1. Introduction

My name is ▮▮▮▮▮▮▮▮▮▮ a consultant psychiatrist who has practiced psychiatry for the past ▮▮▮▮ and as a consultant for ▮▮▮▮ I have worked both in the public and private sectors, mostly in Victoria, but have also had experience working in the public sector of Western Australia and New South Wales. For a good part of my career, I worked as a ▮▮▮▮▮▮▮▮▮▮▮▮ working and collaborating with other medical specialists. I have also undergone training in ▮▮▮▮▮▮▮▮▮▮▮▮ and simulation of neural networks. I will produce succinct evidence (elaborated in references) regarding vitamin D during this Pandemic and the proposal to build an Artificial Intelligence System that may mitigate mistakes such as those made during this Pandemic.

2. Actions taken during the pandemic

I had commenced collaborating with a world expert in vitamin D and other micronutrients in health and illness, Professor ▮▮▮▮▮▮▮▮, early in the Pandemic. We wrote three papers and made international presentations and attempted to inform authorities about our opinion and findings (see the evidence below). In Australia, I sent two emails to the Premier of Victoria, requesting that the Chief Medical Officer consider my pleas. Further, when an Aboriginal community in NSW was affected, I sent another email to the labour representative for Aboriginal affairs.

I have not had any feedback/response nor any evidence that Health Authorities took note of our recommendations. Below, is the evidence that emerged early (mostly 2020) in the Pandemic that vitamin D is important in prophylaxis and adjunctive acute treatment of COVID-19 is presented.

3. Accumulation of evidence indicating the need to use vitamin D status as a prognosticator and as a prophylactic and treatment agent early in the Pandemic

a) The efficacy demonstrated by the end of **2020** for management of COVID-19 with vitamin D has been confirmed by a pooled sample of hundreds of studies. They all converge to a similar level of efficacy already gleaned in **2020**.

b) Evidence was also present in **2020**, that a serum vitamin D level equivalent to 50ng/mL would reduce infection rate by half.

c) Independent sources of evidence prior to and during the early pandemic converged to demonstrate that achieving a vitamin D serum level of 50ng/mL (125 nmol/l) would reduce mortality and that the natural state of human being living under the sun is to have that level of vitamin D.

d) Pooled studies as the pandemic progressed have demonstrated that early treatment with vitamin D is essential in reducing morbidity and saving lives. Delay in giving high dose vitamin D from onset of symptoms to a 6-day delay reduced the efficacy from 100% to 0%.

e) Further, it was known and advocated in **2021**, that calcifediol is the form of vitamin D that should be used in acute treatment in preference to calcitriol (the active form of D), in order to achieve adequate serum levels rapidly (within hours). If calcitriol was used even in high bolus doses (100 000 IU inadequate, 2-300 000 IU adequate), the time to achieve adequate serum concentrations was several days. Thus, early use of

calcifediol could have prevented hospitalisation and ICU bed usage by millions of people around the World.
(Please see accompanying file of slides for illustration of this evidence).

4. The Explanation for why adequate/optimal vitamin D levels resulted in the remarkable outcomes outlined above

Seventy-five percent of the immune system functions dependent on having sufficient vitamin D in the bloodstream whereas deficiency, increases vulnerability to diseases, especially infections like SARS-CoV-2.

COVID-19, the disease caused by SARS-COV-2 is a systemic disease which results in two broad paths that can lead to death:

1) Cytokine Storm, that causes excess inflammation, particularly in the lungs resulting in Adult Respiratory Distress Syndrome (ARDS)
2) Thromboembolism that leads to Pulmonary embolism, heart attacks and stroke

Vitamin D, at optimum levels (50ng/mL or 125 nmol/l) enhances immunity and protects against poor prognosis by, the following actions:

1) It turns on genes within immune cells such as macrophages, that produce antimicrobial peptides that control and eliminate pathogens. In addition, these chemicals prevent cytokine storms.
2) Vitamin D also helps cells important in antibody production such as T-helper cells, transforming them into an anti-inflammatory form.
3) It also strengthens skin and mucus membranes and prevent them being leaky for pathogens to enter.
4) It impacts on another system necessary for defence of the body called the renin-angiotensin system (RAS). Angiotensins are products of this system and the second of these Angiotensin II gets converted by Angiotensin-converting Enzyme II (ACEII), to a vasodilator. Angiotensin II causes vasoconstriction (increased blood pressure and thromboembolism. Vitamin D deficiency leads to lowered tissue and circulating ACEII. It should be noted that tissue (cell-membrane) ACEII, through which SARS-COV2 enters human respiratory cells, rapidly consumes them thus further reducing availability of ACEII. The increase in Angiotensin II leads to cytokine storm and vasoconstriction leading to the principle causes of death (ARDS and Pulmonary/Coronary embolism).

5. The reason for the required serum Concentration of vitamin D

As implied previously, there are different forms of vitamin D. Most important is calcifediol (also called calcidiol) which is the precursor of calcitriol, the active form. For the latter to engage in actions within cells (such as turning on genes), the required level required is quite high. The calcifediol levels required to reach adequate levels within a cell is about 50ng/mL (125nmol/L). Once in the cells this gets converted to calcitriol at levels that are about 20 times the concentration of calcitriol in the blood (i.e. it will not cross the membrane into the cell). Thus, in an emergency it is better to use calcifediol. Calcifediol is also called 25(OH)D. The level of this found in populations living in the open is about 40-60 ng/mL (100-150 nmol/L).

6. Risks/Cost of vitamin D

Calculating the costs of intervention must include the economic cost (cost of intervention of a drug or a nutrient), opportunity costs, and cost of investigations and managing adverse

effects. Vitamin D3 has been proven safe, even at high doses of 15,000 IU/day, 20,000 IU/day, 50,000 IU/per week, and single high doses (but not repeat doses) up to 500,000 IU (ESPN guidelines), which are reported devoid of demonstrable adverse effects. Vitamin D is economical; treating a person cost less than US$2/person and, on average, US$8/person/year for prophylactic use. (In Australian dollars the cost could be twice as much).

7. Poor logic in decisions to not recommend vitamin D as a public health measure

Given its low cost and risk and high likelihood of helping reduce the impact of COVID-19, the benefit of using vitamin D was immense and its non-use could be considered disastrous. The following table demonstrates the outcomes of giving or not giving vitamin D, whether its effect is considered real or not. This obvious logic appears to have escaped health administrators, because in modern Evidence-Based Medicine, they are used to complex statistical methods and principles that can lead to wrong conclusions due to faulty logic. The complexities of such faults are discussed in two papers out of a series of papers by us.

	Real (A)	**Not Real (not A)**
Given (B)	Great benefit (A and B)	Small cost (B only – given but not real)
Not Given (not B)	Catastrophe (A only- real effect- not given) (Health and Economic)	No risk (neither A nor B)

8. Mechanisms to prevent Health Authorities making false deductions and wrong decisions in future

1) Educate medical personnel regarding the pitfalls of blindly following logic used for one kind of treatment evaluation (RCT) and applying this to all situations including an emergency and to naturalistic and observational, retrospective studies.
2) Instead of using standard statistical methods that could be used (knowingly or unknowingly) in submerging the true effects of related confounders (such as vitamin D level and its antecedent causes), aim to use more modern machine learning paradigms using appropriate logic.
3) Use a built in and complete logical system congruent with how humans think into machine learning AI algorithms capable of designing and evaluating studies appropriate for observational clinical data in a future pandemic. Such logic and algorithms could be potentially developed to be used in portable devices such as laptops, that would bring the strength of large databases and labs to the fingertips of clinicians. This would permit more rapid clinical consensus to emerge, freeing clinicians from excessive regulatory oversight.

It is conceivable, based on current knowledge that option 3 above is feasible to implement.