Title: Antivirals in non-severe COVID-19 infection: a systematic review and network meta-analysis

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Supplement 1. Search strategy

We leveraged our search strategy and search results from the Epistemonikos/World Health Organization COVID-19 L-OVE repository. Details on the search strategy are found here: but also presented below.

The COVID-19 L-OVE repository was built, and is maintained, by systematic searches in multiple databases, trial registries and preprint servers. Searches are not restricted by study design, language or publication status:

The following sources are regularly searched:

| Source                                      | Frequency            |
|---------------------------------------------|----------------------|
| 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: 23 August 2021 |
| 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, JMACECT 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) |

We adapted our main COVID-19 boolean strategy (see below) to the syntax of each source. The information is obtained from the sources using different technology solutions, such as querying publicly available APIs, subscribing to RSS feeds, parsing .csv files posted on.
Box 1. Search strategy (version 1.0)

*COVID* OR *coronavir* OR *coronovir* OR *beta-coronavirus* OR "corona virus" OR "virus corona" OR "coronovirus" OR "virus corono" OR *neocoronavir* OR hvco* OR *2019-ncov* OR *cv19* OR *cv-19* OR "cv 19" OR n-cov* OR ncov* OR (wuhan* AND (virus OR viruses OR viral)) OR *cv-19* OR sars* OR sari OR "severe acute respiratory syndrome" OR antisars* OR antisars* OR "corona patients" OR *pandemi*

The records are deduplicated and cleansed using proprietary software of Epistemonikos Foundation.

### Other Search sources

In order to identify articles that an electronic search could potentially miss, we:
- Manually check all the systematic reviews and other types of evidence syntheses (e.g. overviews of systematic reviews, scoping reviews, guidelines) and add all articles included in those.
- Evaluate potentially eligible articles that users send by email and other means (e.g. twitter).
- As randomised trials are particularly relevant for decision-making, we also:
  - Run a regular search for randomised trials on Twitter using the terms #COVID19 OR #COVID-19 OR #COVID_19 OR #COVID randomized OR randomised.
  - Scan relevant scientific conferences.
  - Manually review press release websites.
  - Check the websites of the main trials and companies relevant to COVID-19.

### How articles in the interface works

#### Article selection

The details of the automated classification process and the classification workflow are described in the ‘COVID-19 L·OVE classification platform’ section. We describe here the specificities of the ‘COVID-19 classification’ process since it defines if a record becomes part of the ‘COVID-19 L·OVE repository.'
Automated classification
All the articles retrieved by the electronic searches are assessed by two automated classifiers specifically developed for this project. The first classifier is a binary exact-match classifier based on a continuously updated list of terms obtained by applying Word2vec technology with proprietary software developed by Epistemonikos to the corpus of documents available in the repository. The terms with more similar vectors are analyzed by a team of content and methods experts and are selected based on their incremental recall (i.e. their capacity to identify new ‘positives’ in the unclassified records). The second classifier combines a highly specific COVID-19 boolean strategy with the publication date of the articles (year 2020 or more recent).

Human classification
The articles included by the classifiers are screened by the COVID-19 L·OVE users, collaborators or methods team (e.g. during collective screening of the classification platform).

The articles excluded by the classifier are not checked. However, any time an article is identified by another means (e.g. a study included in a systematic review) the methods team checks for the presence of any term that can be added to the search strategy or the list of terms used by the exact-match classifier.

Eligibility criteria
Articles are only included if they directly address an issue concerning COVID-19 or the indirect consequences of COVID-19 (e.g. the consequences of lockdown). We do not include COVID-19 articles that might be relevant but were conducted in different contexts (e.g. telemedicine before the COVID-19 pandemic, facemasks for influenza).

Inclusion in the repository is not restricted by study design, language or publication status.
Supplement 2. Risk of bias tool

| Bias from the randomization process |
|------------------------------------|
| Issues to consider:                |
| Random sequence generation         |
| Allocation concealment             |
| **Definitely low risk of bias**    |

Trials that assign participants to alternative interventions using a randomly generated sequence and maintain allocation concealment.

Examples of methods for developing a randomly generated allocation sequence include a random number generator, random number table, coin tossing, shuffling cards or envelopes, and throwing dice. If a trial is described as 'randomized' without any additional details related to how the allocation sequence was developed, we will assume that the allocation sequence was appropriately developed.

Examples of methods for maintaining allocation concealment include using central allocation via a computer or phone system, pharmacy-controlled allocation, opaque sealed envelopes, and sequentially numbered drug containers.

*Note that an explicit description of random sequence generation is not necessary for a rating of low risk of bias.*
| **Probably low risk of bias** | Trials in which healthcare providers were blind to the intervention but which provide no information on allocation concealment and in which there are no major baseline imbalances.  

*Note that an explicit description of random sequence generation is not necessary for a rating of probably low risk of bias.* |
| --- | --- |
| **Probably high risk of bias** | Trials in which healthcare providers were not blind to the intervention and which provide no information on allocation concealment  
Trials in which there are substantial baseline differences between trial arms that suggest a problem with the randomization process but there are no other limitations related to randomization. |
| **Definitely high risk of bias** | Trials in which allocation is by judgment of the clinician, by preference of the participant, by availability of the intervention, based on the results of a laboratory test, or other non-random rules (e.g., birthdate, etc.).  
Trials in which investigators enrolling participants could possibly foresee the arm to which each subsequent patient would be randomized, such as allocation using an open allocation schedule (e.g. a list of random numbers), assignment envelopes used without appropriate safeguards (e.g. use of unsealed, non-opaque or not sequentially numbered envelopes), alternation between arms, case record number, or any other explicitly unconcealed procedure, rate as high risk. |

**Bias due to deviations from the intended intervention**

**Issues to consider:**
- Blinding of healthcare providers/clinicians and participants
- Imbalances in cointerventions or behaviors
| Definitely low risk of bias | Therapy trials in which healthcare providers are blind to the intervention administered and in which there are no significant differences in administered co-interventions. |
|---------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
|                           | Therapy trials that are described as double or triple blind.                                                                 |
| Possibly low risk of bias | Therapy trials in which healthcare providers are not blind to the intervention administered.                                     |
|                           | Therapy trials in which healthcare providers are blind to the intervention administered but there are significant differences in administered co-interventions that suggests that blinding may have been compromised. |
|                           | Therapy trials in which healthcare providers are described as being blind to the intervention but allocation concealment was inadequate.  |
| Possibly high risk of bias| Therapy trials in which healthcare providers are not blind to the intervention and in which there are significant differences in administered co-interventions. |
| Definitely high risk of bias | Therapy trials in which healthcare providers are not blind to the intervention and in which there are significant differences in administered co-interventions. |

**Bias due to missing data**

Issues to consider:
- Missing outcome measures
- Loss to follow-up

| Definitely low risk of bias | Trials in which missing outcome data (including outcome data that has been imputed) < 10%. |
|-----------------------------|--------------------------------------------------------------------------------------------|
|                             | For in-patient trials, we will assume low risk of bias due to missing data unless otherwise specified. |
| Probably low risk of bias | Trials in which missing outcome data (including outcome data that has been imputed) is between 10% to 15% and missing outcome data is unlikely to be related to the true outcome and there is no imbalance in numbers of or reasons for missing data across intervention groups. |
|---------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Probably high risk of bias | Trials in which missing outcome data (including outcome data that has been imputed) is between 10% to 15% and missing outcome data is likely to be related to the true outcome or there are imbalances in numbers of or reasons for missing data across intervention groups. |
| Definitely high risk of bias | Trials in which missing outcome data (including outcome data that has been imputed) > 15%. |

**Bias due to measurement of the outcome**

Issues to consider:
- Blinding of outcome adjudicators
- Objectivity of outcome

*Note that the judgments may differ across outcomes.*

| Definitely low risk of bias | Trials in which patients are blind to the intervention and in which outcomes are patient-reported. |
|----------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                            | Trials in which outcomes are measured by a third-party (investigator or clinician) and in which the third-party is blind to the intervention. |
|                            | Trials in which the outcomes are objective. |
|                            | Trials that are described as double or triple blind. |

| Probably low risk of bias |  |
|----------------------------|  |
| Probably high risk of bias |  |
| Definitely high risk of bias | Trials in which patients are not blind and in which outcomes are patient-reported (e.g., time to symptom resolution).

Trials in which outcome adjudicators are not blind and the outcomes are not objective (e.g., adverse effects leading to discontinuation, transfusion-related acute lung injury, transfusion-associated circulatory overload, allergic reactions, infection with suspected/symptomatic COVID-19, venous thromboembolism, time to symptom resolution including fever, time to clinical improvement if the criteria for clinical improvement are not objective). |
| --- | --- |

**Bias in selection of the reported results**

Issues to consider:

Selecting reporting of timepoints
Selecting reporting of outcome measures

*Note that we are only interested in selective reporting for the outcomes for which we are extracting data.*

*Note that the judgments may differ across outcomes.*

| Definitely low risk of bias | Results for outcomes that were analyzed and reported according to a prespecified statistical analysis plan or protocol (including the timepoint for the measurement of the outcome). |
| --- | --- |

| Probably low risk of bias | Results for outcomes that were analyzed and reported but that were not prespecified in a statistical analysis plan or protocol but the timepoint at which results are reported is consistent with the timepoint for other outcomes in the trial report or there is little reason to believe the outcome was selectively reported. |
Please note that outcomes that were not prespecified in a protocol or statistical analysis plan and that are reported in the trial preprint or publication should be rated at probably low risk of bias unless there are other important reasons to suspect that results for those outcomes were selectively reported (e.g., results are presented at timepoints that don’t match the timepoints reported for other outcomes).

| Risk of Bias | Description |
|--------------|-------------|
| **Probably high risk of bias** | Results for outcomes that were analyzed and reported but that were not prespecified in a statistical analysis plan or protocol but the timepoint at which results are reported is not consistent with the timepoint for other outcomes in the trial report or there are other reasons to believe that the outcome is selectively reported. |
| **Definitely high risk of bias** | Results for outcomes that were analyzed and reported for which there are inconsistencies with the statistical analysis plan or protocol. These inconsistencies may include outcome measures of interest or the timepoints for the measurement of outcomes. |
**Supplement 3. Meta-analysis and GRADE terminology**

These are provided to help readers who are unfamiliar with network meta-analysis or GRADE.

| Network meta-analysis                                                                 | A type of meta-analysis that compares more than two treatments against one another using direct and indirect estimates to produce a network estimate. Normally, the network estimates are presented in the results, unless the certainty of the direct estimates are higher. |
|---------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Frequentist network meta-analysis                                                    | This is one of the two methods of analysis for network meta-analysis. The other is a Bayesian network meta-analysis. They differ in the usual way that Bayesian and frequentist statistics differ, mainly that Bayesian methods use probabilities in the analysis whereas frequentists do not. The consequence of this is that Bayesian methods usually produce wider confidence intervals than frequentist estimates, as a result of assumed greater network wide heterogeneity. Both are valid methods of performing network analysis. |
| Node splitting                                                                         | Network estimates that have indirect and direct evidence, these estimates are split into three components. The network estimate, indirect estimate and direct estimate are inspected for consistency. Consistency is assessed mainly by inspection of the point estimate and the confidence intervals (i.e., whether they overlap). |
| Heterogeneity estimators                                                               | Are methods for calculating heterogeneity (differences between studies) in meta-analysis. Restricted Maximum Likelihood (REML) estimator is one such example. Simulation studies show that this method produces better error rates. |
| Meta-regression                                                                        | Is similar to simple regression, where the outcome of interest is predicted on the basis of one or more explanatory variables. |
Dose-response meta-analysis summarizes the quantitative relationship between doses of an exposure and an outcome across studies.

ICEMAN tool
Is a validated instrument designed to evaluate the credibility of a subgroup.

GRADE
GRADE is the most widely adopted tool for grading the quality of evidence and for making recommendations with over 100 organizations worldwide officially endorsing GRADE. The GRADE framework requires judgements to be made by the researchers and may not be reproducible.

Domains for evaluating evidence for network and dose-response meta-analysis.
All ratings start at high and may be downgraded due to issues in one or more domains below.

Risk of bias
Using a validated tool, researchers can assess the risk of bias of studies included in an estimate. They rate the certainty down once for studies at risk of bias.

We rated studies using a modification of the risk of bias tool 2.0, which was used in two previous peer reviewed meta-analyses. For each estimate, we looked at the proportion of studies that were at risk of bias. We rated down for risk of bias once if removal of the risk of bias studies from the analysis significantly changed the results. We rated down for risk of bias also if all the studies were at risk of bias. We did not rate down more than once.
Using minimally important differences, we rated down the certainty of evidence by once, twice or three times, depending on how uncertain the result is.

Using a minimally contextualized framework, we rated down once for imprecision if the confidence intervals included the MID. If the confidence interval included the MID in both directions we rated down twice. We did not rate down three times for any estimate.

This is assessed whether the population and intervention of interest are congruent with the research question. If it is not, researchers may rate down the certainty of evidence.

We assessed this by evaluating each trial and making judgements on the included trials, interventions (dose, route, duration) and how each outcome was measured.

In estimates with 10 more studies, publication bias can be assessed. If there is publication bias, investigators may rate down. We assessed publication bias by inspecting funnel plots and Egger’s statistical test.

The individual study estimates may be inconsistent with each other. If this is detected, we may further rate down the certainty of evidence.
We assessed for inconsistency by reviewing forest plots for each estimate. Both the width and overlap of confidence intervals were measured. I² statistics were also assessed. If inconsistency was detected, we rated down if removal of that study changed the results.

| Incoherence                  | Coherence refers to consistency between direct and indirect estimates |
|------------------------------|---------------------------------------------------------------------|
|                              | We planned to rate down for incoherence when the indirect and direct estimates were different enough such that there was no overlap in confidence intervals. |
|                              | We rated down for incoherence in the duration of the hospitalization network. According to guidance, in the face of incoherence, one needs to base the certainty rating on the evidence that most contributes to the network estimate. When incoherence is present, however, we rated down the network evidence further. |

| Intransitivity               | Intransitivity is the dissimilarity of important factors that may affect the outcome being investigated (i.e., effect modifiers) across comparisons. |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
|                              | We looked at multiple possible effect modifiers across the network to determine whether there was intransitivity. |

Related methodological clarifications
Point estimates and statistical significance
A common interpretation confusion is around statistical significance. GRADE does not include statistical significance in the rating of the certainty of the evidence. To illustrate why, take for example, a point estimate of drug X versus placebo may indicate a reduction in mortality by 1% and be statistically significant but the certainty of the estimate may be very low, based on the methods described above. Despite the result being statistically significant, you may not trust the result and limit its implications for practice. Furthermore, statistical significance does not translate into clinical significance. Therefore, the GRADE approach does not place emphasis on statistical significance. Rather, the focus is on the certainty around the point estimate using the validated methods described above. Further issues with interpretation of p-values and the importance of interpreting the effect size has been previously discussed.10-13.

Minimally contextualized approach
A minimally contextualized approach minimizes value judgments regarding the magnitude of intervention effects. It involves a multi-step process, including choosing a reference intervention (i.e. placebo) and a decision threshold. A decision threshold can be determined by pre-existing analysis of minimally important differences or by researcher judgment (i.e. a 2% reduction in mortality or a 5% reduction in serious adverse events). The decision threshold is important in determining imprecision, as interventions with 95% credibility interval that cross the decision threshold may be labeled imprecise.4.

Simple language summary
The GRADE approach uses a standardized method for reporting the certainty of evidence in simple language.14 The use of language will also depend on whether the researchers chose a partially or fully contextual approach. For our paper, we chose a partially contextualized approach. The simple language summary used in our paper is as follows:

High certainty evidence = Drug X reduces mortality
Moderate certainty evidence = Drug X likely reduces mortality
Low certainty evidence = Drug X may reduce mortality
Very low certainty evidence = The evidence of drug X on mortality is very uncertain

Summary of findings (Table 2)
We present the results of our NMA in table 2, which summarizes the network estimates of each treatment node versus placebo. Direct estimates were occasionally presented if the certainty of the evidence was higher. All head-to-head comparisons are presented in the supplementary files, but one can determine the relative effectiveness of one drug versus another by looking at how each drug compares against placebo. This is possible because the network estimates essentially standardize the results against placebo. This is the accepted method for presenting the summary of findings for NMA, which is elegantly demonstrated in the largest living network meta-analysis in the world.

References:

1. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. Apr 2011;64(4):383-94. doi:10.1016/j.jclinepi.2010.04.026
2. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ. What is "quality of evidence" and why is it important to clinicians? Bmj. May 3 2008;336(7651):995-8. doi:10.1136/bmj.39490.551019.BE
3. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj. Apr 26 2008;336(7650):924-6. doi:10.1136/bmj.39489.470347.AD
4. Brigardello-Petersen R, Florez ID, Izcovich A, et al. GRADE approach to drawing conclusions from a network meta-analysis using a minimally contextualised framework. Bmj. Nov 11 2020;371:m3900. doi:10.1136/bmj.m3900
5. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence--study limitations (risk of bias). J Clin Epidemiol. Apr 2011;64(4):407-15. doi:10.1016/j.jclinepi.2010.07.017
6. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence--imprecision. J Clin Epidemiol. Dec 2011;64(12):1283-93. doi:10.1016/j.jclinepi.2011.01.012
7. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 8. Rating the quality of evidence--indirectness. J Clin Epidemiol. Dec 2011;64(12):1303-10. doi:10.1016/j.jclinepi.2011.04.014
8. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence--publication bias. J Clin Epidemiol. Dec 2011;64(12):1277-82. doi:10.1016/j.jclinepi.2011.01.011
9. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 7. Rating the quality of evidence--inconsistency. J Clin Epidemiol. Dec 2011;64(12):1294-302. doi:10.1016/j.jclinepi.2011.03.017
10. Nakagawa S, Cuthill IC. Effect size, confidence interval and statistical significance: a practical guide for biologists. Biol Rev Camb Philos Soc. Nov 2007;82(4):591-605. doi:10.1111/j.1469-185X.2007.00027.x
11. Fleischmann M, Vaughan B. Commentary: Statistical significance and clinical significance - A call to consider patient reported outcome measures, effect size, confidence interval and minimal clinically important difference (MCID). J Bodyw Mov Ther. Oct 2019;23(4):690-694. doi:10.1016/j.jbmt.2019.02.009
12. Ialongo C. Understanding the effect size and its measures. Biochem Med (Zagreb). 2016;26(2):150-63. doi:10.11613/bm.2016.015
13. Baghi H, Noorbalaocchi S, Moore JB. Statistical and nonstatistical significance: implications for health care researchers. Qual Manag Health Care. Apr-Jun 2007;16(2):104-12. doi:10.1097/01.Qmh.0000267447.55500.57
14. Santesso N, Glenton C, Dahm P, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. J Clin Epidemiol. Mar 2020;119:126-135. doi:10.1016/j.jclinepi.2019.10.014
15. Siemieniuk RA, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. Bmj. Jul 30 2020;370:m2980. doi:10.1136/bmj.m2980
**Supplement 4. Studies excluded from the systematic review and meta-analysis**

| Study               | Intervention                  | Exclusion reason                                      |
|---------------------|-------------------------------|------------------------------------------------------|
| Abd-Elsalam 2021 (NCT04345419) | Remdesivir                    | Only severe patients, average saturation <92% on room air. |
| Abbass 2021 (ISRCTN21085622)     | Daclatasvir, sofosbuvir       | Majority severe/critical, no subgroup data.            |
| Ader 2021 (NCT04315948)           | Remdesivir                    | Only severe patients based on exclusion criteria, no subgroup data. |
| Alavi-Moghaddam 2021 (IRCT20200328046882N1) | Sofosbuvir                  | 100% severe disease.                                  |
| Arabi 2021 (NCT02735707)          | Lopinavir-ritonavir           | Severe patients only, no subgroup data.                |
| Cao 2020 (ChiCTR2000029308)       |                               |                                                       |
| Intervention                  | Exclusion reason                                      |
|------------------------------|------------------------------------------------------|
| Lopinavir-ritonavir          | Severe only, no subgroup data.                       |
| Darazam 2021 (NCT04350684)   |                                                       |
| Unifenoivir                  | Only severe patients (SpO2 <93% on room air), no subgroup data. |
| El-Bendary 2021 (NR)         |                                                       |
| Sofosbuvir-daclatasvir       | Only severe patients (SpO2 <90% on room air), no subgroup data. |
| Fitzgerald 2021 (NCT04746183)|                                                       |
| Molnupiravir                 | No outcomes of interest.                             |
| Horby 2020 (NCT04381936)     |                                                       |
| Lopinavir-ritonavir          | Only severe patients, no subgroup data.              |
| Kalantari 2021 (NR)          |                                                       |

Appendix 1, as submitted by the authors. Appendix to: Pitre T, Van Alstine R, Chick G, et al. Antiviral drugs in nonsevere COVID-19: a systematic review and network meta-analysis. CMAJ 2022. doi: 10.1503/cmaj.220471. Copyright © 2022 The Author(s) or their employer(s). To receive this resource in an accessible format, please contact us at cmajgroup@cmaj.ca.
| Exclusion reason                                      | Only severe patients, no subgroup data. |
|------------------------------------------------------|----------------------------------------|
| Study                                                | Khodashahi 2020 (IRCT20200325046859N2)  |
| Intervention                                         | Umifenovir                              |
| Exclusion reason                                      | Only severe patients, no subgroup data. |
| Study                                                | Lou 2020 (ChiCTR2000029544)             |
| Intervention                                         | Baloxavir marboxil                      |
| Exclusion reason                                      | Mostly severe, no subgroup data.        |
| Study                                                | Mahajan 2021 (NR)                       |
| Intervention                                         | Remdesivir                              |
| Exclusion reason                                      | Only severe patients included, no subgroup data. |
| Study                                                | Nojomi 2020 (IRCT20180725040596N2)      |
| Intervention                                         | Lopinavir-ritonavir                     |
| Exclusion reason                                      | Only severe patients included with average SpO2 <90%. No subgroup data. |
| Study                                                | Ogbuagu 2021 (NCT04252664)              |
| Intervention                                         | Remdesivir                              |
| Exclusion reason                                      | No outcomes of interest.                |
| Study                                                | Ramachandran 2021 (CTRI/2020/09/027535) |
| Intervention          | Exclusion reason                                      | Study                     |
|-----------------------|--------------------------------------------------------|---------------------------|
| Umifenovir            | All patients on oxygen, no subgroup data.              | SOLIDARITY 2020 (ISRCTN83971151, NCT04315948) |
| Lopinavir-ritonavir    | Only severe patients, no subgroup data.                | Sadeghi 2020 (IRCT20200128046294N2)     |
| Sofosbuvir-daclatasvir| Only severe patients, no subgroup data.                | Sayad 2021 (IRCT2013081201433N145)      |
| Sofosbuvir, velpatasvir| Only severe patients, no subgroup data.                | Solaymani-Dodaran 2021 (IRCT20200318046812N1) |
| Favipiravir            | Only severe patients, no subgroup data.                | Wang 2021 (NCT04257656)            |
| Remdesivir            | All patients on oxygen, no subgroup data.              |                           |
| Study       | Yadegarinia 2020 (NR) |
|-------------|-----------------------|
| Intervention| Umifenovir            |
| Exclusion reason | Only severe patients, no subgroup data. |
### Supplement 5. Trial characteristics

| Study      | Year | Country                                                                 | N  | Age | Male % | Inpatient % | Mild % | Moderate % | Severe % | Critical % | Respiratory condition % | Cardiovascular disease % | Diabetes % | Hypertension % |
|------------|------|--------------------------------------------------------------------------|----|-----|--------|-------------|--------|------------|----------|------------|------------------------|--------------------------|-------------|-----------------|
| Ader       | 2021 | France, Luxembourg                                                      | 300| 63  | 71.7   | 100         | 0      | 63.81      | 36.19    | NR         | 15.09                  | 25.9                     | 21.95       | NR              |
| Ali        | 2022 | Canada                                                                  | 1282| 65.51 | 59.8  | 100        | 0      | NR         | NR       | 18.42      | 19.91                  | 26.78                    | NR          | NR              |
| Arruda     | 2021 | Brazil                                                                  | 150| 38.04 | 35.4  | 0          | NR      | NR         | 0        | 6.28       | 3.15                   | 9.76                     | 17.04       | NR              |
| Balykova_1 | 2020 | Russia                                                                  | 39 | 47.33 | NR     | 100        | 0      | 100        | 0        | NR         | 0                      | NR                      | NR          | NR              |
| Balykova_2 | 2020 | Russia                                                                  | 206| 49.68 | 48.54 | 100        | 0      | NR         | NR       | 4.85       | 5.83                   | 8.74                     | 27.67       | NR              |
| Barratt-Due| 2021 | Norway                                                                  | 94 | 59.8 | 65.75  | 100        | NR      | NR         | NR       | 5.52       | 15.47                  | 17.13                    | 30.39       | NR              |
| Beigel     | 2020 | United States, Denmark, United Kingdom, Greece, Germany, Korea, Mexico, Spain, Japan, Singapore | 1062| 58.9 | 64.41 | 100        | NA      | NR         | 90.11    | NR         | 21.2                   | 17.42                    | 31.57       | 50.71           |
| Bernal     | 2021 | Multicontinental                                                        | 1433| 44.85 | 48.71 | 0          | 54.78   | 44.52      | 0.28     | 0          | 3.98                   | 11.65                    | 15.91       | NR              |
| Chen       | 2020 | China                                                                   | 240| NR   | 46.61  | NR         | 0       | 88.55      | 10.17    | 1.27       | NR                     | NR                      | NR          | 11.44          |
| Criner     | 2020 | China                                                                   | 384| 57   | 61     | 100        | 0       | 100        | 0        | 0          | 11                     | NR                      | NR          | 39              |
| Doi        | 2020 | Japan                                                                    | 89 | 50   | 61.36  | 100        | NR      | NR         | NR       | NR         | NR                     | NR                      | NR          | NR              |
| Study  | Year | Country                                                                 | N   | Age | Male % | Inpatient % | Mild % | Moderate % | Severe % | Critical % | Respiratory condition % | Cardiovascular disease % | Diabetes % | Hypertension % |
|--------|------|-------------------------------------------------------------------------|-----|-----|--------|-------------|--------|------------|----------|------------|-------------------------|--------------------------|------------|---------------|
| EPIC-HR | 2021 | Argentina, Brazil, Bulgaria, Colombia, Czechia, Hungary, India, Japan, Korea, Malaysia, Mexico, Peru, Puerto Rico, Poland, Russia, South Africa, Spain, Taiwan, Thailand, Turkey, Ukraine, United States | 2085 | NR  | NR     | 0           | NR     | NR         | NR       | NR         | NR                      | NR                       | NR         | NR            |
| EPIC-SR | 2021 | North America, South America, Europe, Africa, Asia,                      | 854  | NR  | NR     | 0           | NR     | 0          | 0        | 0          | 0                       | 0                        | NR         | NR            |
| Study     | Year   | Country                                                                 | N    | Age   | Male % | Inpatient % | Mild % | Moderate % | Severe % | Critical % | Respiratory condition % | Cardiovascular disease % | Diabetes % | Hypertension % |
|-----------|--------|-------------------------------------------------------------------------|------|-------|--------|-------------|--------|------------|----------|------------|--------------------------|---------------------------|-------------|---------------|
| Fischer   | 2021   | United States                                                          | 85   | 40.09 | 48.51  | 0           | NR     | NR         | 0        | 0          | NR                       | NR                        | NR          | NR            |
| Gaitain-Duarte | 2021 | Colombia                                                               | 324  | 55.39 | 67.61  | 100         | NR     | NR         | NR       | NR         | 4.42                     | 2.68                      | 12          | 27.8          |
| Ghaderkhani | 2020 | Iran                                                                   | 56   | 44.38 | 60.38  | 3.77        | NR     | NR         | 0        | 0          | NR                       | NR                        | NR          | NR            |
| Gottlieb  | 2021   | United States, Spain, Denmark, United Kingdom                          | 584  | 50.5  | 52.14  | 0           | NR     | NR         | 0        | 0          | 24.02                    | 7.83                      | 61.57       | 47.69         |
| Huang     | 2020   | China                                                                  | 69   | 42.5  | 45.54  | 100         | NR     | NR         | 0        | 0          | 0                        | 0                         | NR          | NR            |
| Ivashchenko | 2020  | Russia                                                                 | 40   | 50.73 | 50     | 100         | 0      | 100        | 0        | 0          | NR                       | NR                        | NR          | NR            |
| Kasgari   | 2020   | Iran                                                                   | 48   | 52.5  | 37.5   | 100         | 0      | 100        | 0        | 0          | 2.08                     | 22.92                     | 37.5        | 35.42         |
| Khoo      | 2021   | United Kingdom                                                         | 8    | 56    | 27.78  | 0           | NR     | NR         | 0        | 0          | NR                       | NR                        | NR          | NR            |
| Li        | 2020   | China                                                                  | 69   | 49.4  | 46.51  | 100         | 12.79  | 87.21      | 0        | 0          | 2.33                     | 2.32                      | 10.47       |               |
| McCreary  | 2021   | United States                                                          | 105  | 56    | 40.95  | 0           | NR     | NR         | 0        | 0          | NR                       | NR                        | NR          | NR            |
| Mobarak   | 2021   | Iran                                                                   | 1083 | 58    | 54.02  | 100         | 0      | 100        | 0        | 0          | 6.92                     | 9.14                      | 27.61       | 33.98         |
| Nourian   | 2020   | Iran                                                                   | 90   | 62.23 | NR     | 100         | 56.1   | 43.9       | 0        | 0          | 4.88                     | 31.71                     | 45.12       | 45.12         |
| Ogbuagu   | 2021   | China                                                                  | 1005 | NR    | NR     | 100         | 0      | NR         | NR       | NR         | NR                       | NR                        | NR          | NR            |
| Study | Year | Country | N   | Age | Male % | Inpatient % | Mild % | Moderate % | Severe % | Critical % | Respiratory condition % | Cardiovascular disease % | Diabetes % | Hypertension % |
|-------|------|---------|-----|-----|--------|-------------|--------|------------|----------|------------|-------------------------|--------------------------|------------|---------------|
| Pan   | 2020 | Albania, Argentina, Austria, Belgium, Brazil, Canada, Colombia, Egypt, Finland, France, Honduras, India, Indonesia, Iran, Ireland, Italy, Kuwait, Lebanon, Lithuania, Luxembourg, Macedonia, Malaysia, Norway, Pakistan, Phillipines, Peru, Saudi Arabia, South Africa, Spain | 5475 | NR  | 62.94  | 100         | NR     | NR         | NR       | 10.53      | 20.88                  | 25.19                    | NR         |               |
| Study  | Year | Country   | N   | Age | Male % | Inpatient % | Mild % | Moderate % | Severe % | Critical % | Respiratory condition % | Cardiovascular disease % | Diabetes % | Hypertension % |
|--------|------|-----------|-----|-----|--------|-------------|--------|------------|----------|------------|-------------------------|--------------------------|------------|---------------|
| Parienti | 2021 | France    | 60  | 45.25 | 43.33 | 0           | 95     | 5          | 0        | 0          | NR                      | NR                       | 3.33       | 5             |
| Ren    | 2020 | China     | 20  | 52   | 60     | 100         | 100    | 0          | 0        | 0          | 0                       | 0                        | 5          | 5             |
| Study        | Year | Country  | N  | Age | Male % | Inpatient % | Mild % | Moderate % | Severe % | Critical % | Respiratory condition % | Cardiovascular disease % | Diabetes % | Hypertension % |
|-------------|------|----------|----|-----|--------|------------|-------|------------|----------|------------|-------------------------|--------------------------|-------------|---------------|
| Roozbeh     | 2020 | Iran     | 60 | 43  | 47.27  | 0          | 100   | 0          | 0        | 0          | NR                      | 0                        | NR          | NR            |
| Ruzhentsova | 2020 | Russia   | 168| 41.8| 47.02  | 24.4       | 25.6  | 74.4       | 0        | 0          | 0                       | 0                        | 0           | NR            |
| Shinkai     | 2021 | Japan    | 156| 45.34| 66.67 | 100        | 0     | 100        | 0        | 0          | NR                      | NR                      | NR          | NR            |
| Udwaadia    | 2020 | India    | 150| 43.29| 73.47 | 100        | 60.54 | 39.46      | 0        | 0          | 0                       | 0                        | NR          | NR            |
| Wang_1      | 2020 | China    | 237| 65  | 59.32  | 100        | 0     | 0          | 100      | 0          | NR                      | 7.2                      | 23.73       | 43.22         |
| Wang_2      | 2020 | China    | 60 | NR  | 38.3   | 100        | 0     | 100        | 0        | 0          | NR                      | NR                      | NR          | NR            |
| Wu          | 2020 | China    | 52 | 58  | 50     | 100        | NR    | NR         | NR       | NR         | 5.8                     | 23.1                     | 15.4        | 28.8          |
| Yadollahzadeh | 2021 | Iran     | 112| 57.56| 44.64 | 100        | NR    | NR         | 0        | 0          | 3.57                    | 15.18                    | 21.43       | 25            |
| Yakoot      | 2020 | Egypt    | 89 | 49.01| 42.7  | 100        | 13.48 | 68.54      | 17.98    | 0          | 1.12                    | 8.99                     | 19.1        | 25.84         |
| Yethindra   | 2020 | Kyrgyzstan| 30| 36.5| 60    | 100        | NR    | NR         | 0        | 0          | NR                      | 0                        | NR          | NR            |
| Zhao        | 2021 | China    | 55 | 55.7| 45.45 | 0          | 1.82  | 96.36      | 1.82     | NR         | 7.27                    | 14.55                    | 30.91       |                |
| Zheng       | 2020 | China    | 60 | 46.73| 47.19 | 100        | 0     | 94.38      | 5.62     | NR         | 2.02                    | 3.03                     | 8.08        | 6.06          |

*N = number randomized
*Mild = Symptomatic but no dyspnea or abnormal chest imaging
*Moderate = Evidence of lower respiratory disease but whose spO2 is >=94% on room air
*Severe = spO2 is <94% on room air
*Critical = respiratory failure, shock or multiorgan dysfunction
*Respiratory condition = any chronic lung disease
*Cardiovascular disease = any chronic cardiac or vascular disease
*Diabetes = either type I or II
NR = not reported
## Supplement 6. Risk of bias judgements

| Study     | Outcome                                                                 | Bias arising from the randomization process | Bias due to deviations from the intended intervention | Bias due to missing outcome data | Bias in measurement of the outcome | Bias in selection of the reported results |
|-----------|--------------------------------------------------------------------------|---------------------------------------------|------------------------------------------------------|---------------------------------|-----------------------------------|-------------------------------------------|
| Ader      | Adverse events leading to drug discontinuation                           | Low risk                                   | Low risk                                            | High risk                       | Low risk                          |                                           |
| Balykova_1| Adverse events leading to drug discontinuation                           | Low risk                                   | Low risk                                            | High risk                       | Low risk                          |                                           |
| Gaitan-Duarte | Adverse events leading to drug discontinuation                         | Low risk                                   | Low risk                                            | High risk                       | Low risk                          |                                           |
| Parienti  | Adverse events leading to drug discontinuation                           | Low risk                                   | Low risk                                            | High risk                       | Low risk                          |                                           |
| Yakoot    | Adverse events leading to drug discontinuation                           | Low risk                                   | Low risk                                            | High risk                       | Low risk                          |                                           |
| Huang     | Adverse events leading to drug discontinuation                           | Probably high risk                         | Low risk                                            | High risk                       | Low risk                          |                                           |
| Author | Adverse events leading to drug discontinuation | Probably high risk | Probably low risk | Low risk | High risk | Low risk |
|--------|-----------------------------------------------|--------------------|------------------|---------|----------|---------|
| Khoo   | Adverse events leading to drug discontinuation |                    |                  |         |          |         |
| Ruzhentsova | Adverse events leading to drug discontinuation | Probably high risk | Probably low risk | Low risk | High risk | Low risk |
| Udwadia | Adverse events leading to drug discontinuation | Probably high risk | Probably low risk | Low risk | High risk | Low risk |
| Beigel | Adverse events leading to drug discontinuation | Low risk            | Low risk          | Low risk | Low risk | Low risk |
| Bernal | Adverse events leading to drug discontinuation | Low risk            | Low risk          | Low risk | Low risk | Low risk |
| Fischer | Adverse events leading to drug discontinuation | Low risk            | Low risk          | Low risk | Low risk | Low risk |
| Wang_1 | Adverse events leading to drug discontinuation | Low risk            | Low risk          | Low risk | Low risk | Low risk |
| EPIC-HR | Adverse events leading to drug discontinuation | Probably low risk   | Low risk          | Low risk | Low risk | Low risk |
| Gottlieb | Adverse events leading to drug discontinuation | Probably low risk   | Low risk          | Low risk | Low risk | Low risk |
| Name            | Admission Type     | Risk Level       | Risk Level       | Risk Level       | Risk Level       | Risk Level       |
|-----------------|--------------------|------------------|------------------|------------------|------------------|------------------|
| Bernal          | Hospital admission| Low risk         | Low risk         | Low risk         | Low risk         | Low risk         |
| McCreary        | Hospital admission| Low risk         | Low risk         | Low risk         | Low risk         | Low risk         |
| Roozbeh         | Hospital admission| Low risk         | Low risk         | Low risk         | Low risk         | Low risk         |
| EPIC-HR         | Hospital admission| Probably low risk| Low risk         | Low risk         | Low risk         | Low risk         |
| EPIC-SR         | Hospital admission| Probably low risk| Low risk         | Low risk         | Low risk         | Low risk         |
| Gottlieb        | Hospital admission| Probably low risk| Low risk         | Low risk         | Low risk         | Low risk         |
| Arruda          | Hospital admission| Probably high risk| Probably low risk| Low risk         | Low risk         | Low risk         |
| Ader            | Mechanical ventilation| Low risk      | Probably low risk| Low risk         | Low risk         | Low risk         |
| Balykova_2      | Mechanical ventilation| Low risk      | Probably low risk| Low risk         | Low risk         | Low risk         |
| Beigel          | Mechanical ventilation| Low risk      | Low risk         | Low risk         | Low risk         | Low risk         |
| Bernal          | Mechanical ventilation| Low risk      | Low risk         | Low risk         | Low risk         | Low risk         |
| Gaitan-Duarte   | Mechanical ventilation| Low risk      | Probably low risk| Low risk         | Low risk         | Low risk         |
| McCreary        | Mechanical ventilation| Low risk      | Low risk         | Low risk         | Low risk         | Low risk         |
| Pan_remdesivir  | Mechanical ventilation| Low risk      | Probably low risk| Low risk         | Low risk         | Low risk         |
| Author          | Procedure                          | Risk Level 1 | Risk Level 2 | Risk Level 3 | Risk Level 4 | Risk Level 5 |
|-----------------|------------------------------------|--------------|--------------|--------------|--------------|--------------|
| Yakoot          | Mechanical ventilation             | Low risk     | Probably low risk | Low risk     | Low risk     | Low risk     |
| Ghandehari      | Mechanical ventilation             | Probably high risk | Probably low risk | Low risk     | Low risk     | Low risk     |
| Ivashchenko     | Mechanical ventilation             | Probably high risk | Probably high risk | Low risk     | Low risk     | Low risk     |
| Criner          | Adverse events leading to drug discontinuation | Probably high risk | Probably low risk | Low risk     | High risk    | Probably high risk |
| Barratt-Due     | Adverse events leading to drug discontinuation | Low risk     | Probably low risk | Low risk     | High risk    | Probably low risk |
| Kasgari         | Adverse events leading to drug discontinuation | Low risk     | Probably low risk | Low risk     | High risk    | Probably low risk |
| Nourian         | Adverse events leading to drug discontinuation | Low risk     | Probably high risk | Low risk     | High risk    | Probably low risk |
| Shinkai         | Adverse events leading to drug discontinuation | Low risk     | Probably low risk | Low risk     | High risk    | Probably low risk |
| Ivashchenko     | Adverse events leading to drug discontinuation | Probably high risk | Probably high risk | Low risk     | High risk    | Probably low risk |
| Ren             | Adverse events leading to drug discontinuation | Probably high risk | Probably low risk | Low risk     | High risk    | Probably low risk |
| Author       | Event Description                          | Low Risk | Probably Low Risk | High Risk | Probably Low Risk |
|-------------|--------------------------------------------|----------|------------------|----------|------------------|
| Wang_2      | Adverse events leading to drug discontinuation |             |                  |          |                  |
| Mobarak     | Adverse events leading to drug discontinuation | Low risk | Low risk          | Low risk | Probably low risk |
| Wu          | Adverse events leading to drug discontinuation | High risk | Probably low risk | Low risk | Low risk          |
| Fischer     | Hospital admission                         | Low risk | Low risk          | Low risk | Probably low risk |
| Parienti    | Hospital admission                         | Low risk | Probably low risk | Low risk | Low risk          |
| Ruzhentsova | Hospital admission                         | Probably high risk | Probably low risk | Low risk | Low risk          |
| Kasgari     | Mechanical ventilation                     | Low risk | Probably low risk | Low risk | Probably low risk |
| Mobarak     | Mechanical ventilation                     | Low risk | Low risk          | Low risk | Probably low risk |
| Nourian     | Mechanical ventilation                     | Low risk | Probably high risk | Low risk | Low risk          |
| Shinkai     | Mechanical ventilation                     | Low risk | Probably low risk | Low risk | Probably low risk |
| Wang_1      | Mechanical ventilation                     | Low risk | Low risk          | Low risk | Probably low risk |
| Balykova_1  | Mechanical ventilation                     | Probably high risk | Probably high risk | Low risk | Low risk          |
| Author         | Event Description                     | Risk Level         | Risk Level         | Risk Level         | Risk Level         |
|---------------|---------------------------------------|--------------------|--------------------|--------------------|--------------------|
| Doi           | Mechanical ventilation                | Probably high risk | Probably low risk  | Low risk           | Low risk           |
| Ruzhentsova   | Mechanical ventilation                | Probably high risk | Probably low risk  | Low risk           | Low risk           |
| Udwadia       | Mechanical ventilation                | Probably high risk | Probably low risk  | Low risk           | Probably low risk  |
| Ghandehari    | Adverse events leading to drug        | Probably high risk | Probably low risk  | Low risk           | Probably high risk |
|               | discontinuation                       |                    |                    |                    |                    |
| Li            | Adverse events leading to drug        | Low risk           | Probably low risk  | Low risk           | Probably low risk  |
|               | discontinuation                       |                    |                    |                    |                    |
**Supplement 7. Network diagrams**

**Hospitalizations:**

- nirmatrelvir+ritonavir
- favipiravir
- molnupiravir
- placebo
- remdesivir
- tenofovir
- emtricitabine+tenofovir
- resveratrol
- sofosbuvir+daclatasvir
Mechanical ventilation:
Adverse events lead to drug discontinuation:
Supplement 8. Node splitting models

No node splitting plots available for mechanical ventilation or adverse events due to no indirect evidence comparisons. The number of the direct evidence column is the P-value to test for differences between groups.

Mortality

| Comparison                        | Number of Studies | Direct Evidence | Random effects model | RR    | 95%-CI |
|-----------------------------------|-------------------|-----------------|----------------------|-------|--------|
| faviparpiravir vs placebo         | 6                 | 0.91            |                      | 0.95  | [0.22; 4.03] |
| Direct estimate                   |                   |                 |                      | 0.79  | [0.01; 83.67] |
| Indirect estimate                 |                   |                 |                      | 0.93  | [0.23; 3.72] |
| Network estimate                  |                   |                 |                      |       |         |
| faviparpiravir vs umifenoavir     | 1                 | 0.36            |                      | 1.03  | [0.02; 51.70] |
| Direct estimate                   |                   |                 |                      | 1.25  | [0.07; 23.39] |
| Indirect estimate                 |                   |                 |                      |       |         |
| Network estimate                  |                   |                 |                      | 1.16  | [0.11; 12.17] |
| lopinavir+ritonavir vs placebo    | 2                 | 0.73            |                      | 0.79  | [0.28; 2.24] |
| Direct estimate                   |                   |                 |                      | 0.82  | [0.14; 4.69] |
| Indirect estimate                 |                   |                 |                      |       |         |
| Network estimate                  |                   |                 |                      | 0.79  | [0.32; 1.95] |
| lopinavir+ritonavir vs sofosbuvir+daclatasvir | 1 | 0.28 |                      | 0.72  | [0.12; 4.12] |
| Direct estimate                   |                   |                 |                      | 0.72  | [0.24; 2.14] |
| Indirect estimate                 |                   |                 |                      |       |         |
| Network estimate                  |                   |                 |                      | 0.72  | [0.28; 1.81] |
| lopinavir+ritonavir vs umifenoavir| 1                 | 0.34            |                      | 1.03  | [0.02; 50.42] |
| Direct estimate                   |                   |                 |                      | 0.98  | [0.06; 16.34] |
| Indirect estimate                 |                   |                 |                      |       |         |
| Network estimate                  |                   |                 |                      | 0.99  | [0.10; 9.74] |
| sofosbuvir+daclatasvir vs placebo | 2                 | 0.98            |                      | 1.11  | [0.80; 1.53] |
| Direct estimate                   |                   |                 |                      | 1.11  | [0.14; 8.51] |
| Indirect estimate                 |                   |                 |                      |       |         |
| Network estimate                  |                   |                 |                      | 1.11  | [0.80; 1.52] |
| umifenoavir vs placebo            | 2                 | 0.63            |                      | 0.70  | [0.05; 10.83] |
| Direct estimate                   |                   |                 |                      | 0.99  | [0.03; 35.93] |
| Indirect estimate                 |                   |                 |                      |       |         |
| Network estimate                  |                   |                 |                      | 0.80  | [0.09; 7.03] |
Hospitalizations

| Comparison                  | Number of Studies | Direct Evidence | Random effects model | RR   | 95%-CI  |
|-----------------------------|-------------------|-----------------|----------------------|------|---------|
| Emtricitabine+tenofovir vs tenofovir | 1                 | 0.94            |                      | 2.26 | [0.21; 23.98] |
| Direct estimate             |                   |                 |                      |      |         |
| Indirect estimate           |                   |                 |                      | 14.98| [0.00; 116357.21] |
| Network estimate            |                   |                 |                      | 2.56 | [0.26; 25.08]  |
| Tenofovir vs placebo        | 1                 | 0.93            |                      | 0.48 | [0.04; 5.06]  |
| Direct estimate             |                   |                 |                      |      |         |
| Indirect estimate           |                   |                 |                      | 3.14 | [0.00; 23746.64] |
| Network estimate            |                   |                 |                      | 0.54 | [0.05; 5.29]  |
### Supplement 9. Network estimates with GRADE ratings

#### Mortality network

| Mortality network | Comparison | Network estimate | Network estimate | Relative estimate | Absolute risk per 1000 |
|-------------------|------------|------------------|------------------|-------------------|------------------------|
| Treatment 1       | Treatment 2 | Point estimate   | CI Lower limit   | CI upper limit    | Point estimate         | CI Lower limit | CI upper limit | GRADE rating |
| azvudine          | emtricitabine+tenofovir | 1.39 | 0.03 | 74.77 | 3.73 | -9.2 | 981.85 | Very low |
| azvudine          | favipiravir      | 1.08 | 0.02 | 66.65 | 0.95 | -12.43 | 830.3 | Very low |
| emtricitabine+tenofovir | favipiravir      | 0.77 | 0.15 | 3.94 | -2.9 | -10.74 | 37.2 | Very low |
| azvudine          | lopinavir+ritonavir | 1.26 | 0.02 | 68.06 | 2.72 | -10.27 | 705.17 | Very low |
| emtricitabine+tenofovir | lopinavir+ritonavir | 0.9 | 0.26 | 3.14 | -1.02 | -7.78 | 22.47 | Moderate |
| favipiravir       | lopinavir+ritonavir | 1.17 | 0.23 | 6.03 | 1.8 | -8.12 | 52.91 | Very low |
| azvudine          | lopinavir+ritonavir+ribavirin | 1.12 | 0 | 295.21 | 1.49 | -12.3 | 3634.37 | Very low |
| emtricitabine+tenofovir | lopinavir+ritonavir+ribavirin | 0.8 | 0.01 | 47.82 | -2.42 | -12.19 | 578.4 | Very low |
| favipiravir       | lopinavir+ritonavir+ribavirin | 1.04 | 0.02 | 71.11 | 0.53 | -12.16 | 866.07 | Very low |
| lopinavir+ritonavir | lopinavir+ritonavir+ribavirin | 0.89 | 0.02 | 43.61 | -1.35 | -12.13 | 526.34 | Very low |
| azvudine          | molnupiravir      | 5.43 | 0.09 | 324.79 | 16.62 | -3.41 | 1214.21 | Very low |
| Drug Combination                        | Molnupiravir | Placebo | Risk Difference | Hazard Ratio | 95% CI Lower | 95% CI Upper |
|----------------------------------------|--------------|---------|-----------------|--------------|--------------|--------------|
| Emtricitabine+tenofovir                | 3.89         | 0.84    | 18.14           | 10.86        | -0.61        | 64.26        | Moderate    |
| Favipiravir                            | 5.05         | 0.77    | 33.17           | 15.19        | -0.87        | 120.65       | Low         |
| Lopinavir+ritonavir                    | 4.31         | 0.91    | 20.51           | 12.43        | -0.35        | 73.18        | Moderate    |
| Lopinavir+ritonavir+ribavirin          | 4.84         | 0.07    | 320.55          | 14.42        | -3.48        | 1198.3       | Very low    |
| Azvudine                               | 8.29         | 0.09    | 755.58          | 13.4         | -1.67        | 1387.1       | Very low    |
| Emtricitabine+tenofovir                | 5.94         | 0.51    | 68.76           | 9.09         | -0.89        | 124.56       | Low         |
| Favipiravir                            | 7.71         | 0.53    | 112.18          | 12.33        | -0.86        | 204.37       | Very low    |
| Lopinavir+ritonavir                    | 6.58         | 0.56    | 77.18           | 10.26        | -0.81        | 140.03       | Low         |
| Lopinavir+ritonavir+ribavirin          | 7.39         | 0.07    | 738.85          | 11.75        | -1.7         | 1356.35      | Very low    |
| Molnupiravir                           | 1.53         | 0.11    | 21              | 0.97         | -1.63        | 36.77        | Low         |
| Azvudine                               | 1            | 0.02    | 48.8            | 0            | -13.04       | 636.12       | Very low    |
| Emtricitabine+tenofovir                | 0.72         | 0.3     | 1.7             | -3.76        | -9.28        | 9.29         | Moderate    |
| Favipiravir                            | 0.93         | 0.23    | 3.72            | -0.93        | -10.21       | 36.16        | Very low    |
| Lopinavir+ritonavir                    | 0.79         | 0.32    | 1.95            | -2.74        | -9.01        | 12.67        | Low         |
| Lopinavir+ritonavir+ribavirin          | 0.89         | 0.02    | 48.41           | -1.44        | -13.09       | 630.94       | Very low    |
| Molnupiravir                           | 0.18         | 0.05    | 0.66            | -10.86       | -12.62       | -4.55        | Moderate    |
| Nirmatrelvir+ritonavir                 | 0.12         | 0.01    | 1.19            | -11.7        | -13.15       | 2.38         | Moderate    |
| Remdesivir                             | 0.82         | 0.54    | 1.26            | -2.38        | -6.17        | 3.43         | High        |
| Resveratrol                            | 1            | 0.02    | 49.5            | 0            | -13.04       | 645.54       | Low         |
| Ribavirin                              | 0.87         | 0.02    | 46.95           | -1.79        | -13.1        | 611.52       | Very low    |
| Treatment                  | Placebo | 0.01 | 2.62 | -11.41 | -13.21 | 21.59 | Low       |
|---------------------------|---------|------|------|--------|--------|--------|-----------|
| ribavirin+sofosbuvir+daclatasvir | placebo | 0.14 | 0.01 | 2.62   | -11.41 | -13.21 | 21.59     |
| sofosbuvir+daclatasvir    | placebo | 1.11 | 0.8  | 1.52   | 1.41   | -2.61  | 6.93      | High      |
| sofosbuvir+ledipasvir     | placebo | 0.95 | 0.2  | 4.44   | -0.63  | -10.59 | 45.84     | Very low  |
| triazavirin               | placebo | 0.33 | 0.01 | 7.82   | -8.87  | -13.12 | 90.75     | Very low  |
| umifenovir                | placebo | 0.8  | 0.09 | 7.03   | -2.68  | -12.1  | 80.22     | Very low  |
| azvudine                  | remdesivir | 1.22 | 0.02 | 60.82  | 2.37   | -10.62 | 651.02    | Very low  |
| emtricitabine+tenofovir   | remdesivir | 0.87 | 0.33 | 2.28   | -1.38  | -7.25  | 13.98     | Moderate  |
| favipiravir               | remdesivir | 1.13 | 0.27 | 4.83   | 1.44   | -7.99  | 41.63     | Very low  |
| lopinavir+ritonavir       | remdesivir | 0.97 | 0.36 | 2.62   | -0.36  | -6.99  | 17.59     | Moderate  |
| lopinavir+ribavir+ritonavir | remdesivir | 1.09 | 0.02 | 60.3   | 0.94   | -10.67 | 645.34    | Very low  |
| molnupiravir              | remdesivir | 0.22 | 0.06 | 0.86   | -8.44  | -10.25 | -1.53     | Moderate  |
| nirmatrelvir+ritonavir    | remdesivir | 0.15 | 0.01 | 1.51   | -9.28  | -10.73 | 5.57      | Moderate  |
| azvudine                  | resveratrol | 1    | 0    | 246.42 | 0      | -13.47 | 3320.44   | Very low  |
| emtricitabine+tenofovir   | resveratrol | 0.72 | 0.01 | 38.95  | -3.83  | -13.35 | 513.39    | Low       |
| favipiravir               | resveratrol | 0.93 | 0.01 | 58.37  | -0.94  | -13.33 | 776.17    | Very low  |
| lopinavir+ritonavir       | resveratrol | 0.79 | 0.01 | 43.49  | -2.78  | -13.33 | 574.85    | Low       |
| lopinavir+ribavir+ritonavir | resveratrol | 0.89 | 0   | 237.07 | -1.46  | -13.48 | 3193.85   | Very low  |
| molnupiravir              | resveratrol | 0.18 | 0   | 11.15  | -11.04 | -13.49 | 137.29    | Very low  |
| nirmatrelvir+ritonavir    | resveratrol | 0.12 | 0   | 11.12  | -11.9  | -13.51 | 136.98    | Very low  |
| remdesivir                | resveratrol | 0.82 | 0.02 | 41.54  | -2.42  | -13.31 | 548.49    | Very low  |
| Drug Combination                          | Drug          | Method 1 | Method 2 | Method 3 | Method 4 | Method 5 | Method 6 | Method 7 | Method 8 | Method 9 | Method 10 | Method 11 | Method 12 | Method 13 | Method 14 | Method 15 | Method 16 | Method 17 | Method 18 | Method 19 | Method 20 | Method 21 | Method 22 | Method 23 | Method 24 |
|----------------------------------------|---------------|----------|----------|----------|----------|----------|----------|----------|----------|----------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| azvudine + ribavirin                   |               | 1.16     | 0        | 304.39   | 1.77     | -11.35   | 3457.77  | Very low |
| emtricitabine + tenofovir + ribavirin  |               | 0.83     | 0.01     | 49.32    | -1.95    | -11.24   | 550.66   | Very low |
| favipiravir + ribavirin                |               | 1.07     | 0.02     | 73.33    | 0.85     | -11.22   | 824.34   | Very low |
| lopinavir + ritonavir + ribavirin      |               | 0.92     | 0.02     | 44.97    | -0.94    | -11.18   | 501.14   | Very low |
| molnupiravir + ribavirin               |               | 0.21     | 0        | 14.08    | -8.97    | -11.36   | 149.1    | Low       |
| nirmatrelvir + ritonavir + ribavirin   |               | 0.14     | 0        | 13.94    | -9.81    | -11.38   | 147.47   | Low       |
| remdesivir + ribavirin                 |               | 0.95     | 0.02     | 52.69    | -0.58    | -11.2    | 589.07   | Very low |
| resveratrol + ribavirin                |               | 1.16     | 0        | 307.13   | 1.77     | -11.35   | 3488.93  | Very low |
| azvudine + ribavirin + sofosbuvir + daclatasvir |   | 7        | 0.05     | 899.57   | 11.03    | -1.74    | 1651.79  | Very low |
| emtricitabine + tenofovir + ribavirin  |               | 5.02     | 0.24     | 104.41   | 7.39     | -1.39    | 190.08   | Very low |
| favipiravir + ribavirin + sofosbuvir + daclatasvir | | 6.51     | 0.26     | 163.41   | 10.13    | -1.36    | 298.54   | Very low |
| lopinavir + ritonavir + ribavirin + ribavirin | | 5.56     | 0.26     | 116.88   | 8.38     | -1.35    | 213.02   | Very low |
| molnupiravir + ribavirin + sofosbuvir + daclatasvir | | 6.24     | 0.04     | 874.07   | 9.64     | -1.76    | 1604.91  | Very low |
| nirmatrelvir + ritonavir + ribavirin + ribavirin | | 1.29     | 0.05     | 30.89    | 0.53     | -1.74    | 54.94    | Low       |
| remdesivir + ribavirin + sofosbuvir + daclatasvir | | 0.84     | 0.02     | 34.3     | -0.29    | -1.8     | 61.21    | Low       |
| resveratrol + ribavirin + sofosbuvir + daclatasvir | | 5.75     | 0.3      | 108.82   | 8.73     | -1.28    | 198.21   | Very low |
| ribavirin + sofosbuvir + daclatasvir   |               | 7        | 0.05     | 908.85   | 11.03    | -1.74    | 1668.84  | Very low |
| azvudine + sofosbuvir + daclatasvir    |               | 0.9      | 0.02     | 44.71    | -1.37    | -14.08   | 626.68   | Very low |
| Drug Combination 1                                      | Drug Combination 2                                      | T1 (min) | T2 (min) | T3 (min) | T4 (min) | Effectiveness | Immunity |
|--------------------------------------------------------|--------------------------------------------------------|----------|----------|----------|----------|---------------|-----------|
| emtricitabine+tenofovir                                | sofosbuvir+daclatasvir                                  | 0.65     | 0.26     | 1.63     | -5.04    | -10.63        | 8.97      | Low       |
| favipiravir                                            | sofosbuvir+daclatasvir                                  | 0.84     | 0.2      | 3.48     | -2.28    | -11.43        | 35.61     | Very low  |
| lopinavir+ritonavir                                    | sofosbuvir+daclatasvir                                  | 0.72     | 0.28     | 1.81     | -4.04    | -10.26        | 11.65     | Low       |
| lopinavir+ritonavir+ribavirin                          | sofosbuvir+daclatasvin                                  | 0.81     | 0.01     | 44.04    | -2.77    | -14.13        | 617.15    | Very low  |
| molnupiravir                                           | sofosbuvir+daclatasvin                                  | 0.17     | 0.04     | 0.62     | -11.95   | -13.7         | -5.46     | Moderate  |
| nirmatrelvir+ritonavir                                 | sofosbuvir+daclatasvin                                  | 0.11     | 0.01     | 1.1      | -12.77   | -14.18        | 1.48      | Low       |
| remdesivir                                            | sofosbuvir+daclatasvin                                  | 0.74     | 0.44     | 1.26     | -3.69    | -8.08         | 3.79      | Low       |
| ribavirin                                              | sofosbuvir+daclatasvin                                  | 0.78     | 0.01     | 42.75    | -3.12    | -14.13        | 598.57    | Very low  |
| ribavirin+sofosbuvir+daclatasir                       | sofosbuvir+daclatasvin                                  | 0.13     | 0.01     | 2.41     | -12.49   | -14.24        | 20.25     | Very low  |
| azvudine                                               | sofosbuvir+ledipasvin                                   | 1.05     | 0.02     | 68.76    | 0.63     | -12.44        | 856.93    | Very low  |
| emtricitabine+tenofovir                                | sofosbuvir+ledipasvin                                   | 0.75     | 0.13     | 4.4      | -3.12    | -11.02        | 43.01     | Very low  |
| favipiravir                                            | sofosbuvir+ledipasvin                                   | 0.98     | 0.12     | 7.75     | -0.29    | -11.09        | 85.42     | Very low  |
| lopinavir+ritonavir                                    | sofosbuvir+ledipasvin                                   | 0.83     | 0.14     | 4.96     | -2.1     | -10.88        | 50.14     | Very low  |
| lopinavir+ritonavir+ribavir                            | sofosbuvir+ledipasvin                                   | 0.94     | 0.01     | 67.71    | -0.8     | -12.48        | 843.74    | Very low  |
| molnupiravir                                           | sofosbuvir+ledipasvin                                   | 0.19     | 0.03     | 1.43     | -10.2    | -12.32        | 5.41      | Low       |
| nirmatrelvir+ritonavir                                 | sofosbuvir+ledipasvin                                   | 0.13     | 0.01     | 2        | -11.04   | -12.55        | 12.71     | Low       |
| remdesivir                                            | sofosbuvir+ledipasvin                                   | 0.86     | 0.17     | 4.26     | -1.74    | -10.44        | 41.28     | Very low  |
| resveratrol                                            | sofosbuvir+ledipasvin                                   | 1.05     | 0.02     | 69.58    | 0.63     | -12.45        | 867.35    | Very low  |
| ribavirin                                              | sofosbuvir+ledipasvin                                   | 0.91     | 0.01     | 65.72    | -1.15    | -12.49        | 818.52    | Very low  |
| Drug Combination                        | Triazavirin | Fimasvir | Ganciclovir | Lopinavir | Oseltamivir | Remdesivir | Resveratrol | Umifenovir | Verapamil | Zidovudine | Appendix 1, as submitted by the authors. Appendix to: Pitre T Van Alstine R, Chick G, et al. Antiviral drugs in nonsevere COVID-19: a systematic review and network meta-analysis. CMAJ 2022. doi: 10.1503/cmaj.220471. Copyright © 2022 The Author(s) or their employer(s). To receive this resource in an accessible format, please contact us at cmajgroup@cmaj.ca. |
| Drug Combination                          | Drug 2       | CR | MR | RR  | CI Lower Limit | CI Upper Limit | Absolute Risk per 1000 | GRADE Rating |
|------------------------------------------|--------------|----|----|-----|----------------|----------------|-------------------------|--------------|
| molnupiravir                             | umifenovir   | 0.23 | 0.02 | 2.87 | -7.24          | -9.24          | 17.58                   | Low          |
| nirmatrelvir+ritonavir                   | umifenovir   | 0.15 | 0.01 | 3.56 | -7.99          | -9.35          | 24.1                    | Very low     |
| remdesivir                              | umifenovir   | 1.03 | 0.11 | 9.43 | 0.27           | -8.36          | 79.38                   | Very low     |
| remdesivir                              | umifenovir   | 1.25 | 0.01 | 108.96 | 2.38        | -9.28          | 1016.05                 | Very low     |
| resveratrol                             | umifenovir   | 1.08 | 0.01 | 98.68 | 0.79           | -9.3           | 919.38                  | Very low     |
| ribavirin                               | umifenovir   | 0.18 | 0    | 6.77 | -7.73          | -9.37          | 54.27                   | Very low     |
| ribavirin+sofosbuvir+daclatasvir        | umifenovir   | 1.38 | 0.15 | 12.44 | 3.62           | -7.96          | 107.72                  | Very low     |
| sofosbuvir+ledipasvir                   | umifenovir   | 1.19 | 0.08 | 17.14 | 1.81           | -8.63          | 151.93                  | Very low     |
| triazavirin                             | umifenovir   | 0.42 | 0.01 | 19.27 | -5.48          | -9.33          | 171.94                  | Very low     |
| Hospitalization network                 |              |    |    |     |                |                |                         |              |
| Hospitalization network                 | Comparison   | Network estimate | Network estimate | Relative estimate | Absolute risk per 1000 | GRADE rating |              |
| Treatment 1                             | Treatment 2  |    |     |     |                |                |                         |              |
| emtricitabine+tenofovir                 | favipiravir  | 1.74 | 0.18 | 17.2  | 32.2           | -35.68         | 705.02                  | Very low     |
| emtricitabine+tenofovir                 | molnupiravir | 2.28 | 0.5  | 10.31 | 48.76          | -19.05         | 354.71                  | Very low     |
| emtricitabine+tenofovir                 | nirmatrelvir+ritonavir | 1.38 | 0.31 | 6.07  | 3.116          | -5.658         | 41.574                  | Moderate     |
| Drug Combination                  | Comparator     | RR      | 95% CI     | HR      | 95% CI     | p-value | Effect Size |
|----------------------------------|----------------|---------|------------|---------|------------|---------|-------------|
| emtricitabine+tenofovir          | placebo        | 1.38    | 0.31       | 6.07    | 20.67      | -37.54  | 275.81      | Very low   |
| emtricitabine+tenofovir          | remdesivir     | 4.9     | 0.83       | 28.87   | 59.397     | -2.5891 | 424.4601    | Very low   |
| emtricitabine+tenofovir          | resveratrol    | 4.14    | 0.28       | 60.14   | 56.206     | -12.888 | 1058.606    | Very low   |
| emtricitabine+tenofovir          | sofosbuvir+daclatasvir | 5.32 | 0.4       | 71.05   | 61.0848    | -8.484 | 990.507     | Low        |
| emtricitabine+tenofovir          | tenofovir      | 2.56    | 0.26       | 25.08   | 45.864     | -21.756 | 707.952     | Very low   |
| favipiravir                       | molnupiravir   | 1.31    | 0.22       | 7.75    | 11.81      | -29.72  | 257.17      | Low        |
| favipiravir                       | nirmatrelvir+ritonavir | 5.24 | 0.81       | 33.74   | 34.768     | -1.558  | 268.468     | Moderate   |
| favipiravir                       | placebo        | 0.8     | 0.14       | 4.58    | -10.88     | -46.78  | 194.75      | Very low   |
| favipiravir                       | remdesivir     | 2.82    | 0.38       | 20.97   | 27.7186    | -9.4426 | 304.1431    | Low        |
| favipiravir                       | resveratrol    | 2.39    | 0.14       | 40.62   | 24.881     | -15.394 | 709.198     | Low        |
| favipiravir                       | sofosbuvir+daclatasvir | 3.07 | 0.2       | 48.22   | 29.2698    | -11.312 | 667.6908    | Low        |
| favipiravir                       | tenofovir      | 1.47    | 0.08       | 26.21   | 13.818     | -27.048 | 741.174     | Very low   |
| molnupiravir                      | nirmatrelvir+ritonavir | 4.66 | 2.26      | 9.61    | 30.012     | 10.332  | 70.602      | High       |
| molnupiravir                      | placebo        | 0.7     | 0.5        | 1       | -16.32     | -27.2   | 0           | High       |
| molnupiravir                      | remdesivir     | 2.15    | 0.77       | 5.98    | 17.5145    | -3.5029 | 75.8454     | Low        |
| molnupiravir                      | resveratrol    | 1.82    | 0.19       | 17.24   | 14.678     | -14.499 | 290.696     | Low        |
| molnupiravir                      | sofosbuvir+daclatasvir | 2.34 | 0.27      | 20.02   | 18.9476    | -10.3222 | 268.9428    | Low        |
| molnupiravir                      | tenofovir      | 1.12    | 0.11       | 11.25   | 3.528      | -26.166 | 301.35      | Very low   |
| nirmatrelvir+ritonavir            | molnupiravir   | 0.27    | 0.14       | 0.52    | -27.8      | -32.77  | -18.29      | Moderate   |
| nirmatrelvir+ritonavir            | placebo        | 0.15    | 0.08       | 0.29    | -46.24     | -50.05  | -38.62      | High       |
| Drug Combination 1 | Drug Combination 2 | OR   | CI Lower | CI Upper | Absolute Risk Difference | Absolute Risk Ratio | Relative Risk Estimate | Absolute Risk Estimate |
|-------------------|-------------------|------|----------|----------|---------------------------|---------------------|-----------------------|-----------------------|
| nirmatrelvir+ritonavir | remdesivir        | 0.54 | 0.17     | 1.73     | -7.0058                   | -12.6409            | 11.1179               | Low                   |
| nirmatrelvir+ritonavir | resveratrol      | 0.46 | 0.04     | 4.62     | -9.666                    | -17.184             | 64.798                | Low                   |
| nirmatrelvir+ritonavir | sofosbuvir+daclatasvir | 0.59 | 0.06     | 5.39     | -5.7974                   | -13.2916            | 62.0746               | Low                   |
| nirmatrelvir+ritonavir | tenofovir        | 0.28 | 0.03     | 3.01     | -21.168                   | -28.518             | 59.094                | Very low              |
| remdesivir        | placebo           | 0.28 | 0.11     | 0.75     | -39.17                    | -48.42              | -13.6                 | Low                   |
| remdesivir        | resveratrol      | 0.85 | 0.07     | 9.64     | -2.685                    | -16.647             | 154.656               | Low                   |
| remdesivir        | sofosbuvir+daclatasvir | 1.09 | 0.1      | 11.28    | 1.2726                    | -12.726             | 145.3592              | Low                   |
| remdesivir        | tenofovir        | 0.52 | 0.04     | 6.26     | -14.112                   | -28.224             | 154.644               | Very low              |
| resveratrol       | placebo           | 0.33 | 0.04     | 3.1      | -36.45                    | -52.22              | 114.24                | Low                   |
| resveratrol       | sofosbuvir+daclatasvir | 1.29 | 0.06     | 27.99    | 4.1006                    | -13.2916            | 381.6386              | Low                   |
| resveratrol       | tenofovir        | 0.62 | 0.03     | 15.03    | -11.172                   | -28.518             | 412.482               | Very low              |
| sofosbuvir+daclatasvir | placebo      | 0.26 | 0.03     | 2.17     | -40.26                    | -52.77              | 63.65                 | Low                   |
| sofosbuvir+daclatasvir | tenofovir    | 0.48 | 0.02     | 10.89    | -15.288                   | -28.812             | 290.766               | Very low              |
| tenofovir        | placebo           | 0.54 | 0.05     | 5.29     | -25.02                    | -51.68              | 233.38                | Very low              |

**Mechanical ventilation network**

| Mechanical ventilation network | Comparison | Network estimate | Network estimate | Relative estimate | Absolute risk estimate |
|-------------------------------|------------|------------------|------------------|------------------|-----------------------|
|                               |            |                  |                  |                  |                       |
| Treatment 1  | Treatment 2                     | Point estimate | CI Lower limit | CI upper limit | Point estimate | CI Lower limit | CI upper limit | GRADE rating |
|-------------|--------------------------------|----------------|----------------|---------------|----------------|----------------|----------------|---------------|
| favipiravir | lopinavir+ritonavir            | 2.1366         | 0.605          | 7.545         | 16.2538        | -5.6485        | 93.5935        | Low           |
| favipiravir | molnupiravir                   | 3.2502         | 0.9934         | 10.6342       | 21.286892      | -0.062436      | 91.139532      | Low           |
| favipiravir | placebo                        | 1.3958         | 0.6127         | 3.1797        | 8.7076         | -8.5206        | 47.9534        | Low           |
| favipiravir | remdesivir                     | 3.0125         | 0.6991         | 12.9818       | 20.3665        | -3.06918       | 122.21436      | Low           |
| favipiravir | resveratrol                    | 1.3958         | 0.0259         | 75.1791       | 8.7076         | -21.4302       | 1631.9402      | Very low      |
| favipiravir | ribavirin+sofosbuvir+daclatasvir | 12.562         | 0.6359         | 248.1677      | 27.7488        | -0.87384       | 593.20248      | Very low      |
| favipiravir | sofosbuvir+daclatasvir         | 0.9288         | 0.311          | 2.7741        | -2.3496        | -22.737         | 58.5453        | Very low      |
| favipiravir | sofosbuvir+ledipasvir          | 1.9541         | 0.3743         | 10.2018       | 14.88396       | -9.76092       | 143.54808      | Very low      |
| lopinavir+ritonavir | molnupiravir  | 1.5212         | 0.4225         | 5.4773        | 4.930552       | -5.46315       | 42.355258      | Low           |
| lopinavir+ritonavir | placebo     | 0.6533         | 0.2511         | 1.6994        | -7.6274        | -16.4758       | 15.3868        | Low           |
| lopinavir+ritonavir | remdesivir  | 1.41           | 0.3024         | 6.5735        | 4.1492         | -7.11552       | 56.8497        | Moderate      |
| lopinavir+ritonavir | resveratrol  | 0.6533         | 0.0118         | 36.2406       | -7.6274        | -21.7404       | 775.2932       | Low           |
| lopinavir+ritonavir | ribavirin+sofosbuvir+daclatasvir | 5.8795         | 0.2861         | 120.81        | 11.7108        | -1.71336       | 287.544        | Low           |
| lopinavir+ritonavir | sofosbuvir+daclatasvir       | 0.4347         | 0.1313         | 1.4393        | -18.6549       | -28.6671       | 14.4969        | Low           |
| lopinavir+ritonavir | sofosbuvir+ledipasvir        | 0.9146         | 0.1633         | 5.1208        | -1.33224       | -13.05252      | 64.28448       | Very low      |
| molnupiravir | placebo                        | 0.4118         | 0.1719         | 0.9865        | -12.9404       | -18.2182       | -0.297         | Moderate      |
| molnupiravir | remdesivir                     | 2.1583         | 0.6457         | 7.2136        | 11.721996      | -3.61386       | 63.37872       | Moderate      |
| Treatment                                      | Comparator                  | Odds Ratio | 95% CI           | p Value   | ORI Score | Classification |
|------------------------------------------------|-----------------------------|------------|------------------|-----------|-----------|----------------|
| molnupiravir                                    | resveratrol                 | 0.4633     | 0.0078 - 27.4824 | -11.8074  | -21.8284  | Low            |
| molnupiravir                                    | ribavirin+sofosbuvir+daclatasvir | 3.8649     | 0.194 - 76.9865 | 6.8756    | -1.9344   | Low            |
| molnupiravir                                    | sofosbuvir+daclatasvir      | 0.2858     | 0.0936 - 0.8727  | -23.5686  | -29.9112  | High           |
| molnupiravir                                    | sofosbuvir+ledipasvir       | 0.6012     | 0.1135 - 3.1857  | -6.22128  | -13.8294  | Very low       |
| remdesivir                                      | placebo                     | 0.4633     | 0.0078 - 27.4824 | -11.8074  | -21.8284  | Low            |
| remdesivir                                      | resveratrol                 | 0.4633     | 0.0078 - 27.4824 | -11.8074  | -21.8284  | Low            |
| remdesivir                                      | ribavirin+sofosbuvir+daclatasvir | 4.17       | 0.1858 - 93.5995 | 7.608     | -1.95408  | Low            |
| remdesivir                                      | sofosbuvir+daclatasvir      | 0.3083     | 0.0756 - 1.2572  | -22.8261  | -30.5052  | Moderate       |
| remdesivir                                      | sofosbuvir+ledipasvir       | 0.6487     | 0.0996 - 4.2228  | -5.48028  | -14.04624 | Very low       |
| resveratrol                                     | placebo                     | 1          | 0.02032307 - 0.02032307 | 49.5049505 | 0         | -21.55488924 | Very low       |
| resveratrol                                     | ribavirin+sofosbuvir+daclatasvir | 9         | 0.0711 - 1139.5282 | 19.2     | -2.22936  | 2732.46768    | Low            |
| resveratrol                                     | sofosbuvir+daclatasvir      | 0.6654     | 0.0126 - 35.1343 | -11.0418  | -32.5842  | Low            |
| resveratrol                                     | sofosbuvir+ledipasvir       | 1.4        | 0.022 - 89.2852  | 6.24      | -15.2568  | 1377.24912    | Very low       |
| ribavirin+sofosbuvir+daclatasvir                | placebo                     | 0.11111111 | 0.006315176 - 0.006315176 | 1.955034213 | 0         | -19.55555555 | 21.01075269  | Low            |
| ribavirin+sofosbuvir+daclatasvir                | sofosbuvir+daclatasvir      | 0.0739     | 0.0038 - 1.4222  | -30.5613  | -32.8746  | 13.9326       | Low            |
| ribavirin+sofosbuvir+daclatasvir                | sofosbuvir+ledipasvir       | 0.1556     | 0.0063 - 3.8379  | -13.17264 | -15.50172 | 44.27124      | Very low       |
| ribavirin+sofosbuvir+daclatasvir                | placebo                     | 1.50285542 | 0.730994152 - 1.50285542 | 3.089280198 | 11.0628193 | 5.918128655  | Moderate      |
| sofosbuvir+daclatasvir                          | placebo                     | 2.1039     | 0.4231 - 10.462  | 17.22084  | -8.99964  | 147.6072      | Low            |
| Treatment               | Placebo | OR (95% CI) | p-Value | Hedges' g (95% CI) | Publication Bias | Risk of Bias |
|-------------------------|---------|-------------|---------|--------------------|------------------|--------------|
| Sofosbuvir+ledipasvir   | placebo | 0.714285714 | 3       | 0.170430336        | 2.994011976      | -3.285714285 | -18.235053259 | 43.86826347 | Very low |

Appendix 1, as submitted by the authors. Appendix to: Pitre T Van Alstine R, Chick G, et al. Antiviral drugs in nonsevere COVID-19: a systematic review and network meta-analysis. CMAJ 2022. doi: 10.1503/cmaj.220471. Copyright © 2022 The Author(s) or their employer(s). To receive this resource in an accessible format, please contact us at cmajgroup@cmaj.ca.
## Adverse events leading to drug discontinuation

| Adverse events leading to drug discontinuation | Comparison | Network estimate | Network estimate | Relative estimate | Absolute risk | \( \text{CI Lower limit} \) | \( \text{CI upper limit} \) | \( \text{CI Lower limit} \) | \( \text{CI upper limit} \) | \( \text{GRADE rating} \) |
|----------------------------------------------|------------|-----------------|-----------------|-----------------|--------------|----------------|----------------|----------------|----------------|----------------|
| Treatment 1                                  | Treatment 2| Point estimate  | CI Lower limit  | CI upper limit  |              |                |                |                |                |                |
| azvudine                                     | placebo    | 0               | -3.8255         | 3.8255          |              | 0              | -38.255         | 38.255          | Low            |
| azvudine                                     | emtricitabine+tenofovir | -1.9459       | -6.7587         | 2.8669          | -19.459      | -67.587        | 28.669          | very low        |
| azvudine                                     | favipiravir | -0.6381        | -4.662          | 3.3858          | -6.381       | -46.62         | 33.858          | very low        |
| azvudine                                     | lopinavir+ritonavir | -0.029         | -5.1109         | 5.0529          | -0.29        | -51.109        | 50.529          | very low        |
| azvudine                                     | lopinavir+ritonavir+ribavirin | -0.5522       | -5.7162         | 4.6117          | -5.522       | -57.162        | 46.117          | very low        |
| azvudine                                     | molnupiravir | 0.4456         | -3.4365         | 4.3277          | 4.456        | -34.365        | 43.277          | very low        |
| azvudine                                     | nirmatrelvir+ritonavir | 0.9535        | -2.9012         | 4.8081          | 9.535        | -29.012        | 48.081          | very low        |
| azvudine                                     | novaferon   | 0.7183         | -4.7413         | 6.1778          | 7.183        | -47.413        | 61.778          | very low        |
| azvudine                                     | remdesivir  | -0.2829        | -4.275          | 3.7092          | -2.829       | -42.75         | 37.092          | very low        |
| azvudine                                     | ribavirin   | 0.0663         | -5.1309         | 5.2636          | 0.663        | -51.309        | 52.636          | very low        |
| azvudine                                     | ribavirin+sofosbuvir+daclatasvir | 0             | -5.4485         | 5.4485          | 0            | -54.485        | 54.485          | very low        |
| azvudine                                     | sofosbuvir+daclatasvir | -0.0018       | -4.1468         | 4.1431          | -0.018       | -41.468        | 41.431          | very low        |
| azvudine                                     | sofosbuvir+ledipasvir | 0.0482        | -5.4121         | 5.5085          | 0.482        | -54.121        | 55.085          | very low        |
| azvudine                                     | triazavirin | -1.0986        | -6.0573         | 3.86            | -10.986      | -60.573        | 38.6            | very low        |
| Drug Combination                        | Substances                          | IC50 Values       | Outcome 1 | Outcome 2 | Outcome 3 | Outcome 4 | Outcome 5 | Outcome 6 |
|----------------------------------------|-------------------------------------|------------------|-----------|-----------|-----------|-----------|-----------|-----------|
| azvudine + umifenovir                  |                                    | 0.7073           | -4.7399   | 6.1546    | 7.073     | -47.399   | 61.546    | very low  |
| emtricitabine + tenofovir             | favipiravir                         | 1.3078           | -1.8681   | 4.4837    | 13.078    | -18.681   | 44.837    | Low       |
| emtricitabine + tenofovir             | lopinavir + ritonavir               | 1.9169           | -2.5238   | 6.3577    | 19.169    | -25.238   | 63.577    | very low  |
| emtricitabine + tenofovir             | lopinavir + ritonavir + ribavirin  | 1.3937           | -3.1407   | 5.9281    | 13.937    | -31.407   | 59.281    | very low  |
| emtricitabine + tenofovir             | molnupiravir                        | 2.3916           | -0.6026   | 5.3857    | 23.916    | -6.026    | 53.857    | Low       |
| emtricitabine + tenofovir             | nirmatrelvir + ritonavir            | 2.8994           | -0.0591   | 5.8579    | 28.994    | 0.591     | 58.579    | Low       |
| emtricitabine + tenofovir             | novaferon                           | 2.6642           | -2.2042   | 7.5325    | 26.642    | -22.042   | 75.325    | very low  |
| emtricitabine + tenofovir             | placebo                             | 1.9459           | -0.9745   | 4.8663    | 19.459    | -9.745    | 48.663    | Low       |
| emtricitabine + tenofovir             | remdesivir                          | 1.663            | -1.4725   | 4.7985    | 16.63     | -14.725   | 47.985    | Low       |
| emtricitabine + tenofovir             | ribavirin                           | 2.0122           | -2.5601   | 6.5845    | 20.122    | -25.601   | 65.845    | very low  |
| emtricitabine + tenofovir             | ribavirin + sofosbuvir + daclatasvir| 1.9459           | -2.9101   | 6.8019    | 19.459    | -29.101   | 68.019    | very low  |
| emtricitabine + tenofovir             | sofosbuvir + daclatasvir            | 1.9441           | -1.3839   | 5.272     | 19.441    | -13.839   | 52.72     | Low       |
| emtricitabine + tenofovir             | sofosbuvir + ledipasvir             | 1.9941           | -2.8751   | 6.8633    | 19.941    | -28.751   | 68.633    | very low  |
| emtricitabine + tenofovir             | triazavirin                         | 0.8473           | -3.4518   | 5.1464    | 8.473     | -34.518   | 51.464    | very low  |
| emtricitabine + tenofovir             | umifenovir                          | 2.6532           | -2.2013   | 7.5078    | 26.532    | -22.013   | 75.078    | very low  |
| favipiravir                            | placebo                             | 0.6381           | -0.61     | 1.8863    | 6.381     | -6.1      | 18.863    | Low       |
| favipiravir                            | lopinavir + ritonavir               | 0.6091           | -2.9616   | 4.1798    | 6.091     | -29.616   | 41.798    | very low  |
| favipiravir                            | lopinavir + ritonavir + ribavirin   | 0.0859           | -3.6006   | 3.7723    | 0.859     | -36.006   | 37.723    | very low  |
| favipiravir                            | molnupiravir                        | 1.0838           | -0.3285   | 2.496     | 10.838    | -3.285    | 24.96     | very low  |
| favipiravir                            | nirmatrelvir + ritonavir            | 1.5916           | 0.2566    | 2.9265    | 15.916    | 2.566     | 29.265    | Low       |
| Drug Combination          | Antiviral | Lower CI | Upper CI | Lower CI | Upper CI | Lower CI | Upper CI | Effect Size |
|--------------------------|-----------|----------|----------|----------|----------|----------|----------|-------------|
| favipiravir              | novaferon | 1.3564   | -2.7339  | 5.4466   | 13.564   | -27.339  | 54.466   | very low    |
| favipiravir              | remdesivir| 0.3552   | -1.3362  | 2.0465   | 3.552    | -13.362  | 20.465   | Very low    |
| favipiravir              | ribavirin | 0.7044   | -3.0286  | 4.4374   | 7.044    | -30.286  | 44.374   | very low    |
| favipiravir              | ribavirin+sofosbuvir+daclatasvir | 0.6381 | -3.4374  | 4.7137   | 6.381    | -34.374  | 47.137   | very low    |
| favipiravir              | sofosbuvir+daclatasvir | 0.6363 | -1.3897  | 2.6623   | 6.363    | -13.897  | 26.623   | Very low    |
| favipiravir              | sofosbuvir+ledipasvir | 0.6863 | -3.405   | 4.7776   | 6.863    | -34.05   | 47.776   | very low    |
| favipiravir              | triazavirin | -0.4605 | -3.8534  | 2.9324   | -4.605   | -38.534  | 29.324   | very low    |
| favipiravir              | umifenovir | 1.3454 | -2.7284  | 5.4193   | 13.454   | -27.284  | 54.193   | very low    |
| lopinavir+ritonavir      | lopinavir+ritonavir+ribavirin | -0.5232 | -1.4399  | 0.3934   | -5.232   | -14.399  | 3.934    | Moderate    |
| lopinavir+ritonavir      | ribavirin | 0.0953   | -0.9935  | 1.1841   | 0.953    | -9.935   | 11.841   | Moderate    |
| lopinavir+ritonavir      | umifenovir | 0.7363 | -2.6257  | 4.0983   | 7.363    | -26.257  | 40.983   | Low         |
| lopinavir+ritonavir      | molnupiravir | 0.4746 | -2.9354  | 3.8847   | 4.746    | -29.354  | 38.847   | very low    |
| lopinavir+ritonavir      | nirmatrelvir+ritonavir | 0.9824 | -2.3963  | 4.3612   | 9.824    | -23.963  | 43.612   | very low    |
| lopinavir+ritonavir      | novaferon | 0.7472 | -4.3873  | 5.8818   | 7.472    | -43.873  | 58.818   | very low    |
| lopinavir+ritonavir      | placebo   | 0.029    | -3.3164  | 3.3744   | 0.29     | -33.164  | 33.744   | very low    |
| lopinavir+ritonavir      | remdesivir | -0.254  | -3.7887  | 3.2808   | -2.54    | -37.887  | 32.808   | very low    |
| lopinavir+ritonavir      | ribavirin+sofosbuvir+daclatasvir | 0.029  | -5.039   | 5.1519   | 0.29     | -50.39   | 51.519   | very low    |
| lopinavir+ritonavir      | sofosbuvir+daclatasvir | 0.0271 | -3.6794  | 3.7337   | 0.271    | -36.794  | 37.337   | very low    |
| lopinavir+ritonavir      | sofosbuvir+ledipasvir | 0.0772 | -5.0582  | 5.2126   | 0.772    | -50.582  | 52.126   | very low    |
| lopinavir+ritonavir      | triazavirin | -1.0696 | -5.6681  | 3.5288   | -10.696  | -56.681  | 35.288   | very low    |
| Drug Combination                              | Treatment  | OD      | PD      | Emax   | IC50    | Effect   |
|----------------------------------------------|------------|---------|---------|--------|---------|----------|
| lopinavir+ritonavir+ribavirin                | ribavirin  | 0.6186  | -0.3606 | 1.5977 | 6.186   | -3.606   | 15.977   | Moderate |
| lopinavir+ritonavir+ribavirin                | molnupiravir | 0.9979  | -2.5332 | 4.529  | 9.979   | -25.332  | 45.29    | very low |
| lopinavir+ritonavir+ribavirin                | nirmatrelvir+ritonavir | 1.5057  | -1.9952 | 5.0066 | 15.057  | -19.952  | 50.066   | Low      |
| lopinavir+ritonavir+ribavirin                | novaferon  | 1.2705  | -3.9453 | 6.4863 | 12.705  | -39.453  | 64.863   | very low |
| lopinavir+ritonavir+ribavirin                | placebo    | 0.5522  | -2.9165 | 4.021  | 5.522   | -29.165  | 40.21    | very low |
| lopinavir+ritonavir+ribavirin                | remdesivir | 0.2693  | -3.3824 | 3.921  | 2.693   | -33.824  | 39.21    | very low |
| lopinavir+ritonavir+ribavirin                | ribavirin+sofosbuvir+daclatasvir | 0.5522 | -4.652 | 5.7565 | 5.522 | -46.52 | 57.565 | very low |
| lopinavir+ritonavir+ribavirin                | sofosbuvir+daclatasvir | 0.5504 | -3.2679 | 4.3686 | 5.504 | -32.679 | 43.686 | very low |
| lopinavir+ritonavir+ribavirin                | sofosbuvir+ledipasvir | 0.6004 | -4.6162 | 5.817 | 6.004 | -46.162 | 58.17 | very low |
| lopinavir+ritonavir+ribavirin                | triazavirin | -0.5464 | -5.2353 | 4.1426 | -5.464 | -52.353 | 41.426 | very low |
| lopinavir+ritonavir+ribavirin                | umifenovir | 1.2596  | -2.2252 | 4.7443 | 12.596  | -22.252 | 47.443   | very low |
| molnupiravir                                 | placebo    | -0.5835 | -1.2816 | 0.1147 | -5.835  | -12.816  | 1.147    | Moderate |
| molnupiravir                                 | nirmatrelvir+ritonavir | 0.3687  | -0.4746 | 1.2119 | 3.687   | -4.746   | 12.119   | Moderate |
| molnupiravir                                 | novaferon  | 0.2726  | -3.6782 | 4.2234 | 2.726   | -36.782  | 42.234   | very low |
| molnupiravir                                 | remdesivir | -0.7286 | -2.0474 | 0.5902 | -7.286  | -20.474  | 5.902    | Low      |
| molnupiravir                                 | ribavirin  | -0.3793 | -3.959 | 3.2003 | -3.793  | -39.59   | 32.003   | very low |
| molnupiravir                                 | ribavirin+sofosbuvir+daclatasvir | -0.4456 | -4.3812 | 3.4899 | -4.456 | -43.812 | 34.899 | very low |
| molnupiravir                                 | sofosbuvir+daclatasvir | -0.4475 | -2.1747 | 1.2797 | -4.757 | -21.747 | 12.797 | Low      |
| molnupiravir                                 | sofosbuvir+ledipasvir | -0.3974 | -4.3493 | 3.5544 | -3.974 | -43.493 | 35.544 | very low |
| molnupiravir                                 | triazavirin | -1.5443 | -4.7677 | 1.6792 | -15.443 | -47.677 | 16.792 | Low      |
| Combination                        | Drug          | Odds Ratio (95% CI) | Effect Size | Lower 95% CI | Upper 95% CI |刊名 | Effect Size |
|-----------------------------------|---------------|---------------------|-------------|--------------|--------------|-----|-------------|
| molnupiravir                       | umifenovir    | 0.2617 - 3.6721     | 4.1955      | 2.617        | -36.721      | 41.955 | very low    |
| nirmatrelvir+ritonavir             | novaferon     | -0.2352 - 3.6886    | 3.6886      | -2.352       | -41.59       | 36.868 | very low    |
| nirmatrelvir+ritonavir             | placebo       | -0.9535 - 4.1592    | 4.1592      | -2.871       | -44.37       | 26.627 | very low    |
| nirmatrelvir+ritonavir             | remdesivir    | -1.2364 - 3.6007    | 3.6007      | -12.364      | -24.721      | -0.007 | Moderate    |
| nirmatrelvir+ritonavir             | ribavirin     | -0.8871 - 4.437     | 2.6627      | -8.871       | -44.37       | 26.627 | very low    |
| nirmatrelvir+ritonavir             | ribavirin+sofosbuvir+daclatasvir | -0.9535 - 4.862 | 2.955 | -9.535 | -48.62 | 29.55 | very low |
| nirmatrelvir+ritonavir             | sofosbuvir+daclatasvir | -0.9535 - 2.6199 | 0.7093 | -9.535 | -26.199 | 7.093 | Low |
| nirmatrelvir+ritonavir             | sofosbuvir+ledipasvir | -0.9053 - 4.8301 | 3.0196 | -9.053 | -48.301 | 30.196 | very low |
| nirmatrelvir+ritonavir             | triazavirin   | -2.0521 - 5.2424    | 1.1382      | -20.521      | -52.424      | 11.382 | Low |
| nirmatrelvir+ritonavir             | umifenovir    | -0.2461 - 4.1528    | 3.6606      | -2.461       | -41.528      | 36.606 | very low    |
| novaferon                          | placebo       | -0.7183 - 4.6134    | 3.1769      | -7.183       | -46.134      | 31.769 | very low    |
| novaferon                          | remdesivir    | -1.0012 - 5.0601    | 3.0577      | -10.012      | -50.601      | 30.577 | very low    |
| novaferon                          | ribavirin     | -0.6519 - 5.9007    | 4.5968      | -6.519       | -59.007      | 45.968 | very low    |
| novaferon                          | ribavirin+sofosbuvir+daclatasvir | -0.7183 - 6.2159 | 4.7794 | -7.183 | -62.159 | 47.794 | very low |
| novaferon                          | sofosbuvir+daclatasvir | -0.7201 - 4.9295 | 3.4893 | -7.201 | -49.295 | 34.893 | very low |
| novaferon                          | sofosbuvir+ledipasvir | -0.6701 - 6.1794 | 4.8393 | -6.701 | -61.794 | 48.393 | very low |
| novaferon                          | triazavirin   | -1.8169 - 6.8295    | 3.1957      | -18.169      | -68.295      | 31.957 | very low    |
| novaferon                          | umifenovir    | -0.0109 - 5.5073    | 5.4855      | -0.109       | -55.073      | 54.855 | very low    |
| remdesivir                         | placebo       | 2.829 - 8.584       | 14.243      | 28.29        | -85.84       | 142.43 | very low    |
| remdesivir                         | ribavirin     | 0.3493 - 3.3494     | 4.0479      | 3.493        | -33.494      | 40.479 | very low    |
| Drug Combination                  | Placebo | Remdesivir | Ribavirin | Sofosbuvir + Daclatasvir | Sofosbuvir + Ledipasvir | Triazavirin | Umifenovir | Ribavirin | Triazavirin | Umifenovir |
|----------------------------------|---------|------------|-----------|--------------------------|--------------------------|-------------|------------|-----------|-------------|------------|
| Remdesivir                       | -3.7612| 4.3271     | 2.829     | -37.612                  | 22.431                   | -41.708     | 25.394     | -16.809   | -58.905     | 35.607     |
| Ribavirin + Sofosbuvir + Daclatasvir | 0       | 0.2829     | -1.6809   | 2.2431                   | 2.811                    | -8.157      | 2.5394     | 4.3271    | -5.8905     | 7.073      |
| Ribavirin + Ledipasvir           | -3.7288| 4.3911     | 3.311     | -37.288                  | 43.911                   | -10.986     | 6.1928     | 7.073     | -47.781     | 61.928     |
| Triazavirin                      | -4.1708| 2.5394     | -8.157    | -41.708                  | 25.394                   | -60.992     | 39.02      | -10.986   | -47.781     | 61.928     |
| Umifenovir                       | 2.829   | 5.0327     | 9.903     | -30.521                  | 50.327                   | 61.928      | 7.073      | -47.781   | 61.928      | 7.073      |
| Ribavirin + Placebo              | 38.797  | 38.797     | 0         | -38.797                  | 38.797                   | 0           | 0          | -38.797   | 0           | 38.797     |
| Ribavirin + Sofosbuvir + Daclatasvir | 0.0018  | -4.197     | 4.1933    | -0.018                   | 41.933                   | -60.992     | 39.02      | -10.986   | -47.781     | 61.928     |
| Ribavirin + Ledipasvir           | 0.0482  | -5.4502    | 5.5466    | 0.482                    | 55.466                   | 61.928      | 7.073      | -47.781   | 61.928      | 7.073      |
| Triazavirin                      | -1.0986| 3.902      | -10.986   | -60.992                  | 39.02                    | -12.063     | 4.2604     | -41.603   | 42.604      | 24.389     |
| Umifenovir                       | 0.7073  | 6.1928     | 7.073     | -47.781                  | 61.928                   | 61.928      | 7.073      | -47.781   | 61.928      | 7.073      |
| Sofosbuvir + Daclatasvir         | 0.018   | 15.94      | 15.977    | 0.18                     | 159.4                    | -12.063     | 4.2604     | -41.603   | 42.604      | 24.389     |
| Sofosbuvir + Ledipasvir          | 0.05    | -4.1603    | 4.2604    | 0.5                      | -41.603                  | 42.604      | 24.389     | -46.324   | 24.389      | 24.389     |
| Triazavirin                      | -1.0968| -4.6324    | 2.4389    | -10.968                  | -46.324                  | 24.389      | 24.389     | 24.389    | 24.389      | 24.389     |
| Combination                     | Drug             | OR   | 95% CI   | OR   | 95% CI   | OR   | 95% CI   | Risk   |
|--------------------------------|------------------|------|----------|------|----------|------|----------|--------|
| sofosbuvir+daclatasvir          | umifenovir       | 0.7092 | -3.4843 | 4.9026 | 7.092 | -34.843 | 49.026 | very low |
| sofosbuvir+ledipasvir           | placebo          | -0.482 | -39.444 | 38.48 | -4.82 | -394.44 | 384.8 | very low |
| sofosbuvir+ledipasvir           | triazavirin      | -1.1468 | -6.1603 | 3.8666 | -11.468 | -61.603 | 38.666 | very low |
| sofosbuvir+ledipasvir           | umifenovir       | 0.6591 | -4.838 | 6.1563 | 6.591 | -48.38 | 61.563 | very low |
| triazavirin                     | placebo          | 10.986 | -20.564 | 42.536 | 109.86 | -205.64 | 425.36 | very low |
| triazavirin                     | umifenovir       | 1.8059 | -3.1933 | 6.8052 | 18.059 | -31.933 | 68.052 | very low |
| umifenovir                      | placebo          | -7.073 | -45.852 | 31.706 | -70.73 | -458.52 | 317.06 | very low |
Supplement 10. Heterogeneity estimates

Mortality

Number of studies: \( k = 32 \)
Number of pairwise comparisons: \( m = 36 \)
Number of treatments: \( n = 16 \)
Number of designs: \( d = 17 \)

Random effects model

Quantifying heterogeneity / inconsistency:
\( \tau^2 = 0; \tau = 0 \); \( I^2 = 0\% [0.0\%; 48.0\%] \)

Tests of heterogeneity (within designs) and inconsistency
(between designs):
\[
\begin{array}{cccc}
Q & \text{d.f.} & \text{p-value} \\
\hline
\text{Total} & 6.07 & 19 & 0.9978 \\
\text{Within designs} & 5.97 & 15 & 0.9802 \\
\text{Between designs} & 0.10 & 4 & 0.9988 \\
\end{array}
\]

Hospitalizations

Number of studies: \( k = 10 \)
Number of pairwise comparisons: \( m = 12 \)
Number of treatments: \( n = 9 \)
Number of designs: \( d = 8 \)
Random effects model

Quantifying heterogeneity / inconsistency:
\( \tau^2 = 0; \tau = 0; I^2 = 0\% \ [0.0\%; 84.7\%] \)

Tests of heterogeneity (within designs) and inconsistency (between designs):
\[
\begin{array}{ccc}
\text{Q} & \text{d.f.} & \text{p-value} \\
\text{Total} & 1.61 & 3 \quad 0.6572 \\
\text{Within designs} & 1.45 & 2 \quad 0.4843 \\
\text{Between designs} & 0.16 & 1 \quad 0.6893 \\
\end{array}
\]

**Mechanical ventilation**

Number of studies: \( k = 14 \)
Number of pairwise comparisons: \( m = 14 \)
Number of treatments: \( n = 9 \)
Number of designs: \( d = 8 \)

Random effects model

Quantifying heterogeneity / inconsistency:
\( \tau^2 = 0; \tau = 0; I^2 = 0\% \ [0.0\%; 70.8\%] \)

Tests of heterogeneity (within designs) and inconsistency (between designs):
\[
\begin{array}{ccc}
\text{Q} & \text{d.f.} & \text{p-value} \\
\text{Total} & 3.2 & 6 \quad 0.7836 \\
\text{Within designs} & 3.2 & 6 \quad 0.7836 \\
\end{array}
\]
Adverse events leading to drug discontinuation

Number of studies: $k = 22$
Number of pairwise comparisons: $m = 26$
Number of treatments: $n = 16$
Number of designs: $d = 13$

Random effects model

Quantifying heterogeneity / inconsistency:
$\tau^2 = 0; \tau = 0; I^2 = 0\% [0.0\%; 62.4\%]$

Tests of heterogeneity (within designs) and inconsistency (between designs):

| Q  | d.f. | p-value |
|----|------|---------|
| Total | 7.68 | 9 | 0.5671 |
| Within designs | 7.68 | 9 | 0.5671 |
| Between designs | 0.00 | 0 | -- |

Supplement 11. Subgroup analysis

Mortality subgroups
Remdesivir - risk of bias
### Molnupiravir - risk of bias

| Study            | Remdesivir | Standard care/placebo | Risk ratio with 95% CI | Weight (%) |
|------------------|------------|-----------------------|------------------------|------------|
| **Low risk of bias** |            |                       |                        |            |
| Ali              | Yes        | 5                     | 54                     | 35         | 0.51 [0.17, 1.49] | 15.65 |
| Beigel           | Yes        | 3                     | 72                     | 60         | 0.84 [0.18, 4.02] | 7.42  |
| Gottlieb_2       | Yes        | 0                     | 279                    | 0          | 1.01 [0.02, 50.94] | 1.18  |
| Pan_remdesivir   | Yes        | 11                    | 650                    | 13         | 0.85 [0.38, 1.88] | 26.69 |
| Wang_1           | Yes        | 22                    | 136                    | 10         | 1.09 [0.54, 2.18] | 37.44 |
| **Heterogeneity:** \( \tau^2 = 0.00 \), \( \tau^2 = 0.00\% \), \( H^2 = 1.00 \) |            |                       |                        |            |
| **Test of \( Q = 9 \):** Q(4) = 1.35, p = 0.85 |            |                       |                        |            |
| **High risk of bias** |            |                       |                        |            |
| Criner           | Yes        | 4                     | 380                    | 4          | 0.52 [0.13, 2.06] | 9.60  |
| **Heterogeneity:** \( \tau^2 = 0.00 \), \( \tau^2 = .\%) \), \( H^2 = .\) |            |                       |                        |            |
| **Test of \( Q = 9 \):** Q(0) = 0.00, p = . |            |                       |                        |            |
| **Overall**      |            |                       |                        |            |
| **Heterogeneity:** \( \tau^2 = 0.00 \), \( \tau^2 = 0.00\% \), \( H^2 = 1.00 \) |            |                       |                        |            |
| **Test of \( Q = 9 \):** Q(5) = 1.82, p = 0.87 |            |                       |                        |            |
| **Test of group differences:** Q(1) = 0.47, p = 0.49 |            |                       |                        |            |

Random-effects REML model
### Adverse events leading to drug discontinuation subgroups

| Study     | Molnupiravir | Standard care/placebo | Risk ratio with 95% CI | Weight (%) |
|-----------|--------------|-----------------------|------------------------|------------|
| Low risk of bias |               |                       |                        |            |
| Bernal    | Yes          | No                    | 0.16 [0.04, 0.73]      | 72.83      |
| Fischer   | 0            | 140                   | 0.15 [0.01, 3.61]      | 15.99      |
| Heterogeneity: $\hat{I}^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$ | | | | |
| Test of $\theta = 0$: $Q(1) = 0.00$, $p = 0.96$ | | | | |
| High risk of bias | | | | |
| Khoo      | Yes          | No                    | 0.54 [0.01, 24.33]     | 11.18      |
| Heterogeneity: $\hat{I}^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$ | | | | |
| Test of $\theta = 0$: $Q(0) = 0.00$, $p = 0.8$ | | | | |
| Overall   |              |                       | 0.18 [0.05, 0.66]      |            |
| Heterogeneity: $\hat{I}^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$ | | | | |
| Test of $\theta = 0$: $Q(2) = 0.34$, $p = 0.84$ | | | | |
| Test of group differences: $Q_{1}(1) = 0.34$, $p = 0.56$ | | | | |

Random-effects REML model
Molnupiravir - risk of bias

| Study | Molnupiravir | Standard care/placebo | Risk ratio | Weight |
|-------|--------------|-----------------------|------------|--------|
| Low risk of bias | Yes | No | Yes | No | with 95% CI | (%) |
| Bernal | 10 | 706 | 20 | 697 | 0.50 [0.24, 1.06] | 86.22 |
| Fischer | 2 | 138 | 1 | 61 | 0.89 [0.08, 9.59] | 8.59 |
| Heterogeneity: $I^2 = 0.00, H^2 = 1.00$ | 0.53 [0.26, 1.08] |
| Test of $9_1 = 6_1$, Q(1) = 0.20, p = 0.65 |
| High risk of bias | 1 | 11 | 0 | 6 | 1.62 [0.08, 34.66] | 5.19 |
| Khoo | Heterogeneity: $I^2 = 0.00, H^2 = 1.00$ | 1.62 [0.08, 34.66] |
| Test of $9_1 = 6_1$, Q(0) = 0.00, p = |
| Overall | Heterogeneity: $I^2 = 0.00, H^2 = 1.00$ | 0.56 [0.28, 1.12] |
| Test of $9_1 = 6_1$, Q(2) = 0.69, p = 0.71 |
| Test of group differences: Q₈(1) = 0.49, p = 0.49 |

Random-effects REML model
### Remdesivir - risk of bias

| Study       | Remdesivir | Standard care/placebo | Risk ratio (95% CI) | Weight (%) |
|-------------|------------|-----------------------|---------------------|------------|
|             | Yes No     | Yes No                |                     |            |
| Low risk of bias |            |                       |                     |            |
| Beigel      | 3 52 1 48  |                       | 2.67 [0.29, 24.86]  | 32.84      |
| Gottlieb_2  | 2 277 5 278 |                       | 0.41 [0.08, 2.07]   | 41.20      |
| Heterogeneity: \(i^2 = 0.78\), \(I^2 = 44.07\%\), \(H^2 = 1.79\) | |                       | 0.89 [0.14, 5.48]   |            |
| Test of \(\theta_1 = \theta_2\); \(Q(1) = 1.79\), \(p = 0.18\) | |                       |                     |            |
| High risk of bias |            |                       |                     |            |
| Criner      | 11 373 0 200 |                       | 12.01 [0.71, 202.72] | 25.97      |
| Heterogeneity: \(i^2 = 0.00\), \(I^2 = .\), \(H^2 = .\) | |                       | 12.01 [0.71, 202.72] |            |
| Test of \(\theta_1 = \theta_2\); \(Q(0) = 0.00\), \(p = .\) | |                       |                     |            |
| Overall     |            |                       | 1.82 [0.26, 12.56]  |            |
| Heterogeneity: \(i^2 = 1.67\), \(I^2 = 57.46\%\), \(H^2 = 2.35\) | |                       |                     |            |
| Test of \(\theta_1 = \theta_2\); \(Q(2) = 4.73\), \(p = 0.09\) | |                       |                     |            |
| Test of group differences: \(Q(1) = 2.31\), \(p = 0.13\) | |                       |                     |            |

Random-effects REML model
Supplement 12. Pairwise forest plots for each outcome.

### Mortality pairwise comparisons

| Study | TE vs TE | Risk Ratio | SE | 95% CI  |
|-------|---------|------------|----|---------|
| Deral | 0.92   | 0.0006  | 0.08| [0.87, 0.97] |
| Epravir vs placebo | 0.92 | 0.0006 | 0.08 | [0.87, 0.97] |
| Cobicistat | 0.92 | 0.0006 | 0.08 | [0.87, 0.97] |
| Vela + lopinavir | 0.92 | 0.0006 | 0.08 | [0.87, 0.97] |

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Hospitalization pairwise comparisons

| Study                        | TE    | seTE  | Risk Ratio | RR    | 95%-Ci       |
|------------------------------|-------|-------|------------|-------|--------------|
| emtricitabine+tenofovir vs placebo | 0.08  | 0.9743| 1.08 [0.16; 7.28] |       |              |
| Arruda                       | 0.69  | 1.1972| 2.00 [0.19; 20.90] |       |              |
| Parenti                      | 1.38  | [0.31; 6.07] |       |              |
| Random effects model         |       |       |            |       |              |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.69$ |       |       |            |       |              |
| emtricitabine+tenofovir vs tenofovir | 0.82  | 1.2043| 2.26 [0.21; 23.98] |       |              |
| Arruda                       |       |       |            |       |              |
| tenofovir vs placebo         | -0.74 | 1.2051| 0.48 [0.04; 5.06] |       |              |
| Arruda                       |       |       |            |       |              |
| molnupiravir vs placebo      | -0.36 | 0.1808| 0.70 [0.49; 0.99] |       |              |
| Bemal                        |       |       |            |       |              |
| Fischer                      | 0.28  | 1.1446| 1.33 [0.14; 12.52] |       |              |
| Random effects model         |       |       |            |       |              |
| Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.58$ |       |       |            |       |              |
| nirmatrelvir+ritonavir vs placebo | -2.00 | 0.3525| 0.14 [0.07; 0.27] |       |              |
| EPICH                        |       |       |            |       |              |
| EPICS                        | -1.21 | 0.6547| 0.30 [0.08; 1.08] |       |              |
| Random effects model         |       |       |            |       |              |
| Heterogeneity: $I^2 = 12\%$, $\tau^2 = 0.0383$, $p = 0.29$ |       |       |            |       |              |
| remdesivir vs placebo        | -1.27 | 0.4984| 0.28 [0.11; 0.75] |       |              |
| Gottlieb_2                   |       |       |            |       |              |
| resveratrol vs placebo       | -1.10 | 1.1372| 0.33 [0.04; 3.10] |       |              |
| McCreary                     |       |       |            |       |              |
| sofosbuvir+daclatasvir vs placebo | -1.35 | 1.0850| 0.26 [0.03; 2.17] |       |              |
| Roozbeh                      |       |       |            |       |              |
| favipiravir vs placebo       | -0.23 | 0.8936| 0.80 [0.14; 4.58] |       |              |
| Ruzhentsova                  |       |       |            |       |              |
Mechanical ventilation pairwise comparisons

| Study                              | TE   | seTE  | Risk Ratio | RR   | 95%-CI  |
|------------------------------------|------|-------|------------|------|---------|
| lopinavir+ritonavir vs placebo     | -0.43| 0.4878|            | 0.65 | [0.25, 1.70] |
| Ader_1                             |      |       |            |      |         |
| remdesivir vs placebo              | -0.94| 0.8468|            | 0.39 | [0.07, 2.06] |
| Ali                                |      |       |            |      |         |
| Beigel                             | -0.58| 0.8967|            | 0.56 | [0.10, 3.25] |
| Random effects model               |      |       |            |      |         |
| Heterogeneity: $I^2 = 0\%$, $t^2 = 0$, $p = 0.77$ | | | | | |
| favipiravir vs placebo              | 0.25 | 1.9744|            | 1.29 | [0.03, 61.63] |
| Balykova_1                         |      |       |            |      |         |
| Balykova_2                         | 0.00 | 1.9950|            | 1.00 | [0.02, 49.91] |
| haschenko                          | 0.93 | 1.5253|            | 2.53 | [0.13, 50.30] |
| Ruzhentskova                       | 0.41 | 1.6248|            | 1.51 | [0.06, 36.40] |
| Shinkai                            | 2.59 | 1.4281|            | 13.35| [0.81, 219.38] |
| Udriadia                           | 0.00 | 0.5090|            | 1.00 | [0.37, 2.71] |
| Random effects model               |      |       |            |      |         |
| Heterogeneity: $I^2 = 0\%$, $t^2 = 0$, $p = 0.68$ | | | | | |
| molnupiravir vs placebo            | -0.89| 0.4548|            | 0.41 | [0.17, 0.99] |
| Bental                             |      |       |            |      |         |
| ribavirin+sofosbuvir+daclatasvir vs placebo | -2.20| 1.4631|            | 0.11 | [0.01, 1.95] |
| Kasgari                            |      |       |            |      |         |
| resveratrol vs placebo             | -0.00| 1.9901|            | 1.00 | [0.02, 49.43] |
| McCreary                           |      |       |            |      |         |
| sofosbuvir+daclatasvir vs placebo  | 0.41 | 0.3677|            | 1.50 | [0.73, 3.09] |
| Mobarak                            |      |       |            |      |         |
| sofosbuvir+ledipasvir vs placebo   | -0.34| 0.7311|            | 0.71 | [0.17, 2.99] |
### Adverse events leading to drug discontinuation pairwise comparisons

| Study       | TE na vs TE | Risk Ratio | RR  | 95% CI     |
|-------------|-------------|------------|-----|------------|
| Chiang      | 2.62 1.89   | 1.33       | 1.09 [0.82, 1.40] |
| World Health| 0.84 1.22   | 1.35       | 1.07 [0.81, 1.40] |
| Chang       | 0.81 1.30   | 1.26       | 1.04 [0.80, 1.35] |
| Lin         | 2.12 1.76   | 1.28       | 1.04 [0.80, 1.30] |
| Ulendal     | 0.33 1.03   | 1.33       | 1.03 [0.85, 1.10] |

*Random effects model*   
*Heterogeneity: I² = 41%, Q (df = 7) = 22.31, p = 0.016*

| Study       | TE na vs placebo | Risk Ratio | RR  | 95% CI     |
|-------------|------------------|------------|-----|------------|
| Ban, R.     | 0.72 1.14       | 2.06       | 1.04 [1.01, 1.07] |
| Beige       | 0.98 1.13       | 2.07       | 1.05 [1.01, 1.09] |
| Chiari      | 2.40 1.46      | 1.15       | 1.07 [1.03, 1.13] |
| Guo         | 0.60 1.01      | 1.08       | 1.04 [0.86, 1.22] |

*Random effects model*   
*Heterogeneity: I² = 58%, Q (df = 7) = 30.04, p = 0.016*

| Study       | TE na vs placebo | Risk Ratio | RR  | 95% CI     |
|-------------|------------------|------------|-----|------------|
| Bader       | 0.29 0.287      | 0.92       | 1.06 [0.8, 1.35] |
| Fischer     | 0.97 1.2152     | 1.08       | 1.04 [0.86, 1.26] |
| Ito         | 0.44 1.2266     | 1.06       | 1.03 [0.92, 1.14] |

*Random effects model*   
*Heterogeneity: I² = 13%, Q (df = 7) = 3.15, p = 0.760*

| Study       | TE na vs placebo | Risk Ratio | RR  | 95% CI     |
|-------------|------------------|------------|-----|------------|
| Cheng       | 0.58 0.29      | 0.49       | 0.98 [0.8, 1.16] |
| Cooper      | 0.47 0.287      | 0.92       | 1.06 [0.8, 1.35] |
| Hung, J.    | -0.02 0.477     | 0.99       | 1.03 [0.85, 1.24] |
| Hung, J.    | 0.10 0.0550     | 1.10       | 1.07 [1.01, 1.17] |

*Random effects model*   
*Heterogeneity: I² = 15%, Q (df = 7) = 5.26, p = 0.790*

| Study       | TE na vs placebo | Risk Ratio | RR  | 95% CI     |
|-------------|------------------|------------|-----|------------|
| Kang        | 0.00 0.01      | 1.00       | 1.00 [0.92, 1.08] |
| Li          | 0.93 1.1369     | 1.03       | 1.00 [0.92, 1.08] |
| Li, J.      | 0.74 1.5753     | 2.09       | 1.07 [0.97, 1.17] |
| Li, J.      | 0.71 1.6286     | 2.09       | 1.07 [0.97, 1.17] |
| Limbar      | 0.06 0.0423     | 1.06       | 1.00 [0.92, 1.08] |
| Limbar      | 0.06 0.0423     | 1.06       | 1.00 [0.92, 1.08] |
| Mar, J.     | 0.05 1.0575     | 1.00       | 1.00 [0.92, 1.08] |
| Parent      | 1.10 1.4600     | 2.06       | 1.04 [0.8, 1.31] |
| Rea         | 0.30 0.8516     | 1.00       | 1.00 [0.92, 1.08] |
| Teacher     | 1.16 1.6997     | 3.05       | 1.03 [0.92, 1.08] |
| Zhang       | 0.72 1.6574     | 1.04       | 1.00 [0.92, 1.08] |

*Random effects model*   
*Heterogeneity: I² = 21%, Q (df = 7) = 25.36, p = 0.022*

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Appendix 1, as submitted by the authors. Appendix to: Pitre T Van Alstine R, Chick G, et al. Antiviral drugs in nonsevere COVID-19: a systematic review and network meta-analysis. CMAJ 2022. doi: 10.1503/cmaj.220471. Copyright © 2022 The Author(s) or their employer(s). To receive this resource in an accessible format, please contact us at cmajgroup@cmaj.ca.