# Ongoing Living Update of COVID-19 Therapeutic Options: Summary of Evidence

Ariel Izcovich
Hospital Alemán de Buenos Aires
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# Objetives

- Collect the best available evidence on pharmacological interventions for patients with COVID-19 or exposed to SARS-COV2

- Sustain a “living” update process in which every new piece of evidence is rapidly incorporated to the review

- Analice aquired evidence using standarized tools

# Search

## L·OVE repository

- **>300,000** records  (articles screened 2 million approximately)
- Any type of article
- Automated: 41 databases + preprint + trial registries
  - Main sources screened hourly (eg. Pubmed, medRxiv)
- Manual: many other sources
- Studies included in systematic reviews (coming from any source)
  → **Largest repository** according to our own estimation

# Multiple sources

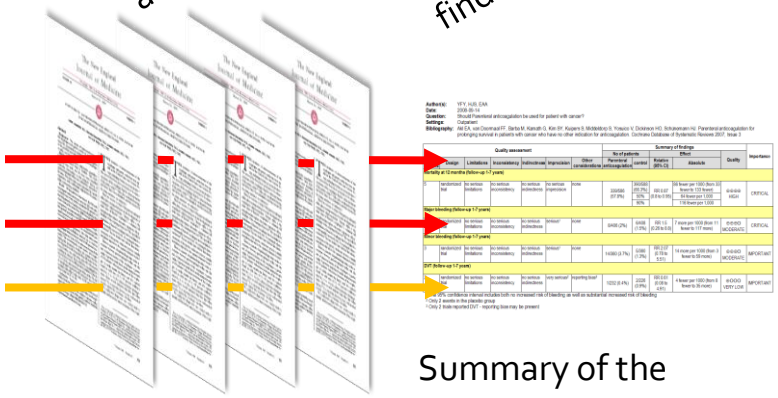
Pubmed/medline (updated several times a day); EMBASE (updated weekly); CINAHL (updated weekly); PsycINFO (updated weekly); LILACS (Latin American & Caribbean Health Sciences Literature) (updated weekly); Wanfang Database (updated every 2 weeks); CBM - Chinese Biomedical Literature Database (updated every 2 weeks); CNKI - Chinese National Knowledge Infrastructure (updated every 2 weeks); VIP - Chinese Scientific Journal Database (updated every 2 weeks); IRIS (WHO Institutional Repository for Information Sharing) (updated weekly); IRIS PAHO (PAHO Institutional Repository for Information Sharing)) (updated weekly); IBECS - Índice Bibliográfico Español en Ciencias de la Salud (Spanish Bibliographic Index on Health Sciences) (updated weekly); Microsoft Academic (last searched: Sept 4, 2020); ICTRP Search Portal (updated daily); Clinicaltrials.gov (updated daily); ISRCTN registry (updated daily); Chinese Clinical Trial Registry (updated daily); IRCT - Iranian Registry of Clinical Trials (updated daily); EU Clinical Trials Register: Clinical trials for covid-19 (updated daily); NIPH Clinical Trials Search (Japan) - Japan Primary Registries Network (JPRN) (JapicCTI, JMACCT CTR, jRCT, UMIN CTR) (updated daily, via ICTRP search portal); UMIN-CTR - UMIN Clinical Trials Registry (updated daily, via ICTRP search portal); JRCT - Japan Registry of Clinical Trials (updated daily, via ICTRP search portal); JAPIC Clinical Trials Information (updated daily, via ICTRP search portal); Clinical Research Information Service (CRiS), Republic of Korea (updated daily, via ICTRP search portal); ANZCTR - Australian New Zealand Clinical Trials Registry (updated daily, via ICTRP search portal); ReBec - Brazilian Clinical Trials Registry (updated daily, via ICTRP search portal); CTRI - Clinical Trials Registry - India (updated daily, via ICTRP search portal); RPCEC - Cuban Public Registry of Clinical Trials (updated daily, via ICTRP search portal); DRKS - German Clinical Trials Register (updated daily, via ICTRP search portal); LBCTR - Lebanese Clinical Trials Registry (updated daily, via ICTRP search portal); TCTR - Thai Clinical Trials Registry (updated daily, via ICTRP search portal); NTR - The Netherlands National Trial Register (updated daily, via ICTRP search portal); PACTR - Pan African Clinical Trial Registry (updated daily, via ICTRP search portal); REPEC - Peruvian Clinical Trial Registry (updated daily, via ICTRP search portal); SLCTR - Sri Lanka Clinical Trials Registry (updated daily, via ICTRP search portal); medRxiv (updated several times a day); bioRxiv (updated several times a day); SSRN Preprints (updated several times a day); ChinaXiv (updated every 2 weeks); SciELO Preprints (updated weekly); Research Square (updated daily);

# GRADE

Outcomes across studies

Summary of findings tables

Certainty of the evidence assessment



Summary of the estimates of effects for every outcome

High
Moderate
Low
Very Low

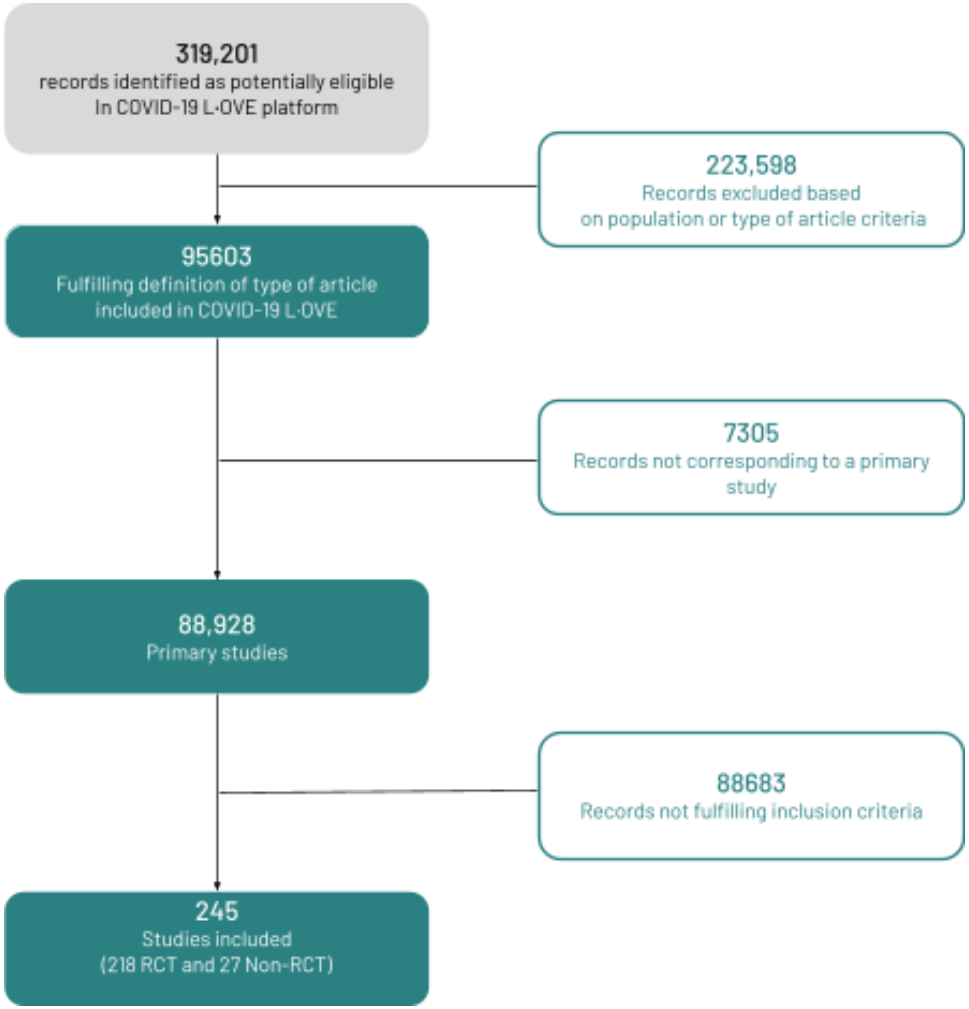
**Downgrade**

1. RoB
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

**Upgrade**

1. Big effect
2. Dose-response gradient
3. Confounders

# Results


319,201
records identified as potentially eligible
In COVID-19 L·OVE platform
223,598
Records excluded based
on population or type of article criteria
95603
Fulfilling definition of type of article
included in COVID-19 L·OVE
7305
Records not corresponding to a primary
study
88,928
Primary studies
88683
Records not fulfilling inclusion criteria
245
Studies included
(218 RCT and 27 Non-RCT)

# Resultados

- 218 RCTs + 27 non-RCTs
- 85 Pharmacological interventions

| Study; publication status | Patients and interventions analyzed | Comorbidities | Additional interventions | Rob and study limitations | Interventions effects vs standard of care (SOC) and GRADE certainty of the evidence |
|---|---|---|---|---|---|
| **99mTc-MDP**<br>**Uncertainty in potential benefits and harms. Further research is needed.** | | | | | |
| **RCT** | | | | | |
| Yuan et al;[10] Preprint; 2020 | Patients with mild COVID-19 infection. 10 assigned to 99mTc-MDP 5/ml once a day for 7 days and 11 assigned to SOC | Median age 61 ± 20, male 42.9% | NR | High for mortality and invasive mechanical ventilation; High for symptom resolution, infection and adverse events<br><br>Notes: Non-blinded study. Concealment of allocation probably inappropriate. | **Mortality:** No information<br><br>**Invasive mechanical ventilation:** No information<br><br>**Symptom resolution or improvement:** No information<br><br>**Symptomatic infection (prophylaxis studies):** No information<br><br>**Adverse events:** No information |

| Intervention | | Overall number of studies including the intervention, n=218 | Mortality (n of studies) | Invasive mechanical ventilation (n of studies) | Symptom resolution (n of studies) | Prevention of infection (n of studies) | Adverse events (n of studies) |
|---|---|---|---|---|---|---|---|
| Hydroxychloroquine or Chloroquine | NEW | 35 | 9 | 7 | 6 | 6 | 9 |
| Ivermectin | | 22 | 7 | 1 | 7 | 3 | 2 |
| Glucocorticoids | | 13 | 11 | 5 | 4 | | 6 |
| Convalecent plasma | NEW | 12 | 11 | 6 | 4 | | 3 |
| Favipiravir | NEW | 11 | 1 | | 6 | | 1 |
| Lopinavir-Ritonavir | NEW | 10 | 3 | 3 | 2 | | 1 |
| Tocilizumab | NEW | 10 | 9 | 8 | 5 | | 9 |
| Azithromycin | NEW | 6 | 3 | 2 | 2 | | 1 |
| Remdesivir | | 6 | 4 (*) | 4 | 3 | | 3 |
| Umifenovir | | 5 | | | | | |
| Colchicine | | 4 | 3 | 2 | | | 1 |
| Interferon beta-1a | | 4 | 3 | 3 | 2 | | |

| | GRADE High- Moderate certainty | GRADE Low certainty |
|---|---|---|
| Beneficial effect | | |
| No significant effect | | |
| Harmfull effect | | |
| Uncertain effect | | |
| No evidence or no estimable effect | | |

| Intervention | | Overall number of studies including the intervention, n=218 | Mortality (n of studies) | Invasive mechanical ventilation (n of studies) | Symptom resolution (n of studies) | Prevention of infection (n of studies) | Adverse events (n of studies) |
|---|---|---|---|---|---|---|---|
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| Tocilizumab | NEW | 10 | 9 | 8 | 5 | | 9 |
| Azithromycin | NEW | 6 | 3 | 2 | 2 | | 1 |
| Remdesivir | | 6 | 4 (*) | 4 | 3 | | 3 |
| Umifenovir | | 5 | | | | | |
| Colchicine | | 4 | 3 | 2 | | | 1 |
| Interferon beta-1a | | 4 | 3 | 3 | 2 | | |
| Sofosbuvir +/- Daclatasvir | | 4 | 2 | 2 | 2 | | |
| Vitamin C | NEW | 4 | 4 | 4 | 2 | | |
| Zinc | NEW | 4 | 1 | 1 | 2 | | |
| Bamlanivimab | | 3 | 1 | | 2 | | 3 |
| IVIG | | 3 | 3 | 2 | | | 1 |
| Mesenchimal cell tranplantation | | 3 | 1 | | 1 | | 1 |
| Vitamin D | | 3 | 1 | 1 | | | 1 |
| ACEIs or ARBs (continuation) | | 2 | 2 | 2 | | | |
| Bromhexine Hydrochloride | | 2 | 1 | 1 | 1 | | 1 |
| Dutasteride | NEW | 2 | | | 1 | | |
| Leflunomide | | 2 | | | | | |
| Mouthwash (povidone iodine or essential oils) | NEW | 2 | | | | | |
| Nitazoxanide | NEW | 2 | 1 | 1 | 1 | | 1 |
| Ozone | | 2 | 2 | | 1 | | 1 |
| Sarilumab | NEW | 2 | 2 | 1 | 1 | | 1 |
| 99mTc-MDP | | 1 | | | | | |
| ACEIs or ARBs (treatment) | NEW | 1 | 1 | 1 | | | |
| Anakinra | | 1 | 1 | 1 | 1 | | 1 |
| Anticoagulants | | 1 | 1 | | | | |
| Aprepitant | | 1 | | | | | |
| Artemisinin | NEW | 1 | | | 1 | | 1 |
| Auxora | | 1 | 1 | 1 | | | |
| Azvudine | | 1 | | | | | |
| Baloxavir | | 1 | | | 1 | | |
| Bamlanivimab + etesevimab | | 1 | 1 | | 1 | | 1 |
| Baricitinib | | 1 | 1 | 1 | 1 | | 1 |
| BCG | | 1 | 1 | | | | |
| Chloroquine nasal drops | | 1 | | | | | |
| Clarithromycin | NEW | 1 | | | | | |
| CIGB-325 | | 1 | | | 1 | | 1 |
| Cofactors | | 1 | | | 1 | | 1 |
| Darunavir-Cobicistat | | 1 | | | | | |
| Electrolyzed saline | | 1 | 1 | | 1 | | |
| Enisamium | | 1 | | | 1 | | |
| Febuxostat | | 1 | | | | | |
| Flebuxamine | | 1 | 1 | 1 | | | 1 |
| Helium (inhaled) | | 1 | | | | | |
| Icatibant | | 1 | 1 | | | | |
| iC1e/K | | 1 | 1 | | | | |
| IFN-alpha2b + IFN-gamma | | 1 | | | | | |
| IFX-1 | | 1 | 1 | | | | 1 |
| INM005 (equine antibodies) | | 1 | 1 | 1 | 1 | | 1 |
| Interferon beta-1b | | 1 | 1 | 1 | 1 | | |
| Interferon beta-1a (inhaled) | | 1 | 1 | 1 | 1 | | 1 |
| Interferon kappa + TFF2 | | 1 | 1 | | | | 1 |
| Itolizumab | | 1 | 1 | 1 | | | 1 |

| Intervention | | Overall number of studies including the intervention, n=218 | Mortality (n of studies) | Invasive mechanical ventilation (n of studies) | Symptom resolution (n of studies) | Prevention of infection (n of studies) | Adverse events (n of studies) |
|---|---|---|---|---|---|---|---|
| Levamizole | | 1 | | | 1 | | |
| Lincomecin | | 1 | | | | | |
| Melatonin | NEW | 1 | 1 | | 1 | | |
| Metisoprinol | NEW | 1 | | | | | |
| Molnupiravir | | 1 | | | | | 1 |
| Mouthwash (hydrogen peroxide) | | 1 | 1 | 1 | 1 | | |
| N-acetylcysteine | | 1 | 1 | 1 | | | 1 |
| Nasal hypertonic saline | | 1 | | | 1 | | |
| Novaferon | | 1 | | | | | |
| Omega-3 fatty acids | | 1 | | | | | |
| Peg-IFN lambda | | 1 | | | | | 1 |
| Progesterone | | 1 | 1 | 1 | | | 1 |
| Prolectin-M | | 1 | 1 | 1 | | | 1 |
| Propolis | | 1 | 1 | 1 | 1 | | |
| Proxalutide | | 1 | 1 | 1 | | | |
| Quercertin | | 1 | 1 | | 1 | | |
| Ramipril | | 1 | 1 | | | 1 | |
| Recombinant Super-Compound IFN | | 1 | 1 | | 1 | | |
| REGN-COV2 (Regeneron) | | 1 | | | | | 1 |
| Ribavirin | | 1 | | | | | |
| Ribavirin + Interferon beta-1b | | 1 | | | | | |
| Ruxolitinib | | 1 | | | 1 | | |
| rhG-CSF | | 1 | 1 | | 1 | | 1 |
| Sofosbuvir/ledipasvir | NEW | 1 | 1 | 1 | 1 | | |
| Steroids (inhaled) | NEW | 1 | | | 1 | | |
| Sulodexide | | 1 | 1 | 1 | | | 1 |
| Telmisartan | | 1 | 1 | 1 | | | |
| Triazavirin | | 1 | 1 | | 1 | | 1 |
| α-Lipoic acid | | 1 | 1 | | | | |

(*) Inconsistent results between included studies. Beigel et al. informed mortality reduction with remdesivir while WHO SOLIDARITY found no significant differences. Pooled estimates show a small non-statitically significant mortality reduction (RR 0.94, 95%CI 0.82 - 1.08).

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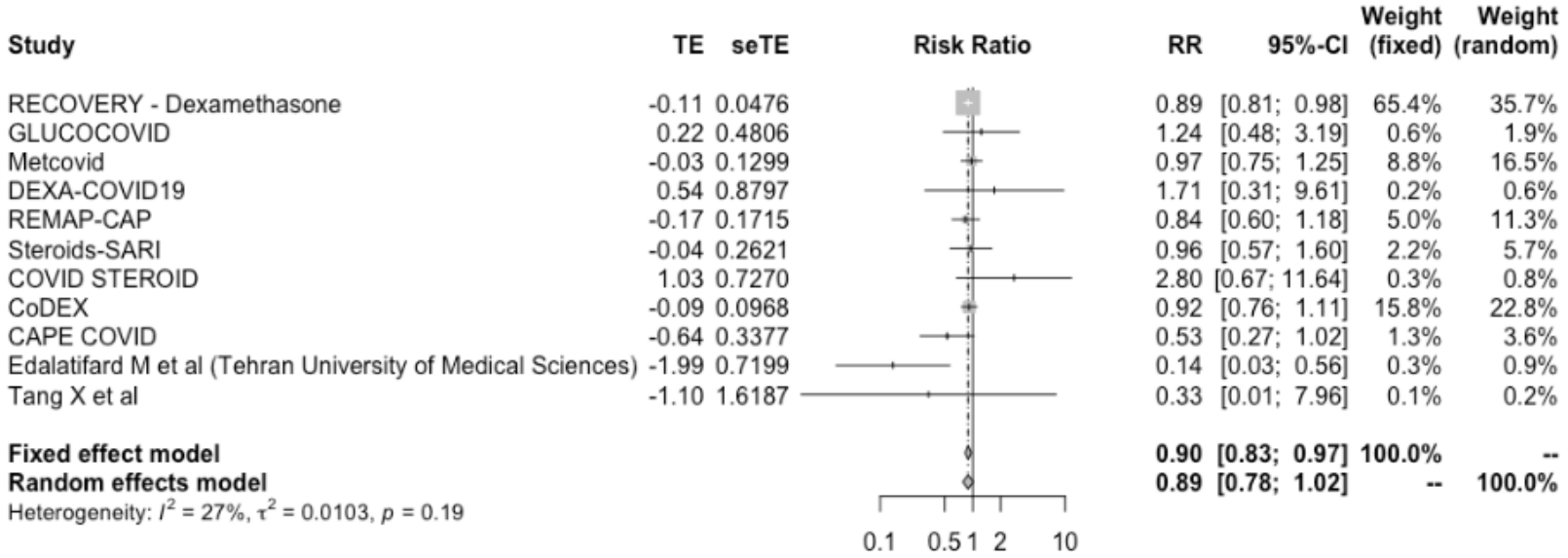
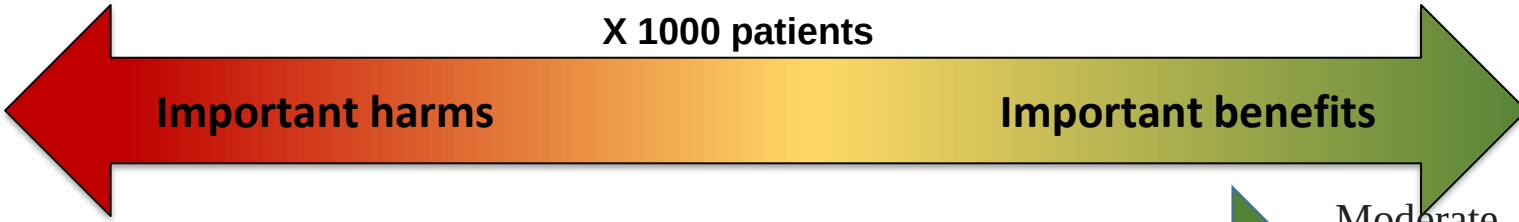
# Systemic steroids

- **13 RCTs, 8065 patients**

All cause mortality: Steroids vs. Standard of care



# Systemic steroids




| | | |
|---|---|---|
| Mortality | - 18 | Moderate Certainty ⊕⊕⊕◯ |
| Invasive mechanical ventilation | - 28 | Moderate Certainty ⊕⊕⊕◯ |
| Time to symptom resolution | 194 | Low Certainty ⊕⊕◯◯ |
| Symptomatic infection (prophylaxis) | No information | |
| Severe adverse events | -11 | Low Certainty ⊕⊕◯◯ |

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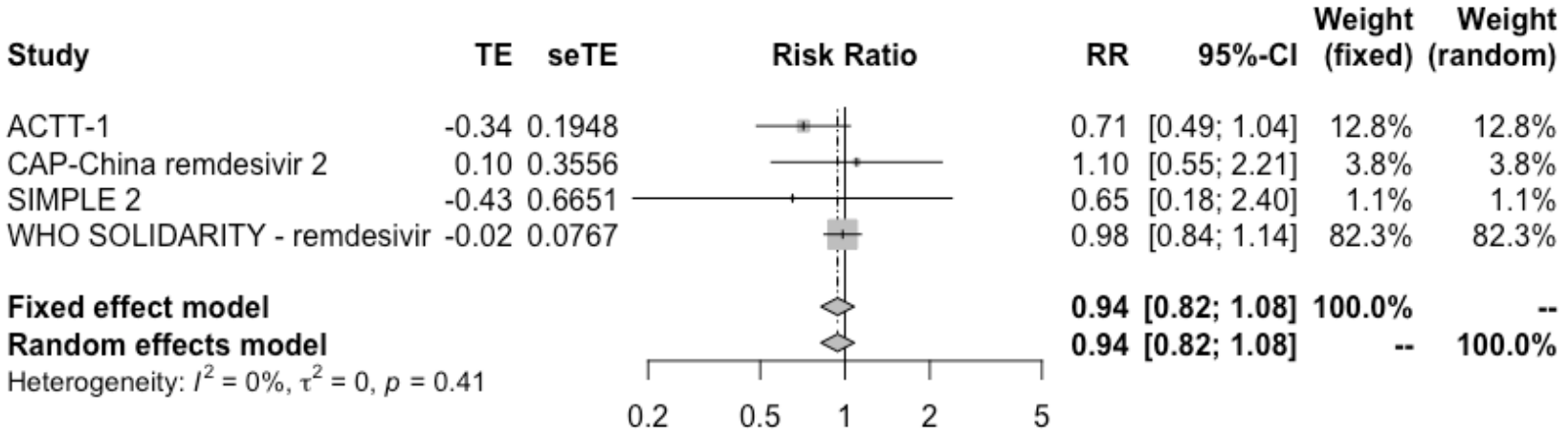
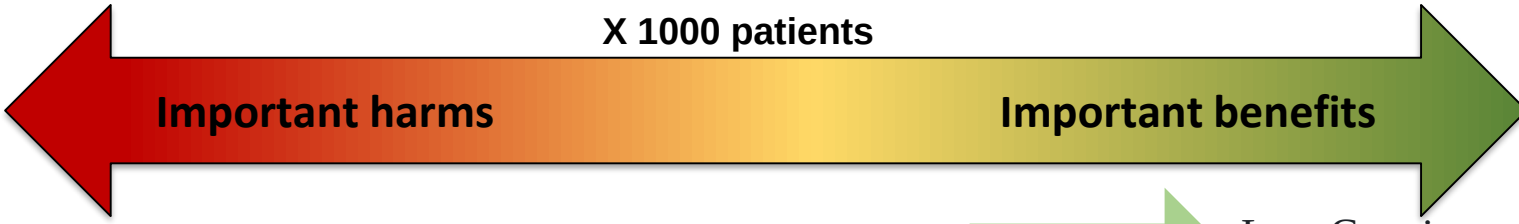
# Remdesivir

- **6 RCT, 15057 patients**

All cause mortality: Remdesivir vs. Standard of care



# Remdesivir




| | | |
|---|---|---|
| Mortality | - 10 | Low Certainty ⊕⊕◯◯ |
| Invasive mechanical ventilation | - 60 | Low Certainty ⊕⊕◯◯ |
| Time to symptom resolution | 103 | Low Certainty ⊕⊕◯◯ |
| Symptomatic infection (prophylaxis) | No information | |
| Severe adverse events | -20 | Low Certainty ⊕⊕◯◯ |

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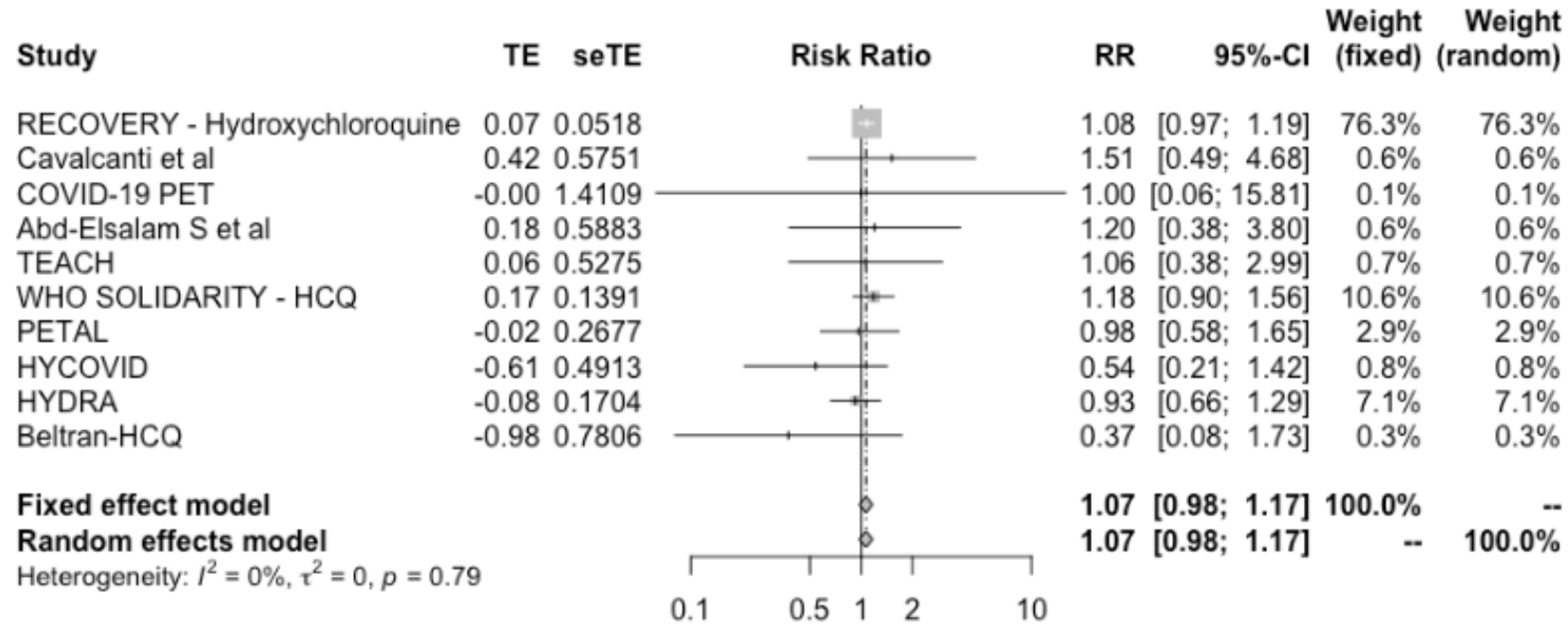
# Hydroxychloroquine

- **36 RCT, 17900 patients**

All cause mortality: HCQ vs. Standard of care

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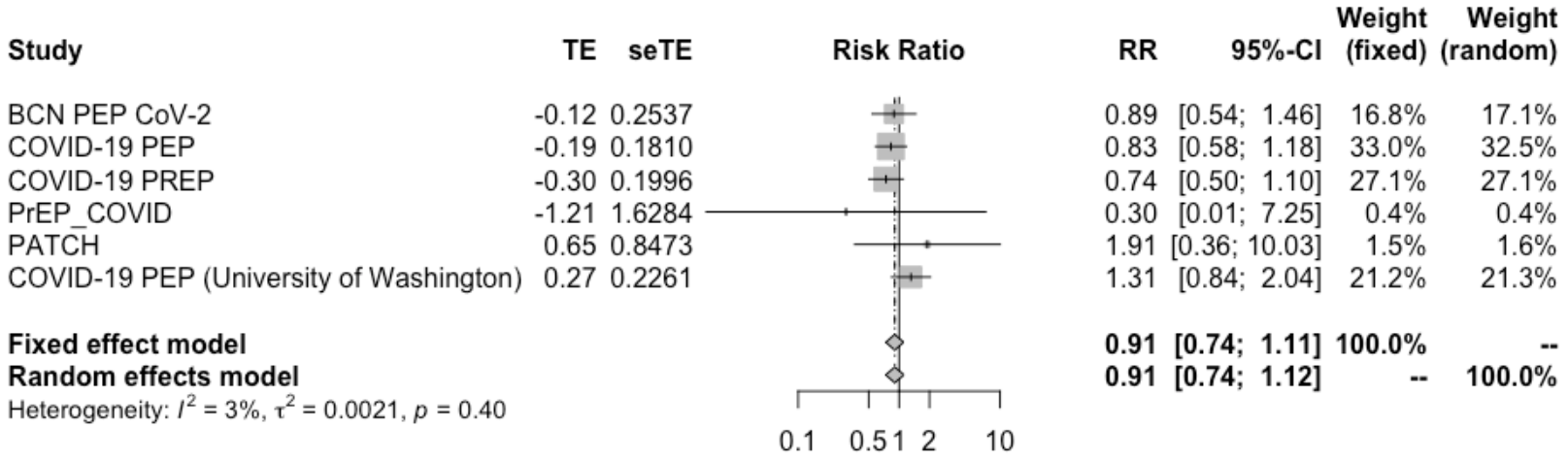
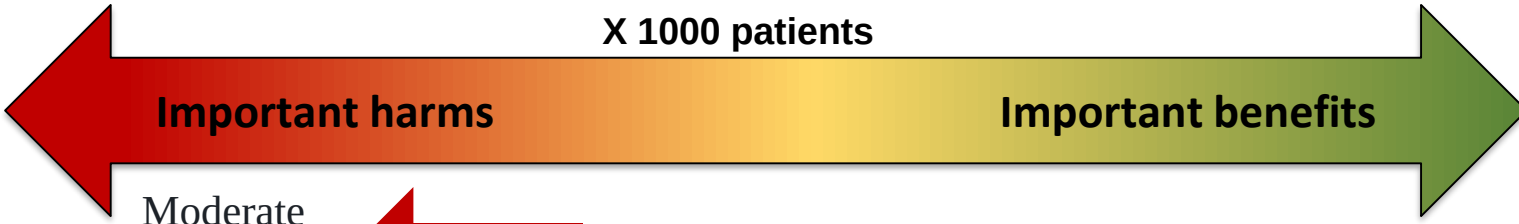
# Hydroxychloroquine

- **36 RCT, 17900 patients**

Symptomatic infection in prophylaxis: HCQ vs. no prophylaxis



# Hidroxicloroquina




| | | | |
|---|---|---|---|
| Mortality | Moderate Certainty ⊕⊕⊕◯ | 11 | |
| Invasive mechanical ventilation | Moderate Certainty ⊕⊕⊕◯ | 9 | |
| Time to symptom resolution | | 30 | Moderate Certainty ⊕⊕⊕◯ |
| Symptomatic infection (prophylaxis) | | -17 | Low Certainty ⊕⊕◯◯ |
| Severe adverse events | | 9 | Low Certainty ⊕⊕◯◯ |

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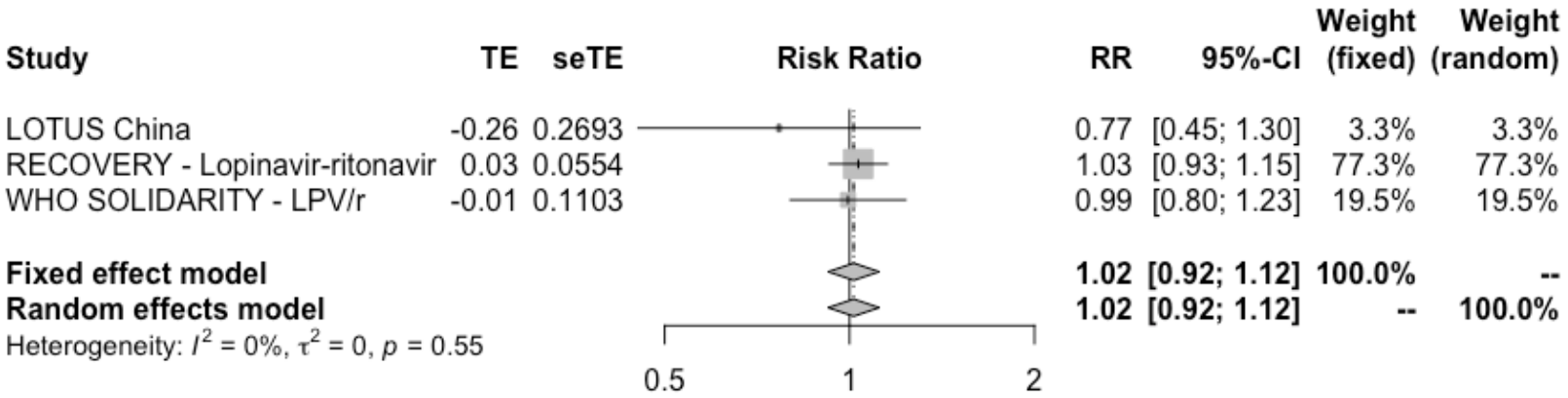
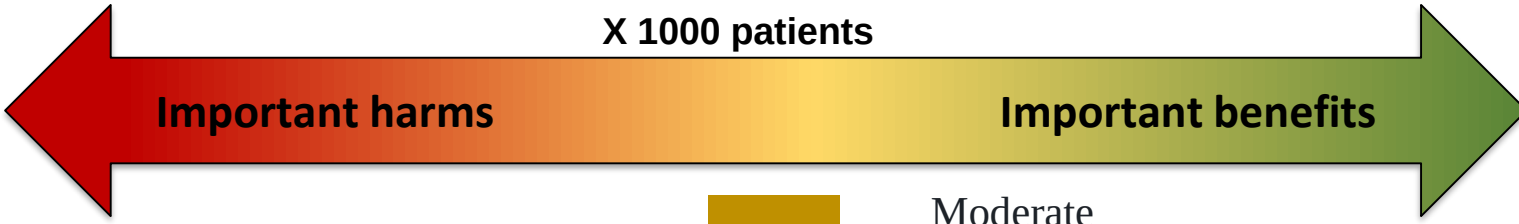
# Lopinavir-Ritonavir

- **10 RCT, 8790 patients**

All cause mortality: LPV vs. Standard of care



# Lopinavir-Ritonavir




| | | |
|---|---|---|
| Mortality | 3 | Moderate Certainty ⊕⊕⊕◯ |
| Invasive mechanical ventilation | 12 | High Certainty ⊕⊕⊕⊕ |
| Time to symptom resolution | 18 | Moderate Certainty ⊕⊕⊕◯ |
| Symptomatic infection (prophylaxis) | No information | |
| Severe adverse events | -41 | Low Certainty ⊕⊕◯◯ |

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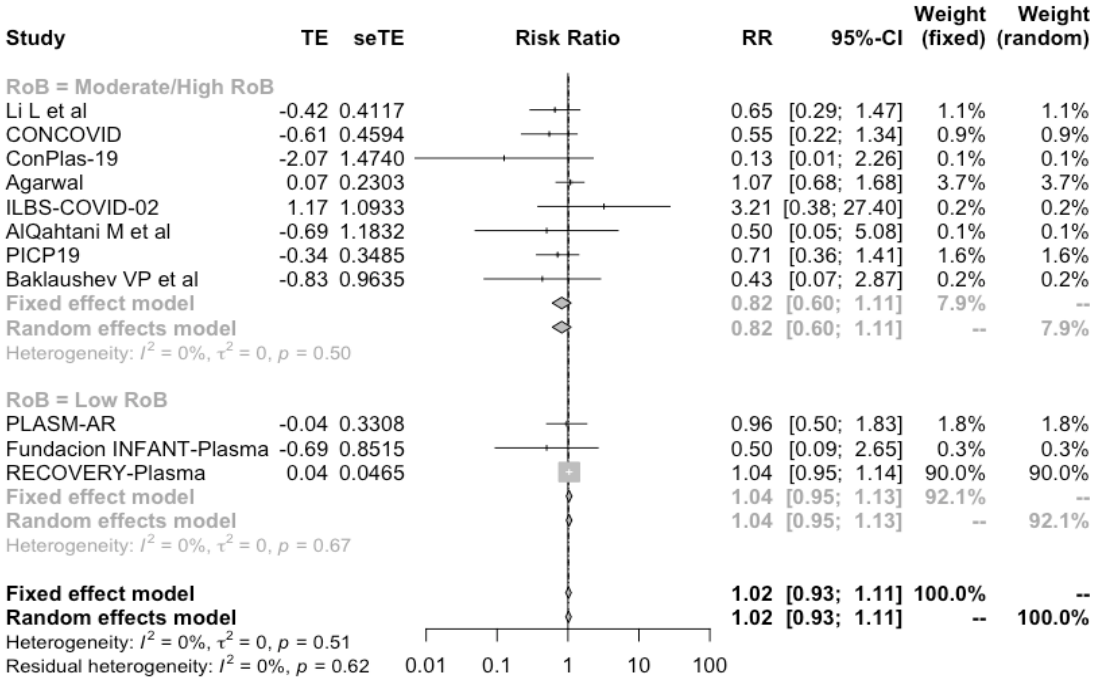
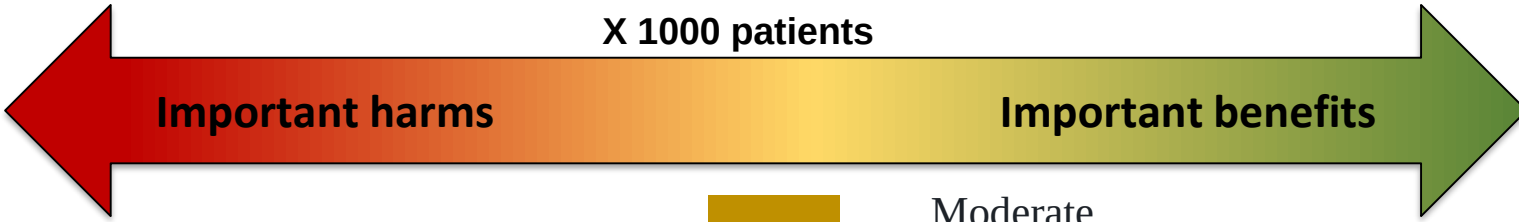
# Convalescent plasma

- **11 RCT, 11848 patients**

All cause mortality: Convalescnet plasma vs. Standard of care



# Convalescent plasma




| | | |
|---|---|---|
| Mortality | 3 | Moderate Certainty ⊕⊕⊕◯ |
| Invasive mechanical ventilation | Very Low Certainty ⊕◯◯◯ | |
| Time to symptom resolution | Very Low Certainty ⊕◯◯◯ | |
| Symptomatic infection (prophylaxis) | No information | |
| Severe adverse events | Very Low Certainty ⊕◯◯◯ | |

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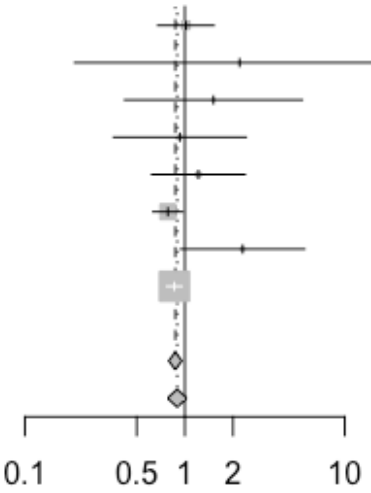
# Tocilizumab

- **10 RCT, 6440 patients**

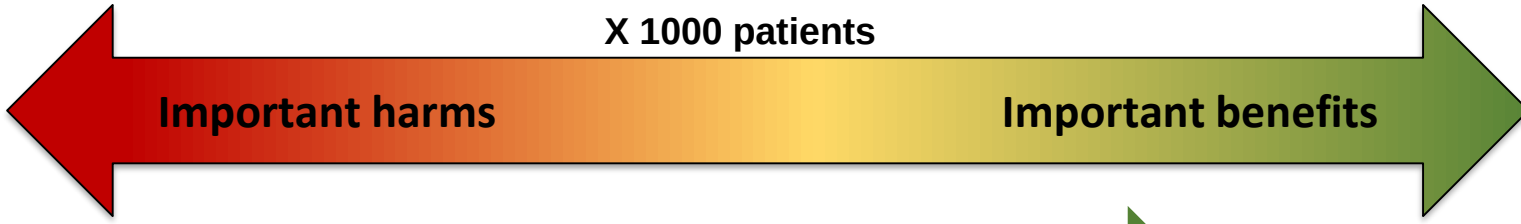
  All cause mortality: Tocilizumab vs. Standard of care

| Study | TE | seTE | RR | 95%-CI | Weight (fixed) | Weight (random) |
|---|---|---|---|---|---|---|
| COVACTA | 0.01 | 0.2064 | 1.01 | [0.68; 1.52] | 5.3% | 10.4% |
| RCT-TCZ-COVID-19 | 0.79 | 1.2117 | 2.20 | [0.20; 23.65] | 0.2% | 0.3% |
| BACC Bay Tocilizumab Trial | 0.41 | 0.6526 | 1.51 | [0.42; 5.42] | 0.5% | 1.2% |
| CORIMUNO-TOCI 1 | -0.07 | 0.4869 | 0.93 | [0.36; 2.42] | 0.9% | 2.1% |
| EMPACTA | 0.19 | 0.3428 | 1.22 | [0.62; 2.38] | 1.9% | 4.1% |
| REMAP-CAP - tocilizumab | -0.24 | 0.1090 | 0.78 | [0.63; 0.97] | 19.0% | 27.6% |
| Veiga | 0.83 | 0.4551 | 2.30 | [0.94; 5.61] | 1.1% | 2.4% |
| RECOVERY-TCZ | -0.15 | 0.0563 | 0.86 | [0.77; 0.96] | 71.1% | 51.9% |
| **Fixed effect model** | | | **0.87** | **[0.79; 0.96]** | **100.0%** | -- |
| **Random effects model** | | | **0.90** | **[0.78; 1.03]** | -- | **100.0%** |

Heterogeneity: $I^2$ = 16%, $\tau^2$ = 0.0067, $p$ = 0.30



# Tociluzumab




| | | |
|---|---|---|
| Mortality | - 16 | Moderate Certainty ⊕⊕⊕◯ |
| Invasive mechanical ventilation | - 35 | High Certainty ⊕⊕⊕⊕ |
| Time to symptom resolution | 60 | Low Certainty ⊕⊕◯◯ |
| Symptomatic infection (prophylaxis) | No information | |
| Severe adverse events | -11 | Moderate Certainty ⊕⊕⊕◯ |

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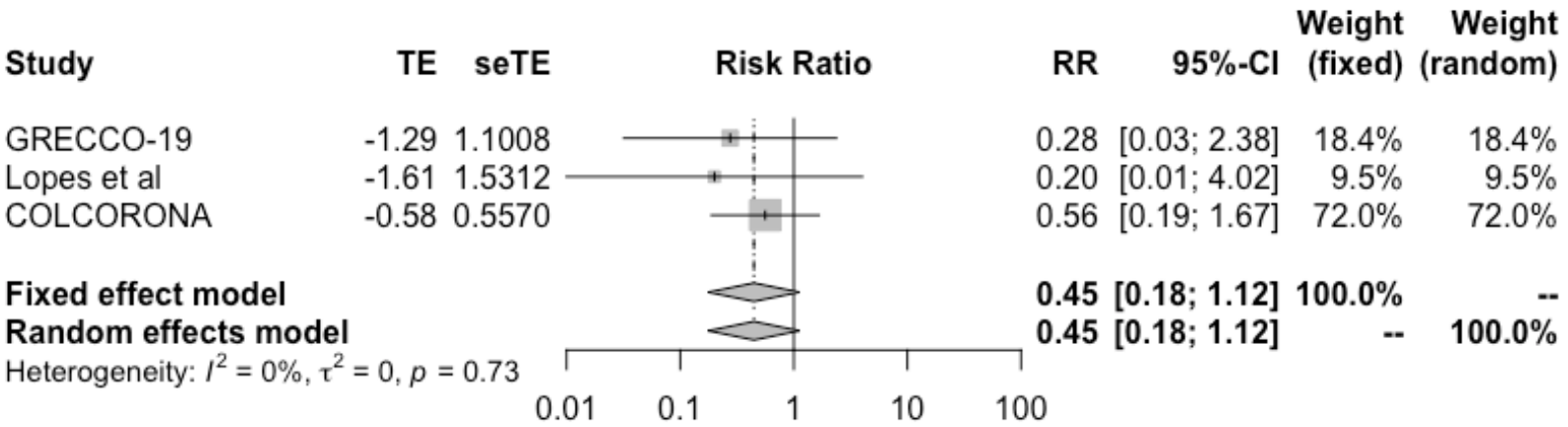
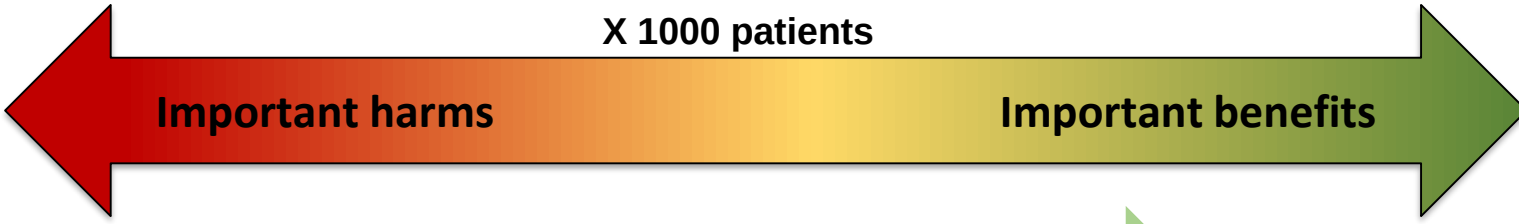
# Colchicine

- **4 RCT, 4731 patients**

  All cause mortality: Colchicine vs. Standard of care



# Colchicine




| | | |
|---|---|---|
| Mortality | - 88 | Low Certainty ⊕⊕◯◯ |
| Invasive mechanical ventilation | - 90 | Moderate Certainty ⊕⊕⊕◯ |
| Time to symptom resolution | No information | |
| Symptomatic infection (prophylaxis) | No information | |
| Severe adverse events | -11 | Moderate Certainty ⊕⊕⊕◯ |

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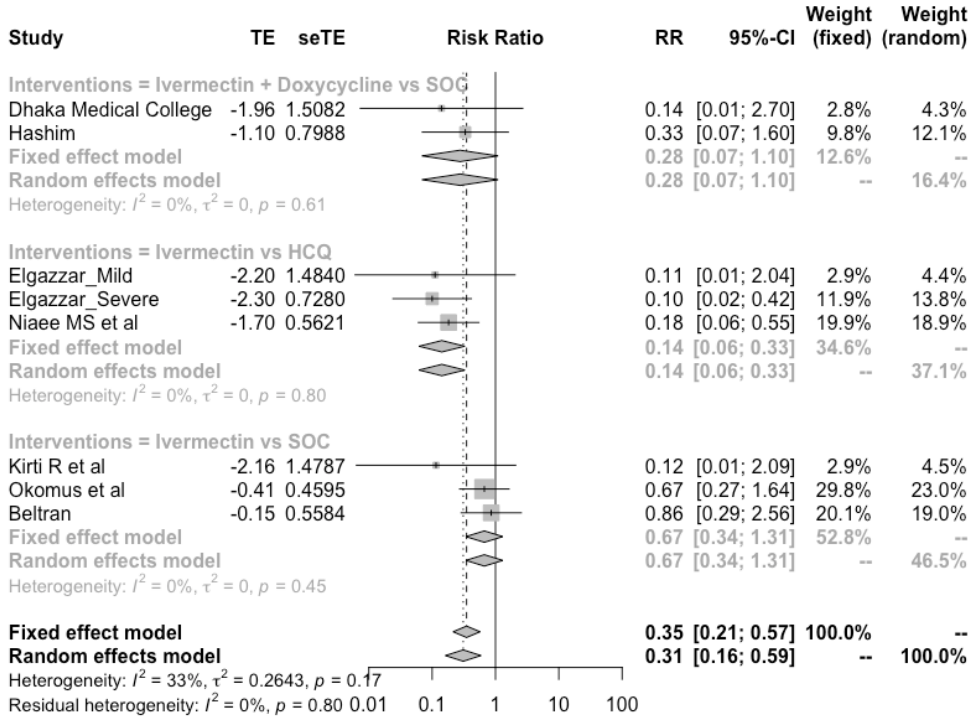
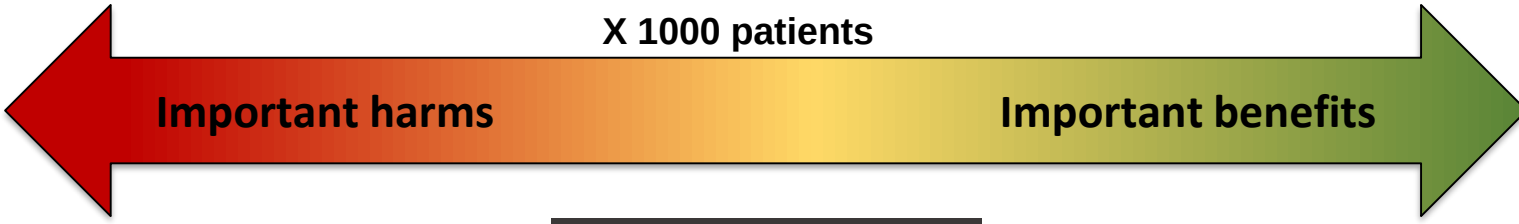
# Ivermectin

- **23 RCT, 3003 patients**

All cause mortality: Ivermectin vs. Standard of care



# Ivermectin

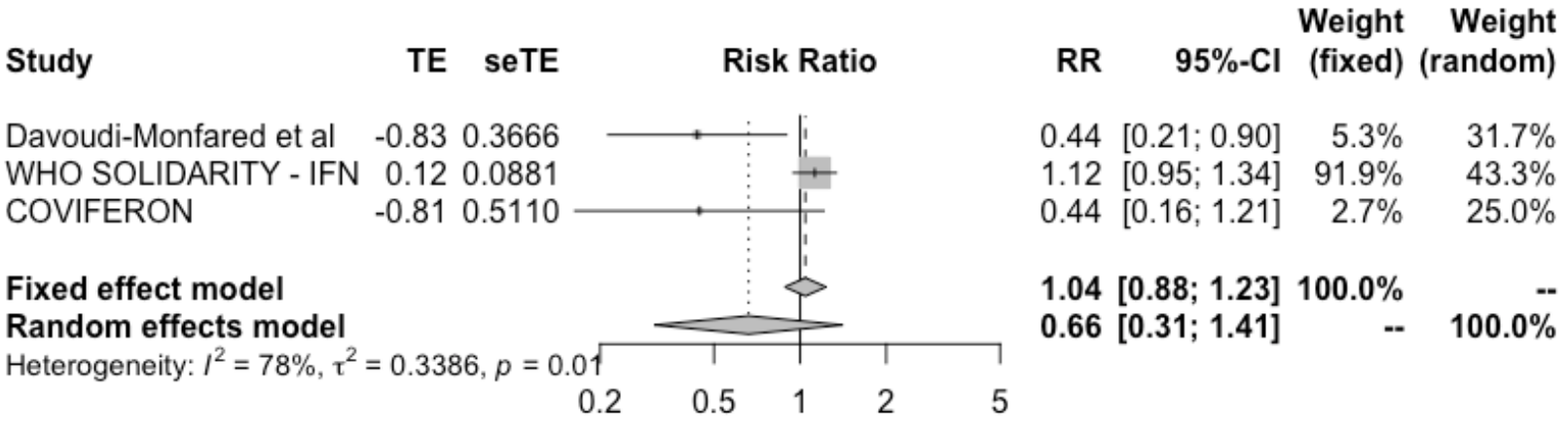



| | |
|---|---|
| Mortality | Very Low Certainty ⊕◯◯◯ |
| Invasive mechanical ventilation | Very Low Certainty ⊕◯◯◯ |
| Time to symptom resolution | Very Low Certainty ⊕◯◯◯ |
| Symptomatic infection (prophylaxis) | Very Low Certainty ⊕◯◯◯ |
| Severe adverse events | Very Low Certainty ⊕◯◯◯ |

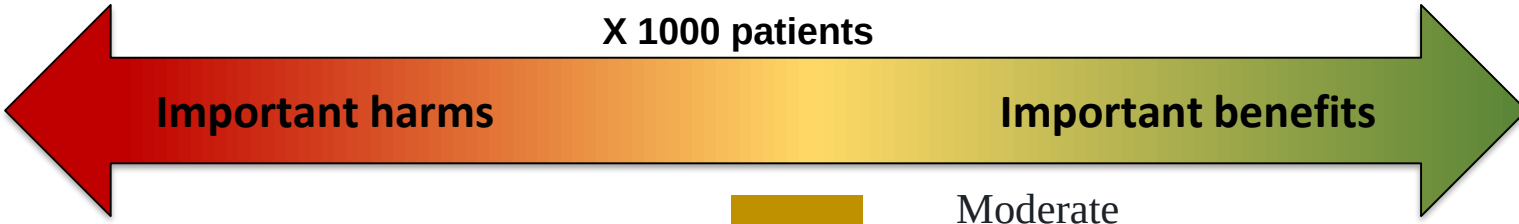
# Interferón Beta-1a

- **5 RCT, 4487 patients**

All cause mortality: Interferón Beta-1a vs. Standard of care



# Interferón Beta-1a




| | | |
|---|---|---|
| Mortality | 6 | Moderate Certainty ⊕⊕⊕◯ |
| Invasive mechanical ventilation | -3 | Moderate Certainty ⊕⊕⊕◯ |
| Time to symptom resolution | Very Low Certainty ⊕◯◯◯ | |
| Symptomatic infection (prophylaxis) | No information | |
| Severe adverse events | No information | |

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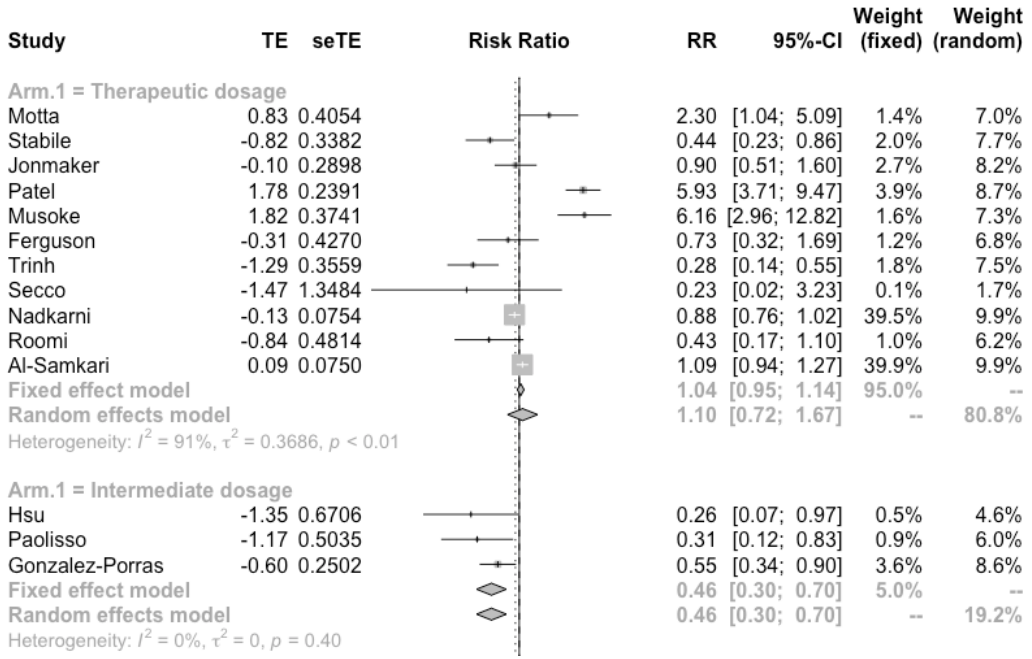
# Anticoagulants

- **14 Non-RCT**

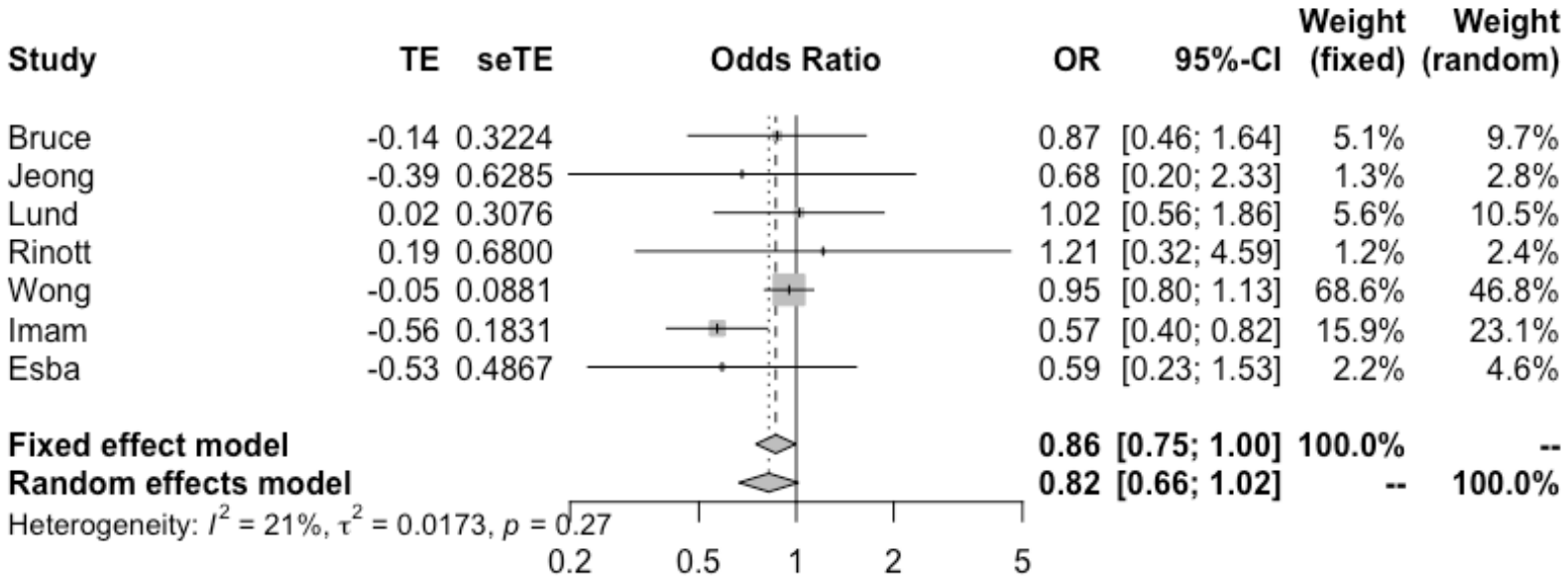
  All cause mortality: Full dose or intermediate dosage vs. prophylactic dosage



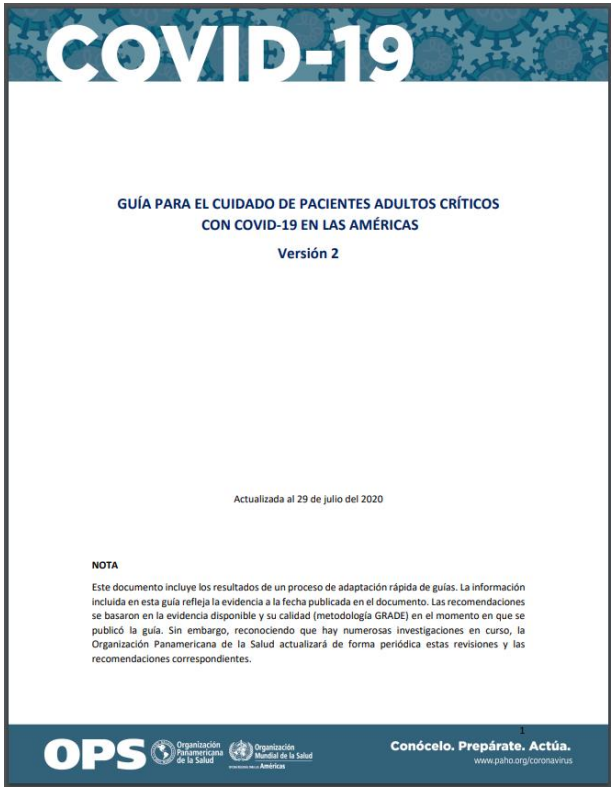
# AINES

- **7 Non-RCT,**

  All cause mortality: NSAID vs. no NSAID



# Manejo de los patients con COVID-19


COVID-19

GUÍA PARA EL CUIDADO DE PACIENTES ADULTOS CRÍTICOS CON COVID-19 EN LAS AMÉRICAS

Versión 2

Actualizada al 29 de julio del 2020

NOTA

Este documento incluye los resultados de un proceso de adaptación rápida de guías. La información incluida en esta guía refleja la evidencia a la fecha publicada en el documento. Las recomendaciones se basaron en la evidencia disponible y su calidad (metodología GRADE) en el momento en que se publicó la guía. Sin embargo, reconociendo que hay numerosas investigaciones en curso, la Organización Panamericana de la Salud actualizará de forma periódica estas revisiones y las recomendaciones correspondientes.

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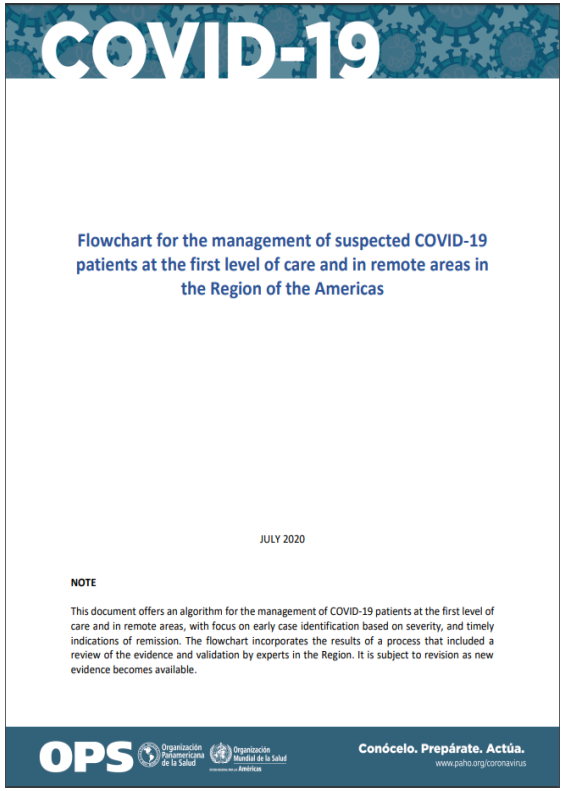
COVID-19

Flowchart for the management of suspected COVID-19 patients at the first level of care and in remote areas in the Region of the Americas

JULY 2020

NOTE

This document offers an algorithm for the management of COVID-19 patients at the first level of care and in remote areas, with focus on early case identification based on severity, and timely indications of remission. The flowchart incorporates the results of a process that included a review of the evidence and validation by experts in the Region. It is subject to revision as new evidence becomes available.

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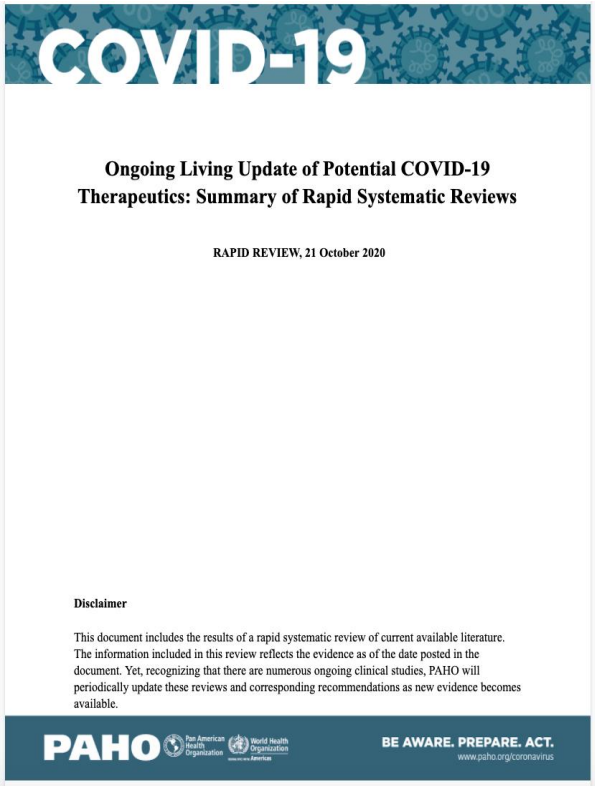
COVID-19

Ongoing Living Update of Potential COVID-19 Therapeutics: Summary of Rapid Systematic Reviews

RAPID REVIEW, 21 October 2020

Disclaimer

This document includes the results of a rapid systematic review of current available literature. The information included in this review reflects the evidence as of the date posted in the document. Yet, recognizing that there are numerous ongoing clinical studies, PAHO will periodically update these reviews and corresponding recommendations as new evidence becomes available.

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BE AWARE. PREPARE. ACT.
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# Thank you!!