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The Impact of Withholding Cost-Effective Early Treatments, such as Vitamin D, on COVID-19: An Analysis Using an Innovative Logical Paradigm

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Abstract

Purpose: While numerous widely accepted nutraceuticals lack randomized clinical trial (RCT) validation, regulatory bodies prioritize RCTs as the primary evidence for testing hypotheses for drug approvals. Despite challenges in authorizing generic therapies for SARS-CoV-2, regulatory bodies promptly granted Emergency Use Authorization for patented agents. This study evaluated whether the clinical trial data yielded adequate evidence to justify the approval of generic compounds, like vitamin D, as adjunct therapy to combat SARS-CoV-2.

Methods: We employed an ancient logic system, seamlessly integrated with modern scientific principles and artificial intelligence principles, to analyze empirical data from 7 papers published in 2020. Subsequently, we compared the results with over 200 scientific papers (including over 100 treatment studies) referenced in a large (big)database. This study aimed to determine if there was substantial evidence in 2020 to support the approval of generic agents such as vitamin D (and ivermectin) for treating COVID-19.

Results: The drug approval process undervalues well-designed observational studies, placing them in a subordinate position to RCTs when assessing effectiveness, even for nutrients. Our utilization of Catuskoti, an innovative logical method, highlights its potential as a catalyst for scientific progress, including big data analysis and integrating artificial intelligence into nutrient and pharmaceutical approval processes.

Conclusions: Analyses conducted within this logical framework affirmed a robust inverse correlation between vitamin D levels and positive clinical outcomes in COVID-19 cases. Emphasizing the broader adoption of Catuskoti logic, particularly in analyzing big data and Machine Learning paradigms, becomes crucial in drug approvals. This approach aims to mitigate harm to individuals in future pandemics by promptly providing a more comprehensive understanding of the relationships between variables.

Keywords: 25(OH)D; 1,25(OH)2D; Epidemiological studies; Pandemic; Randomized-controlled clinical trials; SARS-CoV-2

1. Introduction

The new respiratory virus, SARS-CoV-2, was first detected in Wuhan, China in November 2019. Within two weeks, China warned the world and was able to isolate the viral genome by mid-January 2020 [1]. The first scientific paper regarding the efficacy of an agent, vitamin D, as an essential effective remedy against the virus was published in February 2020 [2].

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During the first few months of the onset of the COVID-19 pandemic in 2020, leading Western health authorities and governments advised against using facemasks [3,4]. They recommended against early, generic therapies like hydroxychloroquine and ivermectin [5,6]. Despite scientific evidence and potential advantages (e.g., wide availability, lack of adverse effects, and economical use), health authorities discounted effective generic agents—early therapies—like vitamin D and ivermectin against this virus [7,8].

At that time, with the experience with the SARS-CoV-1 epidemic in the early 2000s [9] and SARS-CoV-2 from February 2020 onwards [2,10-12], there was considerable knowledge and published scientific evidence on handling the latter disease and the significant benefits incurred from vitamin D sufficiency in controlling respiratory viral infections, including for coronaviruses [13-18].

1.1. The decision-making process for COVID-19-related drug approvals

Decision-makers have ignored the available published data and knowledge for approval of medications, including those previously approved agents for other purposes—repurposed agents—like vitamin D and ivermectin, as early therapies. Nevertheless, regulators promptly approved patented agents, like COVID-19 vaccines, anti-viral agents, and monoclonal antibodies under the Emergency Use Authorization Act (EUA). This disrupted the proper testing of hypotheses, unbiased experimentation, and the free exchange of scientific ideas.

Furthermore, it was a prevalent practice among journal editors to dismiss scientific manuscripts without subjecting them to review by peers, who held critical perspectives on decisions made by prominent health authorities or those highlighting the adverse effects of patented agents approved for COVID-19. Some manuscripts faced rejection with the explanation that their publication would have a detrimental impact on vaccine uptake. This practice persists to the present day. Simultaneously, specific peer-reviewed papers that were critical of vaccines or anti-viral agents or presented evidence of the benefits of generic agents, such as ivermectin or vitamin D, were compelled to withdraw [19], citing reasons unrelated to scientific merit [20].

The term "lack of evidence" is frequently employed to justify the non-approval of generic agents and by authors of systematic reviews and meta-analyses who inaccurately conclude that the mentioned generic agents are ineffective. Meanwhile, regulatory bodies insisted on randomized controlled trials (RCTs) as the sole acceptable evidence for drug and nutrient approvals. This stance persisted despite over 15 positive RCTs published in 2020 (and beyond) for vitamin D and ivermectin effectively controlling SARS-CoV-2 infection [21]. Additionally, more than 20 prospective observational and ecological clinical studies provided substantial evidence that a remedy (or nutrient) was cost-effective and devoid of adverse effects at the recommended doses in combating the rapidly spreading SARS-CoV-2 in 2020.

The EUA-based Fast-track mechanism was provided for developing, testing, and approving vaccines and anti-viral agents [22]. Despite the availability of RCT and other clinical study data for generic medications, regulators failed to approve any of them. In late 2020, vaccines were launched against the SARS-CoV-2 virus with a couple of RCTs for each vaccine, with a special exemption. The preferential status provided under the EUA includes taking shortcuts, relaxing immediate- and longer-term toxicity testing, and other adverse effect studies like genotoxicity using new experimental methods [22]. This article focuses on vitamin D as an example to verify the validity of hypotheses based on the published data available in 2020 to prevent and treat SARS-CoV-2 infection.

1.2. Evidence versus Proof

The initial reactions of health authorities to the COVID-19 pandemic spurred numerous write-ups, categorical statements, and newspaper articles that both praised and criticized them [23]. These writings underscored a lack of logical consistency—challenging the credibility of mainstream media and medicine without sufficient justification and raising concerns about the undue influence of pharmaceutical companies on health agencies and governmental decision-making. As a result, from the early stages of the pandemic, even laypeople could discern the contradictory claims made by health administrators and the inherent ambiguity in their approach.

Evidence and *proof* have different meanings, the former being empirical and the latter a logical conclusion. In science today, concepts such as "necessary and sufficient," excluding confounding factors, generalizability, repeatability, and convergence of evidence to support or refute scientific hypotheses are taken for granted. However, from a logical perspective, the origins of those concepts and the support for their use are not readily evident in the Western sciences, despite the belief that Francis Bacon initiated it in 1620 CE [24].

Bacon [25] was the first European to advocate for the inductive method—the importance of empirical data before inference. However, no evidence indicates that he used that method to develop any logical system. He developed the idea of lists and columns to evaluate causation, allegedly giving rise to the experimental approach. Kant, Popper, and later European philosophers placed logic or deduction ahead of empirical observations. Kant was explicitly influenced by the religious dogma of the day, whereas Popper's appeal to the logical refutability of experiments was more subtle [26,27]. Kolmogorov linked the axioms of probability theory to Boolean logic [28] but did not realize the goal of a complete logical system linking to induction and experimentation beyond statistical tests.

Thousands of years before the common era, the ancient Indian tradition of science and logic expected that one must always start with an empirical fact before making any deduction. It was accepted that a deduction without empirical fact is necessarily invalid. Further, Indian schools of thought considered other forms of knowledge, such as analogy and authority; however, Buddhist scholars rejected both as superfluous. Buddhist preachers and philosophers in that era (2,500 years ago) confined themselves to the empirical (e.g., cause-and-effect) evidence, and deduction was taken in sequence as the appropriate procedure to validate knowledge.

However, a theory of knowledge was present before the emergence of Buddhist logic. The evidence of the philosophy of science of the era from 600 BCE can be gleaned from multiple Buddhist texts, which show the evolution of a series of ideas of Indian and Asian origin. From the sixth-century BCE to the sixth-century CE, three key concepts were developed in Buddhist literature and discourses. The thoughts arise from a paradigm that logically parallels (empirical) practices of ancient Indian and modern science and this paper discusses those putative logical connections to the scientific approach below.

2. Material and Method

2.1. Three Ancient Logical Methods for Making Inferences as a logical base for science

Although the definition of what is considered logical may not always be delineated, numerous medical and scientific arguments focus not necessarily on establishing complex truths but on upholding the validity of beliefs centered around simple linear causation. However, complex dynamics such as equilibria and vicious spirals were often overlooked. What is needed is a more reliable and robust definition of logic that enables readers (scientists) to think beyond conventional boundaries and adopt perspectives that encompass more than just linear relations. In this context, three logical foundations form a paradigm for analyzing a scientific process.

2.1.1. Catuskotic as a unique and innovative logic in science

The principle underlying Dignaga's trilemma, Indian inference, and Western logic share a foundational principle based on dichotomies, simplifying logical arguments. Experiments and deductions become more straightforward by applying the principle of excluded middle. In contrast, Catuskoti introduces complexity by involving a tetralemma. However, this can be conceptualized as an intersection of two dichotomies, potentially leading to iterations that create a more robust error-correcting mechanism in science than a singular paradoxical approach.

2.1.2. The Importance of Catuskoti Logic (quasi truth-functional) to inference

Notably, the second dichotomy of Catuskoti (A and not A and neither A nor not A) is the dual logic of excluded middle (either A or not A—Figure 1). That dichotomy provides the empirical context required to validate the latter reasoning (i.e., logic). Without such validation, one could use inference (or deduction) to make conclusions without referencing empirical evidence. Thus, although statistical inference permits increased precision, the context imposed by Catuskoti leads to valid conclusions. Both validity (accuracy) and precision are fundamental goals in seeking scientific truth. The example of vitamin D levels discussed below concerning COVID-19 illustrated that concept, whereas opposing views are opinions depending principally on inference.

Figure 1 (I) shows the nature of the fourfold logical system that gradually evolved in India in the second to first-millennium BCE, starting from a basic binary logic of excluded middle to the form shown in the sixth-century BCE [Catuskoti (tetralemma) found in Buddhist literature].

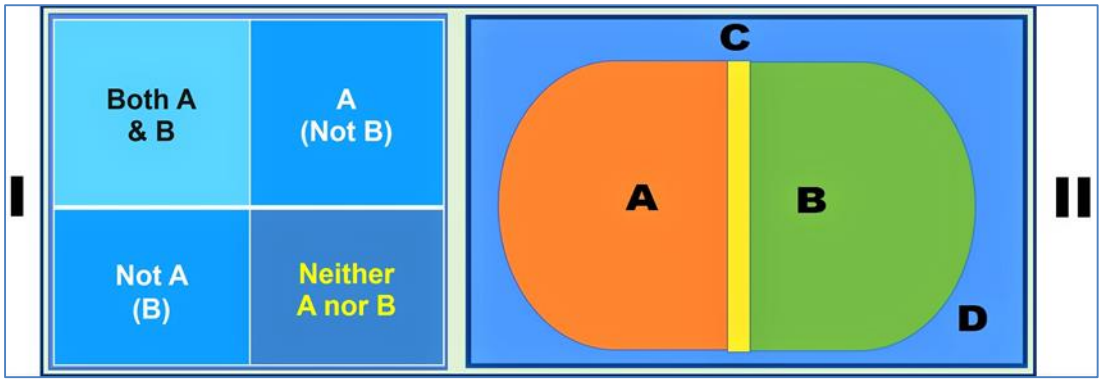

Figure 1 (I) The tabular form of Catuskoti (tetralemma) in Buddhist literature takes the form of the options A, not A (here depicted as B), both A and not A, and neither A nor not A. Here, B, identified as not A, is not the same as the not A in Boolean (binary) logic, which would be all things that are not A. However, B here means either the absence of A or the presence of something other than A, which is either opposite or complementary (thus, items in category B are limited). In contrast, the universe of other possibilities is in the lower right cell (equivalent to the blue section D in the diagram on the right). (II) Diagram of Catuskoti: A, B (not A), C (both A and not A represented by the capsule containing A and B), D (neither A nor, not A). A and B form an exclusive OR (X-OR) relationship. In contrast, C and D include their logical complement (X-NOR) (adapted from [29,30]).

The above figure is the classic Buddhist tetralemma, developed by the time of Siddhartha Gautama, codified as Catuskoti by Nagarjuna (~150–250 CE) [31,32]. It provides examples in *Brahmajala* and other *Sutta* [31,32]. This form of logic is applied to any phenomenon, whether for a dichotomy (A and not A) or alternatives (A and B and neither A nor B). Such is considered a mutually exclusive and exhaustive set [29,30,32,33].

Catuskoti logic may be applied parallel to machine learning, introducing more complex quantum-like logic. Instead of using one type of error-correcting gate (e.g., XOR), if two complementary gates (XOR and XNOR) are used in a recurrent network (e.g., neural), it could enhance the yield (both accuracy and precision) in machine learning by combining hardware and software incorporating Catuskoti like logic [34].

2.1.3. Dignaga's Identity (Correlation) versus Causation

Later, India's sixth-century Buddhist logician Dignaga (480–550 CE) derived a mutually exclusive, exhaustive set of logical relations regarding "Cause and Effect" relationships. Dharmakirti provided the proof in *Nyaya Bindu Tika* (seventh-century CE) [31]. It was developed to analyze empirical knowledge logically.

In that logical system, in contrast to Catuskoti (which was logically related to the existence of phenomena and their error-free identification), the logic used was a separation of phenomena and their relationships, considering that such associations occur according to three conditions:

- At a given instant, the relationship here could only be between similar phenomena classified as logically the same by convention, known as identity (cf. Aristotelian categories and quantum entanglement).
- A relationship between different phenomena at different instants is defined as causation.
- Negation—either classification of objects by identity is false, or an inferred causative relationship is false—and both could not be true at any instant [31].

2.2. Indian Form of Logical Inference

As discussed above, the Catuskoti logic for assertions about the existence of phenomena and the *Dignaga trilemma* of relations form a logic (reason) in which necessary and sufficient (universal) claims are likely to be based on (inductive) observations. Buddhist inference for oneself (based on earlier Indian systems) also involved the following approach concerning premises in an assertion: its

- Presence in the subject of the inference (the quality or phenomenon A),
- Presence in similar instances (generalizability) and
- Absence in dissimilar cases [31].

The above is the logical equivalent of the design of an empirical experiment. Ancient Indians in the Buddhist era were aware of such empirical investigations, evident in *Pyasi sutta* of the Tripitaka [27,35]. The preceding rules for inference are based on empirical observation first, thus compatible with modern experimental (empirical) science.

The three mentioned logical approaches—Catuskoti, followed by Dignaga's trilemma and the Indian approach to inference—form an analytical algorithm (or heuristic) that could guide scientific practice, as shown in Figure 2. Those logical templates could serve as a link between logic and the examination of the validity of empirical hypotheses as follows.

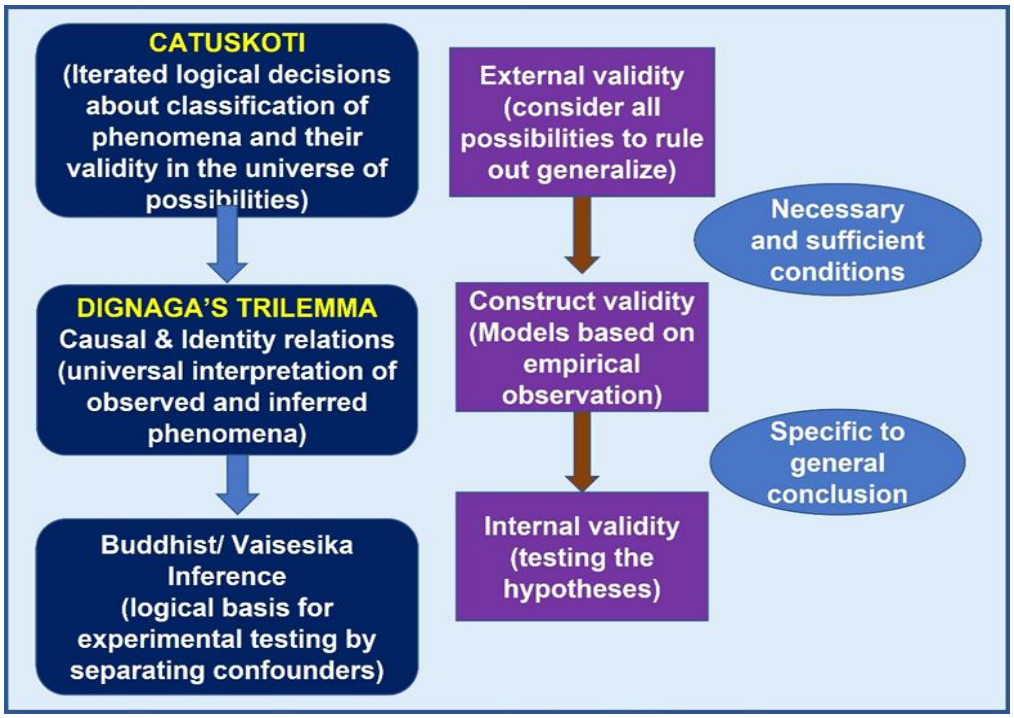

Figure 2 Cascade (a flow diagram) form of Ancient logical systems with Catuskoti (iterated classification of phenomena) and Dignaga's trilemma (causal and identity relations with negation), used sequentially to develop a model of necessary and sufficient conditions. That step is followed by a binary inference (logical base for experimental testing—the A and B in Catuskoti) to guide validation and generalizability. However, the analytical systems appear to precede empirical application here. The logical conclusions are based on previous empirical findings. The logic here is used mainly as an error-correcting mechanism.

Catuskoti permits an iterated examination of multiple possibilities or alternate explanations compared to a primary hypothesis. The primary hypothesis is binary (A or not A). However, the complementary logic (A and not A or neither A nor not A) helps examine alternative hypotheses, an essential part of modern science. The last logical assertion, neither A nor not A, means that entirely different phenomena of confounding factors may also need to be considered.

Logically, the perfect examination of confounding factors would involve the universe of all possibilities. In practice, scientists choose from the most likely confounders. Catuskoti permits further extension by examining the relationship of confounders to the primary factor. So, any confounder could be promoted to A and other members promoted to not A, generating a hypothesis that evaluates the relative contribution of each to an outcome. For example, the mathematical equivalent of such logic would be multiple regression analysis or decision trees.

2.3. Elaborations on Logical Methods

Elaborating on the factors leading to susceptibility to COVID-19 (the disease, not the cause), one would see that the immediate causes are both SARS-CoV-2 viral infection—the (viral)load, directly and indirectly, overwhelmed or weakened the immune system. In contrast, other possibilities must be relegated to "other factors" in part D (as illustrated in Figure 1-II). As part of a further iteration, vitamin D deficiency could be considered an immediate cause (dependency) of low immunity (part A). In contrast, all other susceptibilities could be promoted (from part D to part B) to consider whether they lead to low immunity without vitamin D (i.e., severe vitamin D deficiency).

Dignaga's trilemma offers the concepts of categorical (identity) and cause-and-effect relations, as well as "space and time" constructs for modeling and explanations, thus serving as a logical basis for the construct validity of a hypothesis (Dharmakirti suggests the relationship of space and time to identity and Causation in *Nyaya Bindu Tika*). One could explore various hypotheses, including those designed to explore a question about categories (e.g., variables and nomenclature) or a causal question. That approach covers the universe of possibilities in empirical science in space and time. Any developed construct or explanatory model is based on those constructs. Applying Dignaga's trilemma ensures that such scientific hypotheses are grounded in an empirical base.

Inference for self allows one to logically construct an experiment assessing the index hypothesis against the alternative (e.g., null hypothesis). Doing so provides the logical basis for the internal validity of a putative hypothesis and its relationship to statistical testing; this is clarified below. Thus, the aforementioned logical constructs create an underlying cognitive base for designing experiments and analyzing results and are a form of error correction against any bias that may otherwise creep in.

In addition to providing logical error correction, two analytic methods (Dignaga's trilemma and inference for self) use the logic of excluded middle. They are thus suitable for the development of hypotheses that could be subject to modern statistical error correction. This involves precision but could only lead to accurate conclusions if there is a valid logical basis and empirical evidence. There is a danger that statistics could be used to give precise evidence using data with no scientific validity due to a lack of empirical scientific evidence backing it.

In contrast, Catuskoti is a logic that incorporates Boolean logic (of the excluded middle) but has added complexity to it. Hypotheses generated by it cannot be subject to typical statistical methods but can potentially be addressed by machine learning methods; this was covered in an accompanying article [36].

2.4. Potential errors in the model of determinism and assumption of universal truths

Even if one entertains the idea that, in a conditional empirical world, it is possible to experiment with glimpsing the underlying reality using correct logic, such exploration becomes unattainable within the framework of determinism, rendering both free will and empirical experiments irrelevant [27,37]. Regrettably, the European logical tradition, which places assumed universal truths above empirical observations in the form of laws of nature, endured beyond the European Enlightenment [27,37].

Establishing universal truths within the empirical realm is inherently challenging. Instead, the mechanism employed involves probability, internal validity (through error reduction and enhanced covariance), and statistical analysis to discern cause-and-effect relationships or identities. This statistical approach helps avoid type I errors (rejecting the null hypothesis by chance) and type II errors (failing to reject the null hypothesis due to insufficient statistical power). While standard statistics suffice when dealing with large effect sizes and stringent experimental controls, such luxuries are often unavailable in emergencies like a rapidly spreading pandemic.

Despite the challenges, various statistical methods were developed to assess the probability of "cause-and-effect" findings in naturalistic settings, including techniques such as propensity score and coarsened exact matching [38,39]. Inferential statistics, like multiple regression analysis, also enable the reasoning of causal relationships, even in retrospective studies with multiple correlations. It is crucial to recognize that these statistical tests, based on null hypotheses, are not conducted in isolation. As such, the interpretation of results should be contextualized within the framework of domain expertise and other supporting scientific evidence.

2.5. Statistical Paradigms and Evidence-Based Medicine

Within the paradigm of evidence-based medicine (EBM), designs and methods employed in naturalistic settings are conventionally considered inferior to randomized controlled trials (RCTs) [40]. However, in practical terms, scientists seek repeatable and converging evidence from various perspectives to establish a cause-and-effect relationship, enhancing external validity through generalizability. The influence of determinism and the concept of universal truths may have inadvertently affected EBM. Proponents might unconsciously have believed that absolute precision (associated with determinism) and prediction through deduction or a close analogy (such as RCTs) are equivalent to the best evidence.

Moreover, if an independent explanatory model grounded in other separate experiments or studies exists, providing construct validity, the validations described thus far can collectively contribute to a form of proof. This overall validity

is inferred through convergent validation. However, it is essential to note that precise measurements derived solely from deduction and lacking empirical context may not necessarily be considered valid.

In this context, the validity is derived from both the empirical context and the existing body of scientific knowledge. If a strong connection is absent or tenuous, deductions should be accepted with skepticism, and statistical precision based solely on them may hold little value. Contrary to the notion that RCTs offer unequivocal evidence or proof, it is crucial to recognize that no randomization or RCT is flawless and that empirical methods are essential. Even when subjected to straightforward statistical methods, a degree of error is associated with randomization procedures [35].

Recognizing the fallacy of considering RCTs as inherently superior involves acknowledging that no perfect universal truth is ever "proved" or exists in science. While idealized experiments assume optimized study designs, RCTs provide a certain degree of certainty but fall short of the precision found in controlled physical or biological experiments. They do not establish universal truths and are subject to various constraints. Drawing on Buddhist logic, the algorithm proposed earlier functions as a logical template for cognitive error correction and integrated statistical methods for mathematical error correction. It serves as a guide for decisions regarding the results of both naturalistic and prospective studies, treating them equally. This approach referred to as the Nalanda paradigm for brevity, pays homage to Dignaga, who resided at Nalanda University in India.

3. Results

3.1. Vitamin D Deficiency as an Explanation for Susceptibility to COVID-19—A Base for Logical Analysis

First, the costs of supplementation with vitamin D and calcifediol were considered. Locations for generating calcitriol—intracellularly, in peripheral target cells—need to be considered regarding its mechanisms and efficacy for prevention and using vitamin D as an adjunctive therapy [41,42]. The circulating hormonal form of calcitriol generated in renal tubular cells is crucial for musculoskeletal activities and calcium/magnesium metabolism [43,44]. However, calcitriol circulates in the blood in picomolar concentration: it does not enter extra-renal target cells, like immune cells [45,46], to affect their biology and physiological functions [47,48]. Therefore, immune cells' autocrine and paracrine signaling depends on the intracellular generation of three orders of magnitude higher concentrations of calcitriol in peripheral target cells [42,47,49].

Calculating the costs of intervention must include the economic cost (cost of intervention of a drug or a nutrient), opportunity costs, and cost of investigations and managing adverse effects. Vitamin D_3 has been proven safe, even at high doses of 15,000 IU/day [50,51], 20,000 IU/day [88,89], 50,000 IU/per week [46], and single high doses (but not repeat doses) up to 500,000 IU[115] (ESPN guidelines), which are reported devoid of demonstrable adverse effects [46]. Vitamin D is economical; treating a person costs less than $2/person [52] and, on average, $8/person/year for prophylactic use [53].

In persons with vitamin D deficiency, the reported effect sizes and the efficacies of this nutrient supplementation are high, with virtually no adverse effects, and the costs are exceedingly low. Therefore, the cost-benefit ratio is high for vitamin D. The potential benefits of vitamin D in infections, specifically COVID-19, are discussed below [54,55]. Based on the published data available in 2020 discussed here, the evidence of the capacity of vitamin D to prevent the acquisition of SARS-COV-2 could have been "proven" in 2020. These data also confirmed that vitamin D deficiency is a cause for developing complications from SARS-CoV-2, fulfilling Bradford Hill's criteria for causality [56].

3.2. Cost-Benefit Ratio in Treatment Decisions—Application of Catuskoti logic to a contingency

The cost-benefit ratio could be turned into a simple iteration of Catuskoti logic in which A and B are separate logical constructs (whether a substance is beneficial and should be given or not given). Catuskoti's logic could be applied to a contingency table similar to that used to determine false positive and false negative rates in research and machine learning. Here, the cost (benefit or harm) of giving (or not giving) a substance could be considered logically complementary from the Catuskoti perspective (one dichotomy is classification, and the other a causation paradigm).

Here, the first logical dichotomy is whether a substance is beneficial. If beneficial, the following dichotomy, give or not give, is recursively (one step) iterated with it. Thus, it would be equivalent to accepting that the substance is beneficial (i.e., A and B in Catuskoti); neither A nor B would be not to do anything given no benefit. However, to give (B) when there is no benefit may carry variable harm (that would be small if any harm is considered negligible). Furthermore, not giving when there is a benefit (A) would be catastrophic (Table 1).

Table1. A only (not being given) could lead to a catastrophe (risk huge); B only (given despite not being safe) to some harm (risk small if harm is negligible); not A and not B causes no harm (risk nil) – do nothing; A and B lead to significant benefits (risk is nil due to no harm)

	Benefit (A)	**Harm (not A)**
Given (B)	Great benefit (A and B)	Small risk (B only)
Not Given (not B)	Catastrophe (A only)	No risk (neither A nor B)

Thus, the underlying logic in the contingency table is Catuskoti. Even this one-step iteration displays the logical recursion (between perception and action) that could occur in a mammalian brain. The benefit of giving an efficacious drug with little harm far outweighs not taking the risk of giving an ineffective one with little harm. If the efficacious drug is not given, then the harm is immense (a huge risk). This logic appears natural to any human being. Here, we have provided a rigorous logical framework for such natural logic.

The risk/benefit ratio for giving a harmless drug with minimal evidence at established doses is far lower than that of not giving this drug, given the possibility of its benefit. With vitamin D in mid-2020, the evidence of potential benefit was not just minimal. Both statistical significance and effect size were good and repeatedly found. However, once it is given and the benefit manifests beyond doubt, it would minimize bringing up objections on purely deductive grounds, which is unscientific and unethical. Having used Catuskoti to demonstrate the logic of using vitamin D if there was a chance of it being effective, the evidence for this in mid-2020 can be examined. This evidence came from 7 studies around the world.

3.3. Correlations between Circulating 25-Hydroxyvitamin D and Clinical Outcomes

As highlighted, statistical tests provide a means to assess the inherent validity of inferences drawn from these observations. The consensus across various regions globally, employing diverse study designs, strengthens the external validity of the hypothesis that vitamin D deficiency or insufficiency heightens susceptibility to viral infections, including SARS-CoV-2 infection [57]. These converging findings are reflected in Table 1.

Among the studies discussed, three yielded significant results indicating a relationship between vitamin D level and mortality, while one UK study reported no association. The UK study's failure to demonstrate lives saved is attributed to its improper study design, involving a large bolus dose of vitamin D, and the lack of statistical power due to a small sample size and multiple flawed study designs. In contrast, the study from Iran affirms a statistically significant association with mortality, as depicted in Figure 3.

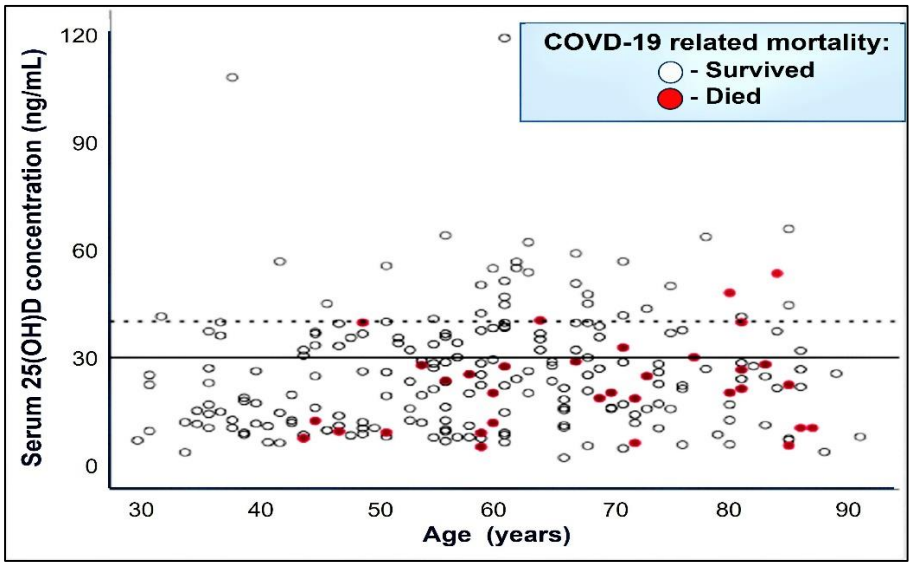

Figure 3. Scatterplot comparing vitamin D level with mortality. Deaths are depicted in red, and the dotted line indicates a vitamin D level of 40 ng/mL (100 nmol/L) (reproduced from Maghbooli et al. [58]).

Three studies (Chicago, Israel, and Iran) evaluated the effect size regarding odds ratio and presented relative risk. The Spanish research performed a post hoc analysis, which provided statistical power for infection risk but not for severity because of the small sample size. The Iranian study gives a relative risk level (1.59) for severity but only the significance for mortality.

3.4. Hypovitaminosis D Significantly Increases Susceptibility to COVID-19

The most robust finding is for susceptibility to infection in the two more extensive studies (Chicago and Israel), which give stratified vitamin D levels for both patient and control groups without COVID-19. The relative risk for infection in the Chicago study is 1.77, and the Israeli study showed an odds ratio for deficiency (1.58) and insufficiency (1.59). Combining data from both studies yields an odds ratio of about 1.5 to acquire COVID-19 for subjects with vitamin D serum levels below 30 ng/mL (i.e., the new definition of vitamin D deficiency) compared with the initial findings.

The results of all study designs converge on an inverse relationship between vitamin D levels (insufficiency/deficiency) and susceptibility to COVID-19, which implies a causal relationship (plausible, consistent, temporal). For the internal validity of the inference that vitamin D deficiency causes vulnerability to the acquisition of COVID-19 and its severity, one can consider the significance and effect size (strength) associated with the results of those studies in 2020. All meticulously designed and conducted studies showed statistically significant evidence that vitamin D deficiency is strongly associated with an increased risk of COVID-19 infection.

3.5. Vitamin D sufficiency reduces hospitalization and deaths from COVID-19

Using hospitalization as a measure of severity and adjusting for confounding factors, the Israeli study failed to show a significant statistical result yet with an odds ratio of 1.95 for the vulnerability to SARS-CoV-2 infection and vitamin D deficiency. That outcome may be due to a relatively small proportion of hospitalized patients (<10%). Given confounding factors such as age, the study may not have had enough numbers in each group to reach significance (a type II error). Thus, despite a trend showing that vitamin D deficiency leads to a more severe infection with SARS-CoV-2, including increased mortality [46], robust evidence indicates that deficiency is associated with an increased risk of infection with increased odds of more than 50% [59,60].

All clinical studies except two (Meltzer et al. [98] and Merzon et al. [40]) collected blood for vitamin D estimates during admission: consistently, they showed significantly low serum 25(OH)D concentrations. That finding raised the possibility of reverse causality (i.e., vitamin D level reduced by the infection). That “reverse causality” merely implies a vicious spiral and is not a good argument against vitamin D supplementation. It is also now known that infections consume vitamin D; thus, unless supplemented, the levels will continue to decline, further aggravating the situation [46,48].

However, the two larger studies mentioned earlier and the epidemiological study discussed below used 25(OH)D concentrations measured “before “the infection and at the time of hospitalization, demonstrating a significant hypovitaminosis of enrolled study subjects [57]. Overall, the effect sizes for all studies mentioned above are comparable, indicating that the measured vitamin D level represented the prior levels and was not caused by the infection (i.e., minimal effect from reverse causality).

3.6. Vitamin D sufficiency prevents the vulnerability to SARS-CoV-2

An extensive epidemiological study from the United States confirmed the above assertion [57]. It showed a significantly reduced infection rate, between deficient vs. adequate levels (risk reduction of 35%; with a 50% increased risk of infection in a deficient subject than that of those with sufficient vitamin D level [defined in that study as 30 ng/mL or 75 nmol/L)] [57]. It also reported an additional 27% risk reduction between adequate and having higher levels of vitamin D. Subjects with elevated levels of 25(OH)D over 55 ng/mL (or 137.5 nmol/L) had 50% less risk of getting infected, compared to deficient subjects (see Figure 4). The study also explored the increased risk of infection for African Americans and those with a darker skin color living in northern latitudes.

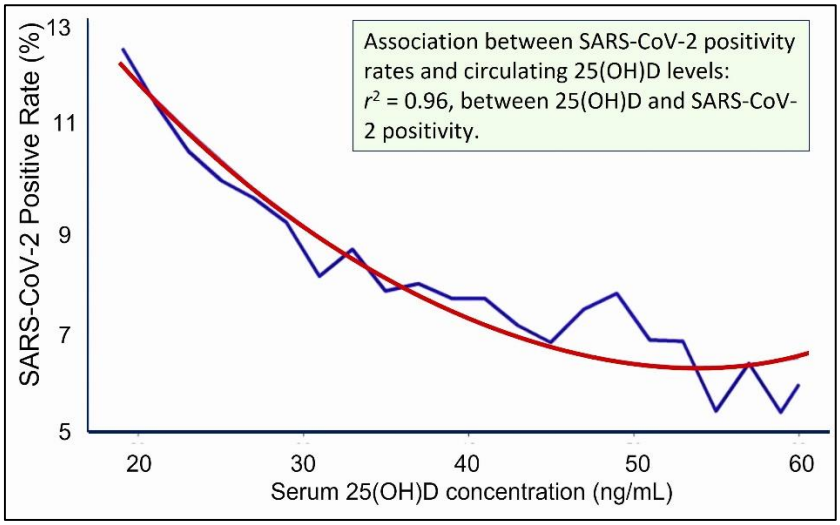

Figure 4. Relation of SARS-CoV-2–positive rate and serum 25-hydroxyvitamin D [25(OH)D] concentrations in the World Health Organization study population (weighted second-order polynomial regression fit to the data). The smooth line is a second-order polynomial fitting the data: (unadjusted odds ratio = 0.979 per 1-ng/mL increment, 95% confidence interval, 0.977–0.980) (reproduced with modifications from Kaufman et al. [57]).

The study utilized vitamin D levels from a database, introducing a temporal separation between the measured 25(OH)D level and COVID-19 susceptibility. Given its extensive scale, the study provided a substantial effect size, reinforcing the assumption that acute hospital samples represented past vitamin D levels and mitigating the possibility of reverse causation. However, it is important to note that infection under these circumstances might have still caused a rapid escalation due to a potential vicious spiral.

3.7. Later studies in 2020

As with naturalistic or retrospective studies, clinical studies with greater power (larger samples) have not been able to look more closely at the severity of COVID-19 associated with 25(OH)D concentrations. Studies in hospital settings also have yielded statistically significant findings of vitamin D deficient patients having a higher prevalence of severity and mortality from SARS-CoV-2. Performing post hoc power analysis on those studies may be worthwhile, considering the robustness of the severity and mortality findings.

There were two dozen vitamin D/COVID-19-related papers published in 2020. Two of these assessed the inference of vitamin D insufficiency as a cause of susceptibility, further advancing the knowledge. The first was a quasi-experimental study from France [61], and the other was a prospective experimental design from India [62]. Both confirmed the hypothesis that vitamin D deficiency increases the vulnerability to poor clinical outcomes in COVID-19, including increased mortality, with the former ensuring a treatment effect.

Many studies have emerged since 2020 and are outlined in https://c19early.org/dmeta.html [21] and briefly covered in the discussion. The relationship of confounders to vitamin D may also alter the significance, which will be addressed next. Based on published data in 2020, one can conclude that internal validity exists for the association between vitamin D insufficiency and COVID-19 susceptibility. Table 2 summarizes these results.

Table 2. Studies exploring vitamin D's impact on COVID-19 [ITU, intensive treatment unit; N/A, unavailable or applicable; OR, odds ratio; RR, relative risk].

N **(Location) Ref.**	**Vitamin D measured Sample(s)**	**Deficient <20 ng/mL**	**Insufficient, 20–30 ng/mL**	**Sufficient >30 ng/mL**	**Statistics, Effect Size, and Significance**
107 (Swiss), D'Avolio et al. [63]	107	PCR^+ (*N* = 27) 11.1	PCR^- (*N* = 80) 24.6		Mann–Whitney *U* Power N/A $p < 0.004$
134 (UK), Panagiotou et al. [64]	134	ITU, 81% (19% >20 ng/mL)	Non-ITU ward 39.1% (60.9% <20 ng/mL)		Student *t*-test, Mann–Whitney *U* Power N/A $p < 0.02$
413 (Spain), Hernández et al. [65]	216 patients, 197 community control	Hospital, 13.9 82.2% deficient	Community, 20.9 52.8% "sufficient"		Student *t*-test Power for infection ~1.00 Power for severity, 0.4 $p < 0.0001$
611 (Iran), Maghbooli et al. [58]	235 patients	Mortality (20%) Severe disease (77.2%)		Mortality (9.7%, 6.3% with >40 ng/ mL) Severe disease (63.6)	Student *t*-test Mann–Whitney *U* $p < 0.04$ RR = 1.59 (severity) $p < 0.02$
4341 (Chicago), Meltzer et al. [59]	499	172 $COVID^+$ (32 = 19%)	143 $COVID^+$ (19 = 13%)	184 $COVID^+$ (20 = 11%)	RR = 1.77 $p < 0.02$
7807 (Israel), Merzon et al. [60]	782 (COVID-19 positive) 7025 (COVID-19 negative)	105 (13.4%) 915 (13.1%) Hospitalization Infection likelihood	598 (76.5%) 5050 (71.8%) Hospitalization Infection likelihood	79 (10.1%) 1060 (15.1%) Hospitalization Infection likelihood	Crude OR: Deficient, 1.58 ($p < 0.0002$) Insufficient, 1.59 ($p < 0.0053$) Adjusted OR: 1.95 ($p = 0.061$); 1.45 ($p < 0.001$)
191,779 (USA), Kaufman et al. [57]	191,779	39,190	27,870 30–34 ng/mL 12,321 >54 ng/mL N/A 20–30 ng/mL and 35–54 ng/mL Reduction in incidence of COVID-19 Deficiency vs. adequate, 35% Adequate vs. high, 27%		Polynomial regression OR = 0.979 per 1-ng/mL increment $R^2 = 0.96$ Student *t*-test and χ^2 $p < 0.001$ $p < 0.001$

3.8. Scientific Evidence that Model Vitamin D's Contribution to the Etiology and Amelioration of COVID-19 (Construct validity; as of 2020)

Sufficiently valid evidence exists for vitamin D deficiency as a cause of susceptibility to COVID-19. Then, one must consider possible mechanisms that could explain such susceptibility/exposure, for which multiple confounding factors could be considered risk factors. Aging and increased body mass index (BMI and higher percentage of body fat) contribute to vitamin D deficiency [i.e., low circulating 25(OH)D concentrations] [46]. They are associated with increased hypertension and cardiovascular diseases (thus associated with vitamin D deficiency) [46].

Independently of other factors, vitamin D deficiency contributes to several metabolic disorders, such as type 2 diabetes, insulin resistance, obesity, and metabolic syndrome [66,67]. Besides the genetic vulnerability, those confounding factors are not as proximal as vitamin D deficiency as a cause of COVID-19 and its risks for complications [68]. Infections such as COVID-19 in older persons and those with comorbidities synergistically increased adverse clinical outcomes and risk of death [236–240,244–246]. This is partly due to adverse effects on innate and adaptive immune systems, as seen in diabetes and neuroendocrine processes [69].

Beyond those factors, clinical outcomes of COVID-19 and other serious infections (e.g., sepsis) are significantly affected by infamm-aging and cytokine storms, driven by over-reactive renin-angiotensin-system (RAS) [70,71]. Low vitamin D activates the latter [72,73]. The likely final common pathway from these factors causing low immunity via vitamin D deficiency must be considered as an explanation.

The phenomena mentioned above help elucidate a disproportionately large number of COVID-19 infectious outbreaks and deaths within facilities for older people (e.g., group homes), developmentally disabled centers, and nursing homes. The residents in these facilities are typically older, often have multiple comorbidities, have a high incidence of low vitamin D and ACE-2 concentrations, and generally experience poor overall health [74].

4. Theoretical Analyses—Vitamin D and COVID-19—Later Studies and Meta-Analyses

4.1. Negative Studies and Study Design Errors

The only negative study from 2020 was published in early 2021 [75] in addition to having inadequate and imbalanced controls and a single high-dose vitamin D treatment given in the late stages of critically ill COVID-19 patients. When this trial was conducted, it was known that a person in the late stage of the disease would not respond to vitamin D, and irrespective of the dose, it is inappropriate to use late therapies. Knowing that it could harm subjects, this RCT with major study design errors should not have been approved by the Institutional Review Board and should not have been used in meta-analyses. Vitamin D takes, on average, three to four days to hydroxylate into 25(OH)D (a rate-limiting step) and be released into the circulation [46].

In those who are acutely ill, as in intensive care unit (ICU) patients, it takes more than a week to raise the circulatory levels of 25(OH)D [42]. Therefore, vitamin D will not help acutely sick patients, irrespective of the dose, as in the ICU set-up. Instead, they should have used partially activated vitamin D, calcifediol [76-78], which increases the serum 25(OH)D within four hours [79,80] and boosts the immune system within a day [81].

Therefore, the failure to respond favorably was not due to the administered initial (high) loading dose of vitamin D but the failure to understand the biology of vitamin D [82] (more discussion in section 3.3). Had the authors used partially activated vitamin D, calcifediol (instead of vitamin D) [41,76,77,83,84], the study would have had a positive outcome—yet still not as good as if that treatment had been administered early in the disease [42]. For more information from 2020, see vdmeta.com, which lists all published studies (positive and negative) using vitamin D, calcifediol, and other early therapies in COVID-19 [21]. A total of five negative studies out of over one hundred and fifty clinical studies on vdmeta.com shared two characteristics:

- Enrolled subjects with advanced COVID-19 (i.e., late-stage disease, as with most ICU patients, where vitamin D would not benefit due to biological reasons).
- Failed to use calcifediol as soon as possible, which acts within 4 hours of administration and boosts the immune system [42].

This vdmeta.com meta-analysis [21] shows that 85% of all studies report a positive effect of vitamin D use, and 93% show a positive impact on vitamin D sufficiency (at least 75 nmol/L or 30 ng/mL). In comparison, all early treatment studies were positive. Overall, an estimated 38% improvement occurs because of vitamin D use (enough before infection

or acute treatment). For sufficiency studies, the gain increases to 55%, indicating that prophylactic supplementation is valuable and cost-effective.

Cui and Tian [85] used an insensitive Mendelian randomization (MR) technique for nutrients to assess how vitamin D concentration affects COVID-19 susceptibility. Some researchers use the MR method as a shortcut (as an alternative for RCTs, particularly for observational studies), as randomization potentially could be simulated on existing larger genetic databases.

One example is using an allele that makes half the Japanese population sensitive to alcohol because of an enzyme deficiency [86]. The single-nucleotide polymorphisms associated with vitamin D were derived from a genetic database without clearly expressing an empirical causal link between the genome and the phenotypes associated with vitamin D deficiency, thus, susceptibility to the presumed clinical outcome. That was a significant weakness of the paper by Cui and Tian [85]. Further, vitamin D supplementation in the vulnerable population may have reduced group statistical differences. That outcome must be further anticipated as a problem because the odds ratios were similar for all examined outcomes. Such results are likely to be due to instrumental error. Hastie and colleagues [87] used UK Biobank data and concluded that vitamin D levels did not contribute to COVID-19 outcomes, but despite critique of the method (88) and refutation by a study on the same database (90), Hastie et al. continued to use inappropriate deductive means (statistics adjusted for related confounders) to minimize the effect found in their 2nd study (89).

4.2. Meta-Analyses: A Contrast between Negative and Positive Findings and Study Design

In addition to the studies listed at vdmeta.com, nine other published meta-analyses were reviewed. Two had negative conclusions regarding the association of vitamin D deficiency with COVID-19 [92,93]. Of the other seven, Shah and colleagues [94] systematically reviewed meta-analyses [95-98].

The five papers above, including Shah and colleagues [94], reported a significant association between the recommended supplementation and improved clinical outcomes related to acute vitamin D treatment. All positive meta-analyses [95-98] looked at pooled data from a moderate number of studies. Negative meta-analyses [92,93] divided studies into four groups of about three each. According to common-sense and Jackson and White [99], using several small studies reduces the statistical power and the validity of using a normal distribution.

Further, in all meta-analyses using tools to grade "quality and bias," most papers are classified as poor or moderate. Therefore, the validity of studies or instruments used to classify retrospective studies should be questioned. Also, one meta-analysis (Chen et al. [92]) wrongly identified that the population sample of Hastie and colleagues [87] accessed about 350,000 of the UK Biobank data but missed the fact that the actual patient sample size was only 449 [87]. Contribution from Kaufman and colleagues' large epidemiological study [57] could have been diluted by a relatively small negative study identified with a large sample size.

5. Applying Logical Proof to Vitamin D in COVID-19

Considering costs and benefits and evidence of vitamin D status in both vulnerability to and amelioration of COVID-19, it is now possible to use the Nalanda paradigm to examine such empirical evidence.

5.1. Logical Assertions in Making Clinical Decisions

The following logical assertions are illustrated in Figures 2 and 5:

- All confounding factors will be placed in part D of the Catuskoti diagram (Figure 1 (II)). Such factors as aging, obesity, diabetes, and having dark skin are not the immediate causes of susceptibility to COVID-19. Instead, those factors are all associated with vitamin D deficiency. Logically, then, using identity relations described by Dignaga, those confounding factors are identified with vitamin D deficiency.
- Low innate immunity and the SARS-CoV-2 virus could be considered in cells A and B in Catuskoti. Both A and B (i.e., C) cause COVID-19, which could be deemed necessary and sufficient (universally) for developing COVID-19 and its complications.
- Identification of vitamin D as the primary pre-existing confounder could now, under Dignaga's causation relation, be considered the immediate (or most proximal) cause of low immunity. So, vitamin D deficiency and insufficiency are associated with poor COVID-19 clinical outcomes in various settings worldwide. This further supports and provides evidence that an epidemiological study practically represents a universal assertion.

After observing the results of the preceding studies, as an experimental design under Buddhist/Vaisesika inference, it is possible to assert that vitamin D deficiency is significantly present in nearly all groups who develop severe COVID-19 disease (see Table 1). Such deficiency is remarkably absent in those with no evidence of infection [63,100], and those with sufficient levels had a significantly lower incidence and severity [57,58,60,64,65,68,100-103]. Therefore, it was necessary to assert sufficient proof that vitamin D deficiency is a significant cause of vulnerability to COVID-19 and that appropriate sun exposure or vitamin D should have been used as a supplement public health approach for prevention. Such reasoning would have permitted immediate actions (rather than disregarding early therapies like vitamin D) and avoided adding to the mistakes made during 2020. Here, the empirical evidence is primary, and deduction is subordinate.

Having shown the proof using the Nalanda paradigm, one could explore the modes of early adjunctive treatments that could have been used during the COVID-19 pandemic. It is very likely that, if left to make decisions without political constraints, clinicians would have come to the same conclusions without even being aware of the logic of the Nalanda paradigm. As an accompanying paper demonstrates, the Nalanda Paradigm provides a rigorous logical basis for how science is usually practiced [36]. The case was made that this logic is natural for human brain functions and should be used in big data analysis using Catuskoiti tetralemma [36]. Further clinical considerations could be made based on additional scientific data for preventative supplementation and vitamin D as an active adjunctive treatment for COVID-19.

5.2. The evidence available for regulatory approval of nutrients or generic agents

The evidence base for vitamin D deficiency as a cause of COVID-19 susceptibility since 2020 has been primarily extended, albeit with limitations. The evidence base for using vitamin D indicates that pretreatment to raise blood levels and the advantage of early treatment (as opposed to late treatment) with doses of vitamin D higher than that currently recommended (and/or calcifediol) is an essential strategy in using the agents effectively [42,81]. Yet many studies ignore such basic facts and use faulty study designs. Despite these limitations, a prominent online meta-analysis of vitamin D and COVID-19 has analyzed published data from 2020 to 2022 and has confirmed our conclusions based on the evidence available in 2020 (https://c19early.org/dmeta.html).

The mentioned large meta-analysis demonstrates an overall 36% improvement when combining prevention (33%), early treatment (69%), and late treatment (47%) with vitamin D_3 (cholecalciferol) or calcifediol [25(OH)calciferol]. It further extends the trends demonstrated in the 2020 publications that the severity and mortality rate are both diminished by vitamin D sufficiency. A random sample of papers in this dataset was critically examined: despite design faults, the significance and effect sizes quoted by the meta-analysis are valid [46].

In acute situations (emergencies), as in critical clinical trials and hospital situations, calcifediol should have been used rather than calcitriol because of the rapidity of its actions (i.e., within 4 hours) and the ability to boost the immune system within a day [42,46]. Based on the biology and physiology of vitamin D metabolites, calcitriol is useless in emergencies like SARS-CoV-2 infection and vitamin D [42,81]. Using calcitriol by Elamir et al. [104] and the use of vitamin D (instead of calcifediol) irrespective of the dose, in seriously ill patients, as in ICU by Murai [75] and others are illogical and expect no benefits.

As illustrated in Figure 5, the pooled statistical data on statistically significant beneficial effects of vitamin D (prevention and treatment) was available to the regulators and public by late 2020. Unlike with vaccines [105,106], the major benefits of over-the-counter vitamin D did not fade away against COVID-19 [107] (Figure 6) [108-112]. As a result of acquired immune resistance by Omicron variants via modified Spike proteins, their immune characteristics significantly deviated from the original SARS-CoV-2.

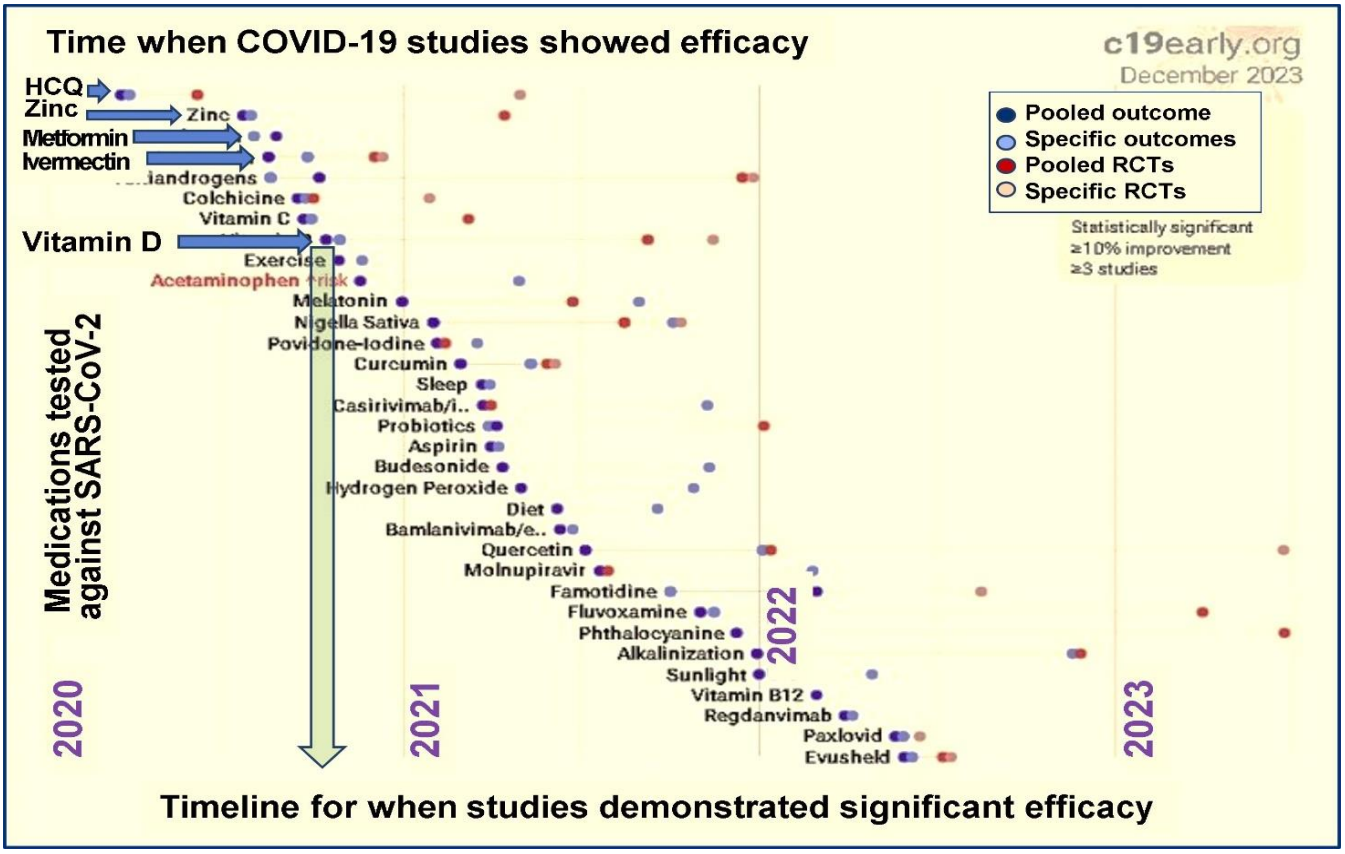

Figure 5: Graphical representation of evidence of the initial reported benefits of various tested agents (depicted on the vertical axis) for SARS-CoV-2 over time (shown on the horizontal axis). Blue arrows indicate, from top to bottom, HCQ (hydroxychloroquine), zinc, metformin, and vitamin D. The vertical green arrow highlights the timeline that underscores vitamin D's substantial clinical outcomes (as per pooled and specific studies and RCT) in the prevention and treatment of COVID-19. Descriptions corresponding to the colored circles are presented in the figure's upper right corner.

In contrast, this had no negative effects on vitamin D and ivermectin. However, the immune evasion capabilities against mRNA and adenovirus vector-based COVID-19 vaccines [113,114], and anti-viral agents [115] markedly reduced the efficacy of all COVID-19 vaccines against the SARS-CoV-2 [108-112]. Consequently, vaccine-derived adaptive immunity failed to prevent new infections and increased re-infection incidence, especially after repeated bivalent booster doses that caused immunoparesis [108-110],[111,112]. Despite more than 70% of the population being vaccinated and boosted with COVID-19 vaccines, it led to breakthrough infections and re-infections [116,117].

To further reinforce the logical conclusion based on the papers that were available early in pre-print servers by July 2020, the chart above demonstrates the timeline for standard statistics to confirm the efficacy of vitamin D. As can be seen, the pooled statistical confirmation occurred in late 2020 while confirmation of acute treatment by RCTs emerged about a year later. The former demonstrates that logical confirmation based on visual perusal of data could occur temporally earlier in sequence to statistical confirmation. During this pandemic, there were logical reasons to try vitamin D both as a prophylactic and an acute treatment in 2020. Considering approximately 25 clinical research publications available by late 2020, by the time the last of these papers (Hernandez et al.) was published. Still, it was unavailable to us earlier—all 25 reported favorable clinical outcomes.

Further, the site c19early.org/dmeta.html did not list one study D'Aviolo, until much later (109th position), despite its availability in a pre-print server in 2020. In this context, we have emulated what would have been available to clinicians in mid-2020 in real time and believe that it was sufficient to reach valid conclusions confirmed statistically within a few months. A few months could make a significant difference in an emergency.

6. Discussion

This manuscript examined evidence that vitamin D deficiency is a key (proximal) cause of susceptibility to COVID-19, developing complications, and death [56]. In this study, published evidence using a heuristic based on ancient Buddhist logic interpretations was tested. Using that logical template allowed us to clarify the context of what logic could offer in medical sciences.

Vitamin D sufficiency is a straightforward reason why people in tropical countries and living outdoors have better survival outcomes during the COVID-19 pandemic despite poverty, being less nourished, and having little vaccination. That finding contrasts with clinical outcomes in people with darker skin who live in temperate countries with a high prevalence of severe vitamin D deficiency, particularly during winter when the viral respiratory illnesses peak. Chronic vitamin D deficiency impaired their immune systems, making them more vulnerable to contracting COVID-19 and developing complications, and dying from it.

As discussed above, such simple logic could relate to more complex modern mathematical techniques. Most scientists and health professionals are less familiar with the logic underlying these complex statistical and mathematical techniques. Thus, a simpler logic model may assist most people in critically examining complex research results. Research that lacks the contextual validity afforded by applying Catuskoti-like logic but uses statistics to justify conclusions without empirical scientific constructs should be suspected and demand caution about their findings and conclusions [36]. For vitamin D and SARS-CoV-2, statistical tests provided the internal validity of the studies analyzed. Studies with geographic diversity or representative samples were used to provide external validity (generalizable).

A theoretical model of vitamin D deficiency's contribution was used for construct validity. The basis of the Nalanda paradigm underlying those approaches was inference (specific application to vitamin D versus the null hypothesis), Catuskoti (generalizability of results by appropriate design and validation against alternate hypotheses), and Dignaga's trilemma (theoretical construct of a causal type), respectively. An easily understandable logical method was utilized to show the fallacy of denying remedies such as vitamin D and ivermectin during the pandemic. That approach was intended to expose possible economic and political factors that may have influenced the lack of affirmative decisions (i.e., the policies were either illogical or influenced by hidden vested interests or both).

Aside from the above discussion, this manuscript has sought to explain philosophical deficits in the conduct of modern science. Specifically, meta-analyses of studies using inappropriate design and statistical methods have tended to either dilute the effect of vitamin D (mixing early and late treatments, improper use of confounders correlated with vitamin D to statistically reduce vitamin D effect) or to entirely suppress vitamin D effect using ambiguous constructs (Mendelian Randomization) and inappropriate sampling (misidentifying sample size, using a fewer number of studies).

This manuscript has also revealed possible faults in standard Cochrane instruments of bias when applied to retrospective data. It highlights the potential inappropriateness of statistical bias measures without domain knowledge about a treatment (strict requirement of using vitamin D as early treatment and the rationale for using calcifediol). This cautionary tale emphasizes the risks associated with blind faith in established methods such as meta-analyses and Cochrane reviews. Similar to conflicted large health agencies and appointed scientific bodies, meta-analyses, and Cochrane reviews have also been found to exhibit various forms of significant bias.

While these methods were developed appropriately for testing the efficacy of standard pharmaceuticals in prospective designs, they fail when it comes to situations "outside the box." Such concerns have been highlighted in this paper using an alternate logical base. It is fitting that the logical base used included Catuskoti, which provided a complementary context to the standard excluded middle or XOR logic. Ignoring this context causes significant problems in modern science when reductionism (while helpful) has supplanted the context in which it is conducted. As a result, a linear, short-sighted approach pervades science.

There is a more ominous aspect of this blind faith in a linear reductionist approach without context awareness. Despite errors in analyses and approvals, authoritative sources continue to rely upon an outdated sufficiency level of vitamin D of 20 ng/mL and supplement doses (of less than 800 IU/day as suggested by groups such as IoM, USPTO, and NIH (USA), SACN and NICE (in the UK) [42,46]. Circularly, regulators used the above conjectures as another reason for not approving any non-patented agents for COVID-19. Although the EBM model was developed mainly to rigorously assess new treatment strategies [149], the drug industry exploited these for their advantage and marketing purposes [118] to suppress generics in favor of propagating patented drugs. Thus, a glaring contradiction exists between EUAs for proprietary drugs vs. non-approval of cost-effective economic, repurposed remedies, including vitamin D.

Applying a consistent logical base to scientific practice makes the equivalence of prospective and retrospective studies easier to see as two sides of the same logical coin—complimentary. In retrospective or naturalistic studies, the applied logic should go beyond Boolean logic (law of the excluded middle) as standard statistical methods require. Utilizing novel machine learning methods such as deep neural networks and Catuskoti-type logic may be necessary to simulate data from naturalistic settings to confront the linear, Boolean thinking that leads to the current Western rejection of remedies that can be logically proven to be efficacious.

7. Conclusion

We applied a relatively straightforward heuristic that concludes that due to its low cost, substantial benefits, and high effect size, widespread vitamin D supplementation is needed, especially for vulnerable groups. Such should have been urgently contemplated to prevent COVID-19 and its complications, serving as an adjunct therapy. This recommendation is particularly relevant for regions at both northern and southern latitudes, developing countries, and those characterized by higher aging populations and ethnic minorities—groups that often have large populations with vitamin D deficiency. Various strategies, outlined below, could have significantly curtailed morbidity and mortality, lessened the strain on intensive care unit resources, reduced the overall COVID-19 case burden, and lowered healthcare costs, especially in developing countries:

A further advantage of such measures described above would have been suppression and possible elimination of the virus from a given population or the world and a rapid return to normality (not the alleged new normal), the supply chains, and the economy to usual. Instead of the unnecessary and burdensome lockdowns and curfews that ruined economies and livelihoods, movement limitations should have been restricted to local areas based on local outbreaks for shorter durations after assuring these communities of food, medical supplies, and water. Contrary to expectations, available data suggest that prolonged, widespread movement restrictions (lockdowns) have increased the prevalence of vitamin D deficiency and, thus, morbidity in the population. This has inadvertently heightened vulnerability to SARS-CoV-2 acquisition and viral spread, contributing to increased mortality.

Considering the emergence of new SARS-CoV-2 variants and anticipation of future epidemics and pandemics, exploring all possible methods to eliminate or suppress the virus is imperative. This includes fostering a resilient population through maintaining adequate vitamin D levels and enhancing local public health measures. As outlined above, the evidence supporting the potential effectiveness of these approaches seems to have been either overlooked or disregarded in 2020, 2021, and even 2022, possibly due to flawed logic and vested interests. It is hypothesized that the identified mistakes (and miscommunications) could have been rectified if a non-Boolean logic system, such as Catuskoti, had been applied within a Deep Learning strategy or other Machine Learning methods, utilizing the available Big Data by mid-2020.

Compliance with ethical standards

Disclosure of conflict of interest: No conflicts of interest are to be disclosed. This study did not receive funding from any sources, nor did it involve any writing assistance.

Author Contributions: Equal contributions from authors—both authors equally contributed to the manuscript from conceptual, designing, writing, and editing.

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