# The Daily COVID-19 Literature Surveillance Summary

## December 09, 2020

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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

**Epidemiology**

- A systematic review of 39 articles (30 retrospective and 9 prospective) on venous thromboembolic events (VTE) in COVID-19 by a team of cardiologists and molecular biologists from the Central South University in Hunan, China found that D-dimer, fibrinogen, and APTT may be useful in predicting thromboembolic events in patients with severe COVID-19.

**Understanding the Pathology**

- Physicians at the Icahn School of Medicine used enzyme-linked immunosorbent assay (ELISA) to screen patients (n=72,401) at Mount Sinai Health System for the SARS-CoV-2 spike protein antibody and found that 30,082 patients tested positive (titer 1:80 or higher) with quantitative microneutralization assay demonstrating that spike protein titer level positively correlated to neutralization titer (Spearman r: 0.87, p<0.000). A subgroup (n=121) had titers drawn at multiple timepoints (30, 82, and 148 days after symptom onset), and their ELISA titers still positively correlated with the neutralization titers after 148 days (r: 0.79; p=0.0001), suggesting that patients infected with SARS-CoV-2 form long lasting neutralizing antibodies and that understanding the kinetics of these antibodies could aid in the vaccine development.

**Management**

- Infectious disease physicians at the Imperial College London reviewed publications about bacterial and fungal coinfection with human coronaviruses and found that in the nine studies, 62/806 patients (8%) experienced coinfections during hospital admission. Because most patients across all studies received broad spectrum antibiotics (1450/2010; 72%), authors suggest the seemingly low occurrence of coinfection may be attributable to empiric antibiotic use and recommend conducting prospective studies to inform antibiotic stewardship during the COVID-19 pandemic.

- Members of the World Association of Perinatal Medicine propose consensus statements regarding SARS-CoV-2 infection in pregnant patients based on their review of the literature. They comment on diagnosis, screening in laboring patients, maternal and fetal complications, vertical transmission, delivery mode, breastfeeding, appropriate setting of care, and use of antiviral medications.

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# CLIMATE

## SCIENCE AND EVIDENCE-BASED REVIEW AND APPROVAL OF COVID-19 VACCINES: A STATEMENT OF SUPPORT FOR THE U.S. FDA

Pai SM, Othman AA, Rusch L, Masters JC, Greene D, Rogge M, Gries JM, Clementi W, Kumar P, Younis I, Salem AH, Gaynes B, Pastino G, Derendorf H.. J Clin Pharmacol. 2020 Dec 4. doi: 10.1002/jcph.1794. Online ahead of print.
Level of Evidence: 5 - Expert Opinion

### BLUF

A position statement by pharmacists from the American College of Clinical Pharmacology (ACCP) commends the U.S. Food & Drug Administration's (FDA) approval and authorization process of COVID-19 vaccines. The authors highlight the FDA's transparency and proactivity in issuing guidelines for clinical trials that define clear primary efficacy endpoints, verify vaccine safety, and specify rigorous design requirements (i.e. randomized, double-blind and placebo-controlled). This position statement is meant to lend explicit confidence in the FDA's approval process regarding future COVID-19 vaccines.

# ADULTS

## VENOUS THROMBOEMBOLIC EVENTS IN PATIENTS WITH COVID-19: A SYSTEMATIC REVIEW AND META-ANALYSIS

Wu T, Zuo Z, Yang D, Luo X, Jiang L, Xia Z, Xiao X, Liu J, Ye M, Deng M.. Age Ageing. 2020 Nov 17:afaa259. doi: 10.1093/ageing/afaa259. Online ahead of print.
Level of Evidence: 2 - Systematic review of surveys that allow matching to local circumstances

### BLUF

A team of cardiologists and molecular biologists from the Central South University in Hunan, China conducted a systematic review of 39 articles (30 retrospective and 9 prospective) published before September 11, 2020 regarding venous thromboembolic events (VTE) in COVID-19 (Figure 1). Results from their analysis, summarized below, indicate that D-dimer, fibrinogen, and APTT may be useful in predicting thromboembolic events in patients with severe COVID-19.

### SUMMARY

- Incidence of pulmonary embolism and VTE in patients with severe COVID-19 (defined as clinical signs of pneumonia plus either respiratory rate > 30 breaths/min OR severe respiratory distress OR SpO2 <90% on room air) was 17% (95% CI: 13-21%) and 42% (95% CI: 25-60%), respectively.
- Patients with COVID-19 and thromboembolic disease were signifciantly more likely to develop severe disease (as defined above) and/or require critical care (Figure 3).

- VTE was more common in older patients (average age of 64.5) and predictable using D-dimer (weighted mean difference [WMD]=4.21 ug/mL; 95% CI: 3.77-4.66 ug/mL), activated partial thromboplastin time (APTT)(WMD=2.03s; 95% CI: 0.83-3.24s), and fibrinogen (WMD=0.49 ug/mL; 95% CI: 0.18-0.79 g/L)(Figure 3).
- Elevated C-reactive protein and white blood cell count and lower lymphocyte counts were also associated with increased VTE risk but these findings were not statistically significant.
- Comorbidities (hypertension, diabetes, pulmonary disease, elevated or decreased BMI) were not associated with increased VTE risk.

### ABSTRACT

BACKGROUND: High incidence of venous thromboembolic complications in COVID-19 patients was noted recently. OBJECTIVE: This study aimed to explore the factors associated with prevalence of venous thromboembolism (VTE) in COVID-19 patients. METHODS: A literature search was conducted in several online databases. Fixed effects meta-analysis was performed for the factors associated with prevalence of VTE in COVID-19 patients. RESULTS: A total of 39 studies were analyzed in this analysis. The incidence of pulmonary embolism and VTE in severe COVID-19 patients were 17% (95% CI, 13-21%) and 42% (95% CI, 25-60%), respectively. VTE were more common among individuals with COVID-19 of advance age. Male COVID-19 patients are more likely to experience VTE. Higher levels of white blood cell (WBC; WMD = 1.34x109/L; 95% CI, 0.84-1.84x109/L), D-dimer (WMD = 4.21 ug/mL; 95% CI, 3.77-4.66 ug/mL), activated partial thromboplastin time (APTT; WMD = 2.03 s; 95% CI, 0.83-3.24 s), fibrinogen (WMD = 0.49 ug/mL; 95% CI, 0.18-0.79 g/L) and C-reactive protein (CRP; WMD = 21.89 mg/L; 95% CI, 11.44-32.34 mg/L) were commonly noted in COVID-19 patients with VTE. Patients with lower level of lymphocyte (WMD = -0.15x109/L; 95% CI, -0.23-0.07x109/L) was at high risk of developing VTE. The incidence of severe condition (OR = 2.66; 95% CI, 1.95-3.62) was more likely to occur among COVID-19 patients who developed VTE. CONCLUSION: VTE is a common complication in severe COVID-19 patients and thromboembolic events are also associated with adverse outcomes.

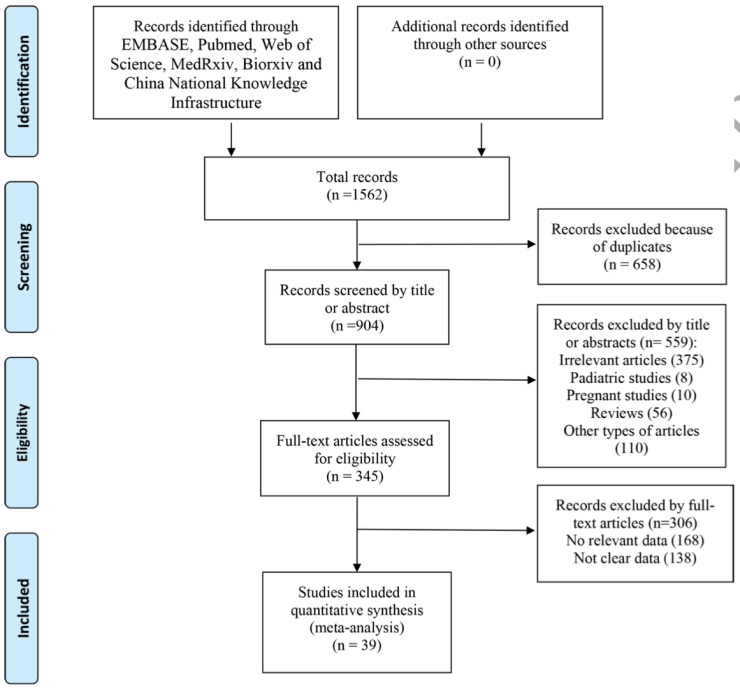



**Figure 1** PRISMA Diagram of Study Selection

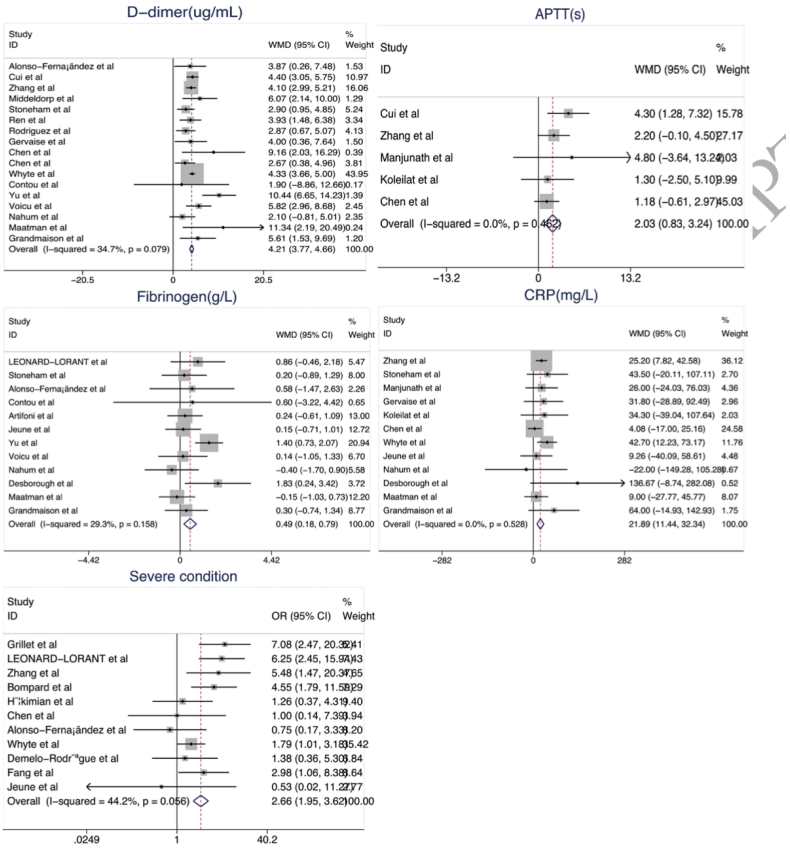



**Figure 3** Meta-analysis of factors (D-dimer, APTT, fibrinogen, CRP, severe condition) associated with prevalence of venous thromboembolic event.

## OPHTHALMIC AND NEURO-OPHTHALMIC MANIFESTATIONS OF CORONAVIRUS DISEASE 2019 (COVID-19)

Ortiz-Seller A, Martínez Costa L, Hernández-Pons A, Valls Pascual E, Solves Alemany A, Albert-Fort M.. Ocul Immunol Inflamm. 2020 Nov 16;28(8):1285-1289. doi: 10.1080/09273948.2020.1817497. Epub 2020 Oct 6.
Level of Evidence: 5 - Case Report

### BLUF

Ophthalmologists from Hospital Universitari Doctor Peset in Valencia, Spain describe the case of a 51-year-old woman who presented with retro-ocular pain and reading impairment two days after testing positive for SARS-CoV-2. The patient had an abnormal pupillary response and multiple bilateral white-yellowish placoid retinal lesions on funduscopic examination. Work up was significant for hypersensitivity with topical dilute 0.1% pilocarpine consistent with Adie's Syndrome and retinal imaging consistent with chorioretinopathy. Authors state this is the first ever reported case of inflammatory chorioretinopathy accompanied by Adie's Syndrome in a patient with COVID-19, and that more research is needed to better understand SARS-CoV-2 infectivity in ocular tissues.

### ABSTRACT

PURPOSE: To describe a case of inflammatory chorioretinopathy and Adie's syndrome possibly associated with COVID-19. METHODS: Observational case report. RESULTS: A 51-year-old woman developed fever, cough, and headache followed by retro-ocular pain and reading impairment. She tested positive for SARS-COV-2 infection by qualitative real-time reverse-transcriptase-polymerase-chain-reaction. The slit-lamp and funduscopic exam revealed abnormal pupillary response and yellowish creamy deep chorioretinal lesions, which were not present in previous examinations. Instillation of pilocarpine demonstrated denervation supersensitivity, and it was suggestive of bilateral Adie tonic pupil. A comprehensive work-up ruled out other systemic, autoimmune, or infectious diseases. CONCLUSIONS: This case illustrates the possible association between multifocal chorioretinitis and Adie's syndrome, and the SARS-COV-2 infection in humans. Further investigation of virus infectivity specifically within ocular tissues has to be conducted.

# ROBUST NEUTRALIZING ANTIBODIES TO SARS-COV-2 INFECTION PERSIST FOR MONTHS

Wajnberg A, Amanat F, Firpo A, Altman DR, Bailey MJ, Mansour M, McMahon M, Meade P, Mendu DR, Muellers K, Stadlbauer D, Stone K, Strohmeier S, Simon V, Aberg J, Reich DL, Krammer F, Cordon-Cardo C.. Science. 2020 Dec 4;370(6521):1227-1230. doi: 10.1126/science.abd7728. Epub 2020 Oct 28.
Level of Evidence: 3 - Local non-random sample

## BLUF

Physicians at the Icahn School of Medicine used enzyme-linked immunosorbent assay (ELISA) to screen patients at Mount Sinai Health System for the SARS-CoV-2 spike protein antibody from March to October 2020 (n=72,401). They found 30,082 patients tested positive (titer 1:80 or higher)(Figure 1) with quantitative microneutralization assay demonstrating that spike protein titer level positively correlated to neutralization titer (Spearman r: 0.87, p<0.000)(Figure 2). A subgroup (n=121) had titers drawn at multiple timepoints (30, 82, and 148 days after symptom onset) and their ELISA titers still positively correlated with the neutralization titers after 148 days (r: 0.79; p=0.0001)(Figure 3). Authors suggest patients infected with SARS-CoV-2 form long lasting neutralizing antibodies and that understanding the kinetics of these antibodies could aid in the vaccine development.

## ABSTRACT

SARS-CoV-2 has caused a global pandemic with millions infected and numerous fatalities. Questions regarding the robustness, functionality, and longevity of the antibody response to the virus remain unanswered. Here we report that the vast majority of infected individuals with mild-to-moderate COVID-19 experience robust IgG antibody responses against the viral spike protein, based on a dataset of 30,082 individuals screened at Mount Sinai Health System in New York City. We also show that titers are relatively stable for at least a period approximating 5 months and that anti-spike binding titers significantly correlate with neutralization of authentic SARS-CoV-2. Our data suggests that more than 90% of seroconverters make detectible neutralizing antibody responses. These titers remain relatively stable for several months after infection.

## FIGURES

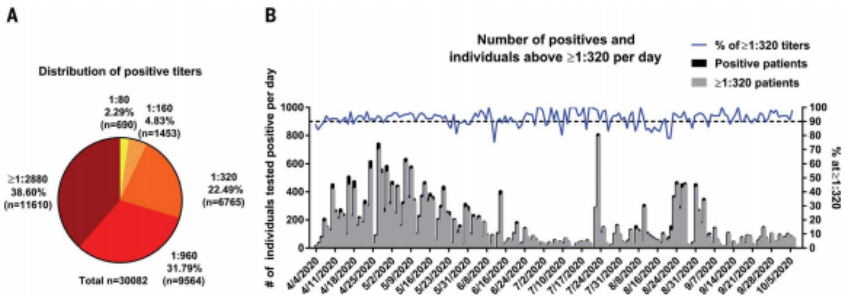



**Fig. 1. SARS-CoV-2 spike antibody titers in 30,082 individuals.** (**A**) The percentage of individuals with antibody titers of 1:80 (low), 1:160 (low), 1:320 (moderate), 1:960 (high), and ≥1:2880 (high). (**B**) Absolute numbers of individuals testing positive and percent of individuals with titers of 1:320 over time. Testing of each sample was performed once in a Clinical Laboratory Improvement Amendments (CLIA)–certified laboratory using an assay that received emergency use authorization (EUA) from the U.S. Food and Drug Administration (FDA).

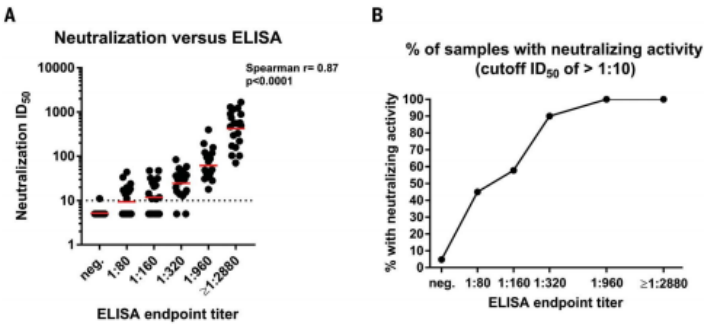



**Fig. 2. Neutralizing activity of serum samples in relation to ELISA titers.** (**A**) A correlation analysis between ELISA titers on the *x* axis and neutralization titers in a micro-neutralization assay on the *y* axis. The Spearman ρ was determined. Red bars indicate the geometric mean. (**B**) The proportion of sera that exert any neutralizing activity in each of the ELISA titer categories. Testing was performed once, using an FDA EUA ELISA in a CLIA laboratory, or twice, following a standardized neutralization protocol.

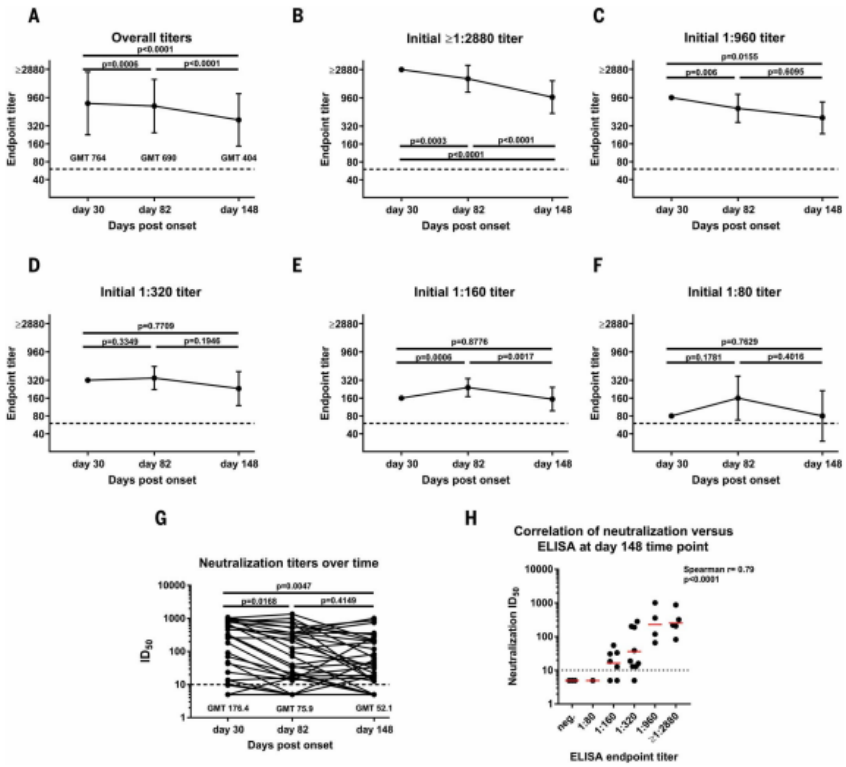



**Fig. 3. Antibody titer stability over time.** (**A**) Titers of 121 volunteers whose blood was initially drawn −30 days after COVID-19 symptom onset and who were then recalled for additional blood draws at −82 days and 148 days after symptom onset. (**B** to **F**) The same data as in (A), but stratified by the initial (day 30) titer. Titers are graphed as geometric mean titers (GMT) with geometric standard error. (**G**) Neutralization titers of 36 individuals over time. A paired one-way analysis of variance corrected for multiple comparison was used to determine statistical significance. (**H**) A correlation analysis between ELISA titers on the *x* axis and neutralization titers in a microneutralization assay on the *y* axis at day 148. Red bars indicate the geometric mean. The Spearman ρ was determined. Testing was performed once, using an FDA EUA ELISA in a CLIA-certified laboratory, or twice, following a standardized neutralization protocol.

# MANAGEMENT

## BACTERIAL AND FUNGAL COINFECTION IN INDIVIDUALS WITH CORONAVIRUS: A RAPID REVIEW TO SUPPORT COVID-19 ANTIMICROBIAL PRESCRIBING

Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, Satta G, Cooke G, Holmes A.. Clin Infect Dis. 2020 Dec 3;71(9):2459-2468. doi: 10.1093/cid/ciaa530.
Level of Evidence: 5 - Review / Literature Review

### BLUF

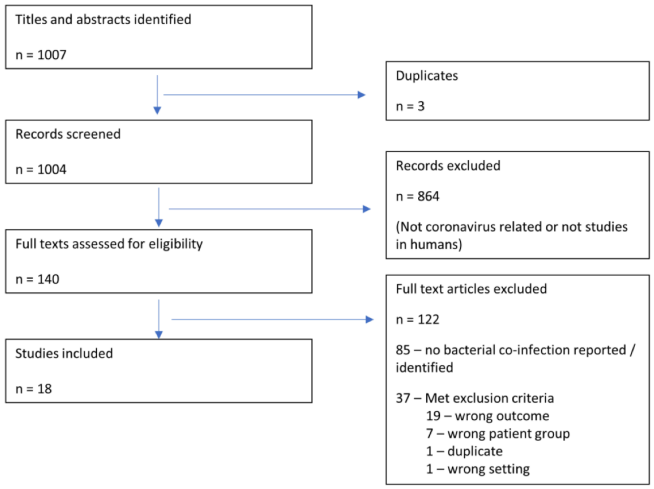
Infectious disease physicians from the Imperial College London reviewed 18 publications about bacterial and fungal coinfection with human coronaviruses (Figure 1). In the nine studies examining COVID-19 patients, they found 62/806 patients (8%) experienced coinfections during hospital admission. Because most patients across all studies received broad spectrum antibiotics (1450/2010; 72%), authors suggest the seemingly low occurrence of coinfection may be attributable to empiric antibiotic use and recommend conducting prospective studies to inform antibiotic stewardship during the COVID-19 pandemic.

### ABSTRACT

BACKGROUND: To explore and describe the current literature surrounding bacterial/fungal co-infection in patients with coronavirus infection. METHODS: MEDLINE, EMBASE, and Web of Science were searched using broad based search criteria relating to coronavirus and bacterial co-infection. Articles presenting clinical data for patients with coronavirus infection (defined as SARS-1, MERS, SARS-COV-2, and other coronavirus) and bacterial/fungal co-infection reported in English, Mandarin, or Italian were included. Data describing bacterial/fungal co-infections, treatments, and outcomes were extracted. Secondary analysis of studies reporting antimicrobial prescribing in SARS-COV-2 even in the absence of co-infection was performed. RESULTS: 1007 abstracts were identified. Eighteen full texts reported bacterial/fungal co-infection were included. Most studies did not identify or report bacterial/fungal coinfection (85/140;61%). 9/18 (50%) studies reported on COVID-19, 5/18 (28%) SARS-1, 1/18 (6%) MERS, and 3/18 (17%) other coronavirus.For COVID-19, 62/806 (8%) patients were reported as experiencing bacterial/fungal co-infection during hospital admission. Secondary analysis demonstrated wide use of broad-spectrum antibacterials, despite a paucity of evidence for bacterial coinfection. On secondary analysis, 1450/2010 (72%) of patients reported received antimicrobial therapy. No antimicrobial stewardship interventions were described.For non-COVID-19 cases bacterial/fungal co-infection was reported in 89/815 (11%) of patients. Broad-spectrum antibiotic use was reported. CONCLUSIONS: Despite frequent prescription of broad-spectrum empirical antimicrobials in patients with coronavirus associated respiratory infections, there is a paucity of data to support the association with respiratory bacterial/fungal co-infection. Generation of prospective evidence to support development of antimicrobial policy and appropriate stewardship interventions specific for the COVID-19 pandemic are urgently required.

### FIGURES

**Figure 1.** PRISMA flow diagram outlining study selection



## CLINICAL MANAGEMENT OF CORONAVIRUS DISEASE 2019 (COVID-19) IN PREGNANCY: RECOMMENDATIONS OF WAPM-WORLD ASSOCIATION OF PERINATAL MEDICINE

Api O, Sen C, Debska M, Saccone G, D'Antonio F, Volpe N, Yayla M, Esin S, Turan S, Kurjak A, Chervenak F.. J Perinat Med. 2020 Nov 26;48(9):857-866. doi: 10.1515/jpm-2020-0265.
Level of Evidence: 5 - Guidelines and Recommendations

### BLUF

Members of the World Association of Perinatal Medicine propose consensus statements regarding SARS-CoV-2 infection in pregnant patients based on their review of the literature. They comment on diagnosis, screening in laboring patients, maternal and fetal complications, vertical transmission, delivery mode, breastfeeding, appropriate setting of care, and use of antiviral medications (see Summary). Authors advise physicians apply these principles to their care of pregnant patients to optimize their care.

### SUMMARY

The World Association of Perinatal Medicine take the following positions based on their review of available literature:
1. RT-PCR is the gold standard for diagnosis. However, a pregnant patient presents with classic symptoms of COVID-19 and is in an outbreak area should be presumed COVID-19 positive even with a negative RT-PCR. Avoid chest CT scans or X-rays as a first-line test for diagnosis.
2. Universal SARS-CoV-2 screening of all pregnant patient admitted for labour should be performed if resources are available.
3. Maternal mortality rates do not appear to be increased in COVID-19.
4. The most significant perinatal effect of infection in the third trimester appears to be preterm delivery. The rates of stillbirth and neonatal death in maternal COVID-19 do not seem to be increased above baseline risk.
5. Further data is needed to understand the vertical transmission risk of maternal COVID-19.
6. The optimal mode and timing of delivery in patients with COVID-19 should chosen based on the clinical situation including clinical status of the patient, gestational age, and fetal well-being.
7. Current evidence suggests that SARS CoV-2 is not detectable in breast milk of mothers with COVID-19 and breastfeeding is not contraindicated.
8. Pregnant patients with mild disease (no shortness of breath or other indication for hospitalization) can be managed at home. Admission with consideration for the ICU should be considered if the patient has increased work of breathing, tachypnea, increasing oxygen need, $PCO2>40$ or $pH<7.35$, hypotension or oliguria despite adequate fluids, chest pain, worsening tachycardia, or altered mental status.
9. No medications have been proven to improve outcomes or approved by the FDA for use in pregnant woman with COVID-19.
- Remdesivir has not yet been studied in pregnant woman, but is currently recommended for severe disease in pregnant woman based on studies performed in other populations.
- Lopinavir/ritonavir is safe for pregnant woman but there is no evidence this is effective in the treatment of COVID-19 for any population.
- Hydroxychloroquine has not yet been demonstrated to be effective in pregnancy or other populations, and high doses should be avoided due to previous studies showing higher rates of mortality and QTc prolongation.
- There is not enough evidence to make a recommendation for or against the use of COVID-19 convalescent plasma.
- Avoid favipiravir due to potential for teratogenicity and embryotoxicity.
- Tocilizumab may be considered as for off-label use as a last resort in pregnant woman if there is concern for cytokine storm.

### ABSTRACT

These guidelines follow the mission of the World Association of Perinatal Medicine, which brings together groups and individuals throughout the world with the goal of improving outcomes of maternal, fetal and neonatal (perinatal) patients. Guidelines for auditing, evaluation, and clinical care in perinatal medicine enable physicians diagnose, treat and follow-up of COVID-19-exposed pregnant women. These guidelines are based on quality evidence in the peer review literature as well as the experience of perinatal expert throughout the world. Physicians are advised to apply these guidelines to the local realities which they face. We plan to update these guidelines as new evidence become available.

## REGN-COV2 ANTIBODIES PREVENT AND TREAT SARS-COV-2 INFECTION IN RHESUS MACAQUES AND HAMSTERS

Baum A, Ajithdoss D, Copin R, Zhou A, Lanza K, Negron N, Ni M, Wei Y, Mohammadi K, Musser B, Atwal GS, Oyejide A, Goez-Gazi Y, Dutton J, Clemmons E, Staples HM, Bartley C, Klaffke B, Alfson K, Gazi M, Gonzalez O, Dick E Jr, Carrion R Jr, Pessaint L, Porto M, Cook A, Brown R, Ali V, Greenhouse J, Taylor T, Andersen H, Lewis MG, Stahl N, Murphy AJ, Yancopoulos GD, Kyratsous CA.. Science. 2020 Nov 27;370(6520):1110-1115. doi: 10.1126/science.abe2402. Epub 2020 Oct 9.

Level of Evidence: 5 - Mechanism-based reasoning

### BLUF

Staff scientists from Regeneron Pharmaceuticals conducted an in vivo study comparing the efficacy of their neutralizing antibody cocktail REGN-COV2 (REGN10987 and REGN10933) in both rhesus macaques (mild COVID-19 disease model) and golden hamsters (moderate to severe disease model). They found that the cocktail reduced viral load in the upper (nasopharyngeal swab) and lower (bronchoalveolar lavage) respiratory tract in rhesus macaques (Figure 1, 2). When administered prophylactically or therapeutically, the cocktail also mitigated pathological sequelae (reduced interstitial lung pathology in rhesus macaques, limited weight loss in hamsters)(Figure 3). Authors imply these findings support the potential utility of REGN-COV2 antibodies as a therapeutic and preventative agent, and encourage follow up of its current clinical trials (clinicaltrials.gov NCT04426695, NCT04425629, and NCT04452318).

### ABSTRACT

An urgent global quest for effective therapies to prevent and treat COVID-19 disease is ongoing. We previously described REGN-COV2, a cocktail of two potent neutralizing antibodies (REGN10987+REGN10933) targeting non-overlapping epitopes on the SARS-CoV-2 spike protein. In this report, we evaluate the in vivo efficacy of this antibody cocktail in both rhesus macaques, which may model mild disease, and golden hamsters, which may model more severe disease. We demonstrate that REGN-COV-2 can greatly reduce virus load in lower and upper airways and decrease virus induced pathological sequelae when administered prophylactically or therapeutically in rhesus macaques. Similarly, administration in hamsters limits weight loss and decreases lung titers and evidence of pneumonia in the lungs. Our results provide evidence of the therapeutic potential of this antibody cocktail.

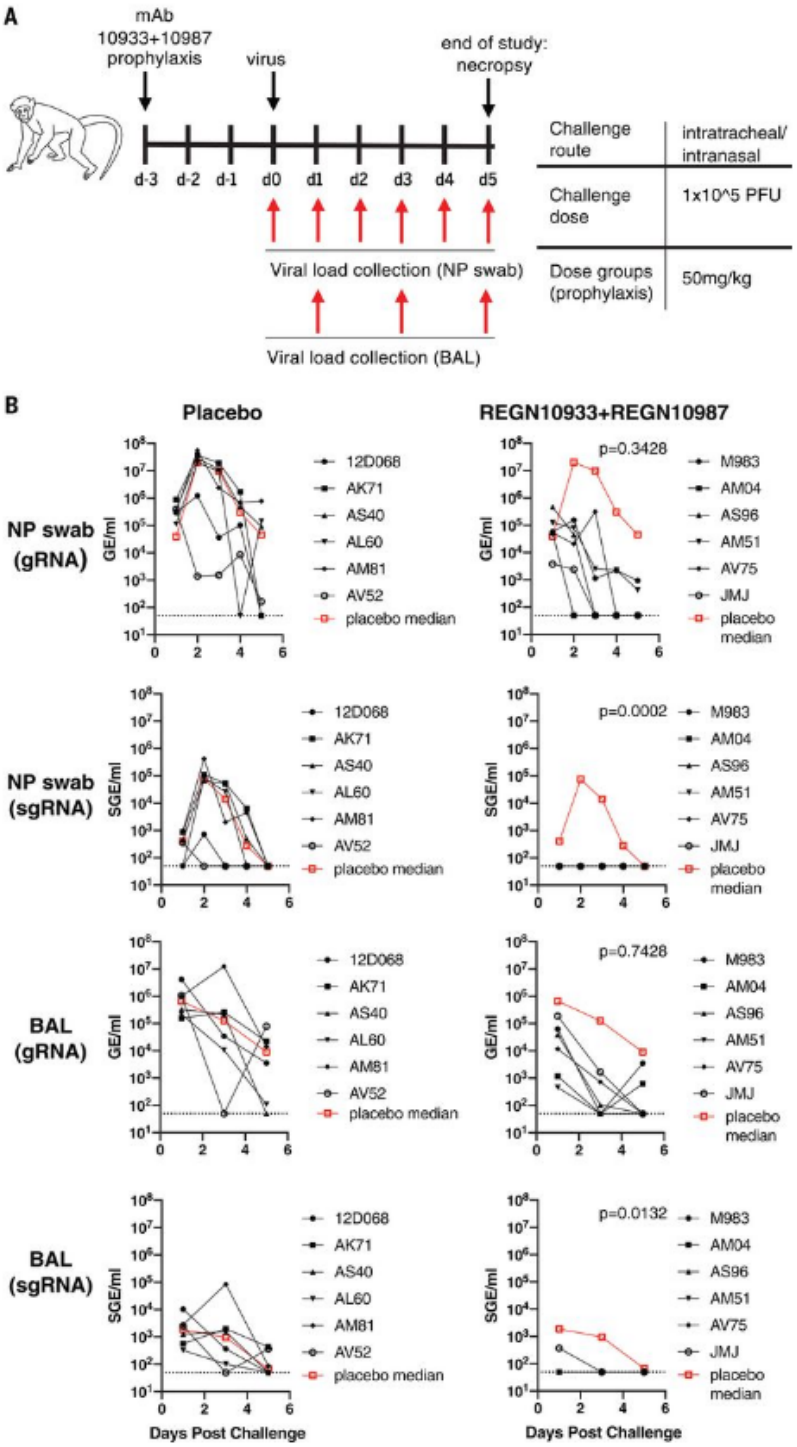



Fig. 1 Prophylactic efficacy of REGN-COV2 in the rhesus macaque model of SARS-CoV-2 infection (NHP study 1).

(A) Overview of study design. d, day.

(B) Impact of REGN-COV2 prophylaxis on viral gRNA and sgRNA in nasopharyngeal (NP) swabs and BAL fluid. The numbers in the graph legends represent animal codes. The dotted lines indicate limit of detection (LOD = 50 GE/ml for gRNA and LOD = 50 SGE/ml for sgRNA). For detailed statistical analysis, refer to tables S2 and S3. GE, genomic equivalents; SGE, subgenomic equivalents.

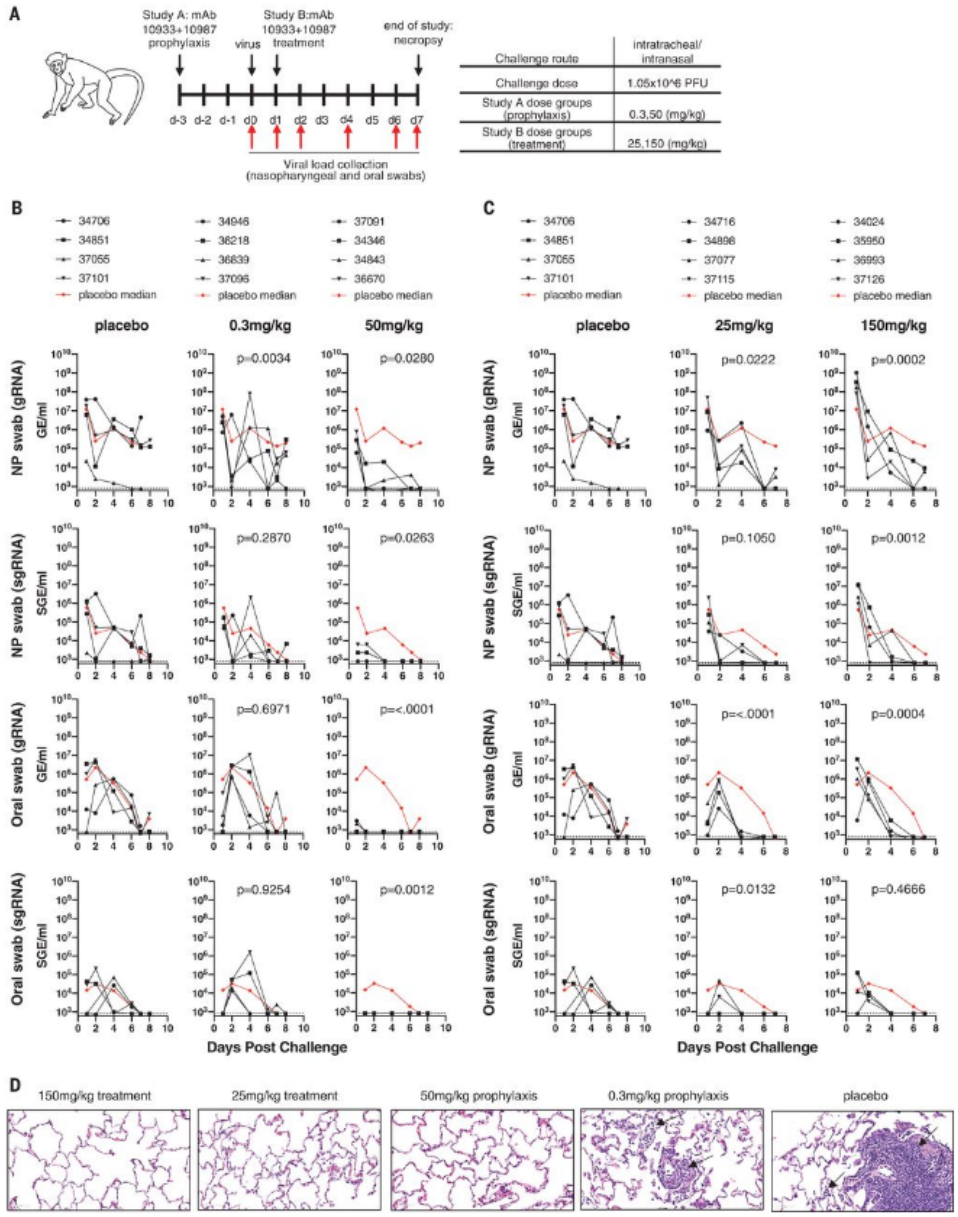



Fig. 2 Prophylactic and therapeutic efficacy of REGN-COV2 in the rhesus macaque model of SARS-CoV-2 infection (NHP study 2).

(A) Overview of study design.

(B) Impact of REGN-COV2 prophylaxis on viral gRNA and sgRNA in nasopharyngeal swabs and oral swabs [Study A, as shown in (A)].

(C) Impact of REGN-COV2 treatment on viral gRNA and sgRNA in nasopharyngeal swabs and oral swabs [Study B, as shown in (A)]. In (B) and (C), the numbers in the graph legends represent animal codes, and the dotted lines indicate limit of detection (LOD = 800 GE/ml for gRNA and LOD = 800 SGE/ml for sgRNA).

(D) Representative images of histopathology in lungs of treated and placebo animals. The black arrows point to inflammatory cells. For detailed statistical analysis, refer to tables S2 and S3.

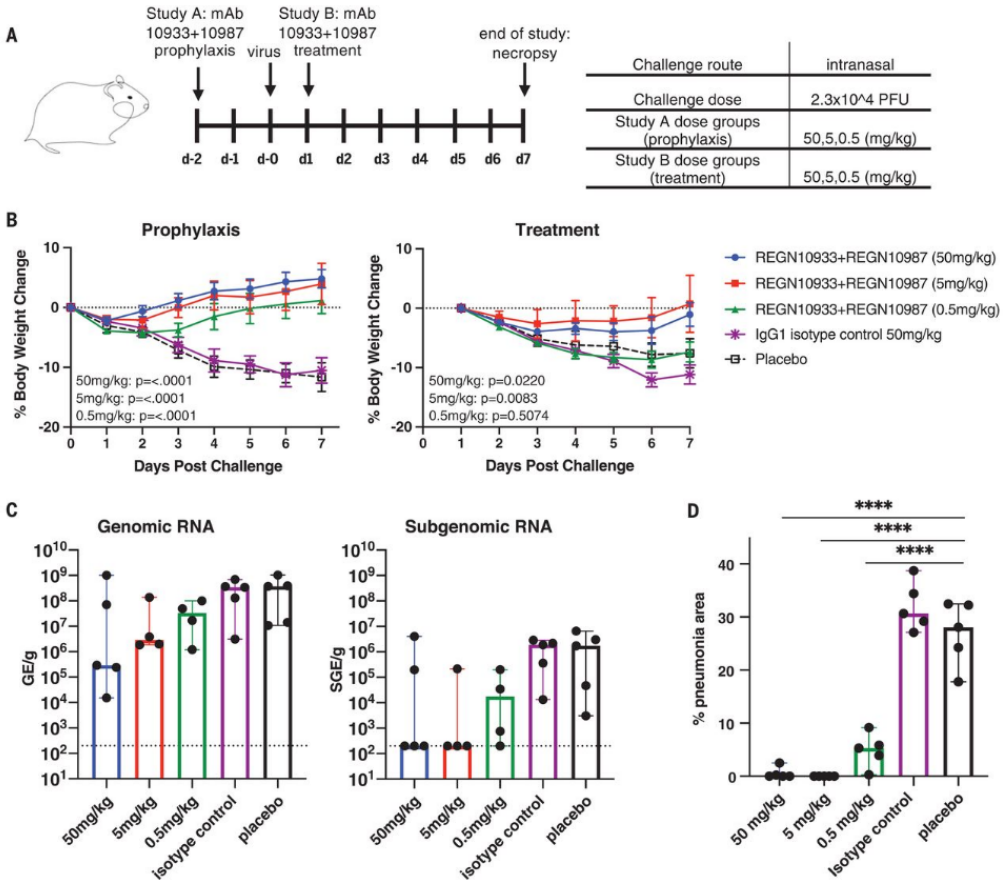



Fig. 3 Efficacy of REGN-COV2 in treatment and prophylaxis in the golden Syrian hamster model of SARS-CoV-2 infection.

(A) Overview of study design.

(B) Impact of REGN-COV2 on weight loss in prophylaxis and treatment groups. Error bars represent mean with error. IgG1, immunoglobulin G1.

(C) Impact of REGN-COV-2 prophylaxis on levels of gRNA and sgRNA in hamster lungs (7 days after infection). No statistical significance was observed between any treatment groups and placebo. The dotted lines indicate limit of detection (LOD = 200 GE/ml for gRNA and LOD = 200 SGE/ml for sgRNA), and error bars represent median with 95% confidence intervals.

(D) Impact of REGN-COV2 prophylaxis on percent area of lung exhibiting pathology typical of pneumonia (****$p < 0.0001$ indicates significant differences). Error bars represent median with 95% confidence intervals. For detailed statistical analysis, refer to tables S4 and S5.

# ACKNOWLEDGEMENTS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