## Covid-19 and Vitamin D, 2-Page Summary

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

#### This document is for medical professionals only.

**June 2020 UPDATE**: We have now published 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 Model for Vitamin D in COVID-19 Outcomes** 

This document is no longer being updated.

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.

Full report: bit.ly/VitDCovid19Info

Call for data: we ask ICUs to test serum levels, add D3 to treatment plans, measure outcomes and report. Please also measure 25(OH)D serum levels in post mortem examinations up to 10 days after death, especially in cases with no apparent comorbidities. Early clinical evidence will support clinical trial applications. **Please Test, Treat, Measure, Report.** 

#### High Level Summary

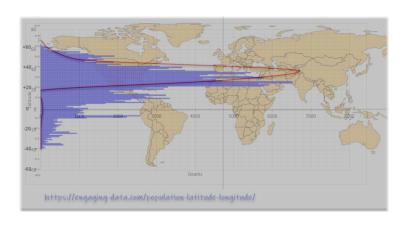
- Vitamin D deficiency is common during winter (Oct Mar) in northern latitudes above 20 degrees and (Apr - Sep) in southern latitudes 20 degrees below the equator. (Mithal et al. 2009)(Isaia et al. 2003)(Garland and Garland 2006)(Giustina et al. 2019)
- Coronaviruses and influenza viruses in the past have displayed very strong seasonality with winter appearances (Gaunt et al. 2010). Severe Covid-19 outbreaks have happened above 20 degree winter latitudes whereas outbreaks in the southern summer hemisphere have been mild and case fatalities relatively low. Case fatalities show a striking relationship to latitude. (23-Mar-2020. See Figure 1).
  - The most severe outbreak in the north has been Italy where it is noted vitamin D deficiency is one of the highest in Europe (Watkins 2020).
  - 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 (Mithal et al. 2009). [NB: Other factors no doubt contribute in
    both countries but culture and behaviour account for speed of spread not case fatality rates].
- Research suggests SARS-Cov-2 virus enters cells via ACE2(Hoffmann et al., n.d.). Coronavirus viral replication downregulates ACE2(Dijkman et al. 2012) dysregulating the renin-angiotensin system (RAS) and leads to a cytokine storm(Ji et al. 2020)(Chen et al. 2010) in the host, causing Acute Respiratory Distress Syndrome (ARDS).
- Research shows that Vitamin D acts to rebalance RAS(Kong et al. 2013)(Yuan W n.d.) and attenuates lung injury(Kong et al. 2013)(Xu et al. 2017).
- Research shows that Vitamin D supplementation increases immunity and reduces inflammatory responses(Jiménez-Sousa et al. 2018) and the risk of acute respiratory tract infection(Martineau et al. 2017).
- Vitamin D deficiency is strongly associated with ARDS(Dancer et al. 2015) and poor mortality outcomes(Ednan K. Bajwa, Ishir Bhan, Sadeq Quraishi, Michael Matthay, B. T. Thompson 2016), as well as being associated with many comorbidities associated with Covid-19 case fatalities.
- High dose oral Vitamin D has been shown to improve mortality in patients with severe vitamin D deficiency.(Christopher 2016)
- Chronic vitamin D deficiency induces lung fibrosis through activation of the RAS.(Et al 2017)
- Vitamin D is a steroid hormone naturally produced 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

("Vitamin D and Health - SACN" 2016). NICE recommends daily supplements for all UK adults all year("Colecalciferol - NICE, BNF" n.d.) ("Scenario: Prevention of Vitamin D Deficiency in Adults - NICE" 2018)

• "25(OH)D was found to be stable in various experiments for at least 10 days postmortem." (Priemel M 2010)

# Deaths + population vs latitude reveals a striking northern hemisphere bias

**Figure 1** - Covid-19 case fatalities by latitude vs population. Severe outbreaks to 23rd March 2020 have only happened north of 20° latitude (winter).



### Bibliography

Chen, I-Yin, Shin C. Chang, Hung-Yi Wu, Ting-Chun Yu, Wen-Chin Wei, Shiming Lin, Chung-Liang Chien, and Ming-Fu Chang. 2010. "Upregulation of the Chemokine (C-C Motif) Ligand 2 via a Severe Acute Respiratory Syndrome Coronavirus Spike-ACE2 Signaling Pathway." *Journal of Virology* 84 (15): 7703.

Christopher, Kenneth B. 2016. "Vitamin D and Critical Illness Outcomes." Current Opinion in Critical Care 22 (4): 332-38.

"Colecalciferol - NICE, BNF." n.d. NICE. Accessed March 24, 2020. https://bnf.nice.org.uk/drug/colecalciferol.html.

Dancer, Rachel C. A., Dhruv Parekh, Sian Lax, Vijay D'Souza, Shengxing Zheng, Chris R. Bassford, Daniel Park, et al. 2015. "Vitamin D Deficiency Contributes Directly to the Acute Respiratory Distress Syndrome (ARDS)." *Thorax* 70 (7): 617–24.

Dijkman, Ronald, Maarten F. Jebbink, Martin Deijs, Aleksandra Milewska, Krzysztof Pyrc, Elena Buelow, Anna van der Bijl, and Lia van der Hoek. 2012. "Replication-Dependent Downregulation of Cellular Angiotensin-Converting Enzyme 2 Protein Expression by Human Coronavirus NL63." *The Journal of General Virology* 93 (Pt 9): 1924–29.

Ednan K. Bajwa , Ishir Bhan , Sadeq Quraishi , Michael Matthay , B. T. Thompson. 2016. "Low Vitamin D Status Occurs in 90% of Patients with ARDS and Is Associated with Longer Duration of Mechanical Ventilation." 2016.

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

Et al, Shi Y. 2017. "Chronic Vitamin D Deficiency Induces Lung Fibrosis through Activation of the Renin-Angiotensin System. - PubMed - NCBI."

https://www.ncbi.nlm.nih.gov/pubmed/28607392#.
Garland, Cedric F., and Frank C. Garland. 2006. "Do Sunlight and Vitamin D Reduce the Likelihood of Colon Cancer?" *International Journal of Epidemiology* 35 (2): 217–20.

Gaunt, E. R., A. Hardie, E. C. J. Claas, P. Simmonds, and K. E. Templeton. 2010. "Epidemiology and Clinical Presentations of the Four Human Coronaviruses 229E, HKU1, NL63, and OC43 Detected over 3 Years Using a Novel Multiplex Real-Time PCR Method." *Journal of Clinical* 

Microbiology 48 (8): 2940–47.
Giustina, Andrea, Robert A. Adler, Neil Binkley, Roger Bouillon, Peter R. Ebeling, Marise Lazaretti-Castro, Claudio Marcocci, Rene Rizzoli, Christopher T. Sempos, and John P. Bilezikian. 2019. "Controversies in Vitamin D: Summary Statement From an International Conference." The Journal of Clinical Endocrinology and Metabolism 104 (2): 234–40.

Hoffmann, Markus, Hannah Kleine-Weber, Nadine Krüger, Marcel Müller, Christian Drosten, and Stefan Pöhlmann. n.d. "The Novel Coronavirus 2019 (2019-nCoV) Uses the SARS-Coronavirus Receptor ACE2 and the Cellular Protease TMPRSS2 for Entry into Target Cells." https://doi.org/10.1101/2020.01.31.929042.

Isaia, G., R. Giorgino, G. B. Rini, M. Bevilacqua, D. Maugeri, and S. Adami. 2003. "Prevalence of Hypovitaminosis D in Elderly Women in Italy: Clinical Consequences and Risk Factors." Osteoporosis International: A Journal Established as Result of Cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 14 (7): 577–82.

Jiménez-Sousa, María Ángeles, Isidoro Martínez, Luz María Medrano, Amanda Fernández-Rodríguez, and Salvador Resino. 2018. "Vitamin D in Human Immunodeficiency Virus Infection: Influence on Immunity and Disease." *Frontiers in Immunology* 9. https://doi.org/10.3389/fimmu.2018.00458.

Ji, Xiaoyang, Chunming Zhang, Yubo Zhai, Zhonghai Zhang, Yiqing Xue, Chunli Zhang, Guangming Tan, and Gang Niu. 2020. "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." medRxiv, February, 2020.02.24.20025437.

Kong, Juan, Xiangdong Zhu, Yongyan Shi, Tianjing Liu, Yunzi Chen, Ishir Bhan, Qun Zhao, Ravi Thadhani, and Yan Chun Li. 2013. "VDR Attenuates Acute Lung Injury by Blocking Ang-2-Tie-2 Pathway and Renin-Angiotensin System." *Molecular Endocrinology* 27 (12): 2116.

Martineau, Adrian R., David A. Jolliffe, Richard L. Hooper, Lauren Greenberg, John F. Aloia, Peter Bergman, Gal Dubnov-Raz, et al. 2017. "Vitamin D Supplementation to Prevent Acute Respiratory Tract Infections: Systematic Review and Meta-Analysis of Individual Participant Data." BMJ 356 (February). https://doi.org/10.1136/bmj.i6583.

Mithal, A., on behalf of the IOF Committee of Scientific Advisors (CSA) Nutrition Working Group, D. A. Wahl, J-P Bonjour, P. Burckhardt, B. Dawson-Hughes, J. A. Eisman, et al. 2009. "Global Vitamin D Status and Determinants of Hypovitaminosis D." *Osteoporosis International*. https://doi.org/10.1007/s00198-009-1030-y.

Priemel M, Et al. 2010. "Bone Mineralization Defects and Vitamin D Deficiency: Histomorphometric Analysis of Iliac Crest Bone Biopsies and Circulating 25-Hydroxyvitamin D I... - PubMed - NCBI." 2010. https://www.ncbi.nlm.nih.gov/pubmed/19594303.

"Scenario: Prevention of Vitamin D Deficiency in Adults - NICE." 2018. NICE. 2018.

https://cks.nice.org.uk/vitamin-d-deficiency-in-adults-treatment-and-prevention#!scenario:1.

"Vitamin D and Health - SACN." 2016.

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\_data/file/537616/SACN\_Vitamin\_D\_and\_Health\_report.pd f.

Watkins, John. 2020. "Preventing a Covid-19 Pandemic." BMJ 368 (February). https://doi.org/10.1136/bmj.m810.

- Xu, Jun, Jialai Yang, Jian Chen, Qingli Luo, Qiu Zhang, and Hong Zhang. 2017. "Vitamin D Alleviates Lipopolysaccharide-induced Acute Lung Injury via Regulation of the Renin-angiotensin System." *Molecular Medicine Reports* 16 (5): 7432–38.
   Yuan W, Et al. n.d. "1,25-Dihydroxyvitamin D3 Suppresses Renin Gene Transcription by Blocking the Activity of the Cyclic AMP Response Element in the Renin Gene Promoter. PubMed NCBI." Accessed March 24, 2020. https://www.ncbi.nlm.nih.gov/pubmed/17690094.