The Daily COVID-19 Literature Surveillance Summary

January 20, 2021

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COVID-19 Daily Literature Surveillance

COVID19LST

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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

Understanding the Pathology

- Italian microbiologists report on a novel SARS-CoV-2 variant (VOC-202012/01) in a 59-year-old man who presented in November 2020 with persistent SARS-CoV-2 positivity since August. Metagenomic sequencing showed 13 amino acid changes compared to reference sequences, including an N501T substitution in the spike protein, suggesting position 501 mutations were circulating in Italy by August 2020. Because N501Y mutations circulating in the United Kingdom may alter binding affinity, authors recommend surveillance for emerging variations in receptor-binding domain that may contribute to immune escape and viral spread.

Transmission & Prevention

- Infectious disease physicians from St George's Hospital in the United Kingdom analyzed samples from 66,001 patients who had PCR and/or a serological SARS-CoV-2 assay performed during the first wave of the COVID-19 pandemic (February to July 2020). They found patients who had evidence of SARS-CoV-2 infection via PCR or antibody during the first wave of the pandemic (n=10,727) had a significantly lower risk of a positive PCR during the second wave (August to December 2020) compared to those with no prior infection (RR 0.0578, 95%CI 0.0288-0.1160). The authors suggest prior infection with SARS-CoV-2 confers some protection against future infection and encourage further research to determine the duration of protection and explore strain-specific immunity.

- In this study, an interdisciplinary group of researchers report on phase 1-2a trial interum results of the candidate vaccine Ad26.COV2.S for COVID-19. These phases were to determine the safety and reactogenicity of the high dose schedule (given once) and low dose schedule (given twice) of the vaccine. The safety of the vaccine was determined by self-reported events characterized as either "adverse events" or "serious adverse events". Reactogenicity, was measured using an ELISA assay to detect for SARS-CoV-2 S-specific binding antibodies. The results of this study indicate that the vaccine has an acceptable safety and reactogenicity profile after a single vaccination with either the high or low dose. In addition, a single dose of the Ad26.COV2.S vaccine elicited a strong humoral response in a majority of vaccine patients (90%). This study offers promising data on a potential vaccine candidate by demonstrating its safety and efficacy in human subjects.

Management

- A systematic review conducted by Debre Tabor University in Ethiopia analyzed 9 articles published internationally from 2019 through September 2020 surrounding Vitamin D and COVID-19 outcomes and found 7 studies (77.8%) that demonstrated vitamin D deficiency correlated with increased likelihood of COVID-19 infection, need for hospitalization, disease severity, odds of ICU admission, and mortality. Although two studies included in this review found no association between Vitamin D levels and COVID-19 infection outcome, the corresponding authors attributed this to the timing of vitamin D sampling in the patients. Overall, authors suggest that these findings support maintaining appropriate Vitamin D levels for the general public through supplementation or sunlight exposure to improve COVID-19 outcomes.

R&D: Diagnosis & Treatments

- A prospective cohort study was conducted at three primary care centers by the Departments of Health and multiple hospitals in Alicante, Spain between September 15 and October 29, 2020 to assess the performance of RT-PCR saliva testing for COVID-19 through three different methods of collection on 577 patients who were either symptomatic or asymptomatic with known exposure to COVID-19 prior to receiving the gold standard comparator RT-PCR nasopharyngeal swab (NPS). Results showed that supervised collection (SVC) had the best performance with 86% sensitivity compared to 66.7% sensitivity of self-collected (SC) samples and a higher sensitivity was achieved when cycle threshold was low resulting in 100% sensitivity in symptomatic and 88.9% sensitivity in asymptomatic patients with RT-PCR. These findings suggest that saliva specimens perform comparably to the NPS samples and are considered effective for detection of SARS-CoV-2 in the community.

Resources

- An expert in health economics from the Frankfurt School of Finance and Management in Germany created a model to analyze the cost-effectiveness of expanding or maintaining intensive care unit (ICU) bed reserve capacity to prepare for a second wave of the COVID-19 pandemic. With full bed utilization, they found the last staffed bed added cost €21,958 per life-year gained with a positive return on investment. Net monetary benefit remained positive with utilization above 2%. The author concludes ICU bed expansion is cost effective even at a large vacancy rate and advocates for more cost-effectiveness analysis to improve hospital preparedness and determine appropriate capacity increases.

TABLE OF CONTENTS

UNDERSTANDING THE PATHOLOGY

FIRST DETECTION OF SARS-COV-2 SPIKE PROTEIN N501 MUTATION IN ITALY IN AUGUST, 2020

Fiorentini S, Messali S, Zani A, Caccuri F, Giovanetti M, Ciccozzi M, Caruso A.. Lancet Infect Dis. 2021 Jan 12:S1473-3099(21)00007-4. doi: 10.1016/S1473-3099(21)00007-4. Online ahead of print.
Level of Evidence: 5 - Case Report

BLUF

Italian microbiologists report on a novel SARS-CoV-2 variant (VOC-202012/01) in a 59-year-old man who presented in November 2020 with persistent SARS-CoV-2 positivity since August. Metagenomic sequencing showed 13 amino acid changes compared to reference sequences, including an N501T substitution in the spike protein, suggesting position 501 mutations were circulating in Italy by August 2020. Because N501Y mutations circulating in the United Kingdom may alter binding affinity, authors recommend surveillance for emerging variations in receptor-binding domain that may contribute to immune escape and viral spread.

COVID-19 AND HYPOGONADISM: SECONDARY IMMUNE RESPONSES RULE-OVER ENDOCRINE MECHANISMS

Sengupta P, Dutta S.. Hum Fertil (Camb). 2021 Jan 13:1-6. doi: 10.1080/14647273.2020.1867902. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

Experts in reproductive endocrinology from MAHSA University in Kuala Lumpur, Malaysia discuss five proposed methods by which SARS-CoV-2 depletes testosterone. The proposed mechanisms include oxidative stress impeding function of Leydig cells, androgen facilitated viral entry via TMPRSS2 gene activation, virus induced anti-ACTH antibodies decreasing glucocorticoid levels, and Leydig cell damage (Figure 1). Authors suggest the multiple mechanisms by which SARS-CoV-2 causes hypogonadism may affect male COVID-19 patients' reproductive health.

ABSTRACT

Men show higher vulnerability to severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection (COVID-19) and present with depleted testosterone levels. Reports pertaining to high luteinizing hormone (LH), while diminished levels of in COVID-19 patients negate the hypothalamic-pituitary-testicular (HPT) axis mediated lowering of testosterone. Although not evidenced, high testicular expression of angiotensin-converting enzymes-2 (ACE2), that aids viral entry into cells, may suggest direct viral-testicular invasion. However, secondary inflammation and oxidative stress (OS), owing to SARS-CoV-2 infection, are more likely to impair steroidogenesis. Moreover, blockage of ACE2 aided angiotensin II into angiotensin (1-7) conversion may also affect testosterone synthesis. SARS-CoV-2, by mimicking adrenocorticotrophic (ACTH) hormones, may trigger host antibodies against the ACTH molecules to suppress host stress response. This commentary concisely presents the possible mechanisms by which SARS-CoV-2 infection may affect testosterone levels, which possibly result in compromised male reproductive health.

FIGURES

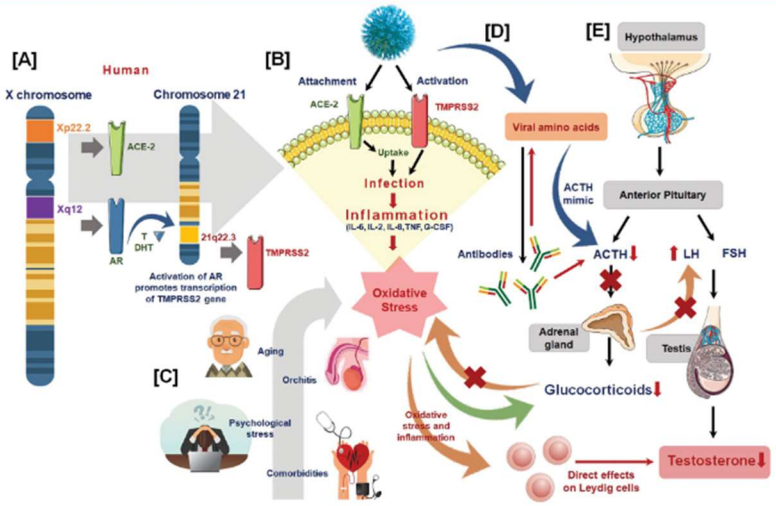


Figure 1. Possible mechanisms of SARS-CoV-2 infection mediated testosterone depletion. (A) androgen receptor and ACE2 are located in chromosome-X, while androgen receptor activation is needed to trigger *TMPRSS2* gene transcription, aiding SARS-CoV-2 entry into host cells; (B) SARS-CoV-2 infection triggers inflammatory responses and oxidative stress-mediated disruptions of Leydig cell functions; (C) Advanced age, psychological, and other co-morbidities associated with COVID-19 may also lead to oxidative stress; (D) Viral amino acids may mimic ACTH molecules and stimulate production of antibodies against host ACTH, thereby reducing glucocorticoid levels and suppressing host response to combat stress; (E) Hypothalamic–pituitary–testicular (HPT) axis may not be affected by SARS-CoV-2 infection, thus due to low testosterone level, LH level remains high in COVID-19 patients. ACE2: angiotensin-converting enzyme 2; AR: androgen receptor; T: testosterone; DHT: dihydrotestosterone; TMPRSS2: transmembrane protease serine-2; IL: interleukin; TNF: tumour necrosis factor; G-CSF: granulocyte colony-stimulating factor; ACTH: adrenocorticotrophic hormone; LH: luteinizing hormone; FSH: follicle-stimulating hormone.

ILLUMINATING THE IMMUNOPATHOLOGY OF SARS-COV-2

Saksena S, Chattopadhyay P.. Cytometry B Clin Cytom. 2021 Jan 4. doi: 10.1002/cyto.b.21988. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

Researchers associated with NYU Langone Medical Center and BD Biosciences conducted this literature review on the effect of COVID-19 on the immune system and found that the immunological markers IL-6, IL-10 are associated with a more severe inflammatory response and a high risk of developing respiratory failure. Flow cytometry for profiling of immune dysfunction in COVID-19 patients showed that patients with severe disease have more activated CD8+ T cells in comparison to activated CD4+, CD8+, follicular helper T cells, IgM, and IgG in mild-to-moderate COVID-19. Authors hope that recent discoveries of the specific immune responses to COVID-19 can help target the development of specific prophylactics and therapeutics.

ABSTRACT

Over a remarkably short period of time, a great deal of knowledge about severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection has been acquired, through the focused and cooperative effort of the international scientific community. Much has become known about how the immune response is coordinated to fight infection, and how it becomes dysregulated in severe disease. In this review, we take an in-depth look at the many immune features associated with the host response to SARS-CoV2, as well as those that appear to mark severe disease.

PRIOR COVID-19 SIGNIFICANTLY REDUCES THE RISK OF SUBSEQUENT INFECTION, BUT REINFECTIONS ARE SEEN AFTER EIGHT MONTHS

Breathnach DAS, Riley PA, Cotter MP, Houston AC, Habibi MS, Planche TD.. J Infect. 2021 Jan 12:S0163-4453(21)00010-4. doi: 10.1016/j.jinf.2021.01.005. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Infectious disease physicians from St George's Hospital in the United Kingdom analyzed samples from 66,001 patients who had PCR and/or a serological SARS-CoV-2 assay performed during the first wave of the COVID-19 pandemic (February to July 2020). They found patients who had evidence of SARS-CoV-2 infection via PCR or antibody during the first wave of the pandemic (n=10,727) had a significantly lower risk of a positive PCR during the second wave (August to December 2020) compared to those with no prior infection (RR 0.0578, 95%CI 0.0288-0.1160)(Figure 1, Tables 1, 2). The authors suggest prior infection with SARS-CoV-2 confers some protection against future infection and encourage further research to determine the duration of protection and explore strain-specific immunity.

FIGURES

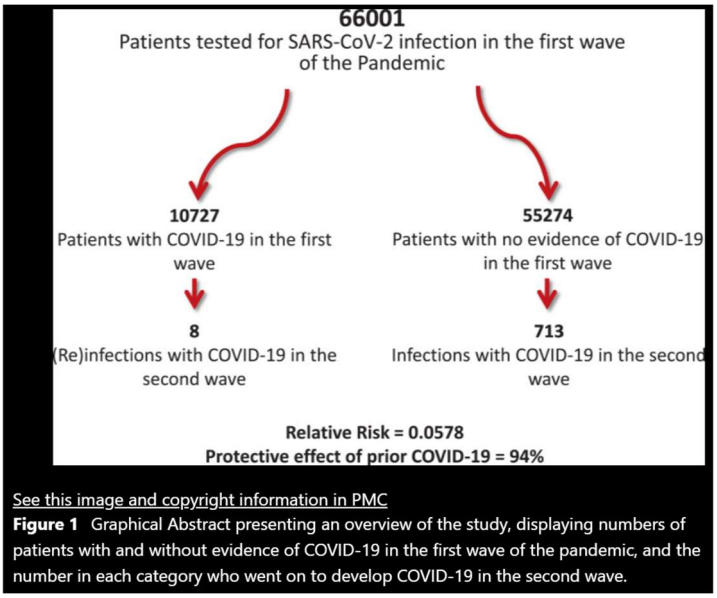


Figure 1 Graphical Abstract presenting an overview of the study, displaying numbers of patients with and without evidence of COVID-19 in the first wave of the pandemic, and the number in each category who went on to develop COVID-19 in the second wave.

Table 1: Patient numbers and demographics

	Total	SARS-CoV-2 infection in first wave	SARS-CoV-2 PCR+ in second wave	Reinfections
Number	66001	10727	721	8
% Female	60%	60%	62%	100%
Average age	50 years	53 years	54 years	55 years

Table 2: SARS-CoV-2 infections in the second wave of the Pandemic, in patients with and without evidence of infection in the first wave.

		Subsequent PCR Positive, August - December (> 90 day interval)			
		Yes	No	Proportion positive in second wave	Relative Risk (95% confidence interval)
Laboratory evidence of prior SARS-CoV-2	Yes	8	10719	0·00075	0·0578
	No	713	54561	0·01290	(0·0288 to 0·1160)

INTERIM RESULTS OF A PHASE 1-2A TRIAL OF AD26.COV2.S COVID-19 VACCINE

Sadoff J, Le Gars M, Shukarev G, Heerwegh D, Truyers C, de Groot AM, Stoop J, Tete S, Van Damme W, Leroux-Roels I, Berghmans PJ, Kimmel M, Van Damme P, de Hoon J, Smith W, Stephenson KE, De Rosa SC, Cohen KW, McElrath MJ, Cormier E, Scheper G, Barouch DH, Hendriks J, Struyf F, Douoguih M, Van Hoof J, Schuitemaker H.. N Engl J Med. 2021 Jan 13. doi: 10.1056/NEJMoa2034201. Online ahead of print.
Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

BLUF

In this study, an interdisciplinary group of researchers report on phase 1-2a trial interum results of the candidate vaccine Ad26.COV2.S for COVID-19. These phases were to determine the safety and reactogenicity of the high dose schedule (given once) and low dose schedule (given twice) of the vaccine. The safety of the vaccine was determined by self-reported events characterized as either "adverse events" or "serious adverse events". Reactogenicity, was measured using an ELISA assay to detect for SARS-CoV-2 S-specific binding antibodies. The results of this study indicate that the vaccine has an acceptable safety (figure 1) and reactogenicity profile (figure 2) after a single vaccination with either the high or low dose. In addition, a single dose of the Ad26.COV2.S vaccine elicited a strong humoral response in a majority of vaccine patients (90%). This study offers promising data on a potential vaccine candidate by demonstrating its safety and efficacy in human subjects.

ABSTRACT

BACKGROUND: Efficacious vaccines are urgently needed to contain the ongoing coronavirus disease 2019 (Covid-19) pandemic of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A candidate vaccine, Ad26.COV2.S, is a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector encoding a full-length and stabilized SARS-CoV-2 spike protein. METHODS: In this multicenter, placebo-controlled, phase 1-2a trial, we randomly assigned healthy adults between the ages of 18 and 55 years (cohort 1) and those 65 years of age or older (cohort 3) to receive the Ad26.COV2.S vaccine at a dose of 5x1010 viral particles (low dose) or 1x1011 viral particles (high dose) per milliliter or placebo in a single-dose or two-dose schedule. Longer-term data comparing a single-dose regimen with a two-dose regimen are being collected in cohort 2; those results are not reported here. The primary end points were the safety and reactogenicity of each dose schedule. RESULTS: After the administration of the first vaccine dose in 805 participants in cohorts 1 and 3 and after the second dose in cohort 1, the most frequent solicited adverse events were fatigue, headache, myalgia, and injection-site pain. The most frequent systemic adverse event was fever. Systemic adverse events were less common in cohort 3 than in cohort 1 and in those who received the low vaccine dose than in those who received the high dose. Reactogenicity was lower after the second dose. Neutralizing-antibody titers against wild-type virus were detected in 90% or more of all participants on day 29 after the first vaccine dose (geometric mean titer [GMT], 224 to 354) and reached 100% by day 57 with a further increase in titers (GMT, 288 to 488), regardless of vaccine dose or age group. Titers remained stable until at least day 71. A second dose provided an increase in the titer by a factor of 2.6 to 2.9 (GMT, 827 to 1266). Spike-binding antibody responses were similar to neutralizing-antibody responses. On day 14, CD4+ T-cell responses were detected in 76 to 83% of the participants in cohort 1 and in 60 to 67% of those in cohort 3, with a clear skewing toward type 1 helper T cells. CD8+ T-cell responses were robust overall but lower in cohort 3. CONCLUSIONS: The safety and immunogenicity profiles of Ad26.COV2.S support further development of this vaccine candidate. (Funded by Johnson & Johnson and the Biomedical Advanced Research and Development Authority of the Department of Health and Human Services; COV1001 ClinicalTrials.gov number, NCT04436276.).

Figure 1. Solicited Adverse Events in Cohorts 1 and 3 after the First Vaccine Dose.

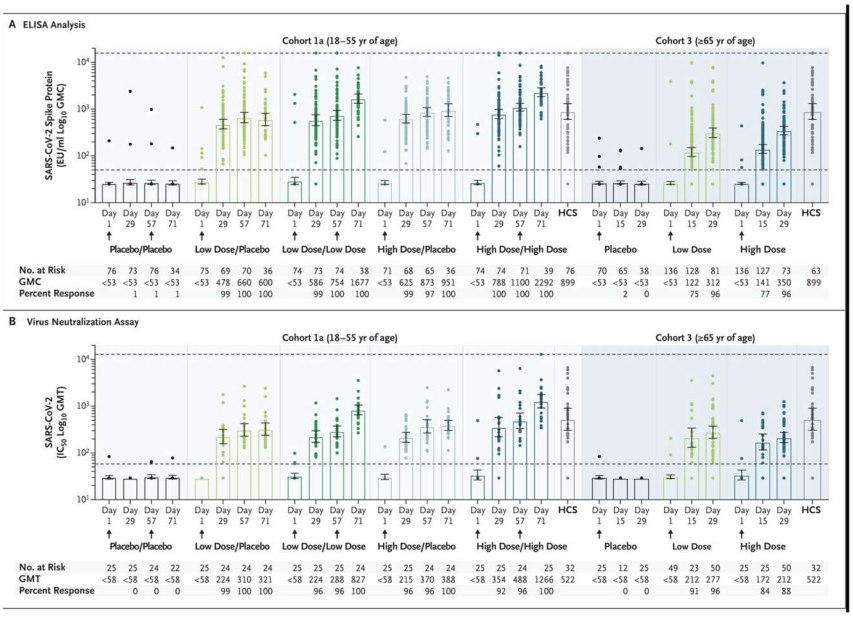


Figure 2. Humoral Immunogenicity

EFFECTS OF VITAMIN D ON COVID-19 INFECTION AND PROGNOSIS: A SYSTEMATIC REVIEW

Yisak H, Ewunetei A, Kefale B, Mamuye M, Teshome F, Ambaw B, Yideg Yitbarek G.. Risk Manag Healthc Policy. 2021 Jan 7;14:31-38. doi: 10.2147/RMHP.S291584. eCollection 2021.
Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

A systematic review conducted by Debre Tabor University in Ethiopia analyzed 9 articles published internationally from 2019 through September 2020 (See Figure 1) surrounding Vitamin D and COVID-19 outcomes and found 7 studies (77.8%) that demonstrated vitamin D deficiency correlated with increased likelihood of COVID-19 infection, need for hospitalization, disease severity, odds of ICU admission, and mortality (See Table 1). Although two studies included in this review found no association between Vitamin D levels and COVID-19 infection outcome, the corresponding authors attributed this to the timing of vitamin D sampling in the patients. Overall, authors suggest that these findings support maintaining appropriate Vitamin D levels for the general public through supplementation or sunlight exposure to improve COVID-19 outcomes.

ABSTRACT

Introduction: Vitamin D status is related to risks of influenza and respiratory tract infections. Vitamin D has direct antiviral effects primarily against enveloped viruses, and coronavirus is an enveloped virus. The 2019 coronavirus disease had a high mortality rate and impacted the whole population of the planet, with severe acute respiratory syndrome the principal cause of death. Vitamin D can adequately modulate and regulate the immune and oxidative response to infection with COVID-19. The goal of this systematic review was thus to summarize and decide if there were a link between vitamin D status and COVID-19 infection and prognosis. Methods: The protocol of this study is documented in the Prospero database and can be accessed with the protocol number CRD42020201283. PubMed and Google Scholar were used for a literature search from August 2020 to September 2020. We restricted the year of publication of reviewed articles to 2019-2020, and the selected language was English. Studies that used secondary data, feedback, or analysis of reviews were removed. To assess the standard of studies included, the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) method was used. Results: Of the nine studies reviewed, seven (77.8%) showed that COVID-19 infection, prognosis, and mortality were correlated with vitamin D status. Conclusion: Most of the articles reviewed showed that blood vitamin D status can determine the risk of being infected with COVID-19, seriousness of COVID-19, and mortality from COVID-19. Therefore, maintaining appropriate levels of Vitamin D through supplementation or natural methods, eg, sunlight on the skin, is recommended for the public to be able to cope with the pandemic.

FIGURES

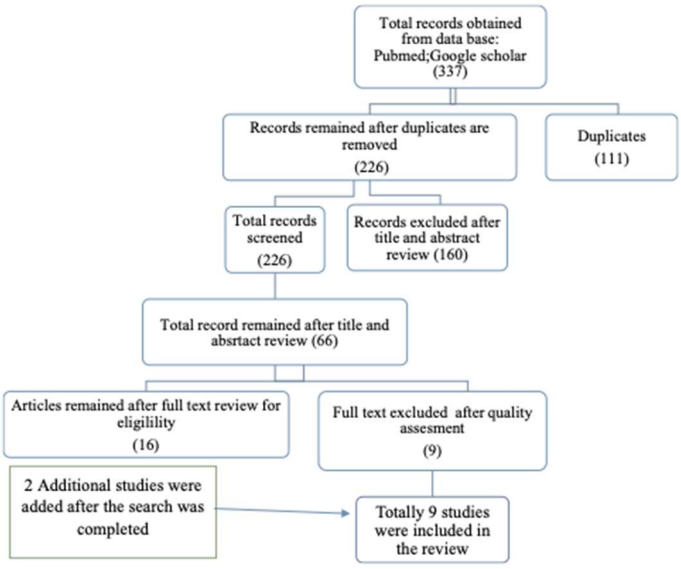


Figure 1: Flow diagram showing the method of selection for papers included in this systematic review.

Authors, Years	Country	Setting	Design	Period	Sample Size	Effect of Vitamin D on COVID-19
Mendy et al	USA	UC	CS	March 13–May 31, 2020	689	Vitamin D was linked with length of hospital stay, disease harshness, and admission to ICU.
Hastie et al	Multinational	UK Biobank	CS	March 16–April 14, 2020	449	Vitamin D status was not linked with COVID-19 status.
Raisi-Estabragh et al	UK	UK Biobank	PC	16 March–18 May, 2020	1326	No important relation between the 25(OH) D status adjusted for the season and COVID-19 positivity.
Daneshkhah et al	Multinational	Nationwide	CS	March 21–April 1, 2020	793	Patient-level CRP information was used as a cytokine-storm proxy marker and interrelated with vitamin D status, and indicated a possible correlation between vitaming D status and COVID-19 severity.
Ali	20 European countries	Global Coranz Virus data portal	RC	April 8–May 20, 2020	1,000,000	A significant correlation was observed for levels of mean vitamin D with COVID-19 cases (p=0.033) but not with death (P=0.123) per million of population
Merzon et al	Israel	Leumit Health Services (LHS) database	CS	February 1–April 30 2020	782	An independent risk factor for COVID-19 infection and hospitalization appeared to be low plasma 25(OH)D levels.
Fasano et al	Italy	Single tertiary center in Lombardy	case-controlled survey	Three months	105	COVID-19 patients were vitamin D nonsupplemented than unaffected patients.
Carpagnano et al	Italy	Policlinico di Bari	Retrospective, observational study	March 11–April 30, 2020	42	There was a significantly greater mortality risk due to COVID-19 in patients with severe vitamin D deficiency.
Entrenas et al	Spain	Spanish patients hospitalized for COVID-19	RCT	Five days	76	Administration of a high dose of calcifediol or 25(OH)D significantly reduced the need for ICU treatment of patients requiring hospitalization due to proven COVID-19.

Abbreviations: UC, University of Cincinnati; RCT, randomized controlled trial; CS, cross-sectional; RC, retrospective cohort; PC, prospective cohort.

Table 1: Characteristics of Studies Included

ASSOCIATION BETWEEN CHRONIC USE OF IMMUNOSUPPRESIVE DRUGS AND CLINICAL OUTCOMES FROM CORONAVIRUS DISEASE 2019 (COVID-19) HOSPITALIZATION: A RETROSPECTIVE COHORT STUDY IN A LARGE US HEALTH SYSTEM

Andersen KM, Mehta HB, Palamuttam N, Ford D, Garibaldi BT, Auwaerter PG, Segal J, Alexander GC.. Clin Infect Dis. 2021 Jan 7:ciaa1488. doi: 10.1093/cid/ciaa1488. Online ahead of print.
Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

A multidisciplinary team of researchers associated with John Hopkins Medicine conducted a retrospective cohort study to analyze disease severity in 2,121 COVID-19 patients, 108 of whom were on chronic immunosuppressant medications. Results suggest that chronic immunosuppression does not cause significant changes to risk of mechanical ventilation (p=0.74), mortality (p=0.73), or length of stay (p=0.08) in comparison to patients who didn't use immunosuppressive medications (Table 2). Authors note limitations due to small sample size and the observational nature of the study, however these findings are important in understanding the relationship between COVID-19 and chronic use of immunosuppressive medications.

ABSTRACT

BACKGROUND: It is unclear whether chronic use of immunosuppressive drugs worsens or improves the severity of coronavirus disease 2019 (COVID-19), with plausible mechanisms for both. METHODS: Retrospective cohort study in 2121 consecutive adults with acute inpatient hospital admission between 4 March and 29 August 2020 with confirmed or suspected COVID-19 in a large academic health system, with adjustment for confounding with propensity score-derived stabilized inverse probability of treatment weights. Chronic immunosuppression was defined as prescriptions for immunosuppressive drugs current at the time of admission. Outcomes included mechanical ventilation, in-hospital mortality, and length of stay. RESULTS: There were 2121 patients admitted with laboratory-confirmed (1967, 93%) or suspected (154, 7%) COVID-19 during the study period, with a median age of 55 years (interquartile range, 40-67). Of these, 108 (5%) were classified as immunosuppressed before COVID-19, primarily with prednisone (>7.5 mg/day), tacrolimus, or mycophenolate mofetil. Among the entire cohort, 311 (15%) received mechanical ventilation; the median (interquartile range) length of stay was 5.2 (2.5-10.6) days, and 1927 (91%) survived to discharge. After adjustment, there were no significant differences in the risk of mechanical ventilation (hazard ratio [HR], .79; 95% confidence interval [CI], .46-1.35), in-hospital mortality (HR, .66; 95% CI, .28-1.55), or length of stay (HR, 1.16; 95% CI, .92-1.47) among individuals with immunosuppression and counterparts. CONCLUSIONS: Chronic use of immunosuppressive drugs was neither associated with worse nor better clinical outcomes among adults hospitalized with COVID-19 in one US health system.

Table 2. Unadjusted Clinical Outcomes by Immune System Status Prior to COVID-19

	Immune System Status Prior to COVID-19		
	Immunosuppressed (n = 108)	Immunocompetent (n = 2013)	*P*
Discharged alive, n (%)	95 (88)	1832 (91)	.2848
Remains hospitalized as of 29 August 2020, n (%)	6 (6)	33 (2)	.0032
Mechanical ventilation, n (%)	17 (16)	294 (15)	.7452
<2 days after admission	6 (35)	161 (55)	
2–7 days	7 (41)	113 (38)	
>7 days	4 (24)	20 (7)	
Median (IQR) time to mechanical ventilation, days	3.0 (1.3–6.8)	2.6 (0.4–3.7)	.0159
In-hospital death, n (%)	7 (7)	148 (7)	.7348
<2 days after admission	0	10 (7)	
2–7 days	1 (14)	23 (16)	
>7 days	6 (86)	115 (78)	
Median (IQR) time to death, days	27.2 (7.9–56.7)	13.3 (8.1–22.7)	.2453
Length of stay, median (IQR), days	6.9 (2.8–13.2)	5.1 (2.5–10.5)	.0853
Among those discharged	6.1 (2.2–10.1)	4.8 (2.3–9.1)	.2136
Among those still admitted as of 29 August 2020	13.2 (10.3–18.8)	18.3 (9.2–24.2)	.7407
Among those who died	27.2 (7.9–56.7)	13.3 (8.1–22.6)	.2453

For counts, the *P* value was calculated using a chi-square test. For median times, the *P* value was calculated using the Wilcoxon rank-sum test for difference in medians.
Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range.

Table 2. Unadjusted Clinical Outcomes by Immune System Status Prior to COVID-19

PERFORMANCE CHARACTERISTICS OF A RAPID SARS-COV-2 ANTIGEN DETECTION ASSAY AT A PUBLIC PLAZA TESTING SITE IN SAN FRANCISCO

Pilarowski G, Lebel P, Sunshine S, Liu J, Crawford E, Marquez C, Rubio L, Chamie G, Martinez J, Peng J, Black D, Wu W, Pak J, Laurie MT, Jones D, Miller S, Jacobo J, Rojas S, Rojas S, Nakamura R, Tulier-Laiwa V, Petersen M, Havlir DV; CLIAHUB Consortium, DeRisi J.. J Infect Dis. 2021 Jan 4:jiaa802. doi: 10.1093/infdis/jiaa802. Online ahead of print.
Level of Evidence: 3 - Non-consecutive studies, or studies without consistently applied reference standards

BLUF

Researchers from multiple departments at the University of California, Latino Task Force-COVID-19, and California Department of Public Health compared the Abbott Binax-CoV2 rapid antigen test to RT-PCR for community screening at a public transit hub, using a dilution-series of lab cultured SARS-CoV-2 to compare the sensitivity and specificity of the 2 testing methods (Figure 1). They found that using a cycle threshold (Ct) of <30, the sensitivity of Binax-CoV2 was 93.3% and specificity was 99.9%. Though the criteria for reading the Binax-CoV2 results is subjective, with its sensitivity depending on the viral kinetics of the test population, the authors still suggest that the Binax-CoV2 assay test can be utilized in both symptomatic and asymptomatic individuals with high viral loads and is beneficial for rapidly identifying infectious individuals.

ABSTRACT

We evaluated the performance of the Abbott BinaxNOW TM Covid-19 rapid antigen test (Binax-CoV2) to detect virus among persons, regardless of symptoms, at a public plaza site of ongoing community transmission. Titration with cultured SARS-CoV-2 yielded a human observable threshold between 1.6x10 4-4.3x10 4 viral RNA copies (cycle threshold (Ct) of 30.3-28.8). Among 878 subjects tested, 3% (26/878) were positive by RT-PCR, of which 15/26 had Ct<30, indicating high viral load. 40% (6/15) of Ct<30 were asymptomatic. Using this Ct<30 threshold for Binax-CoV2 evaluation, the sensitivity of Binax-CoV2 was 93.3% (14/15), 95% CI: 68.1-99.8%, and the specificity was 99.9% (855/856), 95% CI: 99.4-99.9%.

Figure 1

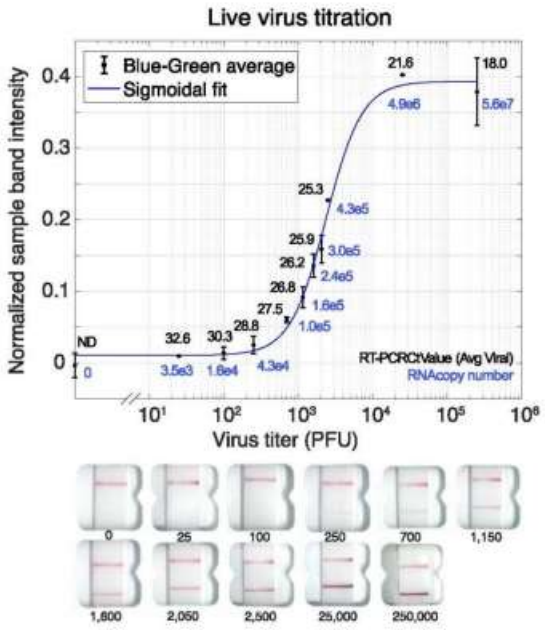


Figure 1. Titration of in vitro grown SARS-CoV-2 and detection on Binax-CoV2 assay. Normalized Binax-CoV2 sample band intensity (blue-green average) for cards loaded with a known amount of virus. Error bars represent standard deviation of sample band intensity of technical replicates. RT-PCR testing was performed at the CLIAHUB consortium [10]. Corresponding RT-PCR Ct values (average of N and E gene probes) are printed in black and the corresponding RNA copy number printed in blue. Note that Ct and genome copy number correlation varies by RT-PCR platform. Representative card images from each datapoint are shown below.

PERFORMANCE OF SALIVA SPECIMENS FOR THE MOLECULAR DETECTION OF SARS-COV-2 IN THE COMMUNITY SETTING: DOES SAMPLE COLLECTION METHOD MATTER?

Fernández-González M, Agulló V, de la Rica A, Infante A, Carvajal M, García JA, Gonzalo-Jiménez N, Cuartero C, Ruiz-García M, de Gregorio C, Sánchez M, Masiá M, Gutiérrez F.. J Clin Microbiol. 2021 Jan 8:JCM.03033-20. doi: 10.1128/JCM.03033-20. Online ahead of print.
Level of Evidence: 2 - Individual cross sectional studies with consistently applied reference standard and blinding

BLUF

A prospective cohort study was conducted at three primary care centers by the Departments of Health and multiple hospitals in Alicante, Spain between September 15 and October 29, 2020 to assess the performance of RT-PCR saliva testing for COVID-19 through three different methods of collection (see summary) on 577 patients who were either symptomatic or asymptomatic with known exposure to COVID-19 prior to receiving the gold standard comparator RT-PCR nasopharyngeal swab (NPS). Results showed that supervised collection (SVC) had the best performance with 86% sensitivity compared to 66.7% sensitivity of self collected (SC) samples (See Table 3) and a higher sensitivity was achieved when cycle threshold was low resulting in 100% sensitivity in symptomatic and 88.9% sensitivity in asymptomatic patients with RT-PCR (See Figures 2+3). These findings suggest that saliva specimens perform comparably to the NPS samples and are considered effective for detection of SARS-CoV-2 in the community.

SUMMARY

The three methods of saliva specimen collection are as follows:
-Supervised collection (SVC): Specimens obtained under supervision of a healthcare worker.
-Oropharyngeal washing (OPW): Rinsing the mouth with 2mL of saline solution and spitting the solution into the collection pot.
-Self-collection (SC): Specimens collected independently by the individual providing the sample by following these written instructions: "To collect saliva, bow your head forward to allow saliva to pool in the front of your mouth and spit up to a minimum of 1 ml of saliva (half a teaspoon) into the collection pot."

ABSTRACT

Background: Data on the performance of saliva specimens for diagnosing COVID-19 in ambulatory patients are scarce and inconsistent. We assessed saliva-based specimens for detecting SARS-CoV-2 by RT-PCR in the community setting and compared three different collection methods.Method: Prospective study conducted in three primary care centres. RT-PCR was performed in paired nasopharyngeal swabs (NPS) and saliva samples collected from outpatients with a broad clinical spectrum of illness. To assess differences in collection methods, saliva specimens were obtained in a different way in each of the participating centres: supervised collection (SVC), oropharyngeal washing (OPW) and self-collection (SC).Results: NPS and saliva pairs of samples from 577 patients (median age 39 years, 44% men, 42% asymptomatic) were collected and tested, and 120 (20.8%) gave positive results. The overall agreement with NPS and kappa coefficients (K) for SVC, OPW and SC were 95% (K=0.85), 93.4% (K=0.76), and 93.3% (K=0.76), respectively. The sensitivity (95% CI) of the saliva specimens varied from 86% (72.6-93.7) for SVC to 66.7% (50.4-80) for SC samples. The sensitivity was higher in samples with lower cycle threshold (Ct) values. The best performance of RT-PCR was observed for SVC, with sensitivity (95% CI) for Ct values <=30 of 100% (85.9-100) in symptomatic, and 88.9% (50.7-99.4) in asymptomatic individuals.Conclusions: Saliva is an acceptable specimen for the detection of SARS-CoV-2 in the community setting. Specimens collected under supervision perform comparably to NPS and can effectively identify individuals with higher risk of transmission in real life conditions.

Saliva type	Positive percent agreement (95% CI)	Negative percent agreement (95% CI)	Overall percent agreement (95% CI)	Performance Agreement (Kappa) (95% CI)
Supervised collection	84.8% (70.5-93.2)	97.7% (93.9-99.3)	95% (91-97.4)	0.85 (0.76-0.93)
Oropharyngeal washing	72% (50.4-87.1)	98.2% (93.1-99.7)	93.4% (87.5-96.8)	0.76 (0.61-0.91)
Self-collection	66.7% (50.4-80)	100% (97.2-100)	93.3% (88.7-96.1)	0.76 (0.64-0.88)

Table 3. Agreement of the different saliva specimens with the nasopharyngeal swabs.

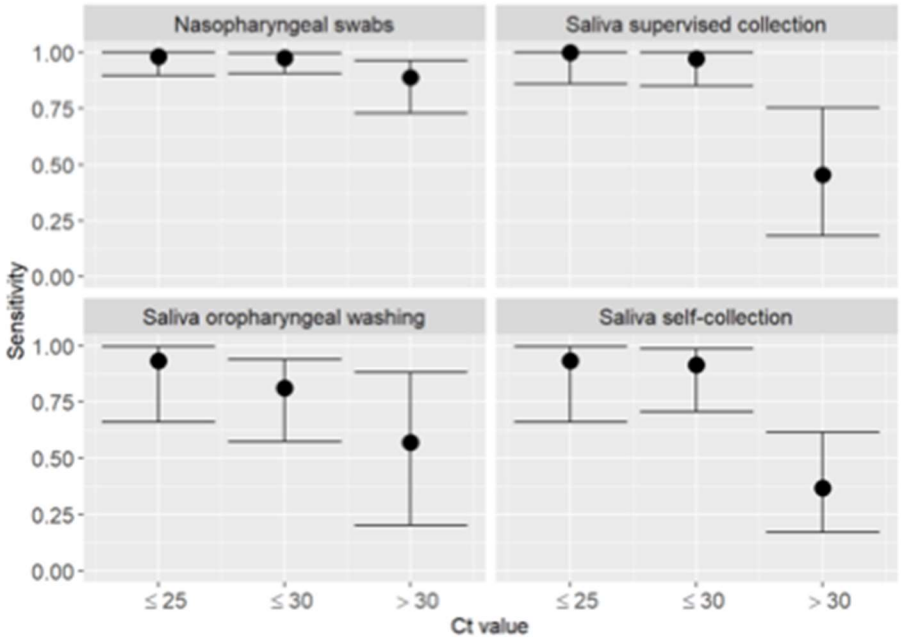


Figure 3. Sensitivity of the different specimens for SARS-CoV-2 detection according tCt value in nasopharyngeal swabs*. *In cases with negative nasopharyngeal swab and positive saliva, the Ct value of the saliva specimen was taken.

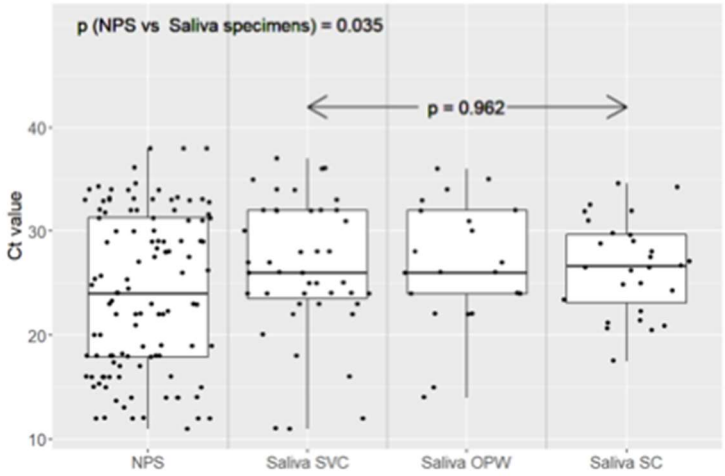


Figure 2. Cycle threshold values for nasopharyngeal swabs and saliva specimens' pairs from all positive individuals.

Each dot represents the Ct value (RT-PCR) for positive: nasopharyngeal swabs (NPS, n=113), saliva obtained under supervised collection (SVC, n=43), saliva obtained after oropharyngeal washing (OPW, n=21) and saliva obtained by self-collection (SC, n=28).

HOW MANY INTENSIVE CARE BEDS ARE JUSTIFIABLE FOR HOSPITAL PANDEMIC PREPAREDNESS? A COST-EFFECTIVENESS ANALYSIS FOR COVID-19 IN GERMANY

Gandjour A.. Appl Health Econ Health Policy. 2021 Jan 12:1-10. doi: 10.1007/s40258-020-00632-2. Online ahead of print.
Level of Evidence: 5 - Modeling

BLUF

An expert in health economics from the Frankfurt School of Finance and Management in Germany created a model to analyze the cost-effectiveness of expanding or maintaining intensive care unit (ICU) bed reserve capacity to prepare for a second wave of the COVID-19 pandemic (Summary). With full bed utilization, they found the last staffed bed added cost €21,958 per life-year gained with a positive return on investment. Net monetary benefit remained positive with utilization above 2% (Figures 1, 2, 3). The author concludes ICU bed expansion is cost effective even at a large vacancy rate and advocates for more cost-effectiveness analysis to improve hospital preparedness and determine appropriate capacity increases.

SUMMARY

The author's model considered the loss of life years when there are no ICU beds left for COVID-19 patients and took into account age-specific life-expectancy changes. He made the clinical value of an additional ICU bed equivalent to the marginal loss of life years if this additional bed were not there. Using these principles he determined the clinical value of an ICU bed in terms of life-years gained as well as decrease in mortality.

Cost analysis considered medical costs (patient costs), hospital costs (operating and infrastructure) and nursing staff costs; payments by the German government for PPE and nursing care were also considered. Costs were determined based on previously reported data or estimated based on publicly available data.

To calculate the return on investment, the author subtracted the cost of an additional bed from the monetary value created and divided this by its additional cost. The net monetary benefit (NMB) was calculated based upon willingness to pay for novel cancer treatments (cancer having a similar disease burden).

ABSTRACT

INTRODUCTION: Germany is experiencing the second COVID-19 pandemic wave. The intensive care unit (ICU) bed capacity is an important consideration in the response to the pandemic. The purpose of this study was to determine the costs and benefits of maintaining or expanding a staffed ICU bed reserve capacity in Germany. METHODS: This study compared the provision of additional capacity to no intervention from a societal perspective. A decision model was developed using, e.g. information on age-specific fatality rates, ICU costs and outcomes, and the herd protection threshold. The net monetary benefit (NMB) was calculated based upon the willingness to pay for new medicines for the treatment of cancer, a condition with a similar disease burden in the near term. RESULTS: The marginal cost-effectiveness ratio (MCER) of the last bed added to the existing ICU capacity is $21,958 per life-year gained assuming full bed utilization. The NMB decreases with an additional expansion but remains positive for utilization rates as low as 2%. In a sensitivity analysis, the variables with the highest impact on the MCER were the mortality rates in the ICU and after discharge. CONCLUSIONS: This article demonstrates the applicability of cost-effectiveness analysis to policies of hospital pandemic preparedness and response capacity strengthening. In Germany, the provision of a staffed ICU bed reserve capacity appears to be cost-effective even for a low probability of bed utilization.

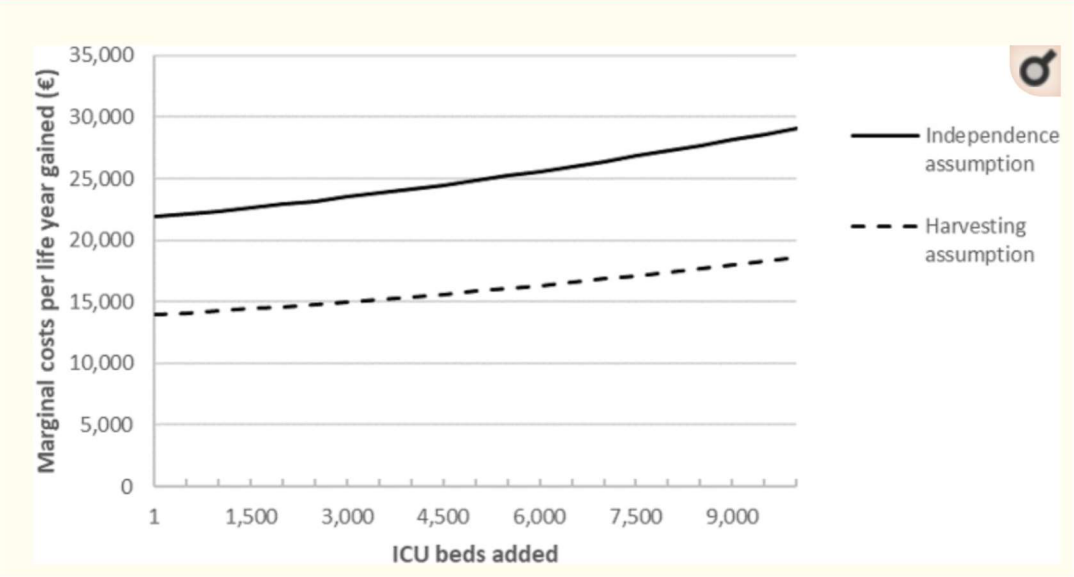
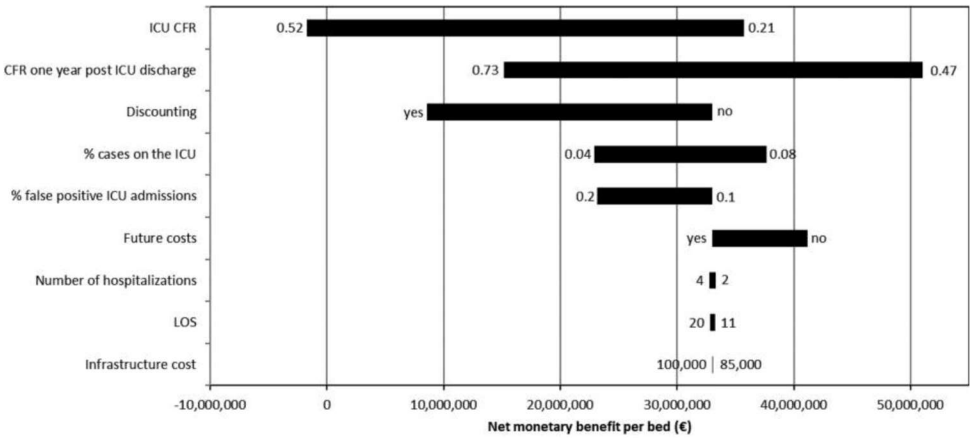


Fig. 1
Marginal costs per life-year gained by adding intensive care unit (ICU) bed capacity



intensive care unit, CFR = case fatality rate, LOS = length of stay

Fig. 2
Tornado diagram demonstrating the results of the one-way sensitivity analysis. The variables are ordered by the impact on the net monetary benefit of the provision of additional ICU bed capacity versus no intervention. The numbers indicate the upper and lower bounds

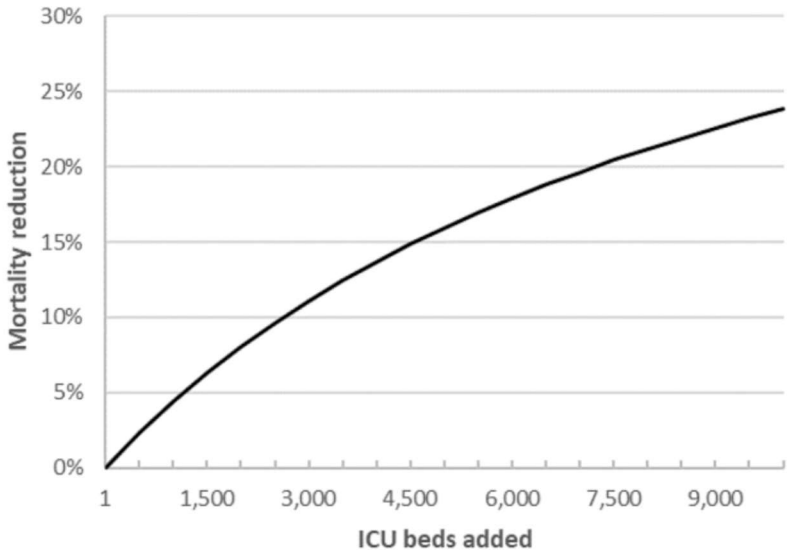


Fig 3. Mortality reduction of intensive care unit (ICU) candidates by increasing ICU bed capacity compared with no increase

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