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Article

Logical Analysis of Response of Health Officials' Worldwide, to Cost-Effective Early Remedies for COVID-19

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Abstract: With the advent of COVID-19, the attitude of health authorities around the world, led mainly by the West, demanded a level of proof as evidence for cheap, non-patented remedies while promoting expensive, patented, and untested remedies by using emergency use authorization and special provisions afforded to the status of a pandemic emergency. Western science has neither a tested nor a valid historical basis of a logical system that informs to authenticate scientific practices. Here we use a logical heuristic derived from ancient Buddhist logic, which is consistent with the conduct of modern science. We applied the heuristic to show that enough evidence was available for using cost-effective early therapies such as vitamin D supplementation as a public health measure during the first half of 2020. Strong supporting evidence has since accumulated. Apart from political and financial decisions incompatible with science and other conflicts of interest, a critical barrier to evaluating and approving early therapies appears to be the fallacy that the randomized controlled trial (RCT) is the superior proof method in medical hypotheses, including those for nutrients. Logically, no reason exists why properly designed retrospective, ecological, and naturalistic studies with adequate sample sizes and applied appropriate statistical methods would not be as valid as RCTs, especially when elucidating a causative factor instead of treatment. That assertion is particularly true for nutrient deficiencies, interventions, and other cost-effective therapies. Leading health authorities' failure or refusal to consider other study types (because of either poor logic or vested interest) probably contributed to the spread of misinformation, symptomatic disease, complications, and deaths from COVID-19. Partial immunity derived from vaccines and the later development of more contagious variants—and thus a sense of acceptance that SARS-CoV-2 had progressed from a pandemic to an endemic—shows the hollowness of the initial promotions and mandates of vaccines as a cure. Adequate knowledge was available in 2020 to advise that SARS-CoV-2 will continue to mutate, with variants emerging a few times per year, making the vaccine less effective. Emerging evidence confirms that natural immunity better protects against new variants than vaccination against the spike protein. Had vitamin D been adopted as part of the public health measure through a broader supplementation program in 2020 or even today (through sun exposure or as a prophylactic or adjunct therapy early on), the viral spread and symptomatic disease may have been suppressed, with minimal lockdowns and quarantine, and economic harm. The pandemic could have been halted with a significantly reduced need for hospitalization, complications, and deaths, potentially saving millions of lives.

Keywords: 25-hydroxyvitamin D; 25(OH)D; 1,25(OH)$_2$D; immunity; pandemic; SARS-CoV-2; logic; cost–benefit; ivermectin; randomized-controlled trial; RCT; epidemiological studies; vitamin D

1. Introduction

Within months of the onset of the COVID-19 pandemic, several Western health authorities advised against using masks [1], recommended hydroxychloroquine (HCQ) [2,3], and discounted vitamin D supplementation's potential advantage as a defense

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against the virus [4,5]. This is despite the predicted major benefits of vitamin D sufficiency in controlling SARS-CoV-2 from February 2020 [6].

The common buzzwords used against and to discredit those economic, early intervention measures have been either alleged lack of evidence, RCTs, or potential (unknown) harm. Such responses had a chilling effect on free experimentation using available knowledge and approved medications for other purposes (i.e., repurpose agents). Some publications may have been suppressed, and others were forced to withdraw [7]. The catchphrase "lack of evidence" implicitly pointed to the belief that randomized controlled trials (RCTs) are the only acceptable standard of proof that a remedy was effective.

The situation was exacerbated by the development of vaccines against the SARS-CoV-2 virus. Western countries, media, and drug companies took center stage, a practice that continues. Special dispensation was given to the development and approval of vaccines under emergency use authorization (EUA)—a fast track for relatively new or experimental methods such as mRNA vaccines and new antiviral agents—while denigrating programs that pursued effective generic agents and vaccines. The critique of the latter may have been justified if not for the uncritical acceptance of the former, for which "lack of evidence" appeared not to apply. In the best-case scenario, the latter had only one or two RCTs per agent with biased data analyses.

Events after those decisions have shown the limitations of dependency on technology, biased decisions, and conflicts of interest, resulting in the failure to control the pandemic. Such contradictions between statements and results indicate significant underlying logical problems with the call for evidence (when empirical evidence already existed) among medical luminaries. They demand not evidence but some proof, an inference made without empirical evidence that could be susceptible to subjective bias.

1.1. Evidence versus Proof

The COVID-19 pandemic and health authorities' initial responses led to many writeups, including newspaper articles [8] pointing out their poor logic (a justified challenge to the credibility of mainstream medicine). Thus, even laypeople could see early on the contradictions in the mindset of health administrators (particularly their attempts to manipulate outcomes and take refuge in evidence). *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," exclusion of confounding factors, generalizability, repeatability, and convergence in seeking evidence to support or refute scientific hypotheses are taken for granted. However, the origins of those concepts and the support for their use, from a logical perspective, are not evident in the Western history of science, despite the belief that Francis Bacon initiated it in 1620 CE [9].

Bacon [10] 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 test causation, allegedly giving rise to the experimental method. 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 [11,12].

By contrast, 2000 years before, Payasi Sutta of the Buddhist Canon (using metaphor) described experimentation, indicating that the knowledge of the experimental method was familiar to the people of ancient India (herein referred to as Indians) [11]. That tradition involves evidence of the evolution of logic, mathematics, and scientific innovation congruently over a long period.

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. A deduction without empirical fact is necessarily invalid. Further, Indian schools of thought considered other forms of knowledge, such as analogy and authority:

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however, Buddhist scholars rejected both as redundant. Buddhist preachers and philosophers confined themselves to the empirical (e.g., cause-and-effect), and deduction was taken in sequence as the appropriate procedure to validate knowledge.

Thus, a pre-Buddhist theory of knowledge was established before the emergence of the Buddhists, 2500 years ago. The evidence of the philosophy of science of the era from 600 BCE can be gleaned from many Buddhist texts, which show the evolution of a series of ideas of Indian and Asian origin. Three concepts developed in Buddhist literature and discourse from the sixth-century BCE to the sixth-century CE. The ideas arise from a paradigm that logically parallels (empirical) practices of ancient Indian and modern science. We show those putative logical connections to scientific practice below.

1.2. The Three Logical Methods for Making Inferences

1.2.1. Catuskoti

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 Table 1 by the sixth-century BCE [Catuskoti (tetralemma) that Buddhist literature].

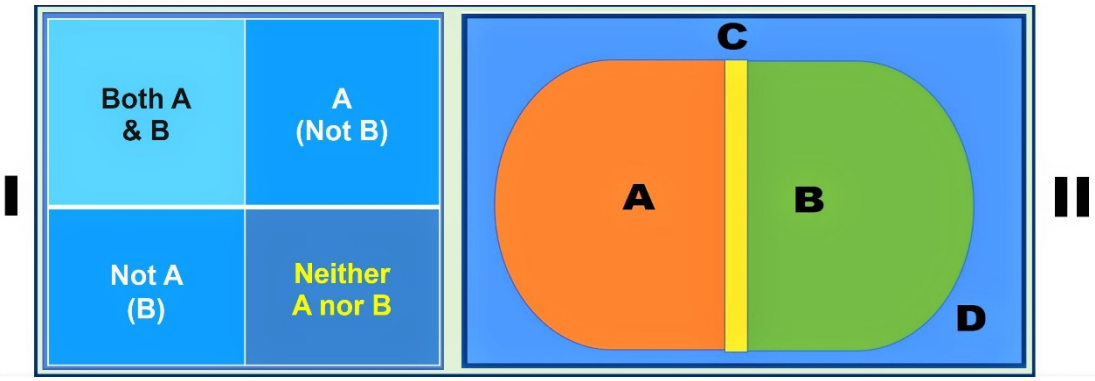

Figure 1. (I) The tabular form of Catuskoti (tetralemma) in Buddhist literature takes the form of the options A, not A (here depicted as B), both A and not A, and neither A nor not A. Here, B, identified as not A, is not the same as the not A in Boolean (binary) logic, which would be all things that 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 cell 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). **(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 form its logical complement (X-NOR), as shown in tables 1 and 2 (figure 1(II) adapted from [13,14]).

This is the classic Buddhist tetralemma, probably developed by the time of Siddhartha Gautama, codified as Catuskoti by Nagarjuna (~150–250 CE) [15,16]. It provides examples, particularly in *Brahmajala Sutta* [15,16]. That 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 [13,14,16,17].

Table 1. XOR error-correcting gate showing the equivalent of A or not A (B) but not both in Catuskoti. Here, vitamin D deficiency is "A" and other confounders are promoted from part D in figure1(II) to part B to test whether they lead to low immunity without vitamin D; either vitamin D deficiency or the confounder but not both should lead to low immunity, A⊕B = 1). Here, A⊕B is the symbol for XOR (exclusive OR).

A	B	A⊕B
0	0	0
1	0	1

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0	1	1
1	1	0

Table 2. XNOR error-correcting gate showing the equivalent of both A and not A (B) or neither A nor not A in Catuskoti. Here, A is SARS-CoV-2 load and B is innate immunity (inputs), and A = B = 1 gives a true output = 1 of susceptibility to COVID-19. In the example of vitamin D deficiency tested against other confounders (A = B = 0), those correlated with SARS-COV-2 as having an impact on susceptibility could be promoted to XOR to test against vitamin D as a cause of low immunity (output in the above XOR table). Thus, the potential exists to model a quantum machine learning paradigm with a theoretical capacity to simulate scientific hypothesis testing, given that XOR and XNOR are complementary and could be suitable as orthogonal axes for a vector space.

A	B	~(A⊕B)
0	0	1
1	0	0
0	1	0
1	1	1

1.2.2. 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. The proof was provided by Dharmakirti in Nyaya Bindu Tika (seventh-century CE) [15]. 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:

1. 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).
2. A relationship between different phenomena at different instants is defined as causation.
3. 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 [15].

1.2.3. Indian Form of Logical Inference

As shown earlier, the Catuskoti logic for assertions about the existence of phenomena and the Dignaga trilemma of relations form a system of logic in which necessary and sufficient (universal) assertions could be made based on (inductive) observations. Buddhist inference for oneself (based on earlier Indian systems) also involved the following approach concerning premises in an assertion: its necessary—

1. presence in the subject of the inference (the quality, or phenomenon A),
2. presence in similar instances (generalizability), and
3. absence in dissimilar instances [15].

The preceding rules for inference are based on empirical observation first, thus compatible with (empirical) science.

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

Catuskoti permits iterated examination of multiple possibilities or alternate explanations compared to a primary hypothesis. The primary hypothesis is binary (A or

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not A). However, the complementary logic (A and not A or neither A nor not A) helps examine alternative hypotheses: an important part of modern science. The last logical assertion, neither A nor not A, means that entirely different phenomena of confounding factors may exist that 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 a further extension by examining the relationship of confounders to the primary factor. So, any member of the confounders 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.

1.3. Elaborations on Logical Methods

Elaborating on the question of factors leading to susceptibility to COVID-19 (the disease, not the cause), one would see that immediate causes are both SARS-CoV-2 infectious (viral)load (A) and overwhelmed (or weakened) immune system (B), whereas many other possibilities would need to be relegated to "other factors" in part D (Figure 1-II). As part of a further iteration, vitamin D deficiency could be considered an immediate cause of low immunity (part A), whereas all other susceptibilities could be promoted (from part D to part B) to consider whether they lead to low immunity without vitamin D. The concept is further clarified using equivalent logic gates in Tables 1 and 2.

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

The inference for self gives the opportunity to logically construct an experiment in which one assesses 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 is clarified below. Thus, the three 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.

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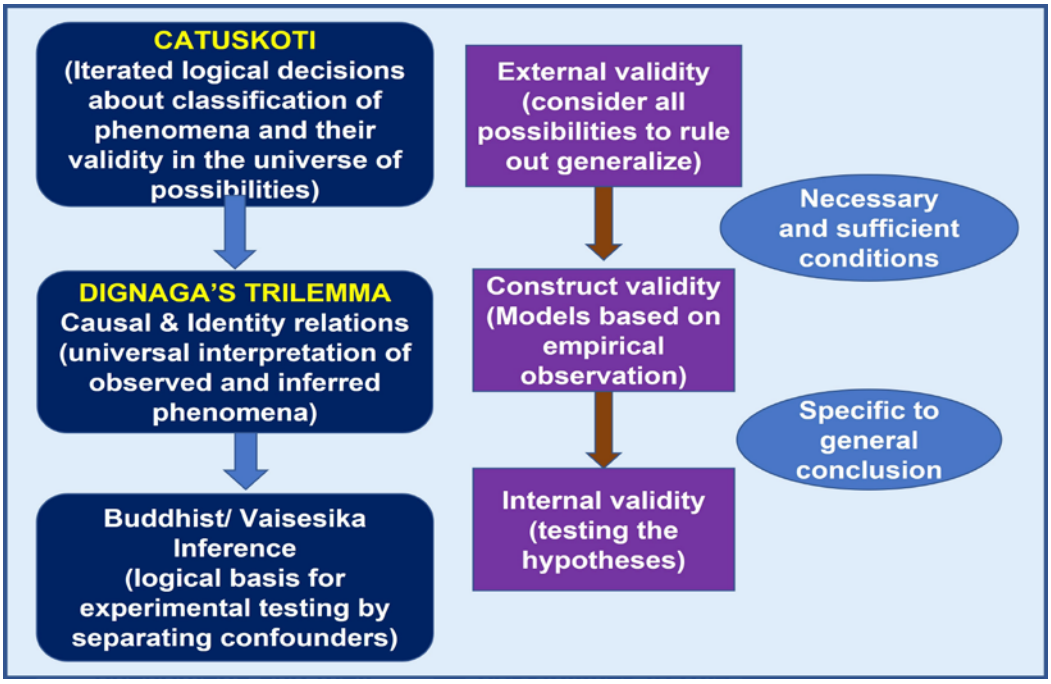

Figure 2. Cascade or flow diagram form of Buddhist logical systems with Catuskoti (iterated classification of phenomena) and Dignaga's trilemma (causal and identity relations with negation), which are used in sequence to develop a model of necessary and sufficient conditions. That step is followed by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

1.4.3. Relationship of the Preceding Logical Algorithm to Mathematics (Statistical Tests)

Whereas the described logical systems offer necessary templates for gross error correction, more precise endeavors (for example, engineering and science, such as navigation and astronomy) would demand more precise error correction involving mathematical techniques. Developments in trigonometry and calculus from the 6th to 16th Centuries CE in India are examples of using mathematics to increase the precision of error correction beyond logic [12,18]. Methods in statistics can be outlined analogously to the three logical systems.

First, statistical tests are generally applied to constructs that logically pose a binary problem (i.e., either A or not A, excluding the middle). Dignaga's trilemma and "inference for self" pose such questions. Regarding Dignaga's trilemma, which deals with the complementary realities of either correlation or causation, correlation coefficients provide initial statistical validation for a correlation. However, according to Dignaga, correlation means a form of classification under one identity and is antithetical to causation. Statistical correlation is not that clear. If a correlation is found, it could be due to identity or causal relation. The commonly used aphorism "correlation is not causation" exemplifies that ambiguity.

For two given temporally separated correlated variables, an excellent logical case can then be made that a causal relationship exists. The objection would, however, be raised that an intervening variable is present, which is the actual cause. Even so, the earlier variable would have a causal relationship even if it is not the most proximal. For the alternative of identity where one is looking for differences or similarities (of group membership), either standard statistics of difference between means or more complex methods such as cluster analysis could be used.

To deal with the issue of intervening confounders, one could use multiple regression analysis, which assesses the strengths of correlation of each of several putative causes while accounting for all others. Those statistical methods depend on the investigators'

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having already logically identified confounding factors and a temporal relationship [19]. For statistics using machine learning, in which the computer algorithm makes decisions about the choice of variables and their temporal relationships, Markov chains or processes can be used [20].

Concerning inference for self, again using binary logic, the statistical alternative usually involves reducing bias and variance between members of the same group and enhancing the variance between (usually) two populations. Examples are the Student *t*-test (for parametric data) and the chi-square test (for nonparametric data) or analysis of variance (sometimes using multivariate analysis) for more complex situations. Similar statistics also could be used to explore group differences for questions concerning identity (classification).

1.5. Catuskoti, Data Science, and Statistics

Catuskoti is the logic least susceptible to algorithmic treatment for statistical processes and requires logical iterating through multiple confounding variables. However, machine learning can use algorithms that deal with multiple variables and generate principal components. This statistical analysis aims to reduce bias (the equivalent of error or deviation from a population norm) and variance, which involves reducing the number of variables by leaving out highly correlated confounding variables.

The problem with the latter is that those essential variables may be disregarded in an analysis. In a later example, vitamin D is considered the proximal causal variable for reduced passive immunity and is the outcome of several other factors, which are confounded as risk factors for COVID-19. If one is unaware of this and applies the algorithm uncritically, vitamin D's importance may be diluted by the statistical technique. Thus, using Catuskoti logic, the investigator may already be able to use external knowledge of basic science to realize vitamin D as an essential variable. Besides, machine learning may have some remedies for missing important data [21]. Room may be available to develop the data science further so that Catuskoti logic could be incorporated into an algorithm.

A decision tree model is one possible strategy for incorporating Catuskoti logic into statistics and scientific data. One example is a random forest [22] with confounding variables as features to allow deriving a variable that may be the candidate variable to be tested in a hypothesis (that uses the logic of the excluded middle or Exclusive-OR). Decision trees make binary decisions and would be the equivalent of iterating through confounding factors in pairs. The method can be used for both categorical and numerical dependent variables. Further discussion is beyond this article's scope. However, decision trees are methods of validation in hypothesis testing and would be congruent with the nature of Catuskoti, which provides logical validity to conclusions of a hypothesis (elaborated later).

Considering the evident inclusion of XOR and XNOR logic within Catuskoti, a room may be available for using that logic to develop new neural network models. Neural networks use the nonlinear logistic function as the statistical procedure, which induces binary decisions in the network. It tries to simulate cortical function in terms of building the identity of a perceived item from simple categories into more complex formations [23]. The advent of the deep learning model in neural networks added another dimension, backpropagation, along with a mathematical concept, gradient descent involving derivatives [24]. Deep learning methods inherently improved algorithms in many modern processes, such as visual object recognition, speech recognition, complex problem solving, drug discovery, and genomics.

Deep learning discovers intricate structures in large data sets using the backpropagation algorithm [24], which is crucial for data analysis of evolving complex subjects such as new and repurposed agents for COVID-19 and their clinical outcomes. As indicated earlier, the origin of the calculus (infinite series) originally involved error correction. Deep learning then brings together three additional forms of error correction:

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binary logic, statistics, and calculus. Deep learning paradigms have been applied to the COVID-19 pandemic, but cost-effective early interventions such as vitamin D, ivermectin, and others have not been examined [25]. Particularly important when the dose-responses are nonlinear, as with nutrients, such as vitamin D.

Meanwhile, reasons exist to consider the mammalian cortex as representing dual or complementary functions in the left and right hemispheres [26]. Theoretically, one can use the dual logic gates of XOR and XNOR as analogies of left and right hemi-cortical functions and thus a suitable model for neural networks. Recursive loops between an XOR-based and an XNOR-based neural network may then obviate backpropagation but solve the challenge of the neural network purely as a forward propagation system. Gradient descent may still be used during the recursion between the two logic systems. We will show that Catuskoti logic functions as a pattern recognition error-correcting system, which is what neural networks do.

The connection between underlying logic and statistical precision can be developed, thus creating a chain of connection between empirical facts and stages of inference. That approach would increase precision in error correction, leading to conclusions, the validity of which is measurable (e.g., using statistical parameters). The difficulties with the practice of modern (Western) science are that its roots involve assumptions of universal truths (ignoring inevitable uncertainty in empirical observations) and adherence to deterministic models of reality, which rely on continuity (see below).

1.6. Potential Errors in the Model of Determinism and Assumption of Universal Truths

Even if we accept that we live in a contingent empirical world, by using correct logic, we can still conduct experiments allowing us to glimpse the underlying reality. Doing so is impossible in the epistemology of determinism, which makes free will and empirical experiments irrelevant [12,18]. Unfortunately, in addition to determinism, the European logic of placing presumed universal truths above empirical observations (in the form of laws of nature) persisted beyond European Enlightenment [12,18].

Universal truths cannot be established in the empirical realm. Instead, the mechanism used is the probability (or internal validity by reducing error and enhancing covariance) of a cause-and-effect relationship determined through statistics (avoiding type I error of rejecting the null hypothesis by chance and type II error of failing to reject the null hypothesis owing to inadequate power). Although the most detailed statistics are necessary when the effect size is large, and if strict experimental controls could be met, such luxury is not available often (in emergencies, such as in a rapidly spreading pandemic).

Nevertheless, appropriate statistical methods have been developed to measure the likelihood of cause-and-effect findings in naturalistic settings. Inferential statistics, such as multiple regression analysis, could infer causal relationships, even in retrospective analyses with multiple correlations. Such statistical tests (null hypothesis) of experimental hypotheses are not performed in a vacuum. The results must be interpreted in the context of other scientific evidence.

1.7. Statistical Paradigms and Evidence-Based Medicine

According to the paradigm of evidence-based medicine (EBM), the designs and methods used in naturalistic settings are considered inferior to those of RCTs only by convention [27]. In practice, scientists seek repeatable and converging evidence (from different perspectives) of a cause-and-effect relationship (external validity by generalizability). The specter of determinism coupled with the idea of universal truths may have inadvertently corrupted EBM as its proponents unconsciously fell for the idea that absolute precision (determinism) or a close analogy (here, RCTs) is equated with the best evidence.

Further, if an independent explanatory model based on other independent experiments or studies (providing construct validity) exists, the forms of the validation

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described so far form a sort of proof in that overall validity can be inferred through convergent validation (That precise measurement based on a deduction devoid of empirical context is not necessarily valid. Here validity is derived from the empirical context and the context of scientific knowledge already available. If such a connection is absent or tenuous, the deduction should be suspect with a statistical precision of little value.)

One could ignore the fallacy of RCTs' being superior by remembering that no perfect universal truth is ever "proved" in science. RCTs are idealized experiments (assuming optimized study designs) and afford a degree of certainty, but not to the extent of a controlled physical or biological experiment. RCTs do not purvey universal truths. The algorithm proposed above, using Buddhist logic, serves as a logical template (for cognitive error correction) and statistical methods to guide decisions regarding such results. That assertion is illustrated concerning the relation between COVID-19 and vitamin D levels. For brevity, this algorithm is referred to as the Nalanda paradigm in honor of Dignaga, who resided at the Nalanda university in India.

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

We first considered the costs of supplementation with vitamin D (converted into a powerful and essential compound, calcitriol, generated within cells in the body). While this sets the stage for considering questions regarding its efficacy for prophylaxis and acute treatment, mechanisms and locations for generating calcitriol must be considered. The overwhelming quantity of circulating calcitriol is generated within proximal renal tubular cells that are crucial for musculoskeletal activities and calcium/magnesium metabolism [28,29]. However, this picomolar calcitriol concentration in the circulation is insufficient to enter extra-renal target cells. Therefore, most non-musculoskeletal functions, as with autocrine and paracrine signaling of immune cells, are driven by a three-orders of the magnitude of calcitriol concentration generated within these cells [30,31].

When calculating the costs of any intervention, it 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 has been proven safe, even at high doses of 15,000 IU/day [32,33] (and is economical, costing less than $8/person/year) [34]. Thus, the costs associated with vitamin D supplementation are exceedingly low. In considering vitamin D's potential benefits, we discuss the following citations, which examine the impact of its deficiency on COVID-19. For comprehensive and critical reviews of the relationship of vitamin D to COVID-19 [35,36].

2.1. Vitamin D and COVID-19: Review of Crucial Papers Published in 2020

2.2.1. Inductive Evidence

This section outlines the evidence for the relationship between vitamin D deficiency and COVID-19 susceptibility in the first half of 2020. If approached logically, the evidence would have shown that vitamin D supplementation is an essential public health measure in the fight against COVID-19. Early in 2020, a postulate was made based on inductive observation (descriptive statistics). That postulate considered the gradation of incidence, morbidity, and mortality associated with COVID-19 according to latitude, season, and age.

People with darker skin living in temperate climatic regions—in higher latitudes—experienced significantly increased morbidity and mortality from COVID-19. The common factor is a higher percentage of people with severe vitamin D deficiency [6,37]. Based on these observations alone, recommendations should have been made in 2020 for enhanced vitamin D supplementation (to attain vitamin D sufficiency in communities) as an effective preventive strategy [32].

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2.2.2. Deductive Evidence and Generalizability

After the preceding inductive observation, several retrospective studies further evaluated the hypothesis of vitamin D deficiency and COVID-19 using (deductive) inference. They showed similar evidence, although the assignment of groups according to vitamin D level may have biased the results. While many researchers considered serum 25(OH)D concentrations of either 20 or 30 ng/L as sufficient [38], others considered either 40 or 50 ng/mL as the minimum serum concentration needed to overcome SARS-CoV-2 infection [36,39-43].

Because of the mentioned diversity, combining those mentioned above two diverse groups of clinical studies in meta-analyses, not surprisingly, would not provide a robust conclusion of the benefits of vitamin D supplementation for COVID-19. Therefore, when designing meta-analyses, individual studies with proper study designs, especially the cut-off limits of measured serum 25(OH)D used for vitamin D adequacy (classification of vitamin D), must be considered before inclusion.

Despite these limitations, relevant odds ratios from published data point to vitamin D deficiency as a strong indicator of the severity of COVID-19 and deaths [44-46]. In addition to the error in the estimation of vitamin D sufficiency by groups like the Institute of Medicine [47,48] and National Dietary Guidelines groups [49,50], Veugelers and Ekwaru [51] and Schwalfenberg [52] pointed out that the doses recommended for achieving even the lower value for sufficiency were made as the result of a major statistical error [51,53-55].

Table 3 summarizes the findings of seven studies submitted for publication in 2020. Five are in hospital settings, one is a population study based on data from extensive health services, and the last is an epidemiological study. Studies were analyzed according to to sample size, vitamin D and COVID-19 status classification, and statistical tests used to emphasize effect size and significance. Five of the six clinical settings used as the index variable for the COVID-19 status and pre-existing vitamin D level as the criterion. One (Chicago study) looked at vitamin D level as the independent variable against which COVID-19 susceptibility was tested.

Table 3. Study designs of papers from six clinical settings examining COVID-19 and insufficient vitamin D levels.

Location	Rx	Infection (dependent variable)	Infection	Severity	Mortality
Chicago		X			
Switzerland			X		
Spain			X		
UK	X			ITU vs. non-ITU ward	NS
Iran				Clinical status	X
Israel			X	Hospital vs. OP	

[ITU, intensive therapy unit; NS, not significant; OP, outpatient].

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

The impact of vitamin D status on susceptibility to infection and its prognosis were assessed from different perspectives in multiple centers around the world (see Table 3 for study design and Table 4 for results).

According to the modern scientific paradigm, because studies mentioned are naturalistic, observational, or cross-sectional and not prospective experimental in design, a conclusion of causation is impossible. However, as pointed out, statistical tests offer ways to evaluate the intrinsic validity of inferences drawn from such observations.

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Vitamin D deficiency or insufficiency increases the susceptibility to viral infections and precedes SARS-CoV-2 infection [56]. The converging findings from various parts of the world using different designs give the hypothesis external validity (see Tables 3 and 4).

Three study results were significant for that relationship. One study reported no association between mortality and vitamin D level, but that was the UK study that either indicates lives saved because of active treatment (including large bolus doses of vitamin D) or lack of power owing to a relatively small sample size. One study (Iran) confirms a statistically significant association with mortality (see Figure 3).

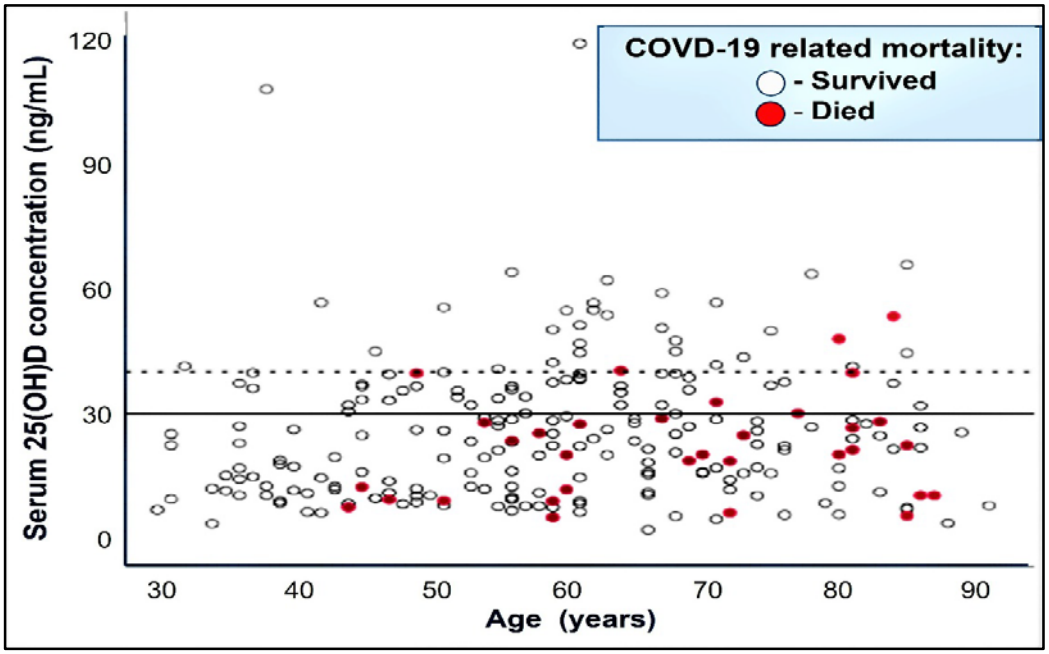

Figure 3. Scatterplot comparing vitamin D level with mortality. Deaths are depicted in red, and the dotted line indicates a vitamin D level of 40 ng/mL (100 nmol/L) (reproduced from Maghbooli et al. [57]). Three studies evaluated the effect size regarding odds ratio or relative risk (Chicago, Israel, and Iran). The Spanish study performed a post hoc analysis of the power of the study, which provided good power for infection risk but not for severity, possibly because of the relatively small sample size. The Iranian study gives a relative risk level (1.59) for severity but only the significance level for mortality.

The most robust finding is for susceptibility to infection in the two more extensive studies (Chicago and Israel), both of which give stratified levels of vitamin D and control groups without COVID-19. The relative risk for infection in the Chicago study is 1.77, and the Israeli study gave the crude 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 compared with the preceding findings.

The results of all study designs converge on a relationship between vitamin D insufficiency/deficiency and susceptibility to COVID-19, which implies a causal relationship. For the internal validity of the inference that vitamin D deficiency causes susceptibility to the acquisition of COVID-19 and its severity, one can consider the significance and effect size associated with the results of those studies. All properly conducted studies showed statistically significant evidence that vitamin D deficiency is associated with an increased risk of COVID-19 infection.

Using hospitalization as a measure of severity and adjusting for confounding factors, the Israeli study failed to show a significant statistical result despite an odds ratio of 1.95, the vulnerability to SARS-CoV-2 infection associated with vitamin D deficiency. That outcome may be due to a relatively small proportion of hospitalized patients (<10%),

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and given confounding factors such as age, the study may not have had enough statistical power to generate the needed effect size. Thus, despite a trend showing that vitamin D deficiency leads to a more severe infection with SARS-CoV2, including increased mortality, robust evidence indicates that deficiency is associated with an increased risk of infection with an increased odds of 50% more [44,58].

All clinical studies except two (Meltzer et al. [98] and Merzon et al. [40]) collected blood for vitamin D estimates during admission, showing low serum 25-hydroxyvitamin D [25(OH)D] concentrations. That finding raised the possibility of reverse causality (i.e., vitamin D level reduced by infection). However, the two larger studies mentioned earlier and the epidemiological study discussed below used 25(OH)D concentrations, measured before infection and hospitalization [56]. The effect sizes for all studies are comparable, indicating that the measured vitamin D level essentially represented prior levels and not cause by the infection.

A mentioned extensive epidemiological study from the United States confirmed the above assertion. That study showed a significantly reduced infection rate between deficient and adequate levels (reducing by 35%; that is, the increased risk of infection in a deficient subject is 50% more than that of a subject with an adequate vitamin D level of 30 ng/mL or 75 nmol/L) [56]. The same study reports a further 27% reduction in the rate of infection between adequate and high levels of vitamin D. Therefore, subjects with high levels of vitamin D (55 ng/mL or 137.5 nmol/L) are almost half as likely to be infected as a deficient subject (see Figure 4). The study also explores the increased risk of infection for African Americans and those with a darker skin color living in northern latitudes.

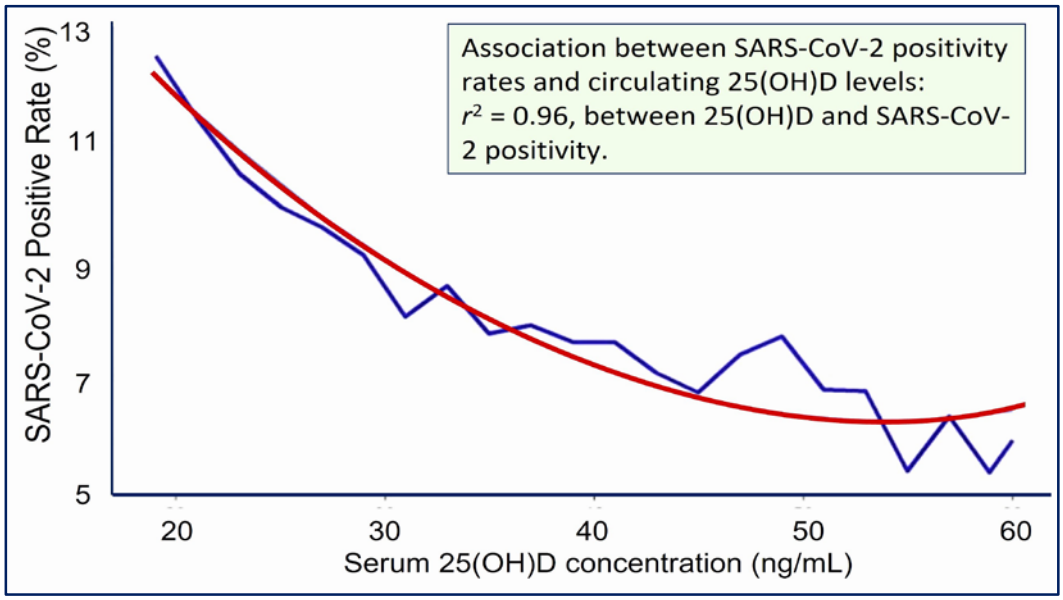

Figure 4. Relation of SARS-CoV-2–positive rate and serum 25-hydroxyvitamin D [25(OH)D] concentrations in the World Health Organization study population (weighted second-order polynomial regression fit to the data). The smooth line is a second-order polynomial fitting the data: (unadjusted odds ratio = 0.979 per 1-ng/mL increment, 95% confidence interval, 0.977–0.980) (reproduced with modifications from Kaufman et al. [56]).

The study used vitamin D levels in a database, thereby giving temporal separation between the measured 25(OH)D level and COVID-19 susceptibility. Because this was a large study, it strengthens the supposition that acute samples taken in hospitals essentially represented past vitamin D levels and were not due to reverse causation.

As with naturalistic or retrospective studies, the studies with greater power have not been able to look more closely at the severity of COVID-19 associated with vitamin D.

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However, studies in hospital settings have yielded statistically significant findings of severity and mortality associated with vitamin D deficiency. Performing post hoc power analysis on those studies may be worthwhile to consider how robust the findings of severity and mortality are. Also, a high effect size of severity was not significant when adjusted for confounders. The relationship of confounders to vitamin D may also alter the significance, which will be covered next. Based on published data, one can conclude that internal validity exists for the association between vitamin D insufficiency and COVID-19 susceptibility. Table 4 summarizes those results.

Table 4. Studies exploring vitamin D's impact on COVID-19

***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. [46]	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. [45]	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. [59]	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. [57]	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. [44]	499	172 COVID⁺ (32 = 19%)	143 COVID⁺ (19 = 13%)	184 COVID⁺ (20 = 11%)	RR = 1.77 $p < 0.02$
7807 (Israel), Merzon et al. [58]	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 ($p < 0.001$)

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191,779 (USA), Kaufman et al. [56]	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 $p < 0.001$ $p < 0.001$

ITU, intensive treatment unit; N/A, not available or applicable; OR, odds ratio; RR, relative risk.

2.4. *Common reasons for the Failure of Nutrient RCTs*

Pharmaceutical agents behave differently from nutrients, which are natural compounds. Moreover, the biological effects of the vitamin D dose-response relationship in humans are nonlinear and, at higher doses, may reflect as a J-shaped curve [60]. Such findings confirm that population-wide vitamin D supplementation can achieve the intended positive clinical outcomes, such as overcoming COVID-19 [6,61-63]. For vitamin D, dosing regimens, binding to vitamin D–binding protein for transportation, saturation and dissociation coefficients, and metabolism of nutrients are much different from those in pharmaceutical agents [64,65]. Consequently, some of the nutrient-related RCTs that treated vitamin D as a pharmaceutical agent (as some aspects of the VITAL clinical study [66]) not surprisingly failed because they.

Therefore, regardless of the size or expenses of the RCT, the reported failures of vitamin D trials [66] were not due to a lack of effect but due to flawed study designs [31], in conjunction with failure to adhere to Heaney's criteria for causality in a biological system [67]. Consequently, those studies report negative results and misleading conclusions because of researchers' failure to understand vitamin D's biology and physiology. Consequently, such studies unnecessarily muddle the literature and regressive of the understanding of the biology of vitamin D. Some studies related to sepsis/ infections, including SARS-CoV-2, failed essentially because of a lack of understanding of how immune cells are boosted by "locally" available proper concentrations of nutrients (e.g., intracellularly generated calcitriol) within those cells. One such fallacy is administering calcitriol, expecting it to enter immune cells and boost them, which does not happen [31].

Other reasons for the flaws in reaching valid conclusions from futile RCTs include failure to (or inadequate numbers) measure baseline (assure deficiency) and achieved concentrations of 25(OH)D (intended biological activity), but reliance upon doses administered. Many such studies had too small sample sizes, administered ineffective vitamin D doses, had an inappropriate frequency of administration, had a too short duration, and allowed participants to take over-the-counter supplements as in the case of the VITAL study and a few others [65,68,69]. Consequently, in their final recommendations, these researchers repeat the jargon that "more RCTs are necessary" and "association is not causation," etc., before a firm conclusion can be reached on the benefits of vitamin D [70] not only in COVID-19 but also in other health ailments. However, hundreds of other studies have confirmed that vitamin D has fulfilled Hill's criteria as a "cause and effect" [71], including COVID-19. Analyses of those studies have been published recently [71].

2.5. *Vitamin D and COVID-19: Later Studies and Meta-Analyses*

In late 2020, two papers were published that assessed the inference of vitamin D insufficiency as a cause of susceptibility further than the earlier papers. The first study was a quasi-experimental study from France [72], and the other was a prospective experimental design from India [73]. Both confirmed the hypothesis that vitamin D

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deficiency increases the vulnerability to poor outcomes in COVID-19, including increased mortality, with the former confirming a treatment effect.

2.5.1. Negative Studies and Study Design Errors

The only negative study from 2020 was published in early 2021 [74]. Significant study design errors were present, including inadequate controls and a single high-dose vitamin D treatment given in the late stages of critically ill COVID-19 patients. When the trial was conducted, it was known that a person in the late stage of the disease would not respond to vitamin D. In part, that lack of response occurs because vitamin D takes more than four days to become active in the body, especially in acutely ill patients [31] but not necessarily because of using an initial (high) loading dose of vitamin D [75] (more discussion in section 3.4). Had the authors used partially activated vitamin D and calcifediol, the study would have had a positive outcome—yet still not as good as if that treatment had been administered early in the disease [31]. For more information since 2020, see vdmeta.com, which lists all published studies (positive and negative) using vitamin D and other early therapies in COVID-19.

All negative studies in vdmeta.com shared two characteristics:

1. They enrolled subjects with advanced COVID-19 (late-stage disease, most patients in intensive care units).
2. They failed to use calcifediol, which acts within 4 hours of administration and boosts the immune system [31].

This meta-analysis (vdmeta.com) shows that 85% of all studies report a positive effect of vitamin D use, and 93% show a positive effect on vitamin D sufficiency (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 improvement increases to 55%, indicating that prophylactic supplementation is valuable.

Cui and Tian [76] used a relatively insensitive Mendelian randomization technique to assess how vitamin D concentration affects COVID-19 susceptibility. Some researchers use that method as a shortcut alternative for RCTs, particularly for observational studies, because control and randomization can be conducted on existing larger genetic databases. One example is the use of an allele that makes half the Japanese population sensitive to alcohol because of an enzyme deficiency [77]. Thus, susceptibility to alcoholism could be examined by using that group as a control against those with alcoholism. The single-nucleotide polymorphisms associated with vitamin D were derived from a genetic database without clear enunciation of an empirical causal link between the genome and the phenotype associated with vitamin D deficiency and, thus, susceptibility to the putative outcome. That was a significant weakness of the paper by Cui and Tian [76].

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 in a similar range for all examined outcomes. The result is likely to be an instrumental error. Hastie and colleagues [78] used UK Biobank data and concluded that vitamin D levels did not contribute to COVID-19 outcomes. Vitamin D levels reportedly did not contribute to the risk of infection, hospitalization, or mortality after controlling for confounders such as obesity, diabetes, and hypertension.

Confounders associated with vitamin D "insufficiency" dilute vitamin D's impact in any regression analysis. Using a method such as the random forest methodology is more appropriate to uncover the most critical factor(s) out of possible confounders. However, the sample size (N = 449) by Hastie and colleagues [78] is too small to make definitive conclusions. By contrast, if the number of confounders is limited to the preceding, performing such an analysis may still be worthwhile. A more detailed critique of

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statistical methods used by Hastie and colleagues is available in a letter to the editor by Davies, Mazess, and Benskin [79].

2.5.2. Positive Studies: Proper Study Designs

In contrast to the negative study mentioned earlier, it is possible to review one of the latest studies reported in the vdmetadata.com analysis. In that study, De Niet and colleagues (2022) [80] used a double-blind control design in which hospitalized COVID-19 patients were treated early with multiple doses of vitamin D_3 (25,000 IU) for up to 6 weeks. Even though calcifediol was not used, each treated patient received 100,000 IU of vitamin D_3 in the first four days, followed by six-weeks of weekly maintenance. The outcomes for the treatment group versus the placebo were favorable and statistically significant, using chi-square and Student *t*-tests. Although the study is weaker, it reported significant findings, such as length of hospital stay (4 days for treatment vs. eight days for placebo), showing a large effect size.

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

In addition to the studies listed at vdmeta.com, we reviewed seven other published meta-analyses. Two had negative conclusions regarding vitamin D deficiency's association with COVID-19 [81,82]. Of the other five, Shah and colleagues [83] was a systematic review of meta-analyses that included others [84-87].

All five, including Shah and colleagues [83], reported a significant association between the recommended supplementation and acute treatment-related improved clinical outcomes. All positive meta-analyses looked at pooled data from a moderate number of studies. Negative meta-analyses divided studies into four groups of about three each. According to common sense and Jackson and White [88], using a number of small studies reduces the statistical power and causes problems with the validity of using the normal distribution.

Further, in all meta-analyses using tools to grade "quality and bias," most papers are classified as poor or moderate. Therefore, the studies or instruments in classifying retrospective studies should be questioned. Also, one meta-analysis (Chen et al. [81]) wrongly identified that the population sample of Hastie and colleagues [78] accessed about 350,000 (the UK Biobank data) but missed the fact that the actual patient sample size was only 449 [78]. Contribution from the remaining large (epidemiological) study of Kaufman and colleagues [56] could have been diluted by a relatively small negative study identified with a large sample size.

2.5.4. Later Studies: Miscellaneous

Vdmeta.com points out that vitamin D supplementation could lead to increased susceptibility to COVID-19 based on admissions data and considers catabolic enzyme induction as one of the reasons. However, enzymes that naturally break down vitamin D should maintain equilibrium. By contrast, people already supplemented if susceptible could have independent vulnerabilities (e.g., genetic or immunological factors) [89].

The contrast in design between positive and negative studies raises an essential point in science practice. Although controls are used to keep confounding factors "constant," experiments also must be conducted to maximize the likelihood of showing a positive (as expected by the hypothesis) effect. For example, to show the interference pattern in Young's famous double-slit experiment [90], the slits must be close enough together. In the preceding example, the positive paper (section 2.5.2) correctly designed the RCT so that the treatment was early and prolonged, as inferred from previous data. The construct validity of the hypothesis must be explored by examining scientific evidence to explain why vitamin D may increase susceptibility to COVID-19.

2.6. More Scientific Evidence Would Model Vitamin D's Contribution to the Etiology and Amelioration of COVID-19 (Construct Validity)

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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, for which multiple confounding factors could be considered risk factors. Aging and increased body mass index contribute to vitamin D deficiency, with both associated with hypertension and cardiovascular diseases and contributing to vitamin D deficiency.

Independently of other factors, vitamin D deficiency contributes to type 2 diabetes, insulin resistance, and metabolic syndrome [91,92]. Other than the genetic vulnerability, those confounding factors are not as proximal as vitamin D deficiency as a cause for COVID-19 and its complications [93]. Innate and adaptive immunities are adversely affected by infections such as COVID-19; advanced age synergistically worsens the outcome, as seen in diabetes and neuroendocrine processes [94]. Beyond those factors, clinical outcomes of COVID-19 and other serious infections (sepsis) are significantly affected by infamm-aging and the cytokine storm [95,96].

The aforementioned phenomena explain a disproportionately large proportion of COVID-19 infectious outbreaks and deaths occurring in facilities for the elderly, the developmentally disabled, and nursing homes. Residents of such facilities tend to have multiple comorbidities, severe vitamin D deficiency, and poor health [97]. Hypovitaminosis is a common determinant among the elderly due partly to lack of sunlight exposure, reduced ability to generate vitamin D in the skin, low appetite, and reduced intestinal absorption of nutrients [96]. Thus, it is logical to assume that vitamin D supplementation and/or adequate daily sun exposure can prevent and treat infections, especially COVID-19 [97]. Considering reverse causality, if an infection causes further reduction, it is likely to exacerbate the immune crisis (another reason for having a sufficient buffer) for people with marginal or low vitamin D levels.

Finally, converging evidence shows that vitamin D has an impact via gene expression and activation of vitamin D receptor-related pathways. For viral diseases, especially COVID-19, the non-hormonal form of active vitamin D (calcitriol) significantly modulates the immune system [31]. It stimulates immune cells, produces antimicrobial peptides, reduces proinflammatory and stimulating anti-inflammatory cytokines, and downregulates the renin-angiotensin hormonal system [33,34,52,98-105]. That system is vital in increasing the concentration of the angiotensin-converting enzyme 2 (ACE2) enzyme, reducing the viral load and angiotensin II, and reducing inflammation and oxidative stress [106]. Vitamin D adequacy should prevent the cytokine storm and acute respiratory distress syndrome, markedly reducing deaths from COVID-19 [107,108].

During SARS-CoV-2 infections at early stages, vitamin D supplementation significantly reduced COVID-19–associated length of hospital stay, reduced frequent need for oxygen, and reduced mortality, mainly with high doses [109]. Moreover, vitamin D deficiency markedly increases both risk of acquiring and the severity of viral infections, especially coronaviruses. Vitamin D deficiency and its rectification can affect viral infections such as influenza [110,111].

2.7. ACE2's Role in SARS-CoV-2 Infections

Susceptibility due to vitamin D deficiency may be postulated mainly for SARS-CoV-2, the virus responsible for COVID-19. The virus enters cells by initial attachment to the ACE2 receptor and later reduces ACE2's availability for its primary function. Thus, vitamin D–deficient subjects may hypothetically have insufficient passive immunity and cause an imbalance in the level of angiotensin II.

In addition to altering immune responses, elevated angiotensin II levels may also lead to increased membrane-bound ACE2 receptor density that might facilitate viral attachment and cellular entry. That process would validate the hypothesis that vitamin D deficiency increases RAS activity and susceptibility to COVID-19. Low vitamin D may be a critical contributor to the excessive cytokine activity seen in COVID-19. Increased

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angiotensin II levels may also lead to some of COVID-19's vascular consequences. Figure 5 shows vitamin D's role concerning other confounders and susceptibility to COVID-19.

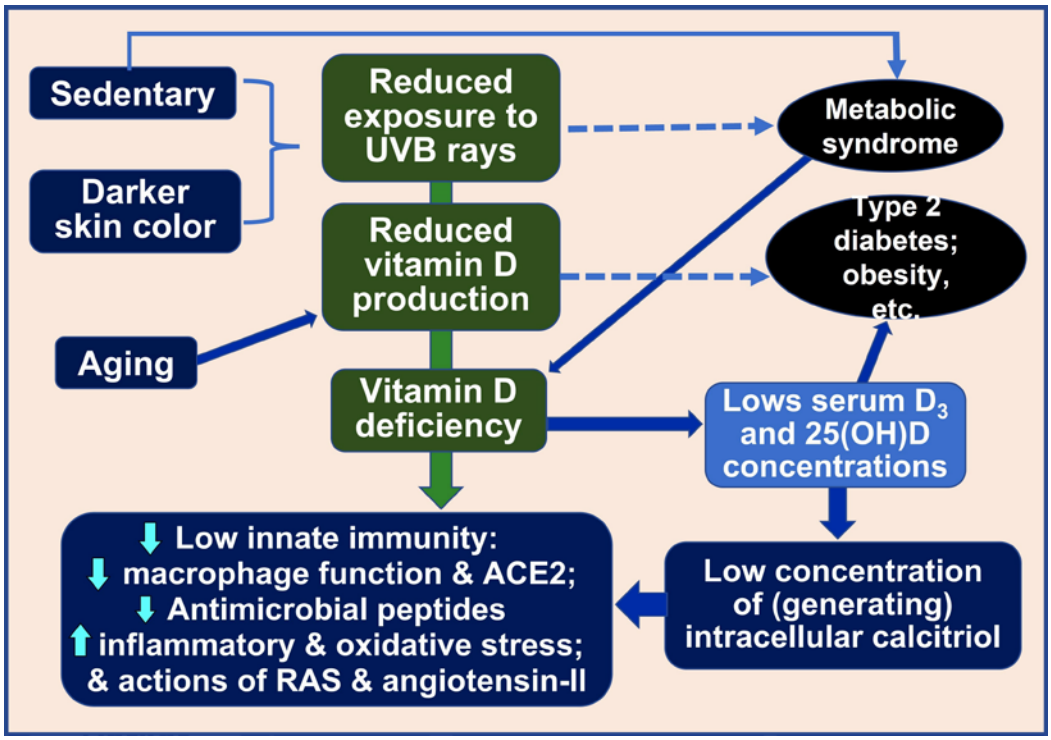

Figure 5. Flowchart showing multiple hypothetical confounding factors all related to vitamin D deficiency. Vitamin D deficiency, in turn, leads to multiple deficits in the innate immune system (low macrophage function, renin–angiotensin, and angiotensin-converting enzyme 2 [ACE2] dysfunction and imbalanced anti-inflammatory function).

Vitamin D sufficiency is an essential protective factor in immune function and several other body systems and conditions, including cardiovascular disease, hypertension, diabetes, cancer, and Alzheimer's disease. [68].

2.8. Interactions of Vitamin D with Caspases

Recently, further evidence has linked vitamin D deficiency to COVID-19 susceptibility via caspase-6 [112]. Moreover, caspase-3 cleaves the vitamin D receptor [113]. Caspase-3 activates caspase-6, although the latter could be activated independently [112]. Meanwhile, vitamin D_3 induces caspase-3 production [114]. A homeostatic loop probably exists between vitamin D and caspases.

Caspase-6 breaks down specific viral proteins, and the fragments can then attach to cellular proteins, vital in producing interferon, thus interfering with its production (see below) [112]. Suppose vitamin D deficiency caused low concentrations of caspase-3 and -6. Then apoptosis (an essential mechanism for suppressing viral replication induced by vitamin D_3 and caspases) also may be slowed. Thus, two cellular mechanisms to suppress viral replication are blocked. Vitamin D deficiency is therefore likely to facilitate increased viral replication as well as the cytokine storm and intravascular consequences of COVID-19.

The caspase-6 enzyme, a cysteine–aspartic acid protease, breaks down cellular structural protein in infected cells, typically facilitating apoptosis. However, it also breaks down the nucleocapsid protein, the products of which inhibit interferon. Therefore, an inhibitor of caspase-6 should reduce the replication and spread of coronaviruses, including SARS-CoV-2, given that there are other paths to apoptosis. Despite that natural preventive mechanism, coronaviruses developed a way to overcome

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it by exploiting caspase-6. Whereas the antiviral drug molnupiravir (Lagevrio) targets viral ribonucleic acid, nirmatrelvir, and ritonavir (Paxlovid) target viral proteases, making viruses develop resistance. In contrast, agents that inhibit caspase-6 seem unlikely to have antiviral drug resistance.

3. 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, we can now consider using the Nalanda paradigm to examine such empirical evidence.

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

1. 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.
2. Low innate immunity and the COVID-19 (SARS-CoV-2) virus could be considered as cells A and B in Catuskoti. Both A and B (i.e., C) cause COVID-19, which could be considered necessary and sufficient (universally) for the development of COVID-19 and its complications.
3. Vitamin D as the identity of all preexisting confounders could now, under Dignaga's causation relation, be considered the immediate (or proximal) cause of low immunity (that vitamin D deficiency and sufficiency appear to be associated with COVID-19 outcome in many settings throughout the world and further confirmation in an epidemiological study practically represents a universal assertion).
4. After observing the results of the preceding studies as an experimental design under Buddhist/Vaisesika inference, we could assert that vitamin D deficiency is significantly present in nearly all groups with severe COVID-19 (see Table 3). Such deficiency is significantly absent in those with no evidence of disease [46,105], and those with sufficient levels had a significantly lower incidence and severity [45,56-59,93,101,104,105,115].

We, therefore, assert that this is necessary and sufficient proof that vitamin D deficiency is a significant cause of vulnerability to severe COVID-19 and that appropriate sun exposure or vitamin D should be used as a supplement for prevention. Such reasoning would have permitted immediate actions and avoided adding to the mistakes made during the first half of 2020. In our proof, empirical evidence is primary, and deduction is subordinate. Having shown the proof by using the Nalanda paradigm, one could explore other forms of critique of illogical decisions made by public health officials during and even before the COVID-19 pandemic.

3.1. The (Il)logical Problem with RCTs' Being the "Gold Standard."

So, how did public health officials miss such logically and statistically apparent facts? Comments made by decision-makers about using vitamin D as a prophylactic appear to imply that the lack of RCTs constitutes a lack of evidence (as in EBM). Requiring RCTs to show vitamin D (a nutrient) deficiency in the etiology of vulnerability to COVID-19 is challenging. Also, drug companies control such RCTs [116,117]: The lack of accepted proof for treatment effect is assumed to mean that the etiology is absent (which is not the case).

However, the absence of evidence is not evidence of absence. Misinterpreting differences that do not reach significance (identifying it as a negative study, when it is not, a type II error) or when insufficient RCT studies are reported does not mean that the particular agent is ineffective [118] or that the researchers found nothing of clinical importance [119]. Therefore, interpreting negative trials (primarily because of study

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design errors) or insufficient numbers of published RCTs as evidence of a treatment's ineffectiveness is incorrect and imprudent. Also, dozens of studies of vitamin D (and ivermectin) in prevention and treatment and their published clinical trial evidence for COVID-19 are ignored, undermined, mistakenly dismissed, or willfully suppressed by regulators and leading health authorities, mainly to maintain EUA status for COVID vaccines.

The insistence on RCTs may follow the (judgmental) assumption that vitamin D deficiency is just an associated factor with other causes of susceptibility to the virus. A series of logical arguments mentioned earlier showed that to be a fallacy. The insistence on having RCTs data, even before evaluating already available evidence or approving nutrient supplements, ignores the serious perils of vitamin D deficiency. That is most likely a fundamental cause of increasing susceptibility to the virus and falsely equates vitamin D supplementation as (an acute) treatment (such as the attitude toward mask-wearing). "Masks could make you worse" was a statement that covered health administrators' lack of masks available for health professionals in early 2020.

Those logical misconceptions (an implicit expectation that RCTs yield universal truths and the false dichotomy of equating replenishing a causal absence as an independent treatment) strangle medical science. In managing COVID-19, the vehement objection by some scientists and doctors to using cost-effective agents, such as vitamin D, ivermectin, and HCQ, are examples. That assertion should not be confused with advocating against the RCT approach but rather reminding that RCTs have their place among other validation methods. Their limitations should be kept in mind by using the correct logic.

3.2. Introducing Bias and Cherry-Picking Studies Leads to False Conclusions

Furthermore, the U.S. Food and Drug Administration's (FDA's) 'emergency' acceptance of mRNA and other COVID vaccines under EUA to prevent SARS-CoV-2 infections and complications of COVID-19 silenced discussion of vitamin D and other reportedly highly successful cost-effective treatments. That occurred not only among prominent health organizations and the mainstream media but also on social media. Those outlets stipulated and confirmed no adequate, approved, and available alternatives (for prevention or treatment) for COVID-19 to justify the approval of COVD vaccines, new monoclonal antibodies, and antiviral therapies [120].

Consequently, vitamin D (as well as other economic supplements and repurposed drugs such as ivermectin) has been subject to a mass media and social media blockade. The costs of withholding such treatments that have no or few risks remain unknown. This is parallel to the massive direct and opportunity costs and loss of livelihood following excessive lockdowns and curfews by authoritarian administrations disregarding the basic biology of the SARS-CoV-2 [121].

Despite overwhelming evidence in favor of vitamin D, several factors led to flawed conclusions by some authors. In the case of Quinn and colleagues [122], selection bias (and subjective analysis of video data, not peer-reviewed articles), intrinsic bias, and unfamiliarity with recently published scientific data on vitamin D and its beneficial effects on human health, particularly on COVID-19. That YouTube analysis could be considered a disservice to the scientific community [122]. A few such analyses are contrary to the overwhelming majority of conclusions from published studies that vitamin D significantly benefits people infected with COVID-19 [122]. Cherry-picking videos or studies in meta-analyses and making unwarranted extrapolations to peer-reviewed publications is fundamentally unscientific. Other review articles may have displayed such bias using pseudo-empirical data or cherry-picking to reach false inferences.

3.3. Biased Assumptions about Confounders Could Lead to Wrong Conclusions

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One critical confounder is having a higher percentage of older adults in the community. Hence in addition to the age factor, comorbidities and vitamin D deficiency contribute to higher rates of complications and death [37,123]. Meanwhile, the same confounders that increase vulnerability to COVID-19 coincide with those with a higher prevalence of severe vitamin D deficiency [6,61,124]. Commonly identified comorbidities include obesity, diabetes, hypertension, and cardiovascular, renal, and cerebrovascular diseases [93,125-127]. The statistical pitfall of the correlation between those confounders and vitamin D levels was discussed earlier.

The fallacy of being distracted by various confounders and insisting on inappropriate increasing levels of evidence during an emergency, as with COVID-19 when a cause (and therefore the remedy) is evident, can be seen in the following excerpt:

> "Suppose, Mālunkyāputta, a man was wounded by an arrow thickly smeared with poison, and his friends and companions, his kinsmen and relatives, brought a surgeon to treat him. The man would say: 'I will not let the surgeon pull out this arrow until I know whether the man who wounded me was a noble or a brahmin or a merchant or a worker.' And he would say: 'I will not let the surgeon pull out this arrow until I know the name and clan of the man who wounded me;…until I know whether the bowstring that wounded me was fiber, reed or sinew or hemp or bark;…until I know whether the shaft that wounded me was wild or cultivated until I know with what kind of sinew the shaft that wounded me was bound—whether that of an ox or a buffalo or a deer or a monkey;…until I know what kind of arrowhead it was that wounded me—whether spiked or razor-tipped or curved or barbed or calf-toothed or lancet-shaped.'" All this would still not be known to that man, and meanwhile, he would die."
>
> —*Shorter Discourse to Malunkyaputta*, Majjima Nikaya 63, *The Tripitaka*.

3.4. Cost-Effective Early Therapies for COVID-19 and Their Inappropriate Use

For any infection, many studies reported that the best clinical outcomes are obtained by administering preventive therapies at the proper dose as soon as possible after infection. Treatments for COVID-19 that started late, as in intensive-care settings, led to worse outcomes than did an early intervention with economic, cost-effective agents such as vitamin D, HCQ, ivermectin, or even expensive therapies such as antiviral agents and monoclonal antibodies.

Here we focus only on cost-effective early therapies, which cost less than $5 to treat a COVID-19 patient. To obtain the best clinical outcomes, it is crucial to administer the proper dose of medication at the right frequency. Figure 6 shows how the effectiveness of medication fades with delayed treatment.

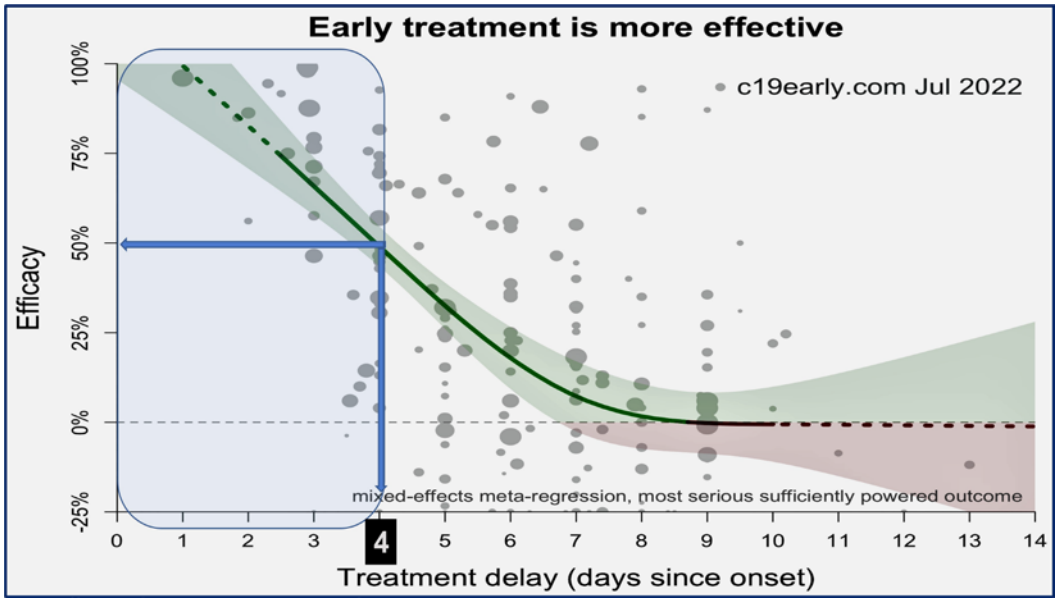

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Figure 6. The importance of starting therapies as soon as possible after diagnosis or hospitalization. The longer the delay, the less effective the treatment (modified from c19early.com).

3.5. Using Inappropriate Therapeutic Serum 25(OH)D Concentrations Leads to Poor Clinical Outcomes

Several peer-reviewed publications confirmed that people with serum 25(OH)D concentrations <12 ng/mL (i.e., severe vitamin D deficiency) are at the greatest risk of SARS-CoV-2 infection, complications, and deaths [36,128,129]. Rapidly raising serum 25(OH)D concentrations using cholecalciferol or calcifediol reduced the risk of complications and deaths from COVID-9 and other infections [68,130-137]. People maintaining serum 25(OH)D concentrations ≥30 ng/mL compared with ≤20 ng/mL not only had significantly lower risk of SARS-CoV-2 infection (hazard ratio [HR] = 0.66 [95% confidence interval (CI), 0.57–0.77]) and a lower risk of severe outcome (HR = 0.72 [95% CI, 0.52–1.00]) and lower mortality (HR = 0.66 [95% CI, 0.46–0.97]). Those findings are further elaborated in section 3.6.

Calcifediol treatment had similar outcomes but with a faster response. A real-time meta-analysis is available online with 89 vitamin D–COVID-19 clinical studies, including 20 RCTs [138] (Vitamin D for COVID-19: real-time analysis of all 300 studies (c19vitamind.com). Ninety-three clinical treatment studies were subject to a meta-analysis which showed improvement (67% for early and 48% for late treatment) compared to 30% for prophylaxis (reasons for this discrepancy of porphylaxis being ineffective in hospitalised patients were discussed earlier). Calcifediol was more effective than cholecalciferol. The analysis includes poorly designed clinical studies. Once again, a positive result in the meta-analysis, even with poorly designed negative studies, shows the robustness of the effect size.

3.6. Acute Treatment with Vitamin D Shows the Need for RCTs, but Poor Design Can Subvert Them

Treatment with loading doses of vitamin D is a sensible and needed approach to rapidly increase serum 25(OH)D concentrations to boost the innate immunity system [93]. That regimen reduces morbidity, complications, and mortality while having minimal risk of adverse effects. The evidence of hypercalcemia with substantial repeated doses of vitamin D is equivocal and could be managed safely through monitoring and treatment [139,140], such as with vitamin K_2 and magnesium. Little if any evidence exists of complications after upfront loading of a single vitamin D megadose [141].

Nevertheless, such intervention requires the level of proof of an RCT. Although exceedingly rare, the adverse effect of high doses of vitamin D is not necessarily as rigorously established as for, say, HCQ or ivermectin. Several RCTs with adequate statistical power have already been published [142,143] (https://vdmeta.com). Those RCTs and other controlled prospective clinical studies have added value: Results lend credibility to the hypothesis and point to adjunctive treatment alternatives. Later meta-analyses further confirmed those findings. The point, however, is that during an emergency, at a minimum, population-wide public health measures could have been considered (because the costs of treatments, as indicated earlier, were minimal).

Poorly designed studies, such as VITAL, inadvertently suggested that vitamin D supplements are unnecessary, extending to the whole population experimental findings on the risk of bone fracture found in a young population sample without available information on vitamin D status [144]. The danger is that the media echoed such and disseminated false narratives worldwide. Whereas, for the COVID-19 pandemic, vitamin D supplementation is an effective preventive and therapeutic tool and should have been considered from early 2020, particularly for people at high risk of vitamin D deficiency. Furthermore, some authors also suggest a possible role of vitamin D dietary

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supplementation in preventing and caring for the post-COVID syndrome (also called "long COVID"), for which no evidence-based therapy is yet available [145].

Contrary to some of VITAL's conclusions, several studies have shown that having a serum 25(OH)D concentration >30 ng/mL (in some studies, a minimum concentration of 40 or 50 ng/mL) significantly reduced morbidity and mortality from COVID [31,57,135-137,146-150]. Other studies reported between 40 and 60 ng/mL for better clinical outcomes [68,130,151,152]. The immune system is robust when serum 25(OH)D concentrations are maintained at >50 ng/mL. It will have positive clinical outcomes [31]. The COVID-19 restrictions (lockdown and curfews) significantly reduced serum 25(OH)D concentrations in children [153].

3.7. Some Published Vitamin D Guidelines and Governmental Recommendations Are Wrong

Several vitamin D guidelines have been published to minimize health risks from vitamin D deficiency [31,154-156], including protecting the musculoskeletal system and stimulating and maintaining proper immune responses. The latter needs more than two-fold higher circulating vitamin D and 25(OH)D concentrations [31]. Nevertheless, virtually all governmental and most scientific societies' recommendations focused only on the musculoskeletal system and ignored the benefits of other body systems.

Despite supporting evidence from thousands of scientific articles, mentioned organizations maintain that serum 25(OH)D concentrations of about 20 ng/mL and a daily intake of 400 IU (10 μg) is sufficient [157]. The government's recommended intake of vitamin D, 10 μg per day, will only maintain serum 25(OH)D concentrations above 25 nmol/L (10 ng/mL) and barely prevent rickets [158]. Such a concentration has virtually no protective effects on the immune system [31,75]. They are outdated.

For example, the European Food Safety Agency and others recommend 800 IU/day for the aging population. Meanwhile, the Scientific Advisory Committee on Nutrition (SACN, UK) and National Institute for Health and Care Excellence (NICE) [158-160], the U.S. Institute of Medicine (IoM), and the European Food Safety Agency recommend an upper limit of 4000 IU/day for adults [161].

The Association of UK Dietitians recently recommended 400 IU per day [162]. Researchers from the Irish TILDA study recommended daily doses of 600–800 IU and 800–1000 IU/day for people older than 70 years [163]. Other researchers recommend 800–2000 IU/day for older adults [164]. Taking such doses fails to increase serum 25(OH)D concentrations above 30 ng/mL. Consequently, for controlling infections such as SARS-CoV-2, daily intakes of <4000 IU for non-obese adults are no better than placebos to boost the immune system [130]. Although those intake levels are adequate to maintain the musculoskeletal system and prevent rickets and osteomalacia, they are uniformly insufficient for all other body systems, especially immune functions [31,165-167].

Despite the availability of data and guidelines [48,67,154], many researchers, including National Institutes of Health-funded studies such as the VITAL study, failed to adhere to the fundamentals. Consequently, it wasted millions of taxpayers' funds. Therefore, conclusions reported from such studies are unreliable and cannot be generalized. In addition to the described use of faulty assumptions and reasoning may also have contributed to decisions about cost-effective remedies such as vitamin D. Besides these, evidence mounts other reasons and conflicts of interest for regulators' unconscionable decisions (see section 4 for information).

3.8. Regulations, Ethics, and COVID Vaccines:

COVID-19 is a global problem [6], which every country dealt with differently, especially in the chosen model and its complications [168-171]. Nevertheless, many countries looked forward and followed the guidance from the WHO and the U.S. Centers for Disease Control and Prevention (CDC) but later found that many of those recommendations were faulty. From SARS-CoV-2's nature as a coronavirus, researchers knew it was likely to evolve into new variants more than once a year [172]. It was evident

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that COVID vaccines will drive mutagenesis and immune evasion by new variants of SARS-CoV-2. That knowledge was available when the pandemic began.

Instead of pursuing time-tested methods of vaccine production (inducing antibodies against the whole viral envelope) [173], the dominant Western nations pursued inadequately tested methods of vaccine production, claiming that these methods could produce larger quantities rapidly, but with no understanding of clinical outcomes and consequences of such judgments. Many of those decisions were based on increasing shareholder values. Companies' primary driver was profit-making, with impunity and legal protections arising from adverse reactions. Such pronounced legal safeguards allowed them to cut corners, take shortcuts, and deal with regulators. Besides, global patent protections hindered developing countries from generating their COVID vaccines at a fraction of the cost. The questionable ethical and legal processes involved in approvals were compounded by the lack of availability and the prohibitive cost charged by vaccine companies.

Had appropriate vaccine production methods been used, prompt relaxation of patent restrictions, and enhanced the global population immunity, along with other public health measures, preventing or delaying the emergence of the world-devastating SARS-CoV-2 variants might have been possible. That would have had the potential for eradicating SARS-CoV-2, which neither industry nor governments want to follow. Physical distancing and universal mask-wearing are easily implemented public health measures; universal screening for vitamin D sufficiency and supplementation could easily have been another.

3.9. Vaccines' Inability to Suppress SARS-CoV-2 Variants: A Reason to Consider Immunomodulatory Treatments

Owing to rapid mutation, SARS-CoV-2 cannot be suppressed or eliminated by vaccines alone. Some mutations make the virus more transmissible (generally less lethal for its survival, but it also could increase lethality in due course) and harder to detect (immune evasion) and treat. Immune competition and immune evasion occur mainly in fully vaccinated (i.e., immunized) persons and some with post-COVID syndrome [174]. As a result of putting all the eggs in the vaccine basket, the world is now faced with SARS-CoV-2's becoming endemic.

Emerging evidence now indicates that people with natural immunity (from past infection) are more protected from severe outcomes of COVID-19 than people with vaccine-mediated immunity [43,175]. That outcome may be particularly true for methods seeking an antibody response to the spike protein alone [176]. Gathering similar data for populations exposed to the traditional vaccines from China and India would be interesting. It is logical to assume that a vitamin D–sufficient population [i.e., for suppressing infections, a circulating 25(OH)D concentration >50 ng/mL] [31] exposed to SARS-CoV-2 would develop mild or no symptoms and produce a higher titer of neutralizing antibodies against the proteins of the whole viral envelope. That approach would allow the formation of a more effective, longer-lasting [43,177] natural immunity template [178] and significantly reduce the risk of the post-COVID syndrome.

The logical course would have been to strengthen both passive and active immunity (at least for susceptible populations) by enhancing population vitamin D levels and deploying vaccines using enhanced traditional methodologies against Spike and core proteins. That would have retarded the emergence of new variants of SARS-CoV-2. Had that approach been carried out earlier, it may have eased the burden of combating the pandemic. The non-susceptible population, if exposed to the virus, could have developed lasting herd immunity, preventing further viral evolution.

4. Regulators' Reasons for Approving No Cost-Effective Early Therapies

When an RCT or a prospective study is designed, it aims to produce outcomes in the future and is looking for predictive validity. By contrast, observational studies are not

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burdened with such. The conceptual problem with prediction is that without past repeatable results, it becomes a superstitious expectation of validation through clever prediction (akin to, e.g., astrology). Prediction should not be tried without past repeated results (such as smoke always being associated with fire). Thus, any prospective experimental design always requires previous observational studies to be analyzed rigorously or else be a repeatability study based on a previous prospective study.

Medical science has many other examples in which RCTs would have been inappropriate or not required, and observational data were accepted: tobacco use and lung cancer, penicillin to treat pneumonia, aspirin for headaches, diuretic for heart failure, appendectomy, and cholecystectomy [27].

Whether because of flawed policies, conflicts of interest, or both, regulatory authorities such as FDA and governing/recommending bodies such as the World Health Organization (WHO), SACN, and CDC refused to accept any unpatented agents or repurposed drugs to prevent and treat COVID-19 [157,159,161]. The standard excuse was "insufficient" RCTs to prove the validity claim that vitamin D is effective against COVID-19. That declaration is despite more than 100 clinical studies that reported using various doses of vitamin D for COVID-19—see vdmeta.com [84,142,167,179,180]. Moreover, convincing RCT data were published by Martineau and others in acute respiratory tract viral infections even in 2017 [181,182] and many since 2020 for COVID-19 [36,129,138].

4.1. Could the Public Rely on Regulatory Authorities for Proper Approval of Drugs?

In medicine (drug approvals) and health care, RCTs are considered superior to observational, ecological, and retrospective clinical studies to show causality. As described, dozens of published RCTs showed significantly reduced SARS-CoV-2 infection, risk of complications, and deaths in the context of treatment with vitamin D [36,129,138]. As a conservative design, using a vitamin D dose of 4000 IU/d for 30 days increased serum 25(OH)D concentration from 18 to 26 ng/mL versus 17 to 19 ng/mL in the control group in the intention-to-treat analysis In the per-protocol analysis, despite raising serum 25(OHD concentration raised only by about ten ng/mL, infection of SARS-CoV-2 in the vitamin D–treated group was reduced by 78% (95% CI, 0.08–0.59) [167].

When overwhelming evidence is reported worldwide concerning cost-effective early therapies, such as vitamin D and ivermectin, should WHO, FDA, and CDC wait until multiple RCT results are available while thousands are dying? That did not happen with any EUA for COVID vaccines, monoclonal antibodies, or antiviral agents. Vitamin D and ivermectin are generic agents; thus, large drug companies are not interested in RCTs or propagating them for the betterment of society. Broader evidence suggests that conflicts of interest of regulators and health organizations prevented the approval of highly cost-effective repurposed agents used to prevent and treat SARS-CoV-2 infection.

4.2. Consequences of Bias and Autocratic Suppression of Critical Evidence

Overall, data from reported clinical studies have satisfied Hill's criteria for causality [183] in a biological system [184]. Despite the vast published information described earlier, policymakers and regulators with conflicts of interest or unfamiliar with the emerging data disregard the health benefits of vitamin D, especially for COVID-19 continue to ignore scientific data.

Meanwhile, governments, regulators, and health authorities, in conjunction with the mass media and social media platforms, blocked information related to effective early therapies such as vitamin D, ivermectin, and melatonin by using the standard pharmaceutical disinformation playbook [116,117,185]. Over the past two years, government authorities and global health agencies have intimidated academics, physicians, and health care workers, directly via threats and through the mass media, not only preventing the dissemination of information but also penalizing them for

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prescribing highly cost-effective repurposed agents that save lives (see https://covid19criticalcare.com/).

4.3. Regulatory Objections to Approving Cost-Effective Repurposed Agents to Prevent and Treat COVID-19

In contrast, despite RCTs' that have less absolute efficacy (as opposed to the reported very high relative efficacy—which is misleading), even with lesser effect sizes, drug regulators accepted one or two RCTs from vaccines, antiviral agents, and monoclonal antibodies as sufficient to approve patented and expensive new COVID agents. Meanwhile, statements and publications, including FDA, CDC, and WHO reports, continue using the misleading "relative" efficacies as percentages that markedly exaggerate real effectiveness instead of using "absolute" reduction of hospitalizations, complications, or deaths. This is a statistical tactic that pharmaceutical companies continue to use to mislead (i.e., grossly exaggerate) the efficacies of drugs.

That behavior seems not to be an accident but rather a deliberate choice to deceive the uninformed public by coercing the regulators. The absolute effectiveness of the agents mentioned is significantly usually less than 5%, which was reported in publications, and more than 90% that are quoted in FDA approval reports from studies that used proper doses of vitamin D and ivermectin [36,150,186,187]. Astonishingly, in September 2022, as per the NBC, FDA stated that no clinical study data are necessary to approve *new* omicron-based vaccines (micron-boosters) under the EUA [188].

The main reason for refusal even to consider repurposed agents such as vitamin D and ivermectin, according to regulators such as FDA and the European Medicines Agency, was that if any such agent were accepted and approved to prevent or treat COVID-19, the EUA status for using vaccines, antiviral agents, and monoclonal antibodies would be automatically revoked. By contrast, after publications of RCTs that used calcifediol [142,148,151,152,189,190], its use was accepted as an effective therapy for COVID-19 in countries such as Spain and Italy [151,191].

Although widely accepted, once selection criteria are taken care of to balance confounders, no logical basis exists to consider prospective data superior to retrospective data. Depending on the circumstances, both methods have pros and cons; if the correct constraints are applied, equivalent results should be obtained. If sufficient to reduce type I and type II errors, the statistical methods used in retrospective studies with small samples should be accepted as valid, especially with convergent evidence. The attachment to RCTs as the gold standard for evidence and the sources of bias shown here hide philosophical assumptions deeply embedded in Western superstition (see section 5).

5. Recapitulating the Deeper Logic behind Errors of Decision-Making

Accepting RCTs as the arbiter of truth carries implicit assumptions: the expectation of universal truths or laws, determinism, and nature as a perfect continuum instead of its empirically evident atomic nature. The assumptions derive from Christian theology, in which deductive proofs are considered superior to empirical ones [11,12,18]. For RCTs, empirical data are obtained from narrow populations: Controls and exclusions further minimize generalizability. That leaves deduction (statistical analysis, often married to the ideal of the continuous distribution—bell curve) as the primary arbiter of truth [192].

5.1. Fallacies Related to Deduction, Universal Truth, and RCTs

Because of underlying assumptions, problems are associated with accepting the bell curve (normal distribution). One is the assumption of continuity: however, most data are not continuous. Even continuous data such as blood vitamin D level ultimately estimate the number of 25(OH)D molecules (as concentration) in a specific volume—1 mL of blood, nonlinear with the dose ingested. Despite these, those data are considered continuous only by convention. For most practical purposes, the distinction does not matter, and the normal distribution approximates the distribution of a large enough data

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set. The actual empirical data are never continuous but appear approximately like a continuum.

A symmetric and specific shape is assumed for the normal distribution. Although physical models of the universe strongly suggest symmetry, that is not the case for samples of data sets in medicine or other sciences. Once again, the shape is approximately related to the idealized normal distribution.

The central limit theorem proves that many empirically based distributions could approximate the normal distribution for large sample sizes. The classical proof uses Taylor's theorem, and by extension, all modern proofs involve limits. The normal distribution is, however, merely a convenient tool to simplify calculations of statistical inference. However, it is often presented as reflecting the underlying reality—a principal influence in placing deduction ahead of the empirical.

Such assumptions can be problematic when dealing with distributions with a skew or long tails and small samples. Those problems are solved by using discrete distributions or statistics with relatively simple logic designed for small samples. Also, assumptions behind normal distributions may plague meta-analyses, especially when studies with small sample sizes are used or the analysis includes few articles [88].

Aligned with the primacy of deductive proof, that approach leads to universal truths. Thus, all other methods (especially empirical evidence) are considered inferior. The retrospective studies have deficits, chief among them potentially missing data. Modern statistics and data science can readily deal with the problem of missing data, as occurs in analyzing large data sets [193].

Thus, no valid logical reasons exist to consider retrospective data (and relatively small samples with large effect sizes) intrinsically inferior to an RCT. An RCT conducted under the auspices of a pharmaceutical company may have considerable room for bias during data collection and interpretation [117]. Further, retrospective data from several sources bring a broader empirical basis and are thus more generalizable than an RCT.

RCTs (with or without placebo) are not always necessary and, in some circumstances, are impossible: A few examples were discussed earlier. Medicine as a discipline should investigate and accept a logical system and philosophies allied to all empirical evidence and not depend solely on RCTs or expert consensus. As discussed above, both have inherent flaws.

5.2. How Did Western Medicine Fail the Test of Logic?

The answer to the question of how Western medicine failed the test of logic may lie in philosophy, which underlies the logical base. First, the principle underlying Dignaga's trilemma, Indian inference, and all Western logic take the form of dichotomies, thus simplifying the logical arguments. However, Catuskoti is more complex and involves a tetralemma. That approach could be simplified to an intersection of two dichotomies, which could iterate to produce a more robust error-correcting mechanism than the approach of one dichotomy. Raju [12] used similar logic as a starting point and a conclusion about structured time (based on empirical evidence) to derive the modern logic of quantum mechanics in the microphysical realm. Similarly, we show that Catuskoti logic also could be used as an error-correcting mechanism in analyzing macrophysical phenomena (such as viruses and immune systems).

Notably, the second dichotomy of Catuskoti (both 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 sort of empirical context required to validate the latter logic. Without that validation, one could use just inference (or deduction) to make conclusions without reference to the empirical. Thus, although statistical inference permits increased precision, the context imposed by Catuskoti leads to valid conclusions. Both validity and precision are fundamental goals in seeking scientific truth. The example of vitamin D levels and COVID-19 has illustrated that concept, whereas opposing views appear to be opinions depending principally on inference.

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5.3. *Applying Logical Models to Western Medical Studies*

Raju's [11] model of levels of underlying rationale in analyzing empirical phenomena as described includes an additional, deeper level below logic, which is the philosophical stance that directs it. According to Raju [11], the underlying dominant philosophy of the Christian church (requirement of eternity, continuity, and determinism, which results from the concept of a transcendent God) may influence Western thinkers to expect universally applicable proofs. Non-Western medical scientists and health professionals could also be considered "colonized" in their ideas.

However, health advisers in non-Western countries may not be influenced by the more profound Western philosophy underlying the inconsistent application of logic. Instead, they may have taken the logic of empiricism at face value and applied it without adhering to any unconscious philosophical position. Although the such application is evident in the early adoption of mask-wearing and later adoption of HCQ and ivermectin by some as treatment alternatives, we know of no country adopting population-wide supplementation of vitamin D. Ironically, some provinces in Spain and Italy have instituted acute treatment with vitamin D in people affected by COVID-19 and on hospital admission. What factors could keep those two nations from submitting to conventional Western wisdom?

An alternative hypothesis could be that Western capitalism, with its attendant influence on educational processes via relationships with the pharmaceutical industry, has influenced the thinking of health bureaucrats [117]. Most research programs being dominated by RCTs, as study designs by pharmaceutical corporations, are targeted to obtain drug approvals. Consequently, they tend to minimize the value and the impact of simpler but more profound science research and inductive observations, such as retrospective, ecological, and naturalistic designs with appropriate statistics as seen. Figure 7 shows philosophy's relations to other levels of scientific discourse.

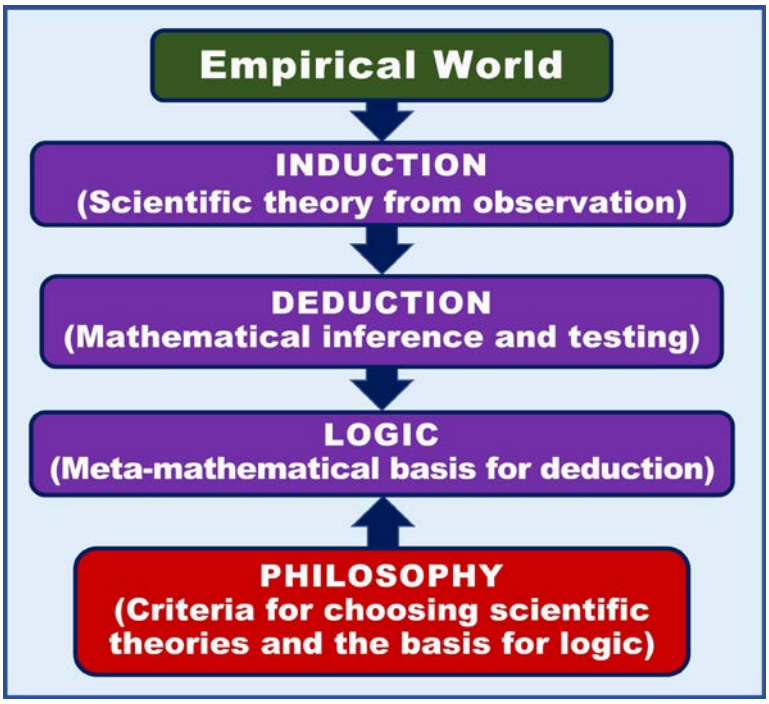

Figure 7. A layered approach to scientific practice (adapted from Raju [11], p. 451).

In contrast to Western philosophy and logic, the Buddhist philosophy, which influenced the Nalanda paradigm and Indian science, asserts reality as impermanent, atomic, and non-deterministic. One could say that empirical observation informs logic and philosophy in that paradigm instead of a force of philosophy and logic that enforces

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axioms on developing theories and hypotheses. In scientific practice, the accepted wisdom is to analyze empirical data and infer explanatory models and philosophy of reality. Although that approach permits a loop providing feedback from established philosophy or model of reality to interpretation of future empirical observations, it is more likely that the model must be adjusted to meet contrary empirical findings. To not accept a contrary empirical finding immediately without reproducibility is reasonable. However, Raju uncovered a deep flaw in science dominated by the West in which superstitious beliefs have long influenced the development of scientific models.

6. Discussion

We examined evidence that vitamin D deficiency is a key (proximal) cause of susceptibility to COVID-19, developing complications and death. We tested the impact of interpreting that evidence by using a heuristic based on ancient Buddhist logic. Using that logical template allowed us to clarify the context that logic could offer in medical sciences.

Vitamin D sufficiency gives a straightforward reason why people in tropical countries and the homeless (living outdoors) have better survival outcomes in COVID-19. That finding contrasts with outcomes in temperate countries, especially people with darker skin with an exceedingly high prevalence of severe vitamin D deficiency, particularly during winter. Their immune systems are thus impaired, making them highly vulnerable to contracting COVID-19 and developing complications.

We showed how such simple logic could relate to more complex modern mathematical techniques. Because most scientists and health professionals are unfamiliar with the logic underlying the most complex statistical and mathematical techniques, a simpler logic model may assist in critically examining complex research results. Research lacking the contextual validity afforded by logically applying Catuskoti-like logic but using mainly statistics to justify conclusions (without empirical scientific constructs) should be suspect. The same logical heuristic can be used to analyze what has happened with vaccines without considering confounders and risks. For an effective strategy against SARS-CoV-2, vitamin D offers a strategy to enhance passive immunity.

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 basic logic 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.

Vaccines enhance active immunity before exposure. If so, one could ask whether using a method that attacks a specific site (spike protein) would be better than a more general one that attacks the whole viral envelope (many sites have been examined for relative potency for antibody action). One could then ask whether vaccines would accelerate the evolution of the virus to resistant variants. How quickly could that happen? One also could ask whether a specific vaccine with or without vitamin D supplementation (passive immunity) would be more effective. If not for geopolitical necessity, the WHO or another organization could have designed a study that examined those finite combinations and permutations, as complex as they may have been.

We used an easily understood logical method to show the fallacy of denying remedies such as vitamin D and ivermectin during the pandemic. That approach was partly intended to expose possible economic and political factors that may have influenced the lack of such a decision (i.e., either illogical or with hidden vested interests). The evidence bases for using vitamin D indicate that pretreatment to raise blood levels and the advantage of early treatment (as opposed to late treatment) with high-dose vitamin D (and/or calcifediol) are essential strategies in using the agents

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effectively. Yet some studies ignore such facts and use faulty study designs as discussed above, sometimes cherry-picking invalid data. Despite that obviousness, those studies also were accepted for publication, so authorities could use them to justify their lack of action.

Further, despite errors in recommendations, they continue for both sufficient levels, and supplement doses (e.g., SACN, IoM, NICE, as described earlier), and supposedly authoritative sources continue to quote them and recommend erroneous levels. That is also used as a reason for not acting. Finally, the contradiction between EUAs for patented drugs and non-approval of economic, repurposed remedies, including vitamin D, is glaring. Although the EBM model was developed mainly to rigorously assess new treatment strategies, the drug industry appears to have exploited for its benefit medical professionals' ambiguous understanding of the evidence base medicine or systems.

Although one could argue that the lack of logical basis for decisions is partly true (as shown in the philosophical basis underlying science, particularly in the West), what is also evident as a reason for indecision is the presence of pharmaceutical lobbies and political campaigns contributions in powerful Western nations. Pharmaceutical disinformation (in analogy with previous campaigns in the tobacco and fossil fuel industries) must be considered an essential factor is influencing Western decision-makers, who are already confused by a superstitious logical and philosophical basis for science.

The preceding was exposed when the reason for not approving cheap remedies (when pressed) was given as the danger such a decision posed to expensive, highly profitable patented drugs under EUA, such as vaccines. That argument is also not genuine because those remedies did not compete with vaccines. However, EUAs were granted because no other agents were supposedly available to prevent or treat COVID-19. Conflating vaccines with other treatment modalities (such as antiviral treatments or immune modulation) exposes the commercial nature of motivations. The relationship between the drug industry and medical politics needs more scrutiny.

Even though we used a heuristic derived from Buddhist logic (Nalanda paradigm) to strengthen the conclusions of empirical studies and their statistical analysis, modern science has fortuitously developed all the procedures necessary to be congruent with such underlying logic. Thus, the approach does not explain the finding that countries that follow Western philosophy failed to apply simple methods to protect their populations against COVID-19. Meanwhile, other nations are less influenced by the pharmaceutical industry, which considers RCTs the most valid method in medical science. For example, the Western nations of Spain and Italy successfully applied some of those more straightforward methods, such as acute treatment with the vitamin D analog calcifediol. 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.

7. Conclusions

Using a relatively simple heuristic leads to the conclusion that because of the low cost and high benefit, population-wide supplementation (at least for vulnerable groups) with vitamin D should be urgently considered to prevent COVID-19 and as an adjunct therapy. That approach would apply especially in northern and southern latitudes and countries with large populations of vitamin D–deficient people. Several approaches summarized below could significantly reduce morbidity and mortality, the use of intensive care unit beds, and the case burden for COVID-19:

- Adequate vitamin D supplementation (population vitamin D sufficiency) to maintain serum 25(OH)D concentration >30 ng/mL (75 nmol/L), preferably >50 ng/mL (125 nmol/L) [31,62,93,194]
- Population-wide use of face masks in all public places

- Targeted use of HCQ and ivermectin under medical supervision as prophylaxis or treatment early in the course of the disease

A further advantage of such measures would be suppression and possible elimination of the virus from a given population or the world and rapidly returning the supply chains and the economy to usual [195,196]. Instead of the unnecessary and burdensome lockdown and draconian curfews that ruined economies and livelihoods, movement limitations should have been restricted to local areas based on local outbreaks. Contrary to expectations, data showed that broader movement restrictions increased the viral spread. As new variants of SARS-CoV-2 emerge and for future epidemics and pandemics, due to the inability of measures to contain viral evolution, all methods to eliminate or suppress it, including a resilient population (due to vitamin D adequacy), must be explored. The evidence for the potential effectiveness of this approach presented above was either missed or ignored in 2020 and 2021, probably because of a combination of poor logic and vested interests.

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