The Daily COVID-19 Literature Surveillance Summary

January 22, 2021

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COVID-19 Daily Literature Surveillance

COVID19LST

Bringing you real time, distilled information for guiding best practices during the COVID-19 pandemic

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

EXECUTIVE SUMMARY

Climate

- A physician with the University of Pennsylvania Department of Medical Ethics and Health Policy discusses the ethics of studying new SARS-CoV-2 vaccines in light of the recent FDA approval of the Moderna and Pfizer/BioNTech vaccinations. The author proposes that moving forward with testing with a multigroup platform trial and comparing approved vaccines to unapproved vaccines would allow for the direct comparison of safety and efficacy among vaccines. The article suggests that this type of trial would eliminate the need for placebo groups, promote vaccinations and the acquisition of public health data, and encourage the participation of vaccine manufacturers to ultimately enable the development of safer vaccines and improve public health.

Epidemiology

- Authors from the University of Genoa and the University of Bologna in Rimini, Italy clarify the current understanding of death caused by COVID-19, established by the World Health Organization (WHO) and coded through the International Classification of Diseases (ICD), stating that COVID-19 should be the official cause of death when the causal chain of events from infection leads directly to death, even when accompanied by pre-existing comorbidities that exacerbate or accelerate death. Accurate classifications of deaths by COVID-19 influence the epidemiology, public health policies, communication, and political decisions made throughout the pandemic.

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CLIMATE

THE ETHICS OF CONTINUING PLACEBO IN SARS-COV-2 VACCINE TRIALS

Rid A, Lipsitch M, Miller FG.. JAMA. 2021 Jan 19;325(3):219-220. doi: 10.1001/jama.2020.25053.
Level of Evidence: 5 - Opinion

BLUF

Researchers from National Institute of Health in Bethesda, MD, Harvard School of Public Health in Boston, MA, and Weill Cornell Medical College in New York, NY discuss the ethics surrounding the vaccination test subjects initially placed in the placebo groups in COVID-19 vaccination trials (Pfizer: n=21,828; Moderna: n= 15,000). They argue that the two main ethical reasons to not vaccinate this group would be 1) loss of valuable research data by eliminating the placebo group and 2) these participants would be receiving the vaccine outside of their priority had they not been in the trial (priority currently belongs to health care personnel, essential workers, high-risk medical conditions, and >65 years of age). In order to maximize benefits and minimize harms, these authors believe that placebo participants should remain enrolled in trials to enable valuable data collection, while also revisiting these recommendations frequently as vaccines become more widely available.

EVALUATING SARS-COV-2 VACCINES AFTER EMERGENCY USE AUTHORIZATION OR LICENSING OF INITIAL CANDIDATE VACCINES

Joffe S.. JAMA. 2021 Jan 19;325(3):221-222. doi: 10.1001/jama.2020.25127.
Level of Evidence: 5 - Expert Opinion

BLUF

A physician with the University of Pennsylvania Department of Medical Ethics and Health Policy discusses the ethics of studying new SARS-CoV-2 vaccines in light of the recent FDA approval of the Moderna and Pfizer/BioNTech vaccinations. The author proposes that moving forward with testing with a multigroup platform trial and comparing approved vaccines to unapproved vaccines would allow for the direct comparison of safety and efficacy among vaccines. The article suggests that this type of trial would eliminate the need for placebo groups, promote vaccinations and the acquisition of public health data, and encourage the participation of vaccine manufacturers to ultimately enable the development of safer vaccines and improve public health.

EPIDEMIOLOGY

COVID-19 AS THE UNDERLYING CAUSE OF DEATH: DISENTANGLING FACTS AND VALUES

Amoretti MC, Lalumera E.. Hist Philos Life Sci. 2021 Jan 8;43(1):4. doi: 10.1007/s40656-020-00355-6.
Level of Evidence: 5 - Expert Opinion

BLUF

Authors from the University of Genoa and the University of Bologna in Rimini, Italy clarify the current understanding of death caused by COVID-19, established by the World Health Organization (WHO) and coded through the International Classification of Diseases (ICD), stating that COVID-19 should be the official cause of death when the causal chain of events from infection leads directly to death, even when accompanied by pre-existing comorbidities that exacerbate or accelerate death. Accurate classifications of deaths by COVID-19 influence the epidemiology, public health policies, communication, and political decisions made throughout the pandemic.

SUMMARY

The WHO defines death from COVID-19 as:

"A death due to COVID-19 is defined for surveillance purposes as a death resulting from a clinically compatible illness, in a probable or confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to COVID disease (e.g. trauma). There should be no period of complete recovery from COVID-19 between illness and death. A death due to COVID-19 may not be attributed to another disease (e.g. cancer) and should be counted independently of preexisting conditions that are suspected of triggering a severe course of COVID-19. COVID-19 should be recorded on the medical certificate of cause of death for ALL decedents where the disease caused, or is assumed to have caused, or contributed to death (WHO 2020, 3)." (Amoretti et al.)

ABSTRACT

In the ongoing pandemic, death statistics influence people's feelings and government policy. But when does COVID-19 qualify as the cause of death? As philosophers of medicine interested in conceptual clarification, we address the question by analyzing the World Health Organization's rules for the certification of death. We show that for COVID-19, WHO rules take into account both facts (causal chains) and values (the importance of prevention).

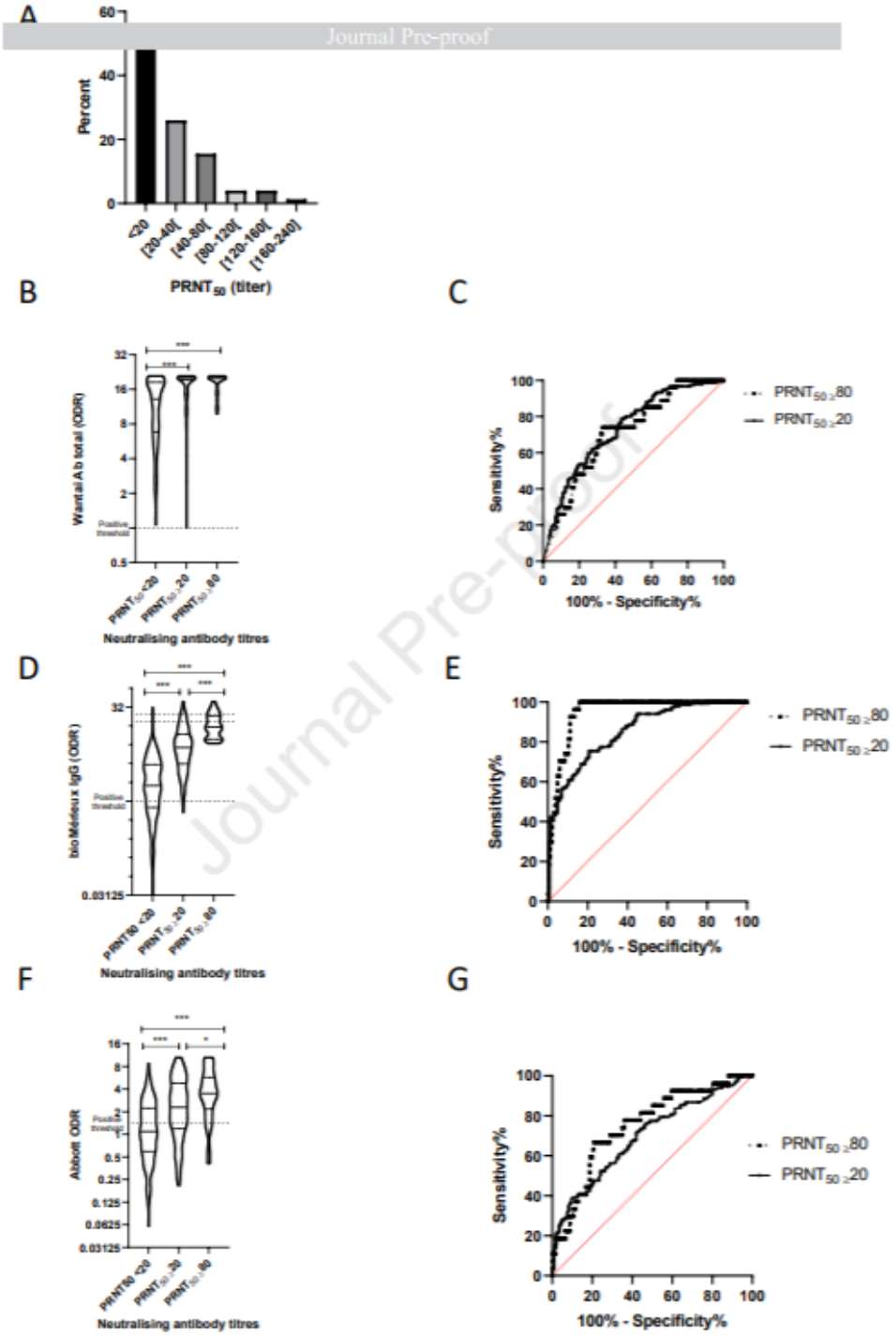
UNDERSTANDING THE PATHOLOGY

SIX-MONTH ANTIBODY RESPONSE TO SARS-COV-2 IN HEALTHCARE WORKERS ASSESSED BY VIRUS NEUTRALISATION AND COMMERCIAL ASSAYS

Antonin Bal, Trabaud MA, Fassier JB, Rabilloud M, Saker K, Langlois-Jacques C, Guibert N, Adèle Paul, Alfaiate D, Massardier-Pilonchery A, Pitiot V, Morfin-Sherpa F, Lina B, Pozzetto B, Trouillet-Assant S; COVID SER STUDY GROUP.. Clin Microbiol Infect. 2021 Jan 12:S1198-743X(21)00005-7. doi: 10.1016/j.cmi.2021.01.003. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

A letter to the editor of the journal "Clinical Microbiology and Infection" penned by researchers in the Laboratoire de Virologie at the Institut des Agents Infectieux in Lyon, France reviews the Trouillet-Assant et al study "Assessment of 90 serological techniques for screening patients for COVID-19 (COVID-SER): a prospective, 91 multicentric study," discussing the potential of virus neutralisation assay (VNA) to assess for antibodies in previously SARS-CoV-2 positive patients. In the study, 6 months after 296 healthcare workers had SARS-CoV-2 infection, 51% had neutralizing antibody (NAb), 55.4% were positive on the Architect Assay, 84.8% on the Vidas Assay, and 100% on the Wantai assay, and those with a NAb titer greater than 80 were more likely to have a Vidas ratio greater than 8 (Figure). This study suggests that certain assays could be utilized to screen for antibodies in recovered SARS-CoV-2 patients.



'Figure'

A. Distribution of neutralisation antibody titres in convalescent subjects (n=296) 6 months after SARS-CoV-2 infection. B-D-F. Violin plots describing ODR according to neutralising antibody titres. Dotted lines described positive threshold recommended by each manufacturer. Comparisons was performed using the Kruskal Wallis test followed by Dunn's test. ***p<0.001, *p<0.05 C-E-G. ROC curves were built to estimate the performance of Wantai (C), bioMérieux (E) and Abbott (G) assays for detecting the presence of neutralising antibodies (PRNT50 ≥ 20-continuous line) and high neutralising antibody titre (PRNT50 ≥ 80-dotted line). ODR-Optical Density Ratio, PRNT-Plaque Reduction Neutralisation Titres.

DEVELOPMENTS IN TRANSMISSION & PREVENTION

CHINA COVID VACCINE REPORTS MIXED RESULTS - WHAT DOES THAT MEAN FOR THE PANDEMIC?

Mallapaty S.. Nature. 2021 Jan 15. doi: 10.1038/d41586-021-00094-z. Online ahead of print.
Level of Evidence: 5 - Opinion

BLUF

An experienced scientific journalist for Nature discusses the COVID-19 vaccine 'CoronaVac', developed by Chinese company Sinovac, being used in mass vaccination programs in Brazil, Indonesia and Turkey. Each country has reported different levels of effectiveness in preventing symptomatic disease in clinical trials (50.4%, 65.3%, and 91.25%, respectively) with minimal adverse effects. They interview multiple experts who agree that although its effectiveness appears lower than for RNA-based vaccines, it could still be profoundly useful in containing SARS-CoV-2.

ROLE OF VITAMIN D IN REGULATING COVID-19 SEVERITY-AN IMMUNOLOGICAL PERSPECTIVE

Kalia V, Studzinski GP, Sarkar S.. J Leukoc Biol. 2021 Jan 19. doi: 10.1002/JLB.4COVR1020-698R. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

American pediatricians and pathologists review the role of vitamin D in the context of COVID-19 severity and propose possible mechanisms for its immunomodulatory properties, such as regulating the production of inflammatory cytokines (Figure 1). Similar to the association observed in other diseases (Table 1), they conclude evidence of a correlation between vitamin D deficiency and COVID-19 severity exists. Authors encourage more research to elucidate the precise role of vitamin D in lung pathology and investigate its utility as a supplement in patient populations at high risk for COVID-19.

FIGURES

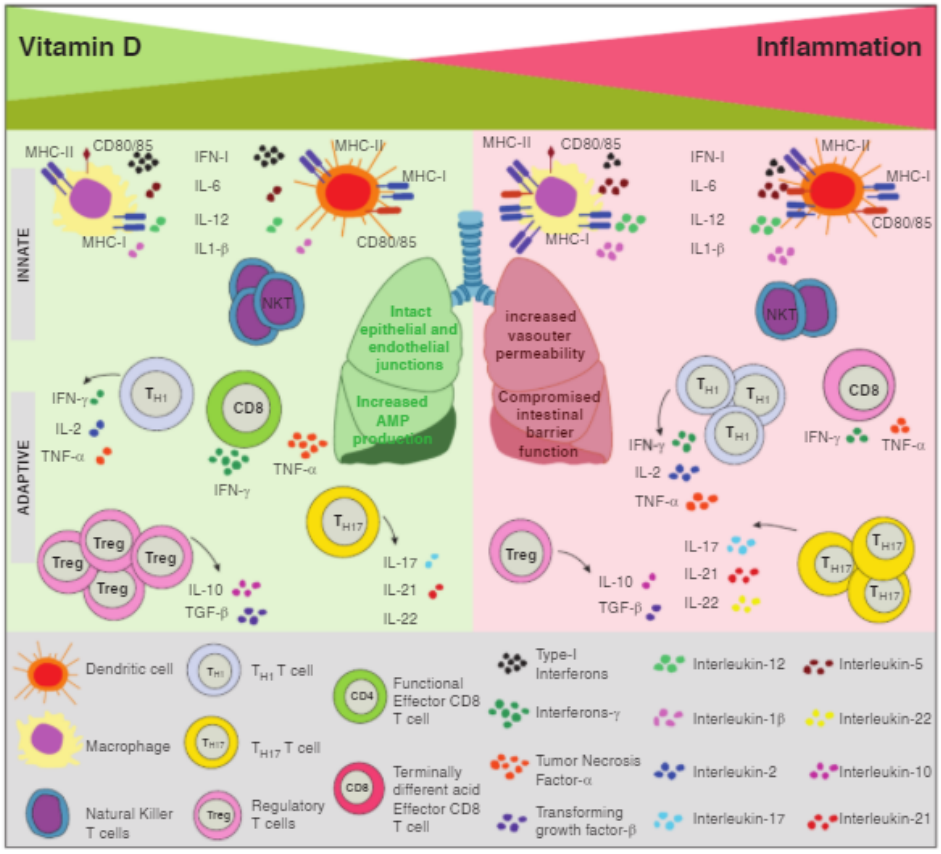


FIGURE 1 **Model of immunomodulation by vitamin D in COVID-19.** The decreasing green shaded triangle indicates decreasing vitamin D status. Increasing intensity of red shade indicates increasing inflammation with decreasing vitamin D levels. Infection in vitamin D sufficient hosts (green half of the figure, corresponding to serum levels of 25(OH)D > 25–30 ng/ml, defined as sufficient) is expected to induce optimal activation of innate immune cells such as macrophages (with robust antimicrobial peptide, AMP, production) and DCs with robust up-regulation of MHC and costimulatory molecules, and regulated production of proinflammatory cytokines. Balanced differentiation of effector CD8 and CD4 T cell subsets under conditions of vitamin D sufficiency is also expected to promote robust antiviral responses, with regulated production of inflammatory cytokines. Vitamin D sufficiency is also predicted to promote the development of immunoprotective NK-T cells, and maintain epithelial junctional integrity and endothelial vascular permeability, thus minimizing pulmonary damage. Contrarily, host vitamin D insufficiency or deficiency (red half of the figure, corresponding to serum levels of 25(OH)D ≤ 10 ng/ml (25 nM) defined as deficient, and 10–20 ng/ml defined as insufficient) is expected to lead to aberrant activation of innate inflammatory mediators such as macrophages and DCs, leading to exacerbated inflammation, more pronounced expansion and terminal differentiation of effector CD8 and inflammatory CD4 T cell subsets, and diminished Treg induction and NK-T cell development. Likewise, the junctional integrity of lung epithelial and vascular endothelial cells is also predicted to be impaired, thus leading to pulmonary edema, lung injury and functional impairment and ARDS. Conditions of vitamin D hyper-supplementation are not depicted in this model. A better understanding of disease-context-dependent immunomodulatory effects of vitamin D in SARS-CoV2 infections at pulmonary sites of viral growth and secondary lymphoid sites of immune activation will illuminate potential beneficial effects of normalizing vitamin D levels to sufficient or hyper-supplemented levels

TABLE 1 Clinical studies showing beneficial effects of vitamin D supplementation

Disease	References
Tuberculosis	Martineau et al.[153] Nursyam et al.[175] Morcos et al.[176] Wejse et al.[177]
Influenza	Aloia and Li-Ng,[43]
AIDS	Arpadi et al.[178] Reviewed in Alvarez et al., 2019 and Teixeira et al.[29,31]
Schistosomiasis	Snyman et al.[179]
Sepsis	Amrein et al.[180] Leaf et al.[181] Quraishi et al.[182] Miroliaee et al.[183,184] Ginde et al.[151]
Coronary disease	Sokol et al.[185] Farrokhian et al.[186] Bahrami et al.[187,188] Manson et al.[28]
Diabetes	Pittas et al.[30]
Multiple sclerosis	Kouchaki et al.[34] Berezowska et al.[35]
Dengue	Ahmed et al.[32] Martinez-Moreno et al.[33]

Selected clinical studies of vitamin D supplementation and meta-analysis of multiple disease-relevant clinical trials showing infection or disease protective effects are presented.

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