EVIDENCE SUMMARY

Should remdesivir be used in the treatment of children with COVID-19 infection?

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Recommendation

1. We suggest the use of remdesivir in hospitalized children with severe COVID-19 infection.

Certainty of Evidence: Very low
Strength of Recommendation: Weak

2. We suggest the use of remdesivir in non-hospitalized children with COVID-19 infection with at least 1 risk factor for disease progression.

Certainty of Evidence: Low
Strength of Recommendation: Weak

Consensus Issues
The recommendations were based on the evidence from one observational study among pediatric patients and 10 randomized controlled trials among patients aged 12 years old and above.

Despite the very low certainty of evidence for hospitalized children, the panel voted for the use of remdesivir. This is due to the significant benefit in decreasing the risk for clinical deterioration (based on WHO progression scale) and the risk reduction in mechanical ventilation use, although this was not statistically significant. The panel also agreed that because there are very limited treatment options for pediatric patients with COVID-19, this would give better guidance to clinicians. The panel emphasized though that remdesivir should be used for pediatric patients with severe COVID-19 following the classification of PIDSP and PSMID (on low flow oxygen support).

The panel voted for the use of remdesivir in non-hospitalized children with COVID-19 infection based on the evidence from one double-blind, placebo controlled randomized controlled trial done among patients aged 12 years old and above. This study showed significant benefit in preventing COVID-19 related hospitalization or all-cause mortality. Remdesivir was given to the patients 7 days from symptom onset and to those with at least one of the following risk factors: hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity, immune compromise, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer or sick cell disease.

Key Findings

- There are no randomized controlled trials (RCTs) to evaluate the use of remdesivir in the treatment of COVID-19 in the pediatric population.
- One observational study (n=77) among pediatric patients described the compassionate use of Remdesivir for all 77 patients. It showed 83% of cases recovered after 28 days of

follow-up. On subgroup analysis, those on invasive ventilation took a significantly longer time to recover and time to discharge than those without, with 32% of patients presenting at least 1 adverse event.

- Pooled results of ten RCTs evaluating the use of Remdesivir in adults outpatients with mild to moderate COVID-19 with risk factors has shown significant benefit in terms of reducing risk for hospitalizations and death. For hospitalized/in-patients, Remdesivir decreased the risk only for clinical deterioration as measured by the WHO progression scale but did not show benefit in other outcomes: all-cause mortality, need for mechanical ventilation and time to clinical improvement. No increased risk of adverse events and serious adverse events were noted. Overall certainty of evidence was rated low to very low due to serious risk of bias, inconsistency, indirectness and imprecision.

Introduction

Remdesivir is an antiviral drug administered intravenously that has been shown to inhibit viral replication. This was initially developed for the Ebola virus and is currently being evaluated as a potential treatment for COVID-19 infection [1].

Previously published RCTs on the use of remdesivir for adult patients with moderate to severe COVID-19 had shorter time to recovery and a lower risk of progression to more severe respiratory disease, safety profiles were similar to placebo and may have greater efficacy when initiated early. Pediatric approval by the US FDA for its use on those 12 years old and above or and weighing ≥40kg was extrapolated from adult trials with pharmacokinetic modeling and safety profile expected to be comparable to adults [2].

Review Methods

A systematic search was done until January 20, 2022 using free text and MeSH terms for coronavirus, SARS-COV-2, COVID-19 in children and remdesivir. The inclusion criteria for this review may be found in Table 1. Only RCTs and observational analytic studies were included. Pubmed, Cochrane Library, Google scholar and COVID-NMA were sought. Preprints were also checked in the medRxiv database. Ongoing studies were also searched in NIH clinicaltrials.gov. Relevant cited references were also manually searched.

Table 1. PICO criteria for remdesivir and COVID-19.

Population	Children with COVID-19
Intervention/Exposure	Remdesivir
Comparison	Usual care, standard of care, placebo, any active control
Outcomes	Hospitalization, mortality, recovery, clinical improvement, need for mechanical ventilation, duration of hospital or ICU stay, adverse events, time to negative viral conversion

Since few to no studies were seen in children on Remdesivir, the Philippine COVID-19 Living Clinical Practice Guidelines (LCPG) Phase 1 on adults was also reviewed as indirect evidence. To update the LCPG, newer clinical trials on the use of remdesivir in adult patients were also included. Available meta-analysis from the COVID-NMA was incorporated in this review. The observational analytic study was appraised using the Newcastle-Ottawa Scale (NOS), Cochrane RoB II for RCTs and AGREE II tool for CPGs. Sub-group analysis by age, dose and severity were done.

Results

The only study on children was a multi-center cohort done in various countries (United States, Spain, United Kingdom, Italy, France and Germany) which included 77 pediatric patients with severe COVID-19 infection who all received Remdesivir through a compassionate use program. There was no control group. The median age was 14 years old (range <2 months to 17 years [IQR 7-16]), 51% (39/77) were on invasive ventilation and 79% (61/77) had at least 1 co-morbid medical condition. A 10-day course was recommended with the following dosing regimen:

- >40kg: Loading dose of 200mg intravenously then 100mg intravenously subsequent days.
- < 40kg: Loading dose of 5mg/kg intravenously on day 1 then 2.5mg/kg/intravenously on subsequent days

Only 62% (48/77) received all 10 doses of Remdesivir in this study. Concomitant medications (hydroxychloroquine, methylprednisolone, anakinra, tocilizumab, hydrocortisone and dexamethasone) were also given to some of the study participants. The study was assessed to be of fair quality using the Newcastle Ottawa Scale.

In 83% (64/77) of patients, there was recovery after 28 days of follow-up. Subgroup analysis by requirement for invasive mechanical ventilation at baseline and age (≤ 12 and > 12 years) were done. Those on invasive ventilation at baseline had significantly longer time to recovery (HR 0.47, 95% CI 0.28-0.78) than those without. The patients aged ≤12 years old also showed significantly longer time to recovery (HR 0.54, 95% CI 0.33-0.89 compared to older cases.

Of 77 patients, 32% experienced at least 1 adverse event. Risk for adverse events was comparable regardless if they were on non-invasive ventilation or not. Adverse events reported were elevated ALT and AST level and anemia. Serious adverse events were elevations in transaminase levels (grade 3 and 4 elevations) and renal adverse events (hematuria, elevations in creatinine levels, toxic nephropathy and renal impairment). Four deaths (4/77, 5%) were reported in this study, all of whom received 9-10 days of remdesivir.

The Philippine COVID-19 LCPG) Phase 1 on adults had a favorable assessment using AGREE Scale. The trials were further updated with 6 new trials resulting in a total of ten (10) RCTs done in adults included in this review (N=10,454) [4-13]. Remdesivir was compared to placebo in three trials [8-9,12] and local standard of care in seven [4-7,10-11,13]. Some treatment interventions used for standard of care included corticosteroids [5-7,10-11,13], anti-coagulation [5,10], antivirals [11] and immunomodulators [5,11]. Nine trials recruited patients with COVID-19 that required hospitalization while one trial focused on non-hospitalized COVID-19 patients [9]. The studies with hospitalized patients included those with mild to critical COVID. Eight RCTs used a 10-day course of Remdesivir while two studies used a 5-day course [10-11]. The study on out-patient use used a 3-day course. The primary outcome of the studies was all-cause mortality, with duration of follow up ranging from 24 to 90 days. Other outcomes reported were time to clinical improvement, need for mechanical ventilation, need for ICU admission, adverse events and serious adverse events. Appendix 2 shows the characteristics of all the included studies.

The overall certainty of evidence was rated to be very low due to serious risk of bias, inconsistency, indirectness and imprecision. The serious risk of bias was mostly due to performance bias, as most of the trials were open label/unblinded as well as detection bias and attrition bias. See risk of bias summary and GRADE evidence summary in Appendix 3-5.

Hospitalized patients

Mortality

Pooled results among nine RCTs (N=9,891) showed that Remdesivir had no effect on all-cause mortality at day 28 (RR 0.91, 95 % CI 0.82-1.01) among adult patients.

Subgroup analysis among adult patients with mild-moderate disease (no oxygen support requirement) at baseline had inconclusive results (RR 0.86, 95% CI 0.55-1.36). Patients with severe disease (those on low flow oxygen support) also did not show significant benefit (RR 0.69, 95% CI 0.41-1.13. I^2=55%). There was no effect among patients with critical disease (those on high flow oxygen support, NIV, mechanical ventilation or ECMO) (RR 1.00, 95% CI 0.87-1.14).

Sub group analysis by treatment duration showed inconclusive effect on mortality for those on the 5-day treatment regimen (RR 0.98, 95% CI 0.37, 2.56; I^2=0%) and no effect for those given the 10-day treatment regimen (RR 0.92, 95% CI 0.83, 1.03; I^2=0%).

Clinical Improvement

Pooled results in four RCTs on adult cases showed that the rate of clinical improvement up to day 28 among those given Remdesivir was comparable to those given placebo or standard treatment (RR 1.07, 95% CI 1.01, 1.13). There was no significant effect seen on time to clinical improvement (RR 1.07, 95% CI 0.91, 1.27; I2=50.7%) as well. However, a decreased risk for clinical deterioration as measured by the WHO progression scale (RR 0.75, 95% CI 0.62,0.89) was reported.

Remdesivir has also shown a reduction in the risk for mechanical ventilation which was not statistically significant and had considerable heterogeneity (RR 0.75, 95% CI 0.56, 1.02; I^2=82%). There is an inconclusive risk for ICU admission (RR 0.98, 95% CI 0.43, 2.22; 1 RCT, n=181).

Non-hospitalized patients

One double-blind placebo-controlled RCT involved 562 non-hospitalized adult patients 12 years old and above with COVID-19, with symptom onset in the previous 7 days and had at least one risk factor for disease progression]. Risk factors included hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity, immune compromise, chronic mild or moderate kidney disease, chronic liver disease, chronic lung disease, current cancer or sickle cell disase. [7] A 3-day course of Remdesivir was given in the intervention group (200mg on Day 1 and 100 mg on day 2 and 3). Overall certainty of evidence for this study was low due to serious indirectness and imprecision. Remdesivir showed a significant benefit in preventing COVID-19 related hospitalization or death from any cause (RR 0.13, 95% CI 0.03, 0.6).

There were eight pediatric patients included in the RCT (3 on remdesivir and 5 on placebo group). Subgroup analysis on these children showed inconclusive results for COVID-19 related hospitalization or death from any cause (RR 1.5, 95% 0.03, 61.3) and safety with mild-moderate COVID-19 (RR 0.58, 95% 0.03-11.2). Only one pediatric patient (placebo group) reported mild fatigue. There were no COVID-19 related hospitalization or death from any cause by Day 28.

Negative Viral Conversion
Remdesivir showed no benefit for negative viral conversion by Day 7 of illness (RR 1.02, 95% 0.76-1.38; 1 RCT n = 196).

Safety
Remdesivir showed no significant risk for adverse events (RR 0.99, 95% CI 0.92, 1.08; I^2=31%) and serious adverse events (RR 0.84, 95% CI 0.67, 1.04; I^2=49%) in hospitalized patients. In the out-patient study, there was also no significant risk for adverse events (RR 0.91, 95% CI 0.75,1.1) but it showed a significant decreased risk for serious adverse events (RR 0.26 95%CI 0.10,0.70). The most common adverse events reported were nausea, headache, cough, diarrhea, dyspnea, fatigue, pyrexia, increased creatinine level, decreased glomerular filtration rate, hypersensitivity reactions and elevation in hepatic enzymes. Serious adverse events included respiratory failure, cardiopulmonary failure and renal failure necessitating kidney replacement therapy

Other Considerations (Evidence to Decision)

Remdesivir is available locally as 100mg of lyophilized powder for reconstitution in a single-use vial, under a compassionate special permit (CSP) for use in the treatment of COVID-19 [14]. The suggested retail price specified in a DOH memorandum is up to Php 8,200 per 100mg vial [15]. Following the recommended dosing of 200mg IV on Day 1 and 100mg IV on Days 2 to 10 for a 10-day course, the total cost per patient (at the SRP) is Php 90,200.00. For outpatient therapy, the total cost per patient is Php 32,800 for the recommended 3-day course. Cost effectiveness and cost utility analysis in the United States showed that remdesivir is more costly and less effective for the treatment of severe COVID-19 compared to Dexamethasone, while in South Africa and Turkey it saved costs by reducing the number of ICU days with higher QALYs [16-18].

Remdesivir has been granted emergency use authorization by the US FDA for the treatment of COVID-19 in adults and children more than 12 years old and weighing at least 40kg. The US NIH recommendations noted that administering IV infusions of remdesivir for up to 5 consecutive days can be difficult in the outpatient setting.

Recommendations from Other Groups

Table 2. Summary of recommendations from other groups

Society/ Regulatory Agency	**Recommendation**
US NIH • February 1, 2022	Recommended **for:** • Non-hospitalized children aged ≥12 years and weighing ≥40 kg at high risk of disease progression, initiate treatment as soon as possible and within 7 days of symptom onset;
• February 24, 2022	• Hospitalized children aged ≥ 12 years with COVID-19 who have risk factors for severe disease and have an emergent or increasing need for supplemental oxygen • Hospitalized children aged ≥16 years with COVID-19 who have an emergent or increasing need for supplemental oxygen regardless of whether they have risk factors for severe disease

	In consultation with a pediatric infectious disease specialist, **remdesivir** can be considered for hospitalized children of all ages with COVID-19 who have an emergent or increasing need for supplemental oxygen
Pediatric Infection Disease Society - USA (September 12, 2020)	Outpatients and hospitalized patients with asymptomatic, mild, or moderate COVID-19 should be managed with supportive care only. **Remdesivir should be used only within the context of a clinical trial in these populations.** Remdesivir is suggested for children with severe COVID-19. Remdesivir should be considered for children with critical COVID-19, unless there are contraindications. ● Severe COVID-19: recommended duration of up to **5 days** of remdesivir therapy for children. ● If used for children with critical COVID-19, a duration of 5-10 days is suggested; consider on a case-by-case basis for children not improving after 5 days of therapy.
National COVID-19 Clinical Evidence Taskforce – Australia October 24, 2021	Use of remdesivir for children or adolescents with COVID-19 outside a trial setting should not be routinely considered (Low certainty of evidence, Conditional)
Philippine COVID Living CPG (March 2021)	We suggest: ● **against** the use of remdesivir in patients with COVID-19 infection who have O2 saturation >94% and do not require oxygen supplementation* ; also in patients with COVID-19 infection who are already on invasive mechanical ventilation*. **for** addition of remdesivir to dexamethasone in patients with COVID-19 infection who have O2 saturation ≤ 94% and/or requiring oxygen supplementation*. * All low certainty of evidence, conditional recommendation
WHO November 20, 2020	Recommend against remdesivir in COVID-19 hospitalized patients. There is no evidence showing improvement in survival or other outcomes.

Research Gaps

Current clinical recommendations on the use of remdesivir have been based on efficacy and safety profiles in trials done among adult patients. There is one ongoing randomized controlled trial that is currently ongoing on the pharmacokinetics and safety of its use in the pediatric population. An update of this review will be done once the results are available.

References

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Appendix 1. Search Yield and Results

Date of Last Search: January 20, 2022

Database	Search Terms	YIELD	ELIGIBLE
Pubmed	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (remdesivir)	2148	9 (2 pediatric)
Cochrane	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (remdesivir)	198	8 (1 pedia)
Google Scholar	Remdesivir AND COVID-19 AND pediatric	3,200	2
COVID-NMA initiative	Remdesivir	13	9
ONGOING TRIALS			
ClinicalTrials.gov https://clinicaltrials.gov/	covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (remdesivir) AND children	30	1
PRE PRINT			
Medrxiv	covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (remdesivir)	1075 4	0

Appendix 2. Table of Included Studies

Title/Author	Patients (n) and Duration of Follow up	Intervention	Control	Outcome	Method
Pediatric (1)					
Compassionate Use of Remdesivir in Children with Severe COVID-19 Goldman, et al (May 2021)	N = 77 Hospitalized patients <18 years old with confirmed COVID-19 infection Follow up: 28 days	Remdesivir course for 10 days	N/A	Mortality Oxygen support requirement Need for invasive ventilation Length of hospital stay Adverse events	Observational (Cohort)
Adult (10)					
Early Remdesivir to prevent progression to severe COVID-19 in outpatients Gottlieb, et al (Dec 2021)	N = 562 (8 pediatric patients) Non-hospitalized patients with COVID-19 with symptom onset within 7 days and one risk factor for disease progression Follow up: 28 days	Remdesivir for 3 day course	Placebo	COVID-19 related hospitalization All cause mortality COVID-19 related medical visit COVID-19 related death Adverse events	Randomized, double blind placebo controlled trial

Remdesivir Efficacy in COVID-19 Treatment: A Randomized Controlled Trial Abd-Elsalam, et al (2021)	N=209 (200 analyzed) Hospitalized Mild to moderate symptoms Age: 18 to 80 years old	Remdesivir 200mg on D1 then 100mg D2-10 (10 day course)	Standard of care (Zinc, NAC, Lactoferrin, Vitamin C)	Duration of hospital stay Need for mechanical ventilation Adverse Events	Randomized controlled open label
Remdesivir plus standard of care alone for the treatment of patietns admitted to hospital with COVID-19 (DisCoVeRy) Ader, et al (Feb 2022, published online Sept 2021)	N= 857 (832 analyzed) Age: ≥ 18 years old Hospitalized patients requiring oxygen support Follow up: 90 days	Remdesivir 200mg on D1 then 100mg D2-10 (10 day course) + Standard of Care	Standard of Care only (dexamethasone, anticoagulants	Clinical Status on Day 15 (WHO ordinal scale) Time to Improvement Change from baselines Time to hospital discharge and duration of hospitalization Time to mech ventilation Mortality Oxygenation and ventilator free days until Day 29 Adverse events	Phase 3 open label RCT
Remdesivir for the treatment of patients in hospital with COVID-19 in Canada: a RCT Ali, et al (Jan 2022)	N = 1282 (1267 analyzed) Hospitalized adults Follow up: 28 days	Remdesivir 200mg on D1 then 100mg D2-10 (10 day course) + Standard of Care	Standard of care	Mortality Change in clinical severity Oxygen and ventilator free days Incidence of new oxygen or mechanical ventilation use Adverse events	Open label RCT

Evaluation of the Effects of Remdesivir and Hydroxychloroquine on Viral Clearance in COVID-19 Barratt, et al (2021)	N = 185 (101 assigned to remdesivir subgroup, 83 analyzed) Age: ≥ 18 years old Admitted in the hospital or ICU Follow up: 90 days	Remdesivir 200mg on D1 then 100mg D2-10 (10 day course) + Standard of Care Additional arm: HCQ	Standard of care	All cause in hospital mortality Need for mechanical ventilation Duration of mechanical ventilation Need for ICU admission Adverse events	Open label RCT
Remdesivir for the Treatment of COVID-19 Beigel, et al (2020)	N=1062 (1048 analyzed) Severe COVID-19 patients	Remdesivir 200mg on D1 then 100mg D2-10 (10 day course)	Placebo	Time to recovery Clinical status Time to discharge Number of days with supplemental oxygen, NIV or high flow and mechanical ventilation Adverse events	Double blind, randomized placebo controlled
Clinical outcomes of using remdesivir in patients with moderate to severe COVID-19: a prospective randomized study Mahajan, et al (2021)	N= 82 (70 analyzed) Age: 18-60 years old Admitted in the hospital Moderate to severe COVID	Remdesivir 200mg on D1 then 100mg D2-4 (5 day course)	Standard of care	Clinical status on Day 12 Mortality Safety Outcomes	Randomized controlled trial

Effect of Remdesivir vs Standard of Care on Clinical Status at 11 days in patients with Moderate COVID-19 Spinner, et al (2020)	N = 596 (584 analyzed) Hospitalized patients with moderateCOVID	Remdesivir 200mg on D1 then 100mg on subsequent days (5 or 10 day course)	Standard of care	Clinical status on day 11 (7-point ordinal scale) Clinical improvement (2-category change from baseline) Time to recovery Adverse events	Double blind Randomized controlled trial
Remdesivir in adults with severe COVID-19: a randomized, double blind placebo controlled multicentre trial Wang (2020)	N = 237 (226 analyzed) Age $\geq$ 18 years old Severe COVID patients Follow up: 28 days	Remdesivir 200mg on D1 then 100mg D2-10 (10 day course)	Placebo	Clinical status (6-point ordinal scale) Clinical improvement (2 points reduction from baseline, or discharge from hospital) Time to clinical improvement Viral load Mortality Adverse events	Double blind Randomized controlled trial
Repurposed Antiviral Drugs for COVID-19 – Interim WHO Solidarity Trial Results WHO (2021)	N = 11,330 (5,025 Remdesivir and control)	Remdesivir 200mg on D1 then 100mg D2-10 (10 day course)	Standard of Care	Mortality Need for mechanical ventilation Duration of hospitalization	

Appendix 3. Study Appraisal

Goldman et al (May 2021) – **Fair Quality**

Table 1. Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Selection

1) Representativeness of the exposed cohort
   a) Truly representative ***(one star)*** *
   b) Somewhat representative ***(one star)***
   c) Selected group
   d) No description of the derivation of the cohort
2) Selection of the non-exposed cohort
   a) Drawn from the same community as the exposed cohort *
   b) Drawn from a different source
   c) No description of the derivation of the non exposed cohort
3) Ascertainment of exposure
   a) Secure record (e.g., surgical record)
   b) Structured interview ***(one star)***
   c) Written self report
   d) No description
   e) Other
4) Demonstration that outcome of interest was not present at start of study
   a) Yes ***(one star)***
   b) No

Comparability

1) Comparability of cohorts on the basis of the design or analysis controlled for confounders
   a) The study controls for age, sex and marital status ***(one star)*** *
   b) Study controls for other factors (list) _____ ***(one star)***
   c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcome

1) Assessment of outcome
   a) Independent blind assessment ***(one star)***
   b) Record linkage ***(one star)***
   c) Self report
   d) No description
   e) Other
2) Was follow-up long enough for outcomes to occur
   a) Yes ***(one star)*** *
   b) No

Indicate the median duration of follow-up and a brief rationale for the assessment above: 28 day follow up

3) Adequacy of follow-up of cohorts
   a) Complete follow up- all subject accounted for ***(one star)*** *
   b) Subjects lost to follow up unlikely to introduce bias- number lost less than or equal to 20% or description of those lost suggested no different from those followed. ***(one star)***
   c) Follow up rate less than 80% and no description of those lost
   d) No statement

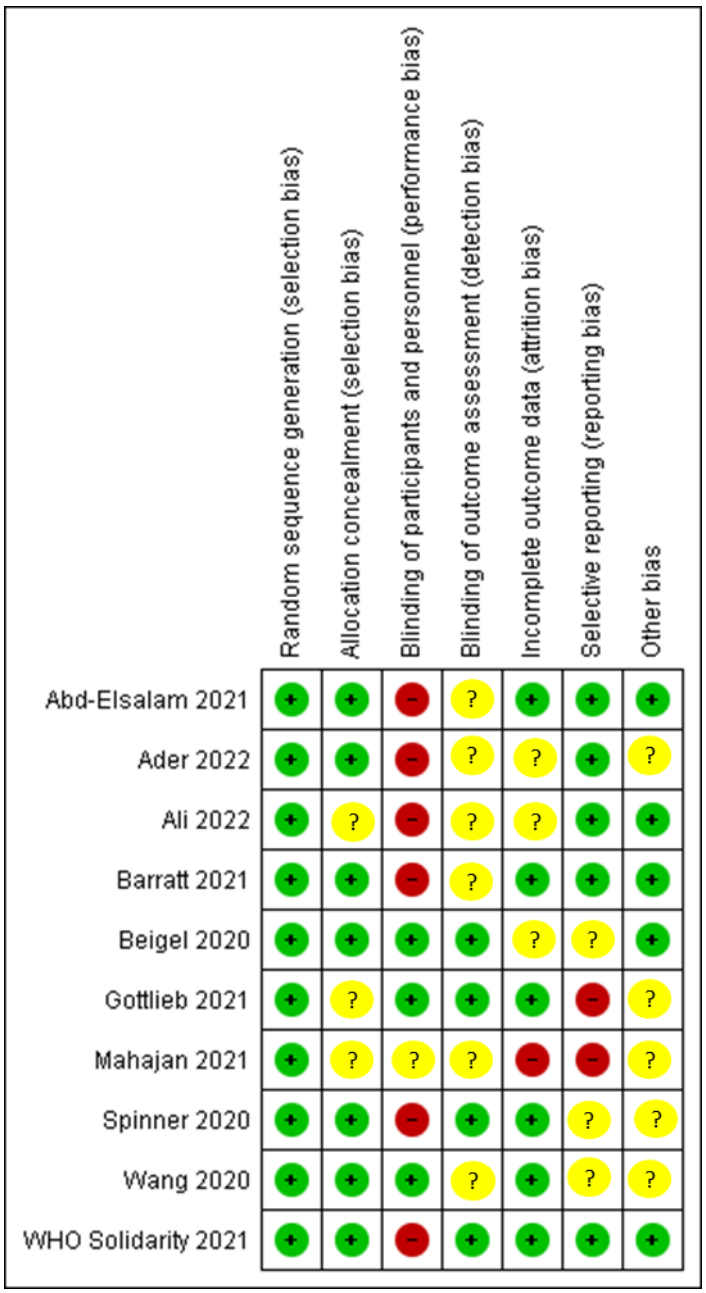

Figure 1. Risk of Bias Summary of Randomized Controlled trials (Adult)

Appendix 4A. GRADE Evidence Profile: Hospitalized Patients

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Question: Should remdesivir compared to placebo or standard of care be used in the treatment for COVID-19 hospitalized patients?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	Placebo or Standard of Care	Relative (95% CI)	Absolute (95% CI)		
Mortality (Day 28)												
9	randomised trials	serious[a]	not serious	serious[b]	not serious	none	554/5092 (10.9%)	591/4799 (12.3%)	**RR 0.91** (0.82 to 1.01)	**11 fewer per 1,000** (from 22 fewer to 1 more)	⨁⨁◯◯ Low	Critical
Mortality (Day 28) - 5 day Remdesivir												
2	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	8/232 (3.4%)	7/141 (5.0%)	**RR 0.98** (0.37 to 2.56)	**1 fewer per 1,000** (from 31 fewer to 77 more)	⨁◯◯◯ Very low	Critical
Mortality (Day 28) - 10 day Remdesivir												
8	randomised trials	serious[a]	not serious	serious[b]	not serious	none	546/4848 (11.3%)	575/4658 (12.3%)	**RR 0.92** (0.83 to 1.03)	**10 fewer per 1,000** (from 21 fewer to 4 more)	⨁⨁◯◯ Low	Criticial
Clinical Improvement												
4	randomised trials	serious[a]	not serious	serious[b]	not serious	none	715/1024 (69.8%)	455/748 (60.8%)	**RR 1.07** (1.01 to 1.13)	**43 more per 1,000** (from 6 more to 79 more)	⨁⨁◯◯ Low	Critical
Clinical Deterioration (WHO Progression Score)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	Placebo or Standard of Care	Relative (95% CI)	Absolute (95% CI)		
5	randomised trials	serious[d]	not serious	serious[b]	not serious	none	189/1565 (12.1%)	229/1269 (18.0%)	**RR 0.75** (0.62 to 0.89)	**45 fewer per 1,000** (from 69 fewer to 20 fewer)	⨁⨁◯◯ Low	Important
Need for Mechanical Ventilation												
5	randomised trials	serious[a]	serious[e]	serious[b]	serious[c]	none	516/4271 (12.1%)	614/4196 (14.6%)	**RR 0.75** (0.56 to 1.02)	**37 fewer per 1,000** (from 64 fewer to 3 more)	⨁◯◯◯ Very low	Critical
Negative Viral Conversion												
1	randomised trials	serious[f]	not serious	serious[b]	serious[c]	none	66/131 (50.4%)	32/65 (49.2%)	**RR 1.02** (0.76 to 1.38)	**10 more per 1,000** (from 118 fewer to 187 more)	⨁◯◯◯ Very low	Important
Serious Adverse Events												
5	randomised trials	serious[g]	not serious	serious[b]	serious[c]	none	329/2158 (15.2%)	346/1875 (18.5%)	**RR 0.84** (0.67 to 1.04)	**30 fewer per 1,000** (from 61 fewer to 7 more)	⨁◯◯◯ Very low	Critical
Adverse Events												
5	randomised trials	serious[g]	not serious	serious[b]	not serious	none	941/2158 (43.6%)	790/1875 (42.1%)	**RR 0.99** (0.92 to 1.08)	**4 fewer per 1,000** (from 34 fewer to 34 more)	⨁⨁◯◯ Low	Critical

CI: confidence interval; **RR:** risk ratio

Explanations

a. Some trials with issues on randomization, missing outcome data, performance bias and detection bias
b. Trials done on adult patients only. No pediatric patients enrolled
c. Wide confidence interval
d. 1 study assessed to have overall high risk of bias
e. Considerable heterogeneity (I2= 82%)
f. Missing outcome data
g. Studies had deviations from intended intervention, missing outcome data and reporting bias

Appendix 5B. GRADE Evidence Profile: Non-hospitalized Patients

Author(s): Melissa A. Dator, MD, Maria Teresa S. Tolosa, MD, FPDS, DipCE; Ma. Lucila M. Perez, MD, MSc, FPPS
Question: Should remdesivir compared to placebo or standard of care be used in the treatment for COVID-19 non- hospitalized patients?
Bibliography: Gottlieb R, 2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	Placebo	Relative (95% CI)	Absolute (95% CI)		
COVID-19 related hospitalization or death from any cause - Day 28												
1 (N=568)	randomised trials	not serious	not serious	serious[a]	serious [,c]	none	2/279 (0.7%)	15/283 (5.3%)	**RR 0.13** (0.03 to 0.60)	**46 fewer per 1,000** (from 51 fewer to 21 fewer)	⨁⨁◯◯ Low	Critical
Adverse events												
1 (N=568)	randomised trials	not serious	not serious	serious[a]	serious[c]	none	118/279 (42.3%)	131/283 (46.3%)	**RR 0.91** (0.75 to 1.10)	**42 fewer per 1,000** (from 116 fewer to 46 more)	⨁⨁◯◯ Low	Critical
Serious adverse events												
1 (N=568)	randomised trials	not serious	not serious	serious[a]	serious[c]	none	5/279 (1.8%)	19/283 (6.7%)	**RR 0.26** (0.10 to 0.70)	**50 fewer per 1,000** (from 60 fewer to 20 fewer)	⨁⨁◯◯ Low	Critical
COVID-19 related hospitalization or death from any cause - Pediatric only												
1 (N=8)	randomised trials	not serious	not serious	not serious	very serious[b]	none	0/3 (0.0%)	0/5 (0.0%)	**RR 1.50** (0.03 to 61.30)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⨁⨁◯◯ Low	Critical

Adverse Event - Pediatric only												
1 (N=8)	randomised trials	not serious	not serious	not serious	serious[b]	none	0/3 (0.0%)	1/5 (20.0%)	**RR 0.58** (0.03 to 11.20)	**84 fewer per 1,000** (from 194 fewer to 1,000 more)	⨁⨁⨁◯ Moderate	Critical

CI: confidence interval; **RR:** risk ratio

Explanations

a. Majority of the population in the study were adults. Only 8 patients were below 18 years old.
b. Wide confidence interval
c. Target sample size of 1264 not met

Appendix 5. Forest Plots

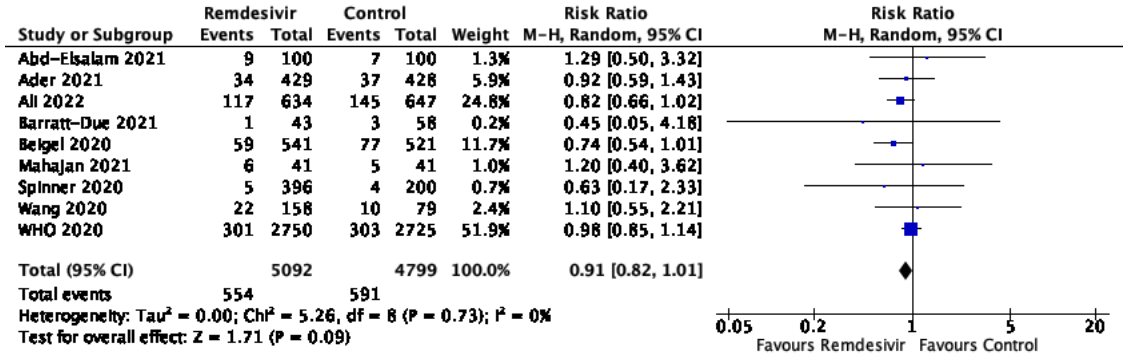

Figure 1. Pooled effect of remdesivir on all-cause mortality at Day 28 among hospitalized patients
(Source: Tan-Lim, Philippine COVID-19 Living CPG)

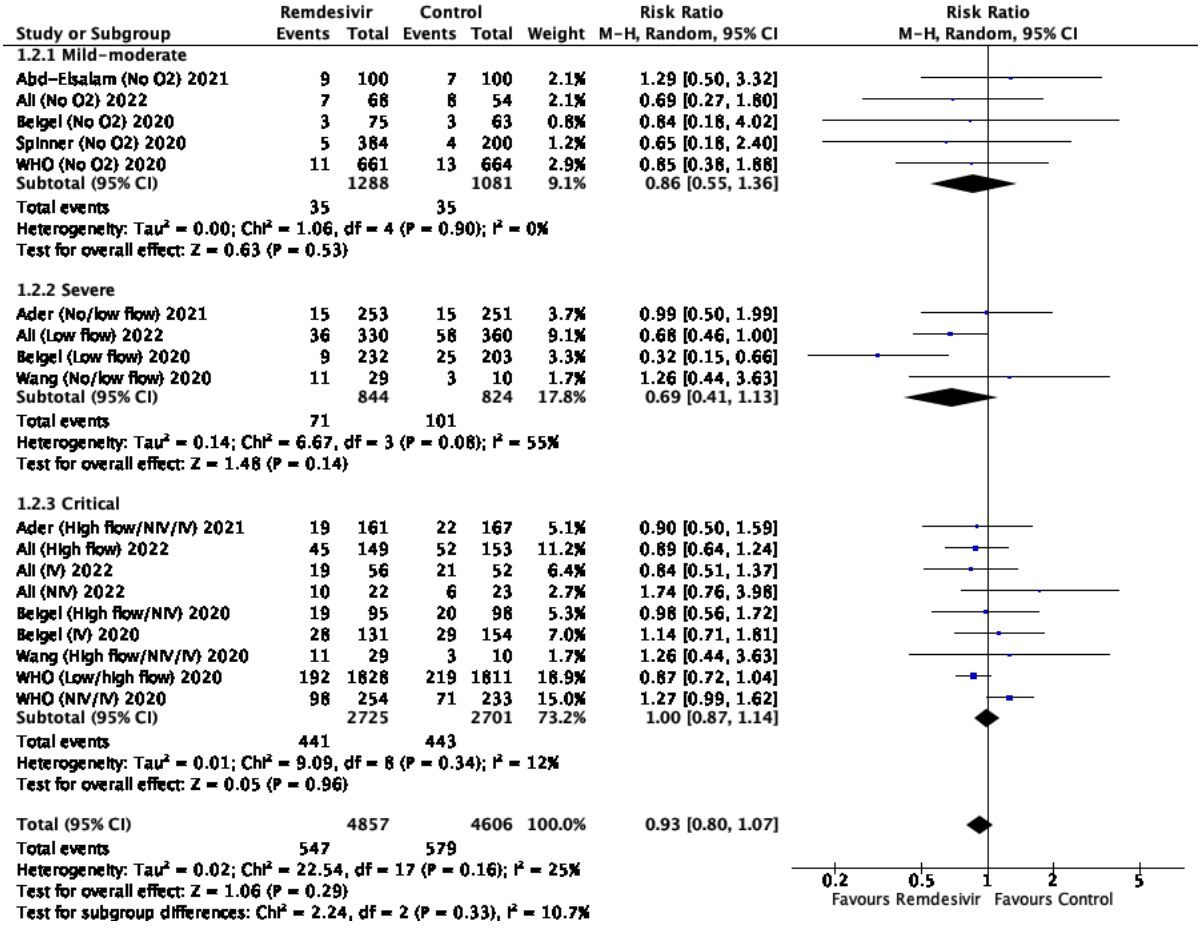

Figure 2. Subgroup analysis for mortality by disease severity
(Source: Tan-Lim, Philippine COVID-19 Living CPG)

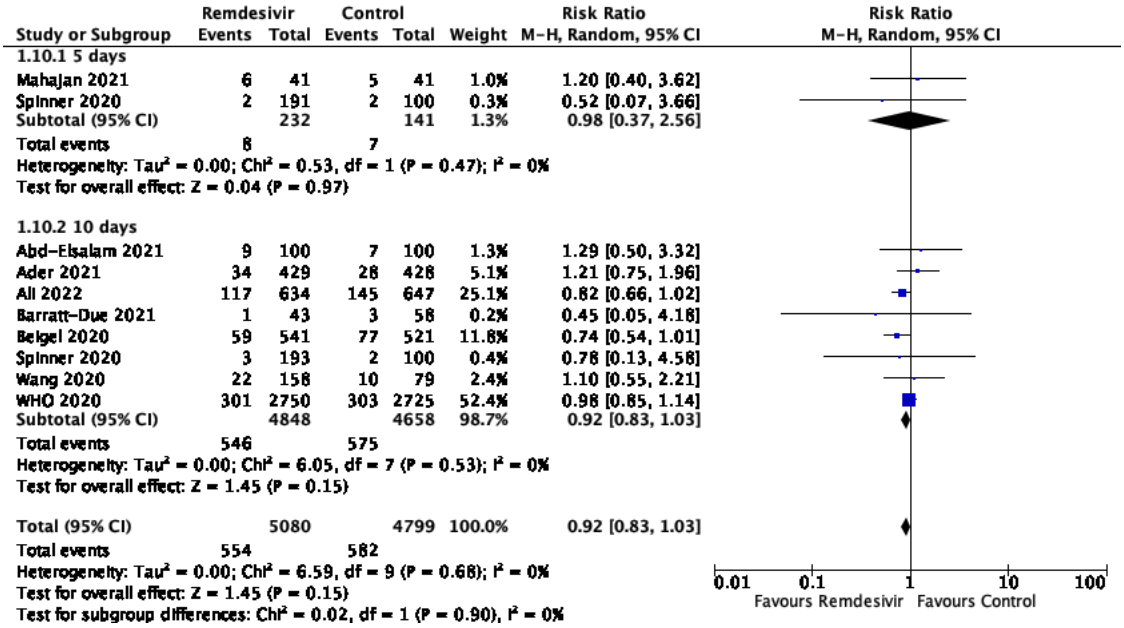

Figure 3. Subgroup analysis for mortality by treatment duration
(Source: Tan-Lim, Philippine COVID-19 Living CPG)

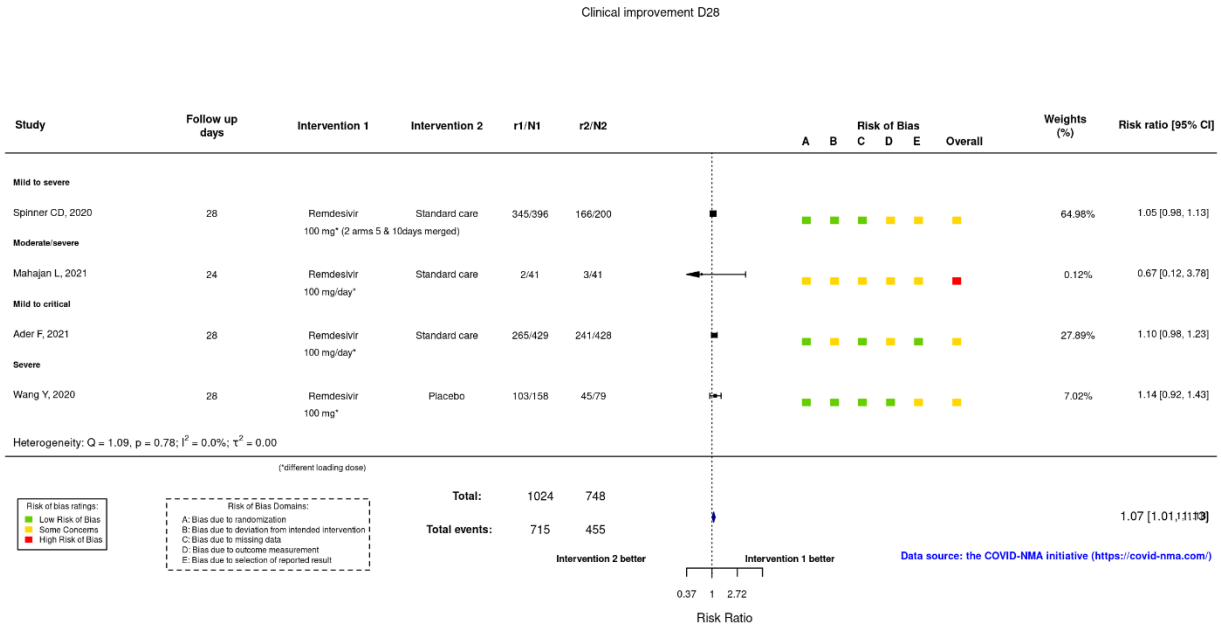

Figure 4. Pooled effect of remdesivir on clinical improvement among hospitalized patients
(Source: www.covid-nma.com)

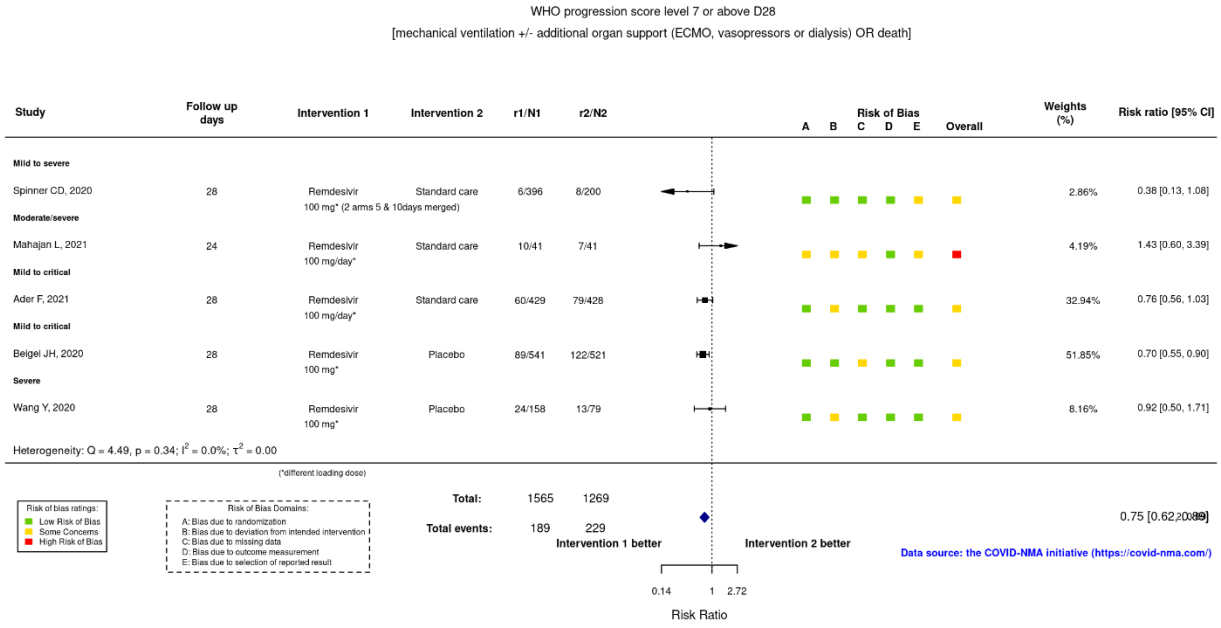

Figure 5. Pooled effect of remdesivir on clinical deterioration using the WHO progression score among hospitalized patients (Source: www.covid-nma.com)

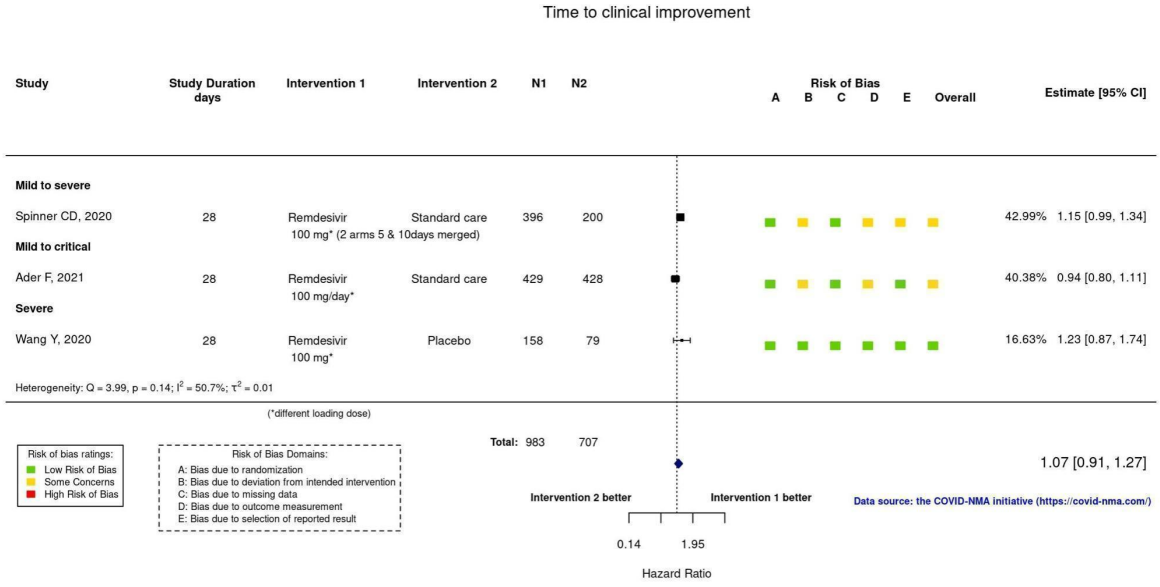

Figure 6. Pooled effect of remdesivir on time to clinical improvement among hospitalized patients (Source: https://www.covid-nma.com)

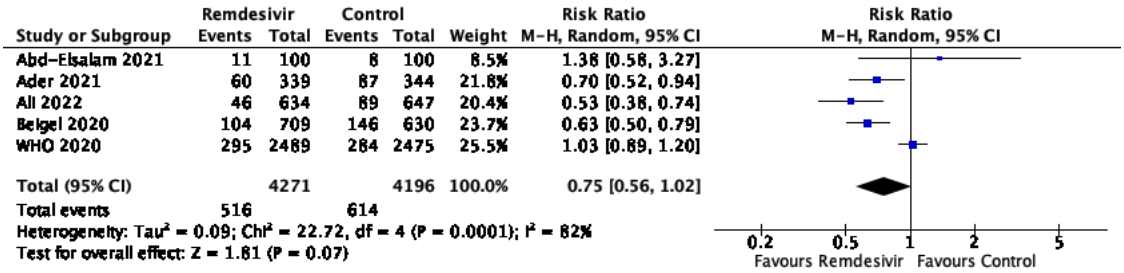

Figure 7. Pooled effect of remdesivir on need for mechanical ventilation among hospitalized patients
(Source: Tan-Lim, Philippine COVID-19 Living CPG)

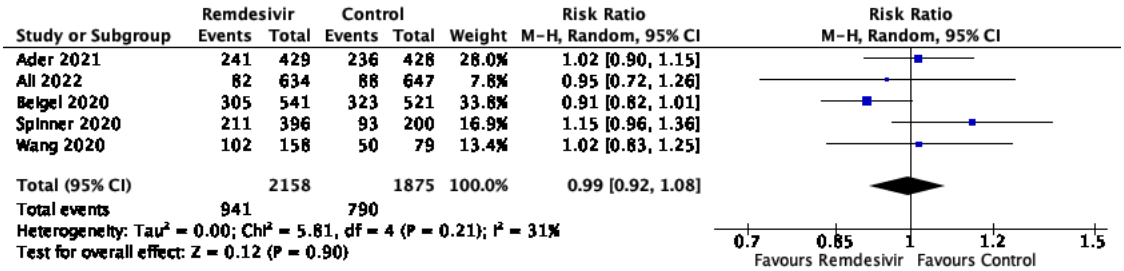

Figure 8. Pooled effect of remdesivir on adverse events among hospitalized patients
(Source: Tan-Lim, Philippine COVID-19 Living CPG)

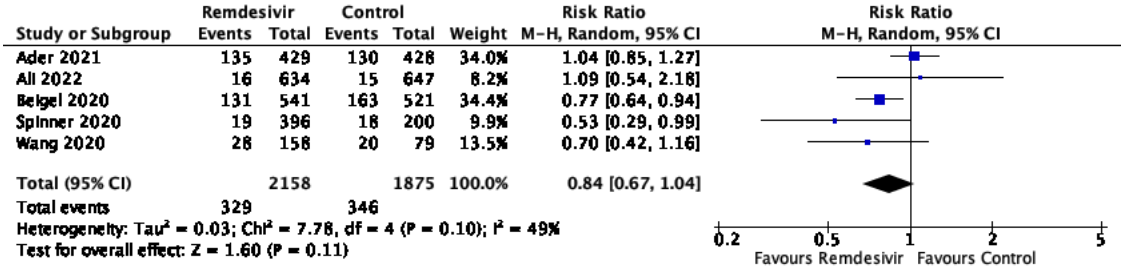

Figure 9. Pooled effect of remdesivir on serious adverse events among hospitalized patients
(Source: Tan-Lim, Philippine COVID-19 Living CPG)

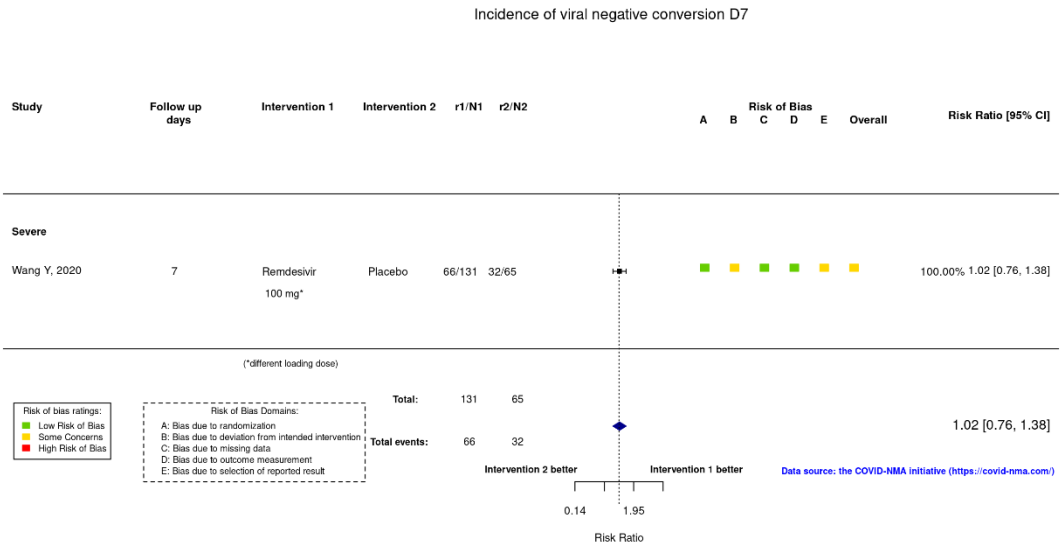

Figure 10. Incidence of viral negative conversion by Day 7 (Source: www.covid-nma.com)

Appendix 6. Table of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
Status to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of Remdesivir in Participants From Birth to < 18 Years of Age with COVID-19 (CARAVAN) NCT04431453 *Status*: Recruiting *Estimated completion*: Feb 2022	Pediatric patients 0 days to <18 years old, to include term and preterm neonates (8 cohorts) with COVID-19 (N = 52)	Remdesivir for 10 days Dose depending on cohorts	*Primary:* Adverse events Laboratory Abnormalities Plasma Concentration of Remdesivir *Secondary*: Oxygenation Use Use of Mechanical Ventilator of ECMO Clinical improvement Time to hospital discharge Days to confirmed RT PCR negative Change to severe COVID Bilirubin concentration in <14 days old Clinical improvements based on PEWS scale Plasma concentrations SBECD Use of other medications other than RDV	Open label Phase 2/3 RCT

Appendix 7: Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 11)

FACTORS	JUDGEMENT (N = 11)								RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (11)		Varies		Uncertain			
Benefits	Large	Moderate (2)	Small (6)	Trivial (2)	Varies	Uncertain (1)			Hospitalized • No significant benefit on all-cause mortality day 28, time to clinical improvement • Significant benefit in reducing risk of clinical deterioration • Non-statistically significant benefit in reducing MV use Non-hospitalized • Significant benefit in reducing COVID-19 related hospitalization or all-cause mortality
Harm	Large	Moderate	Small (6)	Trivial (4)	Varies	Uncertain (1)			• No significant different in adverse events and serious adverse events between intervention and control groups
Certainty of evidence	High	Moderate		Low		Very low (11)			• Rated very low due to serious risk of bias, indirectness and imprecision
Balance of effects	Favors drug	Probably favors drug (6)	Does not favor drug or no drug (1)	Probably favors no drug (1)	Favors no drug	Varies	Uncertain (3)		
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (4)		Probably no important uncertainty or variability (5)		No important uncertainty or variability (1)			
Resources required	Uncertain	Varies	Large costs (9)	Moderate costs (2)	Negligible costs or savings	Moderate savings	Large savings		• Php 32,800.00 for 3-day OPD course • Php 90,200.00 for in-patient course
Certainty of evidence of resources required	No included studies (4)		Very low	Low (1)	Moderate (5)	High (1)			
Cost-effectiveness	No included studies (1)	Varies (3)	Favors the comparison (1)	Probably favors the comparison (2)	Does not favor the comparison or the intervention	Probably favors the intervention (4)	Favors the intervention		
Equity	Uncertain (4)	Varies (1)	Reduced	Probably reduced (4)	Probably no impact (1)	Probably increased (1)	Increased		
Acceptability	Uncertain (6)	Varies	No	Probably no (1)	Probably yes (3)	Yes (1)			
Feasibility	Uncertain (5)	Varies (3)	No (1)	Probably no	Probably yes (1)	Yes (1)			