October 17th update

COVID-NMA

- Summary of Main Results -

Introduction

This is the 7th Summary of Main Results report from the COVID-NMA initiative. It provides an overview of the results as of **October 17th, 2022**, summarizing the evidence regarding treatment of hospitalized and non-hospitalized Covid-19 patients for which there is high or moderate certainty.

Over the past month (September 2022) we have revised all our certainty assessments, applying the **new approach proposed by the GRADE working group for assessing imprecision**[1]. While most of the certainty assessments did not change, some of the updates reported below will be due to these finetuned criteria.

Starting this month, we are including results not only referring to hospitalized patients, but we also present a second table with the results with high or moderate certainty for **outpatients**.

Given the slower pace at which studies are being published and their lower impact on the existing synthesised evidence, from now on we will be preparing these summaries **every three months**, instead of monthly. However, the results on the project's website (covid-nma.com) will continue to be updated every two weeks.

We are also excited to share that another research article arising from the COVID-NMA initiative has recently been published, assessing the *Transparency and reporting characteristics of COVID-19 randomized controlled trials*. A list of all scientific publications arising from the project can be found here.

As a reminder, in March 2022, the COVID-NMA initiative revised its protocol and reduced its scope: Only comparisons evaluating antivirals and immunomodulators have continued to be updated every two weeks (results for other interventions up to that date are still available on the website). Therefore, the most up to date results are available on covid-nma.com, and the list of studies pending data extraction is available here. Feel free to get in touch with us using our contact form and to disseminate this document on twitter (@Covid-NMA).

Updates since the previous report

Since the previous report (updated on September 5th) there have been the following relevant changes (**in addition to all the results related to outpatients**):

- In the updated assessment for **Anakinra**, the certainty associated with its effect on clinical improvement (around 60 days, which indicated little to no difference in the previous update), WHO score ≥ 7 (which indicated a reduction in the risk in the previous update) and adverse events (which indicated little to no difference in the previous update) are now low, and are therefore not reported in the table below any more. The moderate certainty evidence for this intervention therefore indicates that, in hospitalized patients, Anakinra probably reduces the risk of WHO score ≥7 (i.e. mechanical ventilation or death) around 60 days, and it probably results in little to no difference in the likelihood of clinical improvement around 28 days.
- In the updated assessment for **Baricitinib**, the certainty associated with its effect on all-cause mortality (around 28 days, which indicated a likely risk reduction) is now low, and is therefore not reported in the

[1] Schünemann HJ, Neumann I, Hultcrantz M, Brignardello-Petersen R, Zeng L, Murad MH, Izcovich A, Morgano GP, Baldeh T, Santesso N, Cuello CG. GRADE guidance 35: update on rating imprecision for assessing contextualized certainty of evidence and making decisions. Journal of Clinical Epidemiology. 2022 Aug 5.

table below any more. The evidence for the other outcomes remains with little changes: In hospitalized patients, Baricitinib results in little to no difference in clinical improvement around 28 days; it is likely to reduce the risk of WHO score ≥7 (i.e. mechanical ventilation or death, around 28 days) and the risk of all-cause mortality (around 60 days); and it probably does not increase the risk of adverse events but probably decreases the risk of serious adverse events.

- In the updated assessment for **Camostat Mesilate** all outcome results have low or very low certainty and this intervention has therefore been removed from the summary table below.
- In the updated assessment for **Convalescent plasma**, the certainty associated with its effect on WHO score ≥7 (which indicated little to no difference) is now low. The evidence for the remaining outcomes remains with little changes: Convalescent plasma probably results in little to no difference on clinical improvement around 28 days, the risk of WHO score ≥7 (i.e. mechanical ventilation or death) around 28 days, the risk of adverse events or all-cause mortality (around 28 days).
- Regarding **Corticosteroids**, there is now moderate certainty that they probably have little to no effect on the risk of adverse events. The evidence for the remaining outcomes remains with little changes: Corticosteroids probably increase clinical improvement (around 28 days) slightly and reduce the risk of all-cause mortality (around 28 days) in hospitalized patients.
- There is now moderate certainty for the effectiveness of **Favipiravir** on all-cause mortality (around 28 days), which is probably increased. This intervention has now been added to the summary table below.
- There is now moderate certainty for the effectiveness of **Hyperimmune anti-Covid-19 Intravenous Immunoglobulin** on WHO score ≥7 (around 28 days) and of all-cause mortality (around 28 days), which are probably reduced. This intervention has now been added to the summary table below.
- In the updated assessment for **Lopinavir + Ritonavir**, the certainty associated with its effect on clinical improvement (around 28 days) and viral negative conversion (both of which indicating that there were probably little to no effects of the intervention), is now low, and are therefore not reported in the table below any more. The moderate certainty evidence remaining indicates that this intervention probably results in little to no difference in the risk of all-cause mortality (around 28 days).
- There is now moderate certainty for the effectiveness of **Otilimab** on all-cause mortality (around 28 days), which is probably reduced, while there probably is little to no difference in the risk of adverse outcomes. There probably is no increased likelihood of clinical improvement (around 28 days). This intervention has now been added to the summary table below.
- In the updated assessment for **Remdesivir** there is now moderate certainty that this intervention has little to no effect on the likelihood of viral negative conversion. The other outcome for which there was already moderate certainty remains unchanged: it is probably that there is little to no difference in the risk of mortality around 28 days.
- In the updated assessment for **Ruxolitinib** all outcome results have low or very low certainty and this intervention has therefore been removed from the summary table below.
- In the updated assessment for **Sotrovimab**, the certainty associated with its effect on serious adverse events (which indicated a likely risk increase) is now low, and is therefore not reported in the table below any more. For this intervention there is now only moderate certainty in the results for clinical improvement (around 28 days), which indicate little to no difference.
- There is now moderate certainty for the effectiveness of **Nezulcitinib** (**TD-0903)** on all-cause mortality (around 28 days) and adverse events, which are probably reduced. This intervention has now been added to the summary table below.
- There is now moderate certainty in the effect of **Tocilizumab** on the risk of all-cause mortality around 60 days, which is probably reduced. This is consistent with the results indicating a reduced risk of all-cause mortality around 28 days. Tocilizumab has little to no effect on clinical improvement (around 28 days) and adverse events.
- There is now moderate certainty for the effectiveness of **Vilobelimab** on clinical improvement (around 28 days), and all-cause mortality around 28 days and around 60 days, which are all probably reduced. This intervention has now been added to the summary table below.

- There were other updates in the results for **Auxora** and **Canakinumab**, but they were only minor changes.

What is the current evidence regarding treatment of hospitalized Covid-19 patients?

Updated on October 17th, 2022

Pharmacologic treatments in hospitalized patients

Critical outcomes of interest: Clinical improvement (around day 28 or day 60), WHO Clinical Progression Score ≥ 7 (around day 28 or day 60), all-cause mortality (around day 28 or day 60), viral negative conversion (around day 7), adverse events and serious adverse events.

For most pharmacological treatments in hospitalized patients, the certainty of the evidence is still low or very low. Below is a summary of pharmacological interventions that have **results in favor of a beneficial effect** compared with placebo or standard care. We only highlight outcomes of moderate and high certainty; other outcomes are of low or very low certainty.

- **Anakinra** (a monoclonal antibody) probably reduces the risk of WHO score ≥7 (i.e. mechanical ventilation or death) around 60 days in hospitalized patients. It probably results in little to no difference in the likelihood of clinical improvement around 28 days . It is one of the interventions that have been authorized in the EU to treat Covid-19.
- **Baricitinib** (a kinase inhibitor) results in little to no difference in clinical improvement around 28 days. It is likely to reduce the risk of WHO score ≥7 (i.e. mechanical ventilation or death, around 28 days) and the risk of all-cause mortality (around 60 days). It probably does not increase the risk of adverse events and probably decreases the risk of serious adverse events.
- **Casirivimab + Imdevimab (REGN-COV2)** (Monoclonal antibody combination) probably reduces the risk of all-cause mortality (around 28 days), although there is little to no effect on the likelihood of clinical improvement around 28 days and around 60 days. It is one of the interventions that have been authorized in the EU to treat Covid-19.
- **Corticosteroids** increase clinical improvement (around 28 days) slightly and reduce the risk of all-cause mortality (around 28 days) in hospitalized patients, with probably little to no risk increase in adverse events. We pooled together oral and intravenous corticosteroids of participants with various disease severity. Of note, the largest study (the RECOVERY trial) found in subgroup analysis that “differences in mortality varied considerably according to the level of respiratory support that the patients were receiving at the time of randomization”, and that “the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support.”
- **Hyperimmune anti-Covid-19 Intravenous Immunoglobulin** (an immunomodulator) probably reduces the risk of WHO score ≥7 (around 28 days) and of all-cause mortality (around 28 days).
- **Otilimab** (a monoclonal antibody) is likely to reduce the risk of all-cause mortality (around 28 days), while there probably is little to no difference in the risk of adverse outcomes. There probably is no increased likelihood of clinical improvement (around 28 days).
- **Nezulcitinib (TD-0903)** (a kinase inhibitor) is likely to reduce the risk of all-cause mortality around 28 days, as well as the risk of adverse events.
- **Tocilizumab** (a monoclonal antibody) reduces the risk of all-cause mortality around 28 days and is likely to reduce all-cause mortality around 60 days in hospitalized patients, although it probably results in little to no difference on clinical improvement around 28 days. It probably results in little to no difference in the risk of adverse events. It is one of the interventions that have been authorized in the EU to treat Covid-19.
- **Vilobelimab** (a monoclonal antibody) probably increases the likelihood of clinical improvement (around 28 days) and probably reduces the risk of all-cause mortality around 28 days and around 60 days.

For the treatments below there are outcomes with moderate or high certainty indicating **uncertainty of benefit or harm**

- We found that for **Remdesivir** (an anti-viral), which is one of the interventions recommended by the NIH and which has been authorized in the EU to treat Covid-19, the risk estimate for all-cause mortality (around 28 days) and its wide confidence interval (RR 0.91, 95% CI 0.74 to 1.11) point to uncertainty of benefit or harm. It probably results in little to no increase in viral negative conversion (around 7 days).

For the treatments below there are outcomes with moderate or high certainty indicating **no evidence of beneficial effects** (e.g. clinical improvement or reduction in mortality) or an increase in the risks of negative effects (e.g. serious adverse events) compared with placebo or standard care:

- **Auxora** (an immunomodulator) probably decreases the risk of serious adverse events, but evidence regarding its effectiveness has still very low certainty.
- **Bamlanivimab** (a monoclonal antibody) probably results in little to no difference on clinical improvement around day 60.
- **Canakinumab** (a monoclonal antibody) probably results in little to no difference on clinical improvement around 28 days.
- **Convalescent plasma** results in little to no difference on clinical improvement around 28 days. There is probably little to no difference in the risk of all-cause mortality (around 28 days) and the risk of adverse events.
- **Favipiravir** (an anti-viral) is likely to increase the risk of all-cause mortality (around 28 days) in hospitalized patients.
- **Lopinavir + Ritonavir** (an anti-viral) probably results in little to no difference on all-cause mortality (around 28 days).
- **Sotrovimab** (a monoclonal antibody) probably results in little to no difference in clinical improvement around day 60. While the NIH recommends this intervention for outpatients, it has not been recommended for hospitalized patients. Similarly, this intervention has been authorized in the EU to treat Covid-19, but only in patients who do not require supplemental oxygen and are at increased risk of the disease becoming severe.

For another intervention authorized by the European Medicines Association (Ritonavir alone) we have not yet identified randomized controlled trials reporting its effectiveness.

Summary table on next page…

Summary Table: Pharmacologic treatments in hospitalized patients

(Updated on October 17th , 2022)

Legend:

Moderate/**High** certainty of benefit
Moderate/**High** certainty of little or no difference
Moderate/**High** certainty of harm
Low/Very low certainty of evidence

Treatment (vs standard care or placebo)	Treatment effectiveness							Adverse events	
	Clinical improvement (D28)	**Clinical improvement (D60)**	**WHO progression score (level ≥7) (D28)**	**WHO progression score (level ≥7) (D60)**	**All-cause mortality (D28)**	**All-cause mortality (D60)**	**Viral negative conversion (D7)**	**Adverse events**	**Serious adverse events**
Anakinra	1.04 (0.94-1.16)	low certainty	very low certainty	0.54 (0.3 - 0.96)	low certainty	very low certainty	low certainty	low certainty	low certainty
Auxora		very low certainty	very low certainty	very low certainty	very low certainty	very low certainty		low certainty	0.68 (0.47 - 0.99)
Bamlanivimab (LY-CoV555)		0.98 (0.90 - 1.07)	low certainty		low certainty	low certainty		low certainty	low certainty
Baricitinib	**1.02 (1.00 - 1.05)**	low certainty	0.81 (0.68 - 0.97)		low certainty	0.73 (0.59 - 0.89)		0.96 (0.88 - 1.05)	0.80 (0.67 - 0.95)
Canakinumab	1.05 (0.96-1.14)		low certainty		low certainty	low certainty		low certainty	low certainty
Casirivimab + Imdevimab (REGN-COV2)	1.02 (0.99 - 1.04)	1.04 (0.97 - 1.12)	low certainty		0.93 (0.86 - 1.01)	low certainty			
Convalescent plasma	**1.00 (0.98-1.02)**	low certainty	low certainty	low certainty	0.98 (0.93 - 1.03)	very low certainty	very low certainty	1.08 (0.99-1.18)	low certainty
Corticosteroids	**1.05 (1.02 – 1.08)**	low certainty	low certainty	very low certainty	**0.91 (0.85-0.98)**	very low certainty	very low certainty	1.09 (0.84 - 1.4)	very low certainty
Favipiravir	low certainty	very low certainty	low certainty	very low certainty	1.43 (0.71 - 2.88)	very low certainty	low certainty	very low certainty	very low certainty
Hyperimmune anti-Covid-19 Intravenous Immunoglobulin	low certainty		0.57 (0.32 - 1.02)		0.61 (0.34 - 1.09)		very low certainty	very low certainty	low certainty
Lopinavir + Ritonavir	low certainty		low certainty	very low certainty	1.02 (0.92-1.12)	low certainty	low certainty	low certainty	very low certainty
Otilimab	1.06 (0.96 - 1.17)	low certainty			0.88 (0.72 - 1.08)	low certainty		1.03 (0.94 - 1.14)	low certainty
Remdesivir	low certainty		low certainty		0.91 (0.74-1.11)	low certainty	1.06 (0.88 - 1.27)	very low certainty	very low certainty
Sotrovimab		1.05 (0.97 - 1.15)	low certainty		low certainty	low certainty		low certainty	low certainty
Nezulcitinib (TD-0903)	low certainty		low certainty		0.41 (0.17 – 1.00)			0.34 (0.12 - 0.96)	low certainty
Tocilizumab	1.05 (1.00-1.11)	very low certainty	low certainty		**0.88 (0.81-0.94)**	0.91 (0.8 - 1.04)		1.03 (0.95 - 1.12)	very low certainty
Vilobelimab	1.14 (0.92 - 1.41)				0.74 (0.56 - 0.98)	0.76 (0.59 - 0.99)		low certainty	low certainty

All values are RR (95% CI). Bolded results have a high level of certainty, while non-bolded results have a moderate level of certainty. Last updated: October 17th 2022. Click on the treatment to access the corresponding site at covid-nma.com.

What is the current evidence regarding treatment of Covid-19 outpatients?

Updated on October 17th, 2022

Pharmacologic treatments in outpatients

Critical outcomes of interest: Clinical improvement (around day 28 or day 60), WHO Clinical Progression Score ≥ 7 (around day 28 or day 60), all-cause mortality (around day 28 or day 60), viral negative conversion (around day 7), adverse events and serious adverse events.

For most pharmacological treatments in outpatients, the certainty of the evidence is still low or very low. Below is a summary of pharmacological interventions that, in outpatients, have **results in favor of a beneficial effect** compared with placebo or standard care. We only highlight outcomes of moderate and high certainty; other outcomes are of low or very low certainty.

- **Bamlanivimab + Etesevimab** (a monoclonal antibody) probably reduces the risk of hospitalisation or death and of all-cause mortality (around 28 days) in outpatients, although it probably increases the risk of serious adverse events. It probably results in little to no difference in the risk of adverse events.
- **Convalescent plasma** probably reduces the risk of hospitalisation or death, and of all-cause mortality (around 28 days) in outpatients.
- **Ensitrelvir** (an anti-viral) probably increases the likelihood of viral negative conversion (around 7 days), although it probably increases the risk of adverse outcomes. The wide confidence intervals for the risks of hospitalisation or death point to uncertainty of benefit or harm regarding this outcome.
- **Inhaled corticosteroids** probably reduce, in outpatients, the risk of hospitalisation or death and of all-cause mortality (around 28 days). It probably results in little to no difference in the risk of a WHO ≥7 (around 28 days).
- **Molnupiravir** (an anti-viral) is likely to reduce the risk of hospitalisation or death, of all-cause mortality (around 28 days) and of serious adverse events in outpatients. It probably results in little to no difference in the risk of adverse events.
- **Nirmatrelvir/ritonavir** (an anti-viral) probably reduces the risk of hospitalisation or death, of all-cause mortality (around 28 days), and of serious adverse events in outpatients. It probably results in little no to difference in the risk of adverse outcomes. This medicine has received Conditional marketing authorisation by the EMA to treat Covid-19.
- **Regdanvimab (CT-P59)** (a monoclonal antibody) is likely to reduce the risk of hospitalisation or death in outpatients, although it probably results in an increased risk of serious adverse events. The wide confidence intervals for the risks of all-cause mortality (around 28 days and around 60 days) point to uncertainty of benefit or harm regarding these outcomes. It is one of the interventions that have been authorized in the EU to treat Covid-19.
- **Remdesivir** (an anti-viral) probably reduces, in outpatients, the risk of hospitalisation or death and the risk of serious adverse events, but it probably results in little to no difference in the risk of adverse events. It is one of the interventions that have been authorized in the EU to treat Covid-19.
- **Sotrovimab** (a monoclonal antibody) probably results in a reduction in the risk of hospitalisation or death and of serious adverse events in outpatients. It probably results in little to no difference in the risk of adverse events. The wide confidence intervals for the risks of all-cause mortality (around 28 days and around 60 days) point to uncertainty of benefit or harm regarding these outcomes. It is one of the interventions that have been authorized in the EU to treat Covid-19.

For the treatments below there are outcomes with moderate or high certainty indicating **no evidence of beneficial effects** (e.g. clinical improvement or reduction in mortality) or an increase in the risks of negative effects (e.g. serious adverse events) compared with placebo or standard care:

- **Camostat Mesilate** (an anti-viral) probably increases the risk of adverse events in outpatients.
- **Casirivimab + Imdevimab (REGN-COV2)** (Monoclonal antibody combination) probably reduces the risk of adverse events and serious adverse events in outpatients, but the evidence regarding treatment

effectiveness has still low certainty. It is one of the interventions that have been authorized in the EU to treat Covid-19.

- **Favipiravir** (an anti-viral) probably results in an increased risk of hospitalisation or death in outpatients, as well as of severe adverse events. It probably results in little to no difference in the risk of adverse events.
- **Lopinavir + Ritonavir** (an anti-viral) probably results in an increased risk of serious adverse events in outpatients.

Summary table on next page…

Summary Table: Pharmacologic treatments in outpatients

(Updated on October 17th , 2022)

Legend:

Moderate/**High** certainty of benefit
Moderate/**High** certainty of little or no difference
Moderate/**High** certainty of harm
Low/Very low certainty of evidence

Treatment (vs standard care or placebo)	Treatment effectiveness								Adverse events	
	Clinical improvement (D28)	Clinical improvement (D60)	Hospitali-sation or death	WHO progression score (level ≥7) (D28)	WHO progression score (level ≥7) (D60)	All-cause mortality (D28)	All-cause mortality (D60)	Viral negative conversion (D7)	Adverse events	Serious adverse events
Bamlanivimab + Etesevimab	low certainty		0.23 (0.11 - 0.49)			0.05 (0.01 - 0.39)		low certainty	0.91 (0.65 - 1.28)	1.43 (0.59 - 3.45)
Camostat Mesilate	very low certainty		low certainty			very low certainty			1.2 (0.97 - 1.47)	
Casirivimab+Imdevimab (REGN-COV2)			low certainty			low certainty			0.7 (0.53 - 0.93)	0.18 (0.03 - 1.16)
Convalescent plasma			0.82 (0.66 - 1.02)	low certainty	very low certainty	low certainty	0.17 (0.02 - 1.41)	very low certainty	very low certainty	low certainty
Ensitrelvir			0.38 (0.03 - 5.02)			low certainty		1.14 (1.07 - 1.22)	1.3 (1.01 - 1.68)	low certainty
Favipiravir			1.58 (0.81 - 3.09)	low certainty		low certainty		low certainty	1.02 (0.87 - 1.18)	1.5 (0.71 - 3.15)
Inhaled corticosteroids			0.81 (0.58 - 1.13)	1.01 (0.57 - 1.8)		0.74 (0.31 - 1.74)	very low certainty	very low certainty	low certainty	very low certainty
Lopinavir + Ritonavir			very low certainty			very low certainty	low certainty	low certainty	low certainty	1.6 (0.81 - 3.14)
Molnupiravir	low certainty		0.67 (0.49 - 0.92)	low certainty		0.19 (0.04 - 0.86)		very low certainty	0.99 (0.9 - 1.09)	0.73 (0.52 - 1.02)
Nirmatrelvir/ritonavir			0.13 (0.07 - 0.27)			0.04 (0 - 0.63)			0.95 (0.82 - 1.1)	0.24 (0.15 - 0.41)
Regdanvimab (CT-P59)			0.35 (0.22 - 0.56)	low certainty		0.5 (0.05 - 5.53)	0.5 (0.05 - 5.53)	low certainty	low certainty	1.54 (0.61 - 3.92)
Remdesivir			0.28 (0.1 - 0.74)			low certainty			0.9 (0.75 - 1.09)	0.26 (0.1 - 0.7)
Sotrovimab			0.2 (0.08 - 0.48)	low certainty		0.2 (0.01 - 4.16)	0.11 (0.01 - 2.06)	low certainty	0.93 (0.74 - 1.16)	0.34 (0.18 - 0.68)

All values are RR (95% CI). Bolded results have a high level of certainty, while non-bolded results have a moderate level of certainty. Last updated: October 17th 2022. Click on the treatment to access the corresponding site at covid-nma.com.

Acknowledgements

This work received some funding from the Agence Nationale de la Recherche (ANR), the World Health Organization (WHO), Cochrane France, Center of Research in Epidemiology and StatisticS (CRESS), Centre d'Epidémiologie Clinique (GHU Cochin, Hôtel Dieu), the French Ministry of Higher Education and Research, the French Ministry of Health, Assistance Publique Hôpitaux de Paris (APHP), Université de Paris Cité, Centre national de la recherche scientifique (CNRS), the Federal Ministry of Education and Research, Germany and the European Union's Horizon 2020 Research and Innovation Programme under agreement No. 101037867