

Vitamin D and COVID-19: Is There a Lack of Risk/Reward Understanding Among Health Authorities?

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Abstract

The COVID-19 (SARS-CoV-2 infection) crisis is affecting the whole world; many people have died, even more have gotten very sick, and people in many regions have been directly affected in their daily lives due to lockdowns of society. A series of studies by various medical researchers strongly indicates that vitamin D supplements can offer preventive effects against COVID-19. Looking at the dichotomy of seasonal variations in COVID-19, patterns of infection seen in countries toward the southern and northern hemispheres seems to give additional compelling support to this hypothesis. The seasonal variations in the northern and southern hemispheres in relation to COVID-19 appear to be in line with previous studies in vitamin D serum levels in those populations. These findings, combined with the knowledge that vitamin D supplements in moderate dosages have minimal to no risk, mean that the risk/reward of taking vitamin D is very good. Yet, while health authorities in numerous countries must be well aware of the potential preventive benefits from taking vitamin D, they seem more focused on finding a definitive answer before taking action. This seems to be a grave mistake based on the information at this point in time. Potentially, hundreds of thousands of people could be saved if health authorities would recommend vitamin D to the population, even with the qualification that studies are still underway to ascertain their efficacy. If a stronger stand were taken on the positive use of vitamin D, authorities could also make sure that particular at-risk groups could obtain such supplements, the elderly in nursing homes and assisted living facilities, for example.

At this point, the discussion should not be about whether it is helpful to take vitamin D during the COVID-19 pandemic or not, but rather about what dose to take and how to distribute vitamin D effectively among the population. Even if very promising vaccines are now entering production, it will likely take many months before they are available to all vulnerable groups. Further, one does not need to be an “anti-vaxxer” to understand that there can be considerable risk with a new vaccine. We recommend that health authorities act now and recommend vitamin D supplements based on risk/reward analysis.

Keywords: COVID-19, Vitamin D, Seasonality, Risk/Reward, Decision under uncertainty.

1. Vitamin D likely has positive effects against COVID-19 and minimal risk for side effects in moderate doses

In May 2020, Zemb et al. [1] addressed new research on COVID-19, stating that “Randomized controlled trials showed that vitamin D decreases acute respiratory infections (ARIs).” They also concluded that “daily vitamin D supplementation with moderate doses is safe and cheap” and therefore “even a small decrease in COVID-19 infections would easily justify this intervention.”

Meltzer et al. [2] found the relative risk of testing positive for COVID-19 was 1.77 times greater for patients with likely deficient vitamin D status, compared with patients with likely sufficient vitamin D status in a study of 489 patients. Kaufman et al. [3] have similar findings and conclude that “SARS-CoV-2 NAAT positivity is strongly and inversely associated with circulating 25(OH)D levels.”

Maghbooli et al. [4] carried out a study in which they show vitamin D sufficiency reduced risk for adverse clinical outcomes in patients with COVID-19 infection. A pilot study done by Castillo et al. [5] has shown that administration of a high dose of Calcifediol or 25-hydroxyvitamin D significantly reduced the need for ICU treatment of patients requiring hospitalization due to proven COVID-19.

Along these lines of thought, a series of other researchers have indicated that vitamin D likely can be beneficial against COVID-19, see for example [6, 7, 8, 9].

The evidence of a correlation between low vitamin D and poor outcomes in COVID-19 disease is extensive. The latest in a long line of such papers was published in Nature Scientific Reports on 19 November 2020 [10] and concludes:

“Vitamin D level is markedly low in severe COVID-19 patients. Inflammatory response is high in vitamin D deficient COVID-19 patients. This all translates into increased mortality in vitamin D deficient COVID-19 patients. As per the flexible approach in the current COVID-19 pandemic authors recommend mass administration of vitamin D supplements to population at risk for COVID-19.”

A broader review of the literature yields 17 publications in September alone, including one RCT, of which 15 are supportive of a role for vitamin D in COVID-19 and 2 found no association. We conducted a Pubmed search which returned 73 publications, of which 70 were supportive of a role for vitamin D in COVID-19. The National Institute for Health and Care Excellence (NICE, UK) has already pointed out shortcomings [11] in the Spanish RCT, which found a reduction in admission to ICU of 96% for those treated with vitamin D [5].

However, the discerning reader may note the emergence of a certain pattern in the numbers above. These papers if looked at individually are, in general, not providing any solid evidence of causality between vitamin D and resistance towards COVID-19, and could individually be described as weak, but if one looks at the collected information from all of these studies combined with others’ findings, then at least the risk/reward for recommending vitamin D to prevent COVID-19 disease seems strong, as we will suggest in this paper.

The paucity of the case against vitamin D

What are the arguments made against vitamin D supplementation? The primary argument is that “the evidence” is not of sufficient quality to warrant any recommendations being made with respect to ARTIs / flu or COVID-19. We address these objections in turn.

In June 2020, the Scientific Advisory Committee on Nutrition in the UK (SACN) published [11] a rapid review of vitamin D and ARTIs, concluding that “overall, the evidence at this time does not support recommending vitamin D supplementation to prevent ARTIs....” The report shows no evidence of increased risk (excluding bolus doses), and a majority of the papers examined therein showed a benefit, although not all of the papers concurred. This meant that the gold-standard test was not met, leading to the conclusion of no “beneficial effect.” The absence of downside was not considered.

In June 2020, The National Institute for Health and Care Excellence (NICE) in the UK published a review [12] of the evidence regarding vitamin D and COVID-19. The most unfortunate aspect of this paper is that within a few paragraphs it manages to contradict itself:

“There is no evidence to support taking vitamin D supplements to specifically prevent or treat COVID-19.

Evidence was from 5 published studies in peer-reviewed journals... Four of the studies found an association or correlation between a lower vitamin D status and subsequent development of COVID-19.”

Perhaps, being charitable, the authors were under time pressure and didn’t realize that they had become used to using “no evidence” to mean “insufficient evidence.” However, it might be preferable in future to consider the proper use of language, particularly in matters of great national and international importance.

The four studies that found an association are, quite rightly, deemed to be relatively low-quality evidence on account of being observational studies or surveys (at least when considered individually), and having numerous limitations. The fifth study [13] is noteworthy for being cited multiple times as evidence against vitamin D supplementation.

This paper, by Hastie et al., reviewed biobank data and reported that there was no link between catching COVID-19 in 2020 and the blood levels of vitamin D measured in 2006-2010. This bears repeating: the evidence against supplementation includes the assertion that blood samples from 10-14 years ago do not correlate with disease today. We count numerous other studies in recent months that found the opposite in relation to blood samples taken recently [2, 14].

Also, we would like to point out that it would likely be a mistake to consider many of the smaller sample studies in isolation; rather, they should be seen as pieces of a larger “puzzle” where we think the overall sum of the pieces strongly indicates that vitamin D has preventive effects against COVID-19. In a pandemic with deadly outcomes, we do not have the luxury of waiting to see if we can reach a final conclusion. Risk/reward analysis should weigh heavily on decision makers, as will be discussed further, but first we will look at the seasonality in serum levels, and also good indications of seasonality in COVID-19 that are already emerging in the data.

2. Seasonality

Direct exposure to sunlight (on the skin) plays an important role in the human body's vitamin D production. A series of studies shows population serum levels both in the northern and southern hemispheres is seasonal with respect to spring, summer, fall and winter, see [15, 16, 17, 18, 19,20], for example.

As an example, the UK has one of the highest levels of vitamin D deficiency in Europe [21]; in the winter months, at least 30-40% of the UK population is deficient in vitamin D, see [22]. Up to 94% of some Black, Asian, and minority ethnic (BAME) communities have been found to be deficient in winter [23]. Deficiency is likely to be higher this year given lockdowns and will likely be considerably higher in populations that have to shield. Charts showing average seasonal levels of serum concentrations of vitamin D can be found in [24], for example.

If there is a causal relationship between COVID-19 resistance and vitamin D serum levels, then one should likely see seasonal patterns in number of infected people, as well as in mortality statistics. The magnitude of these numbers should be in opposition for the northern and southern hemispheres, since when it is winter in Australia, it is summer in Europe and the US, and vice versa. In other words, we would expect to see an increase in both infections and death rates now in Europe, the US, and Russia, due to falling vitamin D serum levels across these populations, *ceteris paribus*. Naturally, several other factors also play an important role, including how much the people within a population are in contact with each other and thereby spreading the virus, the use of facemasks, rigorous hand washing hygiene measures, and so forth. So, one will not get a complete picture from studying data alone, as the amount of contact can change dramatically on short notice due to the official close down of a particular region, for example. However, if the vitamin D serum levels play an important role, one should expect to see patterns in the data, especially for large populations.

The COVID-19 pandemic has lasted for many months already, so it is an opportune time to look for seasonal variations. If we evaluate recent data, even a simple visual representation clearly seems to support this hypothesis. See Figures in Appendix A that represent countries far south in the southern hemisphere. The pattern in Australia seems to fit this hypothesis very well, where the COVID-19 infections peaked in their winter months (July, August, and September), and have dropped dramatically moving into the Australian summer. Similarly, countries like Bolivia, South Africa, Argentina, and Chile all have dramatic decreases in the numbers of infected people and numbers of deaths now that they have entered the summertime. In some countries like Madagascar, the seasonality is less clear, but overall, countries in the southern hemisphere seem to follow a clear pattern. Longer days and more sun exposure are linked to increased vitamin D serum levels. We cannot absolutely guarantee causality between falling rates of COVID-19 infection and increasing vitamin D serum levels in the southern hemisphere, but it is a plausible connection if seen in combination with the extensive research that exists on vitamin D in relation to the human immune system, flu seasons, and respiratory infections.

See Appendix B for seasonal variations in COVID-19 in select countries considerably far north in the northern hemisphere. Again, in most countries we see low activity of COVID-19 in the

summer, and increased infections now that there is less sun and falling vitamin D serum levels in the population this fall.

We could complete a range of advanced statistical studies about seasonality, but it is unlikely to bring us much closer to a final conclusion. At this stage we will not get clear-cut statistical evidence of seasonality in COVID-19 infection; for that one would likely need to have more data now and also wait for an ongoing COVID-19 pandemic, which would last for years. However, the indications appear to be strong. Often a simple visual inspection of significant patterns can be good enough and sometimes even better than long, complex analysis. Such patterns must not be seen in isolation, but instead must be combined with knowledge we have about seasonality in D vitamin serum level and other research on vitamin D in relation to COVID-19 and immune response in general. Clearly, there is ample room for further research.

3. Risk/Reward consideration for decisions under uncertainty

When it comes to vitamin D in relation to COVID-19, one should make a strong distinction between the perspective of researchers and that of decision makers, who are focused on saving lives and trying to control the pandemic. A researcher's aim is to get to the bottom of a question. From a research standpoint, one should naturally complete thorough and rigorous research before drawing final conclusions. Correlation and causality are not the same thing, so one can be tricked by correlations. For example, the seasonal effects in relation to COVID-19, of which we have good indications in many countries, could be linked to the fact that people are inside more often and thus in closer contact with others in the fall and winter than they are during the summer. Still, based on the extensive research available on vitamin D, we think it is a high probability that vitamin D serum levels also play an important role; one factor does not exclude another factor. As a counterpoint, our impression was that people actually socialized more in the summer in several countries in Europe, as the rates of COVID-19 infection were seen to diminish. This took place when there were fewer lockdowns in much of Europe during the summer than there were in the spring and late fall.

Preferably, a researcher will have access to large scale Randomised Control Trials, where one group is given placebo supplements, while the other group is given vitamin D, and one can follow up closely on serum levels in both groups. Such studies will take time and could be finalized long after the peak of the COVID pandemic has come and gone.

In contrast, from the decision-maker's standpoint, several key elements emerge. First, we already have good indications that vitamin D is beneficial in preventing COVID-19. Second, we have been exposed to vitamin D for thousands of years, actually since the beginning of the human existence, both from the Sun and from uptake from food. A series of studies show the safety of vitamin D supplements, for moderate dosages and even for high dosages. Based on historical studies, combined with the seasonal patterns in vitamin D serum levels and infection rates of COVID-19 by hemisphere, from a risk/reward perspective it would seem highly beneficial to recommend vitamin D supplements, with a low risk of adverse effects.

In addition to protecting individuals, vitamin D supplements may also reduce the rapid spread of the virus, as people will become less likely to infect others. Obviously, this is hard to quantify at this time, but one would likely get good indications about a change in infection rates, even after a couple of months of vitamin D supplementation for people within a given geographic area, or a formal study. In other words, it makes sense to recommend vitamin D supplements, in addition to other measures taken.

One could argue that recommending vitamin D before we are “sure” about its benefits could be counterproductive, as it could make people overconfident and reduce their focus on other important preventive measures. However, this can be mitigated by effort to convey clear and correct information, based on the knowledge we have at the moment.

Granted there are other risks to consider in recommending that a population should take vitamin D supplements, although it is minimal if one gives proper information. As an example, some vitamin D supplements are sold combined with vitamins A, which is known to be toxic in high dosages. However, health authorities should not underestimate the populations’ ability to process information. Naturally, a clear message, with valid information about vitamin D supplements must be part of such a campaign. On a different level, even though vitamin D seems to be very beneficial in the context of fighting the pandemic, it is important to emphasize that it is not a proxy for immortality. The most vulnerable group for COVID-19 is seen in people who are already seriously ill and facing potential death. All one can expect from vitamin D is increased viral resistance in the population and reduced impact on our lives as the spread of COVID-19 is reduced through such resistance. If managed carefully, better control of COVID-19 through such means could also be beneficial for the economies and functionality of countries. A long-term lockdown, or many repeated lockdowns, could lead to many severe side effects, including peoples’ mental health, rates of long-term unemployment, educational impacts on young people, and other individual, familial, and societal stresses.

To be clear, we are not trying to undermine other types of efforts to attack COVID-19. Large pharmaceutical firms are working aggressively on developing vaccines and results are starting to point to delivery by next year. The goal of this paper is not to promote vitamin D as opposed to or at the expense of continuing the research on vaccines. Yet, we know that the risk of taking vitamin D supplements is minimal, while administering a new vaccine may have unknown long-term effects that are not apparent right now. At the logistical level, even once we have several vaccines ready for production, they may not be available to a substantial percentage of the global population for many months. It is best to act now, with simple and reliable measures and strengthen ourselves for the road ahead.

Epistemic versus Phronetic

The claim to be “following the science” is a defining feature COVID-19 pandemic in most of at least the western world. It betrays a failure to think clearly by prioritising the epistemic over the phronetic when making decisions under uncertainty. This approach has shown the limits of Evidence-Based Medicine (“EBM”) and a lack of *phronesis* on the part of political and public health leaders. We argue that the advice regarding Vitamin D is a casualty of this approach given the high probability of it being beneficial and the very low probability of associated health risks. The policy inertia is a function of an inability to apply good judgement and to see beyond the

bounds of EBM. In such circumstances of decision making under uncertainty the general (non-naïve) Precautionary Principle applies and a decision not to act is also a decision with both public health and moral consequences.

The limits of EBM

We do not dispute the value of EBM; rather we dispute the blanket application of EBM in making policy and ethical decisions under uncertainty. Just because the answer in part relies on scientific evidence does not mean the scientific evidence is the only component. This nothing but-ism reflects a failure to understand that different types of question require different types of knowledge and different ways of thinking. EBM reflects one way of thinking, but it may not be appropriate in the early phase of a pandemic caused by a novel pathogen where, by definition, evidence will be scarce. Writing for HBR Martin et al. [25] set out the problem:

“The experience of the 2020 pandemic offers a powerful lesson: A critical skill a leader must bring to the table is the ability to figure out what kind of thinking is required to address a given challenge. Bring the wrong kind of thinking to a problem and you’ll be left fruitlessly analyzing scientific data when what’s desperately needed is a values-informed judgment call.”

The distinctions drawn by the authors reflect problem solving capabilities outlined by Aristotle:

“Techne was craft knowledge: learning to use tools and methods to create something. *Episteme* was scientific knowledge: uncovering the laws of nature and other inviolable facts that, however poorly understood they might be at the moment, “cannot be other than they are.” *Phronesis* was akin to ethical judgment: the perspective-taking and wisdom required to make decisions when competing values are in play — when the answer is not absolute, multiple options are possible, and things *can* be other than what they are”

We argue that *phronesis* is the appropriate way of thinking about decision making under uncertainty and that waiting for certainty is itself a decision with potentially serious consequences. The erroneous EBM-based approach claims that unless a certain standard of evidence is met then no action can be taken. This is susceptible to a *reductio ad absurdum* as Smith & Pell show in their 2003 paper [26] which points out that the lack of Randomised Control Trials (“RCTs”) supporting the use of parachutes means from an EBM perspective that their use cannot be recommended.

We also observe that, while claiming to be “following the science” which is another way of describing the epistemic approach, many decisions during the pandemic have not relied on gold-plated evidence: the decision to stop intubation was based on the observation that it was harmful in many cases; the decision to place hypoxic patients in the prone position was equally based on observation; and recommendations to wear masks in many countries relied on phronetic judgements rather than on available evidence. This constitutes tacit acknowledgment of the limitations of an approach which claims only to consider EBM.

Vitamin D – the phronetic choice?

Ideal interventions are low cost, low risk, with a high probability of upside. Masks fall into this category, as Greenhalgh et al. [27] have rightly argued since April. Vitamin D is another such intervention: its safety is well-established, its effects on immune function are well-documented, its correlation with worse outcomes in COVID-19 disease are very well established, and it is cheap and widely available. Given that vaccines will be available initially only to a small proportion of the global population, there remains an urgent need for cheap and safe interventions such as vitamin D.

Dose Safety

From the perspective of someone who must make a decision amidst uncertainty, the first question is: “*What happens if I am wrong?*” The National Institute for Health and Care Excellence [28] and Public Health England in the UK already recommend supplementation of vitamin D for musculoskeletal health. The UK recommendation is 400iu for adults and children over 1 year, despite the fact that vitamin D is fat soluble. The safety of this dose has not been questioned. Vitamin D toxicity leads to elevated levels of calcium in the blood, which can lead to deposition in soft tissue and demineralisation of the bones [29]. The question then is: “*What doses of supplementary vitamin D may result in toxicity?*” The answer is given by research into blood levels of those given long-term supplements of 1,000, 5,000, or 10,000iu per day for 5 months [30]. None of these led to levels anywhere near toxicity: the NHS reference range for serum vitamin D is 50-200 nmol/L; the 10,000iu per day dose equated to average serum levels of approx. 160 nmol/L. Research has suggested toxicity occurs > 375-750 nmol/L²⁵. So, doses even of 10,000iu per day lead to blood levels of vitamin D well below toxic levels. Publications also indicate a role for Vitamin K / K2 in mediating calcium uptake, and thus in preventing hypercalcaemia [31,32]. Thus, we can consider including vitamin K2 with higher doses of vitamin D, but in adding another supplement to the mix, the risk/reward must also be considered, a discussion that is outside the scope of this paper.

We note that Dr Fauci, Director of the National Institute of Allergy and Infectious Diseases (NIAID, USA), has confirmed he is taking a vitamin D supplement of 6,000iu and that he recommends others to take a supplement as well.¹

4. Conclusion

A series of studies and medical experts have indicated that vitamin D supplements can help prevent COVID-19 infection and also have been shown to make the symptoms in those already infected less severe. We know from both from research and historical experience that vitamin D supplements in moderate dosages have minimal risk. Combining this knowledge with studies showing strong negative correlation in seasonal vitamin D serum levels in North-South hemisphere populations and clear indications of seasonality in the spread of COVID-19 and mortality rates means that health authorities should recommend that people take vitamin D

¹“If you are deficient in vitamin D, that does have an impact on your susceptibility to infection. So I would not mind recommending, and I do it myself taking vitamin D supplements,” Dr Fauci said during an Instagram Live session: <https://www.instagram.com/p/CE7tWzinTI8/>.

supplements, in particular within vulnerable groups. This is based on a well-considered risk/reward decision process, where there is substantial upside and very little downside; communications would be clear around the recommendations and studies would continue, as we advance our understanding of the pandemic and possible approaches to its mitigation.

Our background has entailed deep engagement with decision making under uncertainty and the situation here is striking in that context. The pandemic is not a classical research situation where there is a painless luxury of time in waiting for more research so we can come to a final conclusion. In a pandemic, there is an unprecedented degree of urgency, where hundreds of thousands if not millions of lives could be lost if we are not acting optimally, even given limited information. Decision making based on a good understanding of risk-reward analysis should therefore outweigh other considerations that would constitute norms in a more normal environment.

In summary, the case for vitamin D is as follows: little downside, low cost, lives at stake, and a high probability of a beneficial effect. *Not* to act is also a choice.

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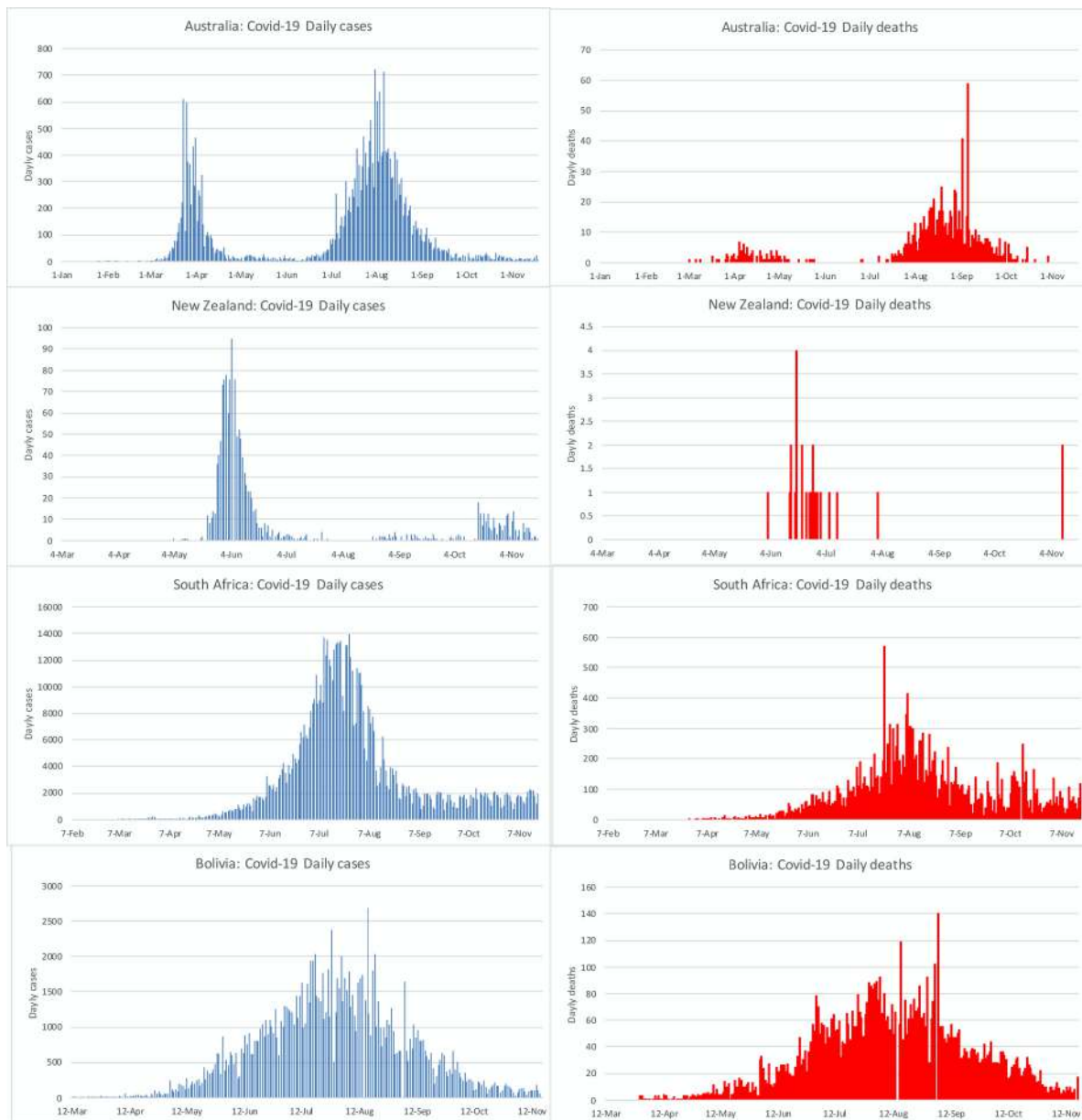
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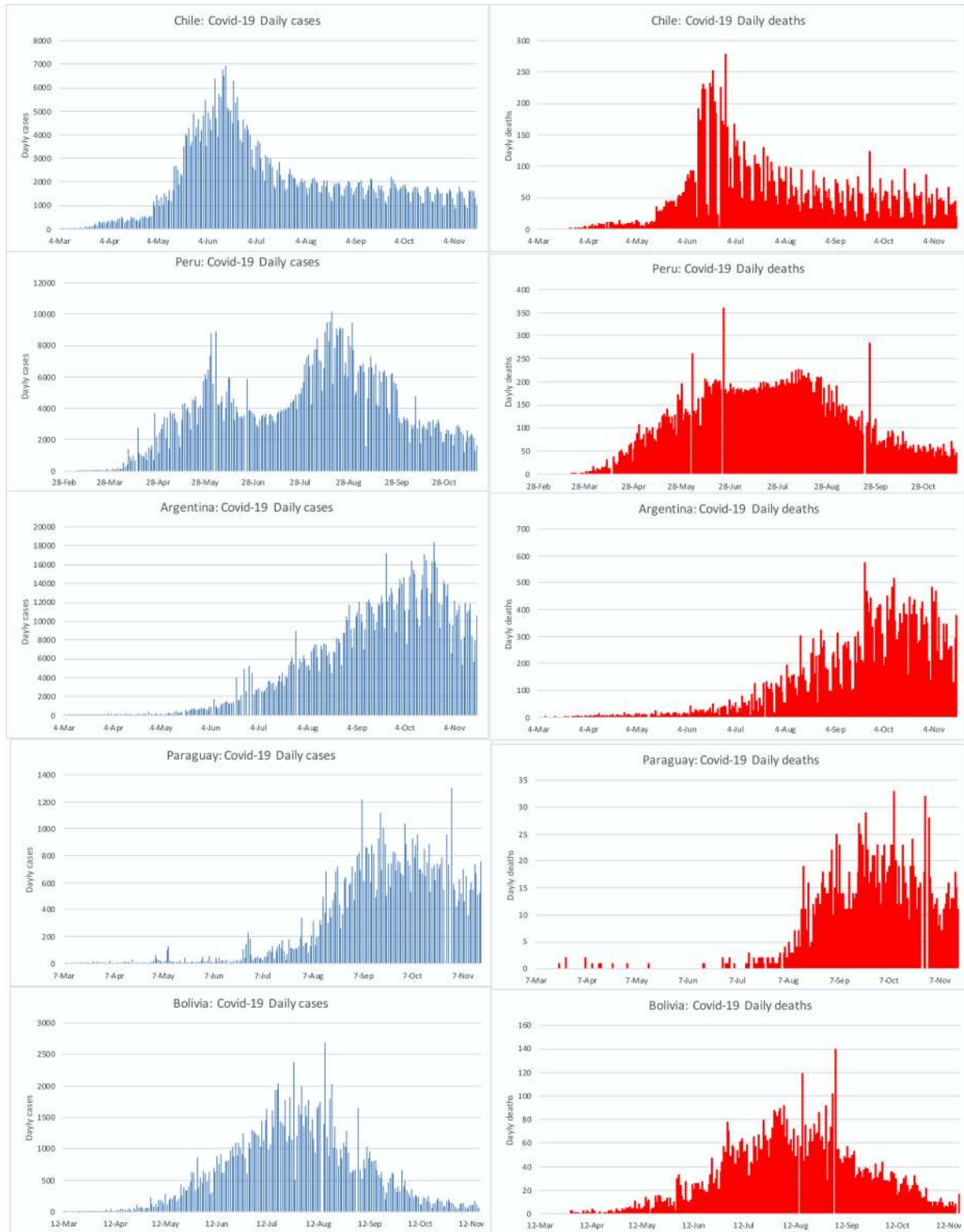
Conflict of Interest and other information

The authors declare no conflict of interest. The authors are not involved in any business involving vitamin D directly or indirectly. However, the authors have spent much of their careers on understanding decision making under uncertainty, where risk/reward analysis is critically important.

Appendix A: COVID-19 in the Southern Hemisphere

The data we have used are publicly available from <https://ourworldindata.org/coronavirus-source-data>. We have removed one or two extreme spikes in a few countries, as these spikes made it hard to see the trends in the remaining data. These spikes are likely due to corrections in number of deaths. If this study was about tail events, then it would be wrong to remove such spikes, but in this case removing them just makes it easier to see the seasonal trends. In the southern hemisphere, we have included most countries that have decent data collection. In the northern hemisphere, we have simply taken a number of the largest countries. It is possible to check more countries through the website mentioned above, which updates every day, or at worldometers.info, for example.





Appendix B: COVID-19 in the Northern Hemisphere

