Pharmacologic treatment for COVID-19: living systematic review and network meta-analysis

Supplementary Material

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Search Strategy for English databases

Database	Strategy
Medline (Ovid) 1946-	(coronavir* OR corona virus* OR betacoronavir* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR 2019nCoV OR wuhan virus*).mp. OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*).mp. OR Coronavirus Infections/ OR Coronavirus/ OR betacoronavirus/ Limits: 2020- OR (novel coronavir* OR novel corona virus* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR 2019nCoV OR wuhan virus*).mp. OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*).mp. OR ((wuhan OR hubei OR huanan) AND (coronavir* OR betacoronavir*)).mp. Limits: 2019-
Embase (Ovid) 1947-	(coronavir* OR corona virus* OR betacoronavir* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR 2019nCoV OR wuhan virus*).mp. OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*).mp. OR Coronavirus infection/ OR coronavirinae/ OR exp betacoronavirus/ Limits: 2020- OR (novel coronavir* OR novel corona virus* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR 2019nCoV OR wuhan virus*).mp. OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*).mp. OR ((wuhan OR hubei OR huanan) AND (coronavir* OR betacoronavir*)).mp. Limits: 2019-
CAB Abstracts (Ovid) 1910-	(coronavir* OR corona virus* OR betacoronavir* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR 2019nCoV OR wuhan virus*).mp. OR ((wuhan OR

	hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*).mp. OR exp Betacoronavirus/ Limits: 2020- OR (novel coronavir* OR novel corona virus* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR 2019nCoV OR wuhan virus*).mp. OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*).mp. OR ((wuhan OR hubei OR huanan) AND (coronavir* OR betacoronavir*)).mp. Limits: 2019-
Global Health (Ovid) 1910-	(coronavir* OR corona virus* OR betacoronavir* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR 2019nCoV OR wuhan virus*).mp. OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*).mp. OR exp Betacoronavirus/ Limits: 2020- OR (novel coronavir* OR novel corona virus* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR 2019nCoV OR wuhan virus*).mp. OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*).mp. OR ((wuhan OR hubei OR huanan) AND (coronavir* OR betacoronavir*)).mp. Limits: 2019-
PsycInfo (Ovid) 1806-	(coronavir* OR corona virus* OR betacoronavir* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR 2019nCoV OR wuhan virus*).mp. OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*).mp. Limits: 2020- OR (novel coronavir* OR novel corona virus* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR 2019nCoV OR wuhan virus*).mp. OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*).mp. OR ((wuhan OR hubei OR huanan) AND (coronavir* OR betacoronavir*)).mp. Limits: 2019-

Cochrane Library	#1(coronavir* OR "corona virus" OR betacoronavir* OR covid19 OR "covid 19" OR nCoV OR "CoV 2" OR CoV2 OR sarscov2 OR 2019nCoV OR "novel CoV" OR "wuhan virus"):ti,ab,kw OR ((wuhan OR hubei OR huanan) AND ("severe acute respiratory" OR pneumonia*) AND outbreak*):ti,ab,kw #2MeSH descriptor: [Coronavirus] this term only #3MeSH descriptor: [Coronavirus Infections] this term only #4MeSH descriptor: [Betacoronavirus] this term only #5 #1 OR #2 OR #3 OR#4 Limits: 2020- OR #1 ("novel coronavirus" OR "novel corona virus" OR covid19 OR "covid 19" OR nCoV OR "novel CoV" OR "CoV 2" OR CoV2 OR sarscov2 OR 2019nCoV OR "wuhan virus"):ti,ab,kw OR ((wuhan OR hubei OR huanan) AND ("severe acute respiratory" OR pneumonia*) AND outbreak*):ti,ab,kw OR ((wuhan OR hubei OR huanan) AND (coronavir* OR betacoronavir*)):ti,ab,kw Limits: 2019-
Scopus 1960-	TITLE-ABS-KEY (coronavir* OR "corona virus" OR betacoronavir* OR covid19 OR "covid 19" OR ncov OR "CoV 2" OR cov2 OR sarscov2 OR 2019ncov OR "novel CoV" OR "wuhan virus") OR (TITLE-ABS-KEY (wuhan OR hubei OR huanan) AND TITLE-ABS-KEY ("severe acute respiratory" OR pneumonia*) AND TITLE-ABS-KEY (outbreak*)) AND (LIMIT-TO (PUBYEAR , 2020)) OR TITLE-ABS-KEY ("novel coronavirus" OR "novel corona virus" OR covid19 OR "covid 19" OR ncov OR "CoV 2" OR cov2 OR sarscov2 OR 2019ncov OR "novel CoV" OR "wuhan virus") OR TITLE-ABS-KEY ((wuhan OR hubei OR huanan) AND ("severe acute respiratory" OR pneumonia*) AND outbreak*) OR TITLE-ABS-KEY ((wuhan OR hubei OR huanan) AND (coronavir* OR betacoronavir*)) AND (LIMIT-TO (PUBYEAR , 2020) OR LIMIT-TO (PUBYEAR , 2019))
Academic Search Complete (Ebsco)	TI,AB,SU((coronavir* OR "corona virus" OR betacoronavir* OR covid19 OR "covid 19" OR nCoV OR "CoV 2" OR CoV2 OR sarscov2 OR 2019nCoV OR "novel CoV" OR "wuhan virus") OR ((wuhan OR hubei OR huanan) AND ("severe acute respiratory" OR pneumonia*) AND (outbreak*))) Limits: Dec. 2019-, peer-reviewed
Africa Wide Information (Ebsco)	TI,AB,SU((coronavir* OR "corona virus" OR betacoronavir* OR covid19 OR "covid 19" OR nCoV OR "CoV 2" OR CoV2 OR sarscov2 OR 2019nCoV OR "novel CoV" OR "wuhan virus") OR

	((wuhan OR hubei OR huanan) AND ("severe acute respiratory" OR pneumonia*) AND (outbreak*))) Limits: 2020-, peer-reviewed OR TI,AB,SU(("novel coronavirus" OR "novel corona virus" OR covid19 OR "covid 19" OR nCoV OR "CoV 2" OR CoV2 OR sarscov2 OR 2019nCoV OR "novel CoV" OR "wuhan virus") OR ((wuhan OR hubei OR huanan) AND ("severe acute respiratory" OR pneumonia*) AND outbreak*) OR ((wuhan OR hubei OR huanan) AND (coronavir* OR betacoronavir*))) Limits: 2019-, peer-reviewed
CINAHL (Ebsco)	TI,AB,SU((coronavir* OR "corona virus" OR betacoronavir* OR covid19 OR "covid 19" OR nCoV OR "CoV 2" OR CoV2 OR sarscov2 OR 2019nCoV OR "novel CoV" OR "wuhan virus") OR ((wuhan OR hubei OR huanan) AND ("severe acute respiratory" OR pneumonia*) AND (outbreak*))) OR (MH "Coronavirus") OR (MH "Coronavirus Infections") Limits: Dec. 2019-, peer-reviewed
ProQuest Central (Proquest) 1952-	TI,AB,SU((coronavir* OR "corona virus" OR betacoronavir* OR covid19 OR "covid 19" OR nCoV OR "CoV 2" OR CoV2 OR sarscov2 OR 2019nCoV OR "novel CoV" OR "wuhan virus") OR ((wuhan OR hubei OR huanan) AND ("severe acute respiratory" OR pneumonia*) AND (outbreak*))) Limits: Dec. 2019-, peer-reviewed
PubMed Central	TITLE-ABSTRACT((coronavirus OR "corona virus" OR coronavirinae OR coronaviridae OR betacoronavirus OR covid19 OR "covid 19" OR nCoV OR "CoV 2" OR CoV2 OR sarscov2 OR 2019nCoV OR "novel CoV" OR "wuhan virus") OR ((wuhan OR hubei OR huanan) AND ("severe acute respiratory" OR pneumonia) AND (outbreak))) OR "COVID-19" [Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] Limits: Dec. 2019-
Medline (PubMed)	TITLE-ABSTRACT((coronavirus OR "corona virus" OR coronavirinae OR coronaviridae OR betacoronavirus OR covid19 OR "covid 19" OR nCoV OR "CoV 2" OR CoV2 OR sarscov2 OR 2019nCoV OR "novel CoV" OR "wuhan virus") OR ((wuhan OR hubei OR huanan) AND ("severe acute respiratory" OR pneumonia) AND (outbreak))) OR "COVID-19" [Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] Limits: Dec. 2019-

LitCovid (NLM)	https://www.ncbi.nlm.nih.gov/research/coronavirus/
SciFinder (CAS)	References (coronavir* OR "corona virus" OR betacoronavir* OR covid19 OR covid OR nCoV OR "CoV 2" OR CoV2 OR sarscov2 OR 2019nCoV OR "novel CoV" OR "wuhan virus") Limits: 2020- OR References ("novel coronavirus" OR "novel corona virus" OR covid19 OR covid OR nCoV OR "CoV 2" OR CoV2 OR sarscov2 OR 2019nCoV OR "novel CoV" OR "wuhan virus") Limits: 2019-
Virtual Health Library (WHO)	Filter VHL created: https://bvsalud.org/vitrinas/post_vitrines/novo_coronavirus/ **Database changed on 6/16/2020 and integrated into the larger WHO database** Limited: 2019- OR TI,AB:((coronavirus OR "corona virus" OR coronavirinae OR coronaviridae OR betacoronavirus OR covid19 OR "covid 19" OR nCoV OR "CoV 2" OR CoV2 OR sarscov2 OR 2019nCoV OR "novel CoV" OR "wuhan virus") OR ((wuhan OR hubei OR huanan) AND ("severe acute respiratory" OR pneumonia) AND (outbreak))) Limits: 2020- OR TI,AB("novel coronavirus" OR "novel corona virus" OR covid19 OR "covid 19" OR nCoV OR "CoV 2" OR CoV2 OR sarscov2 OR 2019nCoV OR "novel CoV" OR "wuhan virus") OR ((wuhan OR hubei OR huanan) AND ("severe acute respiratory" OR pneumonia) AND outbreak) OR ((wuhan OR hubei OR huanan) AND (coronavirus OR betacoronavirus)) Limits: 2019-
WHO Novel Coronavirus page	Download of their global research on COVID 19 database: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov

	OR Hand search
CDC Novel Coronavirus page	https://www.cdc.gov/coronavirus/2019-ncov/publications.html OR Hand search
EuroSurveillance	https://www.eurosurveillance.org/content/2019-ncov?pageSize=100&page=1
China CDC MMWR	Hand search
Homeland Security Digital Library	Title or Summary: Coronavirus OR "Corona virus" OR Betacoronavirus OR Coronaviridae OR coronavirinae OR Covid OR Covid19 OR nCoV OR CoV OR CoV2 OR Wuhan Limits: 2019-
ClinicalTrials	Condition, disease, other term: Coronavirus OR "Corona virus" OR Betacoronavirus OR Coronaviridae OR coronavirinae OR Covid OR Covid19 OR nCoV OR CoV OR CoV2 OR Wuhan Limits: 2019-
bioRxiv medRxiv chemRxiv (preprints)	Condition, disease, other term: Coronavirus OR "Corona virus" OR Betacoronavirus OR Coronaviridae OR coronavirinae OR Covid OR Covid19 OR nCoV OR CoV OR CoV2 OR Wuhan Limits: 2019-
SSRN (preprints)	Condition, disease, other term: Coronavirus OR "Corona virus" OR Betacoronavirus OR Coronaviridae OR coronavirinae OR Covid OR Covid19 OR nCoV OR CoV OR CoV2 OR Wuhan Limits: 2019-

Search Strategy for Chinese databases

中文数据库检索策略及结果

Database	Strategy
WanFang万方医学 (med.wanfangdata.com.cn)	#1 (主题:(2019冠状病毒 OR 新型冠状病毒 OR 新冠肺炎)*主题:(临床试验 OR 系统评价 OR Meta分析 OR 随机对照实验 OR 对照研究))*Date:2019- #2 (主题:(2019-nCoV OR SARS-CoV-2 OR Novel coronavirus OR nCoV OR new coronavirus)*主题:(临床试验 OR 系统评价 OR Meta分析 OR 随机对照实验 OR 对照研究))*Date:2019- #3 #1 OR #2
CBM	(("2019冠状病毒"[常用字段:智能] OR "新型冠状病毒"[常用字段:智能] OR "新冠肺炎"[常用字段:智能] OR "2019-nCoV"[常用字段:智能] OR "SARS-CoV-2"[常用字段:智能] OR "Novel coronavirus"[常用字段:智能] OR "nCoV"[常用字段:智能] OR "Emerging Coronaviruses"[常用字段:智能] OR "new coronavirus"[常用字段:智能] OR "COVID-19"[常用字段:智能] OR "coronavirus"[常用字段:智能] AND ("Wuhan"[常用字段] OR "Hubei"[常用字段] OR "China"[常用字段])) AND 2019-2020[日期]) AND ("循证文献"[文献类型] OR "临床试验"[文献类型] OR "随机对照试验"[文献类型] OR "综述"[文献类型] OR "Meta分析"[文献类型])
CNKI	在期刊文献类型下： #1主题=("2019冠状病毒" OR "新型冠状病毒" OR "新冠肺炎") AND（主题=临床试验 OR 系统评价 OR 随机对照实验 OR Meta分析） #2主题=(2019-nCoV OR SARS-CoV-2 OR Novel coronavirus OR nCoV) AND (主题=临床试验 OR 系统评价 OR 随机对照实验 OR Meta分析) 2019-[日期]
VIP 维普	#1 (主题:(2019冠状病毒 OR 新型冠状病毒 OR 新冠肺炎)*主题:(临床试验 OR 系统评价 OR Meta分析 OR 随机对照实验 OR 对照研究))* #2 主题=(SARS-CoV-2 OR Novel coronavirus OR nCoV) AND (主题=临床试验 OR 系统评价 OR 随机对照实验 OR Meta分析) Date:2019-
中华医学期刊网（预印本）http://medjournals.cn/2019NCP/index.do	#1主题=("2019冠状病毒" OR "新型冠状病毒" OR "新冠肺炎") AND（主题=临床试验 OR 系统评价 OR 随机对照实验 OR Meta分析） #2主题=(2019-nCoV OR SARS-CoV-2 OR Novel coronavirus OR nCoV) AND (主题=临床试验 OR 系统评价 OR 随机对照实验 OR Meta分析) 2019-[日期]
中科院预印本 http://chinaxiv.org/home.htm	Hand search.

Additional study characteristics

			Publication/Study characteristics					
			Publication status	Study status	Was the trial terminated early for benefit?	Design	Funding	Were patients and/or the public involved in the design or interpretation of results?
First author	Trial name	Trial registration	1=peer-reviewed pub 2=pre-print 3=trial registration 4=data from authors	1=complete 2=ongoing, interim data 3=completed, terminated early 4=ongoing, no data		1=parallel group 2=cluster randomized	1=Industry 2=Government 3=Institutional 4=Not-for-profit foundation 0=None	
Beigel	ACTT-1	NCT04280705	1	2	No	1	1, 2, 4	No
Cao_1	LOTUS China	ChiCTR2000029308	1	1	No	1	2	No
Cao_2	NA	ChiCTR-OPN-2000029580	1	1	No	1	2, 3	No
Chen_1	NR	ChiCTR2000029559	2	1	No	1	2	No
Chen_2	NR	ChiCTR2000030254	2	1	No	1	2	No
Chen_3	NR	ChiCTR2000029387	1	3	No	1	2	No
Chen_4	NR	NCT04261517	1	1	No	1	3	No
Chen_5	NR	ChiCTR2000030054	2	3	No	1	2	No
Davoudi-Monfared	NR	IRCT20100228003449N28	2	1	No	1	1 (provided medication)	No
Goldman	NR	NCT04292899	1	1	No	1	1	No
Guvenmez	NR	NR	1	1	No	1	0	No
Horby	RECOVERY	NCT04381936	2	1	No	1	2, 3, 4	No
Huang	NR	ChiCTR2000029542	1	1	No	1	2	No
Hung	NA	NCT04276688	1	1	No	1	2, 4	No
Li	ELACOI	NCT04252885	2	1	No	1	2	No
Li	NR	ChiCTR2000029757	1	3	No	1	3, 4	No
Lou	NR	ChiCTR2000029544	2	1	No	1	2	No
Silva Borba	CloroCovid-19	NCT04323527	1	2	No	1	2	No
Tang	NR	ChiCTR2000029868	1	3	No	1	1 (provided medication), 2	No
Wang	NR	NCT04257656	1	3	No	1	1 (provided medication), 2	No
Zheng	NR	ChiCTR2000029496	2	1	No	1	2	No
Zhong	NR	ChiCTR2000029851	2	1	No	1	1 (provided medication), 0	No
Zhou	NR	NR	1	1	No	1	0	No

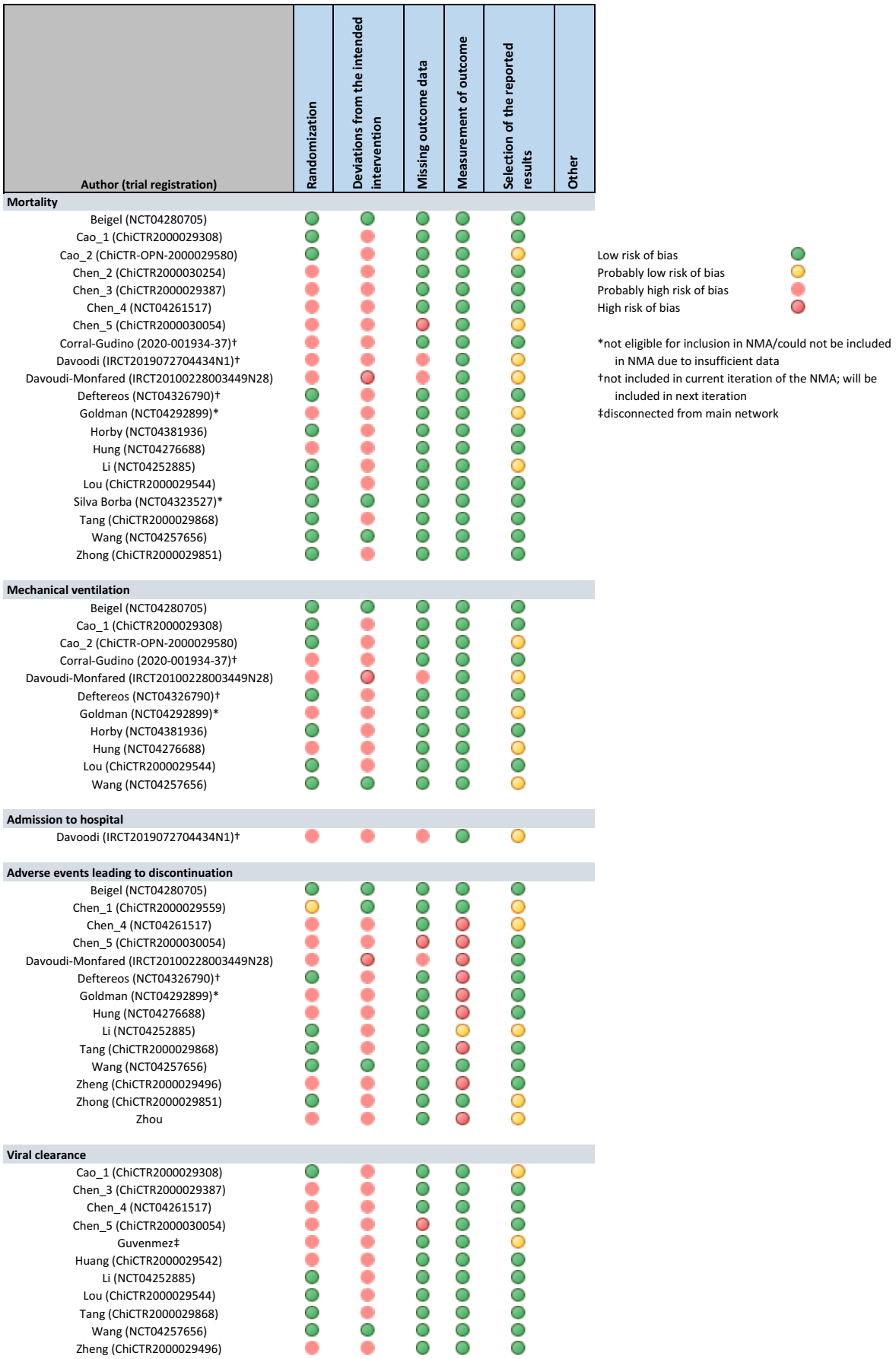
			Baseline patient characteristics												
First author	Trial name	Trial registration	Country	Age	Male (%)	Current or unspecified smokers (%)	Former smokers (%)	Pregnant (%)	Respiratory condition (%)	Cardiovascular disease or coronary heart disease (%)	Diabetes (%)	Hypertension (%)	Steroids (%)	Immunosuppressing medication (%)	ACE inhibitors/angiotensin receptor blockers (%)
Beigel	ACTT-1	NCT04280705	United States, Denmark, United Kingdom, Greece, Germany, Korea, Mexico, Spain, Japan, Singapore	58.9	64.3	NR	NR	0	7.6 (chronic respiratory disease), 2.2 (chronic oxygen requirement), 11.4 (asthma)	11.6 (coronary artery disease), 5 (congestive heart failure)	29.7 (type 2 diabetes), 1.2 (type 1 diabetes)	49.6	NR	NR	NR
Cao_1	LOTUS China	ChiCTR2000029308	China	58	60.3	NR	NR	0	NR	6.5 (cerebrovascular disease)	11.56	NR	NR	NR	NR
Cao_2	NA	ChiCTR-OPN-2000029580	China	63	58.5	9.8	NR	0	NR	7.3 (coronary artery heart disease)	19.5	39	NR	NR	NR
Chen_1	NR	ChiCTR2000029559	China	44.7	46.77	NR	NR	0	NR	NR	NR	NR	NR	NR	NR
Chen_2	NR	ChiCTR2000030254	China	NR	46.61	NR	NR	0	NR	NR	11.44	27.97	NR	NR	NR
Chen_3	NR	ChiCTR2000029387	China	42.5	45.54	NR	NR	0	0 (severe lung disease)	0 (severe heart disease)	NR	NR	NR	NR	NR
Chen_4	NR	NCT04261517	China	48.6	70	NR	NR	0	0 (severe lung disease), 3.33 (COPD)	0 (severe heart disease)	6.67	26.67	NR	NR	NR
Chen_5	NR	ChiCTR2000030054	China	46.92	45.83	NR	NR	NR	NR	NR	18.75	16.67	NR	NR	NR
Davoudi-Monfared	NR	IRCT20100228003449N28	Iran	57.75	53.09	NR	NR	0	1.23 (asthma), 1.23 (COPD)	28.4	27.16	38.27	NR	NR	NR
Goldman	NR	NCT04292899	United States, Italy, Spain, Gernmany, Hong Kong, Singapore, South Korea, Taiwan	61.5	63.73	NR	NR	0	12.34 (asthma)	NR	22.67	49.87	NR	NR	NR
Guvenmez	NR	NR	Turkey	58.75	62.5	NR	NR	0	NR	NR	NR	NR	NR	NR	NR
Horby	RECOVERY	NCT04381936	United Kingdom	66.1	63.62	NR	NR	0.093	20.94 (chronic lung disease), 0.39 (tuberculosis)	27.34 (heart disease)	24.06	NR	NR	NR	NR
Huang	NR	ChiCTR2000029542	China	44	59.09	9.1	NR	0	NR	4.5 (cerebrovascular disease)	9.1	18.2	NR	NR	NR
Hung	NA	NCT04276688	China	51.32	53.54	5.51	NA	0	1.57 (tuberculosis), 1.57 (obstructive sleep apnea)	7.87 (coronary artery disease), 1.6 (cerebrovascular disease)	13.39	28.35	NA	NA	NA
Li	ELACOI	NCT04252885	China	49.4	46.51	NR	NR	0	0	2.33	2.32	10.47	NR	NR	NR
Li	NR	ChiCTR2000029757	China	70	58.3	NR	NR	0	NR	25.24 (cardiovascular disease), 17.48 (cerebrovascular disease), 0 (severe congestive heart failure)	20.39	54.37	NR	NR	NR
Lou	NR	ChiCTR2000029544	China	52.5	72.4	NR	NR	NR	0 (COPD)	13.8	6.9	20.7	NR	NR	NR
Silva Borba	CloroCovid-19	NCT04323527	Brazil	51.1	75.3	8.33	22.9	2.47	7.4 (asthma), 3.6 (tuberculosis)	9.09	25.5	45.5	NR	NR	NR
Tang	NR	ChiCTR2000029868	China	46.1	55	NR	NR	0	NR	0	14	6	NR	NR	NR
Wang	NR	NCT04257656	China	65	59.32	NR	NR	0	NR	7.2	23.73	43.22	38.56	interferon alfa-2b (18.64)	NR
Zheng	NR	ChiCTR2000029496	China	46.73	47.19	NR	NR	NR	0 (severe lung disease)	0 (severe heart disease)	NR	NR	NR	NR	NR
Zhong	NR	ChiCTR2000029851	China	63	76.47	NR	NR	0	NR	5.9	23.53	47.06	NR	NR	NR
Zhou	NR	NR	China	52.1	57.69	NR	NR	0	0 (interstitial pneumonia)	0 (severe heart disease)	NR	0	NR	NR	NR

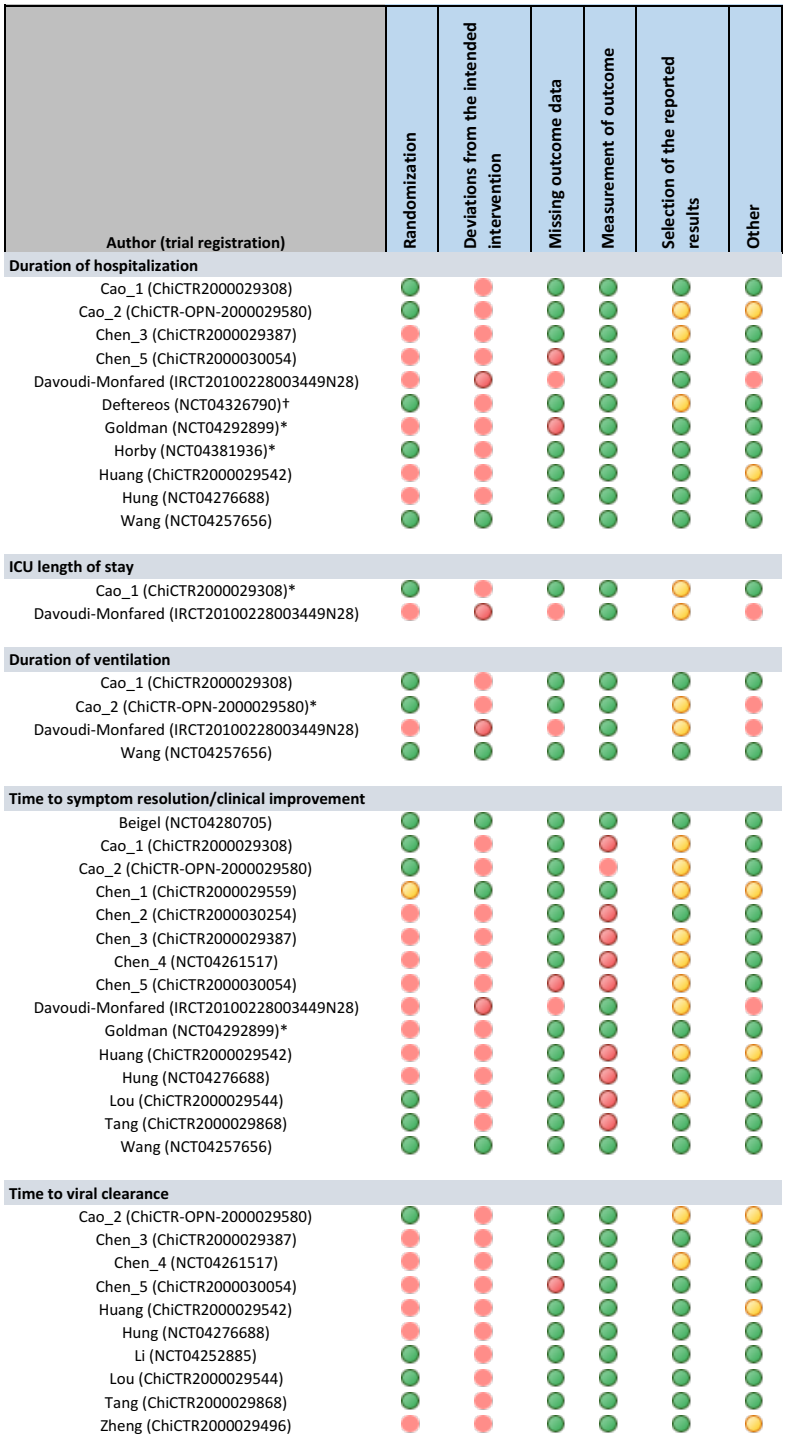
First author	Trial name	Trial registration	Baseline clinical characteristics									
			Inpatient (%)	Intensive care (%)	Confirmed COVID-19 (%)	Illness severity score 1=Sequential Organ Failure Assessment (SOFA) 2=National Early Warning Score 2 (NEWS2)	Illness severity score	Mild illness (%)	Moderate illness (%)	Severe illness (%)	Critical illness (%)	Mechanical ventilation (%)
Beigel	ACTT-1	NCT04280705	100	NR	100	NR	NR	NA	NR	88.7	0	39.6 (supplemental oxygen), 18.5 (non-invasive ventilation or high flow oxygen devices), 25.6 (invasive ventilation or ECMO)
Cao_1	LOTUS China	ChiCTR2000029308.	100	NR	100	2	5	0	0	100	0	69.84 (supplemental oxygen), 15.58 (high-flow nasal cannula or noninvasive ventilation), 0.50 (ECMO or invasive ventilation)
Cao_2	NA	ChiCTR-OPN-2000029580	100	NR	39.5	2	5	0	0	100	0	87.8 (supplemental oxygen), 12.2 (high flow or noninvasive mechanical ventilation)
Chen_1	NR	ChiCTR2000029559	100	NR	100	NR	NR	100	0	0	0	NR
Chen_2	NR	ChiCTR2000030254	NR	NR	42.37	NR	NR	0	88.55	10.17	1.27	NR
Chen_3	NR	ChiCTR2000029387	NR	NR	100	NR	NR	NR	NR	0	0	NR
Chen_4	NR	NCT04261517	100	0	100	NR	NR	0	100	0	0	NR
Chen_5	NR	ChiCTR2000030054	100	NR	68.75	NR	NR	0	100	0	0	72.92 (supplemental oxygen)
oudi-Monfa	NR	IRCT20100228003449N28	100	NR	NR	NR	NR	0	0	100	NR	69.14 (supplemental oxygen), 4.94 (high-flow nasal cannula or non-invasive mechanical ventilation), 24.69 (invasive mechanical ventilation)
Goldman	NR	NCT04292899	100	NR	100	NR	NR	0	0	100	NR	3.27 (invasive ventilation), 27.46 (non-invassive or high flow oxygen), 55.42 (supplemental oxygen)
Guvenmez	NR	NR	100	NR	100	NR	NR	NR	NR	NR	NR	0

First author	Trial name	Trial registration	Baseline clinical characteristics									
			Inpatient (%)	Intensive care (%)	Confirmed COVID-19 (%)	Illness severity score 1=Sequential Organ Failure Assessment (SOFA) 2=National Early Warning Score 2 (NEWS2)	Illness severity score	Mild illness (%)	Moderate illness (%)	Severe illness (%)	Critical illness (%)	Mechanical ventilation (%)
Horby	RECOVERY	NCT04381936	100	NR	81.78	NR	NR	NR	NR	NR	NR	15.67 (invasive mechanical ventilation or ECMO), 60.44 (oxygen with or without non-invasive ventilation)
Huang	NR	ChiCTR2000029542	100	NR	100	1	1	0	63.64	36.36	0	NR
Hung	NA	NCT04276688	100	NR	100	1	0	100	0	0	0	0
Li	ELACOI	NCT04252885	100	NR	100	NR	NR	12.79	87.21	0	0	0 (mechanical ventilation)
Li	NR	ChiCTR2000029757	100	NR	100	NR	NR	0	0	43.69	56.31	29.70 (supplemental oxygen), 43.56 (noninvasive ventilation and/or high flow supplemental oxygen), 24.75 (extracorporeal membrane oxygenation and/or invasive mechanical ventilation)
Lou	NR	ChiCTR2000029544	100	0	100	2	4	NR	NR	NR	0	0
Silva Borba	CloroCovid-19	NCT04323527	100	45.68	76.54	% qSOFA≥2	33.3	0	0	100	NR	88.9 (supplemental oxygen)
Tang	NR	ChiCTR2000029868	100	NR	100	NR	NR	15	84	1	NR	NR
Wang	NR	NCT04257656	100	NR	100	2	4.67	0	0	100	0	82.2 (supplemental oxygen), 15.68 (high-flow nasal cannula or non-invasive ventilation), 0.42 (ECMO or invasive ventilation)
Zheng	NR	ChiCTR2000029496	100	NR	100	NR	NR	0	94.38	5.62	NR	NR
Zhong	NR	ChiCTR2000029851	100	NR	NR	1	4.06	0	0	0	100	5.90 (nasal or mask oxygen), 41.18 (high-flow oxygen or noninvasive ventilation), 52.94 (invasive ventilation)
Zhou	NR	NR	100	0	100	NR	NR	0	100	0	0	NR

First author	Trial name	Trial registration	Oxygen saturation	Quantity of supplemental oxygen (L/min)	ALT (U/L)	CRP (mg/L)	d-Dimer (ng/mL)	LDH (U/L)	Lymphocyte count ($x10^{-9}$/L)	Lymphopaenia (%)
Beigel	ACTT-1	NCT04280705	NR	NR	NR	NR	NR	NR	NR	NR
Cao_1	LOTUS China	ChiCTR2000029308.	NR	NR	33	NR	NR	NR	0.9	61.31
Cao_2	NA	ChiCTR-OPN-2000029580	NR	NR	25	NR	2400	275	1.1	39
Chen_1	NR	ChiCTR2000029559	NR	NR	NR	NR	NR	NR	NR	NR
Chen_2	NR	ChiCTR2000030254	≥98	NR	NR	10.04	NR	NR	0.96	NR
Chen_3	NR	ChiCTR2000029387	97.26	NR	NR	7.78	NR	NR	1.43	NR
Chen_4	NR	NCT04261517	NR	NR	21	NR	NR	NR	1.15	NR
Chen_5	NR	ChiCTR2000030054	97.45	NR	22.31	2.5	NR	NR	1.7	6.25
oudi-Monfa	NR	IRCT20100228003449N28	85.52	NR	42.56	1303	NR	794.48	1.05	NR
Goldman	NR	NCT04292899	NR	NR	33.98	NR	NR	NR	NR	NR
Guvenmez	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

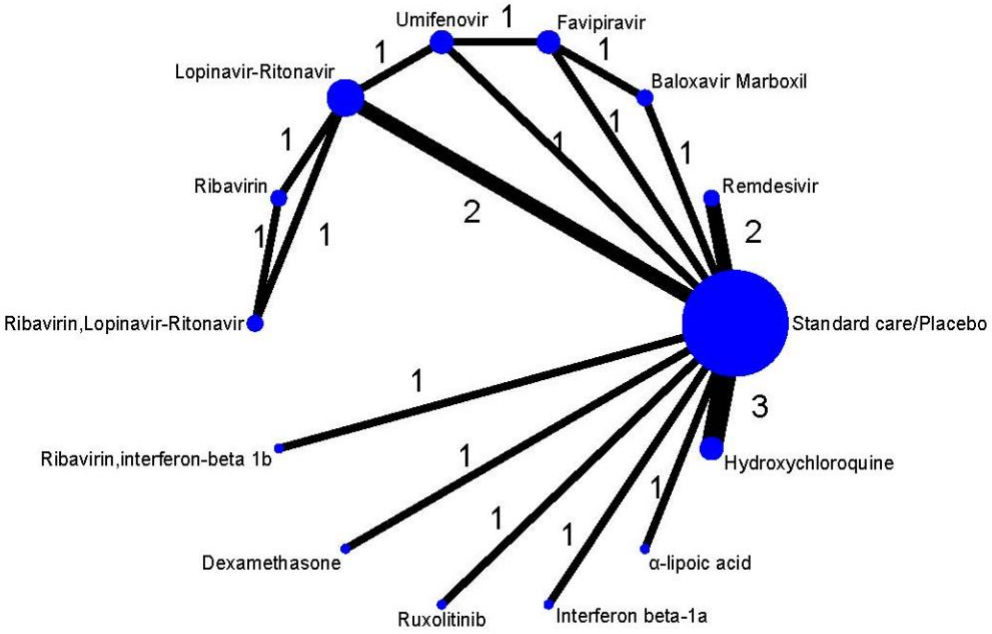
First author	Trial name	Trial registration	Oxygen saturation	Quantity of supplemental oxygen (L/min)	ALT (U/L)	CRP (mg/L)	d-Dimer (ng/mL)	LDH (U/L)	Lymphocyte count ($x10^{-9}$/L)	Lymphopaenia (%)
Horby	RECOVERY	NCT04381936	NR	NR	NR	NR	NR	NR	NR	NR
Huang	NR	ChiCTR2000029542	97.7	NR	18.9	5.51	99	165.5	1.56	NR
Hung	NA	NCT04276688	NA	NA	23.97	30	NR	185.44	1.1	NR
Li	ELACOI	NCT04252885	NR	NR	NR	NR	NR	NR	NR	25.58
Li	NR	ChiCTR2000029757	NR	NR	31.9	14.7	2100	NR	0.82	62.14
Lou	NR	ChiCTR2000029544	NR	NR	22	10.6	NR	249	0.7	NR
Silva Borba	CloroCovid-19	NCT04323527	96	NR	65.2	8.48	NR	948	NR	NR
Tang	NR	ChiCTR2000029868	97.4	NR	32.1	8.6	NR	197.4	1.5	NR
Wang	NR	NCT04257656	NR	NR	26	NR	NR	335.69	0.77	69.1
Zheng	NR	ChiCTR2000029496	NR	NR	NR	NR	NR	NR	NR	NR
Zhong	NR	ChiCTR2000029851	NR	NR	31	NR	32.7	NR	NR	NR
Zhou	NR	NR	NR	NR	NR	5.41	NR	NR	NR	NR


Author (trial registration)
Randomization
Deviations from the intended intervention
Missing outcome data
Measurement of outcome
Selection of the reported results
Other
Mortality
Beigel (NCT04280705)
Cao_1 (ChiCTR2000029308)
Cao_2 (ChiCTR-OPN-2000029580)
Chen_2 (ChiCTR2000030254)
Chen_3 (ChiCTR2000029387)
Chen_4 (NCT04261517)
Chen_5 (ChiCTR2000030054)
Corral-Gudino (2020-001934-37)†
Davoodi (IRCT2019072704434N1)†
Davoudi-Monfared (IRCT20100228003449N28)
Deftereos (NCT04326790)†
Goldman (NCT04292899)*
Horby (NCT04381936)
Hung (NCT04276688)
Li (NCT04252885)
Lou (ChiCTR2000029544)
Silva Borba (NCT04323527)*
Tang (ChiCTR2000029868)
Wang (NCT04257656)
Zhong (ChiCTR2000029851)
Mechanical ventilation
Beigel (NCT04280705)
Cao_1 (ChiCTR2000029308)
Cao_2 (ChiCTR-OPN-2000029580)
Corral-Gudino (2020-001934-37)†
Davoudi-Monfared (IRCT20100228003449N28)
Deftereos (NCT04326790)†
Goldman (NCT04292899)*
Horby (NCT04381936)
Hung (NCT04276688)
Lou (ChiCTR2000029544)
Wang (NCT04257656)
Admission to hospital
Davoodi (IRCT2019072704434N1)†
Adverse events leading to discontinuation
Beigel (NCT04280705)
Chen_1 (ChiCTR2000029559)
Chen_4 (NCT04261517)
Chen_5 (ChiCTR2000030054)
Davoudi-Monfared (IRCT20100228003449N28)
Deftereos (NCT04326790)†
Goldman (NCT04292899)*
Hung (NCT04276688)
Li (NCT04252885)
Tang (ChiCTR2000029868)
Wang (NCT04257656)
Zheng (ChiCTR2000029496)
Zhong (ChiCTR2000029851)
Zhou
Viral clearance
Cao_1 (ChiCTR2000029308)
Chen_3 (ChiCTR2000029387)
Chen_4 (NCT04261517)
Chen_5 (ChiCTR2000030054)
Guvenmez‡
Huang (ChiCTR2000029542)
Li (NCT04252885)
Lou (ChiCTR2000029544)
Tang (ChiCTR2000029868)
Wang (NCT04257656)
Zheng (ChiCTR2000029496)
Low risk of bias
Probably low risk of bias
Probably high risk of bias
High risk of bias
*not eligible for inclusion in NMA/could not be included in NMA due to insufficient data
†not included in current iteration of the NMA; will be included in next iteration
‡disconnected from main network

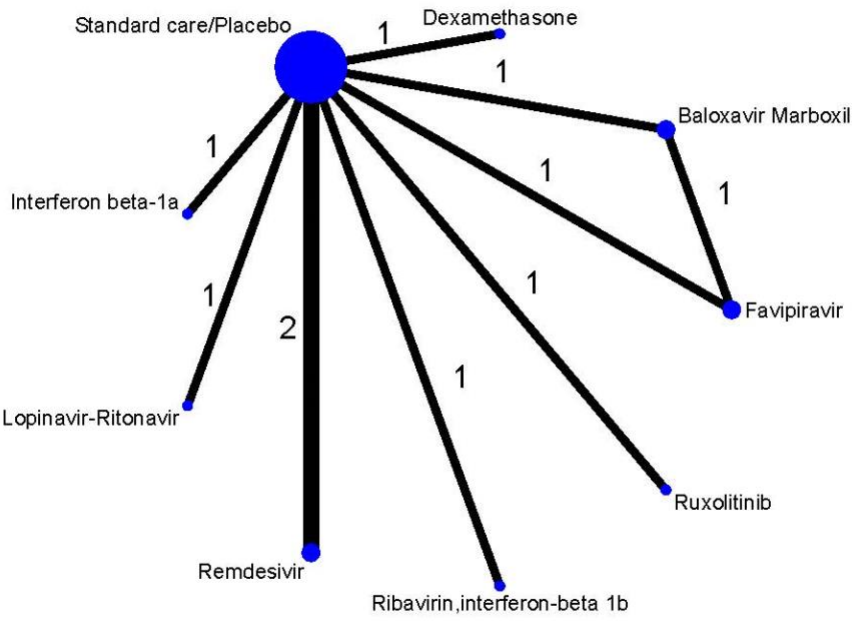

Author (trial registration)
Randomization
Deviations from the intended intervention
Missing outcome data
Measurement of outcome
Selection of the reported results
Other
Duration of hospitalization
Cao_1 (ChiCTR2000029308)
Cao_2 (ChiCTR-OPN-2000029580)
Chen_3 (ChiCTR2000029387)
Chen_5 (ChiCTR2000030054)
Davoudi-Monfared (IRCT20100228003449N28)
Deftereos (NCT04326790)†
Goldman (NCT04292899)*
Horby (NCT04381936)*
Huang (ChiCTR2000029542)
Hung (NCT04276688)
Wang (NCT04257656)
ICU length of stay
Cao_1 (ChiCTR2000029308)*
Davoudi-Monfared (IRCT20100228003449N28)
Duration of ventilation
Cao_1 (ChiCTR2000029308)
Cao_2 (ChiCTR-OPN-2000029580)*
Davoudi-Monfared (IRCT20100228003449N28)
Wang (NCT04257656)
Time to symptom resolution/clinical improvement
Beigel (NCT04280705)
Cao_1 (ChiCTR2000029308)
Cao_2 (ChiCTR-OPN-2000029580)
Chen_1 (ChiCTR2000029559)
Chen_2 (ChiCTR2000030254)
Chen_3 (ChiCTR2000029387)
Chen_4 (NCT04261517)
Chen_5 (ChiCTR2000030054)
Davoudi-Monfared (IRCT20100228003449N28)
Goldman (NCT04292899)*
Huang (ChiCTR2000029542)
Hung (NCT04276688)
Lou (ChiCTR2000029544)
Tang (ChiCTR2000029868)
Wang (NCT04257656)
Time to viral clearance
Cao_2 (ChiCTR-OPN-2000029580)
Chen_3 (ChiCTR2000029387)
Chen_4 (NCT04261517)
Chen_5 (ChiCTR2000030054)
Huang (ChiCTR2000029542)
Hung (NCT04276688)
Li (NCT04252885)
Lou (ChiCTR2000029544)
Tang (ChiCTR2000029868)
Zheng (ChiCTR2000029496)

Network plots

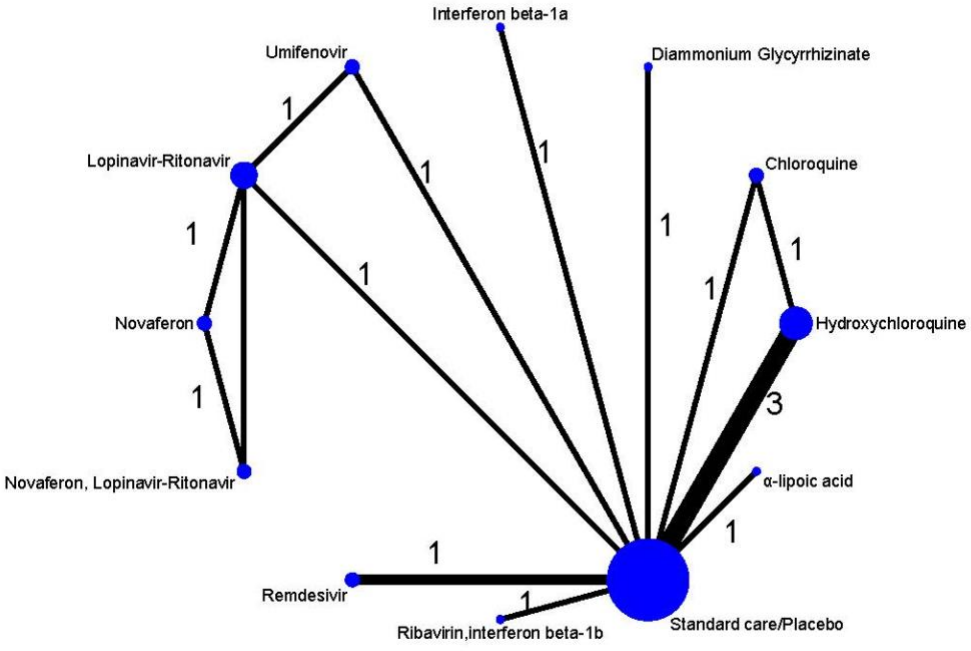
For all of the following network plots, the width of the lines is proportional to the number of trials included for that comparison. The numbers represent the numbers of trials for each comparison.



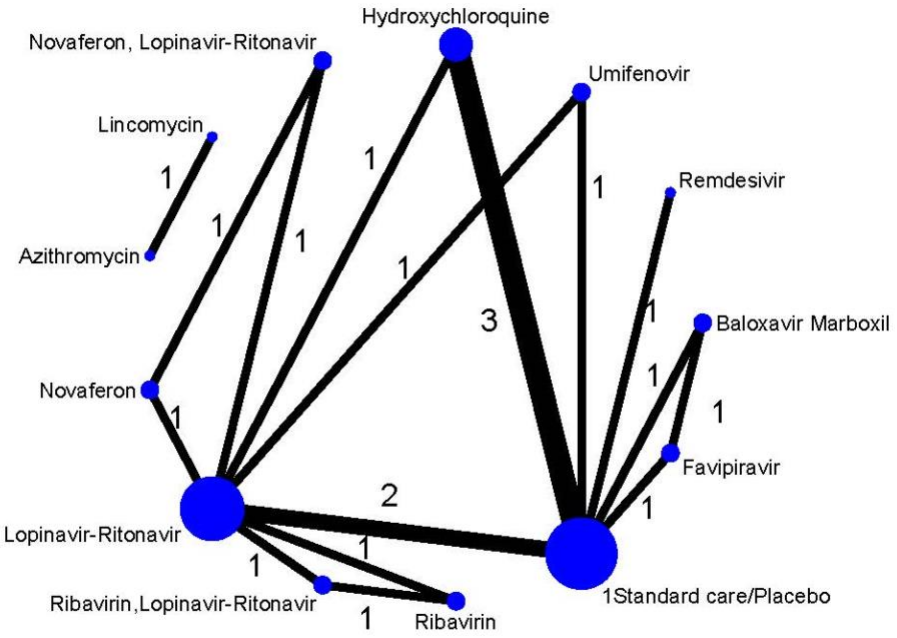
Mortality



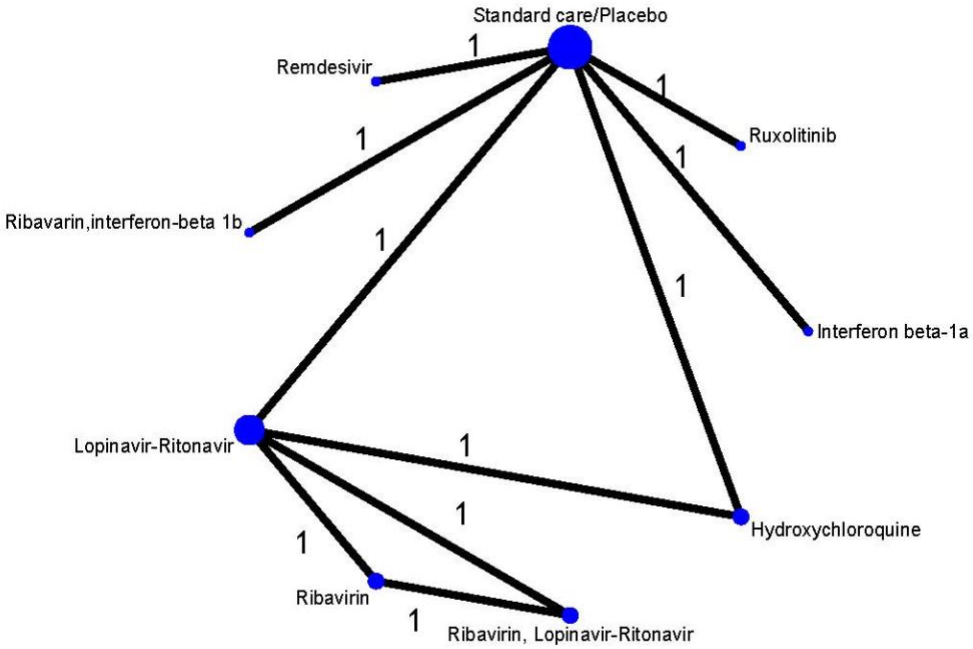
Mechanical ventilation



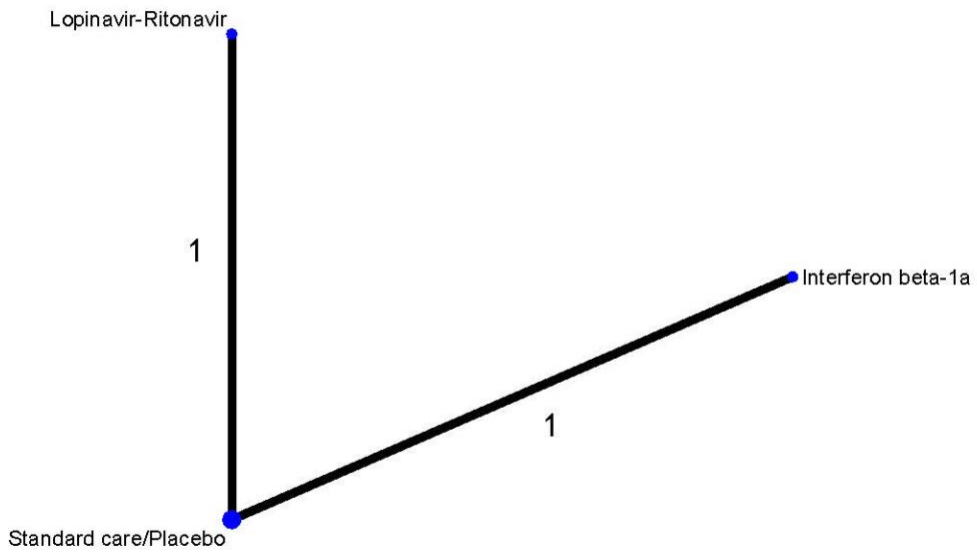
Adverse effects leading to drug discontinuation



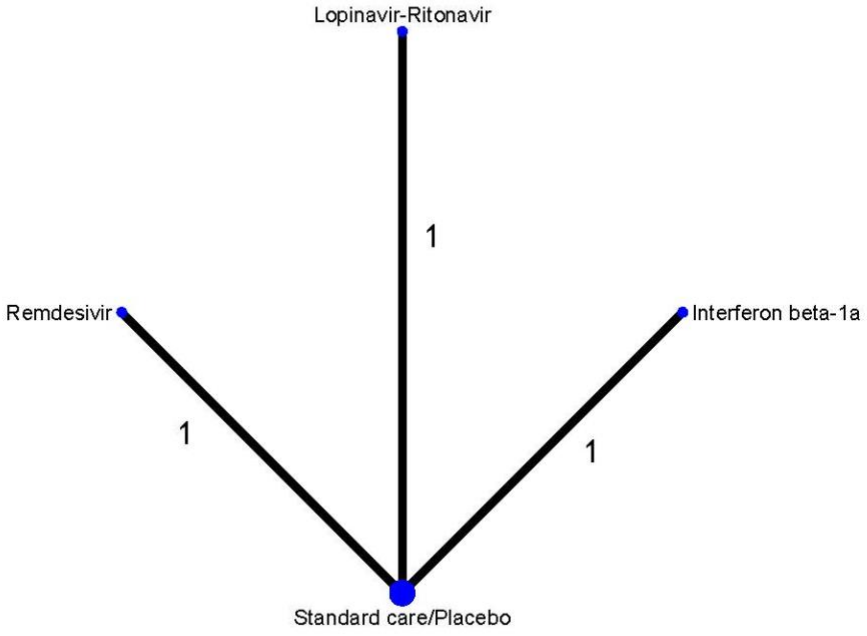
Viral clearance at 7 days (+/- 3 days)



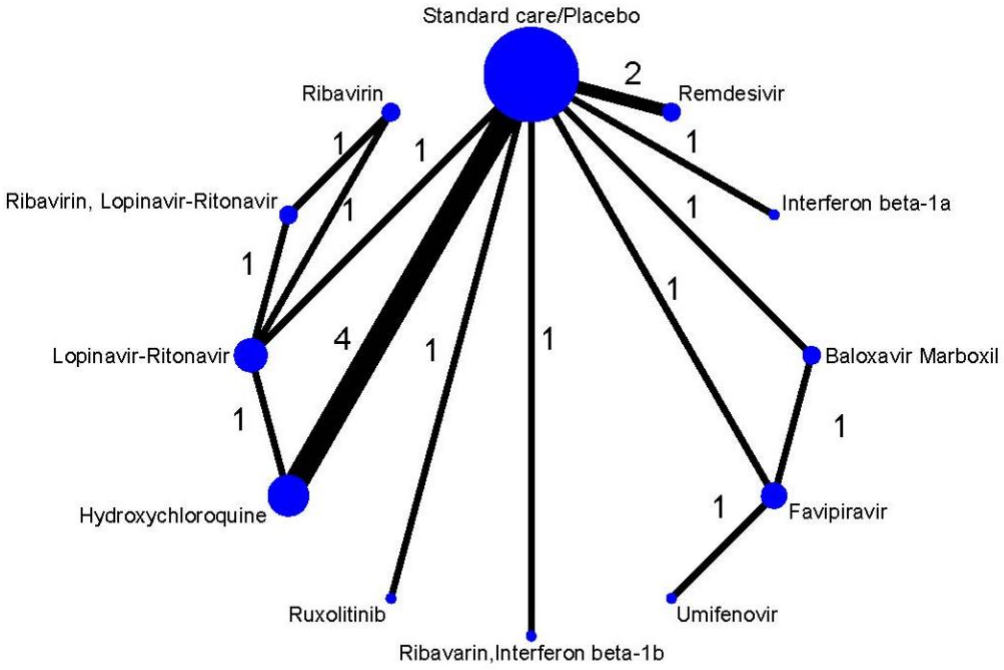
Duration of hospitalization



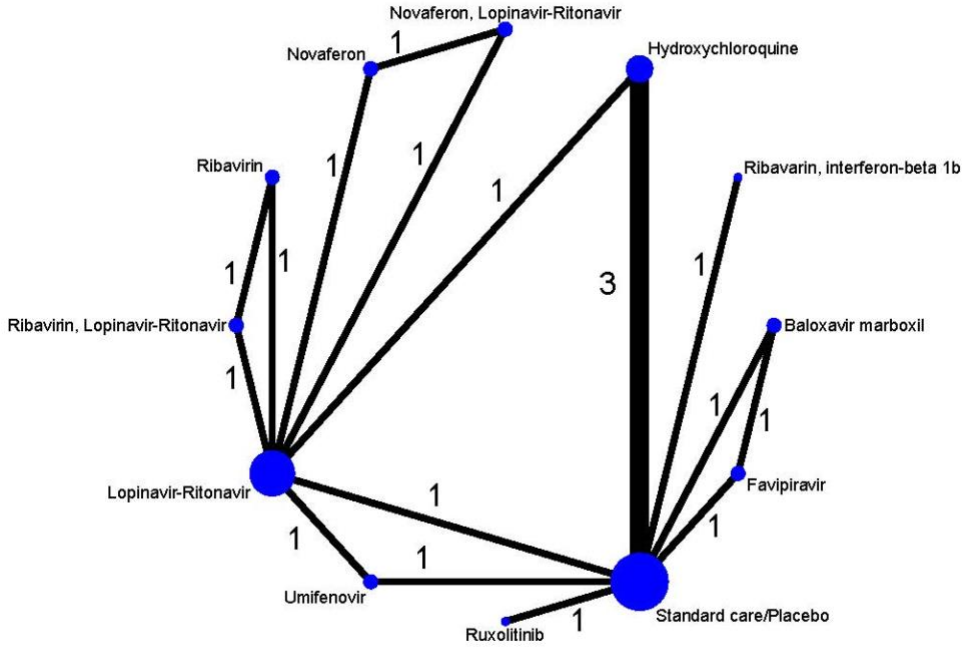
ICU length of stay



Duration of mechanical ventilation



Time to symptom resolution



Time to viral clearance

Mortality									
Intervention	Comparator	Relative effect point estimate (OR)	CI Lower limit	CI upper limit	Risk difference (per 1,000)	CI Lower limit	CI upper limit	Certainty	Reasons
α-lipoic acid	Standard care/Placebo	1.36E-01	9.90E-03	1.26E+00	-267.24	-325.15	53.12	VERY LOW	RoB, imprecisionx2
Baloxavir Marboxil	Standard care/Placebo	2.24E-08	1.67E-112	1.60E+32	-330	-330	670	VERY LOW	RoB, imprecisionx2
Favipiravir	Standard care/Placebo	1.61E+05	8.33E-27	1.25E+48	669.99	-330	670	VERY LOW	RoB, imprecisionx2
Hydroxychloroquine	Standard care/Placebo	5.13E-04	7.22E-31	4.93E+31	-329.75	-330	670	VERY LOW	RoB, imprecisionx2
Lopinavir-Ritonavir	Standard care/Placebo	7.09E-01	3.13E-01	1.59E+00	-71.13	-196.58	109.37	VERY LOW	RoB, imprecisionx2
Remdesivir	Standard care/Placebo	6.59E-01	4.03E-01	1.14E+00	-85.01	-164.24	29.28	LOW	RoB, imprecisionx2
Ribavirin	Standard care/Placebo	3.84E-14	5.58E-42	9.21E+30	-330	-330	670	VERY LOW	RoB, imprecisionx2
Ribavirin,Lopinavir-Ritonavir	Standard care/Placebo	2.61E+17	1.97E-34	1.04E+60	670	-330	670	VERY LOW	RoB, imprecisionx2
Ribavirin,interferon-beta 1b	Standard care/Placebo	6.65E+13	1.43E-40	5.50E+78	670	-330	670	VERY LOW	RoB, imprecisionx2
Umifenovir	Standard care/Placebo	1.16E-08	2.25E-32	1.41E+29	-330	-330	670	VERY LOW	RoB, imprecisionx2
Dexamethasone	Standard care/Placebo	8.41E-01	5.20E-01	1.36E+00	-37.17	-126.01	71.07	VERY LOW	RoB, imprecisionx2
Ruxolitinib	Standard care/Placebo	1.48E-29	9.30E-131	4.85E-03	-330	-330	-327.61	VERY LOW	RoB, imprecisionx2
Interferon beta-1a	Standard care/Placebo	4.47E-01	1.57E-01	1.24E+00	-149.73	-258.2	49.55	VERY LOW	RoB, imprecisionx2
Baloxavir Marboxil	α-lipoic acid	1.81E-07	1.19E-111	1.24E+33	-16.69	-318.06	990.72	VERY LOW	RoB, imprecisionx2
Favipiravir	α-lipoic acid	1.22E+06	5.20E-26	8.61E+48	795.01	-273.66	992.55	VERY LOW	RoB, imprecisionx2
Hydroxychloroquine	α-lipoic acid	4.06E-03	4.79E-30	4.14E+32	-10.97	-313.8	990.56	VERY LOW	RoB, imprecisionx2
Lopinavir-Ritonavir	α-lipoic acid	5.23E+00	4.90E-01	8.11E+01	182.6	-138.55	384.89	VERY LOW	RoB, imprecisionx2
Remdesivir	α-lipoic acid	4.88E+00	4.96E-01	7.04E+01	175.14	-143.13	312.5	VERY LOW	RoB, imprecisionx2
Ribavirin	α-lipoic acid	3.03E-13	5.41E-41	6.54E+31	-30.15	-336.55	988.15	VERY LOW	RoB, imprecisionx2
Ribavirin,Lopinavir-Ritonavir	α-lipoic acid	2.04E+18	1.23E-33	9.26E+60	887.24	-227.25	993.51	VERY LOW	RoB, imprecisionx2
Ribavirin,interferon-beta 1b	α-lipoic acid	5.19E+14	1.17E-39	3.92E+79	889.86	-226.85	993.94	VERY LOW	RoB, imprecisionx2
Umifenovir	α-lipoic acid	9.02E-08	2.45E-31	1.06E+30	-25.69	-333.38	987.75	VERY LOW	RoB, imprecisionx2
Dexamethasone	α-lipoic acid	6.20E+00	6.36E-01	8.81E+01	223.98	-97.08	350.19	VERY LOW	RoB, imprecisionx2
Ruxolitinib	α-lipoic acid	1.10E-28	5.98E-130	3.82E-02	-62.13	-381.91	-3.82	LOW	RoB, imprecision
Interferon beta-1a	α-lipoic acid	3.30E+00	2.83E-01	5.37E+01	106.03	-211.27	321.99	VERY LOW	RoB, imprecisionx2
Favipiravir	Baloxavir Marboxil	9.43E+14	7.26E-24	1.54E+113	0	-1000	1000	VERY LOW	RoB, imprecisionx2
Hydroxychloroquine	Baloxavir Marboxil	5.13E-02	1.57E-32	2.36E+96	0	-1000	1000	VERY LOW	RoB, imprecisionx2
Lopinavir-Ritonavir	Baloxavir Marboxil	3.11E+07	4.69E-33	4.62E+111	183.4	-841.45	411.18	VERY LOW	RoB, imprecisionx2
Remdesivir	Baloxavir Marboxil	3.02E+07	4.21E-33	4.07E+111	198.78	-816.83	339.54	VERY LOW	RoB, imprecisionx2
Ribavirin	Baloxavir Marboxil	3.60E-02	5.96E-62	1.17E+92	0	-1000	1000	VERY LOW	RoB, imprecisionx2
Ribavirin,Lopinavir-Ritonavir	Baloxavir Marboxil	1.05E+24	4.58E-60	1.73E+160	144.45	-1000	1000	VERY LOW	RoB, imprecisionx2
Ribavirin,interferon-beta 1b	Baloxavir Marboxil	1.04E+28	1.77E-33	1.49E+115	0	-995.82	1000	VERY LOW	RoB, imprecisionx2
Umifenovir	Baloxavir Marboxil	2.46E-07	1.42E-43	1.92E+123	0	-1000	1000	VERY LOW	RoB, imprecisionx2
Dexamethasone	Baloxavir Marboxil	3.79E+07	5.24E-33	5.06E+111	253.65	-766.91	376.14	VERY LOW	RoB, imprecisionx2
Ruxolitinib	Baloxavir Marboxil	3.23E-29	2.92E-137	3.84E+60	0	-1000	0	VERY LOW	RoB, imprecisionx2
Interferon beta-1a	Baloxavir Marboxil	2.00E+07	2.73E-33	3.01E+111	110.6	-909.63	348.89	VERY LOW	RoB, imprecisionx2
Hydroxychloroquine	Favipiravir	3.16E-02	3.89E-78	1.72E+35	0	-1000	1000	VERY LOW	RoB, imprecisionx2
Lopinavir-Ritonavir	Favipiravir	4.43E-06	5.92E-49	8.32E+25	-641.33	-851.31	393.48	VERY LOW	RoB, imprecisionx2
Remdesivir	Favipiravir	4.12E-06	5.47E-49	8.06E+25	-693.57	-823.65	327.49	VERY LOW	RoB, imprecisionx2
Ribavirin	Favipiravir	7.34E-17	3.64E-61	3.52E+13	0	-1000	12.99	VERY LOW	RoB, imprecisionx2
Ribavirin,Lopinavir-Ritonavir	Favipiravir	9.02E+12	8.04E-48	3.86E+65	0	-1000	1000	VERY LOW	RoB, imprecisionx2
Ribavirin,interferon-beta 1b	Favipiravir	6.06E+08	1.36E-85	8.48E+92	0	-1000	1000	VERY LOW	RoB, imprecisionx2
Umifenovir	Favipiravir	3.25E-13	7.54E-41	1.56E+27	0	-1000	1000	VERY LOW	RoB, imprecisionx2

Dexamethasone	Favipiravir	5.23E-06	6.74E-49	1.00E+26	-659	-777.48	361.85	VERY LOW	RoB, imprecisionx2
Ruxolitinib	Favipiravir	5.50E-46	2.50E-123	2.34E+14	-999.72	-1000	0	VERY LOW	RoB, imprecisionx2
Interferon beta-1a	Favipiravir	2.82E-06	3.49E-49	5.42E+25	-711.62	-917.14	327.07	VERY LOW	RoB, imprecisionx2
Lopinavir-Ritonavir	Hydroxychloroquine	1.34E+03	1.45E-32	9.58E+29	166.59	-842.65	408.79	VERY LOW	RoB, imprecisionx2
Remdesivir	Hydroxychloroquine	1.31E+03	1.33E-32	9.20E+29	186.91	-817.9	336.11	VERY LOW	RoB, imprecisionx2
Ribavirin	Hydroxychloroquine	2.97E-13	1.26E-69	1.70E+51	0	-1000	1000	VERY LOW	RoB, imprecisionx2
Ribavirin,Lopinavir-Ritonavir	Hydroxychloroquine	1.08E+15	3.71E-50	1.10E+80	72.61	-1000	1000	VERY LOW	RoB, imprecisionx2
Ribavirin,interferon-beta 1b	Hydroxychloroquine	2.08E+13	1.05E-17	1.75E+72	0	-993.74	1000	VERY LOW	RoB, imprecisionx2
Umifenovir	Hydroxychloroquine	1.26E-07	2.04E-55	5.41E+54	0	-1000	1000	VERY LOW	RoB, imprecisionx2
Dexamethasone	Hydroxychloroquine	1.64E+03	1.69E-32	1.15E+30	238.39	-768.38	372.97	VERY LOW	RoB, imprecisionx2
Ruxolitinib	Hydroxychloroquine	2.69E-23	8.10E-142	1.76E+07	-0.12	-1000	0	VERY LOW	RoB, imprecisionx2
Interferon beta-1a	Hydroxychloroquine	8.69E+02	9.11E-33	6.39E+29	97.09	-911.36	345.5	VERY LOW	RoB, imprecisionx2
Remdesivir	Lopinavir-Ritonavir	9.30E-01	3.64E-01	2.51E+00	-13.43	-207.94	157.5	VERY LOW	RoB, imprecisionx2
Ribavirin	Lopinavir-Ritonavir	5.21E-14	7.95E-42	1.45E+31	-214.13	-420.6	832.86	VERY LOW	RoB, imprecisionx2
Ribavirin,Lopinavir-Ritonavir	Lopinavir-Ritonavir	3.61E+17	2.60E-34	1.42E+60	697.56	-369.25	857.73	VERY LOW	RoB, imprecisionx2
Ribavirin,interferon-beta 1b	Lopinavir-Ritonavir	9.39E+13	1.94E-40	8.35E+78	698.01	-366.92	858.32	VERY LOW	RoB, imprecisionx2
Umifenovir	Lopinavir-Ritonavir	1.57E-08	3.40E-32	1.93E+29	-205.04	-417.06	833.78	VERY LOW	RoB, imprecisionx2
Dexamethasone	Lopinavir-Ritonavir	1.19E+00	4.67E-01	3.04E+00	33.6	-163.97	196.57	VERY LOW	RoB, imprecisionx2
Ruxolitinib	Lopinavir-Ritonavir	2.12E-29	1.24E-130	7.05E-03	-258.05	-438.88	-129.8	VERY LOW	RoB, imprecisionx2
Interferon beta-1a	Lopinavir-Ritonavir	6.30E-01	1.68E-01	2.35E+00	-76.02	-290.41	156.17	VERY LOW	RoB, imprecisionx2
Ribavirin	Remdesivir	5.57E-14	8.46E-42	1.33E+31	-217.73	-346.34	810.56	VERY LOW	RoB, imprecisionx2
Ribavirin,Lopinavir-Ritonavir	Remdesivir	3.88E+17	2.98E-34	1.56E+60	728.64	-311.54	827.57	VERY LOW	RoB, imprecisionx2
Ribavirin,interferon-beta 1b	Remdesivir	1.01E+14	2.13E-40	8.36E+78	729.58	-310.49	828.48	VERY LOW	RoB, imprecisionx2
Umifenovir	Remdesivir	1.73E-08	3.38E-32	2.07E+29	-212.9	-343.87	812.09	VERY LOW	RoB, imprecisionx2
Dexamethasone	Remdesivir	1.28E+00	6.09E-01	2.46E+00	48.16	-97.74	174.62	VERY LOW	RoB, imprecisionx2
Ruxolitinib	Remdesivir	2.24E-29	1.36E-130	7.25E-03	-244.4	-358.89	-161.5	VERY LOW	RoB, imprecisionx2
Interferon beta-1a	Remdesivir	6.76E-01	2.07E-01	2.09E+00	-63.94	-223.81	146.37	VERY LOW	RoB, imprecisionx2
Ribavirin,Lopinavir-Ritonavir	Ribavirin	1.68E+28	1.87E-13	2.20E+74	0.73	-0.12	1000	VERY LOW	RoB, imprecisionx2
Ribavirin,interferon-beta 1b	Ribavirin	8.20E+28	9.86E-57	5.07E+97	999.56	-1000	1000	VERY LOW	RoB, imprecisionx2
Umifenovir	Ribavirin	2.27E+08	1.13E-37	6.88E+39	0	-1000	1000	VERY LOW	RoB, imprecisionx2
Dexamethasone	Ribavirin	2.15E+13	9.14E-32	1.50E+41	272.42	-758.03	384.44	VERY LOW	RoB, imprecisionx2
Ruxolitinib	Ribavirin	2.07E-26	2.02E-124	5.40E+31	0	-1000	0	VERY LOW	RoB, imprecisionx2
Interferon beta-1a	Ribavirin	1.09E+13	5.17E-32	8.60E+40	137.07	-902.47	358.2	VERY LOW	RoB, imprecisionx2
Ribavirin,interferon-beta 1b	Ribavirin,Lopinavir-Ritonavir	1.04E+05	4.47E-91	2.22E+69	0	-1000	1000	VERY LOW	RoB, imprecisionx2
Umifenovir	Ribavirin,Lopinavir-Ritonavir	2.15E-26	3.63E-68	6.86E+37	-759.69	-1000	1000	VERY LOW	RoB, imprecisionx2
Dexamethasone	Ribavirin,Lopinavir-Ritonavir	3.23E-18	8.01E-61	4.35E+33	-688.52	-784.17	344.96	VERY LOW	RoB, imprecisionx2
Ruxolitinib	Ribavirin,Lopinavir-Ritonavir	3.22E-54	5.71E-152	2.98E+24	-1000	-1000	0	VERY LOW	RoB, imprecisionx2
Interferon beta-1a	Ribavirin,Lopinavir-Ritonavir	1.75E-18	4.04E-61	1.93E+33	-773.87	-921.47	298.2	VERY LOW	RoB, imprecisionx2
Umifenovir	Ribavirin,interferon-beta 1b	7.88E-23	5.49E-100	1.17E+68	-999.75	-1000	1000	VERY LOW	RoB, imprecisionx2
Dexamethasone	Ribavirin,interferon-beta 1b	1.26E-14	1.51E-79	5.85E+39	-689.19	-785.79	344.31	VERY LOW	RoB, imprecisionx2
Ruxolitinib	Ribavirin,interferon-beta 1b	1.07E-34	6.67E-210	2.61E+07	-1000	-1000	0	VERY LOW	RoB, imprecisionx2
Interferon beta-1a	Ribavirin,interferon-beta 1b	6.63E-15	8.50E-80	3.27E+39	-775.66	-922.18	299.87	VERY LOW	RoB, imprecisionx2
Dexamethasone	Umifenovir	7.20E+07	6.07E-30	3.71E+31	267.65	-759.59	382.04	VERY LOW	RoB, imprecisionx2
Ruxolitinib	Umifenovir	1.00E-27	2.11E-110	1.93E+09	0	-1000	1.71	VERY LOW	RoB, imprecisionx2
Interferon beta-1a	Umifenovir	4.00E+07	3.33E-30	2.05E+31	130.05	-904.37	355.36	VERY LOW	RoB, imprecisionx2

Ruxolitinib	Dexamethasone	1.76E-29	1.10E-130	5.81E-03	-292.31	-400.56	-197.52	VERY LOW	RoB, imprecisionx2
Interferon beta-1a	Dexamethasone	5.31E-01	1.69E-01	1.63E+00	-111.21	-262.68	101.76	VERY LOW	RoB, imprecisionx2
Interferon beta-1a	Ruxolitinib	3.03E+28	8.98E+01	5.09E+129	179.44	68.7	378.99	LOW	RoB, imprecisionx2
Mechanical ventilation									
Intervention	**Comparator**	**Relative effect point estimate (OR)**	**CI Lower limit**	**CI upper limit**	**Risk difference (per 1,000)**	**CI Lower limit**	**CI upper limit**	**Certainty**	**Reasons**
Baloxavir Marboxil	Standard care/Placebo	2.58E+12	3.96E+00	7.03E+34	884	226	884	VERY LOW	RoB, Imprecisionx2
Dexamethasone	Standard care/Placebo	0.71	2.90E-01	1.73E+00	-31	-79	69	VERY LOW	RoB, Imprecisionx2
Favipiravir	Standard care/Placebo	0	0.00E+00	7.68E+13	-116	-116	884	VERY LOW	RoB, Imprecisionx2
Interferon beta-1a	Standard care/Placebo	0.81	0.17	3.8	-20	-94	217	VERY LOW	RoBx2, Imprecisionx2
Lopinavir-Ritonavir	Standard care/Placebo	0.69	0.22	2.12	-33	-88	102	VERY LOW	RoB, Imprecisionx2
Remdesivir	Standard care/Placebo	0.77	0.37	1.54	-24	-70	52	LOW	Imprecisionx2
Ribavirin,interferon-beta 1b	Standard care/Placebo	0	0	0.23	-116	-116	-87	VERY LOW	RoB, Imprecisionx2
Ruxolitinib	Standard care/Placebo	0	0	0	-116	-116	-116	VERY LOW	RoB, Imprecisionx2
Dexamethasone	Baloxavir Marboxil	0	0	0.18	-911	-961	-245	VERY LOW	RoB, Imprecisionx2
Favipiravir	Baloxavir Marboxil	0	0	1.00E-02	-1000	-1000	0	VERY LOW	RoB, Imprecisionx2
Interferon beta-1a	Baloxavir Marboxil	0	0	2.10E-01	-895	-977	-222	VERY LOW	RoBx2, Imprecisionx2
Lopinavir-Ritonavir	Baloxavir Marboxil	0	0	1.80E-01	-911	-970	-243	VERY LOW	RoB, Imprecisionx2
Remdesivir	Baloxavir Marboxil	0	0	0.2	-905	-952	-245	VERY LOW	RoB, Imprecisionx2
Ribavirin,interferon-beta 1b	Baloxavir Marboxil	0	0	0.00E+00	-1000	-1000	-316	VERY LOW	RoB, Imprecisionx2
Ruxolitinib	Baloxavir Marboxil	0	0	0.00E+00	-1000	-1000	-342	VERY LOW	RoB, Imprecisionx2
Favipiravir	Dexamethasone	0	0	1.07E+14	-80	-172	932	VERY LOW	RoB, Imprecisionx2
Interferon beta-1a	Dexamethasone	1.13	0.19	6.63E+00	10	-108	246	VERY LOW	RoBx2, Imprecisionx2
Lopinavir-Ritonavir	Dexamethasone	0.97	0.23	4.00E+00	-2	-111	136	VERY LOW	RoB, Imprecisionx2
Remdesivir	Dexamethasone	1.08	0.34	3.29	6	-100	93	VERY LOW	RoB, Imprecisionx2
Ribavirin,interferon-beta 1b	Dexamethasone	0	0	0.33	-84	-183	-24	VERY LOW	RoB, Imprecisionx2
Ruxolitinib	Dexamethasone	0	0	0	-85	-185	-37	VERY LOW	RoB, Imprecisionx2
Interferon beta-1a	Favipiravir	3.84E+26	0.00E+00	7.79E+88	79	-950	314	VERY LOW	RoBx2, Imprecisionx2
Lopinavir-Ritonavir	Favipiravir	3.31E+26	0.00E+00	6.91E+88	73	-945	205	VERY LOW	RoB, Imprecisionx2
Remdesivir	Favipiravir	3.60E+26	0.00E+00	7.80E+88	85	-927	160	VERY LOW	RoB, Imprecisionx2
Ribavirin,interferon-beta 1b	Favipiravir	7.98E+15	0.00E+00	2.91E+75	0	-1000	26	VERY LOW	RoB, Imprecisionx2
Ruxolitinib	Favipiravir	0	0.00E+00	3.42E+15	0	-1000	0	VERY LOW	RoB, Imprecisionx2
Lopinavir-Ritonavir	Interferon beta-1a	0.85	0.12	5.86	-12	-249	139	VERY LOW	RoBx2, Imprecisionx2
Remdesivir	Interferon beta-1a	0.95	0.17	5.21E+00	-4	-241	101	VERY LOW	RoBx2, Imprecisionx2
Ribavirin,interferon-beta 1b	Interferon beta-1a	0	0	0.32	-94	-331	-15	VERY LOW	RoBx2, Imprecisionx2
Ruxolitinib	Interferon beta-1a	0	0	0	-96	-333	-22	VERY LOW	RoBx2, Imprecisionx2
Remdesivir	Lopinavir-Ritonavir	1.11	0.29	4.16	8	-131	100	VERY LOW	RoB, Imprecisionx2
Ribavirin,interferon-beta 1b	Lopinavir-Ritonavir	0	0	0.34	-82	-217	-19	VERY LOW	RoB, Imprecisionx2
Ruxolitinib	Lopinavir-Ritonavir	0	0	0	-83	-218	-28	VERY LOW	RoB, Imprecisionx2
Ribavirin,interferon-beta 1b	Remdesivir	0	0	0.3	-91	-167	-33	VERY LOW	RoB, Imprecisionx2
Ruxolitinib	Remdesivir	0	0	0	-92	-168	-46	VERY LOW	RoB, Imprecisionx2
Ruxolitinib	Ribavirin,interferon-beta 1b	0	0	2.82E+16	0	-29	0	VERY LOW	RoB, Imprecisionx2
Adverse events leading to discontinuation									

Intervention	Comparator	Relative effect point estimate (OR)	CI Lower limit	CI upper limit	Risk difference (per 1,000)	CI Lower limit	CI upper limit	Certainty	Reasons
Chloroquine	Standard care/Placebo	1.50E+34	5.13E+05	8.21E+89	985.1	984.97	985.1	VERY LOW	RoB, Imprecision
Diammonium Glycyrrhizinate	Standard care/Placebo	1.79E-23	3.41E-54	9.99E+30	-14.9	-14.9	985.1	VERY LOW	RoB, Imprecision
Hydroxychloroquine	Standard care/Placebo	1.60E+06	2.72E+00	3.77E+22	985.06	24.68	985.1	VERY LOW	RoB, Imprecision
Interferon beta-1a	Standard care/Placebo	2.28E+37	1.77E+13	1.20E+77	985.1	985.1	985.1	VERY LOW	RoB, Imprecision
Lopinavir-Ritonavir	Standard care/Placebo	6.73E+30	3.30E+08	2.23E+71	985.1	985.1	985.1	VERY LOW	RoB, Imprecision
Novaferon	Standard care/Placebo	8.94E+49	1.04E-05	8.75E+122	985.1	-14.9	985.1	VERY LOW	RoB, Imprecision
Novaferon, Lopinavir-Ritonavir	Standard care/Placebo	4.62E+04	6.93E-60	2.17E+89	983.67	-14.9	985.1	VERY LOW	RoB, Imprecision
Remdesivir	Standard care/Placebo	1.26E+00	5.12E-01	3.96E+00	3.84	-7.22	41.59	MODERATE	Imprecision
Ribavirin,interferon beta-1b	Standard care/Placebo	3.60E-14	2.96E-46	1.24E-01	-14.9	-14.9	-13.03	VERY LOW	RoB, Imprecision
Umifenovir	Standard care/Placebo	1.60E-12	9.61E-40	2.69E+19	-14.9	-14.9	985.1	VERY LOW	RoB, Imprecision
α-lipoic acid	Standard care/Placebo	4.14E-04	1.65E-40	3.43E+49	-14.89	-14.9	985.1	VERY LOW	RoB, Imprecision
Diammonium Glycyrrhizinate	Chloroquine	1.38E-56	1.86E-122	1.28E+19	-1000	-1000	0	VERY LOW	RoB, Imprecision
Hydroxychloroquine	Chloroquine	1.81E-24	1.19E-86	3.29E-02	-0.04	-957.19	0	VERY LOW	RoB, Imprecision
Interferon beta-1a	Chloroquine	1.16E+09	4.06E-65	7.86E+56	0	0	0.13	VERY LOW	RoB, Imprecision
Lopinavir-Ritonavir	Chloroquine	7.08E-05	1.15E-51	1.72E+51	0	0	0.12	VERY LOW	RoB, Imprecision
Novaferon	Chloroquine	2.13E+20	7.20E-68	9.05E+83	0	-999.98	0.1	VERY LOW	RoB, Imprecision
Novaferon, Lopinavir-Ritonavir	Chloroquine	1.08E-28	1.28E-100	4.55E+56	-1.22	-1000	0	VERY LOW	RoB, Imprecision
Remdesivir	Chloroquine	8.69E-35	1.55E-90	2.59E-06	-981.14	-992.28	-937.73	VERY LOW	RoB, Imprecision
Ribavirin,interferon beta-1b	Chloroquine	6.34E-49	2.60E-125	3.30E-16	-1000	-1000	-994.52	VERY LOW	RoB, Imprecision
Umifenovir	Chloroquine	1.76E-46	1.45E-103	8.37E+04	-1000	-1000	0	VERY LOW	RoB, Imprecision
α-lipoic acid	Chloroquine	1.18E-36	4.84E-107	5.59E+08	-999.94	-1000	0	VERY LOW	RoB, Imprecision
Hydroxychloroquine	Diammonium Glycyrrhizinate	2.90E+29	2.78E-27	1.96E+62	983.57	-240.85	1000	VERY LOW	RoB, Imprecision
Interferon beta-1a	Diammonium Glycyrrhizinate	6.84E+61	2.19E-07	1.09E+115	1000	0	1000	VERY LOW	RoB, Imprecision
Lopinavir-Ritonavir	Diammonium Glycyrrhizinate	1.16E+52	1.13E-09	1.07E+123	1000	0	1000	VERY LOW	RoB, Imprecision
Novaferon	Diammonium Glycyrrhizinate	1.20E+66	1.16E+15	3.37E+137	1000	0	1000	VERY LOW	RoB, Imprecision
Novaferon, Lopinavir-Ritonavir	Diammonium Glycyrrhizinate	9.24E+24	2.94E-53	2.94E+122	0	-1000	1000	VERY LOW	RoB, Imprecision
Remdesivir	Diammonium Glycyrrhizinate	7.29E+22	1.23E-31	3.78E+53	15.49	-988.61	49.71	VERY LOW	RoB, Imprecision
Ribavirin,interferon beta-1b	Diammonium Glycyrrhizinate	6.13E+02	1.14E-76	2.03E+46	0	-1000	1.75	VERY LOW	RoB, Imprecision
Umifenovir	Diammonium Glycyrrhizinate	3.78E+03	1.23E-30	1.98E+47	0	-1000	1000	VERY LOW	RoB, Imprecision
α-lipoic acid	Diammonium Glycyrrhizinate	1.79E+17	8.11E-40	9.15E+58	0	-1000	1000	VERY LOW	RoB, Imprecision
Interferon beta-1a	Hydroxychloroquine	1.24E+30	3.50E+06	2.01E+74	0.04	0	960.42	VERY LOW	RoB, Imprecision
Lopinavir-Ritonavir	Hydroxychloroquine	1.75E+24	7.06E-06	2.80E+67	0.04	0	960.39	VERY LOW	RoB, Imprecision
Novaferon	Hydroxychloroquine	2.84E+41	3.91E-10	5.26E+119	0.01	-922.06	959.5	VERY LOW	RoB, Imprecision
Novaferon, Lopinavir-Ritonavir	Hydroxychloroquine	5.47E-02	4.38E-74	1.35E+77	0	-1000	911.64	VERY LOW	RoB, Imprecision
Remdesivir	Hydroxychloroquine	8.14E-07	3.59E-23	5.06E-01	-975.9	-991.18	-18.55	VERY LOW	RoB, Imprecision
Ribavirin,interferon beta-1b	Hydroxychloroquine	5.70E-24	7.33E-57	2.01E-05	-999.87	-1000	-39.31	VERY LOW	RoB, Imprecision
Umifenovir	Hydroxychloroquine	1.96E-21	6.30E-51	1.05E+15	-998.23	-1000	709.12	VERY LOW	RoB, Imprecision
α-lipoic acid	Hydroxychloroquine	1.96E-12	2.18E-49	4.59E+42	-643.48	-1000	806.68	VERY LOW	RoB, Imprecision
Lopinavir-Ritonavir	Interferon beta-1a	3.06E-04	2.23E-51	1.36E+27	0	0	0	VERY LOW	RoB, Imprecision
Novaferon	Interferon beta-1a	1.18E+08	8.41E-55	1.49E+97	0	-1000	0	VERY LOW	RoB, Imprecision
Novaferon, Lopinavir-Ritonavir	Interferon beta-1a	2.90E-33	2.71E-125	2.17E+54	-1.43	-1000	0	VERY LOW	RoB, Imprecision
Remdesivir	Interferon beta-1a	5.73E-38	1.07E-77	7.41E-14	-981.26	-992.31	-943.51	VERY LOW	RoB, Imprecision
Ribavirin,interferon beta-1b	Interferon beta-1a	3.04E-59	4.50E-102	3.73E-22	-1000	-1000	-998.12	VERY LOW	RoB, Imprecision
Umifenovir	Interferon beta-1a	1.58E-50	1.48E-106	1.17E-04	-1000	-1000	0	VERY LOW	RoB, Imprecision

α-lipoic acid	Interferon beta-1a	1.05E-41	5.60E-109	7.01E+23	-999.99	-1000	0	VERY LOW	RoB, Imprecision
Novaferon	Lopinavir-Ritonavir	1.57E+13	3.04E-54	9.77E+103	0	-996.29	0	VERY LOW	RoB, Imprecision
Novaferon, Lopinavir-Ritonavir	Lopinavir-Ritonavir	1.51E-26	8.14E-96	1.60E+54	-1.41	-1000	0	VERY LOW	RoB, Imprecision
Remdesivir	Lopinavir-Ritonavir	1.93E-31	6.02E-72	3.90E-09	-981.21	-992.29	-939.59	VERY LOW	RoB, Imprecision
Ribavirin,interferon beta-1b	Lopinavir-Ritonavir	5.20E-49	7.93E-91	3.24E-13	-1000	-1000	-996.87	VERY LOW	RoB, Imprecision
Umifenovir	Lopinavir-Ritonavir	6.35E-39	1.18E-94	3.11E-05	-1000	-1000	0	VERY LOW	RoB, Imprecision
α-lipoic acid	Lopinavir-Ritonavir	4.93E-34	2.39E-97	4.98E+24	-999.99	-1000	0	VERY LOW	RoB, Imprecision
Novaferon, Lopinavir-Ritonavir	Novaferon	1.83E-41	5.26E-157	8.28E+44	0	-1000	0	VERY LOW	RoB, Imprecision
Remdesivir	Novaferon	1.49E-50	1.50E-123	1.32E+05	-980.83	-992.2	13.78	VERY LOW	RoB, Imprecision
Ribavirin,interferon beta-1b	Novaferon	4.40E-72	3.17E-137	5.64E-01	-1000	-1000	0	VERY LOW	RoB, Imprecision
Umifenovir	Novaferon	1.40E-60	3.29E-132	2.46E-08	-1000	-1000	0	VERY LOW	RoB, Imprecision
α-lipoic acid	Novaferon	3.65E-58	4.07E-132	4.72E+09	-999.95	-1000	752.13	VERY LOW	RoB, Imprecision
Remdesivir	Novaferon, Lopinavir-Ritonavir	2.77E-05	6.02E-90	1.92E+59	-943.77	-990.59	41.5	VERY LOW	RoB, Imprecision
Ribavirin,interferon beta-1b	Novaferon, Lopinavir-Ritonavir	2.49E-26	4.93E-119	1.16E+55	-995.23	-1000	0.62	VERY LOW	RoB, Imprecision
Umifenovir	Novaferon, Lopinavir-Ritonavir	2.76E-15	7.39E-108	2.16E+44	0	-1000	1000	VERY LOW	RoB, Imprecision
α-lipoic acid	Novaferon, Lopinavir-Ritonavir	1.42E-07	3.39E-97	2.02E+53	0	-1000	1000	VERY LOW	RoB, Imprecision
Ribavirin,interferon beta-1b	Remdesivir	2.74E-14	2.21E-46	9.70E-02	-18.58	-56.25	-6.57	VERY LOW	RoB, Imprecision
Umifenovir	Remdesivir	1.23E-12	7.20E-40	2.10E+19	-15.93	-50.95	987.4	VERY LOW	RoB, Imprecision
α-lipoic acid	Remdesivir	3.18E-04	1.26E-40	2.50E+49	-11.68	-44.8	989.68	VERY LOW	RoB, Imprecision
Umifenovir	Ribavirin,interferon beta-1b	2.45E+03	2.29E-30	8.98E+61	0	-1.41	1000	VERY LOW	RoB, Imprecision
α-lipoic acid	Ribavirin,interferon beta-1b	4.45E+15	8.04E-28	7.06E+64	0.01	-0.82	1000	VERY LOW	RoB, Imprecision
α-lipoic acid	Umifenovir	1.55E+08	5.56E-31	1.91E+55	0	-1000	1000	VERY LOW	RoB, Imprecision
Viral clearance									
Intervention	**Comparator**	**Relative effect point estimate (OR)**	**CI Lower limit**	**CI upper limit**	**Risk difference (per 1,000)**	**CI Lower limit**	**CI upper limit**	**Certainty**	**Reasons**
Baloxavir Marboxil	Standard care/Placebo	1.56	0.03	75.02	109.23	-467.91	486.85	VERY LOW	Risk of bias, Imprecisionx2
Favipiravir	Standard care/Placebo	0.78	0.02	37.65	-61.46	-484.37	474.13	VERY LOW	Risk of bias, Imprecisionx2
Hydroxychloroquine	Standard care/Placebo	1.4	0.19	10.58	82.5	-342.9	413.67	VERY LOW	Risk of bias, Imprecisionx2
Lopinavir-Ritonavir	Standard care/Placebo	0.35	0.02	2.77	-238.91	-478.1	234.68	VERY LOW	Risk of bias, Inconsistency, Imprecisionx2
Novaferon	Standard care/Placebo	1.16	0.01	63.51	36.9	-489.24	484.5	VERY LOW	Risk of bias, Inconsistency, Imprecisionx2
Novaferon, Lopinavir-Ritonavir	Standard care/Placebo	1.78	0.02	98	139.97	-483.56	489.9	VERY LOW	Risk of bias, Inconsistency, Imprecisionx2
Remdesivir	Standard care/Placebo	1.05	0.03	34.43	11.19	-468.95	471.78	LOW	Imprecisionx2
Ribavirin	Standard care/Placebo	0.15	0	8.59	-367.21	-498.58	395.72	VERY LOW	Risk of bias, Inconsistency, Imprecisionx2
Ribavirin,Lopinavir-Ritonavir	Standard care/Placebo	0.08	0	4.93	-423.42	-499.29	331.51	VERY LOW	Risk of bias, Inconsistency, Imprecisionx2
Umifenovir	Standard care/Placebo	0.15	0	3.37	-366.08	-498.29	270.91	VERY LOW	Risk of bias, Imprecisionx2
Favipiravir	Baloxavir Marboxil	0.5	0.01	24.03	-94.97	-722.84	525.91	VERY LOW	Risk of bias, Imprecisionx2
Hydroxychloroquine	Baloxavir Marboxil	0.9	0.01	70.34	-21.5	-658.58	700.49	VERY LOW	Risk of bias, Imprecisionx2
Lopinavir-Ritonavir	Baloxavir Marboxil	0.22	0	15.59	-297.9	-879.16	423.96	VERY LOW	Risk of bias, Inconsistency, Imprecisionx2
Novaferon	Baloxavir Marboxil	0.74	0	180.03	-45.03	-865.24	780.4	VERY LOW	Risk of bias, Inconsistency, Imprecisionx2
Novaferon, Lopinavir-Ritonavir	Baloxavir Marboxil	1.13	0	273.32	15.7	-837.58	812.26	VERY LOW	Risk of bias, Inconsistency, Imprecisionx2
Remdesivir	Baloxavir Marboxil	0.67	0	118.86	-67	-819.04	750.61	VERY LOW	Risk of bias, Imprecisionx2
Ribavirin	Baloxavir Marboxil	0.1	0	24.11	-370.59	-941.38	520.18	VERY LOW	Risk of bias, Inconsistency, Imprecisionx2
Ribavirin,Lopinavir-Ritonavir	Baloxavir Marboxil	0.05	0	13.66	-437.39	-952.95	413.22	VERY LOW	Risk of bias, Inconsistency, Imprecisionx2
Umifenovir	Baloxavir Marboxil	0.1	0	11.5	-388.32	-942.63	391.93	VERY LOW	Risk of bias, Imprecisionx2
Hydroxychloroquine	Favipiravir	1.79	0.02	144.31	120.7	-601.4	756	VERY LOW	Risk of bias, Imprecisionx2

Lopinavir-Ritonavir	Favipiravir	0.44	0	32.39	-148.59	-841.81	498.34	VERY LOW	Risk of bias, Inconsistency, Imprecisionx2
Novaferon	Favipiravir	1.47	0	369.42	58.76	-814.41	843.27	VERY LOW	Risk of bias, Inconsistency, Imprecisionx2
Novaferon, Lopinavir-Ritonavir	Favipiravir	2.26	0	569.65	130.52	-780.46	869.51	VERY LOW	Risk of bias, Inconsistency, Imprecisionx2
Remdesivir	Favipiravir	1.34	0.01	250.9	49.39	-763.34	813.76	VERY LOW	Risk of bias, Imprecisionx2
Ribavirin	Favipiravir	0.19	0	49.41	-222.49	-911.12	615	VERY LOW	Risk of bias, Inconsistency, Imprecisionx2
Ribavirin,Lopinavir-Ritonavir	Favipiravir	0.11	0	27.97	-281.68	-926.91	512.15	VERY LOW	Risk of bias, Inconsistency, Imprecisionx2
Umifenovir	Favipiravir	0.19	0	23.65	-236.35	-914.14	482.26	VERY LOW	Risk of bias, Imprecisionx2
Lopinavir-Ritonavir	Hydroxychloroquine	0.25	0.01	2.6	-282.42	-727.68	193.78	VERY LOW	Risk of bias, Imprecisionx2
Novaferon	Hydroxychloroquine	0.83	0.01	52.39	-37.55	-720.45	582.37	VERY LOW	Risk of bias, Imprecisionx2
Novaferon, Lopinavir-Ritonavir	Hydroxychloroquine	1.27	0.01	81.09	44.08	-688.45	618.18	VERY LOW	Risk of bias, Imprecisionx2
Remdesivir	Hydroxychloroquine	0.75	0.01	42.1	-59.52	-713.27	606.5	VERY LOW	Risk of bias, Imprecisionx2
Ribavirin	Hydroxychloroquine	0.11	0	7.13	-375.73	-824.26	341.37	VERY LOW	Risk of bias, Imprecisionx2
Ribavirin,Lopinavir-Ritonavir	Hydroxychloroquine	0.06	0	4.1	-434.94	-844.08	251.87	VERY LOW	Risk of bias, Imprecisionx2
Umifenovir	Hydroxychloroquine	0.11	0	3.22	-385.19	-833.85	231.28	VERY LOW	Risk of bias, Imprecisionx2
Novaferon	Lopinavir-Ritonavir	3.29	0.09	121.37	221.82	-257.8	739.67	VERY LOW	Risk of bias, Imprecisionx2
Novaferon, Lopinavir-Ritonavir	Lopinavir-Ritonavir	5.04	0.14	188.16	306.6	-209.36	773.72	VERY LOW	Risk of bias, Imprecisionx2
Remdesivir	Lopinavir-Ritonavir	2.94	0.06	290.73	211.88	-441.29	843.15	VERY LOW	Risk of bias, Inconsistency, Imprecisionx2
Ribavirin	Lopinavir-Ritonavir	0.44	0.01	16.47	-79.88	-469.8	495.19	VERY LOW	Risk of bias, Imprecisionx2
Ribavirin,Lopinavir-Ritonavir	Lopinavir-Ritonavir	0.24	0.01	9.57	-127.13	-522.51	400.91	VERY LOW	Risk of bias, Imprecisionx2
Umifenovir	Lopinavir-Ritonavir	0.44	0.01	9.27	-85.12	-527.13	407.59	VERY LOW	Risk of bias, Imprecisionx2
Novaferon, Lopinavir-Ritonavir	Novaferon	1.53	0.04	55.38	46.12	-494.41	626.64	VERY LOW	Risk of bias, Imprecisionx2
Remdesivir	Novaferon	0.9	0	325.92	-17.24	-792.03	818.44	VERY LOW	Risk of bias, Inconsistency, Imprecisionx2
Ribavirin	Novaferon	0.13	0	21.97	-286.45	-891.33	448.12	VERY LOW	Risk of bias, Imprecisionx2
Ribavirin,Lopinavir-Ritonavir	Novaferon	0.07	0	12.6	-353.23	-914.65	336.52	VERY LOW	Risk of bias, Imprecisionx2
Umifenovir	Novaferon	0.13	0	13.54	-308.13	-904.17	348.12	VERY LOW	Risk of bias, Imprecisionx2
Remdesivir	Novaferon, Lopinavir-Ritonavir	0.58	0	216.98	-89.14	-822.24	787.03	VERY LOW	Risk of bias, Inconsistency, Imprecisionx2
Ribavirin	Novaferon, Lopinavir-Ritonavir	0.09	0	14.52	-374.4	-913.59	384.03	VERY LOW	Risk of bias, Imprecisionx2
Ribavirin,Lopinavir-Ritonavir	Novaferon, Lopinavir-Ritonavir	0.05	0	8.25	-445.69	-933.33	273.64	VERY LOW	Risk of bias, Imprecisionx2
Umifenovir	Novaferon, Lopinavir-Ritonavir	0.09	0	8.78	-397.72	-923.12	289.34	VERY LOW	Risk of bias, Imprecisionx2
Ribavirin	Remdesivir	0.15	0	27.76	-293.62	-909.19	552.16	VERY LOW	Risk of bias, Inconsistency, Imprecisionx2
Ribavirin,Lopinavir-Ritonavir	Remdesivir	0.08	0	15.75	-356.14	-924.08	450.64	VERY LOW	Risk of bias, Inconsistency, Imprecisionx2
Umifenovir	Remdesivir	0.15	0	12.52	-303.37	-913.49	417.17	VERY LOW	Risk of bias, Imprecisionx2
Ribavirin,Lopinavir-Ritonavir	Ribavirin	0.55	0.01	23.07	-25.5	-593.2	404.85	VERY LOW	Risk of bias, Imprecisionx2
Umifenovir	Ribavirin	1	0	104.71	0.05	-724.13	566.75	VERY LOW	Risk of bias, Imprecisionx2
Umifenovir	Ribavirin,Lopinavir-Ritonavir	1.83	0.01	204.7	28.87	-633.98	612.46	VERY LOW	Risk of bias, Imprecisionx2
Duration of hospitalization									
Intervention	**Comparator**	**Relative effect point estimate (MD)**	**CI Lower limit**	**CI upper limit**	**Absolute effect**	**CI Lower limit**	**CI upper limit**	**Certainty**	**Reasons**
Hydroxychloroquine	Standard care/Placebo	-5.12	-7.93	-2.23				LOW	Risk of Bias
Interferon beta-1a	Standard care/Placebo	2.54	-1.16	6.22E+00				VERY LOW	Risk of bias, imprecision
Lopinavir-ritonavir	Standard care/Placebo	-1.42	-3.03	2.00E-02				LOW	Risk of bias, imprecision
Remdesivir	Standard care/Placebo	0.35	-3.82	4.53				LOW	Imprecision
Ribavarin,interferon-beta	Standard care/Placebo	-3.6	-5.79	-1.41				LOW	Imprecision
Ribavirin	Standard care/Placebo	1.27	-4.58	7.13E+00				VERY LOW	Risk of bias, imprecision
Ribavirin,Lopinavir-ritonavir	Standard care/Placebo	-0.05	-4.79	4.62E+00				VERY LOW	Risk of bias, imprecision

Ruxolitinib	Standard care/Placebo	0.69	-4.16	5.51E+00				VERY LOW	Risk of bias, imprecision
Interferon beta-1a	Hydroxychloroquine	7.65	2.98	1.23E+01				VERY LOW	Risk of bias, imprecision
Lopinavir-ritonavir	Hydroxychloroquine	3.68	0.51	6.69				LOW	Ris of bias, Imprecision
Remdesivir	Hydroxychloroquine	5.46	0.38	10.51				VERY LOW	Risk of bias, imprecision
Ribavarin,interferon-beta	Hydroxychloroquine	1.52	-2.13	5.05				VERY LOW	Risk of bias, imprecision
Ribavirin	Hydroxychloroquine	6.38	-0.08	12.78				VERY LOW	Risk of bias, imprecision
Ribavirin,Lopinavir-ritonavir	Hydroxychloroquine	5.06	-0.45	1.04E+01				VERY LOW	Risk of bias, imprecision
Ruxolitinib	Hydroxychloroquine	5.81	0.17	1.14E+01				VERY LOW	Risk of bias, imprecision
Lopinavir-ritonavir	Interferon beta-1a	-3.97	-8.01	-2.00E-02				VERY LOW	Risk of bias, imprecision
Remdesivir	Interferon beta-1a	-2.19	-7.73	3.37E+00				VERY LOW	Risk of bias, imprecision
Ribavarin,interferon-beta	Interferon beta-1a	-6.14	-10.42	-1.84E+00				VERY LOW	Risk of bias, imprecision
Ribavirin	Interferon beta-1a	-1.26	-8.21	5.62E+00				VERY LOW	Risk of bias, imprecision
Ribavirin,Lopinavir-ritonavir	Interferon beta-1a	-2.6	-8.62	3.33E+00				VERY LOW	Risk of bias, imprecision
Ruxolitinib	Interferon beta-1a	-1.85	-7.9	4.24E+00				VERY LOW	Risk of bias, imprecision
Remdesivir	Lopinavir-ritonavir	1.79	-2.62	6.28E+00				VERY LOW	Risk of bias, imprecision
Ribavarin,interferon-beta	Lopinavir-ritonavir	-2.17	-4.79	0.57				LOW	Risk of bias, imprecision
Ribavirin	Lopinavir-ritonavir	2.71	-2.92	8.39				VERY LOW	Risk of bias, imprecision
Ribavirin,Lopinavir-ritonavir	Lopinavir-ritonavir	1.39	-3.09	5.85				VERY LOW	Risk of bias, imprecision
Ruxolitinib	Lopinavir-ritonavir	2.13	-2.93	7.22				VERY LOW	Risk of bias, imprecision
Ribavarin,interferon-beta	Remdesivir	-3.95	-8.67	0.76				VERY LOW	Risk of bias, imprecision
Ribavirin	Remdesivir	0.91	-6.28	8.14E+00				VERY LOW	Risk of bias, imprecision
Ribavirin,Lopinavir-ritonavir	Remdesivir	-0.42	-6.72	5.88				VERY LOW	Risk of bias, imprecision
Ruxolitinib	Remdesivir	0.35	-6.05	6.76				VERY LOW	Risk of bias, imprecision
Ribavirin	Ribavarin,interferon-beta	4.87	-1.38	11.14				VERY LOW	Risk of bias, imprecision
Ribavirin,Lopinavir-ritonavir	Ribavarin,interferon-beta	3.54	-1.69	8.72				VERY LOW	Risk of bias, imprecision
Ruxolitinib	Ribavarin,interferon-beta	4.3	-1.05	9.62				VERY LOW	Risk of bias, imprecision
Ribavirin,Lopinavir-ritonavir	Ribavirin	-1.34	-6.39	3.69				VERY LOW	Risk of bias, imprecision
Ruxolitinib	Ribavirin	-0.59	-8.24	7.05				VERY LOW	Risk of bias, imprecision
Ruxolitinib	Ribavirin,Lopinavir-ritonavir	0.76	-6	7.49				VERY LOW	Risk of bias, imprecision
ICU length of stay									
Intervention	**Comparator**	**Relative effect point estimate (MD)**	**CI Lower limit**	**CI upper limit**	**Absolute effect**	**CI Lower limit**	**CI upper limit**	**Certainty**	**Reasons**
Interferon-beta-1a	Standard care/Placebo	-0.81	-5.79	4.17	NA	NA	NA	Very Low	RoB, imprecision
Mechanical ventilation duration									
Intervention	**Comparator**	**Relative effect point estimate (MD)**	**CI Lower limit**	**CI upper limit**	**Absolute effect**	**CI Lower limit**	**CI upper limit**	**Certainty**	**Reasons**
Interferon beta-1a	Standard care/Placebo	3.06	-1.74	7.83	NA	NA	NA	Very low	RoB, imprecisionx2
Lopinavir-ritonavir	Standard care/Placebo	-1.01	-4.12	2.12E+00	NA	NA	NA	Very low	RoB, imprecisionx2
Remdesivir	Standard care/Placebo	-5.26	-15.2	4.96E+00	NA	NA	NA	Low	Imprecision
Lopinavir-ritonavir	Interferon beta-1a	-4.09	-9.77	1.68	NA	NA	NA	Very low	RoB, imprecisionx2
Remdesivir	Interferon beta-1a	-8.33	-19.39	2.98	NA	NA	NA	Very low	RoB, imprecisionx2
Remdesivir	Lopinavir-ritonavir	-4.26	-14.66	6.48E+00	NA	NA	NA	Very low	RoB, imprecisionx2
Time to symptoms resolution									

Intervention	Comparator	Relative effect point estimate (RoM)	CI Lower limit	CI upper limit	Absolute effect (MD)	CI Lower limit	CI upper limit	Certainty	Reasons
Baloxavir marboxil	Standard care/Placebo	1.54	0.47	5	10.07	-9.92	74.8	VERY LOW	RoB x 2, Imprecision x 2
Favipiravir	Standard care/Placebo	1.28	0.41	4	5.27	-11	56.1	VERY LOW	RoB x 2, Imprecision x 2
Hydroxychloroquine	Standard care/Placebo	0.76	0.68	0.84	-4.53	-5.98	-2.99	LOW	RoB x 2
Interferon beta-1a	Standard care/Placebo	1.16	0.9	1.49	3.04	-1.85	9.21	VERY LOW	RoB x 2, Imprecision x 2
Lopinavir-ritonavir	Standard care/Placebo	0.93	0.89	0.98	-1.22	-2	-0.37	LOW	RoB x 2
Remdesivir	Standard care/Placebo	0.86	0.77	0.97	-2.58	-4.32	-0.54	MODERATE	Imprecision
Ribavarin,interferon-beta 1b	Standard care/Placebo	0.63	0.53	0.74	-7.01	-8.86	-4.85	LOW	RoB x 2
Ribavirin	Standard care/Placebo	1.08	0.61	1.89	1.41	-7.37	16.58	VERY LOW	RoB x 2, Imprecision x 2
Ribavirin,Lopinavir-ritonavir	Standard care/Placebo	0.88	0.41	1.89	-2.15	-10.94	16.58	VERY LOW	RoB x 2, Imprecision x 2
Ruxolitinib	Standard care/Placebo	0.95	0.71	1.28	-0.89	-5.44	5.27	VERY LOW	RoB, Imprecision x 2
Umifenovir	Standard care/Placebo	2.13	0.67	6.67	21.09	-6.23	105.97	VERY LOW	RoB x 2, Imprecision x 2
Baloxavir marboxil	Umifenovir	0.73	0.18	2.89				VERY LOW	RoB x 2, Imprecision x 2
Favipiravir	Umifenovir	0.61	0.54	0.69				LOW	RoB x 2
Hydroxychloroquine	Umifenovir	0.36	0.11	1.13				VERY LOW	RoB x 2, Imprecision
Interferon beta-1a	Umifenovir	0.55	0.17	1.79				VERY LOW	RoB x 2, Imprecision x 2
Lopinavir-ritonavir	Umifenovir	0.44	0.14	1.4				VERY LOW	RoB x 2, Imprecision x 2
Remdesivir	Umifenovir	0.41	0.13	1.3				VERY LOW	RoB x 2, Imprecision x 2
Ribavarin,interferon-beta 1b	Umifenovir	0.3	0.09	0.95				VERY LOW	RoB x 2, Imprecision
Ribavirin	Umifenovir	0.51	0.14	1.83				VERY LOW	RoB x 2, Imprecision x 2
Ribavirin,Lopinavir-ritonavir	Umifenovir	0.42	0.11	1.67				VERY LOW	RoB x 2, Imprecision x 2
Ruxolitinib	Umifenovir	0.45	0.14	1.48				VERY LOW	RoB x 2, Imprecision x 2
Baloxavir marboxil	Ruxolitinib	1.61	0.47	5.45				VERY LOW	RoB x 2, Imprecision x 2
Favipiravir	Ruxolitinib	1.35	0.42	4.4				VERY LOW	RoB x 2, Imprecision x 2
Hydroxychloroquine	Ruxolitinib	0.79	0.58	1.09				VERY LOW	RoB, Imprecision x 2
Interferon beta-1a	Ruxolitinib	1.22	0.82	1.8				VERY LOW	RoB x 2, Imprecision x 2
Lopinavir-ritonavir	Ruxolitinib	0.98	0.73	1.33				VERY LOW	RoB x 2, Imprecision x 2
Remdesivir	Ruxolitinib	0.91	0.66	1.25				LOW	RoB, Imprecision
Ribavarin,interferon-beta 1b	Ruxolitinib	0.66	0.46	0.92				LOW	RoB x 2
Ribavirin	Ruxolitinib	1.12	0.59	2.13				VERY LOW	RoB x 2, Imprecision x 2
Ribavirin,Lopinavir-ritonavir	Ruxolitinib	0.93	0.41	2.1				VERY LOW	RoB x 2, Imprecision x 2
Baloxavir marboxil	Ribavirin,Lopinavir-ritonavir	1.73	0.42	7.06				VERY LOW	RoB x 2, Imprecision x 2
Favipiravir	Ribavirin,Lopinavir-ritonavir	1.45	0.37	5.73				VERY LOW	RoB x 2, Imprecision x 2
Hydroxychloroquine	Ribavirin,Lopinavir-ritonavir	0.85	0.4	1.83				VERY LOW	RoB x 2, Imprecision x 2
Interferon beta-1a	Ribavirin,Lopinavir-ritonavir	1.31	0.59	2.92				VERY LOW	RoB x 2, Imprecision x 2
Lopinavir-ritonavir	Ribavirin,Lopinavir-ritonavir	1.06	0.5	2.26				VERY LOW	RoB x 2, Imprecision x 2
Remdesivir	Ribavirin,Lopinavir-ritonavir	0.97	0.45	2.1				VERY LOW	RoB x 2, Imprecision x 2
Ribavarin,interferon-beta 1b	Ribavirin,Lopinavir-ritonavir	0.7	0.32	1.53				VERY LOW	RoB x 2, Imprecision x 2
Ribavirin	Ribavirin,Lopinavir-ritonavir	1.21	0.57	2.56				VERY LOW	RoB x 2, Imprecision x 2
Baloxavir marboxil	Ribavirin	1.43	0.39	5.33				VERY LOW	RoB x 2, Imprecision x 2
Favipiravir	Ribavirin	1.2	0.34	4.31				VERY LOW	RoB x 2, Imprecision x 2
Hydroxychloroquine	Ribavirin	0.71	0.4	1.25				VERY LOW	RoB x 2, Imprecision
Interferon beta-1a	Ribavirin	1.08	0.58	2.02				VERY LOW	RoB x 2, Imprecision x 2
Lopinavir-ritonavir	Ribavirin	0.88	0.5	1.54				VERY LOW	RoB x 2, Imprecision x 2

Remdesivir	Ribavirin	0.81	0.45	1.44				VERY LOW	RoB x 2, Imprecision x 2
Ribavarin,interferon-beta 1b	Ribavirin	0.58	0.32	1.06				VERY LOW	RoB x 2, Imprecision
Baloxavir marboxil	Ribavarin,interferon-beta 1b	2.45	0.74	8.12				VERY LOW	RoB x 2, Imprecision x 2
Favipiravir	Ribavarin,interferon-beta 1b	2.06	0.65	6.54				VERY LOW	RoB x 2, Imprecision x 2
Hydroxychloroquine	Ribavarin,interferon-beta 1b	1.21	0.99	1.47				VERY LOW	RoB x 2, Imprecision
Interferon beta-1a	Ribavarin,interferon-beta 1b	1.86	1.36	2.53				LOW	RoB x 2
Lopinavir-ritonavir	Ribavarin,interferon-beta 1b	1.5	1.26	1.79				LOW	RoB x 2
Remdesivir	Ribavarin,interferon-beta 1b	1.38	1.13	1.7				LOW	RoB x 2
Baloxavir marboxil	Remdesivir	1.77	0.54	5.83				VERY LOW	RoB x 2, Imprecision x 2
Favipiravir	Remdesivir	1.49	0.47	4.7				VERY LOW	RoB x 2, Imprecision x 2
Hydroxychloroquine	Remdesivir	0.87	0.75	1.02				VERY LOW	RoB Imprecision x 2
Interferon beta-1a	Remdesivir	1.34	1.01	1.78				VERY LOW	RoB x 2, Imprecision
Lopinavir-ritonavir	Remdesivir	1.09	0.96	1.23				VERY LOW	RoB x 2, Imprecision
Baloxavir marboxil	Lopinavir-ritonavir	1.63	0.5	5.35				VERY LOW	RoB x 2, Imprecision x 2
Favipiravir	Lopinavir-ritonavir	1.37	0.44	4.31				VERY LOW	RoB x 2, Imprecision x 2
Hydroxychloroquine	Lopinavir-ritonavir	0.8	0.72	0.9				LOW	RoB x 2
Interferon beta-1a	Lopinavir-ritonavir	1.24	0.95	1.61				VERY LOW	RoB x 2, Imprecision
Baloxavir marboxil	Interferon beta-1a	1.32	0.39	4.44				VERY LOW	RoB x 2, Imprecision x 2
Favipiravir	Interferon beta-1a	1.11	0.34	3.58				VERY LOW	RoB x 2, Imprecision x 2
Hydroxychloroquine	Interferon beta-1a	0.65	0.49	0.86				LOW	RoB x 2
Baloxavir marboxil	Hydroxychloroquine	2.03	0.62	6.67				VERY LOW	RoB x 2, Imprecision x 2
Favipiravir	Hydroxychloroquine	1.71	0.54	5.37				VERY LOW	RoB x 2, Imprecision x 2
Baloxavir marboxil	Favipiravir	1.19	0.3	4.7				VERY LOW	RoB x 2, Imprecision x 2
Time to viral clearance									
Intervention	**Comparator**	**Relative effect point estimate (RoM)**	**CI Lower limit**	**CI upper limit**	**Absolute effect (MD)**	**CI Lower limit**	**CI upper limit**	**Certainty**	**Reasons**
Baloxavir marboxil	Standard care/Placebo	2.3	0.58	9.02	10.01	-3.23	61.75	Very Low	RoB, Imprecision
Favipiravir	Standard care/Placebo	1.96	0.52	7.39E+00	7.39	-3.7	49.2	Very Low	RoB, Imprecision
Hydroxychloroquine	Standard care/Placebo	0.94	0.61	1.45E+00	-0.46	-3	3.47	Very Low	RoB, Imprecision, incosistency
Lopinavir-ritonavir	Standard care/Placebo	0.97	0.6	1.55	-0.23	-3.08	4.24	Very Low	RoB, Imprecision, incosistency
Novaferon	Standard care/Placebo	0.85	0.43	1.68	-1.16	-4.39	5.24	Very Low	RoB, Imprecision
Novaferon,Lopinavir-ritonavir	Standard care/Placebo	0.74	0.37	1.46E+00	-2	-4.85	3.54	Very Low	RoB, Imprecision
Ribavarin,interferon-beta 1b	Standard care/Placebo	0.66	0.37	1.18E+00	-2.62	-4.85	1.39	Low	RoB, Imprecision
Ribavirin	Standard care/Placebo	1.21	0.6	2.45E+00	1.62	-3.08	11.17	Very Low	RoB, Imprecision
Ribavirin,Lopinavir-ritonavir	Standard care/Placebo	1.07	0.54	2.14E+00	0.54	-3.54	8.78	Very Low	RoB, Imprecision
Ruxolitinib	Standard care/Placebo	1.1	0.37	3.29	0.77	-4.85	17.63	Very Low	RoB, Imprecision
Umifenovir	Standard care/Placebo	0.98	0.6	1.6	-0.15	-3.08	4.62	Very Low	RoB, Imprecision
Favipiravir	Baloxavir marboxil	0.85	0.2	3.65				Very Low	RoB, Imprecision
Hydroxychloroquine	Baloxavir marboxil	0.41	0.1	1.74				Very Low	RoB, Imprecision
Lopinavir-ritonavir	Baloxavir marboxil	0.42	0.1	1.79E+00				Very Low	RoB, Imprecision
Novaferon	Baloxavir marboxil	0.37	0.08	1.70E+00				Very Low	RoB, Imprecision
Novaferon,Lopinavir-ritonavir	Baloxavir marboxil	0.32	0.07	1.48E+00				Very Low	RoB, Imprecision
Ribavarin,interferon-beta 1b	Baloxavir marboxil	0.29	0.07	1.27E+00				Very Low	RoB, Imprecision
Ribavirin	Baloxavir marboxil	0.53	0.11	2.45E+00				Very Low	RoB, Imprecision

Ribavirin,Lopinavir-ritonavir	Baloxavir marboxil	0.47	0.1	2.16E+00				Very Low	RoB, Imprecision
Ruxolitinib	Baloxavir marboxil	0.48	0.08	2.77E+00				Very Low	RoB, Imprecision
Umifenovir	Baloxavir marboxil	0.43	0.1	1.83E+00				Very Low	RoB, Imprecision
Hydroxychloroquine	Favipiravir	0.48	0.12	1.93E+00				Very Low	RoB, Imprecision
Lopinavir-ritonavir	Favipiravir	0.5	0.12	2				Very Low	RoB, Imprecision
Novaferon	Favipiravir	0.43	0.1	1.91				Very Low	RoB, Imprecision
Novaferon,Lopinavir-ritonavir	Favipiravir	0.38	0.09	1.67				Very Low	RoB, Imprecision
Ribavarin,interferon-beta 1b	Favipiravir	0.34	0.08	1.42				Very Low	RoB, Imprecision
Ribavirin	Favipiravir	0.62	0.14	2.75				Very Low	RoB, Imprecision
Ribavirin,Lopinavir-ritonavir	Favipiravir	0.55	0.12	2.42E+00				Very Low	RoB, Imprecision
Ruxolitinib	Favipiravir	0.56	0.1	3.12				Very Low	RoB, Imprecision
Umifenovir	Favipiravir	0.5	0.12	2.05				Very Low	RoB, Imprecision
Lopinavir-ritonavir	Hydroxychloroquine	1.03	0.57	1.87				Very Low	RoB, Imprecision
Novaferon	Hydroxychloroquine	0.9	0.42	1.96				Very Low	RoB, Imprecision
Novaferon,Lopinavir-ritonavir	Hydroxychloroquine	0.78	0.37	1.71				Very Low	RoB, Imprecision
Ribavarin,interferon-beta 1b	Hydroxychloroquine	0.7	0.34	1.46				Very Low	RoB, Imprecision
Ribavirin	Hydroxychloroquine	1.28	0.58	2.85				Very Low	RoB, Imprecision
Ribavirin,Lopinavir-ritonavir	Hydroxychloroquine	1.14	0.53	2.49				Very Low	RoB, Imprecision
Ruxolitinib	Hydroxychloroquine	1.17	0.36	3.8				Very Low	RoB, Imprecision
Umifenovir	Hydroxychloroquine	1.04	0.55	1.98				Very Low	RoB, Imprecision
Novaferon	Lopinavir-ritonavir	0.88	0.54	1.43				Very Low	RoB, Imprecision
Novaferon,Lopinavir-ritonavir	Lopinavir-ritonavir	0.76	0.46	1.25				Very Low	RoB, Imprecision
Ribavarin,interferon-beta 1b	Lopinavir-ritonavir	0.68	0.32	1.45				Very Low	RoB, Imprecision
Ribavirin	Lopinavir-ritonavir	1.25	0.74	2.1				Very Low	RoB, Imprecision
Ribavirin,Lopinavir-ritonavir	Lopinavir-ritonavir	1.11	0.67	1.84				Very Low	RoB, Imprecision
Ruxolitinib	Lopinavir-ritonavir	1.14	0.35	3.71				Very Low	RoB, Imprecision
Umifenovir	Lopinavir-ritonavir	1.01	0.62	1.64				Very Low	RoB, Imprecision
Novaferon,Lopinavir-ritonavir	Novaferon	0.87	0.53	1.42				Very Low	RoB, Imprecision
Ribavarin,interferon-beta 1b	Novaferon	0.78	0.32	1.91				Very Low	RoB, Imprecision
Ribavirin	Novaferon	1.42	0.7	2.93				Very low	RoB, Imprecision
Ribavirin,Lopinavir-ritonavir	Novaferon	1.27	0.62	2.56				Very Low	RoB, Imprecision
Ruxolitinib	Novaferon	1.29	0.36	4.68				Very Low	RoB, Imprecision
Umifenovir	Novaferon	1.15	0.58	2.3				Very Low	RoB, Imprecision
Ribavarin,interferon-beta 1b	Novaferon,Lopinavir-ritonavir	0.89	0.37	2.19				Very Low	RoB, Imprecision
Ribavirin	Novaferon,Lopinavir-ritonavir	1.64	0.8	3.38				Very low	RoB, Imprecision
Ribavirin,Lopinavir-ritonavir	Novaferon,Lopinavir-ritonavir	1.46	0.72	2.96				Very low	RoB, Imprecision
Ruxolitinib	Novaferon,Lopinavir-ritonavir	1.49	0.41	5.42				Very Low	RoB, Imprecision
Umifenovir	Novaferon,Lopinavir-ritonavir	1.33	0.66	2.66				Very Low	RoB, Imprecision
Ribavirin	Ribavarin,interferon-beta 1b	1.83	0.73	4.57				Very low	RoB, Imprecision
Ribavirin,Lopinavir-ritonavir	Ribavarin,interferon-beta 1b	1.63	0.66	4				Very Low	RoB, Imprecision
Ruxolitinib	Ribavarin,interferon-beta 1b	1.67	0.49	5.67				Very Low	RoB, Imprecision
Umifenovir	Ribavarin,interferon-beta 1b	1.48	0.69	3.19				Very Low	RoB, Imprecision
Ribavirin,Lopinavir-ritonavir	Ribavirin	0.89	0.53	1.49				Very Low	RoB, Imprecision
Ruxolitinib	Ribavirin	0.91	0.25	3.34				Very Low	RoB, Imprecision
Umifenovir	Ribavirin	0.81	0.4	1.65				Very Low	RoB, Imprecision

Ruxolitinib	Ribavirin,Lopinavir-ritonavir	1.03	0.28	3.72				Very Low	RoB, Imprecision
Umifenovir	Ribavirin,Lopinavir-ritonavir	0.91	0.45	1.85				Very Low	RoB, Imprecision
Umifenovir	Ruxolitinib	0.89	0.27	2.94				Very Low	RoB, Imprecision

Therapies for treatment and prophylaxis of COVID-19: introduction and methods for a living systematic review and network meta-analyses

An international collaborative project

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Abstract
Objectives: To compare the effects of therapies for prophylaxis and treatment of COVID-19
Design: Living systematic review and network meta-analysis (NMA).
Data sources: U.S. Centers for Disease Control and Prevention (CDC) COVID-19 Research Articles Downloadable Database, which includes 25 electronic databases.
Study selection: We will include randomized clinical trials (RCT) in which persons exposed to COVID-19 or with suspected, probable or confirmed COVID-19 were treated with pharmaceuticals or blood products aimed at prophylaxis or treatment. Pairs of independent reviewers will screen in duplicate title and abstract and full text of potentially eligible articles.
Methods: After duplicate data abstraction, we will conduct a Bayesian-random effects network meta-analysis for each of the outcomes of interest. We will assess the risk of bias of the included studies using a modification of the Cochrane Risk of Bias 2.0 tool, and the certainty of the evidence using the GRADE approach for NMA. We will classify the interventions in groups from the most to the least effective/ harmful following GRADE guidance using a minimally contextualized approach.
Publication and Updating of Results: We will publish and update the results in *The BMJ* and magicapp.org. We will update the living NMA when the question is no longer of clinical importance, or new evidence that might impact on the conclusions is unlikely to be forthcoming.

Background

COVID-19 is a rapidly evolving global health emergency. As of 27 May 2020, over 5.6 million people have been infected and of these, 335,000 have died,[1] resulting in an enormous perceived need to implement a possibly effective intervention. Public figures,[2] guideline bodies,[3] and government agencies [4] have suggested using interventions without established benefit. Clinicians have responded to these suggestions by administering such interventions to large numbers of patients.[5]

With many teams conducting randomized clinical trials (RCTs) of drug interventions—over 1,000 intervention trials registered as of 10 May 2020 [6]—evidence on the comparative effectiveness of

drug interventions will emerge rapidly. The new environment will amplify the need for evidence based medicine: distinguishing trustworthy from untrustworthy evidence, interpreting the results, and judging net benefits of interventions against standard treatment and one another.[7]

Reliable guidance for COVID-19 will require adherence to standards of trustworthy clinical practice guidelines,[8] including methodically rigorous and rapidly updated evidence summaries. Such summaries will identify interventions with sufficient evidence of net benefit to warrant use. Establishing absence of net benefit in previously highly touted interventions may be equally important. Further, if studies suggest that more than one intervention provides net benefit, clinicians and patients will face the challenge of deciding which intervention to use.

Our living systematic review and network meta-analysis (NMA), updated in real time, will answer this urgent demand for trustworthy evidence on the available therapeutic options. This systematic review is part of the *BMJ Rapid Recommendations* project, a collaborative effort from the MAGIC Evidence Ecosystem Foundation (www.magicproject.org) and *The BMJ*. Our living NMA will thus directly inform *BMJ Rapid Recommendations*,[9] providing trustworthy, actionable, and living guidance to clinicians and patients soon after new and potentially practice-changing evidence is made available. The living NMA will be freely available in user-friendly formats, through *The BMJ* and MAGICapp (www.magicapp.orsg), and ready for re-use and adaptation at national and local levels.

Methods

Structure and organization

The team working in the development of this living systematic review and NMA is composed of the following groups:

a. Oversight group composed of experts in the clinical area and systematic review methodology (RAC, TA, GHG, BR, FL, SM, PV). The role of this team is to ensure that the process follows the highest methodological standards, and that the decisions made are clinically sensible and keep consistency with the needs of the *BMJ Rapid Recommendations*.
b. Core systematic review team leaders. This group is composed of methodologists leading teams in charge of study identification (JB), data abstraction (DZ), data analysis (LG), and assessment of certainty of the evidence and presentation (RBP).
c. Reviewers. This team is composed of clinicians, graduate students, methodologists, and biostatisticians conducting or providing advice for screening, data abstraction, and assessments of certainty of the evidence.

In addition, decisions in this protocol have been made considering the requirements from the *Rapid Recommendations* guideline panel, which includes patients.

Eligibility criteria

We will include RCTs in which persons exposed to COVID-19 or with suspected, probable, or confirmed COVID-19 are treated with pharmacologic or blood products aimed at prophylaxis or

treatment. We will include trials in which researchers compare any intervention against another or against no intervention, placebo, or standard of care, and report any outcome. We will include trials that report results regardless of publication status (peer-reviewed, in press, or pre-print, but not news reports alone) or language. There will be no restrictions on acuity of disease, nor setting.

We will include trials of pharmaceuticals, blood products, vitamins, minerals and, if the drug is one specific molecule, Chinese medicines. We will exclude quasi-randomized studies and randomized trials evaluating external organ support, plasma exchange, oxygen delivery, ventilation strategies, vaccination, nutrition, traditional Chinese herbal medicines (that typically include more than one molecule or a molecule without specific molecular weighted dosing), exercise/rehabilitation, psychological and educational interventions, personal protective equipment, or any other non-drug supportive care interventions.

Data sources and searches

We will search the U.S. Centers for Disease Control and Prevention (CDC) COVID-19 Research Articles Downloadable Database for eligible studies—the most comprehensive database of COVID-19 research articles from December 2019 and which is maintained by the Stephen B. Thacker CDC library [10]. We will update our search daily Monday to Friday to match the update schedule of the database. The database includes 25 bibliographic and grey literature sources: Medline (Ovid and PubMed), PubMed Central, Embase, CAB Abstracts, Global Health, PsycInfo, Cochrane Library, Scopus, Academic Search Complete, Africa Wide Information, CINAHL, ProQuest Central, SciFinder, the Virtual Health Library, LitCovid, WHO COVID-19 website, CDC COVID-19 website, Eurosurveillance, China CDC Weekly, Homeland Security Digital Library, ClinicalTrials.gov, bioRxiv (preprints), medRxiv (preprints), chemRxiv (preprints), and SSRN (preprints).

We will filter the results from the CDC's database through a validated and highly sensitive machine learning model to identify RCTs.[11] We will track preprints of RCTs until publication and data updated to match that in the peer-reviewed publication when discrepant. In addition, we will search six Chinese databases on a biweekly basis: Wanfang, CBM, CNKI, VIP, Chinese Medical Journal Net (preprints), and ChinaXiv (preprints). The search terms for COVID-19 developed by the CDC have been adapted to the Chinese language. For the search of the Chinese literature, we will also include search terms for randomized trials. The search strategy is available in the Supplementary Material.

We will also monitor living evidence retrieval services on an ongoing basis. Two such services are the Systematic and Living Map on COVID-19 Evidence by the Norwegian Institute of Public Health, in collaboration with the Cochrane Canada Centre at McMaster University,[12] and the Living Overview of Evidence (L·OVE) by Epistemonikos Foundation.[13] Our publication will be accompanied with a public call for information sharing, with hopes that investigators will initiate contact and share information when available. RCTs may also be identified organically through informal networks.

Study selection
Pairs of reviewers will independently and in duplicate screen titles and abstracts followed by full texts. A third reviewer will adjudicate conflicts.

Data extraction
For each eligible trial, two reviewers, who have undergone training and have completed calibration exercises, will extract data independently and in duplicate using a standardised, pilot-tested data extraction form. Discrepancies will be resolved by discussion, and when necessary adjudicated by a third person. The study characteristics and baseline participant information that will be extracted is presented in Box 1.

Box 1. Study characteristics and baseline participant information that will be extracted

- Geographic location
- Physical location (outpatient, inpatient, intensive care)
- Patient and public involvement in the study design or interpretation
- Funder (public, private)
- Number randomized
- Number randomized to each intervention
- Dose, frequency, route of administration, and duration for each intervention
- Number who received each intervention
- Mean age
- Percent male
- Severity of illness (non-severe, severe, critically ill)
- Mean oxygen saturation on room air, or mean baseline amount of supplemental oxygen
- Percent receiving mechanical ventilation at baseline
- Percent current and former smokers
- Percent with hypertension
- Percent with underlying chronic respiratory condition including chronic obstructive pulmonary disease (COPD), asthma, and others
- Percent with diabetes
- Percent taking angiotension-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)
- Mean alanine aminotransferase (ALT)
- Mean C-reactive protein (CRP)
- Mean d-dimer
- Mean lactate dehydrogenase (LDH)
- Mean lymphocyte count, and percent with lymphopaenia

Outcomes
We will begin by focusing on the patient-important outcomes listed below, based on the WHO's candidate core outcome set.[14] The list of outcomes may be modified at the discretion of the BMJ

Rapid Recommendations standing panel of experts, which includes frontline healthcare workers and patient-partners. As harms are typically specific to individual pharmacologic therapies, these outcomes will be selected at the time they are needed to support specific linked Rapid Recommendations. We will extract the outcome data closest to the prespecified outcome time point.

The initial outcomes examined for the studies of treatment will include:

- Mortality (time frame: closest to 90 days)
- Mechanical ventilation in patients not initially mechanically ventilated (time frame: closest to 90 days)
- Duration of hospitalization
- Admission to hospital (time frame: closest to 28 days)
- Adverse effects leading to discontinuation of the intervention (time frame: closest to 28 days)
- Time to symptom resolution
- Time until the amount of SARS-CoV2 viral particles is below the threshold set by the RCT authors for being likely no longer infectious (as a surrogate for transmissibility)
- Undetectable nCoV-19 by PCR (time frame: closest to 7 days and not less than 4 days or more than 10 days)

The initial outcomes examined for the studies of prophylaxis will include:

- Symptomatic SARS-CoV2 infection (time frame: closest to 28 days)
- Mortality (time frame: closest to 90 days)
- Admission to hospital (time frame: closest to 28 days)
- Adverse effects leading to discontinuation of the intervention (time frame: closest to 28 days)
- Time to symptom resolution (those not infected will be considered 0)

Other outcomes that will be extracted and reported from the trials, but not initially reviewed will include:

- Ventilator-free days (time frame: 28 days)
- Venous thromboembolism (time frame: closest to 90 days)
- Clinically important bleeding (time frame: closest to 90 days)

Risk of bias assessments

Following calibration exercises, two reviewers, working independently and in duplicate, will use the Clinical Advances Through Research and Information Translation (CLARITY) revisions of the Cochrane tool for assessing risk of bias in randomized trials (RoB 2.0) to rate trials as either 'low risk of bias', 'some concerns – probably low risk of bias', 'some concerns – probably high risk of bias' and 'high risk of bias', across the following domains: bias arising from the randomization process, bias due to departures from the intended intervention, bias due to missing outcome data, bias in measurement of the outcome, bias in selection of the reported results.[15 16] The

response choice 'some concerns' was modified to include a judgement about whether the concerns probably do or do not result in high risk of bias.[16] We will not consider judgements about applicability when considering risk of bias because applicability is judged separately within indirectness domain of the GRADE framework.[17] In addition, the modified tool includes an additional domain to assess risk of bias related to RCTs stopping early for benefit.[18] Reviewers will resolve discrepancies by discussion, and when not possible, adjudication by a third-party research methodologist. A detailed guide for our risk of bias assessments is available in the Supplementary Material. If the body of evidence is rated as high risk of bias for missing data only (i.e., no serious concerns with any other of the risk of bias domains), we may perform sensitivity analyses with worst plausible assumptions to see if results remain robust to missing data.

Treatment nodes

We will perform three separate network meta-analyses: i) pharmacologic treatments for patients with suspected or confirmed COVID-19, ii) blood products for treatment of patients with suspected or confirmed COVID-19, and iii) pharmacologic prophylactic therapy for people exposed to COVID-19.

Treatments will be grouped into common nodes based on molecule but not dose or duration: we will include all doses and durations of the same medication in a single treatment node. When an intervention includes more than one medication, it will be included as a separate node. We will include drugs from the same class within the same node. Chloroquine and hydroxychloroquine will be included in the same node for COVID-19 specific effects and separated for disease-independent adverse effects. Prespecified nodes include angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, anti-interleukin-6 agents (i.e., tocilizumab, sarilumab), glucocorticoids, interferons, JAK inhibitors, statins, antiplatelet agents, and anticoagulants. Antibiotics will be grouped into nodes by class (e.g., macrolides, beta-lactams). The NMA oversight group and the linked Rapid Recommendation panels will make final decisions on how to group treatment nodes.

Data synthesis

We will perform random-effects pairwise meta-analysis for each comparison for each outcome using the Bayesian framework. We will use a plausible prior for variance parameter,[19] and uniform prior for the effect parameter. We will calculate Ratio of Means (RoM) and corresponding 95% credible intervals (CrIs) for continuous outcomes in which we expect variationa cross populations (time to symptoms resolution and time to viral clearance) and mean differences (MDs) and corresponding 95% credible intervals (CrIs) for other continuous outcomes. For dichotomous outcomes, we will calculate odds ratios (ORs) with corresponding CrIs. Absolute effects will be calculated based on the ORs and baseline risk of standard of care.[20] We will create a funnel plot to assess the publication bias when 10 or more studies are available for a specific direct comparison.[21]

We will conduct a random-effects network meta-analysis using the Bayesian framework with same priors for the variance and effect parameters.[19] We will use three Markov-chains with 100,000 iterations after an initial burn-in of 10,000 and a thinning of 10. We will assess the

convergence based on trace plots and the Brooks-Gelman-Rubin statistic, with an acceptable threshold of <1.05 for all nodes. If convergence is not achieved, then we will use 500,000 iterations and a burn-in of 50,000 iterations and a thinning of 10. We will use automated generation of node-splitting models to assess local incoherence and to obtain indirect estimates.[22] We will estimate ranking probabilities and calculate surface under the cumulative ranking curves (SUCRA). For all dichotomous outcomes, we will calculate the absolute treatment effects of the network estimates based-on the odds ratios and the baseline risk using the transitive risks model.[23] To obtain the baseline risk, we will use the highest quality prognostic evidence available at the time of publication, typically based on a systematic review of prognostic studies.[24]

When networks are sparse, between-study heterogeneity variances are often imprecisely estimated. That may generate implausibly wide credible intervals from network estimates, even when the direct and indirect estimates are coherent.[25] When this occurs, we will conduct sensitivity analyses by using empirically informative priors,[26] and fixed effects models.[25] Another situation in which implausibly wide confidence intervals occur is with random effects when the number of studies is small and the heterogeneity is considerable, particularly when study size varies markedly. This is a second situation in which we may opt for fixed effect models.

Pairwise meta-analysis will be conducted using the bayesmeta package of R version 4.0.0 (RStudio, Boston, MA).[27] All network meta-analyses will be performed using the *gemtc* package of R version 4.0.0 (RStudio, Boston, MA),[28] absolute effects in networks will be calculated using *R2jags* package of R version 4.0.0 (RStudio, Boston, MA)[29]. *networkplot* command of Stata version 15.1 (StataCorp, College Station, Texas, USA) will be used to draw the network plots with thickness of edges of the nodes based on inverse variance.[30] The foundational R code that we will use is available in the Supplementary Material.

Subgroups and sensitivity analyses

We will conduct sensitivity analyses and network meta-regression to explore factors that may modify the comparative effect estimates. Specific analyses will be guided by the linked *Rapid Recommendation* guideline panels with the directive to explore a limited number of pre-defined subgroup effects with a specified rationale and anticipated direction of the effect. When sufficient heterogeneity in risk of bias exists, we will perform subgroup analyses comparing studies at low versus high risk of bias. We will classify all studies with at least 1 domain judged at high risk of bias or probably high risk of bias as a high risk of bias study. Ultimately, we will base decisions regarding the credibility of subgroup analyses on the ICEMAN instrument,[31] and follow GRADE guidance on how to deal with low, intermediate, and high credibility subgroup effects.[32]

For all outcomes, we will first include both peer-reviewed and non-peer reviewed data, and then perform a sensitivity analysis by restricting to peer-reviewed publications. When the guideline panel makes a recommendation about a drug class with more than one drug, we will consider performing a sensitivity analysis with individual molecules rather than drug class as the nodes.

Certainty assessment

We will evaluate the certainty of evidence using the GRADE approach for network meta-analysis.[33-35] We will rate the certainty for each comparison and outcome as high, moderate, low, or very low, based on considerations of risk of bias, inconsistency, indirectness, publication bias, intransitivity, incoherence, and imprecision. If and when sufficient effective treatments are available we will, for each outcome, use the GRADE framework to make conclusions by classifying the interventions in groups from the most to the least effective using a minimally contextualized approach.[36]

Updating

Full results will be updated at minimum every two weeks on webpages hosted by BMJ.com and magicapp.org. A summary of the interim results, risk of bias assessments, individual study data summaries, and the date of the search will be posted in a table within the online publication. Results will be updated more frequently if the project steering committee or the linked BMJ Rapid Recommendations guidelines panel judges that there is sufficient new information to possibly change practice and requests an earlier update. Updates will be submitted to international indexes through the mechanism for corrections but labelled as updates. Old versions and details of any changes will be dated and documented in the Supplementary Material. It may be necessary to adjust some of the processes, outcomes, and analytic methods based on the data. The systematic review team will decide together whether changes to the pre-specified protocol are needed and these changes will be documented in the methods section of the updated review.

External review

A standing peer-review committee editorial staff at The BMJ, clinical experts, patients, and statistician(s) will be tasked with providing feedback on the protocol and initial publication, and a subcommittee will peer review updates. The systematic review team will respond to these comments on an urgent basis. Comments from peer reviewers and responses will be made public. The study webpage will include functionality for comments to be made by any member of the public. The systematic review team will endeavor to respond to all public comments in a timely manner.

Publication

The papers will be published in a traditional format for systematic reviews and network meta-analyses. In addition, results will be published in interactive evidence summary and decision aid formats for multiple comparisons and pairwise comparisons on MAGICapp (www.magicapp.org). The publication will include infographics that highlight the key messages from the current state of the evidence.

Determining the end of project

The project will terminate at the discretion of the project oversight group, which includes representation from the MAGIC Evidence Ecosystem Foundation, The BMJ, the WHO, and international collaborators with clinical and research expertise. We anticipate that the project will end when the question is no longer of clinical importance, or new evidence that might impact on the conclusions is unlikely to be forthcoming. If the influx of new RCT results slows, then the project oversight committee may choose to decrease the frequency of updates.

Data access
All extracted data will be made available publicly at the time of the updates to be shared and used freely.

Changes to the protocol
All changes to the protocol are reported in Table 1 and will be updated as necessary.

Discussion
Our living network meta-analysis will provide up to date information to interested users, including healthcare workers, patients, healthcare agencies, guideline bodies, and governments. It will directly inform joint clinical practice guidelines from BMJ Rapid Recommendations.

We anticipate several challenges. First, living systematic reviews require substantial dedication and human resources.[37] To address this, we will organize our large team into smaller groups with specific responsibilities, including i) a study identification team, ii) a data extraction and management team, iii), a data analysis team, iv) a grading and publications team, and v) an oversight team. In addition, *The BMJ* will recruit a standing external review committee that will become familiar with the research methods and respond quickly to updates.

Second, the need for recurrent updates conflicts with traditional publication formats. Frequent updates resulting in new publications can have a devastating effect on a journal's impact factor. It may also be confusing for users who want to find the most recent update. To solve this problem, we plan to i) have a reference website with the links to the latest versions, ii) use headers on previous versions stating that they are outdated with a link to the current version, iii) use PubMed's corrections mechanism so that the updated publication keeps the same digital object identifier (DOI) and PubMed identification number.

Evidence summaries will also be published online with MAGICapp (www.magicapp.org) developed for the purpose of dynamic updating and with electronic publication formats not subject to the limitations of traditional publishing formats thus allowing presentation of evidence summaries in multilayered user-friendly formats.[38]

Third, the optimal methodological and statistical methods may change as the number of RCTs and participants increases. In particular, early NMAs are likely to be sparse, and we may have to use specific analytic methods to accommodate these situations.[25] Our oversight committee and semi-independent guideline panels will provide direction and guidance on whether and how the methods should be adopted to the current situation.

Another major concern with living systematic reviews is limitations in the evidence included, in particular bias. We will assess risk of bias of each study using a standardized tool,[15 16] and assess risk of bias for each comparison using the GRADE framework.[33 34] Publication bias is of particular concern with living reviews: studies with positive results are more likely to be published at all, and when published are likely to be published earlier.[39] We will use the GRADE approach, which

considers publication bias, to rate certainty for the estimated effect for each comparison.[21] Clinical practice guideline panels of whom the majority will be independent of this review, will consider this issue when making recommendations for practice, and their scrutiny may bear on certainty of evidence judgements.[9]

There are at least two other groups planning a similar living systematic review and NMA.[40 41] More than one group performing similar analyses will allow controlled replication and the scientific community to assess reproducibility of the findings. Our review has advantages over the alternatives, including the use of and experience with GRADE for NMA, an established platform in the *BMJ Rapid Recommendations* project; an established collaboration with and early involvement of the publisher (*The BMJ*); and interpretation from a semi-independent *BMJ Rapid Recommendations* guideline panels; inclusion of a dedicated search of the Chinese literature; and co-publication in MAGICapp through its interactive multilayered evidence presentation format.

Conclusions

The COVID-19 pandemic necessitates rapid interpretation of new evidence addressing therapeutic and prophylactic options. Our living systematic review and NMA will provide a reference point for those interested in the most trustworthy evidence regarding these therapies. Our project will facilitate the movement of evidence into practice much sooner than traditional publication methods.

Table 1. Changes to the protocol

Date	Change	Rationale
15 July 2020	Network analyses will only include treatment nodes with at least 100 patients or at least 20 events.	Early analyses with sparse data resulted in implausible and uninformative effect estimates.

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Therapies for treatment and prophylaxis of COVID-19: introduction and methods for a living systematic review and network meta-analyses

Supplementary Material

Table of contents **Page**

Search Strategy for Chinese databases
中文数据库检索策略及结果

Database	Strategy
WanFang 万方医学 (med.wanfangdata.com.cn)	#1 (主题:(2019 冠状病毒 OR 新型冠状病毒 OR 新冠肺炎)*主题:(临床试验 OR 系统评价 OR Meta 分析 OR 随机对照实验 OR 对照研究))*Date:2019- #2 (主题:(2019-nCoV OR SARS-CoV-2 OR Novel coronavirus OR nCoV OR new coronavirus)*主题:(临床试验 OR 系统评价 OR Meta 分析 OR 随机对照实验 OR 对照研究))*Date:2019- #3 #1 OR #2
CBM	(("2019 冠状病毒"[常用字段:智能] OR "新型冠状病毒"[常用字段:智能] OR "新冠肺炎"[常用字段:智能] OR "2019-nCoV"[常用字段:智能] OR "SARS-CoV-2"[常用字段:智能] OR "Novel coronavirus"[常用字段:智能] OR "nCoV"[常用字段:智能] OR "Emerging Coronaviruses"[常用字段:智能] OR "new coronavirus"[常用字段:智能] OR "COVID-19"[常用字段:智能] OR "coronavirus"[常用字段:智能] AND ("Wuhan"[常用字段] OR "Hubei"[常用字段] OR "China"[常用字段])) AND 2019-2020[日期]) AND ("循证文献"[文献类型] OR "临床试验"[文献类型] OR "随机对照试验"[文献类型] OR "综述"[文献类型] OR "Meta 分析"[文献类型])
CNKI	在期刊文献类型下： #1 主题=("2019 冠状病毒" OR "新型冠状病毒" OR "新冠肺炎") AND （主题=临床试验 OR 系统评价 OR 随机对照实验 OR Meta 分析） #2 主题=(2019-nCoV OR SARS-CoV-2 OR Novel coronavirus OR nCoV) AND (主题=临床试验 OR 系统评价 OR 随机对照实验 OR Meta 分析) 2019-[日期]
VIP 维普	#1 (主题:(2019 冠状病毒 OR 新型冠状病毒 OR 新冠肺炎)*主题:(临床试验 OR 系统评价 OR Meta 分析 OR 随机对照实验 OR 对照研究))* #2 主题=(SARS-CoV-2 OR Novel coronavirus OR nCoV) AND (主题=临床试验 OR 系统评价 OR 随机对照实验 OR Meta 分析) Date:2019-
中华医学期刊网（预印本）http://medjournals.cn/2019NCP/index.do	#1 主题=("2019 冠状病毒" OR "新型冠状病毒" OR "新冠肺炎") AND （主题=临床试验 OR 系统评价 OR 随机对照实验 OR Meta 分析） #2 主题=(2019-nCoV OR SARS-CoV-2 OR Novel coronavirus OR nCoV) AND (主题=临床试验 OR 系统评价 OR 随机对照实验 OR Meta 分析) 2019-[日期]
中科院预印本 http://chinaxiv.org/home.htm	Hand search.

Detailed risk of bias assessment guidance

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. Trials that use permuted blocks of random sizes for randomization or minimization procedures.
Probably low risk of bias	Trials that are described as randomized but provide no information on allocation concealment and there are no major baseline imbalances. Randomized trials that are described as ‘double-blind’ or ‘triple-blind’ or indicate that investigators were blinded but provide no additional information on allocation concealment.
Probably high risk of bias	Trials in which there are substantial baseline differences between trial arms that suggests 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 Imbalances in cointerventions or crossovers	
Definitely low risk of bias	Trials in which healthcare providers were blind to the intervention administered and in which there are no significant crossovers or differences in administered co-interventions.
Probably low risk of bias	
Probably high risk of bias	Trials in which healthcare providers were not blind to the intervention administered. Trials in which healthcare providers were blind to the intervention administered but there are significant crossovers or differences in administered co-interventions that suggests that blinding may have been compromised. Trials in which healthcare providers are described as being blind to the intervention but allocation concealment was inadequate.
Definitely high risk of bias	Trials in which there is no blinding of healthcare providers and 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. In such cases, record separate judgments across*	

outcomes and indicate the outcomes that the judgments apply to in parentheses.	
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 (e.g., mortality, mechanical ventilation, admission to hospital, duration of hospital stay, ICU length of stay, ventilator free days, duration of mechanical ventilation). 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. Trials in which outcomes are measured by a third-party (investigator or clinician) and in which the third-party is not blind to the intervention. Trials in which outcome adjudicators are not blind and the outcomes are not objective (e.g., adverse effects leading to discontinuation, time to symptom resolution).
Bias in selection of the reported results	
Issues to consider: Selective reporting of timepoints Selective 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. In such cases, record separate judgments across outcomes and indicate the outcomes that the judgments apply to in parentheses.*	
Definitely low risk of bias	Results for outcomes that were analyzed and reported according to a pre-specified 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.
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.
Definitely high risk of	Results for outcomes that were analyzed and reported for which there are

bias	inconsistencies with the statistical analysis plan or protocol. These inconsistencies may include outcome measures of interest or the timepoints for the measurement of outcomes.

R code for COVID network meta-analysis

```
####Dichotomous data####
####Outcome 1: Mortality#####
library(gemtc)
data<-read.csv("{file location}")
network<-mtc.network(data)

### network plot
#M=data$node
#pdf("{save location}")
#plot(network,layout=igraph::layout.circle, dynamic.edge.width=T, margin=0,
#       edge.color="black",vertex.color="red",vertex.size=M,
#       vertex.shape="circle",vertex.label.dist=-0,
#       vertex.label.cex=1.5,vertex.label.color="blue",vertex.label.degree=pi/1,
#       use.description=FALSE)
#dev.off()

### set model, add "hy.prior=mtc.hy.prior("std.dev", "dunif", 0, "om.scale")" to set Uniform(0,5)
prior
### "hy.prior=mtc.hy.empirical.lor("semi-objective", "pharma-pharma")" to set log-normal prior
based on Turner et al. 2012.
### different model: ??mtc.model
#model <- mtc.model(network,type = "consistency",
#                       likelihood="binom",link="logit",
#                       linearModel="random", n.chain =3,
#                       powerAdjust=NA, dic=TRUE,
#                       hy.prior=mtc.hy.empirical.lor("mortality", "pharma-control"))

### set informative prior based on pairwise MA
model <- mtc.model(network,type = "consistency",
                       likelihood="binom",link="logit",
                       linearModel="random", n.chain =3,
                       powerAdjust=NA, dic=TRUE,
                       hy.prior=mtc.hy.prior("var", "dlnorm", -3.95, 0.5569))

###binom/logit for OR; binom/log for RR; binom/cloglog for HR
results <-mtc.run(model, sampler ="JAGS", n.adapt=50000, n.iter=2000000, thin=1)

# Save Network summary,Posterior summary,convergence diagnostic
sink("{file save location}")
summary(network)
summary(results)
gelman.diag(results)
```

```
sink(NULL)

### Creates a forest plot of the relative effects
pdf("{file save location}",width=8,height = 3)
forest(relative.effect(results,"Standardcare"),digits=4,use.description=T)
dev.off()

###generate league table
mtcresults = as.data.frame(round(exp(relative.effect.table(results)),2))
write.csv(mtcresults, file="{file location}")

### calculating probability of rank, preferredDirection=1 for benifit outcomes
rank.prob<- rank.probability(results, preferredDirection=-1)

####the probability for each treatment to be best, second best, etc.
print(rank.prob)
write.csv(rank.prob, file="C:/Users/Administrator/Desktop/COVID/6-rank/Prbest_mortality.csv")

##Generate quantile ranks
rank.quantiles<-rank.quantiles(rank.prob, probs=c("2.5%"=0.025, "50%"=0.5, "97.5%"=0.975))
write.csv(rank.quantiles, file="{file location}")

# plot a 'rankogram'
pdf("{file location}")
plot(rank.prob, beside=TRUE)
dev.off()

### calculating SUCRA
cumrank.prob <- apply(t(rank.prob), 2, cumsum)
sucra <- round(colMeans(cumrank.prob[-nrow(cumrank.prob),]),4)
write.csv(sucra, file="{file location}")

####Nodesplit analysis
#result.node <- mtc.nodesplit(network, likelihood="binom",link="logit",
#                             linearModel="random", n.chain =3,
#                             n.adapt=50000, n.iter=2000000, thin=1,
#                             hy.prior=mtc.hy.prior("var", "dlnorm", -3.95,0.5569))

#pdf("C:/Users/Administrator/Desktop/COVID/8-nodesplit plots/mortality.pdf")
#plot(summary(result.node),xlim=log(c(0.1,5)),digits=4)
#dev.off()

####Outcome 2: Mechanical ventilation#####
library(gemtc)
```

```
data<-read.csv("{file location}")
network<-mtc.network(data)

### network plot
#M=data$node
#pdf("{file location}")
#plot(network,layout=igraph::layout.circle, dynamic.edge.width=T, margin=0,
#       edge.color="black",vertex.color="red",vertex.size=M,
#       vertex.shape="circle",vertex.label.dist=-0,
#       vertex.label.cex=1.5,vertex.label.color="blue",vertex.label.degree=pi/1,
#       use.description=FALSE)
#dev.off()

### set model, add "hy.prior=mtc.hy.prior("std.dev", "dunif", 0, "om.scale")" to set Uniform(0,5)
prior
### "hy.prior=mtc.hy.empirical.lor("semi-objective", "pharma-pharma")" to set log-normal prior
based on Turner et al. 2012.
### different model: ??mtc.model
#model <- mtc.model(network,type = "consistency",
#                          likelihood="binom",link="logit",
#                          linearModel="random", n.chain =3,
#                          powerAdjust=NA, dic=TRUE,
#                          hy.prior=mtc.hy.empirical.lor("mortality", "pharma-control"))

### set informative prior based on pairwise MA
model <- mtc.model(network,type = "consistency",
                          likelihood="binom",link="logit",
                          linearModel="random", n.chain =3,
                          powerAdjust=NA, dic=TRUE,
                          hy.prior=mtc.hy.prior("var", "dlnorm", -2.34, 0.3303))

###binom/logit for OR; binom/log for RR; binom/cloglog for HR
results <-mtc.run(model, sampler ="JAGS", n.adapt=50000, n.iter=500000, thin=1)

# Save Network summary,Posterior summary,convergence diagnostic
sink("{file location}")
summary(network)
summary(results)
gelman.diag(results)
sink(NULL)

### Creates a forest plot of the relative effects
pdf("{file location}",width=8,height = 3)
forest(relative.effect(results,"Standardcare"),digits=4,use.description=T)
```

```
dev.off()

###generate league table
mtcresults = as.data.frame(round(exp(relative.effect.table(results)),2))
write.csv(mtcresults, file="{file location}")

### calculating probability of rank, preferredDirection=1 for benifit outcomes
rank.prob<- rank.probability(results, preferredDirection=-1)

####the probability for each treatment to be best, second best, etc.
print(rank.prob)
write.csv(rank.prob, file="{file location}")

##Generate quantile ranks
rank.quantiles<-rank.quantiles(rank.prob, probs=c("2.5%"=0.025, "50%"=0.5, "97.5%"=0.975))
write.csv(rank.quantiles, file="{file location}")

# plot a 'rankogram'
pdf("{file location}")
plot(rank.prob, beside=TRUE)
dev.off()

### calculating SUCRA
cumrank.prob <- apply(t(rank.prob), 2, cumsum)
sucra <- round(colMeans(cumrank.prob[-nrow(cumrank.prob),]),4)
write.csv(sucra, file="{file location}")

####Nodesplit analysis
#result.node <- mtc.nodesplit(network, likelihood="binom",link="logit",
#                                      linearModel="random", n.chain =3,
#                                      n.adapt=50000, n.iter=2000000, thin=1,
#                                      hy.prior=mtc.hy.prior("var", "dlnorm", -2.34,0.3303))

#pdf("C:/Users/Administrator/Desktop/COVID/8-nodesplit plots/Mechanical ventilation.pdf")
#plot(summary(result.node),xlim=log(c(0.1,5)),digits=4)
#dev.off()

####Outcome 3: Adverse effects leading to disc####
library(gemtc)
data<-read.csv("{file location}")
network<-mtc.network(data)

### network plot
#M=data$node
```

```
#pdf("{file location}")
#plot(network,layout=igraph::layout.circle, dynamic.edge.width=T, margin=0,
#       edge.color="black",vertex.color="red",vertex.size=M,
#       vertex.shape="circle",vertex.label.dist=-0,
#       vertex.label.cex=1.5,vertex.label.color="blue",vertex.label.degree=pi/1,
#       use.description=FALSE)
#dev.off()

### set model, add "hy.prior=mtc.hy.prior("std.dev", "dunif", 0, "om.scale")" to set Uniform(0,5)
prior
### "hy.prior=mtc.hy.empirical.lor("semi-objective", "pharma-pharma")" to set log-normal prior
based on Turner et al. 2012.
### different model: ??mtc.model
#model <- mtc.model(network,type = "consistency",
#                               likelihood="binom",link="logit",
#                               linearModel="random", n.chain =3,
#                               powerAdjust=NA, dic=TRUE,
#                               hy.prior=mtc.hy.empirical.lor("mortality", "pharma-control"))

### set informative prior based on pairwise MA
model <- mtc.model(network,type = "consistency",
                               likelihood="binom",link="logit",
                               linearModel="random", n.chain =3,
                               powerAdjust=NA, dic=TRUE,
                               hy.prior=mtc.hy.prior("var", "dlnorm", -1.87, 0.4328))

###binom/logit for OR; binom/log for RR; binom/cloglog for HR
results <-mtc.run(model, sampler ="JAGS", n.adapt=50000, n.iter=500000, thin=1)

# Save Network summary,Posterior summary,convergence diagnostic
sink("{file location}")
summary(network)
summary(results)
gelman.diag(results)
sink(NULL)

### Creates a forest plot of the relative effects
pdf("{file location}",width=8,height = 3)
forest(relative.effect(results,"Standardcare"),digits=4,use.description=T)
dev.off()

###generate league table
mtcresults = as.data.frame(round(exp(relative.effect.table(results)),2))
write.csv(mtcresults, file="{file location}")
```

```
### calculating probability of rank, preferredDirection=1 for benifit outcomes
rank.prob<- rank.probability(results, preferredDirection=-1)

####the probability for each treatment to be best, second best, etc.
print(rank.prob)
write.csv(rank.prob, file="{file location}")

##Generate quantile ranks
rank.quantiles<-rank.quantiles(rank.prob, probs=c("2.5%"=0.025, "50%"=0.5, "97.5%"=0.975))
write.csv(rank.quantiles, file="{file location}")

# plot a 'rankogram'
pdf("C:/Users/Administrator/Desktop/COVID/6-rank/rankogram_Adverse effects leading to
disc.pdf")
plot(rank.prob, beside=TRUE)
dev.off()

### calculating SUCRA
cumrank.prob <- apply(t(rank.prob), 2, cumsum)
sucra <- round(colMeans(cumrank.prob[-nrow(cumrank.prob),]),4)
write.csv(sucra, file="{file location}")

####Nodesplit analysis
mtc.nodesplit.comparisons(network)
result.node <- mtc.nodesplit(network, likelihood="binom",link="logit",
                                      linearModel="random", n.chain =3,
                                      n.adapt=50000, n.iter=2000000, thin=1,
                                      hy.prior=mtc.hy.prior("var", "dlnorm", -1.87,0.4328))

pdf("C:/Users/Administrator/Desktop/COVID/8-nodesplit plots/Adverse effects leading to
disc.pdf",width=8,height = 5)
plot(summary(result.node),xlim=log(c(0.1,2)),digits=4)
dev.off()

####Outcome 4: Viral clearance    closest to 7 d#####
library(gemtc)
data<-read.csv("{file location}")
network<-mtc.network(data)

### network plot
#M=data$node
#pdf("{file location}")
#plot(network,layout=igraph::layout.circle, dynamic.edge.width=T, margin=0,
```

```
#         edge.color="black",vertex.color="red",vertex.size=M,
#         vertex.shape="circle",vertex.label.dist=-0,
#         vertex.label.cex=1.5,vertex.label.color="blue",vertex.label.degree=pi/1,
#         use.description=FALSE)
#dev.off()

### set model, add "hy.prior=mtc.hy.prior("std.dev", "dunif", 0, "om.scale")" to set Uniform(0,5)
prior
### "hy.prior=mtc.hy.empirical.lor("semi-objective", "pharma-pharma")" to set log-normal prior
based on Turner et al. 2012.
### different model: ??mtc.model
#model <- mtc.model(network,type = "consistency",
#                                likelihood="binom",link="logit",
#                                linearModel="random", n.chain =3,
#                                powerAdjust=NA, dic=TRUE,
#                                hy.prior=mtc.hy.empirical.lor("mortality", "pharma-control"))

### set informative prior based on pairwise MA
model <- mtc.model(network,type = "consistency",
                               likelihood="binom",link="logit",
                               linearModel="random", n.chain =3,
                               powerAdjust=NA, dic=TRUE,
                               hy.prior=mtc.hy.prior("var", "dlnorm", -2.06, 0.4386))

###binom/logit for OR; binom/log for RR; binom/cloglog for HR
results <-mtc.run(model, sampler ="JAGS", n.adapt=50000, n.iter=500000, thin=1)

# Save Network summary,Posterior summary,convergence diagnostic
sink("{file location}")
summary(network)
summary(results)
gelman.diag(results)
sink(NULL)

### Creates a forest plot of the relative effects
pdf("{file location}",width=8,height = 3)
forest(relative.effect(results,"standardcare"),digits=4,use.description=T)
dev.off()

###generate league table
mtcresults = as.data.frame(round(exp(relative.effect.table(results)),2))
write.csv(mtcresults, file="{file location}")

### calculating probability of rank, preferredDirection=1 for benifit outcomes
```

```
rank.prob<- rank.probability(results, preferredDirection=1)

####the probability for each treatment to be best, second best, etc.
print(rank.prob)
write.csv(rank.prob, file="{file location}")

##Generate quantile ranks
rank.quantiles<-rank.quantiles(rank.prob, probs=c("2.5%"=0.025, "50%"=0.5, "97.5%"=0.975))
write.csv(rank.quantiles, file="{file location}")

# plot a 'rankogram'
pdf("{file location}")
plot(rank.prob, beside=TRUE)
dev.off()

### calculating SUCRA
cumrank.prob <- apply(t(rank.prob), 2, cumsum)
sucra <- round(colMeans(cumrank.prob[-nrow(cumrank.prob),]),4)
write.csv(sucra, file="{file location}")

####Nodesplit analysis
#result.node <- mtc.nodesplit(network, likelihood="binom",link="logit",
#                                      linearModel="random", n.chain =3,
#                                      n.adapt=50000, n.iter=2000000, thin=1,
#                                      hy.prior=mtc.hy.prior("var", "dlnorm", -2.06,0.4386))

#pdf("C:/Users/Administrator/Desktop/COVID/8-nodesplit plots/Viral clearance closest to 7
d.pdf")
#plot(summary(result.node),xlim=log(c(0.1,5)),digits=4)
#dev.off()

####Continuous data####
####Outcome 1: Time to viral load below threshold for transmissibility [days]####
library(gemtc)
data<-read.csv("{file location}")
network<-mtc.network(data)

### network plot
#M=data$node
#pdf("{file location}")
#plot(network,layout=igraph::layout.circle, dynamic.edge.width=T, margin=0,
#       edge.color="black",vertex.color="red",vertex.size=M,
#       vertex.shape="circle",vertex.label.dist=-0,
#       vertex.label.cex=1.5,vertex.label.color="blue",vertex.label.degree=pi/1,
```

```
#         use.description=FALSE)
#dev.off()

### set model, add "hy.prior=mtc.hy.prior("std.dev", "dunif", 0, "om.scale")" to set Uniform(0,5)
prior
### "hy.prior=mtc.hy.empirical.lor("semi-objective", "pharma-pharma")" to set log-normal prior
based on Turner et al. 2012.
### different model: ??mtc.model
#model <- mtc.model(network,type = "consistency",
#                                likelihood="normal",link="identity",
#                                linearModel="random", n.chain =3,
#                                powerAdjust=NA, dic=TRUE,
#                                hy.prior=mtc.hy.empirical.lor("mortality", "pharma-control"))

### set informative prior based on pairwise MA
model <- mtc.model(network,type = "consistency",
                                likelihood="normal",link="identity",
                                linearModel="random", n.chain =3,
                                powerAdjust=NA, dic=TRUE,
                                hy.prior=mtc.hy.prior("var", "dlnorm", -2.06, 0.4386))

###binom/logit for OR; binom/log for RR; binom/cloglog for HR
results <-mtc.run(model, sampler ="JAGS", n.adapt=50000, n.iter=500000, thin=10)

# Save Network summary,Posterior summary,convergence diagnostic
sink("{file location}")
summary(network)
summary(results)
gelman.diag(results)
sink(NULL)

### Creates a forest plot of the relative effects
pdf("{file location}",width=8,height = 3)
forest(relative.effect(results,"Standardcare"),digits=4,use.description=T)
dev.off()

###generate league table
mtcresults = as.data.frame(round(relative.effect.table(results),2))
write.csv(mtcresults, file="{file location}")

### calculating probability of rank, preferredDirection=1 for benifit outcomes
rank.prob<- rank.probability(results, preferredDirection=-1)

####the probability for each treatment to be best, second best, etc.
```

```
print(rank.prob)
write.csv(rank.prob, file="{file location}")

##Generate quantile ranks
rank.quantiles<-rank.quantiles(rank.prob, probs=c("2.5%"=0.025, "50%"=0.5, "97.5%"=0.975))
write.csv(rank.quantiles, file="{file location}")

# plot a 'rankogram'
pdf("C:/Users/Administrator/Desktop/COVID/6-rank/rankogram_Time to viral load.pdf")
plot(rank.prob, beside=TRUE)
dev.off()

### calculating SUCRA
cumrank.prob <- apply(t(rank.prob), 2, cumsum)
sucra <- round(colMeans(cumrank.prob[-nrow(cumrank.prob),]),4)
write.csv(sucra, file="{file location}")

####Nodesplit analysis
#result.node <- mtc.nodesplit(network, likelihood="normal",link="identity",
#                                        linearModel="random", n.chain =3,
#                                        n.adapt=50000, n.iter=500000, thin=1,
#                                       hy.prior=mtc.hy.prior("var", "dlnorm", -2.06, 0.4386))

#pdf("{file location}")
#plot(summary(result.node),xlim=log(c(0.1,5)),digits=4)
#dev.off()


####Outcome 2: Time to symptom resolution [days]####
library(gemtc)
data<-read.csv("C:/Users/Administrator/Desktop/COVID/1-data preparation/1-Time to symptom
resolution_gemtc.csv")
network<-mtc.network(data)

### network plot
#M=data$node
#pdf("C:/Users/Lenovo/Desktop/COVID/2-network plot/mortality.pdf")
#plot(network,layout=igraph::layout.circle, dynamic.edge.width=T, margin=0,
#     edge.color="black",vertex.color="red",vertex.size=M,
#     vertex.shape="circle",vertex.label.dist=-0,
#     vertex.label.cex=1.5,vertex.label.color="blue",vertex.label.degree=pi/1,
#     use.description=FALSE)
#dev.off()
```

```
### set model, add "hy.prior=mtc.hy.prior("std.dev", "dunif", 0, "om.scale")" to set Uniform(0,5)
prior
### "hy.prior=mtc.hy.empirical.lor("semi-objective", "pharma-pharma")" to set log-normal prior
based on Turner et al. 2012.
### different model: ??mtc.model
#model <- mtc.model(network,type = "consistency",
#                   likelihood="normal",link="identity",
#                   linearModel="random", n.chain =3,
#                   powerAdjust=NA, dic=TRUE,
#                   hy.prior=mtc.hy.empirical.lor("mortality", "pharma-control"))

### set informative prior based on pairwise MA
model <- mtc.model(network,type = "consistency",
                   likelihood="normal",link="identity",
                   linearModel="random", n.chain =3,
                   powerAdjust=NA, dic=TRUE,
                   hy.prior=mtc.hy.prior("var", "dlnorm", -2.06, 0.4386))

###binom/logit for OR; binom/log for RR; binom/cloglog for HR
results <-mtc.run(model, sampler ="JAGS", n.adapt=50000, n.iter=500000, thin=10)

# Save Network summary,Posterior summary,convergence diagnostic
sink("{file location}")
summary(network)
summary(results)
gelman.diag(results)
sink(NULL)

### Creates a forest plot of the relative effects
pdf("{file location}",width=8,height = 3)
forest(relative.effect(results,"Standardcare"),digits=4,use.description=T)
dev.off()

###generate league table
mtcresults = as.data.frame(round(relative.effect.table(results),2))
write.csv(mtcresults, file="{file location}")

### calculating probability of rank, preferredDirection=1 for benifit outcomes
rank.prob<- rank.probability(results, preferredDirection=-1)

####the probability for each treatment to be best, second best, etc.
print(rank.prob)
write.csv(rank.prob, file="{file location}")
```

```
##Generate quantile ranks
rank.quantiles<-rank.quantiles(rank.prob, probs=c("2.5%"=0.025, "50%"=0.5, "97.5%"=0.975))
write.csv(rank.quantiles, file="{file location}")

# plot a 'rankogram'
pdf("C:/Users/Administrator/Desktop/COVID/6-rank/rankogram_Time to symptom
resolution.pdf")
plot(rank.prob, beside=TRUE)
dev.off()

### calculating SUCRA
cumrank.prob <- apply(t(rank.prob), 2, cumsum)
sucra <- round(colMeans(cumrank.prob[-nrow(cumrank.prob),]),4)
write.csv(sucra, file="{file location}")

####Nodesplit analysis
#result.node <- mtc.nodesplit(network, likelihood="normal",link="identity",
#                                        linearModel="random", n.chain =3,
#                                        n.adapt=50000, n.iter=500000, thin=1,
#                                       hy.prior=mtc.hy.prior("var", "dlnorm", -2.06, 0.4386))

#pdf("{file location}")
#plot(summary(result.node),xlim=log(c(0.1,5)),digits=4)
#dev.off()


####Outcome 3: Duration of ventilation [days]####
library(gemtc)
data<-read.csv("{file location}")
network<-mtc.network(data)

### network plot
#M=data$node
#pdf("{file location}")
#plot(network,layout=igraph::layout.circle, dynamic.edge.width=T, margin=0,
#     edge.color="black",vertex.color="red",vertex.size=M,
#     vertex.shape="circle",vertex.label.dist=-0,
#     vertex.label.cex=1.5,vertex.label.color="blue",vertex.label.degree=pi/1,
#     use.description=FALSE)
#dev.off()

### set model, add "hy.prior=mtc.hy.prior("std.dev", "dunif", 0, "om.scale")" to set Uniform(0,5)
prior
### "hy.prior=mtc.hy.empirical.lor("semi-objective", "pharma-pharma")" to set log-normal prior
```

```
based on Turner et al. 2012.
### different model: ??mtc.model
#model <- mtc.model(network,type = "consistency",
#                    likelihood="normal",link="identity",
#                    linearModel="random", n.chain =3,
#                    powerAdjust=NA, dic=TRUE,
#                    hy.prior=mtc.hy.empirical.lor("mortality", "pharma-control"))

### set informative prior based on pairwise MA
model <- mtc.model(network,type = "consistency",
                   likelihood="normal",link="identity",
                   linearModel="random", n.chain =3,
                   powerAdjust=NA, dic=TRUE,
                   hy.prior=mtc.hy.prior("var", "dlnorm", -2.34, 0.3303))

###binom/logit for OR; binom/log for RR; binom/cloglog for HR
results <-mtc.run(model, sampler ="JAGS", n.adapt=50000, n.iter=500000, thin=10)

# Save Network summary,Posterior summary,convergence diagnostic
sink("{file location}")
summary(network)
summary(results)
gelman.diag(results)
sink(NULL)

### Creates a forest plot of the relative effects
pdf("{file location}",width=8,height = 3)
forest(relative.effect(results,"Standardcare"),digits=4,use.description=T)
dev.off()

###generate league table
mtcresults = as.data.frame(round(relative.effect.table(results),2))
write.csv(mtcresults, file="C:/Users/Administrator/Desktop/COVID/5-league table/Duration of
ventilation.csv")

### calculating probability of rank, preferredDirection=1 for benifit outcomes
rank.prob<- rank.probability(results, preferredDirection=-1)

####the probability for each treatment to be best, second best, etc.
print(rank.prob)
write.csv(rank.prob, file="{file location}")

##Generate quantile ranks
rank.quantiles<-rank.quantiles(rank.prob, probs=c("2.5%"=0.025, "50%"=0.5, "97.5%"=0.975))
```

```
write.csv(rank.quantiles, file="{file location}")

# plot a 'rankogram'
pdf("{file location}")
plot(rank.prob, beside=TRUE)
dev.off()

### calculating SUCRA
cumrank.prob <- apply(t(rank.prob), 2, cumsum)
sucra <- round(colMeans(cumrank.prob[-nrow(cumrank.prob),]),4)
write.csv(sucra, file="{file location}")

####Nodesplit analysis
#result.node <- mtc.nodesplit(network, likelihood="normal",link="identity",
#                                          linearModel="random", n.chain =3,
#                                          n.adapt=50000, n.iter=500000, thin=1,
#                                         hy.prior=mtc.hy.prior("var", "dlnorm", -2.34, 0.3303))

#pdf("C:/Users/Administrator/Desktop/COVID/8-nodesplit plots/Duration of ventilation.pdf")
#plot(summary(result.node),xlim=log(c(0.1,5)),digits=4)
#dev.off()

####Outcome 4:Duration of hospitalization#####
library(gemtc)
data<-read.csv("{file location}")
network<-mtc.network(data)

### network plot
#M=data$node
#pdf("{file location}")
#plot(network,layout=igraph::layout.circle, dynamic.edge.width=T, margin=0,
#       edge.color="black",vertex.color="red",vertex.size=M,
#       vertex.shape="circle",vertex.label.dist=-0,
#       vertex.label.cex=1.5,vertex.label.color="blue",vertex.label.degree=pi/1,
#       use.description=FALSE)
#dev.off()

### set model, add "hy.prior=mtc.hy.prior("std.dev", "dunif", 0, "om.scale")" to set Uniform(0,5)
prior
### "hy.prior=mtc.hy.empirical.lor("semi-objective", "pharma-pharma")" to set log-normal prior
based on Turner et al. 2012.
### different model: ??mtc.model
#model <- mtc.model(network,type = "consistency",
#                                 likelihood="normal",link="identity",
```

```
#                           linearModel="random", n.chain =3,
#                           powerAdjust=NA, dic=TRUE,
#                           hy.prior=mtc.hy.empirical.lor("mortality", "pharma-control"))

### set informative prior based on pairwise MA
model <- mtc.model(network,type = "consistency",
                           likelihood="normal",link="identity",
                           linearModel="random", n.chain =3,
                           powerAdjust=NA, dic=TRUE,
                           hy.prior=mtc.hy.prior("var", "dlnorm", -2.34, 0.3303))

###binom/logit for OR; binom/log for RR; binom/cloglog for HR
results <-mtc.run(model, sampler ="JAGS", n.adapt=50000, n.iter=500000, thin=10)

# Save Network summary,Posterior summary,convergence diagnostic
sink("{file location}")
summary(network)
summary(results)
gelman.diag(results)
sink(NULL)

### Creates a forest plot of the relative effects
pdf("{file location}",width=8,height = 3)
forest(relative.effect(results,"Standardcare"),digits=4,use.description=T)
dev.off()

###generate league table
mtcresults = as.data.frame(round(relative.effect.table(results),2))
write.csv(mtcresults, file="{file location}")

### calculating probability of rank, preferredDirection=1 for benifit outcomes
rank.prob<- rank.probability(results, preferredDirection=-1)

####the probability for each treatment to be best, second best, etc.
print(rank.prob)
write.csv(rank.prob, file="{file location}")

##Generate quantile ranks
rank.quantiles<-rank.quantiles(rank.prob, probs=c("2.5%"=0.025, "50%"=0.5, "97.5%"=0.975))
write.csv(rank.quantiles, file="{file location}")

# plot a 'rankogram'
pdf("{file location}")
plot(rank.prob, beside=TRUE)
```

```
dev.off()

### calculating SUCRA
cumrank.prob <- apply(t(rank.prob), 2, cumsum)
sucra <- round(colMeans(cumrank.prob[-nrow(cumrank.prob),]),4)
write.csv(sucra, file="{file location}")

####Nodesplit analysis
#result.node <- mtc.nodesplit(network, likelihood="normal",link="identity",
#                                        linearModel="random", n.chain =3,
#                                        n.adapt=50000, n.iter=500000, thin=1,
#                                       hy.prior=mtc.hy.prior("var", "dlnorm", -2.34, 0.3303))

#pdf("{file location}")
#plot(summary(result.node),xlim=log(c(0.1,5)),digits=4)
#dev.off()


###################regression analysis#########
data<-read.csv("{file location}")
study<-read.csv("{file location}")
networkreg<-mtc.network(data=data, studies=study)

# Random effect meta-regression for mortality
regressor <- list(coefficient='shared',
                  variable='coviarate',
                  control='Placebo')
#####coefficient indicates the type of treatment-interaction model: "shared", "unrelated", or
"exchangeable"
#####control, if specified, must be the ID of a treatment in the network

model_reg <- mtc.model(networkreg,
                       type="regression",
                       regressor=regressor,
                       om.scale=NULL,
                       likelihood="binom",link="log",
                       linearModel="random", n.chain =3,
                       om.scale=NULL,hy.prior=mtc.hy.prior("std.dev", "dunif", 0,
"om.scale"))

### run regression model
result_reg <-mtc.run(model_reg, sampler ="JAGS", n.adapt=1000, n.iter=5000, thin=1)

sink("{file location}")
```

```
summary(result_reg)
gelman.diag(result_reg)
sink(NULL)
```

Sensitivity analyses
Network meta-analyses limited to treatments with 100 patients or 20 events

We decided against presenting results from treatment nodes with fewer than 100 patients or 20 events because some of the initial results for comparisons involving these treatments were implausible (e.g., risk ratios more than 1 billion) with extremely wide credible intervals (CIs). We therefore performed a sensitivity analysis to determine whether or not including treatments with very few patients and events substantively changed the effect estimates for comparisons between treatment options with at least 100 patients or 20 events. The primary analysis of this version of the living NMA included treatment nodes with a small number of patients and events. Below, we present the sensitivity analyses excluding treatment nodes with few events. The estimates relative effects and their CIs for comparisons between treatments with at least 100 patients or 20 events are similar regardless of whether or not treatments with fewer patients and events are included in the NMA. In future updates of this living NMA, we will exclude treatment nodes with few patients and events from the primary analysis.

Mortality

Table 1. Mortality: NMA results including only RCTs with at least 100 patients or 20 events

NMA results							
		Relative estimate			**Absolute estimate (per 1,000)**		
Treatment 1	Treatment 2	Point estimate	CI lower limit	CI upper limit	Point estimate	CI lower limit	CI upper limit
Favipiravir	Standard care/Placebo	0.00	0.00	9.24E+05	-330.00	-330.00	670.00
Hydroxychloroquine	Standard care/Placebo	17.12	0.00	1.80E+08	563.98	-330.00	670.00
Lopinavir-Ritonavir	Standard care/Placebo	0.71	0.31	1.59	-71.55	-196.14	108.99
Remdesivir	Standard care/Placebo	0.66	0.41	1.14	-85.00	-163.06	28.59
Umifenovir	Standard care/Placebo	0.00	0.00	180.75	-330.00	-330.00	658.89
Glucocorticoids	Standard care/Placebo	0.84	0.52	1.36	-36.87	-125.26	70.77
Hydroxychloroquine	Favipiravir	9.57E+05	0.00	3.36E+21	454.48	-789.04	1000.00
Lopinavir-Ritonavir	Favipiravir	1.10E+06	0.00	1.67E+18	229.75	-797.36	426.24
Remdesivir	Favipiravir	9.76E+05	0.00	1.56E+18	227.27	-788.18	347.80
Umifenovir	Favipiravir	0.00	0.00	1.95E+04	0.00	-998.11	25.72
Glucocorticoids	Favipiravir	1.25E+06	0.00	2.02E+18	279.66	-734.57	389.03
Lopinavir-Ritonavir	Hydroxychloroquine	0.04	0.00	5.99E+07	-580.06	-841.41	360.91
Remdesivir	Hydroxychloroquine	0.04	0.00	5.32E+07	-622.28	-814.92	303.97
Umifenovir	Hydroxychloroquine	0.00	0.00	5.04E+02	-840.98	-1000.00	535.67
Glucocorticoids	Hydroxychloroquine	0.05	0.00	7.01E+07	-579.45	-768.14	338.70
Remdesivir	Lopinavir-Ritonavir	0.93	0.37	2.49	-13.15	-206.26	157.23
Umifenovir	Lopinavir-Ritonavir	0.00	0.00	244.77	-247.83	-433.65	699.20
Glucocorticoids	Lopinavir-Ritonavir	1.19	0.47	3.03	34.38	-163.35	196.39
Umifenovir	Remdesivir	0.00	0.00	270.24	-238.40	-354.01	730.07
Glucocorticoids	Remdesivir	1.28	0.61	2.45	48.41	-96.19	173.90
Glucocorticoids	Umifenovir	5.58E+09	0.00	7.80E+24	288.40	-686.47	396.23

Mechanical ventilation

Table 2. Mechanical ventilation: NMA results including only RCTs with at least 100 patients or 20 events

NMA results							
		Relative estimate			**Absolute estimate (per 1,000)**		
Treat 1	Treat 2	Point estimate	CI lower limit	CI upper limit	Point estimate	CI lower limit	CI upper limit
Remdesivir	Standard care/Placebo	0.77	0.38	1.52	-24.21	-68.56	50.28
Glucocorticoids	Standard care/Placebo	0.71	0.30	1.67	-30.91	-77.99	63.63
Glucocorticoids	Remdesivir	0.92	0.31	2.82	-6.69	-91.60	95.69

Adverse events leading to discontinuation

Table 3. Adverse events leading to discontinuation: NMA results including only RCTs with at least 100 patients or 20 events

NMA results							
		Relative estimate			Absolute estimate (per 1,000)		
Treat 1	Treat 2	Point estimate	CI lower limit	CI upper limit	Point estimate	CI lower limit	CI upper limit
Hydroxychloroquine	Standard care/Placebo	6.36E+04	3.36	1.28E+15	984.06	33.48	985.10
Remdesivir	Standard care/Placebo	1.28	0.53	3.93	4.06	-7.00	41.16
Remdesivir	Hydroxychloroquine	0.00	0.00	0.43	-971.28	-990.39	-26.30

Viral clearance at 7 days

Table 4. Viral clearance at 7 days: NMA results including only RCTs with at least 100 patients or 20 events

NMA results							
		Relative estimate			**Absolute estimate (per 1,000)**		
Treatment 1	Treatment 2	Point estimate	CI lower limit	CI upper limit	Point estimate	CI lower limit	CI upper limit
Hydroxychloroquine	Standard care/Placebo	1.37	0.17	10.70	78.59	-351.60	414.54
Lopinavir-Ritonavir	Standard care/Placebo	0.34	0.02	2.80	-243.60	-478.96	237.02
Remdesivir	Standard care/Placebo	1.05	0.03	36.92	11.93	-470.96	473.63
Lopinavir-Ritonavir	Hydroxychloroquine	0.25	0.01	2.68	-282.28	-730.65	199.40
Remdesivir	Hydroxychloroquine	0.77	0.01	47.25	-55.42	-717.75	619.98
Remdesivir	Lopinavir-Ritonavir	3.01	0.06	317.58	214.84	-446.62	849.95

Duration of hospitalization

There was only one comparison with more than 100 patients in each group: remdesivir versus standard care.

Intensive care unit length of stay

There were no comparisons with at least 100 patients or 20 events in both groups.

Duration of mechanical ventilation

There was only one comparison with more than 100 patients in each group: remdesivir versus standard care.

Time to symptom resolution

Table 5. Time to symptom resolution: NMA results including only RCTs with at least 100 patients

NMA results							
		Ratio of means			**Absolute estimate (difference in days)**		
Treatment 1	Treatment 2	Point estimate	CI lower limit	CI upper limit	Point estimate	CI lower limit	CI upper limit
Hydroxychloroquine	Standard care/Placebo	0.75	0.68	0.84	-4.68	-5.98	-2.99
Remdesivir	Standard care/Placebo	0.86	0.77	0.97	-2.62	-4.30	-0.56
Lopinavir-Ritonavir	Standard care/Placebo	0.94	0.89	0.98	-1.12	-2.06	-0.37
Hydroxychloroquine	Lopinavir-Ritonavir	0.80	0.72	0.90	-3.74	-5.24	-1.87
Hydroxychloroquine	Remdesivir	0.87	0.75	1.02	-2.43	-4.68	0.37
Lopinavir-Ritonavir	Remdesivir	1.09	0.96	1.23	1.68	-0.75	4.30