV-2 genome, which may modify the affinity to the membrane-bound ACE-2 receptor. Such mutations can modify the affinity to ACE-2 receptors,virulence, as well as the potential for immune evasion [24]. However, dominant variants increase infectiousness as indicated by higher Ro values (replication rate) while exhibiting reduced lethality: in parallel they developed an increased ability to evade immune detection [26]. The virulence of the

newer strains of SARS-CoV-2 strain is comparable to influenza [27], except that it incur long lasting harm, such as the post-COVID syndrome. Nevertheless, less aggresiveness resulting in a decreased need for hospitalization. Additionally, over the past years, the widespread availability of free Rapid Antigen (RAT) kits (intended as a screening tools and not to make diagnosis) has led to a sizable portion of COVID-19 testing being conducted at home or health-related stores. Consequently, positive SARS-CoV-2 data were not consistently captured in general reporting or hospital statistics, potentially causing authorities to overlook, missed, or ignore outbreaks.

1.2. Basic mechanisms involved with gene-directed vaccines

The fundamental mechanism underlying mRNA vaccine technology involves delivering nucleic acid molecules that encode the target antigen, specifically the coding region of the Spike sequences of SARS-CoV-2. These strategically designed sequences utilize host cells to produce foreign mRNA, expressing and amplifying the intended antigen—producing Spike protein sequences in endoplasmic reticulum-Golgi through ribosomes [28]. This intricate process entails synthesizing antigen sequences into corresponding proteins, with some degrading into smaller antigenic peptides by proteasomes [25]. However, the reported critical adverse effects and the dispersion of Spike protein-related mRNA, as suggested by mRNA scatter, indicate that the distribution of this material is not limited to immune cells [29,30].

Once in circulation, antigens interact with immune cells that recognize antigens, such as Toll-like receptor-4, which is distributed extensively in the body. In contrast to traditional protein-based vaccines, mRNA (or DNA) conveys the message to host cells to generate and express Spike proteins on their membrane. The soluble form of these proteins is then shed into circulation to alert the immune system [5]. Consequently, a broad range of cells in the body is exposed to the Spike protein, leading to the reported adverse effects [24].

The antigenic peptides are presented to $CD8^+$ cytotoxic T cells via the major histocompatibility complex (MHC) class I molecular pathway as endogenous antigens, activating cell-mediated immune responses [25]. Additionally, these antigenic peptides, derived from toxic Spike proteins generated by mRNA, are released into the extracellular environment, including the circulation [31]. They are taken up by antigen-presenting cells (APCs) and presented to $CD4^+$ T cells through MHC class II molecules as exogenous antigens. This initiates cellular immune responses through cytokines, activating B cells to produce antibodies and triggering humoral immune responses [32].

1.3. The development of COVID-19 vaccines and new antiviral agents

Novel COVID vaccines against the SARS-CoV-2 virus were developed swiftly, circumventing standard regulatory and safety requirements through EUA [31]. Launching them in late 2020 was considered a significant achievement [33]. The development of this innovative technology for SARS-CoV-2 vaccines was financially supported by the United States taxpayer grant to Big Pharma, benefitting multiple major pharmaceutical companies capable of large-scale vaccine manufacturing [34]. Additional financial subsidies were extended in 2021 to develop antiviral agents. In addition, pharmaceutical companies received special exemptions and fast-track approvals (under the EUA Act) from the FDA to develop, test, and approve these vaccines [9].

The fallacy emerged when vaccine companies and leading health authorities asserted that these vaccines prevented SARS-CoV-2 transmission and propagation, however, they withhold the primary data. The primary reason why governments worldwide purchased expensive COVID-19 vaccines because they were marketed to stop disease transmission. People believed this, which later became a falsehood. This contributed to a broader public distrust and misconceptions about COVID-19 vaccins and directions by health organizations like the WHO [35]. Large health agencies propagated vaccines as the sole solution to the pandemic, prompting many governments to coerce and mandate them [36]. Despite knowing about previous coronaviral infections, vaccine companies failed to design COVID-19 vaccines properly. Instead, they expedited their production by taking shortcuts in vaccine development and testing [31]. This further added to the public distrust. The failure to address and mitigate adverse outcomes proactively and disclose critical information that these vaccines do not prevent infections further eroded their credibility and trust, which later affected the vaccine uptake [25,37].

The EUA and the favorable pharmaceutical agreements with the FDA allowed Big Pharma to bypass standard safety checks in COVID-19 vaccine trials, which would have otherwise taken several years to bring them to market [38]. Conversely, regulators and leading health authorities chose not to authorize using already approved, generic, cost-effective, repurposed agents [39]. Instead, they penalized physicians who used them to save lives. Relaxing of regulations includes otherwise mandatory toxicity studies (such as precluding genotoxicity studies), relaxation of standards of conducting and gathering data, the number of RCTs to confirm their efficacy, and the need for rigorous short-term and long-term adverse effect testing and reporting [31].

Based on the EUA, regulators also lowered the threshold for experimental and untested methods in generating mRNA vaccines and human testing, later expanding and replicating them to new antiviral agents and monoclonal antibodies [40]. It became evident that if regulators were to approve any other agent for preventing or treating SARS-CoV-2, the temporary EUA approval of vaccines and antiviral agents would revoked automatically—a critical reason for the non-approval of any generic agents for the prevention or treatment of SARS-CoV-2 by the regulators.

1.4. Regulatory categorization of COVID-19 vaccines

According to the definitions provided by the European Union (Section IV), New Zealand, and other regulatory bodies, Pfizer-

BioNTech and Moderna's mRNA vaccines were categorized as gene therapies [41]. Additionally, AstraZeneca and J&J's adenoviral (nucleic acid) vector (injections) were identified as modified gene therapies [41]. These vaccines were designed to synthesize large quantities of viral Spike proteins *in vivo* in the recipients, subsequently stimulating memory and plasma cells and leading to the generation of antibodies [42]. Despite claims, Spike proteins remaine in the host for a longer period than anticipated. Therefore, it is unsurprising that the adverse effects on vulnerable people following the SARS-CoV-2 virus and COVID-19 vaccines are similar an continuing.

1.5. Glimpse of virus and vaccine-related adverse effects

With billions of dollars in grant funding and impunity against adverse effects, Big Pharma was incentivized by the FDA to bring the mRNA vaccine to market quickly [35]. Besides, based on agreements and urgency, regulators increased tolerance of big pharma companies taking shortcuts and maintained the secrecy of the approval process [31]. In conjunction with the FDA, Big Pharma refused to share methodology, process, vaccine-related primary RCT data, and reporting adverse effects, using the pretense of patent protection. The vacuum of data availability to independent scientists from pharma and the FDA was striking and unprecedented [43]. Additionally, the subsequent acceptance of bivalent COVID-19 vaccines was without RCT (data), as well as the vaccination of children and young adults [44]. Vaccine companies provided neither safety data related to these groups nor supporting tangible benefits vs. potential harm [45–47].

COVID-19 vaccines have been associated with broader and serious adverse effects [45,48], primarily affecting the cardiovascular and pulmonary systems [49–51]. Similar adverse complications have been reported following SARS-CoV-2 infection [48,52,53]. They also linked to sudden death syndrome [54], a multisystem inflammatory syndrome in adults [55] and Kawasaki-like disease in children [56], as well as adverse outcomes in pregnancy [57], myocarditis [56,58], pericarditis [46], clotting abnormalities (hemagglutinin) [59], and various other adverse effects in cardiological, hematological [60], dermatological [61,62], ocular [63], and neurological systems [53,64].

Inference: The unexpected and broad range of Spike protein-mediated adverse effects began to be reported after the approval and usage of COVID-19 vaccines [52]. These severe adverse effects from COVID-19 vaccines affirmed insufficient testing or withholding of adverse reaction data and insufficient follow-up duration before their broader clinical use was approved [65]. Data confirmed systemic adverse effects (e.g., pulmonary, cardiovascular, and neural effects) stem from disseminating toxic Spike Proteins throughout the body, including the central nervous system. A phenomenon was observed following SARS-CoV-2 infection and after COVID-19 vaccines [52,53,65].

1.6. The progress of vaccines and their efficacy

With a broader uptake, WHO and government sponsorships, vaccines showed promise in early 2021 by decreasing the severity of SARS-CoV-2 infection, as reflected by fewer hospitalizations. However, no reduction in deaths has been demonstrated [33]. However, towards the end of 2021, vaccine efficacy declined. In response, mRNA companies, Pfizer and Moderna developed a hybrid solution—creating bivalent vaccines designed to cover the antigenic sites of emerging Omicron variants [66,67]. Despite assurances from vaccine pharmaceutical companies and leading health authorities regarding high *relative* efficacy and safety and the emphasis on vaccine reliance, opting to rely solely on vaccines to overcome the pandemic appears to have been a mistake [68]. Such has also led to vaccine hesitancy [68].

The diminishing efficacy of vaccines, especially bivalent boosters, coupled with the lack of an alternative plan or effective armamentarium, failed to control COVID-19 with increasing virus outbreaks in 2022, noticeable in industrialized countries with high vaccine uptake [69]. Despite optimistic expectations, outbreaks persisted regardless of the vaccination status in the community [70]. This article critically examines the advantages and disadvantages of COVID-19 vaccines and the potential alternative adjunct therapies based on publicly available information. The data suggested that despite widespread vaccination efforts, the incidence of infections

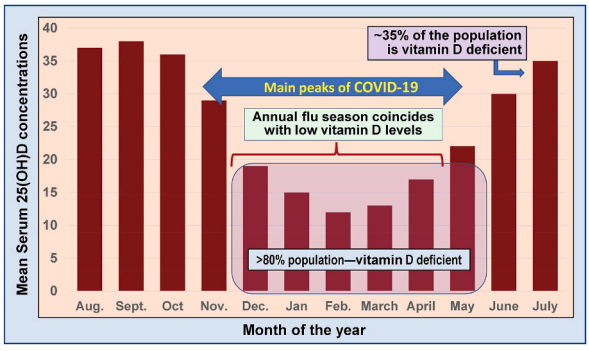

Fig. 1. Winter-associated low serum 25(OH)D levels in the population increase susceptibility to respiratory viral infections, including those caused by SARS-CoV-2 (modified from Wimalawansa, SJ, 2022) [77].

and hospitalizations from SARS-CoV-2 experienced a resurgence and continued, particularly during the winter of 2022 and 2023 [35,53,71].

There is a cyclic decline in the serum 25(OH)D concentration population during winter [72]. This is attributed to a lack of sunlight (i.e., exposure to UVB rays) and inadequate dietary intake and supplementation [73,74]. Hypovitaminosis D weakens the immune system [5], increasing the vulnerability to respiratory viruses: flu viruses, SARS-CoV-2, etc. These viruses spread primarily through airborne mechanisms [75,76]. This phenomenon explains the seasonal escalations of respiratory viral illnesses like flu, respiratory syncytial virus, and SARS-CoV-2 during winter (Fig. 1) [77]. People were infected predominantly in indoor gatherings (inhalation of air with high viral density), and dry air facilitated the spreading of the virus. This behavior change following prolonged curfews and lockdowns had made hypovitaminosis D worse [77,78]. The failure to effectively control SARS-CoV-2 in 2020/21 and mismanaged pandemic guidance resulted in COVID-19 becoming endemic by early 2023 [79].

2. SARS-CoV-2 mutations, vaccine uptake, and viral transmissions

The efficacy of COVID-19 vaccines resulted in fewer hospitalizations from SARS-CoV-2 in early 2021 but it faded by 2022, primarily due to emerging viral mutations and their escape from neutralizing antibodies [33]. Since both mRNA and adenoviral vector COVID-19 vaccines failed to generate mucosal immunity, they failed to prevent infecting others [2,80,81]. This was particularly notable as SARS-CoV-2 viruses and their variants predominantly spread via airborne transmission [2,82]. As a result, there were no significant differences in infectivity rates or viral densities between vaccinated and unvaccinated individuals [81]. Furthermore, new variants like Delta and Omicron continued to acquired new Spike protein mutations [83], rendering them more contagious than the original SARS-CoV-2,[2,84] but less lethal [84], aiding the spread of the virus [4].

2.1. Viral mutations, immune evasion, and lack of effect on viral transmission

Evolving dominant mutated virus increased the affinity of ACE-2-RBD of the virus, enhancing the infectivity [85]. Some viruses become dominant and develop immune evasion capabilities [6,7], rendering them resistant to vaccines [10], and antiviral agents [86]. New Omicron variants have higher R_0 values (the average number of people getting infected from a person) [26], indicating increased infectiousness [87], but generally, they became less lethal than the original SARS-CoV-2 and the Delta variant [26,76]. The loss of vaccine effectiveness due to mutagenesis and the resultant immune evasion and disordered and/or conflicted policies have contributed to the persistence of SARS-CoV-2 outbreaks in 2021 and 2022, becoming endemic. The following sections discuss these aspects and propose cost-effective measures to overcome outbreaks.

2.2. Viral loads and SARS-CoV-2 transmission

As previously discussed, several studies have highlighted the absence of a significant difference in SARS-CoV-2 nasal viral loads between vaccinated and unvaccinated individuals [2,64,88]. This includes the presence of the virus in the nasopharynx, even in asymptomatic cases [2,80,81]. Consequently, fully vaccinated and unvaccinated individuals contribute equally to the spread of the disease [88]. While some variations in reporting exist due to technological differences, the consensus is that, unlike traditional vaccines, COVID-19 vaccines do not prevent disease transmission—from human to human. As a result, mandates for vaccinations have been deemed irrelevant [89] and unjustified [90].

The above points are supported by studies conducted in Israel, showing COVID-19 breakthrough transmission from fully vaccinated healthcare workers to patients [90,91]. various studies have consistently demonstrated no significant difference in the peak viral titers in the upper airways and the culturable viruses between vaccinated and unvaccinated individuals [2,80,81,91]. This evidence challenges the justification for policies mandating compulsory vaccination and the dismissal of unvaccinated healthcare workers [89], frontline workers, and military personnel [2,80].

2.3. Disparity to access vaccines—Industrial nations vs. developing countries

Global distribution of COVID-19 vaccines faced a significant disparity. Wealthier nations secured preferential status through multi-billion-dollar pre-marketing contracts and pre-payments by mRNA vaccine companies—Pfizer and Moderna-with and payments to mRNA vaccine companies. This resulted in they receiving the vaccine supplies first [92]. In contrast, the rollout of vaccines to developing countries faced delays of several months [93]. Many of these countries struggled to secure even a fraction of a percentage of vaccines needed.

Lack of funds prevented them from purchasing expensive COVID-19 vaccines or antiviral agents in sufficient quantities, even for their vulnerable populations. In addition, under public pressure, some of these nations had to compete and spend more than the market price to acquire COVID-19 vaccines [94]. This was escalated because of the lack of raw material supply from the West to manufacture vaccines in countries like India [95]. This disparity underscores the challenges in ensuring equitable access to vaccines worldwide [94].

The focus of big pharma on enhancing upfront profits created major challenges for developing nations, as they lacked the capacity for large pre-payments in (USD) foreign currencies, making it difficult for them to secure delivery contracts [94]. This neglected over four billion people in developing nations without having adequate access to vaccines [95]. This may also contribute to the failure of the development of herd immunity and SARS-CoV-2 infection becoming endemic [92]. and allow vaccine pharma to raise prices for further

vaccines. Consequently, areas like Africa and certain Asian countries were left behind with very low vaccination rates [93]. Ironically, these regions that failed to secure mRNA-based COVID-19 vaccines experienced the lowest mortality from SARS-CoV-2 [96]. The health emergency declared by the World Health Organization (WHO) was managed haphazardly, leading to non-transparent industry practices and creating loopholes that allowed politicians [89], especially in developing countries, to exploit the market for personal gains.

Inference: The mistaken premise that the COVID-19 vaccine would stop propagating SARS-CoV-2 infection drove developing countries to spend precious funds earmarked for essential needs like food and medicine to prioritize vaccine purchases. This stretched their limited foreign reserves, compromising the purchase of essential goods and oil, leading to increased food, medicine, and energy insecurity [93]. The diversion of resources towards vaccine procurement, often at exorbitant prices, was influenced by commissions and additional profits for those involved [92]. This financial strain compromised essential services in emerging economies and developing countries, highlighting the detrimental impact of poor policy and public health decisions affecting the well-being of their populations [95,97].

Developing countries, such as Burundi, Haiti, Chad, Ethiopia, Cameroon, Tanzania, Mali, etc., with lower vaccination rates (ranging from 0.5 to 5 % of the population), experienced notably lower hospitalization and death rates from SARS-CoV-2 [92,95]. Whereas, countries like Sri Lanka, faced challenges after paying double the market rate to obtain COVID-19 vaccines. Poor fiscal policies, extended lockdowns (curfews), and inferior and biassed decision-making led to the dwindling of their foreign reserves and devaluation of currencies. The resulting exchange crisis was exacerbated by unwise decisions, such as banning fertilizer and pesticide importation, significantly reducing crop output and leading to severe food shortages [94]. This crisis, marked by severe shortages of essential goods like food, medicine, and fuel, ultimately led to Sri Lanka declaring bankruptcy in 2022 [98,99].

2.4. Securing COVID-19 vaccines and government mandates to increase uptake

Despite efforts in industrialized countries to boost vaccination uptakes through coercive measures like imposing mandates and vaccine passports and restrictions for unvaccinated people, viral outbreaks persisted, as in most industrialized countries, including the USA [89,100]. Inherent limitations of COVID-19 vaccines, the inability to stimulate mucosal immunity [51], and the high prevelance of vitamin D deficiency played a significant role in the viral spread and the failure to achieve herd immunity and eventually eliminate SARS-CoV-2 [2,80,81].

Relying solely on vaccines at any cost, many administrations enforced vaccine mandates and extended curfews based on the misconception that using vaccination alone will prevent the transmission of SARS-CoV-2 [89]. This approach neglected cost-effective generic, repurposed drugs, and essential traditional public health disease prevention measures. Additionally, governments using their agencies and health authorities utilized Big Tech and mass media to discredit and discourage the use of already approved and widely available repurposed agents, including vitamin D and ivermectin [101,102].

Inference: The lack of transparency, information censorship, and restricting access to scientific publishing prevented healthcare workers and the public from being adequately informed about the benefits and drawbacks of vaccines and alternative therapies [100], along with their efficacy and adverse effects [103,104]. The focus was shifted toward a new vaccination round, using bivalent boosters designed for new mutants. However, these booster vaccines were approved without conducting RCTs [105]. Despite these efforts by prominent health organizations and Western governments, public skepticism increased with a parallel reduction of vaccine uptake in 2022 [70].

2.5. Generation of bivalent vaccines and regulatory framework

In early 2022, vaccine companies acknowledged the fading efficacy of the original COVID-19 vaccine, prompting the development of hybrid bivalent vaccines. These were marketed as an innovative solution against the Omicron variants [1,105]. For bivalent vaccines, pharma emphasized the similarity in the manufacturing process to bypass the need for new RCTs. With little transparency and a lack of credible safety data, including genotoxicity and medium-to longer-term adverse effects, these were promptly approved by the FDA and other regulatory authorities [2,45,101,122,12391]. Regulatory approval for mRNA-based booster/bivalent vaccines, monoclonal antibodies, and antiviral agents was swiftly granted under the Public Health Emergency of International Concern [21] declared by WHO [106,107]. This hasty expedited approval process facilitated rapid market penetration influenced by governmental measures like booster vaccine mandates.

Inference: The untransparent collaboration between Big Pharma and regulators, such as the FDA, led to a critical error by overlooking efficacy and safety testing for bivalent vaccines [66]. Approval for commercialization without adequate testing, safety data, and RCT data was a significant regulatory oversight akin to coercing parents to vaccinate children. Subsequent data revealed that bivalent vaccine boosters had only about a third of the efficacy of the original COVID-19 vaccines, but others disagree [108]. The new Omicron variants had a substantial capability for immune evasion against bivalent booster vaccines [105]. These events have contributed to ongoing outbreaks and the pandemic transitioning to an endemic state [66,84,109,110].

2.6. Insufficient futuristic thinking and planning

The progress of medicine over the last three decades has been remarkable, offering a wide range of choices, advanced diagnostic methods, and innovative interventions [111]; most recently, artificial intelligence. However, information technologies have outpaced practical applications in the medical field. Despite the potential of machine learning and artificial intelligence [79,112], their

integration into medical decisions and policy-making is still in its early stages [79,112]. This lag in incorporating these technologies has resulted in shortcomings in drug and device safety assessments, interactions, and efficacy evaluation [113,114]. Consequently, there have been delays in approving drugs, including cost-effective generic agents [79,112], and making timely healthcare policy decisions, presenting a significant obstacle to progress [79,113].

For instance, since mid-2020, compelling data from multi-disciplinary studies, RCTs [115–117], meta-analyses, and extensive database studies have consistently shown the effectiveness of widely available, unpatented agents and micronutrients in enhancing the immune system capabilities [5,118,119]. These interventions have demonstrated the potential to prevent complications and reduce mortality associated with coronaviruses like SARS-CoV-2 (https://c19early.org/dmeta) [96]. However, regulatory bodies and prominent health authorities have overlooked this evidence.

2.7. Inherent conflicts of interests

Two examples of conflicts of interest are repurposed agents vitamin D [119–121], and ivermectin [122,123]. In late 2020, each agent had over forty reasonably sized peer-reviewed published clinical studies, including RCTs (https://c19early.org) [96]. By the end of 2022, there were over 140. By mid-2023, there were over 250 peer-reviewed publications for each agent [96], still not even considered for evaluation and approvals. In-depth details of all these publications are available free on website—https://c19vitamind.com [96]. Despite this large amount of clinical trial data, regulators and healthcare agencies were unwilling to investigate these agents for their efficacy and safety [112]. Furthermore, the pharmaceutical industry began designing clinical studies and funding for academia to carry out and poorly designed and biased studies and publish them via academic institutes. Some trials were designed to fail, and others intended to discredit generic agents [101,124].

The relevant data supporting the efficacy of early interventions had already been published, and outcomes were well-known. Therefore, authors should have known a high probability of failure of outcomes and, thus, harm to subjects when designing those failed clinical studies [125,126]. Therefore, ethics committees (IRBs) should not have approved such clinical studies.

Most RCTs mentioned above utilized inappropriate and/or insufficient doses of economic agents like vitamin D and ivermectin [127–130]. In some studies, they were administered at the wrong frequency or only as a bolus dose [127,128], in severely ill individuals (e.g., in ICUs) or late in the course of COVID-19 [128,131,132], knowing that such clinical trials will fail. Other failed studies had major study design errors [129,130]. It is noteworthy that most of these generic therapies are most effective when administered early as possible as a preventative or adjunct measure prior to developing complications. Such an approach is intended to provide either prophylactic treatment to prevent symptomatic disease or on admission before complications develop [133].

These repurposed agents had been approved for other conditions, are widely available worldwide without a prescription, and are economical. In addition, they have impressive safety profiles (refer to section 4.8) [96,134,135]. As discussed above, the main reason for not approving these generic agents was the automatic revocation of vaccines, antivirals, and monoclonal antibodies temporarily approved under EUA (i.e., to protect their status). If any of these agents were approved, the previvledged EUA stauts of vaccines and anti-viral agents would be automatically revoked [79].

2.8. The failure to approve repurposed early therapies

Despite four years into the pandemic, regulators have yet to approve any non-patented cost-effective therapies for preventing and treating SARS-CoV-2. This narrow perspective has resulted in missed opportunities to establish logic-based COVID-19 adjunctive algorithms to manage it better using algorithms with complementary therapies, even though it could have pejorative connotations in mainstream medicine [79,112]. Approval of repurposed agents would have saved thousands of lives. Instead, most countries' relied recommended supportive and/or wait-and-see strategy in 2020 [133]. By mid-2020, substantial published data encompassing over 390,000 individuals (i.e., big data) and information on vulnerable patient groups were available [79]. Utilization of these would have offered insights into early diagnosis, age-sex-specific risks, and cost-effective early use of generic agents [112,115]. Yet no steps were taken to integrate this vital information into clinical practice.

The evidence-based medicine paradigm established by big pharma for drug approvals has led regulators to focus solely on pharmaceutical industry-conducted, large, multi-center RCTs as the primary (and the only) evidence for testing medical hypotheses for drug approvals, which was extended to nutrients like vitamin D [5,136]. This preferential approach negatively affects the approval process for unpatented and widely available inexpensive agents, such as vitamin D and ivermectin for SARS-CoV-2, although they were effective [96]. Due to this misconception, well-conducted extensive observational and ecological studies, along with smaller but well-designed and statistically powered RCTs conducted by sources outside the pharma sector, such as academia, were disregarded by regulators in the context of drug approvals. Contrary to this bias, these clinical studies are equally valid for understanding causative factors and assessing effectiveness, even though they may involve generics and nutrient interventions [5].

Inference: Authorities neglected to employ innovative logical methods, extensive data analyses, big-data analysis, and novel machine-learning paradigms for decision-making despite the availability of a large set of data by the end of 2020 [79,112]. Utilizing these approaches could have provided evidence of the efficacies of vitamin D and ivermectin in mid-2020, confirming their clinical relevance, consistency, robust dose responses, and inverse correlations between vitamin D status and COVID-19-related outcomes [73], similar to ivermectin [96]. Integrating new information and engineering technologies into large clinical study datasets could have minimized biases and guesswork used by health authorities over the past three years. The failure to do so resulted in fruitless policies like lockdowns and weak, ambiguous and conflicting clinical recommendations, contributing to increased economic disruptions, healthcare costs, hospitalizations, intensive care usage, and deaths, especially in high-risk groups [79,112].

2.9. Misinformation and data suppression

Throughout the COVID-19 pandemic, there has been a proliferation of misinformation by individuals on social media regarding disease prevention and treatment aspects [137–139]. Numerous challenges in accessing authentic information include preventing the dissemination of the beneficial effects of vitamin D and ivermectin via scientific articles and reviews. Pharmaceutical companies and governments supported the process by sponsoring *fact-checking* organizations [137,140,141]. Besides, a coordinated effort by mainstream media and major social media platforms was used to undermine the use of generics and repurposed medications for COVID-19 [139,142,143]. Additionally, there had been attempts to divert regulatory attention from considering repurposed agents for COVID-19 by presenting sophisticated but irrelevant statistics instead of focusing on straightforward, traditional, and cost-effective analyses and assessments [144].

The cost-effectiveness of the mentioned repurposed agents has been downplayed, and adverse effects have been exaggerated [145], —designed to undermine the public trust. Such disinformation is defined as knowingly sharing false information to cause harm [146]. Even some scientific articles initially published were later found to contain unintentional misinformation [137,140,142,147]. Medical boards and councils have inappropriately taken politically-driven disciplinary actions against physicians who prescribed these cost-effective medications with good intentions and the best judgment to benefit patients [139,141]. The usefulness of generic agents like vitamin D, however, were included in a few, as in Front Line COVID-19 Critical Care Alliance (FLCCC) protocols [148] and World Council of Health treatment guidelines [149]. Repurposed agents like ivermectin (war on ivermectin) [142,143,150] have been addressed in detail elsewhere [119,151,152], and can be explored further on the website https://c19early.org/, which provides published clinical research studies (currenty over 4,500 trials) of all medications tested against SARS-CoV-2 and real-time meta--analyses [96].

Inference: Special interest groups and patient advocacy groups have propagated contradictory recommendations to favor their position, worsening the confusion and hindering the use of repurposed agents and vitamin D [151]. Consequently, big pharma and governments exploited the mass confusion and the lack of unity among scientists to their advantage for marketing patented medications, like and vaccines and anti-viral agents [79]. Big Pharma has employed similar approaches, utilizing their misinformation playbooks [102].

3. Controlling the pandemic with vaccines

As previously illustrated, vaccines developed against the original SARS-CoV-2 had positive effects in 2021, flattening infectious peaks/outbreaks and distributing admissions to hospitals and intensive care facilities (ICUs) that reduced the burden [33,152]. This reduced the overloading of health personnel and facilities, but this advantage diminished toward the end of 2021. This was due to the development of immune evasion by dominant SARS-CoV-2 (Omicron) mutants and the failure of bivalent vaccines [51]. Due to the converging viral mutations occurring within the RBDs of Spike proteins and the consequent reduced immune recognition, the effectiveness of bivalent booster vaccines was reduced to below 40 % [83].

3.1. Benefits derived from COVID-19 vaccines

Despite the failure to prevent the transmission of SARS-CoV-2, [2,80,81] published governmental data during 2021 indicated that COVID-19 vaccines had an impact on reducing hospitalizations [152]. However, by early-2022, the hospitalization rates from Omicron variants of SARS-CoV-2 were increasing [4]. There were few differences between fully vaccinated and boosted individuals and unvaccinated individuals [79]. Notably, the definition of fully vaccinated varies from country to country. In the USA, one dose of Janssen (J&J) viral vector vaccine or two doses of mRNA COVID-19 vaccine constituted complete vaccination.

Several studies have reported the limited capacity and short duration of immunity [153,154] derived from mRNA COVID-19 vaccines [152,155–157]. As a result, the interval between vaccine booster doses was reduced from the intended yearly to six months to maintain circulating antibody levels [157]. However, the ratio of neutralizing antibodies to other antibodies declined, making the response to infection less effective. This decision, however, ignored the importance of T-cell priming and memory cell functions. Besides the short-lived immunity [156], the efficacy of vaccines, including the Omicron-specific bivalent vaccines, is significantly less than it was against the original SARS-CoV-2 virus [157].

3.2. Fundamentals of controlling a pandemic and expectations

During an epidemic or pandemic, an essential public health concept is to prioritize the reduction of the incidence (peaks) of infections, i.e., by reducing the transmissibility (Ro) and curtailing viral spread from person to person [26]. This is vivid with traditional vaccines. An effective vaccine is expected to curtail the transmission of viruses or bacteria. SARS-CoV-2 transmission is primarily airborne, occurring via droplet spread.

Wearing facemasks, observing social distancing, avoiding crowded gatherings, and maintaining good personal hygiene are typical public health disease-preventive measures used against respiratory viral diseases/epidemics. These measures are designed to minimize exposure to high viral loads and curb the spread of the disease, thereby limiting infections and ultimately controlling viral transmission, as in the case of SARS-CoV-2. They aim to flatten infectious peaks, alleviate healthcare burdens, and eventually facilitate herd immunity [103,158]. However, despite widespread vaccination efforts, these intended protective characteristics have not been fully realized.

Inference: As with all previous immunizations, the logical process and expected outcome were that vaccinated individuals would cease becoming infected by others and would not transmit the microbes to unvaccinated persons, such as patients. However, neither of these promises materialized with COVID-19 vaccines. Despite the false claims by Big Pharma that mRNA vaccines prevent the transmission of SARS-CoV-2, institutions like the Centers for Disease Control (CDC) in the USA, the World Health Organization (WHO), and prominent governments propagated this pharma-derived falsehood to boost vaccine uptake and sales. Not until late 2022 did the manufacturers of mRNA COVID vaccines, Pfizer and Moderna, acknowledge that their vaccines do not prevent the spread of the disease or reinfection [2].

3.3. Original COVID-19 vaccines reduced hospitalization but failed to stop SARS-CoV-2 transmission

The COVID-19 outbreaks in 2020 and early 2021 primarily impacted specific vulnerable groups, especially older individuals with co-morbidities, immune-compromised or suppressed individuals, institutionalized persons, and ethnic minorities with darker skin living in temperate countries [159]. A common denominator among these susceptible groups was having a high prevalence of vitamin D deficiency [119,160,161]. Given that approximately 75 % of immune system activities rely on sufficient vitamin D [73], COVID-19 became a pandemic among those with severe vitamin D deficiency [77]. Despite the availability of this critical data, major healthcare agencies overlooked it [79] and took no action to advise the population on strengthening their immune systems to combat the SARS-CoV-2 virus [79]. Consequently, severe hypovitaminosis D persisted and worsened due to prolonged curfews and lockdowns in many countries [77,78]. This contributed to millions unnecessarily developing severe complications requiring hospitalization and thousands succumbing to SARS-CoV-2 [119].

Mass-scale COVID-19 vaccination commenced in late 2020, driven by WHO-enforced strategies adopted by most governments. The USA initially initiated vaccine mandates, which Europe and other nations subsequently replicated without thorough scientific scrutiny. They failed to conduct comprehensive independent investigations and adherence to published scientific data. Following governmental mandates, industrialized countries achieved successful vaccination coverage ranging from 60 to 80 % of their adult populations.

Despite the mass-scale vaccination efforts, since early 2022, SARS-CoV-2 outbreaks and local epidemics have been resurgent, occurring irrespective of vaccination status. These instances have been observed in communities with fully vaccinated, boosted, and unvaccinated individuals. Despite widespread media promotion of vaccination, these local epidemics have shown similar spread patterns among vaccinated and non-vaccinated individuals, irrespective of factors such as access to healthcare, availability, or per capita spending [2,3,80,81].

3.4. Original SARS-CoV-2 vs. Omicron variants—the status and outbreaks

The Omicron variant of SARS-CoV-2 exhibited a rapid spread, surpassing the infectivity of the Delta variant with a doubling of infections every three days. Despite its swifter transmission, Omicron presented as milder, parallel to flu or influenza, and displayed different symptomatology than the original SARS-CoV-2 [4]. Irrespective of the vaccination status, this milder nature resulted in healthy individuals typically not requiring hospitalization. However, individuals with uncontrolled coexisting co-morbidities and those with severe vitamin D deficiency [serum 25(OH)D concentration less than 12 ng/mL] were still at an elevated risk of developing complications and death [159]. Unlike earlier SARS-CoV-2 variants like Alpha and Delta, the two preceding lineages of Omicron (BQ and XBB) that dominated outbreaks in 2022/2023 exhibited increased resistance to mRNA-derived neutralizing antibodies. This resistance (immune evasion) was more noticeable with bivalent booster-generated antibodies [82,84].

New Omicron variants displayed a notable shift in affecting younger age groups compared to the Alpha and Delta variants. This change was attributed to the acquired immune resistance of Omicron variants, driven by mutated Spike proteins, leading to significant

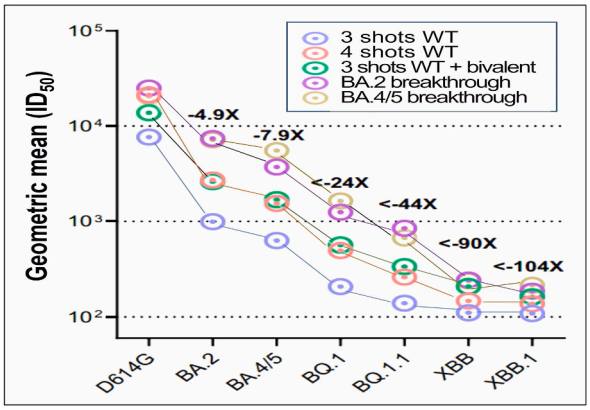

Fig. 2. Compared to pseudo-typed D614G and Omicron subvariants BAs, neutralization of Omicron subvariants BQ.1, BQ.1.1, XBB, and XBB.1c, by sera from five different cohorts—the limit of detection of one hundred (indicated in a dotted line). Values above the bold symbols represent geometric mean, ID50 values (details of the experiment are in the original manuscript) (from Wang et al., Lancet, 2023) [82].

deviations in their immune characteristics from the original SARS-CoV-2. This altered immune profile contributed to immune evasion against mRNA and adenovirus vector-based COVID-19 vaccines [162,163] and antiviral agents [86]. Consequently, vaccine-derived immunity proved less effective in preventing infections caused by new mutants, even with the administration of booster doses [164–166]. immunoparesis resulting from repeated booster doses contributed to reinfections in individuals previously exposed to SARS-CoV-2,[2,154] particularly impacting older adults [66,157].

Fig. 2 illustrates the antigenic drift from the original SARS-CoV-2 and the Omicron variant to XBB and XBB.1. This suggests that these subvariants behave antigenically distinct or, perhaps, as a new virus compared to SARS-CoV-2 [82]. This observation may elucidate why the bivalent vaccine and monoclonal antibodies fail to recognize new subvariants, contributing to the reduced effectiveness of current COVID-19 vaccines and an increased occurrence of breakthrough infections and reinfections [167,168].

Inference: Repetitive administration of COVID-19 booster vaccine doses further weakened the immune system, resulting in diminished responses against pathogenic microbes. This immune suppression, akin to vaccine-acquired immune deficiency syndrome [30], is also called immune paresis, a concern that health authorities should have addressed early.

3.5. Omicron variants and post-COVID syndrome

Mutations represent natural biological phenomena that heighten environmental pressures for viral survival. Increased utilization of COVID-19 vaccines, especially among immun-compromised individuals and those with vitamin D deficiency, despite having bivalent mRNA vaccine booster doses had limited immunity. This may also have contributed to the rate of developing SARS-CoV-2 viral mutations [169]. The dominant variants, such as Delta and Omicron, have higher infectivity than the original SARS-CoV-2 as primarily derived from the mutations in the RBD region, which increased the affinity to the membrane-bound ACE-2 receptors on epithelial cells. However, the resistance to COVID-19 vaccines may also have contributed to it [155,170]. Additionally, convergent evolution has led to diverse combinations of mutations in the virus's RBD [83].

Although the dominant mutants of SARS-CoV-2 exhibit a higher rate of spread (R_0) in the community than the original SARS-CoV-2 virus [169], the occurrence of the post-COVID syndrome (long-COVID) is similar [152], or even higher than those associated with the original virus [171]. Due to the uprising and fatigue of the public due to enforced restrictions, most countries relaxed public health measures, such as wearing facemasks and restrictions on crowded gatherings, way before the WHO's declaration that the pandemic was over. However, some governments continued to propagate expensive COVID-19 vaccines. The Omicron variant outbreaks and endemic spread were fueled by increased local transmission and global travel, dominated by variants like B.1 and XBB mutants, which significantly evade immune recognition by vaccine-derived antibodies [153,162].

Inference: Globally, few or no new SARS-CoV-2 mutants originate from countries or communities with minimal vaccine uptake [70]. Most mutants occur in immune-deficient or fully vaccinated individuals [82]. Moreover, more boosters correlate with an increased likelihood of mutations and reinfection [172,173]. Conversely, repeated vaccine boosters weaken the immune system, making individuals more vulnerable to SARS-CoV-2 mutants [67], reinfections [172,173]. It also increased the risks for re-infections with mutant viruses and other dormant and commensal organisms, such as Mycobacterium tuberculosis and herpes zoster [174].

3.6. Parallels with influenza vaccines

Each year, the characteristics of influenza viruses change. Consequently, vaccines are developed based on predictions of the predominant species in the upcoming winter season. However, these predictions are often inaccurate, resulting in flu vaccines being 'generic' and not specific to the correct species dominating during the following year. As a result, the efficacy of flu vaccines in preventing symptomatic disease, hospitalization, and deaths remains low [12]. This low efficacy has led to distrust in the product, and more adults are now reluctant to take flu vaccines [70]. A similar trend began to emerge in 2022 with SARS-CoV-2 [175]. Initially with

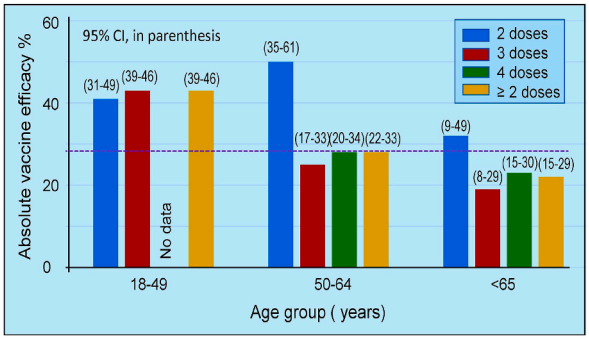

Fig. 3. Absolute effectiveness of vaccines [95 % Confidence Intervals (CI) presented in parenthesis] in Y-axis, against symptomatic SARS-CoV-2 infection for a single bivalent mRNA COVID-19 booster dose. Colored columns illustrate 2, 3, or 4 doses of monovalent vaccine (no data presented for single dose recipients) compared with no booster dose. Data presented by age group (X-axis) vs. number of monovalent COVID-19 vaccine doses received. The average effectiveness of 24 % is presented as a broken horizontal line. The figure was drawn using the data from the CDC's increasing community access to the testing program, USA (Sept.–Nov. 2022, table 3) [179].

high enthusiasm, the uptake of bivalent vaccines was high, but as emerging data became available, the population uptake rapidly decreased despite offering incentives [109,157,175–177].

Recent scientific reports indicate that booster vaccines are relatively ineffective and may not be a solution to control the pandemic (Fig. 2) [109,157,175–177]. Safety concerns regarding serious adverse effects related to COVID-19 vaccines are also growing [21,103, 105,110,178]. The mishandling of COVID-19 by public health authorities has further contributed to the loss of public trust. With increased infectivity from new variants and the diminishing efficacy of bivalent vaccines coupled with immune evasion by mutant SARS-CoV-2 viruses, controlling outbreaks has become challenging, resulting in a transition from a pandemic to an endemic. Fig. 3 illustrates the effectiveness of mono and bivalent COVID-19 vaccines and their susceptibility to immune escape.

Inference: Research, including data from the CDC (Fig. 3), demonstrates a decline in vaccine effectiveness against severe COVID-19, particularly after the second booster [109,179]. As the efficacy of COVID-19 vaccines approaches levels comparable to placebos [179]. Instead of pushing booster doses, health authorities should have explored complementary options to prevent hospitalizations from Omicron variants using other means.

4. Development of mutants and rationale for reduced effectiveness of COVID-19 booster vaccines

4.1. Widespread vaccination is associated with increased SARS-CoV mutants

Variants such as Alpha, Beta, Delta, and Omicron exhibit mutations, deletions, and alterations in the sequence of the NTD antigenic supersite, a larger glycan-free region in the Spike protein within the viral membrane [155]. Deletions in variants B.1.1.523 were identified in early 2021, while B.1.617.2 includes the E484K mutation in most variants [82,180,181]. The E484K mutation is situated within the membrane RBD region, enhancing affinity to ACE-2 receptors and modifying immune detection.

The E484K mutation was also found in B.1.351 and P.1 variants, reducing vaccine efficacy by elevating vaccine resistance. This mutation also diminishes the effectiveness of monoclonal antibodies and convalescent plasma therapy, making them ineffective [181]. Although these new variants evade immunity without increasing virulence, emergent variants like BQ.1.1 and XBB1.5 and future variants might lead to increased virulence [86,163,182]. Consequently, the potential impact of future mutations should be a significant concern [84].

4.2. Viral infections and vaccinations consume vitamin D

The escalation of preexisting and infection-induced vitamin D deficiency (due to lockdowns and increase consumption of vitamin D by immune cells) hinders the entry of D_3 and 25 (OH)D into target cells, preventing the intracellular production of 1,25 $(OH)_2D$ in immune cells [74,126]. This, in turn, disrupts the intracellular autocrine and paracrine signaling functions of calcitriol and activation of VDR (CTR) molecules [73,77], with weakened immune systems. Maintaining a consistent D_3 and calcifediol [25 (OH)D] supply during the infection can overcome this challenge and support a robust immune system. Studies have indicated that vaccinating individuals previously infected and recovered does not confer additional benefits against SARS-CoV-2 or its variants [183]. Furthermore, studies revealed that there is no discernible advantage to administering more than one booster shot to individuals fully vaccinated or recovered from SARS-CoV-2 infection [166].

The robust immune responses triggered by SARS-CoV-2 infections and following vaccinations increased vitamin D/ 25(OH)D utilization. Without continuous vitamin D supplementation during an infection, there is a risk of developing or existing vitamin D deficiency. The administration of more vaccines, particularly booster doses, correlates with a higher rate of depletion of vitamin D stores in the body, an accelerated reduction in serum 25(OH)D concentrations, and more re-infections [73,184].

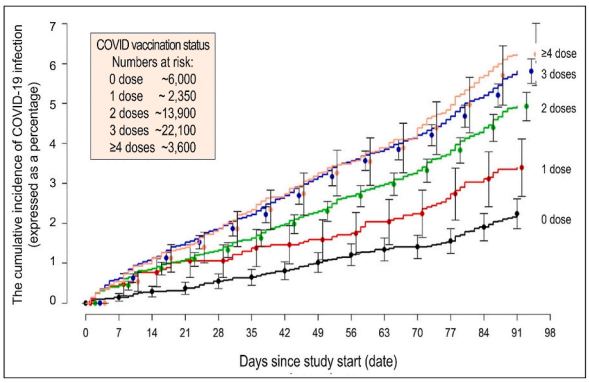

Fig. 4. A Simon-Makuch plot illustrates data from healthcare workers at Cleveland Clinic (n = 51,011) USA—comparisons of the risk of acquiring COVID-19, with and without COVID-19 vaccines and booster doses. Data were analyzed using Cox proportional hazards regression, point estimates, and 95 % confidence intervals. The risk of COVID-19 infection linearly increases with the number of COVID-19 booster doses (adapted from Shrestha, NK et al. with permission; pending peer review [67].

Additionally, zinc and magnesium, which are crucial cofactors for vitamin D's effects on VDR/CTR and other immune functions, are also depleted during this process [185]. The increased consumption of vitamin D exacerbates insufficiencies in zinc and magnesium [74]. Deficiencies in these components result in a dysfunctional innate immune system [5], and immune paresis [30], contributing to delay in recovery, the spread of microbes, and increased complications and deaths. Several datasets indicate Several datasets indicate that higher numbers of COVID-19 booster doses administered are associated with increased vulnerability in the population or individuals and higher infection rates (per the reasons described above) (Fig. 4) [162,165,166,170,186].

The gradual decline in the efficacy of COVID-19 vaccines and bivalent boosters is attributed to many factors. These include mutations that lead to immune evasion by viruses, repeated booster doses causing immune exhaustion and depletion of immune cells, and the increasing deficiency of vitamin D and cofactors, resulting in immune paresis, etc., analog to vaccine-acquired immune deficiency syndrome [30]. The weakening of the immune system is particularly evident, as depicted in Fig. 4, after administering the second booster dose of COVID-19 vaccines.

Inference: Deficiencies in vitamin D and cofactors substantially compromise innate and post-immunization immune responses [166], rendering individuals more susceptible to SARS-CoV-2 reinfections [172,173], infections from mutant viruses [67], and other commensal organisms [174]. Collectively, these factors contribute to heightened morbidity and mortality.

4.3. Development of immune evasions by Omicron variants

Several recent studies have documented the diminishing effectiveness of COVID-19 vaccines [2,3,67,172,173]. An RCT conducted at Cleveland Clinic in the USA involved 51,011 healthcare workers who received bivalent COVID-19 vaccines [67]. 13 weeks follow-up data revealed an increased risk of contracting Omicron variants with the number of vaccine booster doses received [67,166]. The data suggests that the higher the vaccine booster doses, the higher the risk of contracting Omicron disease, as illustrated in Fig. 4.

Additional booster doses decrease immune capabilities and heighten vulnerability to SARS-CoV-2,[67] reinfections [90,172,173], and other infections [174], partially attributed to immune paresis [164]. The effectiveness of current bivalent COVID vaccines in shielding against infection in the BA.4/BA.5 lineages of the Omicron variant is reported to be approximately 30 %, akin to a placebo [67,166]. Strikingly, each successive booster dose correlates with a step-wise escalation in susceptibility to SARS-CoV-2 infection, as depicted in Fig. 4.

4.4. Actions that may help to reduce poor outcomes in future pandemics

Taking preventive measures such as micronutrient sufficiency could naturally strengthen the immune system against microbes and prevent vaccine-associated immunoparesis and the incidence of post-COVID syndrome among both vaccinated and unvaccinated individuals [164–166]. Given the ongoing viral mutations, exploring alternative strategies beyond vaccines alone is imperative. Early therapies incorporating unpatented, repurposed, and widely available agents like vitamin D, ivermectin, and melatonin should be considered [96].

The https://c19early.org/website provides information on over forty generic agents investigated and reported in peer-reviewed literature [96]. The first scientific publication recommending an effective remedy against SARS-CoV-2—vitamin D—was released in February 2020 [187]. The failure to diversify the therapeutic options, influenced by conflicts of interest, pharmaceutical bias, and administrative pressures to maintain the Emergency Use Authorization (EUA) status of patented vaccines and antiviral drugs, resulted in chaos. Replicating such a flawed approach will have disastrous consequences in future pandemics and should be avoided.

Molecular biological techniques offer a practical approach to combating viruses with rapid mutation, aiming to understand and detect them at an early stage. However, it is crucial to identify the complete viral antigenic profile and employ a broader antigenic exposure strategy to induce immunity and antibodies against a broader antigenic spectrum, sensitizing memory cells. The production of such therapies must rapidly address viruses that mutate within a year. Despite the advantages of mRNA technology deployment, the serious adverse effects of Spike protein toxicity and the rapid loss of efficacy raise concerns, making it questionable to use similar choices and technology in the future. As the current mRNA technology is still evolving, introducing insufficiently tested products directly into humans via vaccine injections [188] or orally [189] without establishing proper safety profiles was deemed premature and have serious negative consequences.

4.5. Reported serious adverse events with mRNA vaccines

In the Moderna randomized controlled trial (RCT), serious adverse effects (SAEs) occurred at a rate of 15.1 per 10,000 participants, compared to 6.4 per 10,000 participants in the placebo group—a 2.4-fold higher risk of SAEs than the reduction observed in COVID-19 hospitalization [190]. Similarly, in the Pfizer RCT, the excess risk of SAEs was 10.1 per 10,000 participants, relative to 2.3 per 10,000 in the placebo group [10] —a 4.4-fold higher incidence of SAEs compared to the risk reduction for COVID-19 hospitalization [10,191]. Despite such data, the absolute benefits (in contrast to relative benefits that pharma rested) vs. risks were ignored by the regulators.

Combined mRNA vaccine data was associated with an excess risk of SAEs of 12.5 per 10,000 vaccinated (95 % CI 2.1 to 22.9)—a risk ratio of 1.43 (95 % CI 1.07 to 1.92). The Pfizer RCT had a 36 % higher risk of SAEs in the vaccine group with a risk difference of 18.0 per 10,000 vaccinated (95 % CI 1.2 to 34.9)—a risk ratio 1.36 (95 % CI 1.02 to 1.83), a similar trend [10]. The SAEs and risk ratios in these RCTs are significantly higher in the mRNA-vaccinated groups than in the placebo groups [190,191], but the regulators overlooked these data. Independent scientists' lack of access to primary data further hindered impartial analysis.

4.6. Booster doses: SARS-CoV-2 spread, duration of protection, and impact on mortality

As described above, data confirmed that vaccinated and unvaccinated could harbor, shed the virus, and infect others equally [2,80,81,162]. The primary series of COVID-19 vaccines partially protects from complications, thus reducing hospitalizations, but only for a few months [33,154,192]. Neither antiviral agents nor monoclonal antibody therapies activate the immune system or provide longer-term benefits. These treatments typically cost $500 to $2000 per patient. Nevertheless, they exhibit lower effectiveness than generic agents, such as vitamin D and ivermectin, which costs around two dollars per person [12]. Calcifediol is more effective than vitamin D, which costs about twenty dollars per patient. Many published clinical studies in combating SARS-CoV-2 infection using generic agents against SARS-CoV-2 infection real-time meta-analyses and summarized data available on c19early.org/dmeta.html support these concepts [96].

Given the failure of vaccines to prevent the transmission of SARS-CoV-2, [2,3,48,49,59,67,90,91,172,173] relying on vaccination and mandating status (proof of vaccination) cards or digital identities and segregating people lacks scientific merit. Even in countries like the USA, the UK, Israel, etc., where over 75 % of adults and adolescents are vaccinated, achieving herd immunity or halting viral spread failed [158,193]. The persistence of outbreaks was attributed, in part, to transmission within communities and introduction from outside.

The challenges are compounded by the evasion of vaccine-induced immunity by dominant new variants like the XBB series, along with a reduction in the ability of antibodies to neutralize viruses to under 40 % [153,162]. With emerging new variants developing resistance to vaccines and antiviral agents [86], the reliance on vaccinations alone would fail to prevent COVID-19 outbreaks, establish herd immunity, or eliminate SARS-CoV-2 and its mutant viruses.

In certain Western countries, the proportion of hospitalization attributed to Omicron remains lower among the vaccinated. However, after the introduction of bivalent vaccines, this ratio changed; the reasons for this were discussed above [194]. In these industrialized countries with high vaccination rates, the absolute numbers of infections and re-infections, as well as hospitalization,

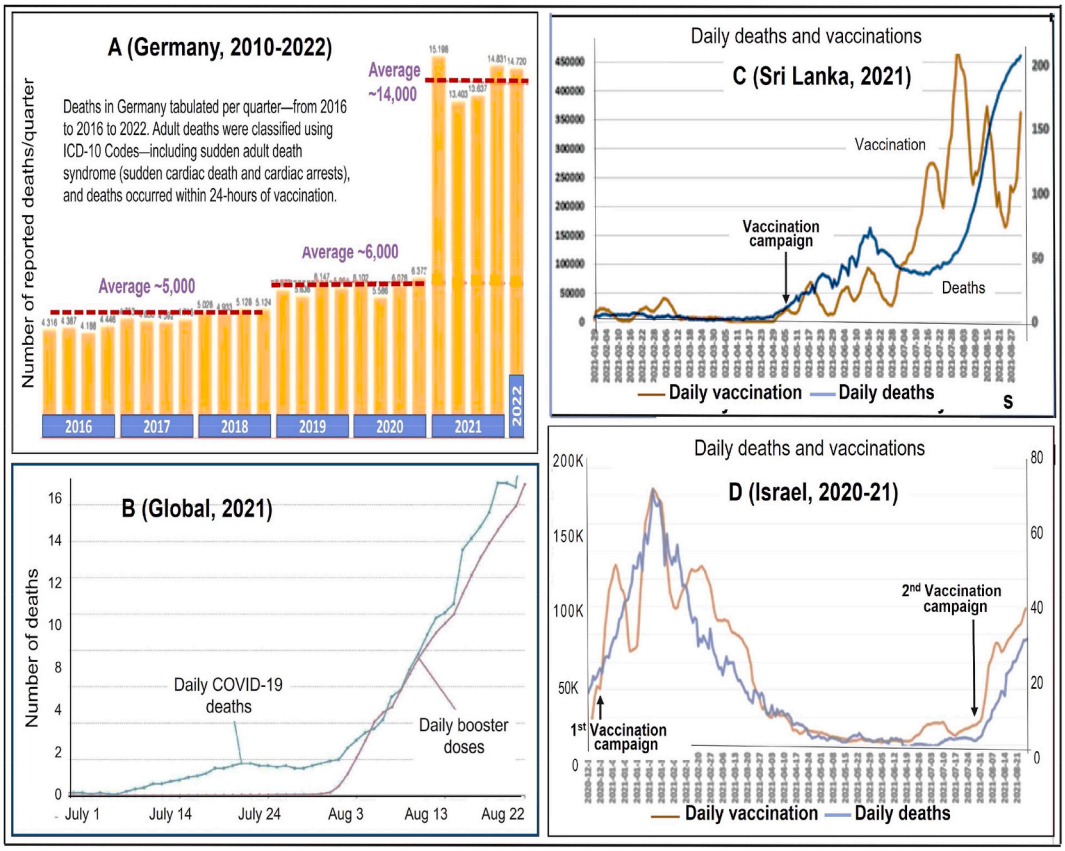

Fig. 5. A) illustrates the change in reported deaths in Germany between 2021 and 2022. Figures C through D depict the parallel relationship between the daily administration of COVID-19 booster vaccine doses and reported deaths. Figure B presents global data, showcasing the daily number of vaccine booster doses administered per 100 people and deaths from COVID-19 (sourced from OneWorld in Data, Human Mortality Database, and World Mortality Dataset, 2023). Figures C and D also provide specific data for Sri Lanka and Israel, respectively. In Figure C, daily vaccination statistics are compared to daily reported deaths from COVID-19 in Sri Lanka from January to September 2021 (adapted from E. Dias). In Figure D, Israel's data illustrates the number of persons fully vaccinated versus daily deaths from COVID-19 from December 2020 to September 2021 (source: https://ourworldindata.org/), highlighting the observed parallelism.

became higher among the fully vaccinated than the unvaccinated [195]. Making firm conclusions, however, requires appropriately adjusting for confounding factors and denominators. For instance, a higher proportion of the vaccinated population comprises older people with co-morbidities. Cautionary measures are warranted unless the observed trend is consistent among younger individuals. Fig. 5 illustrates broader effects using an acute increase in reported sudden deaths in Germany in 2021 and provides comparative data on vaccine uptakes and deaths from 2021 to 22 globally, in Sri Lanka and Israel.

As highlighted earlier, increased complications and hospitalizations can be attributed partly to the immune evasion exhibited by dominant mutant viruses and the immunoparesis of hosts resulting from booster doses or repeated SARS-CoV-2 infections [162,165, 166,170,186]. This pattern has been observed previously with other viruses, especially in individuals who are vitamin D deficient or immune-compromised [196].

Inference: Based on the above data, advocating for multiple booster doses and vaccinating younger children lacks rationale and merit. Instead, the primary focus of vaccination should have been on vulnerable populations to enhance their adaptive immune system, activate memory cells, and prioritize the maintenance of a robust immune system for effective defense against the virus. This becomes particularly evident when considering data demonstrating declining mortality rates in countries during ivermectin treatment campaigns [197].

4.7. Countries with fewer than 15 % vaccinated had no new COVID outbreaks

Approximately 2.8 billion people within 1400 km of the equator experience sufficient sunlight exposure throughout the year. Most individuals in this population maintain their serum 25(OH)D concentrations above 30 ng/mL [74,125], the minimum necessary for certain biological activities, except those deliberately avoiding sun exposure. However, the average serum population serum 25(OH)D concentration in most countries is about 20 ng/mL, including in the USA [198], as well as most developing countries and emerging economies.

Most developing countries mentioned above had insufficient dollars to purchase the required COVID-19 vaccines. With this limited access, their COVID-19 vaccine uptake was between 5 and 15 %; the majority only received the first dose. In contrast, over 70 % of adults in industrialized nations were fully vaccinated, with a similar percentage having received booster doses. Despite these disparities and healthcare inequalities, the tropical countries reported fewer or no COVID-19 outbreaks, hospitalizations, and fewer deaths from 2022 onwards. The difference is these populations had better mean serum 25(OH)D concentrations.

Furthermore, adults in affluent countries received multiple booster vaccine doses, around three boosters per person, yet exhibited lesser protection against SARS-CoV-2, evidenced by re-infections [199]. This significant disconnect is highlighted in Fig. 6, which illustrates the polarized SARS-CoV-2-related deaths expressed per million population in industrialized countries (characterized by higher GDP and per capita health expenditure) with rates of high vaccination (Cluster 1) compared to developing countries with low per capita GDP and low vaccination rates at the time (Cluster 2). As illustrated in Fig. 6, affluent countries (Cluster 1) experienced a four-hundred-fold higher death rate from COVID-19 than developing countries.

4.8. The cost-effectiveness (NNT) of various agents examined against SARS-CoV-2

The website https://c19early.org is a reliable and comprehensive resource featuring over a hundred peer-reviewed clinical research articles focused on three prominent treatments for SARS-CoV-2: vitamin D and ivermectin [96]. This unique site independently compiled data from diverse clinical research teams worldwide, providing individual research study data and collective analyses over forty-five interventional agents published against SARS-CoV-2. This site analyzed individual published clinical studies—321 with

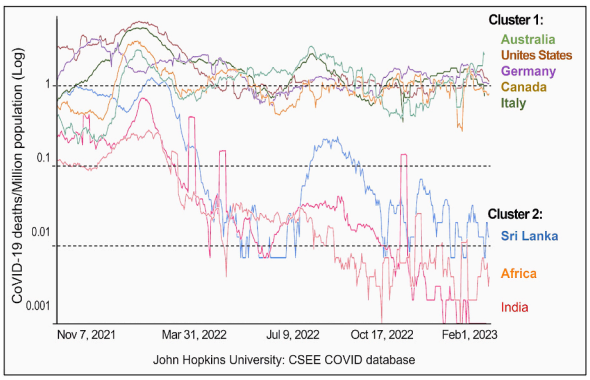

Fig. 6. The data on deaths from COVID-19, spanning from November 2021 to February 2023, presented as the rolling seven-day average deaths per million population, clearly illustrates a stark 400-fold difference in death rates between the two clusters. Cluster 1 comprises industrialized countries with over 70 % of the population fully vaccinated, while Cluster 2 represents African countries with less than 15 % vaccination coverage. Notably, India and Sri Lanka achieved higher vaccination percentages in late 2022, and their death rates were already low before the initiation of vaccination campaigns. The data is expressed as deaths per million population and adapted from Our World COVID data based on the Johns Hopkins University database.

vitamin D and 105 with ivermectin—consisting of several thousand study participants (i.e., reliable big data sets of SARS-CoV-related 4428 clinical studies , by June 2024) [96]. Considering number of clinical trials, countries and participants, costs and efficacy, these two agents emerged as the most cost-effective options for COVID-19. The estimated costs (also imply the number needed to treat: NNT) are reported as $11 for vitamin D and $25 for ivermectin (Table 1).

In addition to the two agents mentioned above (vitamin D and ivermectin), there are other generic agents with reported clinical significance [200]: Fluvoxamine (an antidepressant): 20 clinical studies reported a 40–80 % reduction in hospitalization [201,202]; hydroxychloroquine, 27 clinical studies reporting 80 % reduction in hospitalization; Elderberry (from European black elder - *Sambucus nigra*): Demonstrated a 50 % improvement [203]; Curcumin (oral nano-curcumin): Collective efficacy of 26 clinical studies with a significant p-value of 0.0000093; [204] Nigella (*Nigella sativa*, black cumin seed): 12 clinical studies showing over 50 % reduction in hospitalization [205]; Melatonin 11 clinical studies with a 50 % reduction in mortality [206]; Quercetin: 11 clinical studies showing over 50 % reduction in hospitalization [207]. All agents were reported to have clinically significant anti-viral effects.

In contrast, the anti-viral agent favipiravir, with 67 studies, reported a pooled effect of ~20 % reduction of risks [206], Molnupiravir with ~20 % lower risks [208] (8 % reduction of post-COVID syndrome) [209], Paxlovid (*nirmatrelvir-ritonavir*) ~50 % reduction of risks [210] (1 % improvement of post-COVID syndrome/complications [211], and Remdesivir, 62 clinical studies, 0–10 % Improvement [212] and higher mortality [213]. The pooled effects and mean outcomes were obtained from https://c19early.org/ader.html [96].

4.9. Ivermectin as a cost-effective alternative therapy

Ivermectin is a broad-spectrum antiparasitic drug with additional antiviral activities [214–216]. While several negative studies on ivermectin were published, many were funded by pharmaceutical companies and biased. Some were designed to fail, indicating conflicts of interest. Over a hundred clinical studies and 50+ RCTs have investigated ivermectin—316 clinical trials in 35 countries involving 446,237 subjects with COVID-19. Besides, some RCTs reported a strong association and a significant reduction of mortality with ivermectin use (RR, 0.25; 95 % CI, 0.09–0.70; p = p.008) [215]; other analyses support this [217].

4.9.1. Ivermectin positive studies

Recently published positive clinical studies include seven meta-analyses and a systematic review of trials conducted in 2020 (n = 382); Ragó et al. reported significant benefits associated with ivermectin [218]. These include faster viral clearance, an 81 % reduction in symptomatic disease, 38 % fewer hospitalizations, and a 49 % decrease in mortality [218]. Another meta-analysis, encompassing 15 clinical trials (n = 2438), indicated that prophylactic use of ivermectin resulted in an 86 % reduction in COVID-19 infections (95 % confidence interval 79%–91 %) and a 62 % decrease in mortality risk compared to placebo confirmed by Trail Sequential analysis (95 % CI 0.19–0.73) [219].

Several studies have also affirmed the safety and cost-effectiveness of ivermectin when used at doses ranging from 0.2 to 0.4 mg/kg [220,221]. Additionally, RCT by Varnaseri et al. (n = 110) showed ivermectin significantly reduced ICU admissions (32.7 % vs. 5.5 %; $p < 0.001$), hospitalization duration (6 vs. 4 days; $p < 0.001$), and median time to symptom resolution ($p < 0.05$) compared to the placebo group, with no serious adverse effects reported [222].

However. some of the recent studies on ivermectin were controversial, but well-designed RCTs provided compelling data. The PRINCIPLE study by Hayward et al. (n = 3963) revealed a 36 % reduction in COVID-19-specific symptoms ($p < 0.0001$), with ivermectin demonstrating superiority in primary recovery outcomes with a probability of superiority >0.999 [223]. Early administration of ivermectin resulted in faster recovery, complete symptom alleviation, and sustained relief ($p < 0.0001$), all at a significantly lower cost than other treatments, such as Molnupiravir, which can cost over $700 per patient.

Ivermectin has been the subject of 103 peer-reviewed clinical studies, including 50 RCTs; 142,417 subjects participated and were contributed by 1193 scientists. Real-time meta-analyses of these studies reported significant efficacy ($p < 0.00000001$) in reducing the risk of infection, hospitalization, and mortality and increased viral clearance. A random pooled analysis of 50 RCTs reported that ivermectin demonstrated 85 % effectiveness in reducing the risk of COVID-19 and 49 % efficacious in reducing mortality in early treatment studies.

Table 1
The cost for a life saved (i.e., cost-effectiveness) of several tested agents in SARS-CoV-2*.

High Cost-Effectiveness				Low Cost-Effectiveness			
Agent	Cost	Agent	Cost	Agent	Cost	Agent	Cost
Melatonin	$8	Aspirin	$33	Fluvoxamine	$411	Casirivimab	$203958
Vitamin D	$11	Curcumin	$59	Budesonide	$574	Paxlovid	$206705
Alkalization	$11	Famotidine	$94	Nitazoxanide	$680	Bamlaniv	$301549
Zinc	$15	Probiotics	$99	Azvudine	$1248	Sotrovimab	$325800
Ivermectin	$25	Quercetin	$127	Favipiravir	$1934	Bebtelovimab	$737601
HCQ	$26	Metformin	$133	Tixagev	$74506	Remdesivir	$1558440
Colchicine	$26	Nigella Sativa	$187	Regdanvimab	$139860	Molnupiravir	$2400867

*The cost of an agent needs to save one life) for SARS-CoV-2 infection. Low-cost but low-efficacious agents were excluded (https://c19early.org/) [96].

4.9.2. Negative studies using ivermectin

Nevertheless, there were several negative studies using ivermectin. The TOGETHER study by Reis et al. (n = 679) reported no significant difference between ivermectin and placebo groups in the risk of hospitalization or emergency department visits for COVID-19 [224]. ACTIV-6 study by Naggie et al. used (400 μg/kg for three days) found no significant benefit with ivermectin compared to placebo on time to sustained recovery (defined as three consecutive days without symptoms) (hazard ratio 1·07, 95 %; CI 0·96–1·17.

Nevertheless, TOGETHER [224] and ACTIV-6 [225] RCTs that failed to demonstrate significant benefits of ivermectin had major design errors and potential bias, raising doubts about the validity of conclusions (https://c19ivm.org/). Similarly, the COVID-OUT study by Bramante et al. (n = 1323) initially reported no effect from ivermectin, metformin, or fluvoxamine [226]. However, later analyses suggested a notable reduction in hospitalizations exceeding 50 % [227].

Nevertheless, some evidence on ivermectin in preventing SARS-CoV-2 infection is contradictory [214,215,227–230]. In contrast, well-designed trials with no conflicts of interest showed substantial benefits [11–13,215,217,231]. These conflicting findings underscore the importance of careful independent interpretation and further investigation. Based on local research, ivermectin has been approved and used widely in over forty countries to prevent and treat SARS-CoV-2 [229].

Some of these negative studies were placebo-controlled RCTs. These have been used in a few systematic reviews and meta-analyses that reported equivocal outcomes [214,216,228,229,232,233], and from large, placebo-controlled outpatient trials conducted in the USA (COVID-OUT and ACTIV-6 (two trials, both evaluated 400 μg/kg for three days [226,227], and ACTIV-6, additionally evaluating 600 μg/kg for six days [230], and TOGETHER study, 400 μg/kg for three days [224]. However, subjects in these studies were heterogeneous, and critical study group characteristics like vaccination status and comorbidities (e.g., high BMI) were not comparable, and for unknown reasons, higher in the interventional groups [226]. None of the RCTs mentioned above reported any safety concerns regarding ivermectin.

The Cochrane Reviews encompass all negative studies, including those with significant study design flaws, which dilute potential benefits from investigational agents, such as ivermectin. This selection bias phenomenon is not unique to ivermectin but has also been observed in previous Cochrane reviews evaluating other agents. It underscores an inherent limitation of Cochrane reviews.

Inference: Despite a few negative studies, primarily employing improper doses in late-stage disease, the overall data strongly support positive clinical outcomes when ivermectin is used in the early stages of COVID-19 (early therapy) with appropriate doses. Both vitamin D and ivermectin are low-cost, readily available generic agents that have been shown to have no adverse effects at recommended doses [200]. In many countries these generics are available as over-the-counter without prescriptions. Therefore, these treatments should be made available and accessible for prophylactic use and as adjunct therapies against SARS-CoV-2.

4.10. Consensus on vitamin D and ivermectin—implications for mRNA vaccines

A summary of expert consensus from c19early.org highlights the website as a comprehensive resource providing data from all published clinical studies (positive and negative) on various therapies combating SARS-CoV-2 [96]. The site distinguishes itself as a reliable, dynamic real-time meta-analysis, offering an evolving overview of collective findings. Additionally, it presents calculated evidence on the cost-effectiveness of multiple treatments, incorporating NNT metrics to save one life. The website elucidates the cost-effectiveness of each intervention in terms of US dollar expenditure per life saved, offering valuable insights across diverse therapeutic approaches (Table 1).

As detailed in previous references, the reported negative studies remain below 10 %. These negative studies consistently revealed significant shortcomings in their study designs and flawed statistical methods used [79]. Therefore, such flawed studies should not be included in meta-analyses. Metanalyses of treatments demonstrated a high level of significance ($p < 0.0000000001$), with an overall true efficacy (not *relative* efficacies as reported with COVID-19 vaccines), approximately 50 % in preventing hospitalizations and deaths for each mentioned agent [96]. Sufficient cost-efficacy and safety data supporting these treatments were available by late 2020, which warranted regulatory and approval for clinical use, but never materialized [79].

In contrast to the documented safety issues related to mRNA vaccines [51,234], vitamin D and ivermectin exhibited decades of safety and efficacy (used over billion doses) in managing infections during the pre-pandemic [235–237], and post-pandemic era [238–240]. Despite their established efficacy and safety track record, western health authorities opted for experimental methods with little safety data, influenced by lobbying from the pharmaceutical industry. These contributed to suppressing evidence that supported early treatments with generics that could have saved lives and reduced ICU occupancy and healthcare costs. NIH analyzed vitamin D for COVID-19 and concluded there is insufficient evidence to recommend it [241]. This 2024 update from the NIH is despite 316 clinical trials published, including over 50 RCTs. However, it conveniently overlooked 86 % of the published RCTs but selectively included failed studies, suggesting a significant selection bias that invalidated its conclusions.

Inference: Regulators did not consider alternative approaches to COVID-19 vaccines and antiviral agents for the reasons mentioned above. Relaxation of patents related to mRNA vaccine technology and allowing raw material availability during the early COVID-19 emergency would have permitted countries like India and China with well-established traditional vaccine technology to facilitate developing vaccines in larger-scale at a significantly lower cost.

Despite taking longer, adopting conventional vaccines would have significantly reduced production costs, allowing simultaneous global production at an affordable cost and increased availability of COVID-19 vaccines. It provided the opportunity to thoroughly investigate mRNA technology for its safety and efficacy independent of Pfizer and Moderna companies and test for a broader range of viral antigens before generating and widespread deployment. Considering the serious adverse effects [49,50], and the inability of mRNA vaccines to prevent infections and the spread [2,3,48,49,59,67,91,92,173,174], funding and focusing only on mRNA vaccines may have been an error made in hasty.

5. Discussion

The mRNA and adenoviral vector vaccines were developed only against the Spike protein sequences of SARS-CoV-2 [18]. The bivalent vaccines combined sequences of the original viral RBD sequences and Omicron mutants [105,225,242]. In both instances, the immune recognition was limited to specific regions of the RBD within the Spike protein, excluding core proteins. Consequently, this resulted in the absence of secretory antibodies and mucosal immune protection, allowing spreading of SRS-CoV-2. Ongoing mutations in the Spike protein allowed new variants to evade host immune recognition by neutralizing antibodies, thereby facilitating immune evasion [83]. In addition, booster doses caused immunoparesis, further weakening the host's immune system [164–166]. Collectively, these increased the vulnerability to SARS-CoV-2 infections and re-infections [173], and re-activation of dormant viral and bacterial infections with a secondary flare-up of infections.

Consequently, despite mass vaccination programs covering approximately 5.6 billion people globally, predominantly from industrialized (affluent) countries, hospitalizations and deaths from SARS-CoV-2 and its mutants continued, though at a lower rate. The latter was due to the natural cycle of viral adaptivity and not due to healthcare interventions. Despite expectations to reduce infection and infect others, vaccinated people with mRNA COVID-19 vaccines failed to prevent SARS-CoV-2 infections and viral dissemination. Due to the changing characteristics and behavior of mutant viruses led to immune evasion. The efficacies of the original mRNA and bivalent vaccines against the original SARS-CoV-2 virus and Omicron variants became less than 40%—closer to a placebo by late 2022. Nevertheless, COVID-19 vaccines and boosters were continued to propagate despite less effective and having unacceptably high incidence of severe adverse effects.

As a result, there was a growing need to expand the arsenal of cost-effective agents for prevention and treatment beyond COVID-19 vaccines and antiviral therapies, particularly in anticipation of emerging dominant SARS-CoV-2 variants, and potential future viral pandemics. Over 4500 early treatment clinical studies have been published involving various agents, using many already approved globally and repurposed generic drugs authorized by regulators. Among these clinical studies, 320 have investigated vitamin D, and 105 have examined the use of ivermectin, both are available without a prescription. Despite the availability of compelling clinical studies and randomized controlled trials (RCTs) published in databases [96], demonstrating the cost-effectiveness of vitamin D and ivermectin, regulators continued to overlook them, even to date. Meanwhile, a few conflicted publications sponsored and funded by pharmaceutical companies (e.g., Together, ACTIV-6, COVID-Out, etc.) attempted to discredit the efficacy of these generic agents. The details of these clinical studies are publicly available on the website https://c19ivm.org/meta.html.

Other advantages of these generic agents is their broad-spectrum efficacy against other pathogenic microbes encompassing bacteria, viruses, and parasites, potent anti-inflammatory effects, coupled with their long-established safety record. Unlike COVID-19 vaccines and patented antiviral agents, the effectiveness of these non-proprietary early therapies remains unaltered by viral mutations. With declining efficacy observed in all COVID-19 vaccines and the limited effectiveness and significant adverse effects associated with antiviral agents, regulators and health agencies must promptly evaluate the mentioned widely available, non-patented agents. This assessment should occur preemptively, before the emergence of new dominant variants or the onset of another pandemic.

In parallel, medical societies, scientific organizations, hospitals, and insurance companies should integrate these generic agents into their formularies for the benefit of the public. Scientists and guideline makers must follow science and write and propagate clinical guidance without bias, based on recent publications. Besides ensuring the availability of these highly cost-effective treatments, they must be included in public healthcare guidelines as first-line adjuvant therapies. So that healthcare persons can start these adjunctive therapies on the first encounter with exposed or symptomatic persons. Furthermore, the lessons learned from managing the COVID-19 pandemic should be widely disseminated on websites such as WHO and the US government's CDC, accessible free of charge to the public. This is yet to be materilze. Other resources should emphasize avoiding the errors associated with developing COVID-19 mRNA vaccines and discouraging further use of mRNA technology. Instead, efforts should explore new platforms for developing vaccines using traditional, whole virus-based approaches.

6. Conclusions

The original COVID-19 vaccines effectively reduced hospitalizations but faced major challenges during winter outbreaks, leading to increased hospitalizations and mortality. Adequate vitamin D is critical for most human immune functions, including post-vaccination adaptive immunity. Individuals with low 25(OH)D concentrations have compromised immune systems and have less robust immune responses after vaccination, increasing their susceptibility to infections. Besides, COVID-19 mRNA vaccines predominantly target SARS-CoV-2 Spike proteins, providing limited antibody protection.

Moreover, mRNA-based COVID-19 vaccines provide no mucosal immunity, thus failing to prevent virus transmission. Additionally, mutations in the receptor binding regions of the SARS-CoV-2 viruses allow Omicron mutants to evade immune detection by antibodies. Besides, repeated bivalent vaccine boosters weaken the immune system and increase vulnerability to infection and re-infection. Consequently, exclusive reliance on COVID-19 vaccines to control outbreaks became ineffective. In contrast, Spike protein mutations do not impact the efficacy of repurposed, already approved generic, widely available early therapies like vitamin D and ivermectin, thus remain effective. Regulators should consider approving them as cost-effective adjunct therapies, and health organizations should make them available to address emerging variants and enhance vaccine efficacy in future epidemics and pandemics. Timely implementation of the actions mentioned above has the potential to reduce morbidity, mortality, and healthcare costs, providing a rational, cost-effective approach without serious adverse effects of medications for future outbreaks and pandemics.

Funding

None.

Ethical approval

Not applicable.

Ethics statement

This study does not have issues related to ethical aspects.

Availability of data and materials

Data is included in the article/supp. material is referenced in the article.

CRediT authorship contribution statement

Sunil J. Wimalawansa: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The author declares no conflicts of interest. The author did not receive any funding or writing assistance.

Acknowledgments

The author appreciates the input from Drs. Athula Polonowita and Maneesha Weerasooriya.

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