IMMUNITY INSTITUTE

SARS-CoV-2 and VARIANTS

THE NEED FOR A COMBINED APPROACH

Vaccines *plus* Natural Immunity & Vitamin D

February 6th 2021. Updated 11.2.21 Report Ref. 2021-001.1

PREFACE

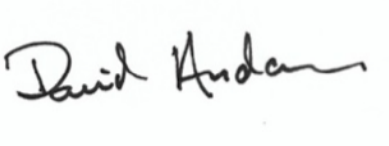
Late 2019 saw the advent of the new and unusually virulent pathogen, Coronavirus SARS-CoV-2, that spread quickly around the world. By mid-January 2021, three variants had emerged in quick succession and had begun establishing themselves in the UK and elsewhere. At time of writing this report the full implications of these variants are being assessed. In particular, which, if any, of the vaccines developed to counter SARS-CoV-2 would be effective against which, if any, variant.

What is certain, however, is that the social and economic life of the UK cannot be brought to a standstill and locked down each time a new variant emerges, whilst assessments are made and, potentially, existing vaccines modified or new vaccines developed.

We must, therefore, have an exit strategy from the present lockdown-based modus. This report proposes just such an exit strategy. It combines a Public Health initiative to optimise natural immunity by eliminating vitamin D deficiency in the population, together with the current vaccine program.

The authors of the report, who include three senior consultant clinicians with decades of front-line experience, encompassing theory, research and practice, together with an independent health researcher, are confident that the proposed strategy will enable a rapid return to near normality. It will also remove the risk of imposing entirely avoidable and repeated future winter lockdowns.

Report Authors



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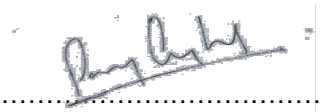

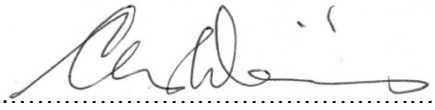

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The Immunity Institute is a nascent organisation set up to provide a free and trusted information source about the vital importance and role of our natural immune system in defending against serious infection. The advent of the new and unusually virulent pathogen, Coronavirus SARS-CoV-2, demands a much wider understanding of 'natural immunity', the result of 500 Million years of evolution, than currently pertains. Natural immunity is critically dependant on systemic reserves of metabolised Vitamin D.

Initially, the Institute will focus on: natural immunity; the role of Vitamin D (which is much more than a 'pre-hormone'); the role of vaccines in immunity; and the potential role of mRNA medicine technology.

The founders and trustees of the Institute (details overleaf) possess between them over 140 years of critical enquiry and a creative, systems approach to health issues. Having said that, it must be understood that the Institute does not purport to provide or prescribe medical advice. Rather it seeks to bridge what is a huge knowledge gap, with both factual reporting of existing knowledge and new research, as well as medical opinion from seasoned medical practitioners.

The Trustees have no commercial interest whatsoever in any of the topics to be covered and provide their time, knowledge and expertise 'pro-bono'.

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Chris Williams is an independent health researcher and 'problem solver'. His interest in health began over 20 years ago following an 'inoperable cancer' diagnosis, a dilemma he successfully managed to deal with.

In professional life he was founder and CEO for some 25 years of an internationally operating UK electronic systems and software company. He retired from this venture in 2008. He lives in Surrey, UK.

CONTENTS

Some important abbreviations used in this report

ng/mL: nanograms per millilitre (1 nanogram is 1 billionth of a gram)

nmol/L: nanomoles per litre (1 nanomole is 1 billionth of a mole)
(To convert ng/mL to nmol/L multiply by 2.5)

25(OH)D: also known as 25(OH)D3 and *calcifediol*, this is the blood circulating form of Vitamin D after Vitamin D3 (*cholecalciferol*) is metabolised in the liver – a process that takes some 7 to 10 days. (This applies whether the intake of Vitamin D3 is by the action of sun on the skin or by supplementation)

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1. PURPOSE OF THIS REPORT

In the absence of an adequate blood level of Vitamin D, the human immune system cannot function (see 2.2). In healthy individuals, subject to adequate systemic Vitamin D, the immune system will resist any pathogen whether virus or microbe, including SARS-CoV-2 and variants. Therefore, in the ongoing Public Health Emergency context of the rapidly mutating and virulent SARS-CoV-2 virus, now with at least 3 identified variants, it is vital to give prominence to Vitamin D sufficiency and natural immunity. Unlike a vaccine, natural immunity is disease (and variant) generic.

Furthermore, it is unacceptable socially, and un-affordable economically, to 'lock-down' as new SARS-COV-2 variants emerge, while assessments are made as to whether vaccine efficacy is maintained and, if not, while new vaccines are developed. Therefore, natural human immunity and its inextricable link to systemic Vitamin D level must also now be embraced in the fight against SARS-CoV-2 and variants.

The purpose of this Report is, therefore, to present some of the conclusive evidence supporting an immediate and urgent national initiative of Vitamin D3 supplementation in order to correct the widespread systemic Vitamin D deficiency in the UK population, and to reduce to a minimum its susceptibility to SARS-CoV-2. Gross systemic Vitamin D deficiency and susceptibility to SARS-CoV-2 is particularly prevalent among the BAME community; more often than not, dangerously so (3.3) and, as now generally accepted, among care home residents.

A Vitamin D sufficiency programme must, therefore, be implemented as a vital, necessary and urgent adjunct to the current vaccine programme. It is of note that since November 2020, in the Spanish Region of Andalucía, such an initiative (using the fast-acting Vitamin D metabolite *calcifediol* [1]) has been in operation in care homes. As David Davis MP informed the UK Parliament on Thursday January 14th 2021, the results have been dramatic and positive. (See Section 4. and Appendix 2/2).

Based on the evidence presented in this report, and their decades of relevant expertise, the authors are confident that together, the proposed Vitamin D Sufficiency and current vaccine programme will have the effect of:

- rapidly reducing the susceptibility of the population to SARS-CoV-2 and variants;
- rapidly reducing the number of those hospitalised, the severity of their disease and mortality, and the requirement for ICU;
- reducing the length of COVID-19 hospital stays;
- allowing the economy to return to 'normal'; and
- removing the risk of imposing entirely avoidable and repeated future winter lockdowns

2. THE REALISATION OF VITAMIN D DEFICIENCY IMPLICATIONS FOR IMMUNITY

2.1. Background

As long ago as 1981, Edgar Hope-Simpson of the UK Epidemiology Research Unit, Cirencester postulated "that a 'seasonal stimulus' intimately associated with solar radiation explained the remarkable seasonality of epidemic influenza" [Ref 1].

Hope-Simpson has since been proved to be correct. In 2006, a review study of 119 papers by Cannell et al 'Epidemic Influenza and Vitamin D' reached the conclusion "vitamin D, or lack of it, may be Hope-Simpson's 'seasonal stimulus'" [Ref.2]. And since 2006 there have been numerous studies that have established the direct link between Vitamin D levels and

[1] Calcifediol administered orally becomes available to the immune system within 2 – 4 hours. Vitamin D3 can take 7+ days to be metabolised to calcifediol and be available.

susceptibility to and severity of influenza. Of particular early note, in 2010, a Japanese RCT involving 334 children concluded that the Vitamin D group, supplementing with1,200 units Vitamin D3 daily, was 58% less likely to catch Influenza A. [Ref 3]

Most recently, in 2017, an international team led by Queen Mary University, London reviewed 25 randomised controlled trials involving some 11,000 participants and concluded: "Vitamin D supplementation was safe and it protected against acute respiratory tract infection overall." [Ref 3a].

2.2. The Immune System and Vitamin D

Thanks to 500 Million years of evolution, humans are endowed with a 'broad spectrum' defensive immune system. If suitably primed, the immune system will resist any would-be pathogenic invader whether microbe or virus. **BUT to do so it must have access to enough blood circulating Vitamin D in order to activate T cell immunity**.

The characterization of this mechanism is relatively new, having emerged since 2010. As reported in ScienceDaily in March 2010 (since when there have been many related papers):

> *"Scientists have found that vitamin D is crucial to activating our immune defences and that without sufficient intake of the vitamin - the killer cells of the immune system - T cells - will not be able to react to and fight off serious infections in the body. The research team found that T cells first search for vitamin D in order to activate and if they cannot find enough of it will not complete the activation process."* [Refs 4 & 4a]

And just as the fuel in a motor car gets used more heavily when going up a steep hill, the reserves of blood circulating Vitamin D become more heavily used when resisting infection – particularly when resisting so virulent a virus as SARS-CoV-2 – and, as we have seen, this virus and its variants each represent a very steep hill.

3. COVID-19 RELATED VITAMIN D RESEARCH

3.1. Vitamin D blood Levels, COVID-19 susceptibility and disease outcomes

Since the start of the COVID-19 pandemic some 30 papers have been published that show that, as with influenza, COVID-19 susceptibility and outcomes are directly associated with blood Vitamin D levels. Twelve of these are cited in Appendix 1, Ref16.

Typical examples of summary findings include:

> May 2020 From University of Birmingham & University Hospitals Birmingham NHS Foundation Trust: *"**Vitamin D deficiency is a risk factor for COVID-19 seroconversion** **[effective immune response]** **for NHS healthcare workers especially in BAME male staff**.*[our underlining]*"* [Ref 16a.]
>
> June 2020 From University of Newcastle upon Tyne and Royal Victoria Infirmary: "***we found that patients requiring ITU admission were more frequently vitamin D deficient than those managed on medical wards, despite being significantly younger.**"* [Ref 16b.]

An early paper published in April 2020, 'Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths' by William B Grant et al [Ref 7] concluded:

> "To reduce the risk of infection, it is recommended that people at risk of influenza and/or COVID-19 consider taking 10,000 units/day of vitamin D_3 for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 units/day. The goal should be to raise

25(OH)D concentrations above 40–60 ng/mL (100–150 nmol/L). For treatment of people who become infected with COVID-19, higher vitamin D_3 doses might be useful."

3.2. Bradford Hill Criteria – Covid-19 – Vitamin D

In 1965, the English statistician Sir Austin Bradford Hill proposed a set of nine criteria to provide epidemiologic evidence of a causal relationship between a presumed cause and an observed effect. The application of these criteria is the accepted methodology to apply when a widespread medical emergency becomes evident and large-scale randomised controlled trials are impractical owing to the need for urgent response, or questionable ethically owing to the high likelihood of mortality in the control group.

Bradford Hill understood the limitations of the randomised controlled clinical trial. He and Sir Richard Doll demonstrated in 1964 the causal role of cigarette smoking in relationships to lung cancer. This was readily accepted as proven without there having been a randomised controlled trial. It is to be hoped that almost sixty years later those with responsibilities for National Health will also understand these limitations. The pragmatic legal concept of weight of evidence is also applicable to health-related decision-making.

(Ref: Doll R, Hill AB. Mortality in Relation to Smoking: Ten Years' Observations of British Doctors. Br Med J 1964; 1 (5395): 1399–1410. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1814562/pdf/brmedj02630-0017.pdf)

In October 2020 a paper applying the Bradford Hill criteria to fourteen observational studies, all providing evidence that blood Vitamin D levels are inversely correlated with the incidence of, or severity of COVID-19 was published. This paper, 'Evidence Regarding Vitamin D and Risk of COVID-19 and Its Severity', by three eminent researcher medics, Joseph Mercola, William B Grant, and Carol Wagner [Ref 8].

Whilst noting that 'Public Health Policy' ideally requires evidence from one or more double blind trials, the authors conclude "The evidence to date generally satisfies Hill's criteria for causality in a biological system, namely, strength of association, consistency, temporality, biological gradient, plausibility (e.g., mechanisms), and coherence, although experimental verification is lacking. Thus, the evidence seems strong enough that people and physicians can use or recommend vitamin D supplements to prevent or treat COVID-19 in light of their safety and wide therapeutic window."

3.3 UK BAME population

As reported in the 2016 'Vitamin D and Health' report from the UK Scientific Advisory Committee on Nutrition, a substantial proportion of the UK population is deficient in Vitamin D (according to SACN, a level of <10ng/mL; 25nmol/L):- some 21% of the white population; *75% of the Asian population; 54% of the black population and 64% of 'other'* darker skinned ethnicities. These BAME deficiency findings are supported by many other research studies both pre- and post- 2016.

With regard to natural vitamin D production by the action of (the UVB component of) sunshine on the skin, numerous studies have shown that people with light (type II) skin can produce Vitamin D3 in their skin at rates 5–10 times faster than dark-skinned (type V) people. Examples of such studies include: Appendix 1 Refs [11], [12], [13], [14] & [15]. This biological fact, combined with cultural practices within some ethnic groups to cover most or all skin when outdoors provides the context for the gross vitamin D deficiency prevalent among many members of the BAME community.

3.4. Meta Analysis of 12 Treatment Studies

With regard to sufficiency and treatment studies [Ref 5] is a meta-analysis of some 38 papers including 12 treatment studies. With regards to the treatment studies, the meta-analysis concludes "Vitamin D is an effective treatment for COVID-19". Summary first page & Study References at Appendix 3.

3.5. Randomised Controlled Trial - Reina Sofia Teaching Hospital, Cordoba, Andalucía, Spain

The most conclusive of the treatment studies is of the randomised controlled trial carried out at the Reina Sophia Teaching Hospital in Cordoba, Andalucía, Spain during last summer. It involved 76 severely ill hospitalised COVID-pneumonia patients; 50 in the treatment group and 26 in the control group. It was reported on in early September. This innovative RCT used the fast-acting Vitamin D metabolite *calcifediol* (taken orally) in its treatment protocol, in addition to the 'standard' treatment.

The treatment group saw a 96% reduction in the requirement for ICU admission compared to the control group: 1 ICU admission v. 13. [Ref 6]

Although NICE dismissed this trial on the basis of a comorbidity 'confounding factor', the trial findings were subsequently independently validated by the MIT Maths Dept. As stated in the MIT report introduction, "Specifically, we show that the probability of obtaining such a large effect size by chance if the treatment had no effect is less than one in a million, that the probability that the effect was due to differences in comorbidities between the treatment and control groups is less than one in 60,000…" [Ref 6a].

3.6. Larger Randomised Controlled Trial in Andalucía: 5 Hospitals; up to 1,000 patients

Arising from the success of the RCT at Reina Sofia Hospital, a larger RCT using calcifediol at 5 Hospitals with up to 1,000 patients was undertaken and has recently concluded. We understand that the results obtained are just as encouraging as those of the earlier Reina Sofia RCT. The report of this larger RCT is presently undergoing peer review.

4. ROLL-OUT OF CALCIFEDIOL MORE WIDELY IN ANDALUCÍA; Dramatic Results

As a result of the trial, early November 2020 saw the Andalucía Regional Government approve the roll-out of calcifediol more widely; to Care Home residents and, other elderly at the discretion of their clinicians (Appendix 2). The result has been a dramatic fall in COVID-19 hospital admissions and mortality rates as shown in the comparative table below. Having said that, coincident with the emergence of new virus variants, deaths/million among the 'under-elderly' have increased in January, and more so elsewhere where calcifediol has not been deployed.

Andalucía *v.* Spain-excluding-Andalucía *v.* UK

	Andalucía: Deaths per million	Spain excluding Andalucía: Deaths per million	UK Deaths per million
November	189	161	175
December	80	133	222
January	128	180	482

Table entries produced from data available on 06.02.21
for Andalucía derived from
from: http://www.juntadeandalucia.es/institutodeestadisticaycartografia/salud/COVID19.html
For UK and Spain derived from: www.worldometers.info
Andalucía population size from Statista.com; UK and Spain population size from worldometer.info

5. PROPOSED VITAMIN D SUFFICIENCY PROGRAMME AND DOSAGE[2] FOR THE SARS-CoV-2 CONTEXT

The study "*SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels*" by Harvey Kaufman, Michael Holick *et al*, published in September 2020 (Ref 16 i) used a retrospective, observational analysis of tests performed at a US national clinical laboratory to determine if circulating 25-hydroxyvitamin D (25(OH)D) levels are associated with severe acute respiratory disease coronavirus 2 (SARS-CoV-2) positivity rates. Over 190,000 SARS-CoV-2 patients were involved.

Aided by the findings of that study and others and based on their expertise and experience the physician authors of this report consider the desirable Vitamin D blood levels for the SARS-CoV-2 context to be as shown in the table below:

25(OH)D Levels for the SARS-CoV-2 context		
	ng/mL	nmol/L
Deficient	<40	<100
Insufficient	40 - 50	100 - 125
Optimal	51 - 70	126 - 175
Too High	> 100	>250

These 25(OH)D ranges also accord with those proposed by other leading Vitamin D and SARS-CoV-2 cognoscent medical professionals e.g. Prof Dr Roger Seheult, Prof. Medicine, UC – (see https://www.youtube.com/watch?v=ha2mLz-Xdpg). Furthermore, it is of interest to note that this SARS-CoV-2 'Optimal' range corresponds with the upper levels of 25(OH)D found in traditionally living African tribes such as the Masai and the Hadzabe. Several research papers on 'Ancestral 25(OH)D levels' have been published by Luxwolda et al, from Gronigen University.

In summary:

51ng/mL - 70ng/mL (is the range considered to be that which will allow the immune system of healthy individuals to successfully resist the virus, possibly with mild cold symptoms.

40ng/mL to 50ng/mL is the range considered to be that which will allow the immune system in healthy individuals to successfully resist the virus, albeit with symptoms of a heavy cold possibly bordering on influenza.

Below 40ng/mL the chances of requiring hospitalisation are considered to be significant, especially in older persons and those with co-morbidities.

With regard to supplementation, in the wider, less vulnerable, non-infected population it is advised that supplementation should be a minimum of 4,000 IU (4,000 units) Vitamin D3 daily. This dosage level should enable the optimal range to be reached within a few months.

For healthy individuals who have not been supplementing and likely to be very deficient, it is suggested that the protocol of a recent Indian RCT be followed in order to rapidly gain 'Sufficiency'. The study in question: 'Short term, high-dose vitamin D supplementation for COVID-19 Disease - a randomised, placebo-controlled study'; Ashu Rastogi *et al.* [Ref 10] In this study, 60,000 units was given on 6 successive days, targeting a blood level of 60ng/mL.

[2] All dosage levels subject to individual medical advice and contraindications – e.g. sarcoid or other granulomatous diseases; renal issues; etc.

Alternatively, the NICE booster dose protocol published in December 17 could be employed. https://cks.nice.org.uk/topics/vitamin-d-deficiency-in-adults-treatment-prevention/management/management/#how-to-treat

For groups at risk of gross deficiency – care home residents, other elderly, and within the BAME community, the fast-acting Vitamin D metabolite, calcifediol, should preferably be used to quickly boost Vitamin D levels, as per the roll-out to care homes in Andalucía.

The Care Home protocol used in Andalucía, under medical supervision, is 1 calcifediol capsule (266 micrograms) once/month or twice/month subject to deficiency assessment. (Appendix 2/2)

> Note: The Vitamin D3 **:** calcifediol equivalence ratio used in Andalucía is 3.2 **:** 1. [Ref 9]. Thus 266 micrograms of calcifediol is deemed equivalent to 34,000 units vitamin D.

The treatment of hospitalised C-19 patients, many of whom are either BAME or elderly should also include fast-acting calcifediol, for obvious reasons.

NB. Both forms of Vitamin D are inexpensive. A year's supply of Vitamin D3 4,000 units is around £10-£15. A course of calcifediol to boost blood levels, or for treatment, is approximately £10; (Producer: Faes Farma)

6. CONCLUSION

On the basis of the foregoing we submit that the evidence to urgently commence use of Vitamin D for both supplementation and treatment is ample and conclusive. Given the high mortality in the UK associated with COVID-19 and the evident severe susceptibility to the disease by particular, large groups within the population, it is vital that SAGE/NICE/PHE must now modify policy given the ample Vitamin D evidence base now available.

If current policy is continued the evidence proves beyond any reasonable doubt that the result will be: a significant number of further unnecessary deaths; and, with current and future SARS-CoV-2 variants, further entirely avoidable and repeated winter lockdowns.

POST SCRIPT

VITAMIN D TOXICITY (VDT) IS AN EXTREMELY RARE OCCURRENCE

Possible Vitamin D Toxicity was cited as the reason not to supplement above 400 IU daily. Now in the UK, official sources cite the possibility of VDT as the reason not to exceed 4,000 IU daily. In the USA official sources suggest no more than 10,000 IU daily will avoid VDT…….

The three physician authors of this report have between them some 120 years of patient-facing experience. In that time just one single case of Vitamin D toxicity was encountered in a patient who had been taking 20,000 IU per day over many years. Putting it into context, by comparison with severe vaccine side-effects, VDT occurrence is less than negligible.

The writers emphasise that, apart from individuals with rare clinical conditions, e.g. sarcoid or other granulomatous diseases; renal issues; etc., a daily supplementation level of 4,000 IU (or equivalent at weekly or monthly intervals) is perfectly safe, as are short-term higher daily doses, as discussed in this Report, in order to achieve 'Sufficiency', then followed on by daily 4,000 IU.

Unfortunately, as indicated earlier, 'officialdom' presents an unhelpful, confusing picture. In the 2016 UK SACN (Scientific Advisory Committee on Nutrition) Report, 'Vitamin D and Health' a daily dose of 400 IU is recommended, with 1,000 IU as the upper limit. In the same report, 'Europe' is reported to have 4,000 IU as its upper limit; and the US Institute of Medicine is reported to state "based on the available data it unlikely that symptoms of toxicity would be observed at daily vitamin D intakes below 250 µg/(10,000 IU)". More recently, the NHS website

https://www.nhs.uk/conditions/vitamins-and-minerals/vitamin-d/ advises “Do not take more than 100 micrograms (4,000 units) of vitamin D a day as it could be harmful.”

Having said that, a major retrospective study reporting in 2018, investigating the occurrence of VDT found only one case, illustrating how extremely rarely it occurs:

Vitamin D Toxicity–A Clinical Perspective. Front. Endocrinol., Sept. 2018 https://doi.org/10.3389/fendo.2018.00550. A relevant extract from this report is given below:

> In statements released over the last decade, the Institute of Medicine (IOM) (15) and the Endocrine Society (14) have both concluded that acute VDT is extremely rare in the literature, that serum 25(OH)D concentrations must exceed 150 ng/ml (375 nmol/l), and that other factors, such as calcium intake, may affect the risk of developing hypercalcemia and VDT. Regardless of additional risk factors for VDT, many studies provided evidence that vitamin D is probably one of the least toxic fat-soluble vitamins, much less toxic than vitamin A (4). Dudenkov et al. (2) researched more than 20,000 serum 25(OH)D measurements performed at the Mayo Clinic from 2002 to 2011 to determine the prevalence of VDT, demonstrated by the presence of hypercalcemia. The number of individuals with a serum 25(OH)D concentration >50 ng/ml (>75 nmol/l) had increased by 20 times during that period. However, relatively high 25(OH)D concentrations coincided with a normal serum calcium concentration. Only one patient, with a25(OH)D concentration of 364 ng/ml (910 nmol/l), was diagnosed with hypercalcemia. Pietras et al. (16) reported that healthy adults in a clinical setting, receiving 50,000 IU of vitamin D_2 once every 2 weeks (equivalent to approximately 3,300 IU/day) for up to 6 years, maintained 25(OH)D concentrations of 40–60 ng/ml (100–150 nmol/l) without any evidence of VDT. Those findings were consistent with the observation by Ekwaru et al. (17) that Canadian adults who ingested up to 20,000 IU of vitamin D_3per day had a significant increase of 25(OH)D concentrations, up to 60 ng/ml (150 nmol/l), but without any evidence of toxicity.

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APPENDIX 1/1 - REFERENCES

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[6] **Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study** J Steroid Biochem Mol Biol. 2020 Oct; 203: 105751. Published online 2020 Aug 29 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7456194/

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Summary Findings: ***"****Vitamin D deficiency is a risk factor for COVID-19 seroconversion [effective immune response] for NHS healthcare workers* ***especially in BAME male staff****."*
https://www.medrxiv.org/content/10.1101/2020.10.05.20206706v1.full.pdf

b. **UK, University of Newcastle upon Tyne and Royal Victoria Infirmary** - Title: Low serum 25-hydroxyvitamin D (25[OH]D) levels in patients hospitalised with COVID-19 are associated with greater disease severity: results of a local audit of practice. June 2020
Summary Findings: *"Subject to the inherent limitations of observational (non-trial) audit data, analysed retrospectively, we found that patients requiring ITU admission were more frequently vitamin D deficient than those managed on medical wards, despite being significantly younger."*
https://www.medrxiv.org/content/10.1101/2020.06.21.20136903v1

c. **Italy, Di Venere Hospital, Bari.** - Title: Vitamin D deficiency as a predictor of poor prognosis in patients with acute respiratory failure due to COVID-19
Summary Findings: *"Patients with severe vitamin D deficiency had a significantly higher mortality risk."*
Journal of Endocrinological Investigation. July 2020
http://www.societaitalianadiendocrinologia.it/public/pdf/hypovitaminosis_d_covid19.pdf

d. **Germany: Division of Clinical Epidemiology and Aging Research, Germany Cancer Research Center, Heidelberg** - Title: Vitamin D Insufficiency and Deficiency and Mortality from Respiratory Diseases in a Cohort of Older Adults: Potential for Limiting the Death Toll during and beyond the COVID-19 Pandemic? [Paper presenting 15 years of follow-up of 9548 adults aged 50–75]
Summary Findings: *"In conclusion, our results, along with evidence from meta-analyses from RCTs regarding results of vitamin D_3 supplementation on various outcomes, suggest that vitamin D_3 supplementation could contribute to lowering mortality from respiratory and other diseases during and beyond the COVID-19 pandemic"*
Nutrients. 2020 Aug; 12(8): 2488.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7468980/

e. **Spain, Reina Sofia University Hospital, Córdoba.** **Randomised Controlled Trial** - Title: Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study
Summary Findings: *"Early calcifediol (25-hydroxyVitamin D) treatment to hospitalised COVID-19 patients significantly reduced intensive care unit admissions - Calcifediol seems to be able to reduce severity of the COVID-19"*
September 2nd 2020
https://www.sciencedirect.com/science/article/pii/S0960076020302764

f. **Germany, University of Heidelberg** - Title: Vitamin D Deficiency and Outcome of COVID-19 Patients.
Summary Findings: *"Our study demonstrates an association between VitD deficiency and severity/mortality of COVID-19"*
Nutrients **2020**, 12(9), 2757
https://www.mdpi.com/2072-6643/12/9/2757

g. **France, University Hospital of Saint-Etienne, University Hospital, Angers.** Title: Vitamin D and survival in COVID-19 patients: A quasi-experimental study
Summary Findings: *Bolus vitamin D3 supplementation during or just before COVID-19 was associated with better survival rate in frail elderly. Vitamin D may be a central biological determinant of COVID-19 outcomes.*
The Journal of Steroid Biochemistry and Molecular Biology
Volume 204, November 2020
https://www.sciencedirect.com/science/article/pii/S096007602030296X?via%3Dihub

h. **USA: Department of Medicine, University of Chicago** - Title: Association of Vitamin D Status and Other Clinical Characteristics With COVID-19 Test Results
Summary Findings: *"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"*
JAMA Netw Open. September 3, 2020
https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2770157

i. **USA, Boston University School of Medicine** - Title: SARS-CoV-2 positivity rates associated with circulating 25-hydroxyvitamin D levels
Summary Conclusion: *"SARS-CoV-2 positivity is strongly and inversely associated with circulating 25(OH)D levels, a relationship that persists across latitudes, races/ethnicities, both sexes, and age ranges."*
PLOS-One. September 17, 2020
https://doi.org/10.1371/journal.pone.0239252

j. **Russia, Clinical Infectious Hospital S.P. Botkin, St Petersburg** - Title: serum 25 (OH) D level in patients with COVID-19
Summary Findings: *"Vitamin D deficiency and obesity have been found to increase the risk of severe course and death of coronavirus infection."* August 2020
https://journal.niidi.ru/jofin/article/view/1073?locale=en_US

k. **Israel: Clalit Health Services** - Title: The link between Vitamin D deficiency and COVID-19 in a large population
Summary Findings: *"Results revealed a significant connection between the prevalence of vitamin D deficiency and COVID-19 incidence."*
SEPTEMBER 4, 2020
https://www.medrxiv.org/content/10.1101/2020.09.04.20188268v1.full.pdf

l. **Mexico**. - Title: Vitamin D deficiency is a risk factor for mortality in COVID-19 patients.
Summary Findings: *"Patients with COVID-19 who require hospitalization have vitamin D deficiency, and levels below 8 ng / mL is a risk factor for mortality from COVID-19, so actions should be taken to improve vitamin D levels such as vitamin D supplementation in this group of patients."*
https://www.medigraphic.com/cgi-bin/new/resumen.cgi?IDARTICULO=93773

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APPENDIX 2/1

Salud tratará con Calcifediol a ancianos en residencias para atenuar los efectos del Covid

Diversos estudios demuestran la capacidad protectora de la vitamina D contra infecciones respiratorias agudas

Andalucía, 10/11/2020

La Consejería de Salud y Familias ha dado a conocer al Consejo de Gobierno el informe del comité técnico de expertos para estudios de suplemento e intervención nutricional frente al Covid-19, en el que recomienda la utilización de Calcifediol en ancianos residentes en centros sociosanitarios para minimizar la incidencia de la infección y atenuar su gravedad en caso de que se produzca.

Entre los argumentos recogidos en el informe, destaca que el sistema endocrino de la vitamina D (SEVD) es bien conocido por sus efectos beneficiosos sobre la homeostasis del calcio y huesos, especialmente en niños, ancianos y pacientes osteoporóticos. Además, tiene diversos efectos extraesqueléticos, especialmente sobre el sistema inmunológico y la función pulmonar.

Además, la deficiencia de vitamina D puede predisponer a un mayor riesgo de infecciones y la suplementación con vitamina D puede disminuir el riesgo de infecciones de las vías respiratorias altas en esos pacientes. Metanálisis de ensayos controlados aleatorios realizados entre 2007 y 2020 revelan efectos protectores de la vitamina D contra las infecciones respiratorias agudas, aunque estos efectos fueron de tamaño modesto y con una heterogeneidad sustancial en los ensayos.

Del mismo modo, el informe señala que un ensayo clínico piloto paralelo, abierto, aleatorizado y doble enmascarado, realizado en el Hospital Universitario Reina Sofía de Córdoba, en 76 pacientes consecutivos hospitalizados con infección por Covid-19, concluyó que la administración de una dosis alta de calcifediol, metabolito principal del sistema endocrino de la vitamina D, redujo significativamente la necesidad de tratamiento en la UCI de estos pacientes.

Así, y dado que en la población anciana existe elevada prevalencia de déficit de vitamina D motivada por diversas causas, como una disminución de la síntesis de colecalciferol (vitamina D3) en la piel, menor exposición solar, disminución de la ingesta de alimentos que la contienen por intolerancia, peor estado nutricional y disminución de la absorción de la misma, la Consejería de Salud y Familias ha decidido recomendar el uso de vitamina D en estos centros de manera generalizada y aplicable a los residentes que, a juicio de su médico, se beneficiarán del suplemento con calcifediol, salvo contraindicaciones.

Finalmente, se ha informado de que la Dirección General de Asistencia Sanitaria del Servicio Andaluz de Salud ha dictado una Instrucción para la recomendación, con fecha 6 de noviembre de 2020, donde establece el traslado de la información del informe del Comité Técnico a los facultativos del SAS que tengan asignados pacientes usuarios de centros sociosanitarios, a fin, de que si lo consideran conveniente y dado el déficit de vitamina D3 en esta población, les prescriban el tratamiento recomendado por el citado comité.

Health will treat elderly people in residences with Calcifediol to mitigate the effects of Covid
Various studies demonstrate the protective capacity of vitamin D against acute respiratory infections
Andalusia, 11/10/2020

The Ministry of Health and Families has released to the Governing Council the report of the technical committee of experts for supplement studies and nutritional intervention against Covid-19, in which it recommends the use of Calcifediol in elderly residents in social health centers to minimize the incidence of the infection and lessen its severity if it occurs.

Among the arguments collected in the report, it stands out that the endocrine system of vitamin D (SEVD) is well known for its beneficial effects on calcium and bone homeostasis, especially in children, the elderly and osteoporotic patients. In addition, it has various extraskeletal effects, especially on the immune system and lung function.

Furthermore, vitamin D deficiency may predispose to an increased risk of infections, and vitamin D supplementation may decrease the risk of upper respiratory infections in these patients. Meta-analysis of randomized controlled trials conducted between 2007 and 2020 reveal protective effects of vitamin D against acute respiratory infections, although these effects were modest in size and with substantial heterogeneity in the trials.

Likewise, the report points out that a parallel, open, randomized and double-masked pilot clinical trial, carried out at the Reina Sofía University Hospital in Córdoba, in 76 consecutive patients hospitalized with Covid-19 infection, concluded that the administration of one dose High levels of calcifediol, the main metabolite of the endocrine system of vitamin D, significantly reduced the need for ICU treatment in these patients.

Thus, and given that in the elderly population there is a high prevalence of vitamin D deficiency motivated by various causes, such as a decrease in the synthesis of cholecalciferol (vitamin D3) in the skin, less sun exposure, a decrease in food intake than contain intolerance, worse nutritional status and decreased absorption, the Ministry of Health and Families has decided to recommend the use of vitamin D in these centers in a generalized way and applicable to residents who, in the opinion of their doctor, are will benefit from the supplement with calcifediol, except for contraindications.

Finally, it has been reported that the General Directorate of Sanitary Assistance of the Andalusian Health Service has issued an Instruction for the recommendation, dated November 6, 2020, where it establishes the transfer of the information from the report of the Technical Committee to the doctors of the SAS that have patient users assigned to social health centers, so that if they consider it appropriate and given the vitamin D3 deficiency in this population, they prescribe the treatment recommended by the aforementioned committee.

ANDALUCIA CARE HOME DOSAGE

From: **Jose Lopez Miranda** <md1lomij@uco.es>
Date: Fri, 15 Jan 2021 at 12:54
Subject: RE: Calcifediol: 1. Committee Report. 2. Elderly Care Home dosage
To: Chris Williams <crwlawnrd@gmail.com>

Dear Chris,
Prof. Isaac Tunez Will send you the committee report.
With regard to the dosage. We recommend to use Calcifediol 0,266 mg [266 micrograms] 1 cap every 2 weeks or every month.
Best regards
José

José López Miranda
Professor of Medicine
Lipid and Atherosclerosis Unit
Department of Medicine
Reina Sofia University Hospital
University of Cordoba
Cordoba, Spain

Tel.: 34-957012830. FAX: 34-957218250. eMail: jlopezmir@uco.es

Vitamin D is effective for COVID-19: real-time meta analysis of 38 studies

Covid Analysis, Dec 17, 2020 (Version 12, Jan 19, 2021)
https://vdmeta.com/

- Vitamin D is effective for COVID-19. Random effects meta-analysis of the 13 treatment studies to date shows an estimated reduction of 73% in the effect measured, RR 0.27 [0.15-0.51].
- Sufficiency studies show a strong association between vitamin D sufficiency and outcomes. Meta-analysis of the 25 sufficiency studies shows an estimated reduction of 50%, RR 0.50 [0.41-0.59].

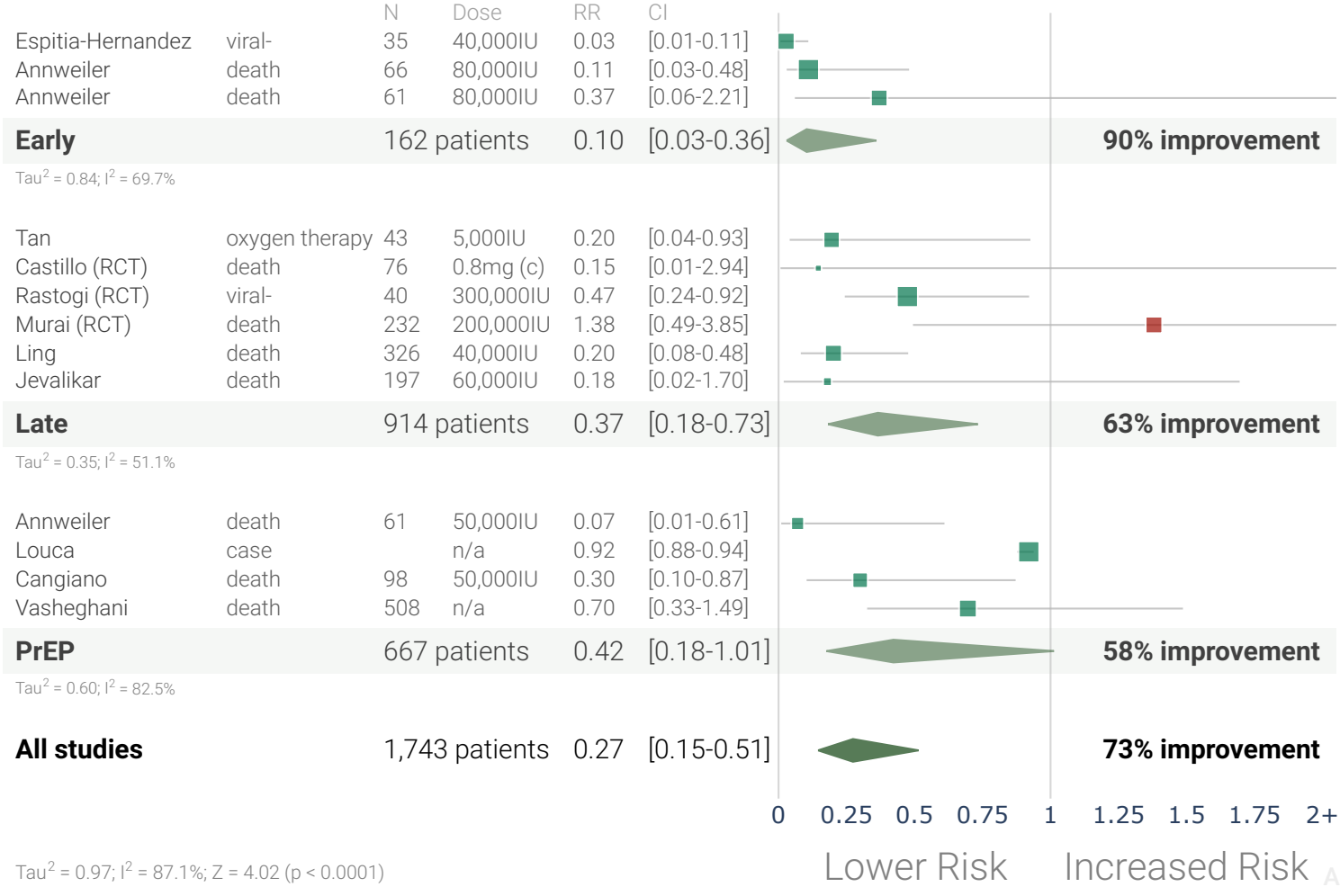
Treatment studies	73% improvement	RR 0.27 [0.15-0.51]
Sufficiency studies	50% improvement	RR 0.50 [0.41-0.59]

Total	38 studies	332 authors	6,384 patients
Treatment	13 studies	131 authors	1,743 patients

Show forest plot for:
Treatment studies
Treatment with exclusions
Treatment mortality
Sufficiency studies

All vitamin D COVID-19 treatment studies

vdmeta.com 1/19/21



Tau² = 0.97; I² = 87.1%; Z = 4.02 (p < 0.0001)

[*Cangiano*], 12/22/2020, retrospective, Italy, Europe, peer-reviewed, 14 authors, dosage 25,000IU 2x per month.	**risk of death, 70.0% lower, RR 0.30, p = 0.04**, treatment 3 of 20 (15.0%), control 39 of 78 (50.0%).
[*Louca*], 11/30/2020, retrospective, United Kingdom, Europe, preprint, 26 authors, dosage not specified.	**risk of COVID-19 case, 8.0% lower, RR 0.92, p < 0.001**, United Kingdom.
	risk of COVID-19 case, 24.0% lower, RR 0.76, p < 0.001, treatment 19444, control 26313, United States.
	risk of COVID-19 case, 19.0% lower, RR 0.81, p < 0.001, treatment 6722, control 20651, Sweden.
[*Vasheghani*], 1/18/2021, retrospective, Iran, Middle East, preprint, 5 authors, dosage not specified.	**risk of death, 30.4% lower, RR 0.70, p = 0.45**, treatment 7 of 88 (8.0%), control 48 of 420 (11.4%), vitamin D supplementation.
	risk of ICU admission, 63.8% lower, RR 0.36, p = 0.009, treatment 13 of 185 (7.0%), control 53 of 323 (16.4%), adjusted per study, vitamin D levels >30ng/mL.

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