Health Information and Quality Authority
An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Interventions in an ambulatory setting to prevent progression to severe disease in patients with COVID-19

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About the Health Information and Quality Authority (HIQA)

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.
- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.
- **Regulating health services —** Regulating medical exposure to ionising radiation.
- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.
- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.
- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.
- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

List of abbreviations used in this report

CADTH	Canadian Agency for Drugs and Technologies in Health
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COVID-19	coronavirus disease 2019
EAG	Expert Advisory Group
ECDC	European Centre for Disease Prevention and Control
EMA	European Medicines Agency
EUnetHTA	European Network of HTA
FDA	Food and Drug Administration
HIQA	Health Information and Quality Authority
HPSC	Health Protection Surveillance Centre
HSE	Health Service Executive
HTA	health technology assessment
NICE	The National Institute for Health and Care Excellence
NIH	National Institutes of Health
NRCT	non-randomised controlled trial
NPHET	National Public Health Emergency Team
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
RCT	randomised controlled trial
WHO	World Health Organization

Interventions in an ambulatory setting to prevent progression to severe disease in COVID-19 patients

Key points

- A rapid evidence review was conducted to identify studies on the effectiveness of (i) pharmaceutical and (ii) non-pharmaceutical interventions, in the ambulatory setting, aimed at reducing progression to severe disease in individuals with confirmed or suspected COVID-19.
- For the purpose of this evidence summary, only controlled trials with published effectiveness data were included. The following studies of interventions were excluded:
  - ongoing trials without published interim or preliminary results
  - trials that enrolled patients from both inpatient and ambulatory settings, but did not report disaggregated data relating to the ambulatory group
  - trials that included interventions against which regulatory agencies (such as the EMA, FDA, MHRA) have issued warnings on the basis of potential harms (such as hydroxychloroquine).
- No trials were identified relating to non-pharmaceutical interventions (lifestyle, physiotherapy, respiratory therapy, psychological therapy, organisational or technological interventions).
- Eight randomised controlled trials (RCTs) were identified relating to nine pharmaceutical interventions. Seven of these trials enrolled adults ≥18 years with one trial enrolling adults and adolescents ≥16 years. At the time of enrolment, all patients had RT-PCR confirmed COVID-19 and were not hospitalised. The median number of participants in trials was 198 (range: 62-577) with a median duration of follow-up of 25 days (range: 5-29).
- None of the nine interventions identified are currently authorised for the treatment of COVID-19 by the European Medicines Agency (EMA); five of the nine interventions are not authorised for any indication by the EMA (casirivimab plus imdevimab, bamlanivimab, bamlanivimab plus etesevimab, nitazoxanide, sulodexide).
- ‘Low certainty’ evidence in support of potential effectiveness was found for two interventions: fluvoxamine versus placebo to prevent clinical deterioration, and the combination monoclonal antibody treatment bamlanivimab plus etesevimab

versus placebo to prevent hospitalisation or emergency department visits. However, both trials were limited by small sample sizes and short durations of follow-up; the results should therefore be considered exploratory in nature. The determination of clinical efficacy and safety will require larger, robust RCTs to be conducted.

  - In one preliminary RCT, patients who received fluvoxamine had a lower risk of clinical deterioration than patients who received placebo (absolute risk difference 8.7% [95% CI: 1.8%-16.4%]; low certainty evidence; 152 participants were followed for 15 days).
  - In one RCT, patients who received the combination monoclonal antibody therapy bamlanivimab plus etesevimab were observed to have a reduced risk of hospitalisations or emergency department visits compared with patients who received placebo (absolute difference 4.9% [95% CI: 0.8%-8.9%]; low certainty evidence; 268 participants were followed for 29 days). No significant difference versus placebo was observed for patients who received bamlanivimab as monotherapy (at any dose, 700mg, 2800mg or 7000mg) , for this outcome.

- 'Very low certainty' evidence was identified from a further two studies (both published as preprints) of two interventions: ivermectin plus doxycycline and sulodexide. Serious concerns were raised with regard to the high risk of bias, small sample sizes and short durations of follow-up within the trials. As such, results from these studies should not be used to inform decision-making with respect to effectiveness. Neither study was considered applicable to the Irish healthcare setting due to differences in usual care provided in the trials.

- No statistically significant difference in the rates of clinical deterioration or hospitalisation was reported for the following interventions, compared with placebo or usual care in the outpatient setting: bamlanivimab (as monotherapy), casirivimab plus imdevimab (at interim analysis of one RCT), ivermectin (as monotherapy), nitazoxanide and peginterferon lambda. Additionally, there were concerns identified in relation to the risk of bias, small sample sizes and short durations of follow-up within a number of these trials. The ivermectin and nitazoxanide trials were considered not applicable to the Irish healthcare setting due to differences in usual care provided in the trials.

- Given the lack of regulatory authorisation of any of the interventions for the treatment of COVID-19 in the ambulatory setting, no robust assessment of safety has been performed to date with respect to their use for this indication. Furthermore, the results presented within the trials herein described are insufficient for establishing the safety profile of the interventions; this is a consequence of small sample sizes, short duration of follow-up, and insufficient assessment and reporting of safety outcomes across the trials.

- In conclusion, there is currently insufficient evidence of either effectiveness or safety to support the use of any pharmaceutical intervention in the community setting to reduce the risk of progression to severe disease in patients who have been diagnosed with COVID-19, unless as part of an ongoing monitored clinical trial. Furthermore, no evidence was identified for the effectiveness or safety of any non-pharmaceutical intervention in the community setting.

Interventions in an ambulatory setting to prevent progression to severe disease in COVID-19 patients

Background

The Health Information and Quality Authority (HIQA) has developed a series of evidence syntheses to inform advice from HIQA to the National Public Health Emergency Team (NPHET). The advice takes into account expert interpretation of the evidence by HIQA's COVID-19 Expert Advisory Group.

This evidence synthesis was requested by NPHET to address the following policy question:

> **"**What is the emerging evidence in relation to (i) pharmaceutical and (ii) lifestyle interventions post diagnosis of COVID-19 in the community aimed at minimising progression to severe disease?"

The following research question was developed to address this policy question:

> What is the evidence on the effectiveness of (i) pharmaceutical and (ii) non-pharmaceutical interventions, in the community setting, aimed at reducing progression to severe disease, in individuals with confirmed or suspected COVID-19?

Methods

A limited scoping of the literature was conducted in advance of this review and a large number of pharmaceutical interventions were identified as prospective candidates for the treatment of COVID-19. For the purpose of this evidence summary, only controlled trials with published effectiveness data were included. The following were excluded:

- ongoing trials without interim or preliminary results
- trials that enrolled patients from both inpatient and ambulatory settings that did not report disaggregated data relating to the outpatient group
- trials that included interventions that regulatory agencies (such as the EMA, FDA, MHRA) have issued warnings against using due to potential harms (such as hydroxychloroquine).

The processes outlined in HIQA's protocol for this review (www.hiqa.ie) were followed. The process through which studies were identified had two components:

1. a database search to identify relevant controlled trials

2. an additional search of publications from select international public health agencies, institutional websites, clinical trial registries and desktop searching (Appendix 1).

Databases were searched on 6 January 2021. Both controlled clinical trials (Randomised Controlled Trials [RCTs] or Non-Randomised Controlled Trials [NRCTs]) and systematic reviews of controlled clinical trials (RCTs or NRCTs) were included.

Only clinical outcomes were included (such as hospitalisation and clinical deterioration); virological outcomes (such as a reduction in viral load) were not considered.

Both pharmaceutical and non-pharmaceutical interventions were included. Pharmaceutical interventions included medications and vitamin or mineral supplementation (such as vitamin D). Non-pharmaceutical interventions included lifestyle interventions (such as smoking cessation and dietary modifications), physiotherapy or respiratory therapy interventions (such as breathing exercises), psychological therapy, organisational interventions (such as community-based assessments and prediction rules) or technological interventions (such as pulse oximetry). Population-level interventions (such as public health recommendations) were not considered.

The quality of individual trials was assessed using the Cochrane Risk of Bias Tool 2 (RoB 2[(1)]). The Grading of Recommendations Assessment, Development and Evaluation (GRADE[(2)]) method was used to evaluate the quality of evidence by outcomes. GRADE assesses the following five domains: (i) risk of bias, (ii) inconsistency, (iii) indirectness, (iv) imprecision and (v) publication bias.

In June 2020, the GRADE team published additional guidance on using GRADE in situations of emergencies and urgencies during the COVID-19 pandemic.[(3)] This publication was used to refine our GRADE assessment of the certainty of the body of evidence. The following seven questions were asked:

1. Are the study designs used appropriate?
2. Are there important limitations in the research design or execution of the research?
3. Are the results consistent across studies when the settings, populations, interventions, comparators, and outcomes are reasonably similar?
4. How directly do the results apply to the population (including setting), intervention, comparator, and outcomes (PICO) of interest?
5. Are the results precise enough or likely due to chance?

6. Is this all the research that has been conducted on the PICO question of interest?
7. Is there anything, in particular very large effects of an intervention, dose response gradients, or unfavourable scenarios still leading to convincing effect that makes us more confident?

There are four possible certainty ratings for each outcome: high, moderate, low and very low. The rating for a RCT starts at 'high' and can be marked down one or two levels for each domain. Outcomes can also be marked up for the following attributes: (i) large magnitude of effect, (ii) dose-response gradient and (iii) all residual confounding would decrease magnitude of effect.

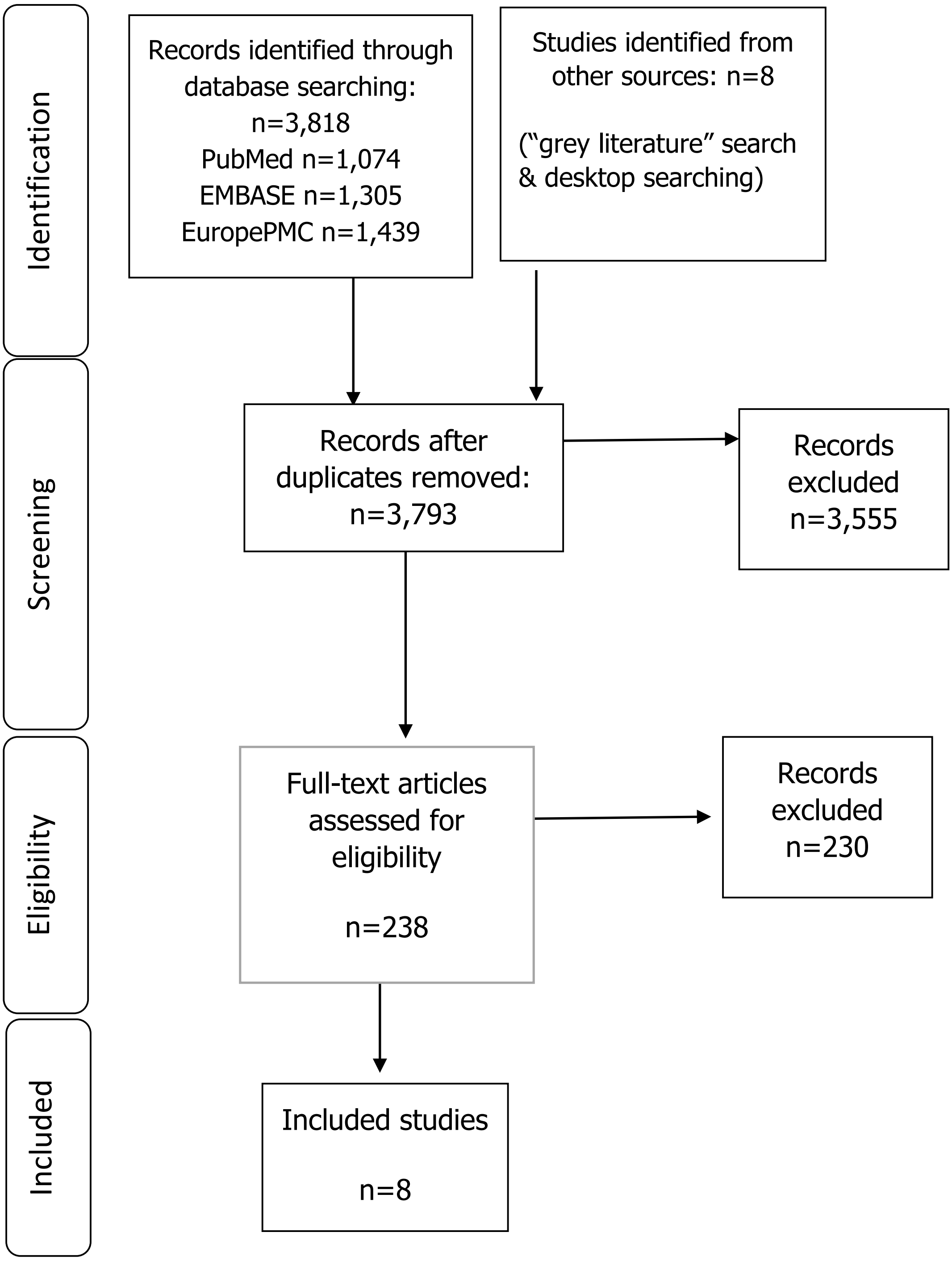
Each of the evidence quality ratings are explained below:

- High – Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate – Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low – Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low – Any estimate of effect is very uncertain.

Results

The collective search resulted in 3,818 citations. Figure 1 provides the PRISMA diagram of study selection.

Figure 1. PRISMA diagram of study selection



Eight RCTs were identified relating to nine pharmaceutical interventions in the community or ambulatory setting and which reported on outcomes associated with the progression of COVID-19 (Table 1).[4-11] No trials or systematic reviews of trials were identified relating to lifestyle interventions, physiotherapy or respiratory therapy interventions, psychological therapy, organisational interventions or technological interventions.

With respect to the eight trials eligible for inclusion, all study participants were adults or adolescents (≥16 years), had not been hospitalised and had RT-PCR confirmed SARS-CoV-2 infection. Six of the eight trials were placebo controlled[4-9] and trials were conducted in both high and middle-income countries. The median number of participants in trials was 198 (range: 62-577) and the median duration of follow-up for the primary endpoint was 25 days (range: 5-29). GRADE evidence profiles for each of the eleven comparisons are provided in Table 2. This is followed by a brief summary of the trials and their findings. Full details of data extraction and quality appraisal (Cochrane Risk of Bias and GRADE assessment) are provided in Appendices 2 and 3.

Table 1 Summary of included studies and primary outcome results: insufficient evidence of effectiveness and safety to support use in ambulatory care

Pharmaceutical intervention	Number of identified trials (number of participants)	Comparator(s)	Study author-reported results	Trial location(s) and applicability to Irish setting
Casirivimab+Imdevimab ("Antiviral antibody cocktail" or REGN-COV2)[9]	1 ongoing trial (N=275)	Placebo	Interim analysis showed a non-significant reduction in medically attended visits*. Absolute risk difference: -3% (95% CI: -16% to 9%).	▪ Study was conducted in USA ▪ Study is potentially applicable to the Irish setting
Bamlanivimab and bamlanivimab plus etesevimab[4]	1 ongoing trial (N=577)	Placebo	Intervention 1: Bamlanivimab 700mg – no significant difference in hospitalisation/emergency department visit versus placebo; absolute risk difference was –4.8% (95% CI, –8.9% to –0.6%; p=0.09). Intervention 2: Bamlanivimab 2800mg no significant difference in hospitalisation/emergency department visit versus placebo; absolute risk difference was –3.9% (95% CI, –8.4% to 0.6%; p=0.21). Intervention 3: Bamlanivimab 7000mg no significant difference in hospitalisation/emergency department visit versus placebo; absolute risk difference was -3.8% (95% CI, –8.3% to –0.8%; p=0.21). Intervention 4: Bamlanivimab 2800mg plus etesevimab 2800mg: significant difference in hospitalisations/emergency department visit versus placebo, absolute risk difference was –4.9% (95% CI, –8.9% to –0.8%; p=0.049).	▪ Study was conducted in USA ▪ Study is potentially applicable to the Irish setting
Fluvoxamine[7]	1 completed preliminary trial (N=152)	Placebo	Fluvoxamine** reduced the risk of clinical deterioration***. Absolute risk difference: 8.7% (95% CI, 1.8%-16.4%) by survival analysis, log-rank χ^2=6.8 and p=0.009.	▪ Study was conducted in USA

				▪ Study is potentially applicable to the Irish setting
Ivermectin[10]	1 completed trial published as a pre-print (N=62)	Usual care (including doxycycline)	The mean time to resolution of all symptoms was not significantly different between groups. Time for resolution of symptoms from date of onset of illness: Intervention: 10.09 days (SD=3.24) Control: 11.5 days (SD=5.32) 95% CI for difference in mean: -0.86 to 3.67	▪ Study was conducted in Bangladesh ▪ 'Usual care' included a range of interventions not used to treat COVID-19 in Ireland ▪ Study was not considered applicable to the Irish setting
Ivermectin + doxycycline[11]	1 completed trial published as a pre-print (N=96)	Usual care	There was no difference in clinical deterioration or mortality (no patients deteriorated in either arm of the trial). The mean time to recovery in mild-moderate patients was 6.34 days (SD=2.4) in the intervention group versus 13.66 days (SD=6.4) in the control group. The intervention was associated with a reduced recovery time (reduction of 7.32 days) in mild-moderate patients. P value: <0.0001.	▪ Study was conducted in Iraq ▪ 'Usual care' included a range of interventions not used to treat COVID-19 in Ireland ▪ Study was not considered applicable to the Irish setting
Nitazoxanide[8]	1 completed trial (N=392)	Placebo	There was no significant difference in the hospitalisation rate or the time to resolution of symptoms (absolute rates not reported).	▪ Study was conducted in Brazil ▪ 'Usual care' included a range of interventions not used to treat COVID-19 in Ireland ▪ Study was not considered applicable to the Irish setting

Peginterferon-lambda[6]	1 completed trial published as a pre-print (N=120)	Placebo	Peginterferon lambda-1a was not associated with a reduction in the time to resolution of symptoms. No difference between the arms in time to clinical progression (adjusted HR 1.38; 95% CI 0.52 to 3.63; p = 0.52).	▪ Study was conducted in USA ▪ Study is potentially applicable to the Irish setting
Sulodexide[5]	1 completed trial published as a pre-print (N=243)	Placebo	Sulodexide was associated with a reduction in the hospitalisation rate and the need for supplemental oxygen. Requirement for hospital care in sulodexide arm versus placebo: RR = 0.6 (95% CI 0.37 to 0.96; p=0.03). There was no significant difference in the total duration of illness or mortality.	▪ Study was conducted in Mexico ▪ Intervention and 'usual care' arms included a number of concomitant medications not used to treat COVID-19 in Ireland ▪ Study was not considered applicable to the Irish setting

Key: CI – confidence interval; HR – hazard ratio; RR – relative risk; SD – standard deviation.
* Medically attended visits could include telemedicine visits, in-person physician visits, urgent care or emergency department visits, and hospitalisation.
**Fluvoxamine was administered at a dose of 100 mg three times daily for 15 days.[12] This is higher than the recommended starting dose for depression (50-100mg daily) or obsessive compulsive disorder (50mg daily). For these authorised indications, it is recommended that the dose should be increased gradually to reduce the potential for undesirable effects. It is recommended that abrupt withdrawal should be avoided, with the dose gradually reduced over one or two weeks to reduce the risk of withdrawal reactions.
***Clinical deterioration defined as: (1) presence of dyspnoea (shortness of breath) or hospitalisation for shortness of breath or pneumonia and (2) decrease in oxygen saturation (<92%) on room air or supplemental oxygen requirement to maintain oxygen saturation of 92% or greater.

Table 2 GRADE Evidence Profiles: Effectiveness of pharmaceutical interventions in the outpatient setting to treat COVID-19

Comparison 1: Casirivimab + Imdevimab (REGN-COV2) versus placebo (source: Weinreich et al.[9])

Outcome: The prevention of a medically attended visit (follow up: 29 days)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)		
1 (275 participants)	Randomised controlled trial	not serious	not serious	not serious	very serious[a]	none	6/182 (3%)	6/93 (6%)	Approx. 49%	-3% (-16% to 9%)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval
[a] Evidence of very serious imprecision due to only 1 RCT, small sample size, short follow-up

Comparison 2: Bamlanivimab (700 mg) versus placebo (source: Gottlieb et al.[4])

Outcome: The prevention of hospitalisation (follow up: 29 days)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)		
1 (101 participants)	Randomised controlled trial	not serious	not serious	not serious	very serious[a]	none	1/101 (1.0%)	9/152 (5.8%)	Not reported	-4.8%; (-8.9 to -0.6)	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval
[a] Evidence of very serious imprecision due to only 1 RCT, small sample size, short follow-up

Comparison 3: Bamlanivimab (2800 mg) versus placebo (source: Gottlieb et al.[(4)])

Outcome: The prevention of hospitalisation (follow up: 29 days)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)		
1 (107 participants)	Randomised controlled trial	not serious	not serious	not serious	very serious[a]	none	2/107 (1.9%)	9/152 (5.8%)	Not reported	-3.9%; (-8.4 to 0.6)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval
[a] Evidence of very serious imprecision due to only 1 RCT, small sample size, short follow-up

Comparison 4: Bamlanivimab (7000 mg) versus placebo (source: Gottlieb et al.[(4)])

Outcome: The prevention of hospitalisation (follow up: 29 days)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)		
1 (101 participants)	Randomised controlled trial	not serious	not serious	not serious	very serious[a]	none	2/101 (2.0%)	9/152 (5.8%)	Not reported	-3.8%; (-8.3 to 0.8)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval
[a] Evidence of very serious imprecision due to only 1 RCT, small sample size, short follow-up

Comparison 5: Bamlanivimab (2800mg) and Etesevimab (2800 mg) versus placebo (source: Gottlieb et al.[(4)])

Outcome: The prevention of hospitalisation (follow up: 29 days)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)		
1 (109 participants)	Randomised controlled trial	not serious	not serious	not serious	very serious[a]	none	1/109 (0.9%)	9/152 (5.8%)	Not reported	-4.9%; (-8.9 to -0.8)	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval
[a] Evidence of very serious imprecision due to only 1 RCT, small sample size, short follow-up

Comparison 6: Fluvoxamine versus placebo (source: Lenze et al.[(7)])

Outcome: The prevention of clinical deterioration (follow up: 15 days)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)		
1 (152 participants)	Randomised controlled trial	not serious	not serious	not serious	very serious[a]	none	0/80 (0.0%)	6/72 (8.3%)	not estimable	8.7% (1.8%-16.4%)[b]	⊕⊕◯◯ LOW	CRITICAL

CI: Confidence interval
[a] Evidence of very serious imprecision due to only 1 RCT, small sample size, short follow-up
[b] Calculated by study authors using survival analysis

Comparison 7: Ivermectin + usual care (that included doxycycline) versus usual care (that included doxycycline) (source: Podder et al.[(10)])

Outcome: Time for resolution of symptoms from date of onset of illness (follow up unclear)

Certainty assessment							Effect (days)		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator		
1 (62 participants)	Randomised controlled trial	Serious[b]	not serious	not serious	very serious[a]	none	10.09 (SD=3.24)	11.5 days (SD=5.32) Difference is non-significant (95%CI - 0.860 to 3.672)	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval
[a] Evidence of very serious imprecision due to only 1 RCT, small sample size, short follow-up
[b] No information on blinding or allocation concealment, not all randomised patients were analysed

Comparison 8: Ivermectin + doxycycline versus usual care (source: Hashim et al.[11])

Outcome: Progression of disease - hospitalisation or death (follow up unclear)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)		
1 (96 participants)	Randomised controlled trial	Serious[b]	not serious	not serious	very serious[a]	none	0/48	0/48	not estimable	not estimable	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval
[a] Evidence of very serious imprecision due to only 1 RCT, small sample size, short follow-up
[b] Issues with randomisation, lack of blinding and measurement bias

Outcome: Time from treatment administration to recovery

Certainty assessment							Effect (days)		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator		
1 (96 participants)	Randomised controlled trial	Serious[b]	not serious	not serious	very serious[a]	none	6.34 (SD=2.4)	13.66 (SD=6.4) Difference of 7.32 days, (p<0.0001)	⨁◯◯◯ VERY LOW	CRITICAL

[a] Evidence of very serious imprecision due to only 1 RCT, small sample size, short follow-up
[b] Issues with randomisation, lack of blinding and measurement bias

Comparison 9: Nitazoxanide versus placebo (source: Rocco et al.[(8)])

Outcome: The prevention of hospitalisation (follow up: 14 days)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)		
1 (392 participants)	Randomised controlled trial	serious[b]	not serious	not serious	very serious[a]	none	5/194, however no patient completed treatment course	5/198	Not reported	Not reported	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval
[a]Evidence of very serious imprecision due to only 1 RCT, small sample size, short follow-up
[b]Some randomised patients were not included in the analysis; some data is missing or not evaluable

Comparison 10: Peginterferon lambda-1a versus placebo (source: Jagannathan et al.[(6)])

Outcome: Time to resolution of symptoms (follow up: 28 days)

Certainty assessment							Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI)	Interpretation		
1 (120 participants)	Randomised controlled trial	not serious	not serious	not serious	very serious[a]	none	aHR 0.94; 95% CI 0.64 to 1.39; p=0.76	No difference observed in time to resolution of symptoms or sustained resolution of symptoms.	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval
[a]Evidence of very serious imprecision due to only 1 RCT, small sample size, short follow-up

Comparison 11: Sulodexide versus placebo (source: Gonzales-Ochoa et al.[(5)])

Outcome: The prevention of hospitalisation (follow up: 21 days)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Relative (95% CI)	Absolute (95% CI)		
1 (243 participants)	Randomised controlled trial	serious[b]	not serious	not serious	very serious[a]	none	22/124 (17.7%)	35/119 (29.4%)	0.6 (95% CI 0.37 to 0.96; p=0.03)	not reported	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval
[a]Evidence of very serious imprecision due to only 1 RCT, small sample size, short follow-up
[b]Blinding was broken during data management

The following sections describe the published results of the nine identified trials for each pharmaceutical intervention. As noted, full details of data extraction and quality appraisal (Cochrane Risk of Bias and GRADE assessment) are provided in Appendices 2 and 3.

1. Bamlanivimab, and bamlanivimab plus etesevimab

One US study on the monoclonal antibody bamlanivimab, as monotherapy or in combination with the monoclonal antibody etesevimab met our inclusion criteria.(4) Bamlanivimab single agent or the combination of bamlanivimab and etesivimab are administered as an intravenous infusion over at least one hour. Patients who received bamlanivimab monotherapy or placebo were enrolled first (between 17 June 2020 and 21 August 2020); patients who received bamlanivimab plus etesevimab or placebo were enrolled between 22 August 2020 and 3 September 2020. The phase II portion of the randomised phase II/III clinical trial included 577 patients. Bamlanivimab and etesevimab are neutralising monoclonal antibodies that bind to the spike protein of SARS-CoV-2, preventing spike protein attachment to the human ACE2 receptor (in the respiratory airway epithelia).

This clinical trial is an ongoing, multipart, phase II/III, randomised, double-blind, placebo-controlled, single-infusion study that included patients with recently diagnosed mild or moderate COVID-19 in the outpatient setting. At the time of enrolment, study participants were all adults (≥18 years), had not been hospitalised and had RT-PCR confirmed SARS-CoV-2 infection. Participants were randomly assigned to receive a single intravenous infusion of the neutralising antibody bamlanivimab in one of three doses (700 mg, 2800 mg, or 7000 mg), or in combination with etesevimab or placebo. Overall, 387 patients (67.1%) had at least one risk factor for severe COVID-19 (aged ≥55 years, BMI ≥30, or ≥1 relevant comorbidity such as hypertension)

Quantitative virologic end points were the primary outcome; clinical outcomes including inpatient hospitalisation (which included emergency department visits) were secondary outcomes. 'Hospitalisation' was defined as a minimum of 24 hours of acute medical care.

The proportion of patients with COVID-19–related hospitalisations or emergency department visits at day 29 was 1.0% (1 event/101 patients) in the 700 mg group, 1.9% (2 events/107 patients) in the 2800mg group, 2.0% (2 events/ 101 patients) in the 7000 mg group, 0.9% (1 event/112 patients) in the combination therapy group, and 5.8% (9 events/156 patients) in the placebo group. The reported absolute difference compared with placebo was –4.8% (95% CI, –8.9% to –0.6%; p=0.09) for the 700 mg group, –3.9% (95% CI, –8.4% to 0.6%; p=0.21) for the

2800 mg group, –3.8% (95% CI, –8.3% to –0.8%; p=0.21) for the 7000 mg group, and –4.9% (95% CI, –8.9% to –0.8%; p=0.049) for the combination group.

In a post-hoc analysis examining hospitalisation among high risk subgroups (those who were 65 years of age or older or who had a BMI of 35kg/m^2 or more), the percentage hospitalised was 2.7%, 3.3% and 5.9% in the 700mg, 2800mg and 7000mg monotherapy groups, respectively and 0% in the combination therapy group compared with 13.5% in the placebo group. However, these results were only statistically significant in the 700mg monotherapy group and in the combination therapy group. One patient in the trial (in the placebo group) was admitted to an intensive care unit.

Secondary outcomes included 'total symptom score' (see Table 1 for definition), 'COVID-19 symptom improvement', and 'COVID-19 resolution'. As all outcomes were disaggregated according to the four interventions and one placebo group, and some by number of days from intervention (days 7, 11, 15 and 22) this resulted in the reporting of 84 separate outcomes. Thus, any reported significant results need to be considered as hypothesis generating and will need to be confirmed in future studies.

No serious adverse events were reported in any of the 309 patients in the monotherapy groups. One serious adverse event was reported in the combination therapy group (urinary tract infection) and one in the placebo group (upper abdominal pain), neither of which were deemed to be related to treatment. The most frequently reported adverse events were nausea and diarrhoea. Immediate hypersensitivity was reported in nine patients (6 in monotherapy groups, 2 in combination group and 1 in placebo group), most of which were mild and occurred during infusion; infusions were completed in all cases. No deaths occurred during the study treatment.

2. Casirivimab + Imdevimab (REGN-COV2)

One US study on the combination therapy casirivimab plus imdevimab (also known as 'antiviral antibody cocktail', or REGN-COV2, administered as a single intravenous infusion over at least one hour) met our inclusion criteria.[9] Both medications included in this therapy are neutralising monoclonal antibodies that bind to the spike protein of SARS-CoV-2, preventing spike protein attachment to the human ACE2 receptor (in the respiratory airway epithelia).

The study is an ongoing, randomised, phase I–III placebo-controlled clinical trial involving symptomatic, ambulatory patients with COVID-19. The publication is an interim analysis of the first 275 patients enrolled (patients were followed for 29 days); randomisation of patients took place between 16 June 2020 and 13 August 2020. Of the 275 enrolled participants, 176 (64%) had at least one risk factor for hospitalisation. Specified risk factors for hospitalisation include an age of more than 50 years, obesity, cardiovascular disease (including hypertension), chronic lung disease (including asthma), chronic metabolic disease (including diabetes), chronic kidney disease (including receipt of dialysis), chronic liver disease, and immunocompromise (immunosuppression or receipt of immunosuppressants).

Study participants were all adults (≥18 years), non-hospitalised, and had RT-PCR confirmed SARS-CoV-2 infection. Patients were randomly assigned (1:1:1) to receive placebo, REGN-COV2 at a dose of 2.4g (low dose), or REGN-COV2 at a dose of 8.0g (high dose). REGN-COV2 contains equal doses of casirivimab and imdevimab.

The pre-specified clinical end point was the percentage of patients with one or more medically attended visits. Medically attended visits could include telemedicine visits, in-person physician visits, urgent care or emergency department visits, and hospitalisation. Disaggregated data relating to hospitalisation were not reported.

Fewer patients in the REGN-COV2 group had a medically attended visit (in both the full analysis set and the serum antibody–negative subgroup), however this difference was non-significant. Results from a subsequent descriptive analysis involving a larger data set indicated that time to alleviation of symptoms was not strongly associated with treatment.

The percentage of patients with hypersensitivity reactions, infusion-related reactions, and other adverse events were similar in the combined REGN-COV2 dose groups and the placebo group.

3. Fluvoxamine

One preliminary trial on oral fluvoxamine, conducted in the US, was identified that met our inclusion criteria.[7] Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) with high affinity for the σ-1 receptor (or S1R). S1R is an endoplasmic reticulum chaperone protein with various cellular functions, including regulation of cytokine production. Study participants (N=152) were all adults (≥18 years), non-hospitalised and had RT-PCR confirmed SARS-CoV-2 infection. Participants were randomly assigned to receive 100 mg of fluvoxamine (N=80) or placebo (N=72) three times daily for 15 days. It is notable that fluvoxamine is usually administered at a lower starting dose and titrated upwards (starting at 50-100mg daily for depression and 50mg daily for obsessive compulsive disorder[12]) to minimise the risk of adverse events. Product authorisations for these indications also recommend that abrupt withdrawal should be avoided, with the dose gradually reduced over one or two weeks to reduce the risk of withdrawal reactions.

A range of risk factors for severe disease were identified at baseline. These included: asthma (21% of participants in the intervention group versus 13% in control);

hypertension (19% of participants in intervention group versus 21% in control); diabetes (11% of participants in intervention group versus 11% in control); hypercholesterolaemia (9% of participants in intervention group versus 10% in control); and hyperthyroidism (8% of participants in intervention group versus 8% in control).

The primary end point was clinical deterioration defined by both the (1) presence of dyspnoea (shortness of breath) or hospitalisation for shortness of breath or pneumonia and (2) decrease in oxygen saturation (<92%) on room air or supplemental oxygen requirement to maintain oxygen saturation of 92% or greater. The primary analysis was the survival analysis for the primary outcome (clinical deterioration) using a log-rank test.

The study was a fully remote (contactless) clinical trial. Study supplies were delivered to self-quarantined study patients as a package left at their door and the study materials consisted of the study medication, an oxygen saturation monitor, an automated blood pressure monitor, and a thermometer. Participants then self-assessed using the equipment provided and confirmed vital signs were within range and oxygen saturation of 92% or greater. Study staff called participants, informed them of eligibility, and instructed them to take the study medication. Dyspnoea (shortness of breath) was measured using a continuous scale (self-reported).

Clinical deterioration occurred in none of the 80 patients in the fluvoxamine group and in 6 of 72 (8.3%) patients in the placebo group (absolute difference, 8.7% [95% CI, 1.8%-16.4%] by survival analysis, log-rank χ^2=6.8 and p=0.009). In the placebo group, cases of clinical deterioration ranged from 1 to 7 days after randomisation and from 3 to 12 days after the onset of COVID-19 symptoms. Four of 6 deteriorated patients were hospitalised, with the length of stay ranging from 4 to 21 days. One patient required mechanical ventilation for 10 days and no patients died.

One serious adverse event and 11 other adverse events were reported in the fluvoxamine group, whereas six serious adverse events and 12 other adverse events were reported in the placebo group. Pneumonia and gastrointestinal symptoms (such as nausea and vomiting) occurred more often in the placebo group compared with those who received fluvoxamine.

4. Interferon (peginterferon lambda-1a)

One US study on interferon (IFN), specifically peginterferon lambda ('lambda'), met our inclusion criteria.[6] Participants were randomly assigned to receive a single 180 mcg subcutaneous injection of peginterferon lambda-1a (N=60 participants) or 0.45 mL subcutaneous injection of saline (placebo; N=60 participants). Interferons are a group of signalling proteins made and released by host cells in response to the presence of several viruses.

The study was a completed Phase II clinical trial, currently published only as a preprint. Study participants were all adults (≥18 years), non-hospitalised and had RT-PCR confirmed SARS-CoV-2 infection. Participants (N=120) had a median of three risk factors (IQR: 2-3) for severe disease at baseline. Risk factors were defined as 'relevant severe disease risk factors' and included the following: presence of temperature of 99.5F or greater, cough, or shortness of breath; age 60 or greater; male sex; black race; Latin ethnicity; BMI greater than 30; ALC less than 1000; ALT greater than 94.

The primary outcome was time to first of two consecutive negative oropharyngeal tests for SARS-CoV-2 by RT-PCR. Time to alleviation of all symptoms, sustained resolution of symptoms and time to clinical progression were included as a secondary outcomes.

No significant difference in time to resolution of symptoms (aHR 0.94; 95% CI 0.64 to 1.39; p=0.76) or sustained resolution of symptoms (aHR 0.92; 95% CI 0.60 to 1.41; p=0.70) was observed. Time to clinical progression was not significantly different between the two arms (aHR 1.38; 95% CI 0.52 to 3.63; p=0.52).

Two serious adverse events (hospitalisation) were reported in each arm. Liver transaminase elevations were more common in the intervention arm versus placebo (15 versus 5; p=0.027); alanine aminotransferase levels were significantly raised in the intervention arm versus placebo, though no associated symptoms were reported and abnormalities were not sustained.

5. Ivermectin (trial comparison: ivermectin plus usual care involving doxycycline, compared to usual care involving doxycycline)

One study, conducted in Bangladesh, on the antiparasitic agent ivermectin as a single-agent oral intervention, met our inclusion criteria.[10]

The study was a completed open label trial that is currently published only as a preprint. Study participants (N=62) were all adults (≥18 years), non-hospitalised and had RT-PCR confirmed SARS-CoV-2 infection. Details on participant risk factors for severe disease were not reported.

Participants were randomly assigned to receive ivermectin (single dose of 200mcg/kg on day 1) plus usual care (N=32 participants) or usual care only (N=30 participants). Usual care consisted of symptom-directed treatment, which included antipyretics, cough suppressants, and doxycycline (100mg as oral capsules every 12 hours for seven days) to treat possible community-acquired pneumonia.

Primary outcomes included recovery time, defined as the time required for the resolution of symptoms, from the date of enrolment in the study and from the onset of initial illness. The mean time to resolution of all symptoms, from either the date of enrolment or the onset of symptoms, was not significantly different between the intervention and control groups.

Safety outcomes were not reported. The mean time to resolution of all symptoms from date of enrolment was 5.31 days (SD=2.48) in the intervention group and 6.33 days (SD=4.23) in the control group, and the mean time to resolution of all symptoms from date of onset of illness was 10.09 days (SD=3.24) in the intervention group and 11.5 days (SD=5.32) in the control group

6. Ivermectin plus doxycycline

One study, conducted in Iraq, on a combination intervention of oral ivermectin plus doxycycline, met our inclusion criteria.(11) This study is currently published only as a preprint. Study participants were all adults or adolescents (≥16 years) and had RT-PCR confirmed SARS-CoV-2 infection. Patients of all disease severities were enrolled. All patients with mild to moderate disease were outpatients (N=48 patients in intervention group and N=48 patients in control group). Only the outpatient component of this trial was included in this review. Details on baseline risk factors pertaining to patients with mild to moderate disease were not reported.

Participants were randomly assigned to receive 200mcg/kg ivermectin orally daily for 2-3 days and 100mg oral doxycycline twice daily for 5-10 days plus standard therapy (N=48 participants) or standard therapy only (N=48 participants). Standard therapy included the following: acetaminophen (paracetamol), Vitamin C, Zinc, Vitamin D3; and azithromycin, oxygen therapy/CPAP, dexamethasone, methylprednisolone or mechanical ventilation if needed. Three outcomes of interest were assessed: time to full recovery, rate of progression to severe disease and mortality.

The mean time to recovery in patients with mild/moderate disease was 6.34 days (SD 2.4) days in the intervention group compared with 13.66 days (SD 6.4) in the control group ($p<0.01$). The prevention of progression to severe disease and mortality could not be estimated as there were no cases of deterioration in either group.

Safety outcomes were not reported.

7. Nitazoxanide

One study on nitazoxanide oral solution, conducted in Brazil, met our inclusion criteria.(8) Nitazoxanide is a broad-spectrum antiparasitic and broad-spectrum antiviral drug.

The study is a completed clinical trial. Study participants (N=392) were all adults (≥18 years), non-hospitalised and had RT-PCR confirmed SARS-CoV-2 infection. Patients were randomly assigned to receive either placebo solution (N=198 patients) or nitazoxanide (500 mg oral solution, three times daily for 5 days, N=194). The primary outcome was complete resolution of symptoms (self-reported); secondary outcomes included hospitalisation. In terms of risk factors at baseline, 12% of participants in the intervention group and 18% of participants in the control group had one or more of the following comorbidities: systemic arterial hypertension, diabetes or asthma.

There was no difference in the proportion patients that reported complete resolution of symptoms (dry cough, fever, and fatigue) between the nitazoxanide and placebo arms after five days of therapy. Ten patients were hospitalised in each arm. However, no patients that completed the full 5-day course of nitazoxanide were hospitalised.

No serious adverse events were reported.

8. Sulodexide

One study on oral sulodexide, conducted in Mexico, met our inclusion criteria.(5) Sulodexide is a highly purified mixture of glycosaminoglycans composed of low molecular weight heparin (80%), a blood thinner, and dermatan sulfate (20%).

The study is a completed clinical trial, currently published only as a preprint. A total of 243 patients (out of 312 randomised patients) were eligible for final data analysis; 124 patients in the sulodexide group and 119 in the placebo group. Study participants were all adults (≥40 years), had not been hospitalised and had RT-PCR confirmed SARS-CoV-2 infection. Hypertension was the most common chronic health condition at baseline, reported in 34.2% (83 of 243), followed by diabetes 22.2% (54 of 243). Patient risk factors according to the 'COVID-19 Health Complication (C19HC) calculator' was similar between groups (67.8% for the sulodexide group and 65.8% for the placebo group; p=0.32).

Primary endpoints were hospitalisation, the duration of illness and the need for oxygen supplementation. Secondary endpoints included the need for mechanical ventilation support and mortality.

Overall, 57 of 243 patients (23.4%) required hospital care during the 21 days of follow-up; 22 of 124 (17.7%) in the sulodexide group and 35 of 119 (29.4%) in the placebo group with a RR of 0.6 (95% CI 0.37 to 0.96; p=0.03); absolute difference=-11.7% (not reported in the study).

Eighty-seven of the 243 patients (35.8%) developed respiratory symptoms requiring oxygen support; 37 of 124 (29.8%) in the sulodexide group versus 50 of 119 (42%) in the control group with an RR of 0.71 (95% CI 0.5 to 1.0; p=0.05). The mean length of duration of oxygen support was 9 ±7.2 days in the sulodexide group versus 11.5 ±9.6 in the placebo group (p=0.02). There was no significant difference in the mean duration of hospital stay. There was a non-significant reduction in mortality in the sulodexide group. The need for mechanical ventilation was not reported.

There was no reported significant difference in safety outcomes between the two groups (novel symptoms or adverse events that resulted in medication cessation).

Study authors concluded that sulodexide treatment in the outpatient setting reduced the need for hospitalisation and supplemental oxygen support. However, there was no significant difference in the total duration of illness or mortality.

Quality of individual studies

There was concern over the quality of a number of studies (Appendix 3). Overall, four studies of the eight studies were considered at high risk of bias(5, 8, 10, 11) and there were some concerns regarding the risk of bias in another study.(7) Only three of the nine studies were considered at low risk of bias.(4, 6, 9) The main methodological concerns included the lack of placebo in the control group in some studies,(10, 11) insufficient or absent blinding of outcome assessors and researchers,(5, 10, 11) and inadequate randomisation procedures.(10, 11) Half of the included trials are currently published only as preprints (4/8), so have not yet been formally peer-reviewed, raising additional concerns about overall quality and the potential for results to change prior to formal publication.

Certainty of evidence

The certainty of evidence was considered 'low' or 'very low' for all outcomes assessed (Table 2). All studies were downgraded for imprecision due to small sample sizes, short durations of follow-up and the fact that only one RCT provided evidence for any one outcome. Five studies were further downgraded due to risk of bias. All preprints that reported statistically significant results were deemed to be of 'very low' certainty. This designation indicates that the estimate of effect is very uncertain and should not be relied upon to inform decision-making.

Applicability of included studies

Four of the eight included studies were not considered applicable to the Irish healthcare setting.(5, 8, 10, 11) The four potentially applicable studies, all of which were undertaken in the US, were the placebo-controlled trials on bamlanivimab and bamlanivimab plus etesevimab,(4) casirivimab plus imdevimab,(9) fluvoxamine,(7) and peginterferon lambda-1a.(6)

The four trials not considered applicable to the Irish healthcare setting were undertaken in developing countries were undertaken in developing countries (Bangladesh,[10] Brazil,[8] Iraq,[11] and Mexico[5]), where the structure and level of healthcare is likely to differ substantially to Ireland. In all four studies, medications were used as part of 'usual care' that were not considered applicable to Ireland, such as the use of concomitant antibiotics (doxycycline and or azithromycin), corticosteroids, ivermectin and high dose Vitamin D3. Furthermore, while all trials reported on ambulatory patients, the baseline rates of progression to severe disease varied greatly, from no cases of clinical deterioration in the placebo group[11] to 29.4%.[5]

Discussion

Pharmaceutical interventions for which relevant trial evidence was identified

This review identified eight RCTs relating to nine pharmaceutical interventions in the community or ambulatory setting which reported on outcomes associated with the progression of COVID-19.[4-11]

Evidence of a potential effect was identified for four pharmaceutical interventions. However, results for two of these were graded as 'very low certainty' evidence and should not be used to inform decision-making. Low certainty evidence of a potential effect was found for two interventions from placebo-controlled trials (lower likelihood of clinical deterioration with fluvoxamine and a lower proportion of hospitalisations of ED visits with combination bamlanivimab plus etesevimab). Both were small trials with short follow-up (15 days and 29 days, respectively). As concluded by the trial authors, clinical efficacy for these outcomes cannot be determined on the basis of these results.

No difference in the rates of clinical deterioration or hospitalisation was found for the following interventions, compared with placebo or usual care in the community or ambulatory setting: casirivimab plus imdevimab (REGN-COV2 interim analysis), bamlanivimab (single agent therapy), ivermectin, nitazoxanide, peginterferon lambda.

While no difference in hospitalisations was reported in the interim analysis of casirivimab plus imdevimab identified by this review,[9] on 28 October 2020 Regeneron Pharmaceuticals announced positive results from an ongoing phase II/III RCT in the outpatient setting on their website.[13] Detailed results from this trial are awaited. Therefore, based on the results of the trial presented in this review, there is currently no published evidence to support the effectiveness of casirivimab plus imdevimab in the community or ambulatory setting.

Status of authorisation, or inclusion in treatment guidelines, of pharmaceutical interventions

None of the potential treatments described above have been authorised by the European Medicines Agency for the treatment of COVID-19. Both casirivimab plus imdevimab (REGN-COV2)[14] and bamlanivimab (LY-CoV555)[15] have been granted emergency use authorization by the FDA for use in the US for the treatment of non-hospitalised patients with mild-moderate COVID-19 who are at high risk for disease progression, high risk being defined within the product monograph according to a list of potential criteria (for example, aged 65 years or older). As noted in this review, 67.1% of participants in the trial on bamlanivimab and bamlanivimab plus esetevimab,[4] and 64% of participants in the trial on casirivimab plus imdevimab,[9] had risk factors at baseline for progression to severe disease and or hospitalisation. Health Canada has also issued interim authorisation of bamlanivimab for such patients at high risk of disease progression.[16] On 1 February 2021, the European Medicines Agency announced that the human medicines committee (CHMP) has commenced a rolling review of casirivimab plus imdevimab based on the findings of the trial discussed within the present review.[17] This review will continue until enough evidence is available to support a formal marketing authorisation application. Bamlanivimab either as monotherapy or in combination with esetevimab is not currently listed as being under consideration by the EMA.

On 12 January 2021, the Canadian Agency for Drugs and Technologies in Health (CADTH) published a health technology review of bamlanivimab for the treatment of outpatients with COVID-19; this took the form of a critical appraisal of the interim analysis of the BLAZE-1 trial.[18] This review detailed the limitations associated with the interim analysis and concluded that a phase III trial comparing bamlanivimab to placebo, including a clinically important primary endpoint and sufficient adjustment for multiple comparisons, is necessary to determine whether bamlanivimab provides a true benefit. Furthermore, CADTH published on 14 January 2021 a Drug Implementation Advice document on the use of bamlanivimab for mild-to-moderate symptoms of COVID-19, which incorporated in part the findings of the CADTH critical appraisal as well as recommendations from other health care organisations and panels of clinical experts.[19] This noted that the document advice panel was unable to identify with certainty a specific patient population or setting in which the benefits of the drug exceed the potential risks. The panel also noted the unique challenges, with respect to infrastructure and healthcare personnel requirements, posed by the administration of bamlanivimab and the associated requirement for post-infusion monitoring.[19] While not considered by CADTH, it is important to note that such challenges would similarly apply to the implementation of other monoclonal antibody infusion treatments (for example, etesevimab, casirivimab plus imdevimab).

None of the remaining interventions for which very limited evidence of a potential beneficial effect was identified in this review (fluvoxamine, ivermectin plus doxycycline, sulodexide) have been authorised by a medicines regulatory authority for use in COVID-19. The National Institutes of Health (NIH) COVID-19 Treatment Guidelines were updated on 14 January 2021 to specifically include a statement on the use of ivermectin.[20] This statement noted that many emerging trials of ivermectin in patients with COVID-19 have significant methodological limitations and incomplete information and that, as such, the NIH guidelines panel could not draw definitive conclusions about the clinical efficacy of ivermectin for the treatment of COVID-19 from these studies. Furthermore, the Panel stated that they had determined that there were insufficient data to recommend either for or against the use of ivermectin for the treatment of COVID-19. Similarly, the Australian National COVID-19 Clinical Evidence Taskforce reviewed the evidence for several potential treatments considered within this review, including casirivimab plus imdevimab, bamlanivimab, fluvoxamine, ivermectin, and peginterferon lambda, in the development of the Australian guidelines for the clinical care of people with COVID-19.[21] In each case, the guideline development panel stated that there was currently limited evidence about the impact of the treatment on patient-relevant outcomes in the treatment of COVID-19. The panel stated that they had significant concerns regarding the potential harms of unproven treatments and therefore recommended that these treatments should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval. As of 2 February 2021, the Australian National COVID-19 Clinical Evidence Taskforce has stated that both ivermectin plus doxycycline and sulodexide are currently under review.[21]

While no safety concerns were identified in included studies of this review, the follow-up period was insufficient to assess the safety profile of any included intervention. It is noted that a number of interventions considered in this review are known to have substantial adverse event profiles based on safety data from use for other indications. Given the lack of authorisation of any of the interventions for the treatment of COVID-19 in the ambulatory setting, no robust assessment of safety has been performed to date with respect to their use for this indication.

Other pharmaceutical interventions

This review did not identify any trials on remdesivir or dexamethasone conducted in the ambulatory setting. These are the only pharmaceutical interventions that have been approved by the EMA for the treatment of COVID-19.[22] Both were recommended by the EMA's human medicines committee (CHMP) for the treatment of COVID-19 in adults and adolescents with pneumonia who require supplemental oxygen. These recommendations do not consider ambulatory patients, although they may be relevant to residents of nursing homes and long term care facilities who have access to quality nursing support and supplemental oxygen. Similarly, the US COVID-19 Treatment Guidelines Panel recommends using dexamethasone in patients with COVID-19 who are mechanically ventilated or require supplemental oxygen[23] based on results of the RECOVERY Trial,[24] and the use of remdesivir in patients who require hospitalisation and supplemental oxygen.[23] It must be noted, however, that data from the RECOVERY trial also indicated that dexamethasone might increase mortality in hospitalised patients who were not receiving oxygen.[25] Additional concerns relating to the RECOVERY trial included the fact that 1,707 patients were considered unsuitable for randomisation; if these patients were excluded because of perceived contraindications (such as uncontrolled diabetes, underlying malignancy or immunosuppression), the full benefit–risk profile across all patient comorbidities remains uncertain.

The World Health Organization (WHO), in the most recent update (17 December 2020) to the living guideline document 'Therapeutics and COVID-19', recommended against using remdesivir in patients with COVID-19, irrespective of disease severity, and also recommended against using corticosteroid therapy in patients with non-severe COVID-19.[26] These recommendations indicate that neither treatment is considered appropriate in the treatment of ambulatory patients.

While extremely limited data were available for the interventions identified in this review, there is substantial research underway with respect to therapeutic interventions for COVID-19. As of 19 January 2021, 1,994 COVID-19 treatment trials have been registered on the WHO trial registries platform, 1,143 of which are still recruiting.[27] This large volume of ongoing studies implies that more reliable and relevant evidence will emerge to inform policy and practice.

Evidence regarding the continued use of certain medications following a COVID-19 diagnosis was outside the scope of this review. The EMA and the FDA have issued statements on Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), a class of medication frequently used in the outpatient setting. Both agencies advised that there is no scientific evidence connecting NSAID use and worsening COVID-19 symptoms.[28, 29] Theoretical concerns have also been raised about Renin-Angiotensin Aldosterone System (RAAS) Inhibitors (including ACE inhibitors and ARB antagonists). However, two recent observational studies found no association between ACE or ARB use and COVID-19 positivity or infection-related morbidity or mortality.[30, 31]

Vitamin/mineral supplementation

This review did not identify any trials that investigated the effects of Vitamin D supplementation in ambulatory COVID-19 patients. Similarly, an evidence review by NICE[32] did not identify any studies in the outpatient setting on the use of vitamin D for either the prevention or treatment of COVID-19. However, the NICE review did identify very low quality evidence from one inpatient trial[33] which reported that people who received calcifediol treatment plus standard care were less likely to be admitted to intensive care than people who received standard care only.

There is conflicting evidence regarding the benefits of Vitamin D in preventing other respiratory viral infections, such as influenza. Several studies using lower doses of Vitamin D support its benefit in preventing respiratory tract infections[34-36] while other studies have shown mixed results.[37] One recent study (January 2021) looked at high-dose supplementation in an older population to reduce the risk, duration, and severity of acute respiratory tract infections.[38] Monthly bolus doses of 60,000

IU of vitamin D did not reduce the overall risk of acute respiratory tract infection, but could slightly reduce the duration of symptoms in the general population over a five-year follow-up period.

No evidence was identified on other vitamin or mineral supplementation interventions, such as Vitamin C or Zinc.

'Long' COVID

All studies in this review measured acute outcomes over a short follow-up period (up to 29 days); the median duration of follow-up for the primary endpoint was 21 days (range: 5-29). None of the included trials investigated the effects of interventions at preventing ongoing symptomatic COVID-19 or post-COVID syndrome (sometimes referred to as 'long COVID').

NICE published a review[39] on 18 December 2020 on managing the long-term effects of COVID-19. For this review, ongoing symptomatic disease was defined as signs and symptoms of COVID-19 that continue for four to 12 weeks and 'post-COVID-19 syndrome' was defined as signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis. The review did not identify any primary intervention studies aimed at reducing progression of acute COVID-19 to ongoing symptomatic illness or post-COVID-19 syndrome.

Two additional reviews focussed on 'long COVID' were identified. The first was a rapid living systematic review that searched for evidence on rehabilitation interventions and service delivery interventions focussed on the post-acute or chronic phases of COVID-19 (published 29 October 2020).[40] No primary intervention studies were retrieved. The second was a rapid narrative review on the management of post-acute COVID-19 in primary care.[41] Indirect evidence suggested that many such patients recover spontaneously with holistic support, rest, symptomatic treatment, and gradual increase in activity. The review also reported indirect evidence that home pulse oximetry may be helpful in monitoring ongoing breathlessness, and that indications for specialist assessment include clinical concern along with respiratory, cardiac, or neurological symptoms that are new, persistent, or progressive. However, no specific intervention studies were identified, and guidance statements were derived from indirect sources.

Lifestyle interventions

No interventions relating to lifestyle interventions, such as dietary or weight-loss interventions, smoking cessation or reduction in alcohol intake were identified, although numerous studies have demonstrated associations between these factors and poorer outcomes in patients with COVID-19. For example, one study investigated the association between current smoking and the risk of developing symptomatic COVID-19 and the severity of illness.[42] Data were consistent with smokers being at an increased risk of developing symptomatic COVID-19. Another prospective cohort study demonstrated significantly increased risk of hospitalisation among obese individuals.[43]

Physiotherapy, respiratory therapy and psychological interventions

No studies relating to physiotherapy, respiratory therapy or psychological interventions were identified which met the inclusion criteria for this review. It is noted, however, that the WHO 'COVID-19 Clinical management: living guidance' (25 January 2021) has a conditional recommendation (based on very low certainty evidence) for the use of pulse oximetry monitoring in the community as part of a package of care. This includes patient and provider education and appropriate follow-up, in symptomatic COVID-19 patients with risk factors for progression to severe disease.[44]

Limitations

Of the four trials that reported statistically significant results, only two reported completed trial results in a peer-reviewed journal; the other two were published as preprints (awaiting peer-review). While the peer-reviewed trials on fluvoxamine and bamlanivimab and bamlanivimab plus etesevimab demonstrated a beneficial effect,[4, 7] both studies were limited by small sample sizes and short durations of follow-up. Similarly, each of the preprints were limited by small sample sizes and short duration of follow-up, and both were deemed at high risk of bias (Appendix 2). Our GRADE assessment of the certainty of evidence for our primary outcome for each of these trials was 'very low' (any estimate of effect is very uncertain). In light of these limitations, the determination of clinical efficacy of any of these interventions would require larger, more robust randomised controlled trials to be conducted.

This review did not identify any published trial data on a number of pharmaceutical interventions that have been reported widely in the media, such as antihistamines (famotidine and cetirizine), aspirin and statins (HMG-CoA reductase inhibitors). Evidence on other interventions widely reported, such as chloroquine or hydroxychloroquine and the antiretroviral medications lopinavir-ritonavir, was excluded from the review due to the strong recommendations against use by a number of organisations, including by the WHO (strong recommendation against use in patients with COVID-19 at any disease severity).[45]

There was a complete absence of published trial evidence on non-pharmaceutical interventions in this review (lifestyle, physiotherapy, respiratory therapy, psychological therapy, organisational or technological interventions). Non-randomised controlled trial designs may be more appropriate than RCTs in the effectiveness assessment for these interventions, however none were identified.

Conclusion

This review identified eight RCTs relating to nine different pharmaceutical interventions. There is currently insufficient evidence of either effectiveness or safety to support the use of any pharmaceutical intervention in the community setting to reduce the risk of progression to severe disease in patients who have been diagnosed with COVID-19 unless as part of an ongoing monitored clinical trial.

Overall, only one trial per intervention was identified, all were limited by small sample sizes and short durations of follow up, with only four of the trials considered potentially applicable to the Irish setting. In light of these limitations, the determination of clinical efficacy and safety of any of these interventions for the treatment of COVID-19 would require larger, more robust randomised controlled trials to be conducted.

No evidence was identified for the effectiveness or safety of any non-pharmaceutical intervention (lifestyle, physiotherapy, respiratory therapy, psychotherapy, organisational or technological interventions) in the community or ambulatory setting.

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Appendix 1 Search of national and international public health agencies

Source	Website
Agency for Care Effectiveness (ACE), Singapore	https://www.cebm.net/oxford-covid-19/
Australian National COVID-19 Clinical Evidence Taskforce	https://covid19evidence.net.au/
BMJ Best Practice Coronavirus disease 2019 (COVID-19)	https://bestpractice.bmj.com/topics/en-gb/3000201/management-recommendations
Canadian Agency for Drugs and Technologies in Health	https://covid.cadth.ca/category/treatment/
Centre for Evidence-Based medicine (CEBM) COVID-19 Evidence Service	https://www.cebm.net/oxford-covid-19/
Cochrane COVID-19 living evidence project	https://covid-nma.com/living_data/index.php#table1
eCOVID19 RecMap	https://covid19.evidenceprime.ca/about
European Society of Intensive Care Medicine	https://www.esicm.org/resources/coronavirus-public-health-emergency/#GUIDELINES
European Network of HTA (EUnetHTA)	https://eunethta.eu/Covid-19-treatment/
HTA Austria's Horizon Scanning System (HSS) for Covid-19 interventions	https://eprints.aihta.at/1234/
Infectious Diseases Society of America (IDSA)	https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/
National Centre for Pharmacoeconomics (Ireland)	http://www.ncpe.ie/research/covid-19/
National Institutes for Health (NIH, US)	https://covid19treatmentguidelines.nih.gov/whatsnew/
National Institute for Health and Care Excellence (NICE, UK)	https://www.nice.org.uk/Covid-19#rapid-es
Norwegian Institute of Public health – map of COVID-19 evidence	https://www.fhi.no/en/qk/systematic-reviews-hta/map/
US National Library of Medicine clinical trials database	https://clinicaltrials.gov/
WHO Country & Technical Guidance - Coronavirus disease (COVID-19) and WHO PAHO (Pan American	https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance-publications

Health Organization World Health Organization)	https://iris.paho.org/handle/10665.2/52719

All websites were searched on the 19 January 2021.

Appendix 2 Data extraction tables

First author, year Study ID Study design Trial status Country	Population Intervention Comparator Duration of follow-up	Primary and secondary outcomes of interest	Results
Bamlanivimab and bamlanivimab plus etesevimab			
Gottlieb 2021 **NCT04425629** **DOI:10.1001/jama.2021.0202** **Final phase 3 portion of phase 2-3 (BLAZE-1), double-blind, placebo-controlled RCT.** **Published JAMA** **USA**	**Population:** N=577 participants randomised (553 completed trial) 5 arms: n=101 single infusion of Bamlanivimab 700mg; n=107 2800mg; n=101 7000mg; n=112 combination treatment 2800mg of Bamlanivimab and 2800mg of Etesevimab; n=156 placebo Study participants were aged 18 ≥years, tested positive for SARS-CoV-2 infection, had 1 or more mild to moderate symptoms, and presented within 3 days of their first positive test result for SARS-CoV-2 (either direct antigen or reverse transcriptase–polymerase chain reaction). Median age: Monotherapy 700mg 39 years; Monotherapy 2800mg 45 years Monotherapy 7000mg 46 years; Combination therapy 44 years; Placebo 46 years	**Primary clinical outcome:** SARS-CoV-2 log viral load from baseline to day 11 (±4 days). **Secondary outcomes:** Time to viral clearance; proportion of patients with viral clearance at days 7, 11, 15, and 22; viral load area under the curve [AUC] at day 29. Proportion of patients with a COVID-19–related hospitalisation, emergency department visit, or death) at day 29. Hospitalisation rate among patients aged 65.	**Absolute risk (hospitalisation or emergency department visit):** Day 29 1.0% (1/101 patients) in the 700mg monotherapy group, 1.9% (2/107 patients) in the 2800mg monotherapy group, 2.0% (2/101 patients) in the 7000mg monotherapy group, 0.9% (1/112 patients) in the combination therapy group, and 5.8% (9/156 patients) in the placebo group. The difference vs placebo was –4.8% (95% CI, –8.9% to –0.6%; p=0.09) for the 700mg monotherapy group; - 3.9% (95% CI, -8.4% to 0.6%, P=0.21) for the 2800mg monotherapy group; -3.8% (95% CI, -8.3% to 0.8%, P=0.21) for the 7000mg monotherapy group; -4.9% (95% CI -8.9% to -0.8%,P=0.049) for the combination group **Hospitalisation rate among patients aged ≥65 or with a BMI ≥ 35 (post-hoc analysis) for Interventions 1-4 and placebo respectively** Lower hospitalisation rate in interventions 1-4 compared with those who received placebo: 2.7% in the 700mg group, difference of –10.8% (95% CI, –21.4% to –0.1%); 3.3%- in the 2800mg group, difference of –10.1% (95% CI, –21.4% to 1.2%); 5.9% in the 7000mg group,

	Median duration of symptoms pre randomisation: 4-5 days **Participant characteristics: (5 arms)** 51-85% female; 86.5-94.6% white; 37.5 - 48.5% Hispanic; 69.3 - 82.2% mild symptoms; 17.8 - 30.7% moderate; BMI median 27.2 - 30.4; 4/5 days median duration of symptoms; SARS-CoV-2 cycle threshold mean 22.7 - 24.5 **Intervention 1:** Bamlanivimab 700 mg **Intervention 2:** Bamlanivimab 2800 mg **Intervention 3:** Bamlanivimab 7000 mg **Intervention 4:** combination treatment (2800 mg of Bamlanivimab and 2800 mg of Etesevimab) **Comparator:** Placebo **Follow-up:** 29 days for the primary endpoint	≥ or with a BMI of ≥35 (post-hoc analysis). Total symptom score* - days 7,11,15 and 22. COVID-19 symptom improvement -days 7,11,15 and 22. COVID-19 symptom resolution - days 7,11,15 and 22.	difference of –7.6% [95%CI, –19.8% to 4.6%]); 0% in the combination group, difference of –13.5% (95%CI, –22.7% to –4.2%); *P* = .04); 13.5% placebo. 1 patient in the study (in the placebo group) was admitted to the intensive care unit. **Total symptom score* for Interventions 1-4 and placebo respectively** **Day 7** 1.98 (SD 2.49) change from baseline vs. placebo -0.48 (95% CI,-1.17 to 0.21, p=0.17); 2.07 (SD 2.93) change from baseline vs. placebo -0.33 (95% CI,-1.01 to 0.35, p=0.34); 2.22 (SD 2.97) change from baseline vs. placebo -0.39 (95% CI,-1.08 to 0.30, p=0.27); 2.14 (SD 2.98) change from baseline vs. placebo -0.31 (95% CI,-0.98 to 0.37, p=0.37); 1.88 (SD 2.50) **Day 11** 1.06 (SD 1.58) change from baseline vs. placebo -0.78 (95% CI, -1.37 to 0.20, p=0.009); 1.59 (SD 2.24) change from baseline vs. placebo -0.32 (95% CI,-0.91 to 0.26, p=0.27); 1.56 (SD 2.61) change from baseline vs. placebo -0.45 (95% CI,-1.04 to 0.13, p=0.13); 1.28 (SD 2.48) change from baseline vs. placebo -0.60 (95% CI,-1.18 to 0.03, p=0.04); 1.88 (SD 2.50) **Day 15** 1.00 (SD 2.25) change from baseline vs. placebo -0.16 (95% CI,-0.71 to 0.38, p=0.56); 1.20 (SD 2.03) change from baseline vs. placebo -0.07 (95% CI,-0.60 to 0.46, p=0.80); 1.00 (SD 2.07) change from baseline vs. placebo -0.39 (95% CI,-0.93 to 0.15, p=0.16); 1.04 (SD 2.43) change from baseline vs. placebo -0.25 (95% CI,-0.78 to 0.28, p=0.35); 1.24(SD 2.05) **Day 22** 0.46 (SD 1.16) change from baseline vs. placebo -0.17 (95% CI,-0.60 to 0.25, p=0.42); 0.74 (SD 1.67) change from baseline vs. placebo -0.03 (95% CI,-0.45 to

			0.38, p=0.88); 0.71 (SD 1.54) change from baseline vs. placebo -0.22 (95% CI,-0.64 to 0.21, p=0.32); 0.76 (SD 2.00) change from baseline vs. placebo -0.03 (95% CI,-0.38 to 0.44, p=0.89); 0.77 (SD 1.67) **COVID-19 symptom improvement for Interventions 1-4 and placebo respectively** **Day 7** 46.5% had symptom improvement, % change from baseline vs. placebo 5.7 (95% CI,-6.7 to 18.2, p=0.44); 34.6% had symptom improvement, % change from baseline vs. placebo -6.2 (95% CI, -18.1 to 5.7, p=0.36); 45.5% had symptom improvement, % change from baseline vs. placebo 4.8 (95% CI,-7.7 to 17.2, p=0.52); 45.9% had symptom improvement, % change from baseline vs. placebo 5.1 (95% CI,-7.1 to 17.3, p=0.45); 40.8% **Day 11** 59.4% had symptom improvement, % change from baseline vs. placebo 16.0 (95% CI, 3.6 to 28.4, p=0.02); 44.9% had symptom improvement, % change from baseline vs. placebo 1.4 (95% CI,-10.8 to 13.7, p=0.90); 58.4% had symptom improvement, % change from baseline vs. placebo 15.0 (95% CI, 2.6 to 27.4, p=0.02); 53.2% had symptom improvement, % change from baseline vs. placebo 9.8 (95% CI,-2.5 to 22.0, p=0.13); 43.4% **Day 15** 62.4% had symptom improvement, % change from baseline vs. placebo 7.8 (95% CI,-4.6 to 20.1, p=0.24); 58.9% had symptom improvement, % change from baseline vs. placebo 4.3 (95% CI,-8.0 to 16.5, p=0.53); 68.3% had symptom improvement, % change from baseline vs. placebo 13.7 (95% CI, 1.7 to 25.8, p=0.04); 63.3% had symptom improvement, % change

			from baseline vs. placebo 8.7 (95% CI,-3.3 to 20.7, p=0.17); 54.6% **Day 22** 69.3% had symptom improvement, % change from baseline vs. placebo 6.1 (95% CI,-5.7 to 18.0, p=0.35); 64.5% had symptom improvement, % change from baseline vs. placebo 1.3 (95% CI,-10.5 to 13.2, p=0.90); 70.3% had symptom improvement, % change from baseline vs. placebo 7.1 (95% CI,-4.6 to 18.9, p=0.28); 71.6% had symptom improvement, % change from baseline vs. placebo 8.4 (95% CI,-3.0 to 19.8, p=0.18); 63.2% **COVID-19 symptom resolution for Interventions 1-4 and placebo respectively** **Day 7** 36.6% had symptom resolution, % change from baseline vs. placebo 5.1 (95% CI,-6.97 to 17.0, p=0.42); 30.8% had symptom resolution, % change from baseline vs. placebo -0.7 (95% CI,-12.2 to 10.7, p=>99); 33.7% had symptom resolution, % change from baseline vs. placebo 2.1 (95% CI,-9.7 to 13.9, p=0.78); 34.9% had symptom resolution, % change from baseline vs. placebo 3.3 (95% CI,-8.3 to 14.9, p=0.60); 31.6% **Day 11** 50.5% had symptom resolution, % change from baseline vs. placebo 13.7 (95% CI, 1.2 to 26.1, p=0.04); 40.2% had symptom resolution, % change from baseline vs. placebo 3.3 (95% CI,-8.7 to 15.4, p=0.61); 43.6% had symptom resolution, % change from baseline vs. placebo 6.7 (95% CI,-5.6 to 19.1, p=0.30); 45.9% had symptom resolution, % change from baseline vs. placebo 9.0 (95% CI,-3.1 to 21.1, p=0.16); 36.8% **Day 15** 55.4% had symptom resolution, % change from baseline vs. placebo 9.4 (95% CI,-3.1 to 21.9, p=0.16);

			55.1% had symptom resolution, % change from baseline vs. placebo 9.1 (95% CI,-3.2 to 21.4, p=0.17); 59.4% had symptom resolution, % change from baseline vs. placebo 13.4 (95% CI, 0.9 to 25.8, p=0.04); 57.8% had symptom resolution, % change from baseline vs. placebo 11.7 (95% CI,-0.5 to 23.9, p=0.08); 46.1% **Day 22** 67.3% had symptom resolution, % change from baseline vs. placebo 9.4 (95% CI,-2.6 to 21.5, p=0.15); 58.9% had symptom resolution, % change from baseline vs. placebo 1.0 (95% CI,-11.2 to 13.2, p=0.90); 61.4% had symptom resolution, % change from baseline vs. placebo 3.5 (95% CI,-8.8 to 15.8, p=0.60); 68.8% had symptom resolution, % change from baseline vs. placebo 10.9 (95% CI,-0.8 to 22.6, p=0.09); 57.9% **Safety outcomes:** Serious adverse events occurred in 0% (0/309) in Bamlanivimab monotherapy groups, in 0.9% (1/112) in the Bamlanivimab and Etesevimab combination group (UTI-deemed unrelated) and in 0.6% (1/156) in the placebo group (upper abdominal pain-deemed unrelated). The most frequently reported adverse events were nausea (3% to 5%) and diarrhoea (0.9% to 4.5%). Immediate hypersensitivity were reported in 9 patients (6 in monotherapy groups, two in combination group and one in placebo group)- most occurred during infusion and were reported as mild- no changes in vital signs and symptoms included pruritus, flushing, rash and facial swelling. Infusions were completed in all instances.
Casirivimab + Imdevimab (REGN-COV2)			
Weinreich 2020 **NCT04425629**	**Population:**	**Primary clinical outcome:** The percentage of patients	**Absolute risk:**

DOI: 10.1056/NEJMoa2035002 **Phase 1-3, double-blind, placebo-controlled RCT** **Ongoing, published interim results (NEJM)** **USA**	N=275 participants randomised (269 completed trial) in a 1:1:1 assignment: N=93 in placebo arm, N=92 in low-dose intervention arm and N=90 in high-dose intervention arm. Study participants were all non-hospitalised adults (≥18 years), and had RT-PCR confirmed SARS-CoV-2 infection with symptom onset no more than 7 days before randomisation. Both the intervention and placebo were administered intravenously in a 250ml normal saline infusion given over a period of 1 hour. Median age: 44 years Median duration of symptoms pre randomisation: 3 days **Intervention 1:** Low dose REGN-COV2 intravenous infusion (equal doses of casirivimab and imdevimab), at a dose of 2.4g **Intervention 2:** High dose REGN-COV2 (equal doses of casirivimab and imdevimab), at a dose of 8.0g **Comparator:** Placebo **Follow-up:** 29 days for the primary endpoint	with one or more COVID-19 related medically attended visits through day 29. Medically attended visits could include telemedicine visits, in-person physician visits, urgent care or emergency department visits, and hospitalisation. Disaggregated data relating to hospitalisation was not reported.	In the full analysis set, 6 of 93 patients (6%) in the placebo group and 6 of 182 patients (3%) in the combined REGN-COV2 group had a medically attended visit; absolute difference versus placebo: −3 percentage points; 95% CI: −16 to 9 (non-significant). **Relative risk:** Approximately 49% relative difference in the percentage of patients with medically attended visits (6% in placebo group versus 3% in combined REGN-COV2 group). **Safety outcomes:** The percentages of patients with hypersensitivity reactions, infusion-related reactions, and other adverse events were similar in the combined REGN-COV2 dose groups and the placebo group. An adverse event of special interest was reported in 2 of 93 patients (2%) in the placebo group and in 2 of 176 patients (1%) in the combined REGN-COV2 dose groups.
Fluvoxamine			
Lenze 2020	**Population:**	**Primary end point:** Clinical deterioration	**Absolute risk:** Clinical deterioration occurred in 0 of 80 patients in the fluvoxamine group and in 6 of 72 (8.3%)

NCT04342663 **DOI: 10.1001/jama.2020.22760** **Double-blind, placebo-controlled RCT** **Completed, published (peer-reviewed)** **USA**	N=152 participants; N=80 intervention arm and N=72 in placebo arm. Study participants were all adults (≥18 years), non-hospitalised and had RT-PCR confirmed SARS-CoV-2 infection with symptoms occurring within 7 days of the first dose of study medication. **Intervention:** 50mg fluvoxamine taken as oral capsules immediately after baseline assessment, followed by 100mg twice daily for 2 days, followed by 100mg three times daily through day 15. After the 15 days were completed, participants were given the option to receive a 6-day open-label course of fluvoxamine, in a change from the original study protocol. **Comparator:** Placebo **Follow-up:** 15 days for primary outcome	defined by (1) presence of dyspnoea (shortness of breath) or hospitalisation for shortness of breath or pneumonia and (2) decrease in oxygen saturation (<92%) on room air or supplemental oxygen requirement to maintain oxygen saturation of 92% or greater. The primary analysis was the survival analysis for the primary outcome (clinical deterioration) using a log-rank test. All endpoints were self-reported; the primary endpoint was corroborated by phone discussion with participants and review of medical records. **Secondary endpoints:** Severity of deterioration, number of days requiring supplemental oxygen, hospitalisation, and ventilator support.	patients in the placebo group: absolute difference, 8.7% [95% CI, 1.8%-16.4%] by survival analysis, log-rank χ^2=6.8 and p=0.009). For the non-prespecified outcome of hospital or emergency department care received during the 30 days after day 15 of the trial, among fluvoxamine-treated participants, 1 of 80 received care (hospitalised for headache) compared with 1 of 72 placebo-treated participants (emergency department visit for costochondritis). **Relative risk:** N/R **Secondary outcomes:** ▪ In the placebo group, cases of clinical deterioration ranged from 1 to 7 days after randomisation and from 3 to 12 days after the onset of COVID-19 symptoms. ▪ Four of the 6 patients that deteriorated were hospitalised, with the length of stay ranging from 4 to 21 days. One patient required mechanical ventilation for 10 days; no patients died. **Safety outcomes:** The fluvoxamine group had 1 serious adverse event and 11 other adverse events, whereas the placebo group had 6 serious adverse events and 12 other adverse events. Pneumonia and gastrointestinal symptoms (such as nausea and vomiting) occurred more often in the placebo group compared with those who received fluvoxamine.
Ivermectin with Doxycycline			
Hashim A, 2020 **NCT04591600**	**Population:**	**Primary Outcomes:** 1. Time to recovery.	**Primary Outcomes** **1. Time to recovery**

DOI: 10.1101/2020.10.26.20219345 **RCT** **Completed, published as preprint** **Baghdad, Iraq**	N= 96 mild-moderate participants (48 assigned to intervention and 48 assigned to standard care). All patients with mild-moderate disease were outpatients. All of the recruited COVID-19 patients were diagnosed by clinical, radiological and laboratory PCR testing. Inclusion criteria of the patients enrolled in the clinical trial were mild-moderate cases who were symptomatic for no more than 3 days. Mean age: 48.7±8.6 years (range: 16-86) **Intervention:** 200mcg/kg of ivermectin orally plus 100mg doxycycline orally daily for 2-3 days and twice per day for 5-10 days, plus standard therapy **Comparator:** Standard care therapy <u>Standard care</u> ▪ Acetaminophen 500mg as needed ▪ Vitamin C 1000mg twice a day ▪ Zinc 75-125 mg/day ▪ Vitamin D3 5000IU/day ▪ Azithromycin 250mg/day for 5 days ▪ Oxygen therapy/ CPAP if needed ▪ Dexamethasone 6 mg/day or methylprednisolone 40mg twice per day, if needed ▪ Mechanical ventilation, if needed. **Follow-up:** Unclear.	2. Percentage of patients who progressed to a more advanced stage of disease. 3. Mortality rate.	The mean time to recovery in mild-moderate patients was 6.34 days (SD=2.4) in the intervention group versus 13.66 days (SD=6.4) in the control group. The intervention reduced recovery time about 7.32 days in mild-moderate patients. P value: <0.0001. **2. Progression of the disease** No patient with mild/moderate symptoms progressed to severe disease in either arm of the trial. **3. Mortality rate** No patient with mild/moderate symptoms died in either arm of the trial. Safety outcomes not reported.

Ivermectin			
Podder 2020 **URL:** **http://www.imcjms.com/registration/journal_full_text/353** **Open-label RCT** **Completed, published as preprint** **Ibrahim Medical College Journal of Medical Science** **Bangladesh**	**Population:** N=62 participants; N=32 in intervention arm and N=30 in control arm. Mean age 39.16±12.07 COVID-19 profile: mild, N=50 (80.6%); moderate, N=12 (19.4%) Study participants were adults (age 18+), enrolled from a single health centre outpatient department, following COVID-19 symptom onset within the past 7 days and RT-PCR confirmed SARS-CoV-2 infection. Both the intervention and control arm received 'usual care' symptom-directed treatment, which included antipyretics, cough suppressants, and doxycycline (100mg as oral capsules every 12 hours for 7 days) to treat possible community-acquired pneumonia. **Intervention:** Single dose of ivermectin, 200mcg/kg, on day 1 of randomisation, plus usual care as described above. **Control:** Usual care, as described above **Comparison:** Ivermectin + doxycycline versus doxycycline **Follow-up:**	**Outcomes** ▪ Recovery time was defined as the time required for the resolution of symptoms, from the date of enrolment in the study and from the onset of initial illness. ▪ Duration of time until resolution of the following indices were measured: fever, cough, shortness of breath, and full recovery from all symptoms. ▪ Negative result on repeat RT-PCR, day 10.	**Time for resolution of symptoms from date of enrolment:** The mean time to resolution of all symptoms was not significantly different (p>0.05, specific value not reported) between the intervention and control groups: Intervention: 5.31 days (SD=2.48) Control: 6.33 days (SD=4.23) 95% CI for difference in mean: -0.766 to 2.808 **Time for resolution of symptoms from date of onset of illness:** The mean time to resolution of all symptoms was not significantly different (p>0.05, specific value not reported) between the intervention and control groups: Intervention: 10.09 (SD=3.24) Control: 11.5 days (SD=5.32) 95% CI for difference in mean: -0.86 to 3.672 **Safety outcomes** No results reported

	Maximum follow-up not reported. Repeat RT-PCR on day 10 after the first positive test result, and symptom assessment performed via semi-structured questionnaire, with both face-to-face and telephone communication.		
Nitazoxanide			
Rocco 2020 **NCT04552483** **DOI: 10.1183/13993003.03725-2020** **Double blind, randomised, placebo-controlled RCT** **Completed, published (European Respiratory Journal)** **Brazil**	**Population:** N=392 participants; N=194 in the intervention arm and N=198 in placebo arm. Study participants were adults (age 18+) with one or more of fever, dry cough and fatigue, and with RT-PCR confirmed SARS-CoV-2 infection. The study was conducted at 7 sites in Brazil. Patients were based at home. **Intervention:** 500mg nitazoxanide 3 times daily for 5 days, taken as an oral solution (25ml of a 25mg/ml solution) **Comparator:** Placebo (colour-matched solution) **Follow-up:** Participants returned to the study sites the day after the 5-day intervention course to return self-reported symptom journals and provide nasopharyngeal and blood samples. Adverse events were monitored by review of the electronic medical record, physical examination, vital signs and laboratory tests from enrolment through day 14.	**Primary end point:** Complete resolution of symptoms of interest (dry cough, fever, fatigue) after 5 days of the intervention. **Secondary endpoints:** Reduction in viral load, improvement in laboratory parameters (including markers of inflammation), and incidence of hospital admission over a 14-day period.	**Absolute risk:** Overall, ten patients (5 from each arm) were hospitalised due to clinical deterioration; none had completed the 5-day course of therapy at this point. Two patients, both in the nitazoxanide arm, required intensive care unit admission. Complete resolution of symptoms (dry cough, fever, fatigue) did not differ between the arms after 5 days of therapy **Relative risk:** N/R **Adverse events:** 6 patients in the nitazoxanide arm and one patient in the placebo arm discontinued therapy due to moderate diarrhoea and vomiting within the first 2 days; both had experienced improvement of COVID-19 symptoms. Mild and moderate adverse events were experienced by patients in both arms (nitazoxanide, 30.9%; placebo, 30.4%) during the 5-day course of therapy.

Peginterferon lambda-1a			
Jagannathan 2020 **NCT04331899** **DOI: 10.1101/2020.11.18.20234161** **Phase 2, single-blind, randomised, placebo-controlled trial** **Completed, published (pre-print)** **USA**	**Population:** N=120 participants, with 110 completing 28 days of follow up; N=60 intervention arm and N=60 in placebo arm. Median age: 36 years (range 18-71). Median duration of symptoms prior to randomisation: 5 days 40% of patients were SARS-CoV-2 IgG positive at enrollment Study participants were adults (18-65 years, subsequently amended to include up to 75 years of age) with RT-PCR confirmed (FDA EUA test) SARS-CoV-2 infection. The trial was conducted in the Stanford Health Care System; participants were based at home. **Intervention:** 180 mcg of peginterferon lambda-1a, delivered subcutaneously **Comparator:** Subcutaneous saline injection **Follow-up:** Daily symptom questionnaire (self-completed), self-reporting of in-home measurements of temperature and oxygen saturation. In-person follow-up on days 1, 3, 5, 6, 10, 14, 21, 28, with assessment of symptoms and vitals and collection of oropharyngeal swabs. Blood draws at days 5 and 14 to assess for safety events.	**Primary endpoint:** Time to first of 2 consecutive negative oropharyngeal tests (RT-PCR). **Secondary endpoints:** (1) Time to alleviation of all symptoms, as self-reported (time to first day of no reported symptoms) (2) Oropharyngeal viral RNA levels over time (3) Oropharyngeal viral RNA area under the curve (4) Incidence of emergency department visits or hospitalisations within 28 days of intervention initiation **Exploratory outcomes** (1) Time until sustained resolution of symptoms (2) Progression of disease, defined as admission to the emergency	**Participant characteristics:** **Absolute risk:** N/R **Relative risk (secondary and exploratory outcomes):** No difference observed in time to resolution of symptoms or sustained resolution of symptoms. No difference between the arms in time to clinical progression (adjusted HR 1.38; 95% CI 0.52 to 3.63; p = 0.52). **Adverse events:** 25 (42%) participants in intervention group and 21 (25%) in placebo group experienced adverse events. Two serious adverse events (hospitalisation) were reported in each arm. Liver transaminase elevations were more common in the intervention arm versus placebo (15 vs 5; p= 0.027); ALT levels were significantly raised in the intervention arm versus placebo, though there were no associated symptoms and abnormalities were not sustained.

		department, hospitalisation, or worsening cough or shortness of breath, defined as an increase in severity of 2 points or more on a 5-point scale.	
Sulodexide			
Gonzalez-Ochoa 2020 **ISRCTN59048638** **DOI: 10.1101/2020.12.04.20242073** **Placebo-controlled RCT** **Completed, published as preprint** **Mexico**	**Population:** N=243 participants; N=124 intervention arm and N=119 in placebo arm. Study participants were all adults (≥18 years), non-hospitalised and had RT-PCR confirmed SARS-CoV-2 infection and any two symptoms of COVID-19 with no more than 3 days from symptom onset to trial entry. Median age: 52 ±10.6 years **Intervention:** 500RLU sulodexide capsules twice daily for three weeks (as reported in study) **Comparator:** Placebo **Follow-up:** Three weeks **Concomitant medications:** Both intervention and comparator groups were not precluded from the use of concomitant medications, such as ivermectin, corticosteroids, hydroxychloroquine and oseltamivir.	**Primary endpoints:** Hospitalisation, the duration of illness and the need for oxygen supplementation. **Secondary endpoints**: The need for mechanical ventilation support and mortality	<u>**Primary endpoints:**</u> **Absolute risk:** 57/243 patients (23.4%) required hospital care during the 21 days of follow-up; 22/124 (17.7%) in the sulodexide group and 35/119 (29.4%) in the placebo group (absolute difference=-11.7%; not reported in study) **Relative risk:** Requirement for hospital care in sulodexide arm versus placebo: RR = 0.6 (95% CI 0.37 to 0.96; p=0.03) **Other primary endpoints:** The mean duration of days in hospital was 6.2 ±4.1 in the sulodexide group versus 7.8 ±4.5 in the placebo group; p=0.21 37 participants in the sulodexide arm (35.8%) developed respiratory symptoms requiring oxygen support versus 50 (42%) in the placebo arm. RR 0.71 (95% CI 0.5 to 1.0; p=0.05) The mean length of duration of oxygen support was 9 ±7.2 days in the sulodexide group versus 11.5 ±9.6 in the placebo group (p=0.02). <u>**Secondary endpoints:**</u> ▪ There were 3 deaths in the sulodexide arm (2.4%) versus 7 in the placebo arm (5.8%). RR 0.41 (95% CI 0.10 to 1.55, p=0.19).

			▪ The need for mechanical ventilation was not reported. **Safety outcomes:** There was no reported significant difference in safety outcomes between the 2 groups.

Key: ALT – alanine aminotransferase; CPAP – continuous positive airways pressure; EUA – Emergency Use Authorized; NEJM – New England Journal of Medicine; RCT – randomised controlled trial

Appendix 2 Quality appraisal

Risk of Bias in included studies (Cochrane Risk of Bias Version 2.0)

Gottlieb 2020[4] (Bamlanivimab LY-CoV555)		
Domain	Judgement (Low/High/Some concerns)	
Bias arising from the randomisation process	Low	
Bias due to deviations from the intended interventions	Low	
Bias due to missing outcome data	Low	
Bias in measurement of outcome	Low	
Bias in selection of the reported result	Low	
Other bias: Industry funding	*Yes*	
Overall bias	**Low**	If not considered 'low-risk' state reason N/A

Hashim 2020[11] (Ivermectin+docycycline)		
Domain	**Judgement (Low/High/Some concerns)**	
Bias arising from the randomisation process	High	
Bias due to deviations from the intended interventions	High	
Bias due to missing outcome data	Low	
Bias in measurement of outcome	High	
Bias in selection of the reported result	Low	
Other bias: Industry funding	*No*	
Overall bias	**High**	If not considered 'low-risk' state reason ▪ Allocation not fully random. ▪ Not information on blinding provided. ▪ Not placebo controlled.

Gonzalez-Ochoa 2020[5] (Sulodexide)		
Domain	**Judgement (Low/High/Some concerns)**	
Bias arising from the randomisation process	Low	
Bias due to deviations from the intended interventions	Low	
Bias due to missing outcome data	Low	
Bias in measurement of outcome	High	
Bias in selection of the reported result	Low	
Other bias: Industry funding	*Yes*	
Overall bias	High	If not considered 'low-risk' state reason Blinding was broken during data management

Jagannathan 2020[6] (Peginterferon lambda-1a)		
Domain	**Judgement (Low/High/Some concerns)**	
Bias arising from the randomisation process	Low	
Bias due to deviations from the intended interventions	Low	
Bias due to missing outcome data	Low	
Bias in measurement of outcome	Low	
Bias in selection of the reported result	Low	
Other bias: Industry funding	*Unclear*	
Overall bias	**Low**	If not considered 'low-risk' state reason N/A

Lenze 2020[7] (Fluvoxamine)		
Domain	**Judgement (Low/High/Some concerns)**	
Bias arising from the randomisation process	Low	
Bias due to deviations from the intended interventions	Low	
Bias due to missing outcome data	Low	
Bias in measurement of outcome	Some concerns	
Bias in selection of the reported result	Low	
Other bias: Industry funding	*No*	
Overall bias	**Some concerns**	If not considered 'low-risk' state reason All outcomes were self-reported

Rocco 2020[8] (Nitazoxanide)		
Domain	**Judgement (Low/High/Some concerns)**	
Bias arising from the randomisation process	Low	
Bias due to deviations from the intended interventions	Low	
Bias due to missing outcome data	High	
Bias in measurement of outcome	Low	
Bias in selection of the reported result	Low	
Other bias: Industry funding	*No*	
Overall bias	**High**	If not considered 'low-risk' state reason ▪ Some randomised patients were not included in the analysis. ▪ Some data is missing or not evaluable.

Podder 2020[10] (Ivermectin)		
Domain	**Judgement (Low/High/Some concerns)**	
Bias arising from the randomisation process	High	
Bias due to deviations from the intended interventions	High	
Bias due to missing outcome data	High	
Bias in measurement of outcome	High	
Bias in selection of the reported result	Low	
Other bias: Industry funding	*Unclear*	
Overall bias	**High**	If not considered 'low-risk' state reason
		▪ No information on concealment/blinding. ▪ Unclear if there were deviations from intended interventions. ▪ Not all randomised patients analysed. ▪ Unclear how many patients analysed for outcome of interest. ▪ Investigator prompting may have influenced reporting for outcomes.

Weinreich 2020[9] (Casirivimab + Imdevimab (REGN-COV2))		
Domain	**Judgement (Low/High/Some concerns)**	
Bias arising from the randomisation process	Low	
Bias due to deviations from the intended interventions	Low	
Bias due to missing outcome data	Low	
Bias in measurement of outcome	Low	
Bias in selection of the reported result	Low	
Other bias: Industry funding	*Yes*	
Overall bias	**Low**	If not considered 'low-risk' state reason
		N/A

GRADE assessment of the certainty of the body of evidence per outcome

Outcome 1: Casirivimab + Imdevimab (REGN-COV2) versus placebo for the prevention of medically attended visit

Certainty of evidence question	Response	Downgrade?
1. Are the study designs used appropriate?	Yes (1 RCT)	No
2. Are there important limitations in the research design or execution of the research?	No	No
3. Are the results consistent across studies when the settings, populations, interventions, comparators, and outcomes are reasonably similar?	N/A	No
4. How directly do the results apply to the population (including setting), intervention, comparator, and outcomes (PICO) of interest?	They are applicable	No
5. Are the results precise enough or likely due to chance?	They are not precise enough (1 interim analysis of an RCT of 275 participants followed for 29 days)	2 Levels
6. Is this all the research that has been conducted on the PICO question of interest?	Yes (database search supplemented by grey literature search and search for preprints)	No
7. Is there anything, in particular very large effects of an intervention, dose response gradients, or unfavourable scenarios still leading to convincing effect that makes us more confident?	No	No
Overall result: Low certainty		

N/A – not applicable. RCT – randomised controlled trial

Outcomes 2 to 5: Bamlanivimab or bamlanivimab plus etesevimab versus placebo for the prevention of hospitalisation

Certainty of evidence question	Response	Downgrade?
1. Are the study designs used appropriate?	Yes (1 RCT)	No
2. Are there important limitations in the research design or execution of the research?	No	No
3. Are the results consistent across studies when the settings, populations, interventions, comparators, and outcomes are reasonably similar?	N/A	No
4. How directly do the results apply to the population (including setting), intervention, comparator, and outcomes (PICO) of interest?	They are applicable	No
5. Are the results precise enough or likely due to chance?	No they are not precise enough (1 RCT of 577 participants followed for 29 days)	2 Levels
6. Is this all the research that has been conducted on the PICO question of interest?	Yes (database search supplemented by grey literature search and search for preprints)	No
7. Is there anything, in particular very large effects of an intervention, dose response gradients, or unfavourable scenarios still leading to convincing effect that makes us more confident?	No	No
Overall result: Low certainty		

N/A – not applicable. RCT – randomised controlled trial

Outcome 6: Fluvoxamine versus placebo for the prevention of clinical deterioration

Certainty of evidence question	Response	Downgrade?
1. Are the study designs used appropriate?	Yes (1 RCT)	No
2. Are there important limitations in the research design or execution of the research?	Yes – all outcomes were self-reported	1 Level
3. Are the results consistent across studies when the settings, populations, interventions, comparators, and outcomes are reasonably similar?	N/A	No
4. How directly do the results apply to the population (including setting), intervention, comparator, and outcomes (PICO) of interest?	They are applicable	No
5. Are the results precise enough or likely due to chance?	They are not precise enough (1 RCT of 152 participants followed for 15 days) As it is a preliminary study the results must be confirmed by larger scale RCTs	2 Levels
6. Is this all the research that has been conducted on the PICO question of interest?	Yes (database search supplemented by grey literature search and search for preprints)	No
7. Is there anything, in particular very large effects of an intervention, dose response gradients, or unfavourable scenarios still leading to convincing effect that makes us more confident?	No	No
Overall result: Very low certainty		

N/A – not applicable. RCT – randomised controlled trial

Outcome 7: Ivermectin + usual care (that included doxycycline) versus usual care (that included doxycycline)

Certainty of evidence question	Response	Downgrade?
1. Are the study designs used appropriate?	Yes (1 RCT)	No
2. Are there important limitations in the research design or execution of the research?	Yes No information on concealment/blinding. Unclear if there were deviations from intended interventions. Not all randomised patients analysed. Unclear how many patients analysed for outcome of interest. Investigator prompting may have influenced reporting for outcomes.	2 Levels
3. Are the results consistent across studies when the settings, populations, interventions, comparators, and outcomes are reasonably similar?	N/A	No
4. How directly do the results apply to the population (including setting), intervention, comparator, and outcomes (PICO) of interest?	They are applicable	No
5. Are the results precise enough or likely due to chance?	They are not precise enough (1 RCT of 62 participants)	2 Levels
6. Is this all the research that has been conducted on the PICO question of interest?	Yes (database search supplemented by grey literature search and search for preprints)	No
7. Is there anything, in particular very large effects of an intervention, dose response gradients, or unfavourable scenarios still leading to convincing effect that makes us more confident?	No	No
Overall result: Very low certainty		

N/A – not applicable. RCT – randomised controlled trial

Outcome 8: Ivermectin + doxycycline versus usual care

Certainty of evidence question	Response	Downgrade?
1. Are the study designs used appropriate?	Yes (1 RCT)	No
2. Are there important limitations in the research design or execution of the research?	Yes Allocation not fully random. Not information on blinding provided. Not placebo controlled	2 Levels
3. Are the results consistent across studies when the settings, populations, interventions, comparators, and outcomes are reasonably similar?	N/A	No
4. How directly do the results apply to the population (including setting), intervention, comparator, and outcomes (PICO) of interest?	They are applicable	No
5. Are the results precise enough or likely due to chance?	They are not precise enough (1 RCT of 96 participants)	2 Levels
6. Is this all the research that has been conducted on the PICO question of interest?	Yes (database search supplemented by grey literature search and search for preprints)	No
7. Is there anything, in particular very large effects of an intervention, dose response gradients, or unfavorable scenarios still leading to convincing effect that makes us more confident?	No	No
Overall result: Very low certainty		

Outcome 9: Nitazoxanide versus placebo

Certainty of evidence question	Response	Downgrade?
1. Are the study designs used appropriate?	Yes (1 RCT)	No
2. Are there important limitations in the research design or execution of the research?	Yes Blinding was broken during data management	1 Level
3. Are the results consistent across studies when the settings, populations, interventions, comparators, and outcomes are reasonably similar?	N/A	No
4. How directly do the results apply to the population (including setting), intervention, comparator, and outcomes (PICO) of interest?	They are applicable	No
5. Are the results precise enough or likely due to chance?	They are not precise enough (1 RCT of 392 participants)	2 Levels
6. Is this all the research that has been conducted on the PICO question of interest?	Yes (database search supplemented by grey literature search and search for preprints)	No
7. Is there anything, in particular very large effects of an intervention, dose response gradients, or unfavourable scenarios still leading to convincing effect that makes us more confident?	No	No
Overall result: Very low certainty		

Outcome 10: Peginterferon lambda-1a versus placebo

Certainty of evidence question	Response	Downgrade?
1. Are the study designs used appropriate?	Yes (1 RCT)	No
2. Are there important limitations in the research design or execution of the research?	No	No
3. Are the results consistent across studies when the settings, populations, interventions, comparators, and outcomes are reasonably similar?	N/A	No
4. How directly do the results apply to the population (including setting), intervention, comparator, and outcomes (PICO) of interest?	They are applicable	No
5. Are the results precise enough or likely due to chance?	They are not precise enough (1 RCT of 120 participants)	2 Levels
6. Is this all the research that has been conducted on the PICO question of interest?	Yes (database search supplemented by grey literature search and search for preprints)	No
7. Is there anything, in particular very large effects of an intervention, dose response gradients, or unfavourable scenarios still leading to convincing effect that makes us more confident?	No	No
Overall result: Low certainty		

Outcome 11: Sulodexide versus placebo for the prevention of hospitalisation

Certainty of evidence question	Response	Downgrade?
1. Are the study designs used appropriate?	Yes (1 RCT)	No
2. Are there important limitations in the research design or execution of the research?	Yes – blinding was broken by the lead researcher. Study has not yet gone through the peer review process (pre-print)	2 Levels
3. Are the results consistent across studies when the settings, populations, interventions, comparators, and outcomes are reasonably similar?	N/A	No
4. How directly do the results apply to the population (including setting), intervention, comparator, and outcomes (PICO) of interest?	They are applicable	No
5. Are the results precise enough or likely due to chance?	They are not precise enough (1 RCT of 243 participants followed for 3 weeks)	2 Levels
6. Is this all the research that has been conducted on the PICO question of interest?	Yes (database search supplemented by grey literature search and search for preprints)	No
7. Is there anything, in particular very large effects of an intervention, dose response gradients, or unfavourable scenarios still leading to convincing effect that makes us more confident?	No	No
Overall result: Very low certainty		

Appendix 3 Excluded studies and reasons (from full text review)

First Author	Title	Exclusion reason
AbiSaleh 2020	Statement of the Lebanese pulmonary society, the Lebanese society of critical care medicine & the Lebanese society of anaesthesiology	Wrong study design
A'Court 2020	COVID-19 and cardiac considerations in the community	Wrong study design
Agarwal 2020	COVIDCare@Home: Lessons from a Family Medicine Led Remote Monitoring Program	Wrong study design
Akhavan 2020	Risk Stratification of COVID-19 Patients Using Ambulatory Oxygen Saturation in the Emergency Department	Wrong study design
AlaviDarazam 2020	An investigation into the beneficial effects of high-dose interferon beta 1-a, compared to low-dose interferon beta 1-a (the base therapeutic regimen) in moderate to severe COVID-19: A structured summary of a study protocol for a randomized controlled I trial	Wrong study design
Ansarin 2020	Effect of bromhexine on clinical outcomes and mortality in COVID-19 patients: A randomized clinical trial	Wrong setting
Arafath 2020	Covid 19 disease - A case series of cases reported with different treatment approaches	Wrong study design
Aranda-Abreu 2020	Observational study of people infected with SARS-Cov-2, treated with amantadine	Wrong study design
Axfors 2020	Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19: an international collaborative meta-analysis of randomized trials	Formal recommendation against
Ayaz 2020	Out-patient management of patients with COVID-19 on home isolation	Wrong study design
Ayerbe 2020	The association between treatment with heparin and survival in patients with Covid-19	Wrong study design
Barro 2020	Management of the COVID-19 epidemic by public health establishments-Analysis by Fédération Hospitalière de France	Wrong study design
Barzin 2020	Development and Implementation of a COVID-19 Respiratory Diagnostic Center	Wrong study design
Bashash 2020	COVID-19 prognosis: What we know of the significance and prognostic value of liver-related laboratory parameters in SARS-CoV-2 infection	Wrong study design
Bass 2020	Procalcitonin and COVID-19: A Reliable Clinical Tool	Wrong study design
Bastiani 2020	EPICOVID19: Psychometric assessment and validation of a short diagnostic scale for a rapid Covid-19 screening based on reported symptoms	Wrong study design
Bates 2020	Use of a portable computed tomography scanner for chest imaging of COVID-19 patients in the urgent care at a tertiary cancer center	Wrong setting
BayonaHuguet 2020	The organization of primary care teams from the COVID-19 pandemic	Wrong study design

Beattie 2020	Near Me at Home: codesigning the use of video consultations for outpatient appointments in patients' homes	Wrong intervention
Beauchet 2020	Telemedicine for housebound older persons during the Covid-19 pandemic	Wrong study design
Beck 2004	Community health orientation, community-based quality improvement, and health promotion services in hospitals: Practitioner application	Wrong study design
Bellos 2020	Development of a novel risk score for the prediction of critical illness amongst COVID-19 patients	Wrong study design
Berrocal 2020	Zinc and Vitamin a Deficiency Predisposes to the Need for Intubation and ICU Admission in Patients With COVID-19. An Observational Study	Wrong study design
Bhapkar 2020	A critical analysis of CTRI registered AYUSH studies for COVID- 19	Wrong study design
Bhaumik 2020	Community health workers for pandemic response: a rapid evidence synthesis	Wrong study design
Bicher 2020	Supporting Austria through the COVID-19 Epidemics with a Forecast-Based Early Warning System	Wrong study design
Blazey-Martin 2020	Primary Care Population Management for COVID-19 Patients	Wrong study design
Blecher 2020	Crisis as opportunity: how COVID-19 can reshape the Australian health system	Wrong study design
Bonning 2020	Respiratory clinics and rural and Aboriginal health	Wrong study design
Bradley 2020	128 Operation Kick the King: a Non-Governmental Organization's Response to the United States Novel Corona Virus 2019 Pandemic	Wrong study design
Bressy 2020	Technological devices in COVID-19 primary care management: the Italian experience	Wrong study design
Bright 2020	A Preliminary Study on Various Types of 4-Aminoquinolines for Pre- or Post-Exposure Prophylaxis and for Treatment in Severe COVID-19	Wrong study design
Browne 2020	Please do not forget about us: The need for patient-centered care for people with kidney disease and are at high risk for poor COVID-19 outcomes	Wrong study design
Bryant 2020	Planning and clinical role of acute medical home care services for COVID-19: consensus position statement by the Hospital-in-the-Home Society Australasia	Wrong study design
Byrne 2020	Telehealth and the COVID-19 Pandemic	Wrong study design
Capobussi 2020	3D printing technology and internet of things prototyping in family practice: building pulse oximeters during COVID-19 pandemic	Wrong outcomes
Carlberg 2020	Preliminary Assessment of a Telehealth Approach to Evaluating, Treating, and Discharging Low-Acuity Patients With Suspected COVID-19	Wrong study design
Carr 2020	Evaluation and Improvement of the National Early Warning Score (NEWS2) for COVID-19: a multi-hospital study	Wrong outcomes
Castelnuovo 2020	Low Dose Hydroxychloroquine is Associated with Lower Mortality in COVID-19: A Meta-Analysis of 27 Studies and 44,684 Patients	Formal recommendation against drug

Cawood 2020	A Review of Nutrition Support Guidelines for Individuals with or Recovering from COVID-19 in the Community	Wrong study design
Chan 2020	Enhancing the Triage and Cohort of Patients in Public Primary Care Clinics in Response to the Coronavirus Disease 2019 (COVID-19) in Hong Kong: An Experience from a Hospital Cluster	Wrong outcomes
Chang 2020	Ready for a long fight against the COVID-19 outbreak: An innovative model of tiered primary health care in Taiwan	Wrong outcomes
Chen 2020	Antiviral activity and safety of darunavir/Cobicistat for the treatment of COVID-19	Wrong setting
Chen 2020	Effectiveness of Convalescent Plasma for Treatment of COVID-19 Patients	Wrong patient population
Chivese 2020	A meta-review of systematic reviews and an updated meta-analysis on the efficacy of chloroquine and hydroxychloroquine in treating COVID19 infection	Wrong outcomes
Choi 2020	Community Treatment Centers for Isolation of Asymptomatic and Mildly Symptomatic Patients with Coronavirus Disease, South Korea	Wrong study design
Chua 2020	Early prognostication of COVID-19 to guide hospitalisation versus outpatient monitoring using a point-of-test risk prediction score	Wrong study design
Cramer 2020	Multivitamins for acute respiratory tract infections: a rapid review	Wrong patient population
Crespo-Facorro 2020	Aripiprazole as a candidate treatment of COVID-19 identified through genomic analysis	Wrong study design
Dambha-Miller 2020	Currently prescribed drugs in the UK that could up or down regulate ACE2 in COVID-19 disease: A systematic review	Wrong outcomes
Dambha-Miller 2020	Drug treatments affecting ACE2 in COVID-19 infection: A systematic review protocol	Wrong study design
Das 2020	Effect of Vitamin D deficiency on COVID-19 status: A systematic review	Wrong study design
Das 2020	Efficacy and Safety of Anti-malarial Drugs (Chloroquine and Hydroxy-Chloroquine) in Treatment of COVID-19 Infection: A Systematic Review and Meta-Analysis	Formal recommendation against drug
Davoodi 2020	Febuxostat therapy in outpatients with suspected COVID-19: A clinical trial	Wrong comparator
Delgado-Enciso 2020	Patient-Reported Health Outcomes After Treatment of COVID-19 with Nebulized and/or Intravenous Neutral Electrolyzed Saline Combined with Usual Medical Care Versus Usual Medical care alone: A Randomized, Open-Label, Controlled Trial.	Wrong intervention*
Desborough 2020	Australia's national COVID-19 primary care response	Wrong study design
DeSpiegeleer 2020	The effects of ARBs, ACEIs and statins on clinical outcomes of COVID-19 infection among nursing home residents	Wrong study design
DeVoe 2020	A Practice-Based Research Network (PBRN) Roadmap for Evaluating COVID-19 in Community Health Centers: A Report From the OCHIN PBRN	Wrong outcomes

deZulueta 2020	Touch matters: COVID-19, physical examination, and 21st century general practice	Wrong study design
DiCastelnuovo 2020	Low dose hydroxychloroquine is associated with lower mortality in COVID-19: a meta-analysis of 26 studies and 44,521 patients	Formal recommendation against drug
Dorner 2020	131 A Novel Mobile Integrated Health Program for COVID-19 Response	Wrong outcomes
Douillet 2020	Outpatient management or hospitalization of patients with proven or suspected SARS-CoV-2 infection: the HOME-CoV rule	Wrong study design
Dunlop 2020	The coronavirus outbreak: The central role of primary care in emergency preparedness and response	Wrong study design
Duran 2020	Stemming COVID-19 in Cuba: Strengths, strategies, challenges	Wrong study design
Ehrenpreis 2020	Rapid Review: Nonsteroidal Anti-inflammatory Agents and Aminosalicylates in COVID-19 Infections	Wrong study design
ElBiali 2020	Cannabinoids and COVID-19	Wrong study design
Elliott 2020	Home visits: A practical approach	Wrong study design
ElSayed 2020	Promising preventive and therapeutic effects of taibuvid nutritional supplements for COVID-19 pandemic: Towards better public prophylaxis and treatment (a retrospective study)	Wrong study design
ErÅ‘ss 2020	Personalised health education against health damage of COVID-19 epidemic in the elderly Hungarian population (PROACTIVE-19): protocol of an adaptive randomised controlled clinical trial	Wrong patient population
Falvey 2020	The Essential Role of Home- and Community-Based Physical Therapists During the COVID-19 Pandemic	Wrong study design
Farsalinos 2021	Improved strategies to counter the COVID-19 pandemic: Lockdowns vs. primary and community healthcare	Wrong study design
Farshchian 2020	Outpatient Teledermatology Implementation During the COVID-19 Pandemic: Challenges and Lessons Learned	Wrong patient population
Favalli 2020	Impact of corticosteroids and immunosuppressive therapies on symptomatic SARS-CoV-2 infection in a large cohort of patients with chronic inflammatory arthritis	Wrong study des
Fenton 2020	An Expanded COVID-19 Telemedicine Intermediate Care Model Using Repurposed Hotel Rooms	Wrong study design
Ford 2020	Leveraging health system telehealth and informatics infrastructure to create a continuum of services for COVID-19 screening, testing, and treatment	Wrong study design
Francis 2020	Predictors of adverse outcome in patients with suspected COVID-19 managed in a ‘virtual hospital’ setting: a cohort study	Wrong study design
Fu 2020	An open-label, randomized trial of the combination of IFN-Îº plus TFF2 with standard care in the treatment of patients with moderate COVID-19	Wrong patient population

GÃ¶pel 2020	Test and treat COVID 65 plus - Hydroxychloroquine versus placebo in early ambulatory diagnosis and treatment of older patients with COVID19: A structured summary of a study protocol for a randomised controlled trial	Formal recommendation against drug
Gao 2020	Application of Telemedicine During the Coronavirus Disease Epidemics: A Rapid Review and Meta-Analysis	Wrong patient population
Gbinigie 2020	Should chloroquine and hydroxychloroquine be used to treat COVID-19? A rapid review	Formal recommendation against drug
Gibbons 2020	6 Lung Ultrasound versus Chest X-ray for the Diagnosis of COVID-19 Pneumonia	Wrong outcomes
Gong 2020	Cloud-Based System for Effective Surveillance and Control of COVID-19: Useful Experiences From Hubei, China	Wrong study design
Govind 2020	Clozapine treatment and risk of COVID-19	Wrong study design
Greenhalgh 2020	Covid-19: a remote assessment in primary care	Wrong study design
GuÃ©rin 2020	Azithromycin and Hydroxychloroquine Accelerate Recovery of Outpatients with Mild/Moderate COVID-19	Wrong study design
Haldane 2020	National primary care responses to COVID-19: a rapid review of the literature	Wrong study design
Harskamp 2020	[COVID-19: care at home or in hospital? Considerations in primary care]	Wrong study design
Herzik 2021	The impact of COVID-19 on pharmacy transitions of care services	Wrong study design
Hippisley-Cox 2020	Protocol for the development and evaluation of a tool for predicting risk of short-term adverse outcomes due to COVID-19 in the general UK population	Wrong study design
Ho 2020	Highlights of traditional Chinese medicine frontline expert advice in the China national guideline for COVID-19	Wrong study design
Hossain 2020	Repurposing therapeutic agents against SARS-CoV-2 infection: most promising and neoteric progress	Wrong study design
Hozayen 2020	Outpatient and Inpatient Anticoagulation Therapy and the Risk for Hospital Admission and Death Among COVID-19 Patients	Wrong study design
Huaroto 2020	COVID-19. Ambulatory management during intense community transmission	Wrong study design
Hunter 2020	Benefits and risks of zinc for adults during covid-19: rapid systematic review and meta-analysis of randomised controlled trials	Wrong study design
Ientile 2020	Covid-19 what community pharmacies are doing in the hardest-hit states	Wrong study design
Ilich 2020	Nutritional and behavioral approaches to body composition and low-grade chronic inflammation management for older adults in the ordinary and covid-19 times	Wrong study design
Isaksen 2020	Chloroquine, but not hydroxychlorquine, prolongs the QT interval in a primary care population	Wrong study design

Jacobson 2020	COVID Care Clinic: A Unique Way for Family Medicine to Care for the Community During the SARS-CoV-2 (COVID-19) Pandemic	Wrong outcomes
Jacquelin 2020	[Together against COVID-19, the nurses ensured continuity of care at home]	Wrong study design
Jenkins 2020	The evolving role of family physicians during the coronavirus disease 2019 crisis: An appreciative reflection	Wrong study design
Jeong 2020	Self-Assessment Questionnaire for Efficient and Safe Evaluation of Patients with Mild COVID-19	Wrong study design
Jin 2020	Chemoprophylaxis, diagnosis, treatments, and discharge management of COVID-19: An evidence-based clinical practice guideline (updated version)	Wrong outcomes
Jolliffe 2020	Vitamin D supplementation to prevent acute respiratory infections: systematic review and meta-analysis of aggregate data from randomised controlled trials	Wrong outcomes
Juranek 2020	The Effect of Non-Pharmaceutical Interventions on the Demand for Health Care and Mortality: Evidence on COVID-19 in Scandinavia	Wrong outcomes
Kalin 2020	What is the Efficacy and Safety of Rapid Exercise Tests for Exertional Desaturation in Covid-19: A rapid review protocol	Wrong patient population
Kalin 2020	What is the Efficacy and Safety of Rapid Exercise Tests for Exertional Desaturation in Covid-19: A Rapid Systematic Review	Wrong outcomes
Kalirathinam 2020	Comprehensive physiotherapy management in COVID-19 â€“ A narrative review	Wrong study design
Kalra 2020	Clinical tools for cardiorespiratory assessment and rehabilitation: A primary care perspective	Wrong indication
Kana 2020	Remote clinician-based home management of COVID-19 associated pneumonia in a resource limited setting	Wrong study design
Kaye 2020	The efficacy of IL-6 inhibitor Tocilizumab in reducing severe COVID-19 mortality: a systematic review	Wrong indication
Kearon 2020	The Role of Primary Care in a Pandemic: Reflections During the COVID-19 Pandemic in Canada	Wrong study design
Keeney 2020	Physical Therapy in the COVID-19 Pandemic: Forging a Paradigm Shift for Rehabilitation in Acute Care	Wrong study design
Kennedy 2020	The UK IBD Registry COVID-19 Risk Tool; Patient Generated Data Can Improve the Hospital Record	Wrong study design
Kerkhoff 2020	Evaluation of a novel community-based COVID-19 'Test-to-Care' model for low-income populations	Wrong outcomes
Khadka 2020	The Use of Medicinal Plant to Prevent COVID-19 in Nepal	Wrong outcomes
Khanna 2020	Utilizing the Learning Health System Adaptation to guide Family Medicine Practice to COVID-19 response	Wrong study design
Kienle 2020	Addressing COVID-19 Challenges in a Randomized Controlled Trial on Exercise Interventions in a High-risk Population	Wrong study design
Kinar 2020	Predicting individual risk for COVID19 complications using EMR data	Wrong study design

Koenig 2020	2019-nCoV: The identify-isolate-inform (3I) Tool applied to a novel emerging coronavirus	Wrong study design
Krenitsky 2020	Primed for a pandemic: Implementation of telehealth outpatient monitoring for women with mild COVID-19	Wrong study design
Ladapo 2020	Randomized Controlled Trials of Early Ambulatory Hydroxychloroquine in the Prevention of COVID-19 Infection, Hospitalization, and Death: Meta-Analysis	Formal recommendation against drug
Lane 2020	Risk of depression, suicidal ideation, suicide and psychosis with hydroxychloroquine treatment for rheumatoid arthritis: a multi-national network cohort study	Wrong study design
Lepere 2021	COVID-19: Can early home treatment with Azithromycin alone or with Zinc help prevent hospitalisation, death, and long-COVID-19? A review	Wrong intervention
Levitan 2020	Pulse Oximetry as a Biomarker for Early Identification and Hospitalization of COVID-19 Pneumonia	Wrong study design
Li 2020	A simple algorithm helps early identification of SARS-CoV-2 infection patients with severe progression tendency	Wrong intervention
Li 2020	Challenges and responsibilities of family doctors in the new global coronavirus outbreak	Wrong study design
Li 2020	Modifiable lifestyle factors and severe COVID-19 risk: Evidence from Mendelian randomization analysis	Wrong study design
Li 2020	The Effects of Immunomodulators on a Veteran Population During the COVID-19 Pandemic	Wrong study design
Lin 2020	Retooling Primary Care in the COVID-19 Era	Wrong study design
Ling 2020	High-dose cholecalciferol booster therapy is associated with a reduced risk of mortality in patients with covid-19: A cross-sectional multi-centre observational study	Wrong study design
Liu 2020	Telehealth for Noncritical Patients With Chronic Diseases During the COVID-19 Pandemic	Wrong intervention
Llor 2020	[Coronavirus and primary care]	Wrong study design
LopezdelaIglesia 2020	HYDROXICLOROQUINE FOR PRE-EXPOSURE PROPHYLAXIS FOR SARS-CoV-2	Wrong outcomes
Lu 2020	Effectiveness and Safety of Glucocorticoids to Treat COVID-19: A Rapid Review and Meta-Analysis	Wrong study design
Ludy 2020	105 Studying the Impacts of To-Go Medications for Vulnerable Populations Discharged from the Emergency Department during the COVID-19 Pandemic	Wrong study design
Luo 2020	How can traditional Chinese medicine contribute to the therapeutic approach in coronavirus disease 2019 (COVID-19)? A review of the registered clinical trials	Wrong study design
Luo 2021	Characteristics of registered clinical trials on traditional Chinese medicine for coronavirus disease 2019 (COVID-19): A scoping review	Wrong study design
Macias 2020	Similar incidence of Coronavirus Disease 2019 (COVID-19) in patients with rheumatic diseases with and without hydroxychloroquine therapy	Wrong patient population

Mainous 2020	A Towering Babel of Risk Information in the COVID-19 Pandemic: Trust and Credibility in Risk Perception and Positive Public Health Behaviors	Wrong study design
Mansab 2020	The performance of national COVID-19 'Symptom Checkers'™: A comparative case simulation study	Wrong study design
Maor 2020	Compassionate use of convalescent plasma for treatment of moderate and severe pneumonia in COVID-19 patients and association with IgG antibody levels in donated plasma	Wrong patient population
Martinez-Lacalzada 2020	Predicting critical illness on initial diagnosis of COVID-19: Development and validation of the PRIORITY model for outpatient applicability	Wrong intervention
Mohammad 2020	Ambulatory care practice in the COVID-19 era: Redesigning clinical services and experiential learning	Wrong study design
Motta 2020	An emergency system for monitoring pulse oximetry, peak expiratory flow and body temperature of patients with COVID-19 at home: Development and preliminary application	Wrong patient population
Murr 2020	The pandemic in family practice â€" a practice report on sars-cov-2	Wrong study design
Nakakubo 2020	Proposal of COVID-19 Clinical Risk Score for the management of suspected COVID-19 cases: a case control study	Wrong study design
Napoli 2020	A panel of broad-spectrum antivirals in topical ophthalmic medications from the drug repurposing approach during and after the coronavirus disease 2019 era	Wrong study design
NeJhaddadgar 2020	Effectiveness of telephone-based screening and triage during COVID-19 outbreak in the promoted primary healthcare system: a case study in Ardabil province, Iran	Wrong study design
Neyens 2020	A spatial model to optimise predictions of COVID-19 incidence risk in Belgium using symptoms as reported in a large-scale online survey	Wrong intervention
Nguyen 2020	Applicability of the CURB-65 pneumonia severity score for outpatient treatment of COVID-19	Wrong intervention
Oh 2020	SARS-CoV-2 intervened by NSAIDs: A network pharmacology approach to decipher pathway and interactive genes	Wrong study design
Ohrling 2020	Management of the emergency response to the SARS-CoV-2 (COVID-19) outbreak in Stockholm, Sweden, and winter preparations	Wrong study design
O'Keefe 2020	Initial Experience in Predicting the Risk of Hospitalization of 496 Outpatients with COVID-19 Using a Telemedicine Risk Assessment Tool	Wrong outcomes
Olagundoye 2020	Recommendations for a national Coronavirus disease 2019 response guideline for the care of older persons in Nigeria during and post-pandemic: A family physician's perspective	Wrong study design
Olivares 2020	Covid-19 in Chile. The experience of a Regional reference Center. Preliminary report	Wrong study design
Olsen 2020	Large-Scale Air Medical Operations in the Age of Coronavirus Disease 2019: Early Leadership Lessons From the Front Lines of British Columbia	Wrong setting
O'Neill 2020	Covid-19 in care homes: The many determinants of this perfect storm	Wrong study design

Ong 2020	Safety and potential efficacy of cyclooxygenase-2 inhibitors in coronavirus disease 2019	Wrong study design
Oteo 2020	A short therapeutic regimen based on hydroxychloroquine plus azithromycin for the treatment of COVID-19 in patients with non-severe disease. A strategy associated with a reduction in hospital admissions and complications	Wrong study design
PantaleÃ³n-Matamoros 2020	Use of Artificial Intelligence Techniques in the Prediction of the Pre and Asymptomatic Patient to COVID-19	Wrong study design
Parida 2020	Nature to Nurture- Identifying Phytochemicals from Indian Medicinal Plants as Prophylactic Medicine by Rational Screening to Be Potent Against Multiple Drug Targets of SARS-CoV-2	Wrong study design
Parikh 2020	Pediatric Otolaryngology Divisional and Institutional Preparatory Response at Seattle Children's Hospital after COVID-19 Regional Exposure	Wrong patient population
Park 2020	Out-of-Hospital Cohort Treatment of Coronavirus Disease 2019 Patients with Mild Symptoms in Korea: an Experience from a Single Community Treatment Center	Wrong study design
Park 2020	Strengthening the UK primary care response to covid-19	Wrong study design
Paxton 2020	Chloroquine Administration in Breastfeeding Mothers Associates with Increased HIV-1 Plasma Viral Loads	Wrong study design
Peng 2020	[Prediction of severe outcomes of patients with COVID-19]	Wrong study design
Pereda 2020	Therapeutic Effectiveness of Interferon Alpha 2b Treatment for COVID-19 Patient Recovery	Wrong setting
PieraCarbonell 2020	[Thrombosis and COVID-19: Key primary care in the interdisciplinary approach]	Wrong study design
Prencipe 2020	Pump up the lung and be stronger against COVID-19	Wrong study design
Rajoli 2020	Dose prediction for repurposing nitazoxanide in SARS-CoV-2 treatment or chemoprophylaxis	Wrong study design
Rawaf 2020	Chloroquine and hydroxychloroquine effectiveness in human subjects during coronavirus: a systematic review	Wrong study design
Reinders 2020	Use of low molecular weight heparin (LMWH) in primary care is plausible in patients with COVID-19	Wrong study design
Rentsch 2020	Early initiation of prophylactic anticoagulation for prevention of COVID-19 mortality: a nationwide cohort study of hospitalized patients in the United States	Wrong patient population
Rentsch 2020	Hydroxychloroquine for prevention of COVID-19 mortality: a population-based cohort study	Wrong study design
Rhee 2020	Effects of a DPP-4 inhibitor and RAS blockade on clinical outcomes of patients with diabetes and COVID-19	Wrong study design
Sánchez-Duque 2020	Coronavirus disease 2019 (COVID-19) in Latin America: Role of primary care in preparedness and response	Wrong study design
Velez 2020	A practical approach for the compassionate use of convalescent plasma in patients with severe COVID-19 in developing countries	Wrong patient population

Saiz-RodrÃ-guez 2020	Outpatient treatment of COVID-19 with steroids in the phase of mild pneumonia without the need for admission as an opportunity to modify the course of the disease: A structured summary of a randomised controlled trial	Ongoing study - no published results
Schinköthe 2020	A Web- and App-Based Connected Care Solution for COVID-19 In- and Outpatient Care: Qualitative Study and Application Development	Wrong study design
Schmidt 2020	Access to Care During a Pandemic: Improving Planning Efforts to Incorporate Community Primary Care Practices and Public Health Stakeholders	Wrong study design
Schmidt 2020	The Ambulatory Management of COVID-19 Via the German Department of Health	Wrong study design
Scholz 2020	COVID-19 Outpatients â€" Early Risk-Stratified Treatment with Zinc Plus Low Dose Hydroxychloroquine and Azithromycin: A Retrospective Case Series Study	Wrong study design
Segal 2020	Establishing clinical pharmacist telehealth services during the COVID-19 pandemic	Wrong study design
Shah 2020	Novel Use of Home Pulse Oximetry Monitoring in COVID-19 Patients Discharged From the Emergency Department Identifies Need for Hospitalization	Wrong study design
Sharma 2020	A review on connection between BCG vaccination and COVID 19 cases: Facts and figures	Wrong intervention
Shih 2020	Remdesivir for coronavirus 2019 (COVID-19): More promising but still unproven	Wrong study design
Singh 2020	Efficacy and Safety of Hydroxychloroquine and Chloroquine for COVID-19: A systematic review	Formal recommendation against drug
Stemler 2020	Web-based, rapid and contactless management of ambulatory patients for SARS-CoV-2-testing	Wrong study design
Stokes 2020	The relative effects of non-pharmaceutical interventions on early Covid-19 mortality: natural experiment in 130 countries	Wrong intervention
Sudhir 2020	A primary care alternative to a hospital-based approach to COVID-19 in India	Wrong study design
Suillot 2020	Call your doctor: prospective description study of telemedicine during the first COVID-19 outbreak in a Swiss primary care practice	Wrong intervention
Sulaiman 2020	The Effect of Early Hydroxychloroquine-based Therapy in COVID-19 Patients in Ambulatory Care Settings: A Nationwide Prospective Cohort Study	Wrong study design
Swargiary 2020	Simeprevir and Eltrombopag as Potential Inhibitors of SARS-CoV2 Proteases: A Molecular Docking and Virtual Screening Approach to Combat COVID-19	Wrong study design
Talarico 2020	Psychiatric side effects induced by chloroquine and hydroxychloroquine: a systematic review of case reports and population studies	Wrong study design
Tan 2020	A cohort study to evaluate the effect of combination Vitamin D, Magnesium and Vitamin B12 (DMB) on progression to severe outcome in older COVID-19 patients	Wrong patient population
Tan 2020	Association of hyperlipidemia and statin use with severity of COVID-19	Wrong study design
Tapp 2020	The Changing Face of Primary Care Research and Practice-Based Research Networks (PBRNs) in Light of the COVID-19 Pandemic	Wrong study design

Thakre 2020	Review on efficacy of herbal antiviral drugs against COVID-19	Wrong study design
Thomas 2020	Emerging Pharmacotherapy for COVID-19 Treatment: An Integrative Review	Wrong outcomes
Ulrich 2020	Treating COVID-19 with hydroxychloroquine (TEACH): A multicenter, double-blind randomized controlled trial in hospitalized patients	Wrong setting
Vanassche 2020	A randomized, open-label, adaptive, proof-of-concept clinical trial of modulation of host thromboinflammatory response in patients with COVID-19: the DAWn-Antico study	Wrong setting
Vanasse 2020	Hydroxychloroquine (HCQ): an observational cohort study in primary and secondary prevention of pneumonia in an at-risk population	Wrong study design
vanderVelden 2020	Oseltamivir in human coronavirus infection: Post-hoc analysis of 2016-2018 data	Wrong patient population
vanPaassen 2020	Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes	Wrong patient population
Verity 2020	Does total triage and remote-by-default consulting impact vulnerable groups: A pilot study	Wrong intervention
Veronese 2020	Use of corticosteroids in Coronavirus disease 2019 pneumonia: A systematic review of the literature	Wrong study design
Vila-Corcoles 2020	COVID-19 TARRACO Cohort Study: Development of a predictive prognostic rule for early assessment of COVID-19 patients in primary care settings	Wrong intervention
Vindrola-Padros 2020	Remote home monitoring (virtual wards) during the COVID-19 pandemic: a living systematic review	Wrong study design
Vishvakarma 2020	Thiazolidinones: Potential Human Novel Coronavirus (SARS-CoV-2) Protease Inhibitors Against COVID-19	Wrong outcomes
Wang 2020	Development and Validation of a Diagnostic Nomogram to Predict COVID-19 Pneumonia	Wrong study design
Wilcock 2021	What is the value of community oximetry monitoring in people with SARS-CoV-2? A prospective, open-label clinical study	Wrong study design
Wilkinson 2020	Rapid Evidence Review of Harm Reduction Interventions and Messaging for People Who Inject Drugs During Pandemic Events: Implications for the On-Going COVID-19 Response	Wrong outcomes
Williams 2020	Seek COVER: Development and validation of a personalized risk calculator for COVID-19 outcomes in an international network	Wrong study design
Wong 2020	OpenSAFELY: Do adults prescribed Non-steroidal anti-inflammatory drugs have an increased risk of death from COVID-19?	Wrong study design
Wycliffe 2020	Age and chest radiography as possible parameters for rapid triage in COVID-19 outbreak surge	Wrong study design
Wynants 2020	Systematic review and critical appraisal of prediction models for diagnosis and prognosis of COVID-19 infection	Wrong outcomes
Xiang 2020	Exploring drugs and vaccines associated with altered risks and severity of COVID-19: a UK Biobank cohort study of all ATC level-4 drug categories	Wrong study design

Xuan 2020	PMU67 IMPACT OF PHARMACIST-PROVIDED TRANSITION OF CARE SERVICES ON HOSPITAL READMISSIONS	Wrong patient population
Yan 2020	Role of Drugs Affecting the Renin-Angiotensin-Aldosterone System on Susceptibility and Severity of COVID-19: A Large Case-Control Study from Zheijang Province, China	Wrong study design
Yang 2020	Characteristics of registered studies for Coronavirus disease 2019 (COVID-19): A systematic review	Wrong outcomes
Yates 2020	A Proposed Randomized, Double Blind, Placebo Controlled Study Evaluating Doxycycline for the Prevention of COVID-19 Infection and Disease In Healthcare Workers with Ongoing High Risk Exposure to COVID-19	Wrong patient population
Ying-Hui 2020	Chemoprophylaxis, diagnosis, treatments, and discharge management of COVID-19: An evidence-based clinical practice guideline (updated version)	Wrong outcomes
Young 2003	An outcome analysis of chest x-ray examination for detecting severe acute respiratory syndrome in general practice	Wrong study design
Yuan 2020	The application of Temporary Ark Hospitals in controlling COVID-19 spread: The experiences of one Temporary Ark Hospital, Wuhan, China	Wrong study design
Zampino 2021	Remote Outpatient Management During COVID-19 Lockdown: Patient-Derived Quality Assessment	study design
Zeng 2020	Efficacy of Traditional Chinese Medicine, Maxingshigan-Weijing in the management of COVID-19 patients with severe acute respiratory syndrome: A structured summary of a study protocol for a randomized controlled trial	Wrong outcomes
Zhai 2020	From Isolation to Coordination: How Can Telemedicine Help Combat the COVID-19 Outbreak?	Wrong study design
Zhang 2020	Current therapeutic options for coronavirus disease 2019 (COVID-19): lessons learned from severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS) therapy: A systematic review protocol	Wrong study design
Zhao 2020	ConceptWAS: a high-throughput method for early identification of COVID-19 presenting symptoms	Wrong outcomes
	[Recommendations on the identification and transfer of children with critical diabetes during the COVID-19 outbreak]	Wrong patient population

*In this trial, an experimental agent was used (neutral electrolysed saline), both nebulised and intravenously, for which no equivalent pharmaceutical product was identified (anywhere, including Ireland).

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