TRANSFUSION TRANSMITTED DISEASES

Review

SARS-CoV-2 infection rebound among patients receiving antiviral agents, convalescent plasma, or no treatment: a systematic review with meta-analysis

Mario Cruciani, Ilaria Pati, Francesca Masiello, Vanessa Piccinini, Simonetta Pupella, Vincenzo De Angelis

National Blood Centre, Italian National Institute of Health, Rome, Italy

Background - There is some evidence showing rebound of COVID-19 infections in patients treated with nirmatrelvir-ritonavir between 2 and 8 days following cessation of the antiviral treatment. COVID-19 rebound is not unique to patients treated with nirmatrelvir-ritonavir, but is also observed in molnupiravir recipients, in patients who did not receive any antiviral treatment and in patients who received convalescent plasma (CP).

Materials and methods - This was a systematic review with meta-analysis of clinical trials evaluating rates of virologic and clinical rebound in COVID-19 patients receiving antiviral agents, CP or no treatment. Both randomized clinical trials and controlled cohort studies were considered. The methodological quality of trials was assessed using ROB-2 and ROBIN-1 checklists, and the GRADE approach.

Results - Data were available from 16 trials. The occurrence of virologic rebound was more commonly observed among nirmatrelvir recipients than among untreated patients (relative risk [RR]=2.12; 95% confidence interval [CI]: 1.38-3.28; p=0.0007). No differences were observed in the occurrence of virologic rebound between nirmatrelvir-ritonavir and molnupiravir recipients (RR=1.01; 95% CI: 0.71-1.43). Similar rates of virologic rebounds were observed in molnupiravir recipients and untreated patients (RR=1.14; 95% CI: 0.81-1.6). One study in the pre-omicron period compared rates of virologic rebound between patients receiving standard of care with or without CP: no differences were observed between groups (RR=1.04; 95% CI: 0.55-1.99). Rates of clinical rebound were reported in seven trials, five evaluating nirmatrelvir-ritonavir and untreated patients, and two evaluating nirmatrelvir-ritonavir and molnupiravir recipients. No statistically significant differences between groups were observed. For all these comparisons, the certainty of the available evidence was graded as low or moderate.

Discussion - Virologic rebound of COVID-19 infections appears to be mild and self-limited, and was observed more commonly in nirmatrelvir-ritonavir recipients than in untreated patients, but was also observed in patients treated with molnupiravir or CP.

Keywords: *SARS-CoV-2 infection, Rebound, nirmatrelvir-ritonavir, molnupiravir, convalescent plasma.*

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Correspondence: Ilaria Pati
e-mail: ilaria.pati@iss.it

INTRODUCTION

Convalescent plasma (CP), small-molecule antivirals, monoclonal antibodies, and repurposed drugs have all been suggested as treatments for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection but only a few drugs have been approved or have emergency use authorization for this purpose in USA, Europe and other countries[1-3]. Among these drugs, the nirmatrelvir-ritonavir combination has been object of extensive clinical investigation and continues to represent an effective oral treatment against SARS-CoV-2[4]. Recently some concerns have been raised related to the fact that some patients treated with nirmatrelvir-ritonavir experienced rebound coronavirus disease 2019 (COVID-19) infections following the cessation of antiviral treatment[5,6]. Population data from the USA showed that COVID-19 rebound is not unique to nirmatrelvir-ritonavir recipients, but is also observed in molnupiravir recipients[7,8]. Moreover, viral rebound has been reported in patients who did not receive any antiviral treatment and in patients receiving CP[9,10]. Several reports document that some patients with normal immune response who have completed a 5-day course of antiviral agents for laboratory-confirmed infection and have recovered can experience recurrent illness 2 to 8 days following cessation of treatment[8]. COVID-19 rebound is characterized by a recurrence of symptoms (clinical rebound) or a new positive viral test after having tested negative (virologic rebound). Both the recurrence of illness and positive test results improved or resolved (at a median of 3 days) without additional anti-COVID-19 treatment[8]. Based on information from the case reports, COVID-19 rebound did not represent reinfection with SARS-CoV-2 or the development of resistance to antiviral agents.

SARS-CoV-2 virologic rebound after clearance of test positivity or symptom resolution continues to be reported, particularly in nirmatrelvir-ritonavir recipients[11-15]. Taking this in consideration, we performed a systematic review with meta-analysis to evaluate rates of rebound in nirmatrelvir-ritonavir recipients, in recipients of other antiviral agents or CP, and in untreated patients.

MATERIALS AND METHODS

This systematic review is conducted according to recommended Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist guidelines[16] (**Figure 1**, *Online Supplementary* **Table SI**). The protocol is registered in the Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42024498898.

Literature search

We searched MEDLINE (through PubMed), EMBASE, Epistemonikos, medRxiv and bioRxiv databases for the period from February 2020 to December 2023, without search restrictions. The Medical Subject Heading (MeSH) and search query used were: "("COVID-19" OR "SARS-CoV-2" OR "coronavirus disease 2019") AND ("treatment", "nirmatrelvir-ritonavir", "molnupiravir", "remdesivir", "convalescent plasma", "monoclonal antibodies") AND ("rebound/virologic rebound").

Type of studies, interventions, outcomes and data extraction

We planned to include studies evaluating rates of virologic rebound in individuals with a confirmed diagnosis of COVID-19 receiving treatment with antiviral agents, monoclonal antibodies, CP or no treatment. When available, we also extracted rate of "clinical rebound", or

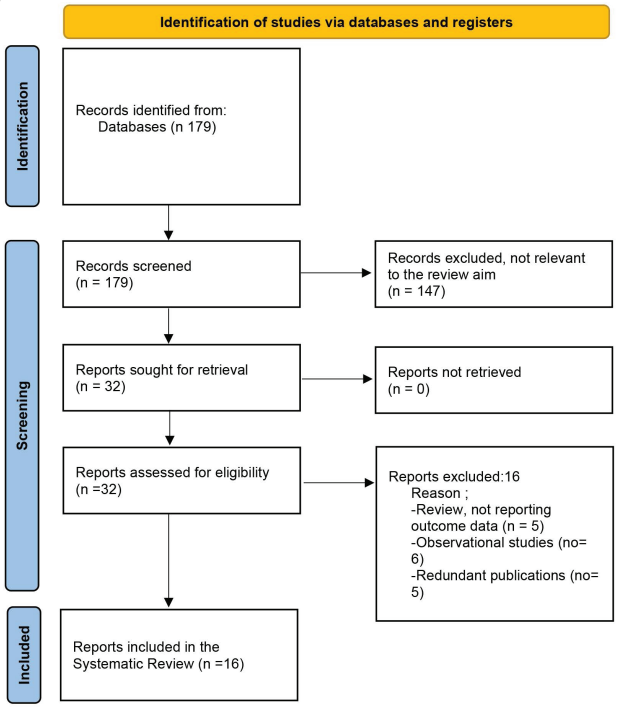

Figure 1 - Flow chart of the study selection process

other clinical outcomes (e.g., progression of disease, need of hospitalization, death). Only comparative studies (both randomized clinical trials and controlled cohort studies) were considered for the analysis. Case reports, case series, and review articles were excluded from the analysis. We included trials that enrolled participants with disease of any severity.

All titles were screened by two assessors (MC and IP). Eligibility assessment was based on the title or abstract and on the full text if required. Full texts of possibly eligible articles were obtained and assessed independently by two reviewers (MC and IP). Both reviewers compared the articles identified. The two assessors also independently extracted quantitative and qualitative data from each selected study, with disagreements resolved through discussion and on the basis of the opinion of a third reviewer (FM). The following parameters were extracted from each study: study design and periods, characteristics of COVID-19 patients and setting (hospitalized or not), main characteristic in the experimental group and in controls, sample size, and main results.

Assessment of methodological quality of included studies

Two review authors (MC and IP) independently assessed the risk of bias of each study included following the domain-based evaluation described in the Cochrane Handbook for Systematic Reviews of Interventions[17]. Within-trial risk of bias was assessed using the Cochrane Risk of Bias 2 (ROB 2) tool for randomized controlled trials (RCT) and the Risk of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) tool for non-RCT[17]. The Cochrane ROB tool for RCT addresses five specific domains: sequence generation and allocation concealment, blinding, incomplete data, selective outcome reporting, and other issues relating to bias. The methodological quality of observational studies is assessed with the ROBINS-1 tool[18]. This tool includes seven specific bias pre-intervention and post-intervention domains. The domains are: (i) confounding; (ii) selection of participants; (iii) classification of intervention; (iv) deviation from interventions (or biases that arise when there are systematic differences between the care provided to experimental intervention and comparator groups, beyond the assigned interventions); (v) missing outcomes; (vi) measurement of outcomes; and (vii) selection of reported result overall. For both RCT and non-RCT we have presented our assessment of risk of bias using two summary figures: (i) a summary of bias for each item across all studies and (ii) a cross-tabulation of each trial by all the "risk of bias" items.

"Summary of findings" tables

For the outcome virologic rebound, we used the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the quality of the body of evidence associated with this outcome and constructed "Summary of findings" tables using REVMAN 5.4[19,20]. These tables present key information concerning the certainty of evidence, the magnitude of the effects of the interventions examined, and the sum of available data for the main outcomes. The "Summary of findings" tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE approach, which defines the certainty of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The certainty of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias.

Statistical methods

The treatment effect was measured as a risk ratio (RR) with a 95% confidence interval (95% CI). The study weight was calculated using the Mantel-Haenszel method. We explored clinical heterogeneity and assessed statistical heterogeneity using the I^2 statistic, which examines the percentage of total variation across studies that is due to heterogeneity rather than to chance. If significant heterogeneity was detected, a random effect method of study weight calculation was performed. Calculations were done with REVMAN 5.4.

RESULTS

The main characteristics of the 16 included studies (3 RCT and 13 comparative, non-RCT) are summarized in **Table I**. Data on SARS-CoV-2 virologic rebound were available from 24 reports, ten reporting rates of virologic rebound in nirmatrelvir-ritonavir recipients compared to untreated patients, four in molnupiravir recipients compared to untreated patients, nine in nirmatrelvir-ritonavir recipients compared to

Table I - *Main characteristics of the studies included in the review*

First author [ref]	Study design and study period	Comparisons	Rebound related Outcomes	Risk factors	Main results
Wang [7]	Retrospective cohort of nation-wide electronic health records, with propensity-score matching. Between January and June 2022	13,644 COVID-19 pts, treated with NR (No.=11,270) or with MOV (No.=2,374) within 5 days of their COVID-19 infection	Three types of COVID-19 rebound outcomes (COVID-19 infections, COVID-19 related symptoms, and hospitalizations) were examined	After propensity-score matching, there were no significant differences in COVID-19 rebound risks between NR and MOV	There were no significant differences in COVID-19 rebound risks (infection, symptoms and hospitalization) between NR and MOV: COVID-19 rebound occurred both after NR and MOV, especially in pts with underlying medical conditions
Smith-Jeffcoat [9]	Individuals included in this analysis were drawn from a prospective COVID-19 case-ascertained household transmission study in the United States, March 2022-May 2023	130 outpatients receiving NR and 241 untreated pts. Participants who reported taking MOV, RDV, BEB, or >1 COVID-19 medication were excluded	Virologic and clinical rebound	Propensity score matching was used to selected treated and untreated pts. Treated and untreated participants had similar baseline characteristics	NR treated participants had greater occurrence of symptom rebound (32% *vs* 20%; p=0.009) and viral load rebound (27% *vs* 7%; p<0.001)
Alupo [10]	Randomized open-label clinical trial. Participants were hospitalized, and enrolled between September and December 2020	Convalescent plasma + standard of care (69 pts) *vs* standard of care (67 pts)	VR	Rebound cases were more prevalent among pts who had at least one co-morbidity, with HIV co-infected pts having the highest rebound rates	There was no difference in the rebound rates in the study arms; participants with hypertension had higher rebound rates compared to those with other comorbidities
Edelstein [14]	Prospective observational cohort studies, from March 2022 to May 2023. Ambulatory pts	NR (72 pts) or no treatment (55 pts)	Primary: VR within 20 days of the participant's initial positive test result; Secondary: viral load measurements on days 5, 10, and 14. VR defined as a viral load at days 10 and 14 of at least 2.7 $\log_{10}$ copies/mL and at least 0.5 $\log_{10}$ copies/mL greater than the result at day 5. Clinical rebound also reported	Participants in NR were older, received more COVID-19 vaccinations, and more commonly had immunosuppression. In multivariable models, only NR use was associated with VR (adjusted odds ratio, 10.02 [CI: 1.13 to 88.74]; p=0.038)	15 participants taking NR had VR *vs* 1 untreated. Eight of 16 participants with VR also reported symptom rebound; 2 were completely asymptomatic
Harrington[21]	MMWR reporting data from 2 RCT (EPIC-HR-and EPIC-SR trials)[21,38]. In pre-omicron and omicron periods; outpatients	NR (1,532 pts) *vs* placebo (1,511 pts)	VR at days 10 and 14, and clinical rebound	Pts from EPIC-HR and the 2021/ pre-omicron and 2022/omicron enrolment periods of EPIC-SR. Patient characteristics were similar in the two groups	Rates of VR were similar between NR and placebo recipients. Viral RNA rebound after NR treatment was not associated with COVID-19-related hospitalization or death
Dai [22]	A prospective observational study of 36 outpatients newly diagnosed with SARS-CoV-2 infection. Between March and May 2022	NR (11 pts) and untreated (25 pts)	VR	Participants in the NR group were older (44 *vs* 16 years) and more likely to have comorbidities; there was a median of 3 prior COVID-19 vaccine doses in both groups. All sequenced viruses were BA.2 or a sub-lineage	One out of 25 individuals in the untreated group (4%) had VR compared to 3 out of 11 (27%) in the NR group. One case of NR-associated rebound was asymptomatic

COVID-19: coronavirus disease 2019; NR: nirmatrelvir- ritonavir; MOV: molnupiravir; pts: patients; BEB: bebtelovimab; MMWR Morbidity and Mortality Weekly Report; VR: virologic rebound; HIV: human immunodeficiency virus; RCT: randomized controlled trial; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; ICU: intensive care unit; RDV: Remdesivir.

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Table I - *Main characteristics of the studies included in the review (follows from previous page)*

First author[ref]	Study design and study period	Comparisons	Rebound related Outcomes	Risk factors	Main results
Li[23]	A cohort of hospitalized adult pts with mild-to-moderate COVID-19 at high risk of progression to severe disease. Between 5 March and 5 April 2022	258 pts treated with NR and 224 nontreated pts. Pts included in this analysis were not treated with any other COVID-19-specific medications such as RDV or monoclonal antibodies	VR	Pts in the treatment group were on average 4 years younger and had 1 fewer day of delay between symptom onset and hospitalization. They were more likely to smoke but less likely to have diabetes or hypertension than nontreated pts	COVID-19 recurrence occurred in 2 pts in the treatment group and in 3 pts in the control group
Pandit[24]	A prospective, observational study between August and November 2022. Participants (outpatients) were assigned to the treatment or control group based on their decision to take NPR	127 in the NR group and 43 in the control group	Viral and symptoms rebound	There were no notable differences in age, gender, preexisting conditions, between groups, but there was a higher rate of white participants in NR group compared to controls	VR incidence was 14.2% in the NPR treatment group and 9.3% in the control group. Symptom rebound incidence was higher in the treatment group (18.9%) compared to controls (7.0%)
Schilling[25]	A RCT (Platcov). Between June 2022 and 2023. The laboratory team were masked to treatment allocation and the clinical investigators were masked to the virology results until the study group was terminated	209 outpatients were enrolled and concurrently randomly assigned to MOV (No.=65), ritonavir-boosted nirmatrelvir (No.=59), or no study drug (No.=85)	VR was an exploratory outcome. Clinical rebound also reported	Two pts were excluded from the analyses because they withdrew from the study on day 0, resulting in a modified intention-to-treat population of 207	VR occurred more frequently following NR (6 of 58) compared with the no study drug (1 of 84; p=0.018) or MOV (1 of 65; p=0.051). Of these 8 pts, 3 reported evidence of symptom rebound, all in the ritonavir-boosted nirmatrelvir group
Wong CKH[26]	A retrospective cohort study of hospitalized pts with a confirmed diagnosis of COVID-19. From February to July 2022 (during the omicron BA.2.2 variant wave)	MOV (No.=563), NR (No.=242), or no oral antiviral treatment (No.=3,787), for a total of 4,592 pts with non-oxygen-dependent COVID-19 at baseline	VR	More pts in the NR and control groups received concomitantly RDV and immunomodulators compared to MOV recipients. In a post-hoc logistic regression adjusting for potential baseline confounders, no significant difference in the incidence of viral burden rebound was observed across the three groups. Immunocompromised status was associated with increased odds of viral burden rebound across the groups, regardless of antiviral treatment	The incidence of viral burden rebound did not differ significantly across the 3 groups (16 of 242 pts [6.6%] receiving NR, 27 of 563 [4.8%] receiving MOV, and 170 of 3,787 [4.5%] in the control group). Viral burden rebound was not associated with adverse clinical outcomes (death or ICU admission or need of mechanical ventilation)
Tadmor[27]	A retrospective cohort study of COVID-19 pts with chronic lymphocytic leukemia from electronic records. From January to September 2022	NR (89 pts), MOV (23 pts), no treatment (219 pts). 28 pts also received monoclonal antibodies (tixagevimab/cilgavimab)	VR	A multivariate regression model was used to evaluate the association between covariates (myeloproliferative disorders, antivirals, and monoclonal antibodies) and rebound	There were 2 rebounds in MOV recipients, 8 in NR recipients, and 8 in untreated pts. In the multivariate analysis, independent predictors of rebound were myeloproliferative disorders and use of antivirals. No hospitalizations or deaths during rebound were observed

COVID-19: coronavirus disease 2019; NR: nirmatrelvir- ritonavir; MOV: molnupiravir; pts: patients; BEB: bebtelovimab; MMWR Morbidity and Mortality Weekly Report; VR: virologic rebound; HIV: human immunodeficiency virus; RCT: randomized controlled trial; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; ICU: intensive care unit; RDV: Remdesivir.

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Table I - *Main characteristics of the studies included in the review (follows from previous page)*

First author[ref]	Study design and study period	Comparisons	Rebound related Outcomes	Risk factors,	Main results
Chen[28]	Retrospective cohort studies, between April and May 2022	NR (58 pts) and MOV (27 pts)	VR, symptoms rebound	Pts receiving NR were younger, had better renal function, fewer risk factors for disease progression, and lower levels of inflammatory markers compared to those receiving MOV. Logistic regression analyses were performed to analyze the risk factors for VR among pts receiving oral antiviral agents. For sensitivity analyses; only univariable logistic regression analysis were performed due to relatively small numbers of VR and total pts. Initial lymphopenia was associated with VR after antivirals among the overall population	The overall proportion of VR (No.=11) was 12.9%. VR was more common among pts receiving NR No.=10 *vs* No.=1. Of them, 5 patients experienced symptomatic rebound
Han[29]	Prospective cohort study in Korea between August and November 2022. Outpatient setting. The predominant variant was the omicron subvariant BA.5	Among the 150 pts, 93 (62%) and 57 (38%) received NR therapy and MOV, respectively	VR, symptom score during rebound	Patients taking MOV were more likely to have diabetes, chronic kidney disease, and solid organ transplants than those taking NR. Regardless of type of antiviral therapy, high initial symptom scores were associated with more frequent rebound	There was no significant difference in the clinical rebounds associated with NR and MOV therapy: 5/93 (5.4%) of NR recipients and 6/57 (10.5%) of MOV recipients
Quian[30]	A retrospective cohort study among outpatients. with a pre-existing systemic autoimmune rheumatic disease, who had COVID-19 onset between January and May, 2022	Overall, 704 pts: 307 received NR, 105 monoclonal antibodies, 7 MOV, 5 combination therapy (including RDV) and 278 were untreated. Rebound data available only for NR and MOV recipients	VR	Pts who received outpatient treatment were more likely to be female (78% *vs* 74%) and white (86% *vs* 80%), less likely to have severe kidney impairment (1% *vs* 3%), and less likely to be unvaccinated (2% *vs* 6%) than those who received no outpatient treatment	Among 311 pts who received NR, 24 (7.7%) had COVID-19 rebound. Among seven pts who received MOV, one (14.3%) had COVID-19 rebound. No rebound data available for the remaining pts
Tiseo[31]	Prospective observational study between January 2022 and July 2022	562 outpatients:114 (20.3%) received MOV, 252 (44.8%) NR, and 196 (34.9%) 3-day RDV	VR	Pts who received RDV were older, more frequently had more than two comorbidities, were more frequently affected by cardiovascular disease, and were more commonly solid organ transplant recipients compared with pts in the orally administered antiviral treatment groups. Adequate COVID-19 vaccination status was higher in pts treated with NR	Overall, 7 (1.3%) pts reported a rebound of symptoms after the complete course of antivirals: 2/109 (1.8%) in the NR group and 5/236 (2.1%) in the MOV group. No rebound in RDV recipients

COVID-19: coronavirus disease 2019; NR: nirmatrelvir- ritonavir; MOV: molnupiravir; pts: patients; BEB: bebtelovimab; MMWR Morbidity and Mortality Weekly Report; VR: virologic rebound; HIV: human immunodeficiency virus; RCT: randomized controlled trial; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; ICU: intensive care unit; RDV: Remdesivir.

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Table I - *Main characteristics of the studies included in the review (follows from previous page)*

First author[ref]	Study design and study period	Comparisons	Rebound related Outcomes	Risk factors,	Main results
Wong GLH[32]	A territory-wide, retrospective cohort study of 12,629 hospitalized pts, from January to March 2022	MOV (746 pts), NR (195 pts), no treatment (11,688 pts)	VR, deaths	At baseline, compared with antiviral nonusers, MOV or NR users were older and had more comorbidities, including digestive diseases, diabetes, history of malignant tumor, and lower complete vaccination rate. Compared with NR users, MOV users were older and had more cardiovascular diseases, diabetes, cerebrovascular events, respiratory diseases, and kidney diseases, as well as a lower complete vaccination rate	VR occurred in 68 nonusers (0.6%), 2 NR users (1.0%), and 6 MOV users (0.8%). Among 76 pts with VR, 12 of 68 nonusers, 1 of 6 MOV users, and neither of the NR users died of COVID-19.

COVID-19: coronavirus disease 2019; NR: nirmatrelvir- ritonavir; MOV: molnupiravir; pts: patients; BEB: bebtelovimab; MMWR Morbidity and Mortality Weekly Report; VR: virologic rebound; HIV: human immunodeficiency virus; RCT: randomized controlled trial; SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; ICU: intensive care unit; RDV: Remdesivir.

molnupiravir recipients, and one in CP recipients compared to untreated patients[7,9,10,14,21-32]. Data on clinical rebound were available from seven trials, five reporting rates of virologic rebound in nirmatrelvir-ritonavir recipients compared to untreated patients, and two in nirmatrelvir-ritonavir recipients compared to molnupiravir recipients[7,9,21,23-25,31].

Sixteen reports, including five with already reported data, four not reporting rates of rebound, and six observational studies were excluded from the analysis[5,6,8,11-13,33-42].

Methodological quality of included studies

The methodological quality of studies, as assessed by the ROB 2 tool for RCT and ROBIN-1 tool for non-RCT was summarized in risk of bias graphs (*Supplementary* **Figure S1**).

Risk of bias and heterogeneity in included studies

With regard to randomized studies: we assessed the EPIC HR and HS trials to be at low risk of bias. The study by Schilling *et al*. was assessed to be at high risk of performance bias (open label) and at unclear risk of attrition bias (viral rebound reported, although the study was not designed to characterize this fully)[21,25]. The study by Alupo *et al*. was assessed to be at high risk of performance bias (open label) and at unclear risk of selection, detection, attrition and other bias[10].

With regard to the cohort studies, all these studies but one[9] were judged to be at high risk and/or at unclear risk of bias for selection and confounding, mostly because there were several unbalanced characteristics at admission between groups, often because the variable that was being examined to predict the outcome of interest also predicted whether an individual received one or the other interventions of interest. However, in five studies, control for confounding was performed through multiple logistic regression or propensity score matching[7,9,14,26,27]. Most of the cohort studies were judged at low risk of bias for the domains of measurement classification of interventions, deviation from intended interventions, missing data and measurements of outcomes.

There was moderate/substantial heterogeneity for the outcome "virologic rebound" in the comparison between nirmatrelvir-ritonavir recipients and untreated patients (I^2=59%) and considerable heterogeneity for the outcome "clinical rebound" for the same comparison (I^2=84%). For these comparisons, we performed subgroup analyses according to the presence of selection bias

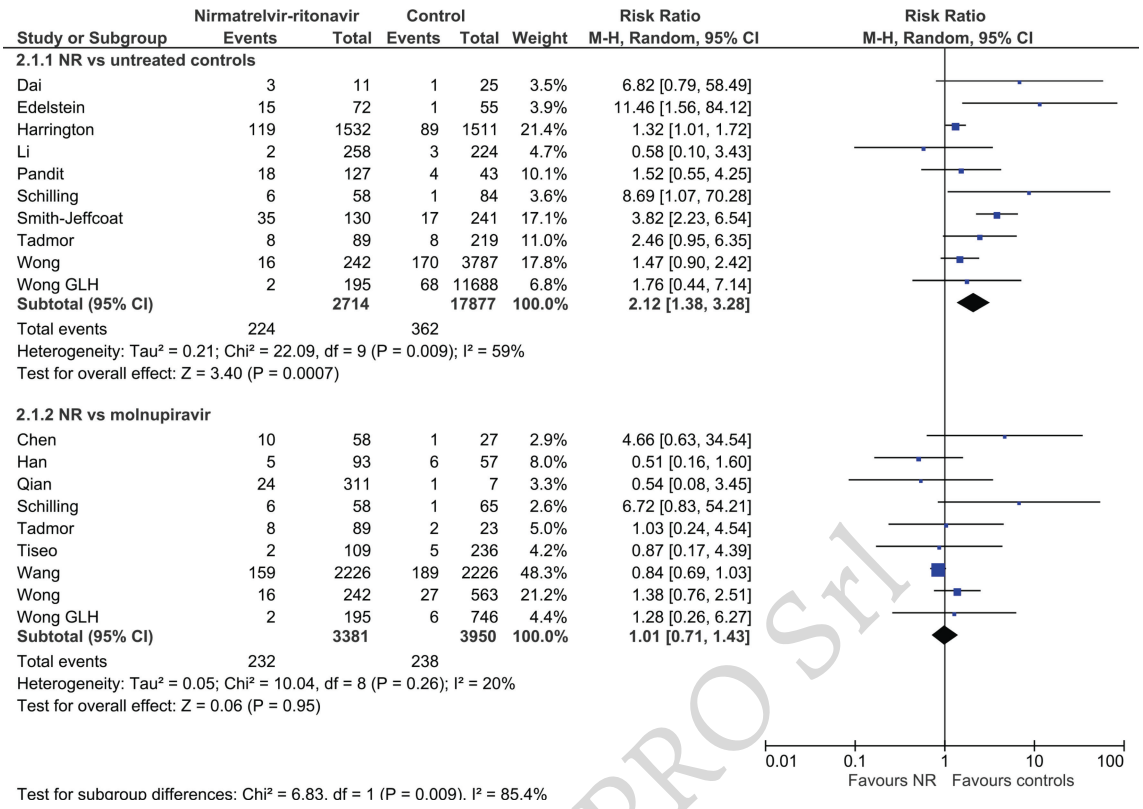

Figure 2 -Forest plots of comparisons. Rates of virologic rebound in nirmatrelvir-ritonavir recipients compared to untreated patients (analysis 2.1.1) and to molnupiravir recipients (analysis 2.1.2)
M-H: Mantel-Haenszel; 95% CI: 95% confidence interval; NR: nirmatrelvir-ritonavir.

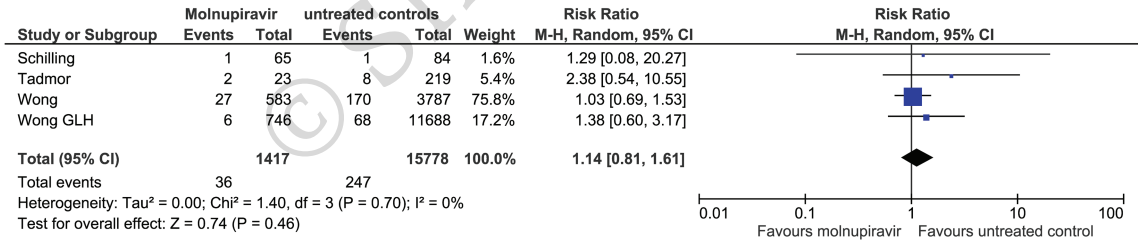

Figure 3 - Forest plots of comparisons. Rates of virologic rebound in molnupiravir recipients compared to untreated patients
M-H: Mantel-Haenszel; 95% CI: 95% confidence interval.

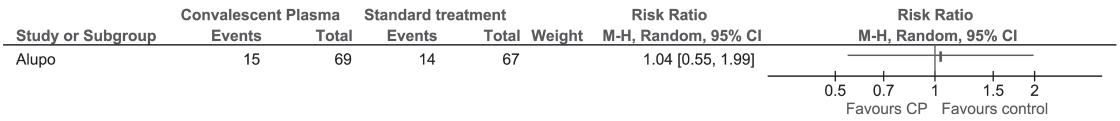

Figure 4 - Forest plots of comparisons. Rates of virologic rebound in recipients of convalescent plasma compared to control
M-H: Mantel-Haenszel; 95% CI: 95% confidence interval; CP: convalescent plasma.

and confounding, underlying risk factors at baseline, study size (< or >100 participants) and timing of the study (retrospective or prospective). However, these factors had little influence on the effect size and I^2 value. For other comparisons statistical heterogeneity was not important or not applicable.

Effects of interventions

Forest plots of the comparisons for virologic rebound are shown in **Figures 2-4**, and for clinical rebound in **Figure 5**.

Virologic rebound

The occurrence of virologic rebound was more commonly observed among nirmatrelvir recipients than among untreated patients (RR=2.12; 95% CI: 1.38-3.28; p=0.0007). These data were reported from two RCT and eight cohort studies (4 with propensity logistic regression/propensity score matching); the level of certainty of the evidence was graded as low due to risk of bias and inconsistency (I^2=59).

No differences were observed in the occurrence of virologic rebound between nirmatrelvir-ritonavir and molnupiravir recipients (RR=1.01; 95% CI: 0.71-1.43): the data were from one RCT and eight cohort studies (3 with logistic regression/propensity score matching). The level of certainty of the evidence was graded as moderate due to risk of bias (**Table II**). Likewise, similar rates of virologic rebound were observed in molnupiravir recipients and untreated patients (RR=1.14; 95% CI: 0.81-1.61) from four trials (1 RCT, 3 cohort studies) (moderate levels of certainty due to risk of bias).

The study by Alupo *et al*. compared the occurrence of virologic rebound between patients receiving standard of care with or without CP[10]. No differences in the rate of virologic rebound were observed between the groups (RR=1.04, 95% CI: 0.55-1.99), and this was graded as low-level of evidence due to risk of bias and imprecision (small size study and low number of events).

Clinical rebound

This outcome was reported in seven trials, five (including 2 RCT) evaluating nirmatrelvir-ritonavir

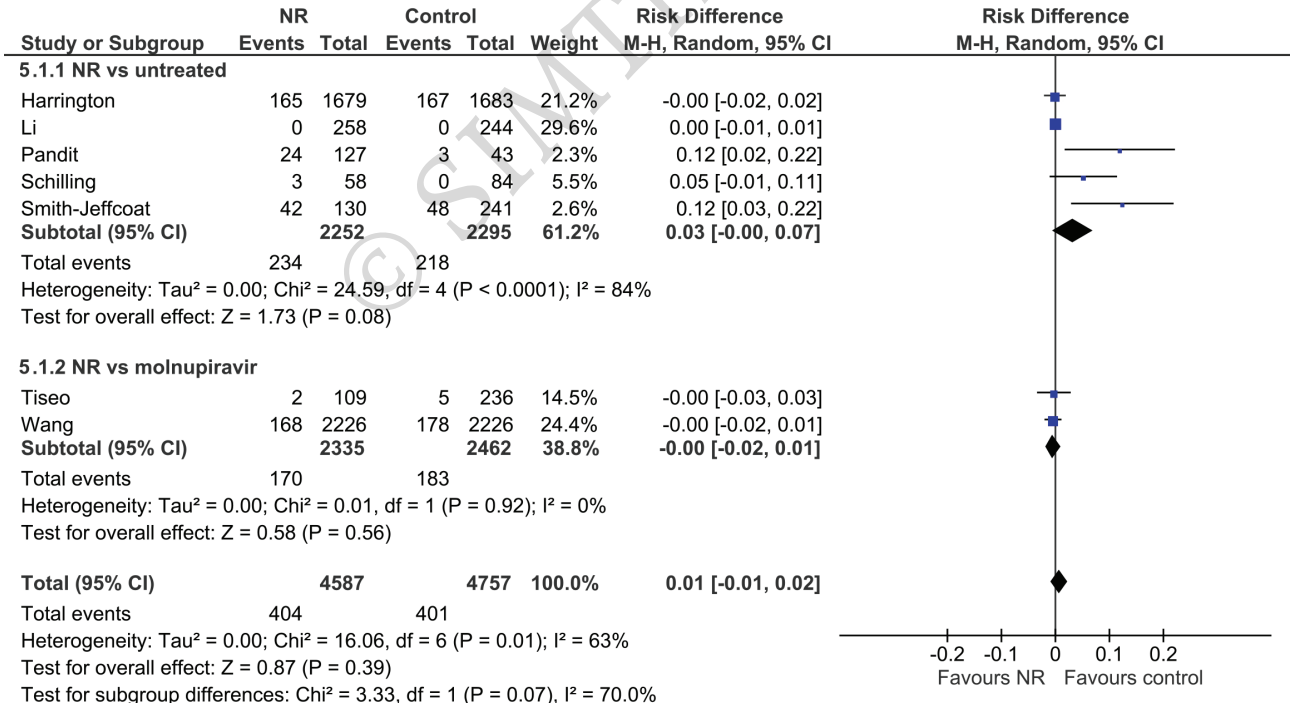

Figure 5 - Forest plots of comparisons. Rates of clinical rebound in nirmatrelvir-ritonavir recipients compared to controls (untreated patients (analysis 5.1.1) and molnupiravir recipients (analysis 5.1.2)
M-H: Mantel-Haenszel; 95% CI: 95% confidence interval; NR: nirmatrelvir-ritonavir.

Table II - *Summary of findings*

- ***Patient or population:*** **COVID-19 infected subjects.**
- ***Settings:*** **inpatients and outpatients.**
- ***Comparison:*** **rates of virologic rebound and clinical rebound among COVID-19 infected individuals receiving nirmatrelvir-ritonavir, molnupiravir, convalescent plasma or no treatment.**

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	N. of participants (study)	Quality of evidence (GRADE)	Comments
	Assumed risk in the control group	Corresponding risk in the intervention group				
Virologic rebound						
Nirmatrelvir-ritonavir *vs* untreated patients	362/17,887 (2.0 %)	4.2 % (2.7-6.5)	RR 2.12 (1.38-3.28)	20,591 (10)	⊕⊕⊖⊖ **low**[1]	There was evidence that nirmatrelvir-ritonavir recipients had higher rate of virologic rebound compared to untreated subjects
Nirmatrelvir-ritonavir *vs* molnupiravir	238/3,950 (6.0 %)	6.0 % (4.2-8.5)	RR 1.01 (0.71-1,43)	7,331 (9)	⊕⊕⊕⊖ **moderate**[2]	No significant differences in virologic rebound between nirmatrelvir-ritonavir and molnupiravir recipients
Molnupiravir *vs* untreated patients	247/15,778 (1.5 %)	1.71 % (1.2-12.4)	RR 1.14 (0.81-1.61)	16,595 (4)	⊕⊕⊕⊖ **moderate**[2]	No significant differences in virologic rebound between molnupiravir recipients and untreated patients
Convalescent plasma + SOC *vs* SOC without convalescent plasma	14/67 (20.8 %)	21.6 % (11.4-41.3)	RR 1.04 (0.55-1.99)	139 (1)	⊕⊕⊖⊖ **low**[3]	No significant differences in virologic rebound between convalescent plasma recipients and controls
Clinical rebound						
Nirmatrelvir-ritonavir *vs* no treatment	218/2,295 (9.4 %)	Clinical rebound was 3 % higher (from 0 to 7 % higher)	RD 0.02 (0.00-0.07)	4,547 (5)	⊕⊕⊖⊖ **low**[4]	Higher rate of clinical rebound in nirmatrelvir-ritonavir recipients compared to untreated pts., but the difference is not statistically significant.
Nirmatrelvir-ritonavir *vs* molnupiravir	183/2,462 (7.4 %)	Clinical rebound was 7.4 % (from 2 % lower to 1 % higher)	RD –0.0 (–0.02/0.01)	4,797 (2)	⊕⊕⊕⊖ **moderate**[2]	No significant differences of clinical rebound between nirmatrelvir-ritonavir and molnupiravir recipients

*The assumed risk is the mean control group risk across studies. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
GRADE Working Group grades of evidence: **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** 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 quality:** We are very uncertain about the estimate.
[1]Downgraded for ROB (mostly confounding and selection) and inconsistency due to heterogeneity (I^2=59). [2] Downgraded for ROB. [3]Downgraded for ROB and imprecision (small number of participants). [4]Downgraded for ROB and inconsistency (I^2=85). CI: confidence interval; RR: risk ratio; RD: risk difference; SOC: standard of care; ROB: risk of bias.

and untreated patients, and two observational studies evaluating nirmatrelvir-ritonavir and molnupiravir between nirmatrelvir-ritonavir and untreated patients there was a trend favoring a higher rate of clinical rebound of COVID-19 symptoms among nirmatrelvir-ritonavir recipients compared to untreated patients (risk difference=0.02; 95% CI: 0.00-0.07; p=0.08) (low certainty of evidence due to risk of bias and inconsistency [I^2=84]). Data from an observational study did not report symptom rebound in remdesivir recipients[31].

Other outcomes

Results from an observational study showed that among 76 patients with viral rebound, 12 of 68 patients not receiving antiviral agents, one of six molnupiravir recipients, and

neither of the two nirmatrelvir-ritonavir recipients died of COVID-19[32]. No progression of disease or deaths were reported among patients who experienced rebound in the remaining trials.

DISCUSSION

While many small molecules were repurposed as antiviral agents during the early stages of the COVID-19 pandemic, oral antivirals developed against SARS-CoV-2 for outpatients were not authorized and available until December 2021, when nirmatrelvir-ritonavir and molnupiravir were approved[3,38,43]. Shortly after, intravenous remdesivir was also approved for outpatient use[44]. In December 2021, nearly 2 years after the first use of CP, the Food and Drug Administration approved outpatient use of CP, but only for immunocompromised patients[45,46]. While monoclonal antibodies have been withdrawn due to resistance of viral variants BQ.1.* and XBB.*[3,47,48], other antiviral agents (e.g., nirmatrelvir-ritonavir, remdesivir, molnupiravir) are still advised for treating COVID-19. For more than 1 year (January 2020-March 2021), COVID-19 CP, collected from individuals who have recovered from SARS-CoV-2 infection, represented the only specific, antibody-based passive immunotherapy available against this potentially life-threatening viral disease[49]. Additionally, there has been renewed interest in the clinical use of CP in immunocompromised patients as the new variants of SARS-CoV-2 have emerged[50].

Concerns have been raised about rebound COVID-19 infections, which occur between 2 and 8 days following the cessation of antiviral treatment[8]. Population data from the USA showed that COVID-19 rebound is not unique to nirmatrelvir-ritonavir recipients, but it is also observed in molnupiravir recipients, and has been reported in patients who did not receive any antiviral treatment and in patients receiving CP[5-10]. To enhance our understanding of COVID-19 rebound, we have performed a systematic review and meta-analysis of the available evidence. Data on SARS-CoV-2 rebound were available from 16 trials (3 RCT and 13 non-RCT) reporting rates of virologic rebound and/or clinical rebound in patients treated with antiviral agents (nirmatrelvir-ritonavir or molnupiravir, and in 1 trial also remdesivir), in patients not receiving treatment and in CP recipients. The results of our analysis show that the occurrence of virologic rebound was more common among nirmatrelvir-ritonavir recipients than among untreated patients (RR=2.12; 95% CI: 1.38-3.28; p=0.0007; low certainty of evidence), while no difference was observed between nirmatrelvir-ritonavir and molnupiravir recipients (RR=1.01; 95% CI: 0.71-1.43; moderate level of certainty); similar rates of virologic rebound were observed in molnupiravir recipients and untreated patients (RR=1.14; 95% CI: 0.81-1.6; moderate level of certainty). One study compared the occurrence of virologic rebound between patients receiving standard of care with or without CP, and found no differences in the rate of virologic rebound between the groups (RR=1.04, 95% CI: 0.55-1.99; low level of evidence)[10]. The outcome clinical rebound was reported in five trials evaluating nirmatrelvir-ritonavir and untreated patients, and in two observational studies evaluating nirmatrelvir-ritonavir and molnupiravir recipients. No statistically significant differences between groups were observed, although in the comparison between nirmatrelvir-ritonavir-treated and untreated patients there was a trend favoring a higher rate of clinical rebound of COVID-19 symptoms among nirmatrelvir-ritonavir recipients compared to untreated patients (risk difference=0.02; 95% CI: 0.00-0.07; p=0.08; low certainty of evidence).

People receiving antiviral treatment might be at higher risk of rebound compared with people not receiving treatment because of host factors or treatment-induced viral suppression early in the course of illness. However, rebound has also been reported among people not receiving treatment, and might reflect viral fluctuation that is part of the natural disease process early in the course of illness.

Viral rebound might occur in people on antiviral treatment because they are at high risk of severe disease and might have host factors, such as immunosuppression, that contribute to the natural variability in viral dynamics[51]. Patients receiving antiviral treatment might be at higher risk for rebound given the viral suppression related to early treatment in the disease course, and resumption of viral replication after completion of treatment because of delayed viral clearance. This elevated risk could be due to early discontinuation of antiviral treatment or the need for longer courses of treatment among certain subjects,

such as those who are immunocompromised[27].

Of note, in the large majority of trials no associations were observed between rebound and progression of disease, hospitalization and death. Also, there was no evidence that rebound represents reinfection or resistance to treatment[24].

By late December 2021, the predominant variant was omicron[49,52]. Except in rare cases, the original version of omicron is no longer circulating, nor is the original strain of the SARS-CoV-2 virus and the early, more severe alpha and delta variants. Currently, there is a long list of circulating omicron subvariants, including more than a dozen XBB strains. With the exception of the study by Alupo *et al.*, and a subset of the Epic HR and SR studies[10,21,38] all the studies included in the current analysis were conducted in the omicron era. The study by Alupo *et al.* was conducted between September and December 2020, when the alpha variant was the variant of concern[10]. The Epic HR and SR trials started enrolling patients in July 2021 before the emergence of omicron, and were concluded in the omicron period[21,38].

The findings in this systematic review are subject to several limitations. First, standardized definitions for symptom, viral, and clinical rebound were not used across studies. Using standard definitions to accurately reflect outcomes could improve interpretability and comparisons of data across studies and settings. Another limitation is related to viral kinetics. The original EPIC-HR study assessed outcomes for patients at only two time points, while other studies tracked patients more frequently. As a consequence, not all the studies included in the current review captured the full extent of virologic rebound as the study by Edelstein *et al.* did[14]. In this latter study SARS-CoV-2 viral load was assayed three times a week for 2 weeks and weekly thereafter. Of note, viral rebound can occur in people who do and do not receive antiviral treatment, and might reflect viral fluctuation that is part of the natural disease process[37]. Moreover, few studies correlated symptoms with viral load, which makes the significance of recurrence of mild symptoms difficult to understand because symptoms are subjective and might not represent viral reactivation. Most of the included trials (13/16) were observational cohort studies, and were judged at high or unclear risk of bias for selection and confounding, mostly because there were several unbalanced characteristics at admission between groups, often because the variable that predicted the outcome of interest also predicted whether an individual received one or the other interventions of interest. However, to mitigate the risk of bias, five of the 13 observational studies performed multiple logistic regression or propensity score matching to control for confounding. Finally, ascertainment bias is also possible given that patients receiving antiviral treatment are closely followed, and more likely to report recurrent symptoms, which would explain the large availability of case reports being associated with nirmatrelvir-ritonavir, the most commonly used antiviral agent for COVID-19.

There was from moderate/substantial to considerable heterogeneity for the outcomes "virologic rebound" and "clinical rebound" in the comparison between nirmatrelvir-ritonavir heterogeneity for this outcome in the comparison between recipients and untreated patients. Factors that could potentially be responsible for the observed heterogeneity were the frequency of viral load measurements and definition of clinical rebound. For instance, as mentioned above, when the virologic analyses in the study by Edelstein *et al.*[14] were restricted to only three time points, as was done in the EPIC-HR study[38], viral rebound was detected in only three of 124 (2.4%) patients, and 13 of the 16 (81.2%) rebound events that were detected with more frequent specimen collections (3 times a week for 2 weeks and weekly thereafter), were not captured.

There was a large variability in the definition of clinical rebound[9,21,23-25]. Methods for determining symptom rebound varied across studies, from patient-reported records to predefined lists of symptoms, and not all the studies reporting it had clinical rebound as a predefined outcome. Hence, is not surprising that there was considerable heterogeneity for this outcome in the comparison between nirmatrelvir-ritonavir recipients and untreated patients.

Some individuals with viral rebound are reported to have culturable virus up to 16 days after the initial diagnosis and it is possible that transmission to close contacts may occur during the rebound period[12,13,33]. Additionally, the precise time therapy is initiated, within-host viral dynamics, individuals' specific response to treatment, and the timing of adaptive immunity play important roles

in determining whether viral rebound occurs[33]. These important factors vary from individual to individual and may explain why only some individuals show viral rebound after completing treatment. In the case of rebound following antiviral treatment, immune evasion due to early viral suppression has been hypothesized as a possible cause[48,52]. Otherwise, it is possible that antiviral exposure might be insufficient due to individual pharmacokinetics or insufficient duration or that SARS-CoV-2 persists in inaccessible sanctuary tissues[5,53,54]. Emergence of SARS-CoV-2 resistance to antiviral agents as a cause of viral rebound is unlikely, considering that in previous studies on COVID-19 rebound, resistance mutations were not identified[11]. In the current systematic review, no associations were observed between rebound and progression of diseases, hospitalization and death. Hence, despite the possibility of rebound, these data confirm the importance of continuing to offer antiviral treatment to individuals with COVID-19 who are at increased risk of progression to severe COVID-19.

AUTHORS' CONTRIBUTIONS

MC and IP conceived the study. MC determined the methodology, extracted data and prepared the original draft of the manuscript. IP and FM extracted data and reviewed and edited the manuscript. SP, VP and VDA reviewedand edited the manuscript. All the Authors have read and agreed to the published version of the manuscript.

The Authors declare no conflict of interests.

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title, line 2
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Lines 42-54
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Lines 54-56
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Lines 66-72
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Literature search, lines 61-64
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Lines 61-64
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Lines 66-76
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Lines 71-76
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Lines 66-68
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Lines 1067-70
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Assessment of methodological quality of included studies-lines 77-88
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Lines 99-102
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Lines 66-69
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	74-76
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Tables 1 and 2, fig 1-5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	REVMAN 5. ROB-2 and ROBIN 1

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Lines 100-102
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	GRADE assessment
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	GRADE assessment.
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	GRADE assessment
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Fig. 1, lines 104-109.
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Lines 110-111
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Suppl. Fig. 1. Graphs of ROB
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Forest plots, figures 2-5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Suppl. Fig. 1, lines 113-125
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Figg. 2-5, SOT table
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Effect of interventions, lines 126-onwards
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not performed
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not performed
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	SOT
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Lines 162-176
	23b	Discuss any limitations of the evidence included in the review.	Lines 186-201
	23c	Discuss any limitations of the review processes used.	Lines 186-201
	23d	Discuss implications of the results for practice, policy, and future research.	Lines 203-214
OTHER INFORMATION			
Registration and	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	A PROSPERO protocol has

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Table SI - *PRISMA 2020 checklist (follows from previous page)*

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
protocol			been registered. Lines 58-59
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Lines 58-59
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	No amendements were made
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Lines 328-329
Competing interests	26	Declare any competing interests of review authors.	No competing interest
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	All the templates used (from REVMAN, GRADE, PRISMA) are publicly available

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

Figure S1 - A) Risk of bias summary (ROBIN-1): review authors' judgements about each risk of bias item for each included non-randomized trial study. B) Risk of bias summary (ROB 2): review authors' judgements about each risk of bias item for each RCT included.