Covid-19 and Vitamin D Information

Dr Gareth Davies (PhD), Dr Joanna Byers (MBChB), Dr Attila R Garami (MD, PhD)

Author Bios

This document is for medical professionals only.

June 2020 UPDATE: We have now published v3 of our full research in preprint on medRxiv which includes a causal inference analysis verifying a causal link between vitamin D status and COVID-19 outcomes:
Evidence Supports a Causal Role for Vitamin D Status in COVID-19 Outcomes

This document is no longer being updated.

Call for data: we ask ICUs to test serum levels, add D3 to treatment plans, measure outcomes and report. Early clinical evidence will support clinical trial applications.
Please Test, Treat, Measure, Report.

A 2-page summary of this report can be found here: bit.ly/VitDCovid19SummaryShort
Posters for GPs and ICUs: bit.ly/VitDCovid19Posters

Evidence strongly suggests Vitamin D supplements could be effective in preventing Covid-19, and play a key role in treating patients if added to existing treatment plans, especially if this is done early in the disease progression.

This is **not** to be taken as a reason to stop isolating and social distancing! **This document is for medical professionals only.** Until further advised everyone should continue to social distance and isolate. **The authors have been self-isolating for weeks and continue to do so.**

TL;DR Summary

- Vitamin D deficiency is common during winter in northern latitudes above 20 degrees and southern latitudes 20 degrees below the equator.
- Severe Covid-19 outbreaks have only happened above 20 degree latitudes (23rd March 2020). Outbreaks in the southern summer hemisphere have been mild so far.
- SARS-Cov-2 virus enters cells via ACE2 receptors. Viral replication downregulates ACE2 dysregulating the renin-angiotensin system and leads to a cytokine storm in the host, causing Acute Respiratory Distress Syndrome (ARDS).
- Vitamin D deficiency is strongly associated with ARDS, poor mortality outcomes as well as being associated with the majority of comorbidities associated with Covid-19 case fatalities.
- Vitamin D acts to rebalance RAS and attenuates lung injury.

- Vitamin D supplementation reduces the risk of acute respiratory tract infection.
- Vitamin D is a steroid hormone naturally produces in the skin in summer exposure to UVB light. It is considered safe to take as cholecalciferol (D3) oral supplements in doses up to a maximum of 4,000iu/d for short periods.
- For healthy young individuals, NICE recommendations advise “all adults living in the UK, including people at increased risk of vitamin D deficiency, should take a daily supplement containing 400 international units (IU [10 micrograms]) of vitamin D throughout the year, including in the winter months”.
- Young people with known Vitamin D deficiency and those older than 60 and should supplement with 2,000iu/d during winter. The Scientific Advisory Committee on Nutrition (SACN, 2016) does not recommend routine monitoring of serum vitamin D levels during long-term supplementation with vitamin D. Furthermore, expert opinion in the National Osteoporosis Guideline Group 2017 (NOG 2017) is that routine monitoring of serum 25(OH)D levels is unnecessary for people on long-term maintenance doses of vitamin D (up to 2000 IU a day).
- Please note prolonged supplementation at higher levels carries a risk of hypercalcaemia (Contraindications, British National Formulary) and should only be undertaken with professional advice.
- If you are able to get exposure to natural sunlight then your body will synthesize Vitamin D and you are less likely to need supplements to maintain healthy levels.

Supporting Evidence

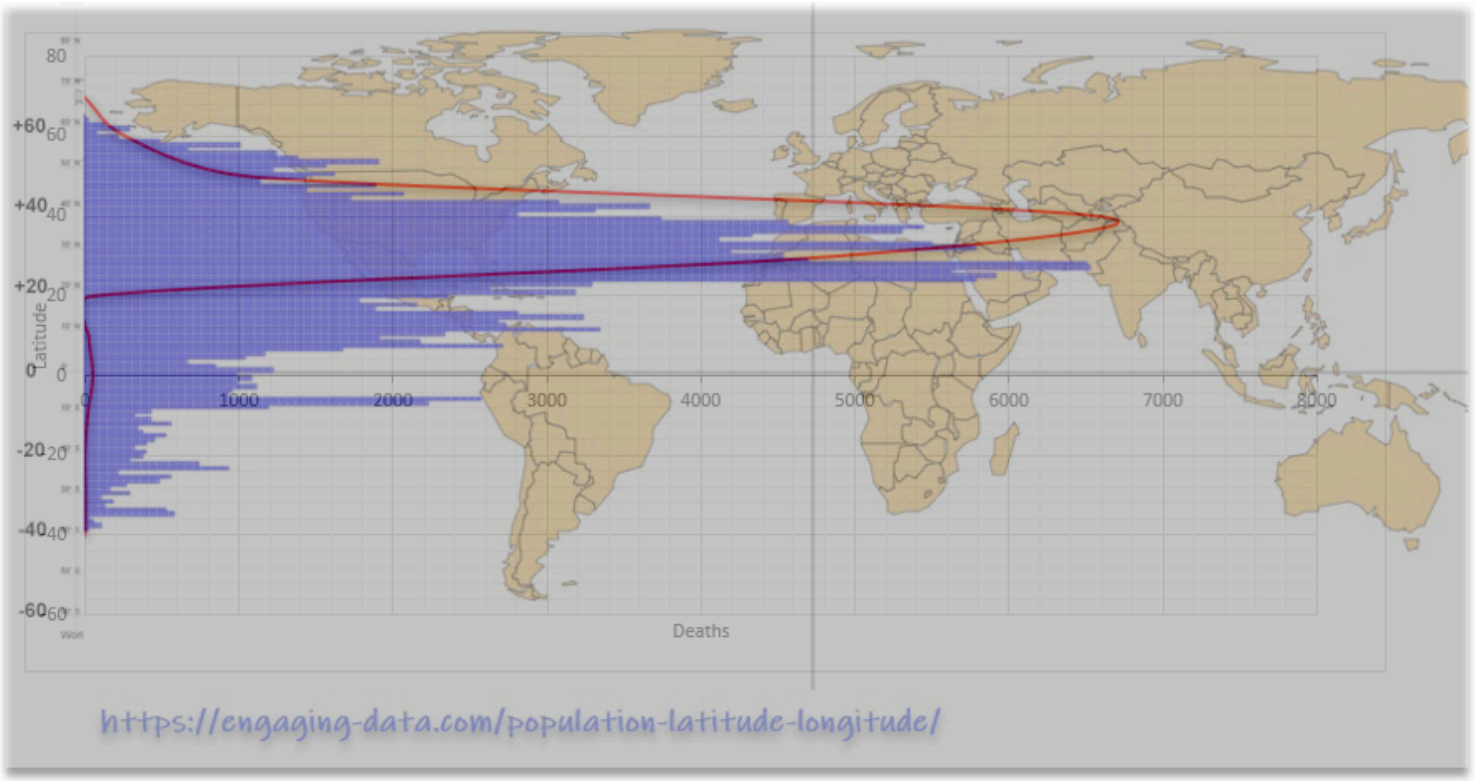
Coronavirus Seasonality and Correlation with Latitude

Summary of findings in this section

- **Coronaviruses and influenza viruses in the past have displayed very strong seasonality with winter appearances.**
- **Covid-19 severe outbreaks have so far only happened north of the 20º latitude line in the current winter hemisphere.**
- **Vitamin D deficiency occurs during winter since Vitamin D is synthesised in the skin during summer exposure to UVB rays.**
- **Italy has one of the worst Vitamin D deficiency rates in Europe and has paid the highest death toll. Italy found serum levels of Vitamin D lower than 12 ng/ml (<30 nmol/L) in as many as 76% of 700 women tested between the ages 60-80 yrs.**
- **Japan is an outlier in the north, with only a very mild outbreak and has the lowest incidence of Vitamin D deficiency thanks to its high fish-content diet. (No doubt other factors also contribute in both countries). Prevalence of hypovitaminosis D (<30 nmol/L) in women over 30 years old in Japan is only 10.3% and in active elderly (25(OH)D <75 nmol/L) is below 5%.** [Social, cultural and behavioural differences account for slower spread but not lower case fatality rates.]

Deaths by latitude with population by latitude shows a striking northern hemisphere bias

Plotting Covid-19 deaths by latitude (22nd March 2020) and overlaying with population reveals a striking northern (winter) hemisphere bias above the 20 degree latitude line in the severity of outbreaks. In tropical latitudes and southern hemisphere locations, the Covid-19 outbreaks have been very mild. Case Fatality Rates in lower latitudes have been very low relative to northern locations.



Previous Coronavirus and influenza outbreaks have also shown strong seasonality

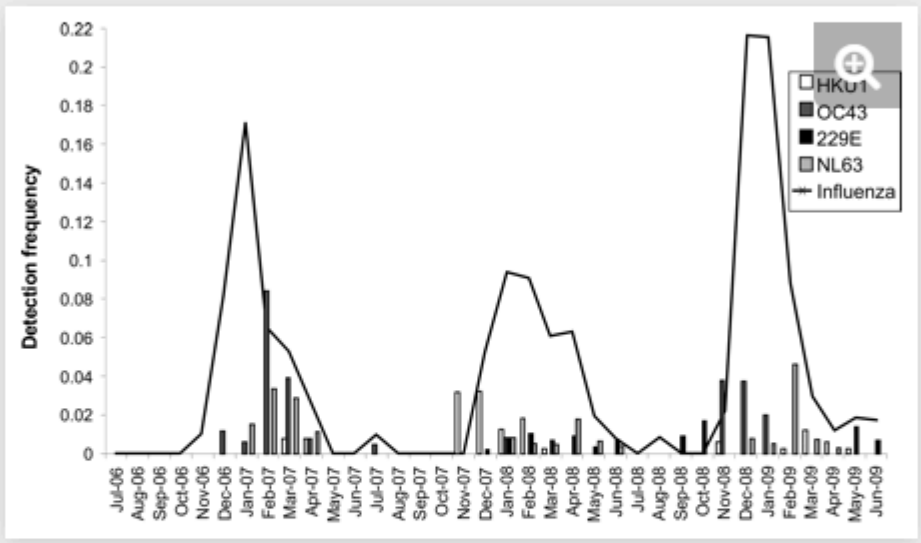


FIG. 2. Open in new tab | Download powerpoint

Coronavirus and influenza virus (A and B combined) detection frequencies by month over the 3 years of the study.

Source: https://jcm.asm.org/content/48/8/2940

“Four human coronaviruses (HCoV-229E, HCoV-HKU1, HCoV-NL63, and HCoV-OC43) are associated with a range of respiratory outcomes, including bronchiolitis and pneumonia … we conducted a large-scale comprehensive screening for all four coronaviruses by analysis of 11,661 diagnostic respiratory samples collected in Edinburgh, United Kingdom, over 3 years between July 2006 and June 2009 using a novel

four-way multiplex real-time reverse transcription-PCR (RT-PCR) assay. Coronaviruses were detected in 0.3 to 0.85% of samples in all age groups. Generally, **coronaviruses displayed marked winter seasonality between the months of December and April and were not detected in summer months**, which is comparable to the pattern seen with influenza viruses. HCoV-229E was the exception; detection was confined to the winter of 2008 and was sporadic in the following year."

Italy (latitude 39º to 45º north) most severe outbreak, high CFR

Andrea Guistina, Professor of Endocrinology,
Anna Maria Formenti Vita-Salute San Raffaele University, Milano
Wrote to the BMJ noting:
"Italy is the Country that is paying the highest death toll to Covid19 infection in the whole world (reaching today the impressive number of 4000 in less than four weeks and exceeding already by far the number of deaths of slightly more than 3.200 so far reported in China)) (3). From the analysis of epidemiological data available particularly in the Chinese Literature but also in the reports of the Italian Ministry of Health the majority of deaths is concentrated in the elderly with common, although not necessarily deadly per se, comorbidities such as hypertension, diabetes or obesity(4). In fact, it has been suggested that the elevated mean age of the Italian population (5) could be a predisposing factor to the severity and elevated mortality related to Covid infection. This has led to the hypothesis that Italians may die with Coronavirus infection rather than for Coronavirus infection, Nevertheless, a convincing explanation on the reason(s) of this so far anomalous and deadly impact of Covid in Italy and particularly in the Northern Regions has not so far been provided. Interestingly, epidemiological data report that **Italy is one of the Countries with the highest prevalence of hypovitaminosis D in Europe**. A study from Isaia et al on 700 women aged 60-80 yrs in **Italy found values of 25OH vitaminD lower than 5 ng/ml in 27% of the women and lower than 12 ng/ml in as many as 76%**. (6) Moreover, the same group found a very high prevalence of hypovitaminosis D in elderly women with diabetes (7). Finally, another Italian study found a winter prevalence of hypovitaminosis D up to 32% of healthy postmenopausal women and to 82% in patients engaged in long-term rehabilitation programmes because of various neurological disorders.(8). Obesity has also been suggested to be linked to low vitamin D and higher vitamin D requirements (9)"

No doubt Italian culture which is normally socially very close has also contributed to the rapid spread of infection.

Japan is an outlier in the North (latitude 30º to 45º north)

Japan's recovery rates are 7 times higher than deaths. In all other norther territories, deaths and recovery rates have followed a 1:1 ratio until the outbreaks have been brought under control.
Japan is a more socially distant culture, and compliance with hygiene recommendations has been high.
Japan also has a strikingly low incidence of Vitamin D deficiency compared to Europe. This is attributed to its high fish-content diet.

http://users.metu.edu.tr/azulfu/OseopIntRevVitD_.pdf
"Overall, the vitamin D status in Japan is relatively better in the regions in South Asia and positively related to fish consumption [49–51]. Prevalence of hypovitaminosis D (<30 nmol/L) in women over 30 years old is only 10.3% [49] and **in active elderly (25(OH)D <75 nmol/L) is below 5%** [50]."
"The vitamin D status within different European countries shows a high variation [53]. A serum 25(OH)D lower than Osteoporos Int 25 nmol/l was found in 2% to 30% of adults, but this percentage may increase to 75% or more in older persons in institutions [4]."

SARS-Cov-2 biochemistry and ARDS

Summary of findings in this section

- **SARS-Cov-2 virus enters cells via ACE2 receptors.**
- **Viral replication downregulates ACE2 dysregulating the renin-angiotensin system**
- **Imbalance in the steady-state cytokine regulatory axis involving RAS and IP-10 leads to a cytokine storm in the host causing Acute Respiratory Distress Syndrome (ARDS).**

ACE-2: The Receptor for SARS-CoV-2

https://www.rndsystems.com/resources/articles/ace-2-sars-receptor-identified

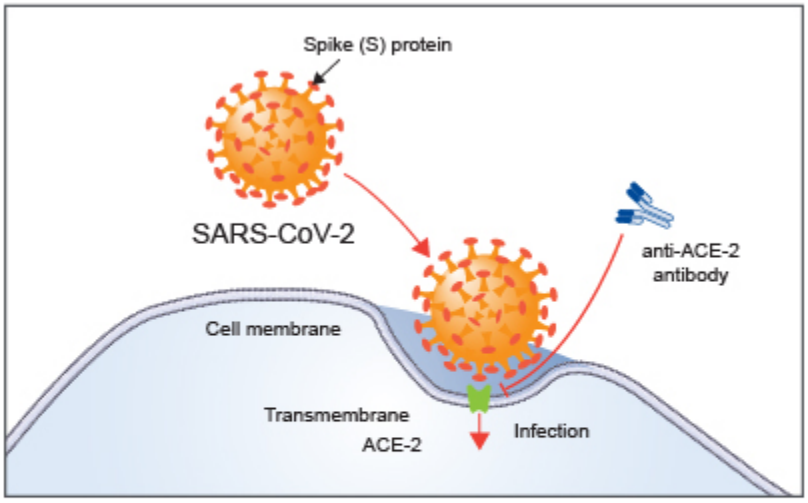


Figure 1. ACE-2 is the host cell receptor responsible for mediating infection by SARS-CoV-2, the novel coronavirus responsible for coronavirus disease 2019 (COVID-19). Treatment with anti-ACE-2 antibodies disrupts the interaction between virus and receptor.

ACE-2

ACE-2 is a type I transmembrane metallocarboxypeptidase with homology to ACE, an enzyme long-known to be a key player in the Renin-Angiotensin system (RAS) and a target for the treatment of hypertension.14 It is mainly expressed in vascular endothelial cells, the renal tubular epithelium, and in Leydig cells in the testes.15,16 PCR analysis revealed that ACE-2 is also expressed in the lung, kidney, and gastrointestinal tract, tissues shown to harbor SARS-CoV.17-19 The major substrate for ACE-2 is Angiotensin II.20 ACE-2 degrades Angiotensin II to generate Angiotensin 1-7, thereby, negatively regulating RAS.15,20 ACE-2 has also been shown to exhibit a protective function in the cardiovascular system and other organs.15

ACE-2 is an Entry Receptor for SARS-CoV-2

Based on the sequence similarities of the RBM between SARS-CoV-2 and SARS-CoV, several independent research groups investigated if SARS-CoV-2 also utilizes ACE-2 as a cellular entry receptor. Zhou et al. showed that SARS-CoV-2 could use ACE-2 from humans, Chinese horseshoe bars, civet cats, and pigs to gain entry into ACE-2-expressing HeLa cells.5 Hoffmann et al. reported similar findings for human and bat ACE-2.21 Additionally, Hoffmann et al. showed that treating Vero-E6 cells, a monkey kidney cell line known to permit SARS-CoV

replication, with an Anti-ACE-2 Antibody (R&D Systems, Catalog # AF933) blocked entry of VSV pseudotypes expressing the SARS-CoV-2 S protein.21

Replication-dependent downregulation of cellular angiotensin-converting enzyme 2 protein expression by human coronavirus NL63

https://www.ncbi.nlm.nih.gov/pubmed/22718567

Like severe acute respiratory syndrome coronavirus (SARS-CoV), human coronavirus (HCoV)-NL63 employs angiotensin-converting enzyme 2 (ACE2) as a receptor for cellular entry. **SARS-CoV infection causes robust downregulation of cellular ACE2 expression levels and it has been suggested that the SARS-CoV effect on ACE2 is involved in the severity of disease**. We investigated whether cellular ACE2 downregulation occurs at optimal replication conditions of HCoV-NL63 infection. The expression of the homologue of ACE2, the ACE protein not used as a receptor by HCoV-NL63, was measured as a control. A specific decrease for ACE2 protein level was observed when HCoV-NL63 was cultured at 34 °C. Culturing the virus at the suboptimal temperature of 37 °C resulted in low replication of the virus and the effect on ACE2 expression was lost. We conclude that **the decline of ACE2 expression is dependent on the efficiency of HCoV-NL63 replication, and that HCoV-NL63 and SARS-CoV both affect cellular ACE2 expression during infection**.

GD Note: If SARS-Cov-2 similarly downregulates ACE2 (which appears to be the case), then this will trigger RAS and lead to cytokine storm which in turn leads to ARDS.

TWIRLS, an automated topic-wise inference method based on massive literature, suggests a possible mechanism via ACE2 for the pathological changes in the human host after coronavirus infection

https://www.medrxiv.org/content/10.1101/2020.02.24.20025437v1

Extract: “Using the TWIRLS system, we found that an important regulatory factor angiotensin-converting enzyme 2 (ACE2) may be involved in the host pathological changes on binding to the coronavirus after infection. **After triggering functional changes in ACE2/AT2R, an imbalance in the steady-state cytokine regulatory axis involving the Renin-Angiotensin System and IP-10 leads to a cytokine storm.**”

Into the Eye of the Cytokine Storm

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3294426/

Upregulation of the Chemokine (C-C Motif) Ligand 2 via a Severe Acute Respiratory Syndrome Coronavirus Spike-ACE2 Signaling Pathway

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2897593/

Dysregulation of inflammatory cytokines and adhesion molecules may be involved in lung injury that causes acute respiratory distress syndrome. High levels of proinflammatory cytokines such as interleukin-6, transforming growth factor β (TGF-β), and tumor necrosis factor alpha (TNF-α) were detected in the sera and ACE2+ cells of SARS patients (12, 45). Elevated levels of cytokines, including alpha interferon (IFN-α), IFN-β, IFN-γ, CCL3, CCL5, and CXCL10, were also detected in SARS-CoV-infected macrophages, dendritic cells, and a colon carcinoma cell line (1, 5, 25). It is possible that the high fatality rate of SARS results from a severe immune response caused by cytokines and chemokines.

Vitamin D biochemistry, RAS and ARDS

Summary of findings in this section

- **Chronic Vitamin D deficiency induces lung fibrosis through activation of the RAS.**
- **Vitamin D deficiency contributes directly to the acute respiratory distress syndrome (ARDS).**
- **Low Vitamin D Status Occurs in 90% of Patients with ARDS and Is Associated with Longer Duration of Mechanical Ventilation.**
- **Vitamin D prevents experimental lung fibrosis and predicts survival in patients with idiopathic pulmonary fibrosis.**
- **Vitamin D alleviates lipopolysaccharide-induced acute lung injury via regulation of the renin-angiotensin system.**
- **VDR Attenuates Acute Lung Injury by Blocking Ang-2-Tie-2 Pathway and Renin-Angiotensin System.**
- **1,25-dihydroxyvitamin D3 suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin gene promoter.**
- **Vitamin D supplementation is safe and protects against respiratory tract infection.**
- **Studies in HIV patients show Vitamin D induces anti-inflammatory responses through direct effects on T-cells. Vitamin D promotes an anti-inflammatory response by inhibiting the maturation of dendritic cells, downregulating antigen presenting molecules (MHC-class II), costimulatory molecules (e.g., CD40, CD80, and CD86), and pro-inflammatory cytokines (e.g., IL-12 and IL-23); Simultaneously, Vitamin D enhances anti-inflammatory cytokine (IL-10) and T-cell inhibitory molecule (PD-1).**

Chronic vitamin D deficiency induces lung fibrosis through activation of the renin-angiotensin system

https://www.ncbi.nlm.nih.gov/pubmed/28607392#

Excerpt: “Chronic vitamin D deficiency destructs lung structures, impairs lung development and stimulates ECM deposition. RAS components are also found to increase. These effects seem to worsen with prolonged vitamin D deficiency. By giving RAS blockers, these changes can be largely rescued. However, a smooth muscle relaxant whose regulatory effect on blood pressure is independent of RAS does not show similar effects. This study demonstrated that chronic vitamin D deficiency may induce RAS activation, which subsequently stimulates the expression of profibrotic factors and activates the fibrotic cascade.”

GD Note: In some Covid-19 patients, lung function can decline by 20-30% after recovery. Pulmonary fibrosis is suspected.

Vitamin D deficiency contributes directly to the acute respiratory distress syndrome (ARDS)

https://scholar.harvard.edu/kennethbchristopher/publications/vitamin-d-deficiency-contributes-directly-acute-respiratory

Low Vitamin D Status Occurs in 90% of Patients with ARDS and Is Associated with Longer Duration of Mechanical Ventilation

https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2016.193.1_MeetingAbstracts.A1846

Vitamin D alleviates lipopolysaccharide-induced acute lung injury via regulation of the renin-angiotensin system

https://www.spandidos-publications.com/10.3892/mmr.2017.7546

It is established that vitamin D exhibits anti-inflammatory effects, however, the specific effect of vitamin D on ALI remains largely unknown. The aim of the present study was to investigate whether, and by which mechanism, vitamin D alleviates lipopolysaccharide (LPS)-induced ALI. The results demonstrated that a vitamin D agonist, calcitriol, exhibited a beneficial effect on LPS-induced ALI in rats; calcitriol pretreatment significantly improved LPS-induced lung permeability, as determined using Evans blue dye. Results from reverse transcription-quantitative polymerase chain reaction, western blotting and ELISA analysis demonstrated that calcitriol also modulated the expression of members of the renin-angiotensin system (RAS), including angiotensin (Ang) I-converting enzymes (ACE and ACE2), renin and Ang II, which indicates that calcitriol may exert protective effects on LPS-induced lung injury, at least partially, by regulating the balance between the expression of members of the RAS.

VDR Attenuates Acute Lung Injury by Blocking Ang-2-Tie-2 Pathway and Renin-Angiotensin System

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3857197/

Taken together, **these observations provide evidence that the vitamin D-VDR signaling prevents lung injury by blocking the Ang-2-Tie-2-MLC kinase cascade and the renin-angiotensin system.**

1,25-dihydroxyvitamin D3 suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin gene promoter

https://www.ncbi.nlm.nih.gov/pubmed/17690094

We have shown that 1,25-dihydroxyvitamin D(3) (1,25(OH)(2)D(3)) down-regulates renin expression. To explore the molecular mechanism, we analyzed the mouse Ren-1c gene promoter by luciferase reporter assays. Deletion analysis revealed two DNA fragments from -2,725 to -2,647 (distal fragment) and from -117 to +6 (proximal fragment) that are sufficient to mediate the repression. Mutation of the cAMP response element (CRE) in the distal fragment blunted forskolin stimulation as well as 1,25(OH)(2)D(3) inhibition of the transcriptional activity, suggesting the involvement of CRE in 1,25(OH)(2)D(3)-induced suppression. EMSA revealed that 1,25(OH)(2)D(3) markedly inhibited nuclear protein binding to the CRE in the promoter. ChIP and GST pull-down assays demonstrated that liganded VDR blocked the binding of CREB to the CRE by directly interacting with CREB with the ligand-binding domain, and the VDR-mediated repression can be rescued by CREB, CBP, or p300 overexpression. **These data indicate that 1,25(OH)(2)D(3) suppresses renin gene expression at least in part by blocking the formation of CRE-CREB-CBP complex.**

Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data.

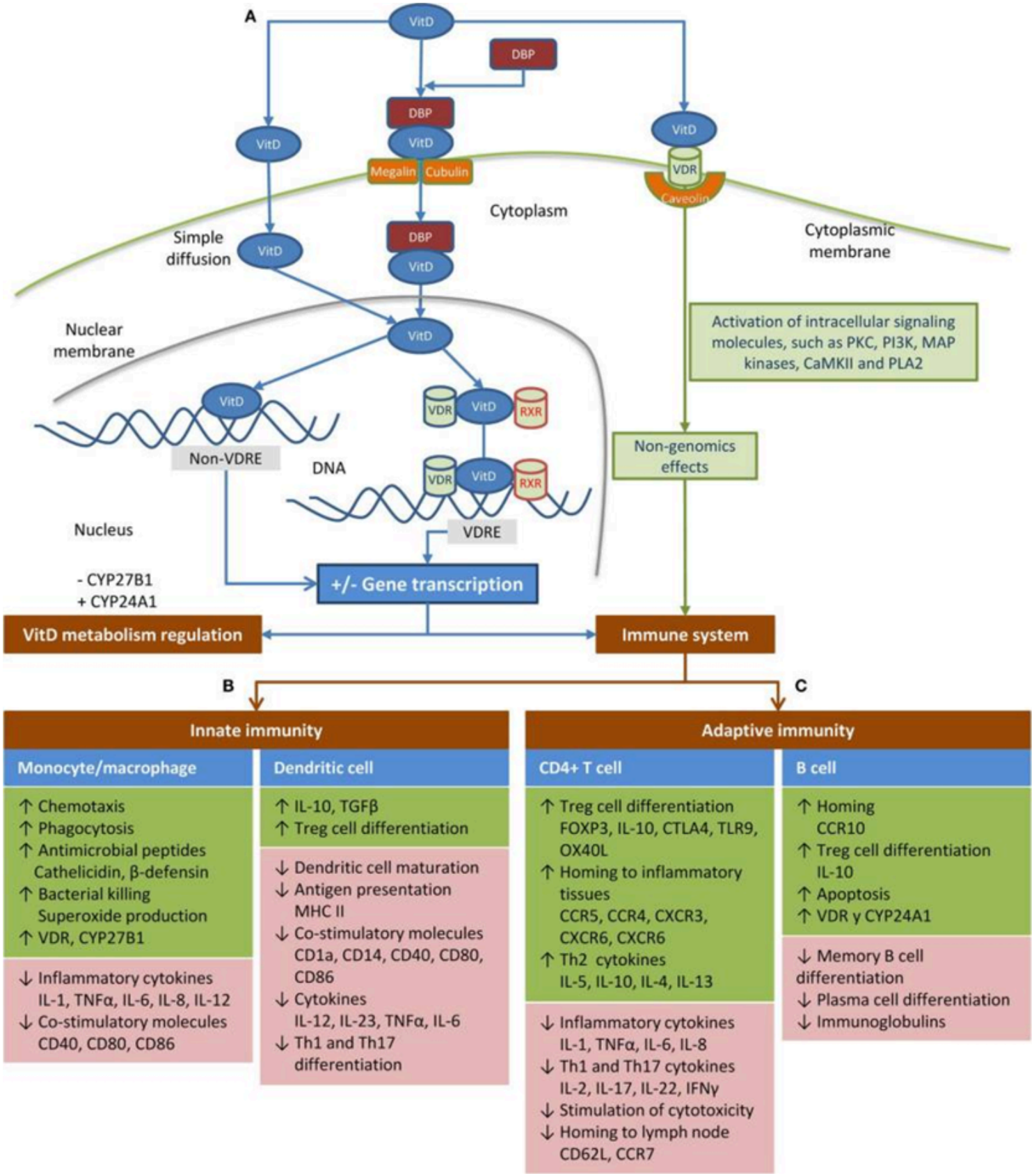
BMJ 2017; 356 doi: https://doi.org/10.1136/bmj.i6583 (Published 15 February 2017)
Cite this as: BMJ 2017;356:i6583

https://www.bmj.com/content/356/bmj.i6583

Conclusion: Vitamin D supplementation was safe and it protected against acute respiratory tract infection overall. Patients who were very vitamin D deficient and those not receiving bolus doses experienced the most benefit.
GD Note: Daily supplementation with vitamin D appears to protect against acute respiratory tract infection. “Over-dosing” once in a while does not. It may make it worse.

Vitamin D in Human Immunodeficiency Virus Infection: Influence on Immunity and Disease

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5857570/
Excerpt: “High levels of VitD and VDR expression are also associated with natural resistance to HIV-1 infection. Conversely, **VitD deficiency is linked to more inflammation and immune activation**, low peripheral blood CD4+ T-cells, faster progression of HIV disease, and shorter survival time in HIV-infected patients. VitD supplementation and restoration to normal values in HIV-infected patients **may improve immunologic recovery during combination antiretroviral therapy, reduce levels of inflammation and immune activation, and increase immunity against pathogens**. Additionally, VitD **may protect against the development of immune reconstitution inflammatory syndrome events, pulmonary tuberculosis, and mortality** among HIV-infected patients. In summary, this review suggests that VitD deficiency may contribute to the pathogenesis of HIV infection. Also, **VitD supplementation seems to reverse some alterations of the immune system, supporting the use of VitD supplementation as prophylaxis, especially in individuals with more severe VitD deficiency.**”



Schematic of transport and mechanism of action of vitamin D (VitD) in the body. **(A)** A small fraction of VitD circulates in the serum as a "free" steroid, having easy access to the intracellular compartment. The remaining VitD is transported in the blood while bound to the vitamin D-binding protein (DBP) (1, 2), which seems to critically regulate the bioavailability of VitD (7). This protein-bound fraction (bound to DBP) is actively transported into the cell by megalin or cubulin. Calcitriol is considered the main ligand of the vitamin D receptor (VDR) to trigger the

effects of VitD, because its affinity is 1,000 times greater than calcidiol (8). When VitD binds to VDR in the nucleus of target cells, it forms a complex with the retinoic acid X receptor (RXR), which controls transcriptional activity of target genes. This heterodimer binds to VitD response elements (VDREs), a predefined promoter DNA sequence, initiating gene transcription processes, which covers around 5% of the human genome and 36 different cell types (4). However, there are genes regulated by VitD that do not contain VDREs (9). These genes may be regulated by microRNAs, phosphorylation, or other modifications of proteins, which affect their stability or the activity of proteases that target them (9). Additionally, non-genomic effects have been reported when the VDR is situated on the cell membrane (VDRm) complexed to caveolin (5), which immediately activates several intracellular pathways, such as mitogen-activated protein kinases, protein kinase C (PKC), protein kinase A, and Ca2+-calmodulin kinase II through the activation of several signaling molecules (5). VitD may reduce its synthesis by inhibiting CYP27B1 and increases its degradation by inducing CYP24A1 (6). **(B)** VitD modulates the function of monocytes/macrophages and dendritic cells (DCs) in response to infections. In monocytes/macrophages, 1,25(OH)2D leads to the expression of multi-target genes, among which are cathelicidin microbial peptide (10, 11), human β-defensin 4 (DEFB4) (12), and genes involved in autophagy and phagosome maturation, all of which are involved in the intracellular destruction of pathogens (7, 13). Furthermore, 1,25(OH)2D enhances the chemotactic and phagocytic capacity of macrophages (14). Moreover, **VitD also promotes an anti-inflammatory response** by inhibiting the maturation of DCs, resulting in a phenotype characterized by the downregulation of antigen presenting molecules (MHC-class II), costimulatory molecules (e.g., CD40, CD80, and CD86), **and pro-inflammatory cytokines** (e.g., IL-12 and IL-23); **while an anti-inflammatory cytokine (IL-10) and T-cell inhibitory molecule (PD-1) are enhanced** (15–22). Therefore, VitD induces hypo-responsiveness and allows a shift in the T-cell polarization from the pro-inflammatory Th1 and Th17 responses to a more tolerogenic Th2 response (16, 17, 20, 22–24), which leads to an altered alloreactive T cell activation (25). **(C) VitD induces anti-inflammatory responses through direct effects on T-cells.** Specifically, 1,25(OH)2D inhibits the proliferation of T-cells by blocking mitosis and IL-2 production (26, 27), limits the differentiation of Th1/Th17 cells, which favors Th2 differentiation (28–32), and induces the generation of IL-10 secretory Treg cells (32–34). Additionally, T-cell proliferation is significantly reduced when DCs are exposed to 1,25(OH)2D3 (16). T-cell cytokines also regulate VitD metabolism by monocytes. Thus, the Th1 cytokine IFN-γ induces CYP27B1, leading to the conversion of 25(OH)D to 1,25(OH)2D, whereas the Th2 cytokine IL-4 promotes upregulation of CYP24A1 (35). Stimulation of B-cells with 1,25(OH)2D leads to apoptosis, impaired plasma cell differentiation, decreased antibody production, inhibition of memory B-cell formation, and increased production of IL-10 (32, 36–41).

Vitamin D and comorbidities associated with covid-19 case fatalities

Summary of findings in this section

- **Vitamin D is causal in reducing development of all cancers, including colorectal cancer.**
- **Mortality rates for colorectal cancer have been shown to correlate with latitude.**
- **Vitamin D insufficiency/deficiency plays a causative role in the prevalence of Crohn's Disease.**
- **People living near the equator are at low risk of developing inflammatory bowel disease, however, upon migration to developed countries in temperate climates, the risk of IBD increases.**
- **Regular doses of vitamin D (VTD)—about 2000 IU/d—early in life have been shown to reduce the risk of developing type 1 diabetes (up to an 80% reduction projected over the next 30 years)**
- **Vitamin D is implicated in procognitive and neuroprotective functions, including the reduction of Alzheimer's disease hallmarks**

- **Nicotine (smoking) downregulates ACE2 almost certainly worsening Covid-19 outcomes for smokers and ex-smokers.**

Vitamin D and gastrointestinal diseases: inflammatory bowel disease and colorectal cancer

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3036961/
GD Note: The abstract doesn't summarise findings, but the paper shows Vitamin is causal in reducing development of all cancers, including colorectal cancer, and that it has long been noted that cancer mortality including mortality from CRC increases with geographical latitude [Garland and Garland, 1980]; Recently, one group observed that 1,25D signalling is a direct inducer of NOD2 expression arguing strongly that **vitamin D insufficiency/deficiency does play a causative role in the prevalence of CD** [Wang et al. 2010]; IBD also correlates to latitute and shows seasonal variations consistent with Vitamin D playing a key role.
GD Note 2: GI Symptoms found in nearly half of patients with covid-19.

Vitamin D and diabetes - Improvement of glycemic control with vitamin D3 repletion

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2426990/
GD Note: Diabetes is another comorbidity associated with high case fatality rate of covid-19.

Vitamin D and Dementia

https://www.ncbi.nlm.nih.gov/pubmed/29214280
Excerpt: "Emerging evidence suggests that low vitamin D concentrations are potentially involved in the pathogenesis of dementia. This is of particular interest when considering the high prevalence of vitamin D deficiency in elderly adults and the urgent need to identify modifiable risk factors for dementia. Studies have found that vitamin D is implicated in procognitive and neuroprotective functions, including the reduction of Alzheimer's disease hallmarks such as amyloid beta and phosphorylated tau. Cross-sectional studies have consistently found that vitamin D concentrations are significantly lower in individuals with Alzheimer's disease and cognitive impairment compared to healthy controls. Longitudinal studies support an association between low vitamin D concentrations and an increased risk of dementia and cognitive decline"
GD Note: dementia is yet another comorbidity associated with high CFR w.r.t. covid-19.

Nicotine and the renin-angiotensin system

https://www.ncbi.nlm.nih.gov/pubmed/30088946
Extract: "The literature presented in this review strongly suggests that nicotine alters the homeostasis of the RAS by upregulating the detrimental angiotensin-converting enzyme (ACE)/angiotensin (ANG)-II/ANG II type 1 receptor axis and downregulating the compensatory ACE2/ANG-(1-7)/Mas receptor axis, contributing to the development of CVPD."
GD Note: The reason for this line of investigation was smoking was implicated in higher case fatality rates especially in males in China. Italy and Spain both have a strong cultural history of smoking too.

Rapid Response Letters to BMJ

12th Mar 2020 Rapid response to: Preventing a covid-19 pandemic [pub date: 28 Feb]

Attila R Garami
MD, PhD, Senior Biomarker Consultant
https://www.bmj.com/content/368/bmj.m810/rr-24

20th March 2020 Rapid Response: Re: Preventing a covid-19 pandemic Can high prevalence of severe hypovitaminosis D play a role in the high impact of Covid infection in Italy?

Andrea Giustina
Professor of Endocrinology
Anna Maria Formenti
Vita-Salute San Raffaele University, Milano
IRCCS San Raffaele Hospital, via Olgettina 60, 20132 Milano, Italy
https://www.bmj.com/content/368/bmj.m810/rr-36

Reports from Severe Outbreak Locations

Italy - Report on the characteristics of COVID-19 positive deceased patients

Report sulle caratteristiche dei pazienti deceduti positivi a COVID-19 in Italia Il presente report è basato sui dati aggiornati al 17 Marzo 2020

https://www.epicentro.iss.it/coronavirus/bollettino/Report-COVID-2019_17_marzo-v2.pdf

English Translation by Google:

Report on the characteristics of COVID-19 positive deceased patients in Italy This report is based on data updated to 17 March 2020

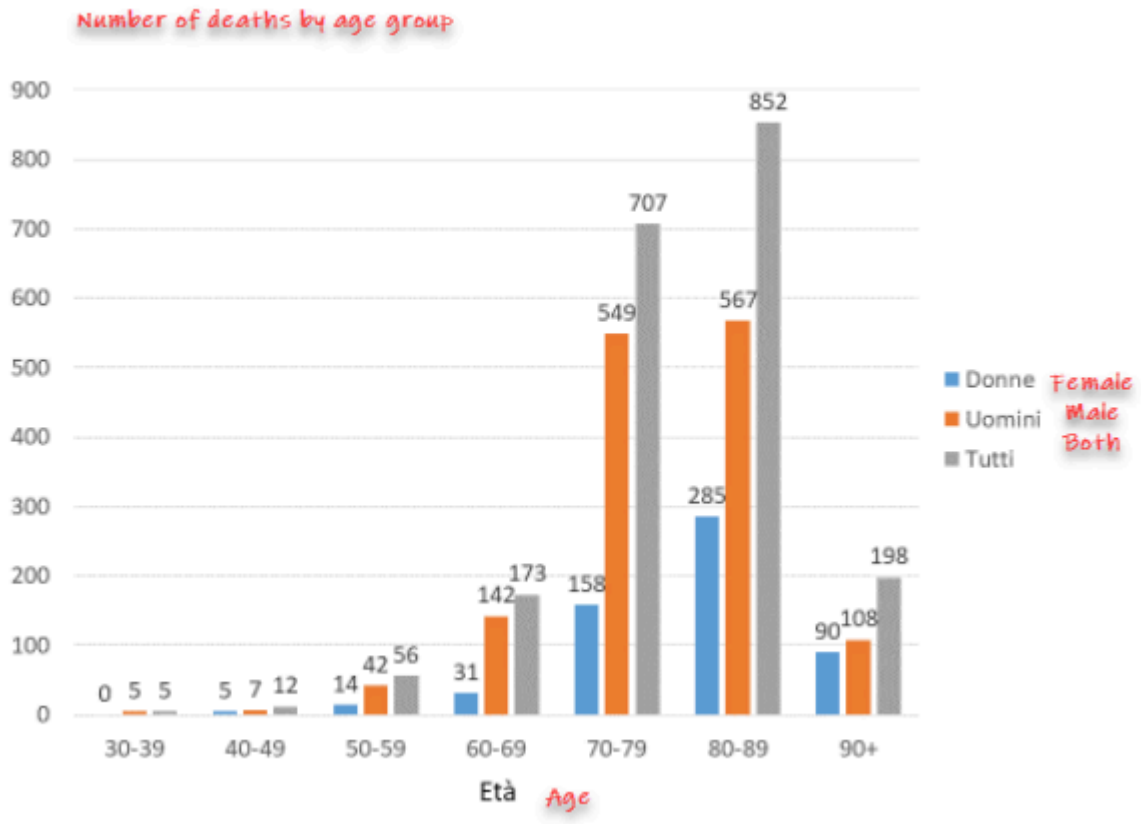
https://translate.google.com/translate?hl=en&sl=auto&tl=en&u=https%3A%2F%2Fwww.epicentro.iss.it%2Fcoronavirus%2Fbollettino%2FReport-COVID-2019_17_marzo-v2.pdf

Excerpts
“The mean age of deceased and positive COVID-19 patients is 79.5 years (median 80.5, range 31-103, Range InterQuartile - IQR 74.3-85.9). There are **601 women (30.0%)**. *Figure 1* shows that the median age

of the patients COVID-19 positive deaths is more than 15 years higher than that of patients who contracted the infection (median age: patients who died 80.5 years - patients with infection 63 years).

Figure 2 shows the number of deaths by age group. Women who died after contracting COVID-19 infection they are older than men (median ages: women 83.7 - men 79.5)."

Figura 2. *Numero di decessi per fascia di età*



"*Table 1* presents the most common pre-existing chronic pathologies (diagnosed before contracting infection) in deceased patients. **This figure was obtained in 355/2003 deaths (17.7% of the sample total).** The average number of pathologies observed in this population is 2.7 (median 2, Deviation Standard 1.6). Overall, 3 patients (0.8% of the sample) had 0 pathologies, 89 (25.1%) had 1 pathology, 91 had 2 pathologies (25.6%) and 172 (48.5%) had 3 or more pathologies."

Table 1. *Most common diseases observed in patients who died as a result of COVID-2019 infection*

diseases	***N***	***%***
Ischemic heart disease	*117*	*33.0*
Atrial fibrillation	*87*	*24.5*
Stroke	*34*	*9.6*
Hypertension	*270*	*76.1*
Diabetes mellitus	*126*	*35.5*
Dementia	*24*	*6.8*
COPD	*47*	*13.2*
Active cancer in the past 5 years	*72*	*20.3*
Chronic liver disease	*11*	*3.1*
Chronic renal failure	*64*	*18.0*
Number of pathologies		
0 pathologies	*3*	*0.8*
1 pathologies	*89*	*25.1*
2 pathologies	*91*	*25.6*
3 or more pathologies	*172*	*48.5*

GD Note: It's unclear what methodology they used nor categorisation scheme, but almost all of the above conditions are either associated with or can be caused or aggravated by low vitamin D levels. It could simply be a correlation since Vitamin D is essential for normal function, but adds strength to the hypothesis and case for clinical study and data collection. 355 patients isn't a large enough sample to draw conclusions from in this respect.
https://www.medicinenet.com/vitamin_d_deficiency/article.htm

Notes about Virus Types

Common Features of Enveloped Viruses and Implications for Immunogen Design for Next-Generation Vaccines

https://www.cell.com/cell/pdf/S0092-8674(18)30231-9.pdf
"The group of enveloped viruses carrying class I fusion proteins includes respiratory viruses such as the **influenza viruses** (four genera in the **Orthomyxovirus** family: influenza A, B, C and D), the respiratory syncytial virus (RSV, Pneumoviridae family) and the related measles, mumps and parainfluenza viruses in the Paramyxoviridae family, which also includes the recently emerged zoonotic Hendra and Nipah encephalitis viruses that cause serious disease in humans. Other respiratory virus members of the Class

I group include the **coronaviruses** (CoVs) (Coronaviridae family) responsible for seasonal respiratory infections (NL73 CoV and HKU1 CoV, for instance), as well as the zoonotic severe acquired respiratory syndrome (SARS CoV) and Middle-Eastern respiratory syndrome coronaviruses (MERS CoV). The Retroviridae family, exemplified by HIV and the human T cell leukemia viruses (HTLVs), represent a very important subset of class I viruses. Last but not least, several important hemorrhagic fever agents have class I fusion proteins, the most notable ones being Lassa virus together with other members of the Arenaviridae family, and Ebola virus and relatives in the Filoviridae family."

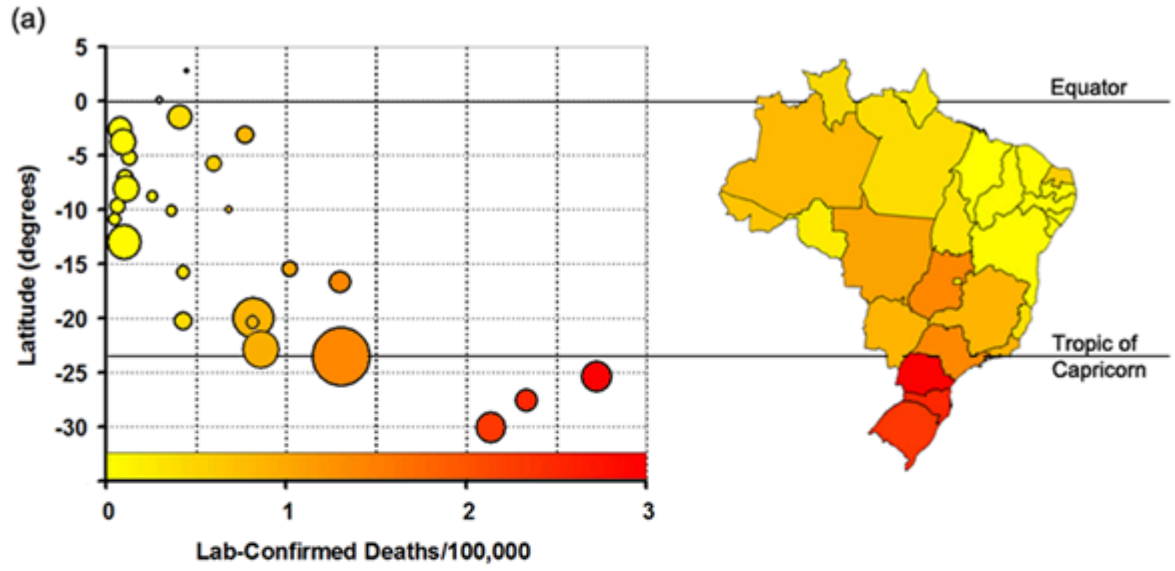
Historical Supporting Evidence

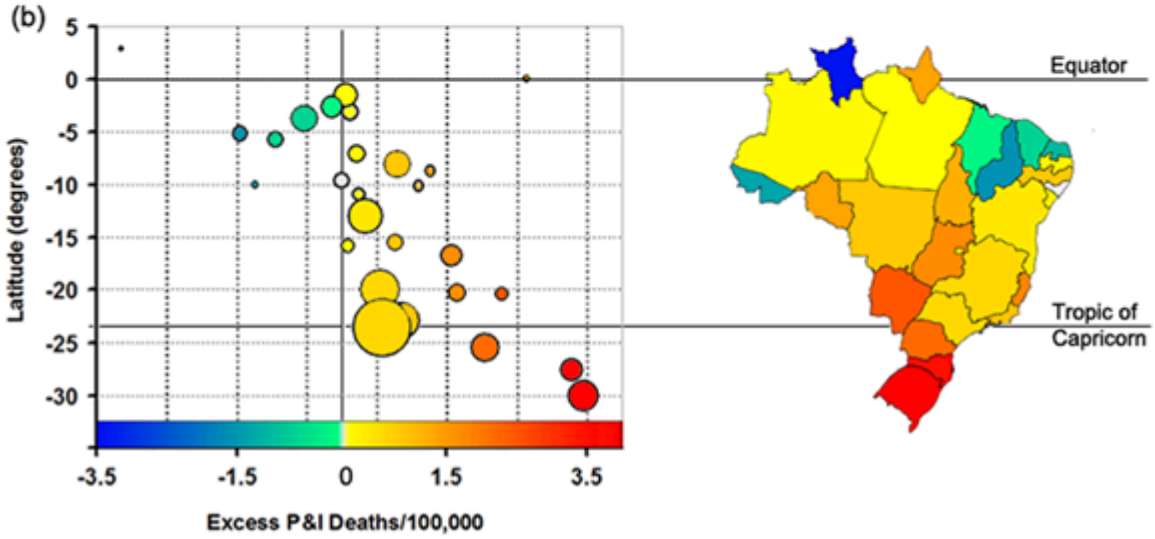
Were Equatorial Regions Less Affected by the 2009 Influenza Pandemic? The Brazilian Experience

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0041918

Extract from the abstract: "Our results suggest, however, that tropical regions of the Southern Hemisphere may have been disproportionally less affected by the pandemic, and that climate may have played a key role in this regard."

GD Notes: This paper details some fascinating correlations between latitude and influenza mortality. Interpret with care though as many things change because of climate, including habits, transport etc. not just weather. One fascinating difference is that the number of reported deaths of seniors over 65 was very low. This pattern is the opposite to covid19 in China and Europe. No data for Brazil yet. Note that life expectancy also varies by latitude, and income very likely will too. Also note, this virus H1N1 **isn't** a coronavirus but **is** a so-called enveloped virus. See Notes about Virus Types.





Seasonality in risk of pandemic influenza emergence

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5654262/

https://www.sciencedirect.com/science/article/pii/S1201971210024975

“Conclusions: **In temperate latitudes even pandemic influenzas often show a clear seasonality.** The data support the hypothesis that high fluences of UVB radiation (vitamin D level), as occur in the summer, act in a protective manner with respect to influenza.”

Questions and answers on influenza pandemics

https://www.ecdc.europa.eu/en/pandemic-influenza/facts/questions-and-answers

The seasonality of pandemic and non-pandemic influenzas: the roles of solar radiation and vitamin D

https://www.ijidonline.com/article/S1201-9712(10)02497-5/fulltext

“Non-pandemic influenzas mostly occur in the winter season in temperate regions. UVB calculations show that at high latitudes very little, if any, vitamin D is produced in the skin during the winter. Even at 26°N (Okinawa) there is about four times more UVB during the summer than during the winter. **In tropical regions there are two minor peaks in vitamin D photosynthesis, and practically no seasonality** of influenza. Pandemics may start with a wave in an arbitrary season, while secondary waves often occur the following winter. Thus, it appears that a low vitamin D status may play a significant role in most influenzas.

Conclusion: In temperate latitudes even pandemic influenzas often show a clear seasonality. The data support the hypothesis that high fluences of UVB radiation (vitamin D level), as occur in the summer, act in a protective manner with respect to influenza.”

3.3 Mechanisms behind seasonality

Being the main source of vitamin D, UVB radiation may affect influenza via the immune system. It was demonstrated in two independent studies[81, 82] that children who were regularly exposed to artificial UVB radiation had around two times lower incidence rates of upper respiratory tract infections, influenza, and sore throat than non-exposed children, and the phagocytic activity of macrophages increased significantly in all exposed subjects in a dose-dependent manner.

The impact of rurality on morbidity and mortality from the 1918 pandemic influenza in England, Wales, New Zealand, and Japan was investigated.[83, 84, 85] The influenza morbidity in villages was higher than or similar to that in towns and cities, while the mortality appeared to be lowest in villages, revealing significant differences compared to all cities and towns. The differences in mortality rates between urban and rural regions may be related to many factors, including differences in vitamin D status. People living in rural areas have significantly higher vitamin D levels compared to those living in urban areas.[86, 87]

3.4 Seasonal variations in host immunity or in pathogen virulence

An argument for the seasonal effect on the host are that outbreaks of genetically similar strains occur simultaneously at similar latitudes across different continents.[1] There seems to be, in many cases, a continuous presence of pathogens throughout the year.[88] Circadian variations of hormones, like melatonin, change with the season.[88, 89] This may lead to a seasonal variation in immunity.[89] Thus, mice exhibit circadian variations of susceptibility to pathogens, with the highest susceptibility in the morning.[90]

The same virus strain appears to be present in the hosts over longer periods, two years or more, but leading to manifest disease only under favorable conditions, mainly related to host immune weakening.[88] One might expect variations in the immune system to play a major role. The preventive effect of vitamin D supplementation against influenza has also been demonstrated in intervention studies.[11] Furthermore, Ginde et al.[91] found that serum levels of vitamin D were inversely associated with upper respiratory tract infections.

UV radiation interacts with the immune system in several ways, as already mentioned. We believe that the main mechanism involves vitamin D photosynthesis in the skin.

3.5 The influence of vitamin D on the immune response

Vitamin D plays an important immunomodulatory function in primates. Deficiency has been linked with several autoimmune

General articles with supporting/countering anecdata or data

Why do dozens of diseases wax and wane with the seasons—and will COVID-19?

https://www.sciencemag.org/news/2020/03/why-do-dozens-diseases-wax-and-wane-seasons-and-will-covid-19

“Nathanson suspects that, at least for viruses, their viability outside the human body is more important. The genetic material of some viruses is packaged not only in a capsid protein, but also in a membrane called an envelope, which is typically made of lipids. It interacts with host cells during the infection process and helps dodge immune attacks. Viruses with envelopes are more fragile and vulnerable to adverse conditions, Nathanson says, including, for example, summertime heat and dryness.

A 2018 study in *Scientific Reports* supports the idea. Virologist Sandeep Ramalingam at the University of Edinburgh and his colleagues analyzed the presence and seasonality of nine viruses—some enveloped, some not—in more than 36,000 respiratory samples taken over 6.5 years from people who sought medical care in their region. “Enveloped viruses have a very, very definite seasonality,” Ramalingam says.”

“For the novel coronavirus SARS-CoV-2, we have reason to expect that like other betacoronaviruses, it may transmit somewhat more efficiently in winter than summer, though we don’t know the mechanism(s) responsible. The size of the change is expected to be modest, and not enough to stop transmission on its own. Based on the analogy of pandemic flu, we expect that SARS-CoV-2, as a virus new to humans, will face less immunity and thus transmit more readily even outside of the winter season.”

Older Historical Papers

The Open-Air Treatment of PANDEMIC INFLUENZA

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4504358/

Excerpt: The H1N1 “Spanish flu” outbreak of 1918–1919 was the most devastating pandemic on record, killing between 50 million and 100 million people. Should the next influenza pandemic prove equally virulent, there could be more than 300 million deaths globally. The conventional view is that little could have been done to prevent the H1N1 virus from spreading or to treat those infected; however, there is evidence to the contrary. Records from an “open-air” hospital in Boston, Massachusetts, suggest that some patients and staff were spared the worst of the outbreak. **A combination of fresh air, sunlight, scrupulous standards of hygiene, and reusable face masks appears to have substantially reduced deaths among some patients and infections among medical staff.**

16. Markel H, Lipman HB, Navarro JA, et al. Nonpharmaceutical interventions implemented by US cities during the 1918–1919 influenza pandemic. JAMA. 2007;298:644–654. [PubMed] [Google Scholar]

17. Hatchett RJ, Mecher CE, Lipsitch M. Public health interventions and epidemic intensity during the 1918 influenza pandemic. Proc Natl Acad Sci USA. 2007;104:7582–7587. [PMC free article] [PubMed] [Google Scholar]

UV light on virus activity

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC373989/
From 1944

Success of Open air treatments in 1918

https://medium.com/@ra.hobday/coronavirus-and-the-sun-a-lesson-from-the-1918-influenza-pandemic-509151dc8065

Background Information

This document summarises actionable findings from Seasonal Mimicry Approaches for Combating Covid-19 (short permalink: bit.ly/Covid19Seasonal).

Author Bios

Dr Gareth Davies (Gruff) has BSc in Physics and PhD in Medical Physics from Imperial College, London; Gruff is a Codex World's Top 50 Innovator; Machine Learning & Data Scientist, Software Engineer; Award-winning Serial Tech Entrepreneur; he has more than three decades of complex system modelling experience with a science and medical background. He worked for 2 years as a consultant at the NHS Modernisation Agency and The NHS Institute for Innovation and Improvement.

Dr Joanna Byers is a UK medical doctor (MBChB, University of Birmingham) with years of clinical experience across general medicine, palliative care and oncology, as well as primary care and expedition medicine. She is interested in the development of integrated multi disciplinary systems for adaptive approaches to preventative health and is currently undertaking an MSc in Occupational Therapy with the University of Essex. She has a diploma in Healthcare Management, Leadership and Innovation from the University of Plymouth and currently assists as a facilitator for Public Health teaching at the University of Cambridge Medical School.

Dr Attila R Garami (MD, PhD) is a senior biomarker consultant for innovative biomedical approaches in Switzerland. After his medical degree from Hungary, he earned a PhD in Multidisciplinary Medical Sciences. He has a highly multidisciplinary background including tropical diseases, immunology, biochemistry and molecular biology from Max-Planck-Institutes, Tübingen in Germany - where he

earned a reputation as an outstanding research fellow. He specialised in growth- and cancer-related signal transduction pathways from Friedrich-Miescher-Institute for Biomedical Research, Basel in Switzerland. He took part in the pioneering establishment of the multidisciplinary biomarker field in pharma environment and for decades he has been working as a consultant specializing in innovative biomarkers.