EVIDENCE SUMMARY

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

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Recommendation

We suggest <u>against</u> the routine use of intravenous immunoglobulin for children with COVID-19 infection.

Certainty of Evidence: Very Low
Strength of Recommendation: Weak

Consensus Issues
The recommendation was based on the evidence from one retrospective cohort study in children and seven randomized controlled trials in hospitalized adults with moderate to severe COVID-19. Although the evidence in adults showed a significant benefit in reducing clinical deterioration, duration of hospital stay and ICU admission, the evidence was rated as very low due to serious risks of bias, indirectness and imprecision. On the other hand, the evidence in pediatric patients was inconclusive. Coupled with the high cost of the treatment, the panel decided to vote against the routine use of the drug. However, the panel agreed that IVIG may be considered especially when no other treatment option is available. In special circumstances such as MIS-C, expert opinion should be sought.

Key Findings

There were no randomized controlled trials (RCT) found on the use of intravenous immunoglobulin (IVIG) in the treatment of COVID-19 infection in children during the search. However, there was one retrospective cohort study which compared the use of IVIG+CS with CS alone among pediatric patients with Multisystem Inflammatory Syndrome in Children (MIS-C). This showed that addition of IVIG demonstrated tendency towards harm for the composite outcome (use of inotropic support or mechanical ventilation on or after day 2 or death) and inconclusive findings for the other outcomes. When IVIG alone was compared with CS alone (IVIG vs CS) among patients with MIS-C, results were inconclusive for the same composite outcome and for the other outcomes.

Since data on children is limited, indirect evidence was also used through extrapolation of results from the studies included in the Philippine COVID 19 Adult Living Clinical Practice Guideline Phase II as well as from the new adult RCTs found in the search. Pooled results of the seven (7) RCTs on adults showed that the use of IVIG resulted in significant benefit on clinical deterioration, shorter duration of hospital stay and of ICU admission but no significant difference for the rest of the outcomes and adverse events.

The overall certainty of evidence was very low. Thus, there is still insufficient evidence on the use of IVIG for the treatment of COVID -19 in children.

Introduction

Intravenous immunoglobulin has been considered as a treatment for COVID-19 due to its anti-inflammatory and immunomodulatory effects. It is used as first line treatment for Kawasaki disease due to its anti-inflammatory effect [1].

MIS-C is a newly defined clinical syndrome associated with SARS-CoV-2 infection characterized by fever, systemic inflammation, and multiple organ dysfunction [2-4]. As reported in studies, the incidence of MIS-C is 316 per 1 million SARS-CoV-2 infections or approximately 1 in 3000 children and adolescents or patients less than 21 years old who had SARS-CoV-2 infection with a median age of 9 years old (75% of cases with no comorbidities) and highest among Black and Hispanic/Latino children [5-8]. Patients with MIS-C often have severe symptoms of cardiac injury or dysfunction [9], critically ill with as high as 80% of children requiring ICU admission and a mortality rate of 1% to 2% for hospitalized patients as reported in the United States [10]. Due to the similarity of the features of Kawasaki disease and MIS-C such as fever, rash, conjunctivitis, mucosal symptoms, and swollen hands and feet, IVIG was proposed as a potential drug of choice for the treatment of MIS-C [11,12].

Despite several clinical trials done in adults on the use of IVIG for the treatment of COVID-19 infection, there has been insufficient evidence to recommend IVIG as treatment [13]. This review looks into the effectiveness of IVIG as treatment of pediatric COVID-19 infection and MIS-C.

Review Methods

A systematic search was conducted from January 3, 2022 to January 5, 2022 in the following sites: Pubmed (Medline), Cochrane Library, Google Scholar, COVID-NMA Living Data and the Living Evidence on COVID-19. Ongoing studies were checked in the WHO clinical trial registry, NIH *clinicaltrials.gov* and various trial registries, and preprints from MedRxiv, chinaXiv and bioRxiv. MeSH and free text search were done. Search terms included coronavirus infections, COVID-19, severe acute respiratory syndrome, coronavirus 2 or SARS-CoV-2, intravenous immunoglobulin, immunoglobulin, IVIG, children, pediatric and adolescent. Only randomized trials and cohort studies and studies were included. The inclusion criteria were as follows:

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

Population	Children with COVID-19
Intervention/Exposure	Intravenous immunoglobulin
Comparison	Usual care, standard of care, placebo, any active control
Outcomes	Mortality, clinical improvement, hospitalization, ICU admission

Since few to no studies in children were found, indirect evidence was obtained using the Philippine COVID 19 Adult Living Clinical Practice Guideline (ALCPG) Phase II. To update the CPG, newer RCTs in adults were located using the same search terms but, this time with adults as population. All studies were appraised using Newcastle Ottawa Scale (NOS) for the cohort study, Cochrane RoB for RCTs and AGREE II for the Philippine ALCPG II.

Planned subgroup analysis for age, dose and COVID severity was not done due to unavailability of data in the pediatric study

Results

During the search, there were no randomized clinical trials found in children on the use of IVIG for the treatment of COVID-19 infection, however there were cohort studies found on the use of

IVIG compared with IVIG+CS for the treatment of MIS-C [14-17]. Among the cohort studies found, only one retrospective cohort study investigated the use of IVIG alone, corticosteroids alone and IVIG+CS for the treatment of MIS-C. The remaining three (3) retrospective cohort studies investigated the use of IVIG compared with IVIG plus corticosteroids for the treatment of MIS-C which did not fit the PICO criteria (intervention and comparison), thus only one cohort study was included in this review. Outcomes of interest included in the cohort study were reduction in the score for disease severity on the ordinal scale and composite outcome: inotropic support or mechanical ventilation or death. This cohort study was appraised as poor using the Newcastle-Ottawa Scale with a total score of 6 stars (Appendix 3).

Since there were no other studies found in children aside from the cohort study on MIS-C, indirect evidence was used in the form of the Philippine COVID 19 Adult Living Clinical Practice Guideline (ALCPG) Phase II which had an overall good quality using AGREE II. (Appendix 3) Three (3) new RCTs (Appendix 2) were added to update the ALCPG making a total of seven (7) RCTs.

The included studies have a very low overall certainty of evidence due to very serious risk of bias, for being an observational study and imprecision in 2 critical outcomes for the study on MIS-C and for the adult RCTs were downgraded due to indirectness, inconsistency and imprecision in 2 critical outcomes (Appendix 4).

Efficacy

MIS-C

Patient outcomes from the single cohort study on the use of IVIG alone compared with CS alone among patients with MIS-C showed inconclusive findings for the composite outcome: use of inotropic support or mechanical ventilation on or after day two (2) or death and for the outcome reduction in the score for disease severity on the ordinal scale by day 2 (RR 0.75, 95% CI [0.42, 1.33], n=237and RR 0.94, 95% CI [0.58, 1.54], n=212, respectively).

Among patients with MIS-C showed that addition of IVIG to CS resulted in a tendency to increased risk for the composite outcome: use of inotropic support or mechanical ventilation on or after day 2 or death (RR 1.89, 95% CI [1.08, 3.30], n=230) compared to CS alone. Findings were inconclusive for the outcome reduction in the score for disease severity on the ordinal scale by day 2 (RR 1.28, 95% CI [0.80, 2.06], n=212). The outcomes have very low certainty of evidence.

Adult Studies

Pooled estimates of patient outcomes on the use of IVIG showed statistically significant benefit for clinical deterioration or WHO progression level 7 or above (RR 0.39, 95% CI [0.20, 0.79], n=84, 2 RCTs), with shorter duration of hospital stay (MD -9.80, 95% CI [-11.38, -8.22], n=100, 1 RCT) and duration of ICU admission (MD -1.00, 95% CI [-1.92, -0.08], n=100, 1 RCT). Pooled estimates however, were inconclusive for all-cause mortality at Day 28 (RR 0.73, 95% CI [0.45, 1.19], n=533, 7 RCTs), Clinical Improvement at Day 28 (RR 1.35, 95% CI [0.93, 1.95], n=230, 3 RCTs), need for ICU admission (RR 0.89, 95% CI [0.72, 1.10], n=84, 1 RCT), and need for mechanical ventilation (RR 0.85, 95% CI [0.46, 1.59], n=264, 3 RCTs). The rest of the outcomes namely clinical improvement at Day 7, Viral Clearance at Day 3 and Day 8 were likewise inconclusive. The forest plots are shown in Appendix 5.

Safety

Risk for adverse events (RR 1.06, 95% CI [0.89, 1.27], n=356, 4 RCTs) and serious adverse events (RR 1.39, 95% CI [0.82, 2.38], n=340, 4 RCTs) were not statistically significant.

Adverse events reported include hypersensitivity reaction (e.g. mild rash and lip swelling, anaphylaxis), infusion reactions (e.g. headache, chills, myalgia, wheezing, tachycardia, lower back pain, nausea, hypotension), transfusion related acute lung injury (TRALI), hemolysis, thrombotic events, renal failure, aseptic meningitis syndrome, transmission of infectious pathogens [13].

The cohort study on children reported adverse events or IVIG-related complications which occurred in approximately 1.8% of patients treated with IVIG [4]. Adverse events reported in the study include mild rash and lip swelling and other complications which were not specified [16].

Other Considerations (Evidence to Decision)

Intravenous immunoglobulin and methylprednisolone have been available and used locally for the treatment of Kawasaki disease and systemic lupus erythematosus (SLE) respectively. IVIG has been available in hospitals and various suppliers and methylprednisolone is mostly available in hospitals and local drugstores. The estimated cost of IVIG and methylprednisolone was retrieved from the 2020 Philippine Drug Price Reference Index [18]. Table 2 shows the estimated cost of IVIG and methylprednisolone.

Table 2. Estimated Cost of IVIG and Methylprednisolone

	IVIG 2 g/kg over 8-12 hours (maximum dose:100g) [15]	**Methylprednisolone** 1-2 mg/kg/dose (max: 30 mg/dose) IV q12h for 3-5 days [15]
Preparations available:	50mg/ml (100ml) or 5g per vial	125mg/ml(2ml)
Cost per preparation based on 2020 DPRI (Range of Cost from lowest to highest)	9,650 (1,600 – 16,000)	613.77 (613.77-995)
Total Cost of Treatment (Range)	20 vials: 193,000 (32,000 – 320,000)	3 vials: 1,841.31 (1,841.31-2,985)
Total Cost of Treatment [IVIG + Steroid] (Range)	194,841.31 (33,841.31 – 322,985)	

*Values were taken from the 2020 Philippine Drug Price Reference Index; Dosages were based on the PPS and PIDSP INTERIM GUIDELINES ON THE SCREENING, CLASSIFICATION, AND MANAGEMENT OF PEDIATRIC PATIENTS WITH SUSPECTED OR CONFIRMED CORONAVIRUS DISEASE 2019 (COVID-19) Ver. 5. Updated 1/8/2022.

There were no studies found on patient's values and preference, equity, acceptability and feasibility in the literature search done but based on the availability and the varied use of IVIG and methylprednisolone, it can somehow be inferred that they are widely acceptable.

Recommendations from Other Groups

There were no available guidelines on the use of IVIG for the treatment of COVID-19 infection in children; however, the PIDSP and PPS interim guidelines recommend the use of IVIG plus steroids for the treatment of MIS-C [12]. The Australian guideline taskforce is currently developing recommendations [18].

Since there were no available guidelines on the use of IVIG in children with COVID 19 infection, guidelines in adults were used. The Philippine COVID 19 Adult Living CPG suggests against the use of IVIG in moderate to severe COVID 19 [19] while the Surviving Sepsis Campaign Guidelines also suggest against its' routine use but in critically-ill adults with COVID-19 (updated March 2021) [20]. The Australian Living Guidelines allow the use of immunoglobulin for the treatment of COVID-19, only in the context of randomized trials with appropriate ethical approval (updated December 2021) [19]. The US NIH found insufficient evidence to support its use pending results of clinical trials (updated April 2021) [13]. WHO, IDSA, and American Thoracic Society/European Respiratory Society have no recommendation on the use of IVIG for the treatment of COVID 19 infection.

Research Gaps

Currently, there are no randomized trials on the use of IVIG for the treatment of COVID 19 in children, hence the available sources of data are from observational studies in children and from randomized trials in adults which is an indirect form of evidence.

As of January 13, 2022, there are 26 ongoing studies during the search of which only 2 studies are conducted in children. One of the 2 studies is a randomized open label study of COVID-19 Therapy in Children with Pediatric Inflammatory Multisystem Syndrome –Temporally Associated with SARS COV 2 (PIMS-TS) in Switzerland or the SWISSPED-RECOVERY trial with the expected completion date on July 2022. The other one is an observational study on MIS-C (Appendix 6).

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Appendix 1. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE OF SEARCH	RESULTS	
			Yield	Eligible
Medline	("covid 19"[Supplementary Concept] OR "COVID-19 drug treatment"[Supplementary Concept] OR "COVID-19 serotherapy"[Supplementary Concept] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[Supplementary Concept] OR "2019-nCoV"[All Fields] OR "2019nCoV"[All Fields] OR "cov 2"[All Fields] OR "covid 19"[All Fields] OR "SARS Coronavirus 2"[All Fields] OR "sarscov 2"[All Fields] OR "sarscov 2"[All Fields] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[All Fields] OR "coronavirus 2"[All Fields] OR "covid 19"[All Fields] OR "covid 19"[All Fields] OR "2019-nCoV"[All Fields] OR "2019nCoV"[All Fields] OR "corona virus disease 2019"[All Fields] OR "cov2"[All Fields] OR "covid 19"[All Fields] OR "COVID19"[All Fields] OR "nCov 2019"[All Fields] OR "nCoV"[All Fields] OR "new corona virus"[All Fields] OR "new coronaviruses"[All Fields] OR "novel corona virus"[All Fields] OR "novel coronaviruses"[All Fields] OR "SARS Coronavirus 2"[All Fields] OR "SARS2"[All Fields] OR "sarscov 2"[All Fields] OR "Severe Acute Respiratory Syndrome Coronavirus 2"[All Fields] OR (("19"[Title/Abstract] OR "2019"[Title/Abstract] OR "2019-nCoV"[All Fields] OR "Beijing"[All Fields] OR "China"[All Fields] OR "covid 19"[All Fields] OR "epidem*"[Title/Abstract] OR "epidemic*"[All Fields] OR ("epidemies"[All Fields] OR "epidemy"[All Fields]) OR "new"[Title/Abstract] OR "novel"[Title/Abstract] OR "outbreak"[All Fields] OR "pandem*"[All Fields] OR "sarscov 2"[All Fields] OR "Shanghai"[All Fields] OR "Wuhan"[All Fields]) AND ("Coronavirus Infections"[MeSH Terms] OR "coronavirus"[MeSH Terms] OR "coronavirus*"[All Fields] OR "corona virus*"[All Fields] OR "cov"[Title/Abstract] OR "pneumonia virus*"[Title/Abstract])) AND 2019/12/01:3000/12/31[Date - Publication] AND ("Intravenous Immunoglobulin"[All Fields] OR ("immunoglobulins, intravenous"[MeSH Terms] OR ("immunoglobulins"[All Fields] AND "intravenous"[All Fields]) OR "intravenous immunoglobulins"[All Fields] OR "ivig"[All Fields]) OR ("immunoglobulin s"[All Fields] OR "immunoglobuline"[All Fields] OR "immunoglobulines"[All Fields] OR "immunoglobulins"[MeSH Terms] OR "immunoglobulins"[All Fields] OR "immunoglobulin"[All Fields])) AND ((("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "drug therapy"[MeSH Subheading] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields] OR ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields]) OR (("paediatrics"[All Fields] OR "pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "paediatric"[All Fields] OR "pediatric"[All Fields]) AND ("patient s"[All Fields] OR "patients"[MeSH Terms] OR "patients"[All Fields] OR "patient"[All Fields] OR "patients s"[All Fields])) OR ("pedia"[All Fields] AND ("patient s"[All Fields] OR "patients"[MeSH Terms] OR "patients"[All Fields] OR "patient"[All Fields] OR "patients s"[All Fields])) OR ("adolescences"[All Fields] OR "adolescency"[All Fields] OR	1/3/22	486	2 (MIS-C) 6 Adults

	"adolescent"[MeSH Terms] OR "adolescent"[All Fields] OR "adolescence"[All Fields] OR "adolescents"[All Fields] OR "adolescent s"[All Fields]))			
CENTRAL	"COVID-19" OR "COVID-19 diagnostic testing" OR "COVID-19 drug treatment" OR "COVID-19 serotherapy" OR "COVID-19 vaccine" OR "severe acute respiratory syndrome coronavirus 2" OR "2019-nCoV" OR "2019nCoV" OR "cov 2" OR "Covid-19" OR "sars coronavirus 2" OR "sarscov 2" OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2" OR "coronavirus 2" OR "COVID 19" OR "COVID-19" OR "2019 ncov" OR "2019nCoV" OR "corona virus disease 2019" OR "cov2" OR "COVID-19" OR "COVID19" OR "nCov 2019" OR "nCoV" OR "new corona virus" OR "new coronaviruses" OR "novel corona virus" OR "novel coronaviruses" OR "SARS Coronavirus 2" OR "SARS2" OR "SARS-COV-2" OR "Severe Acute Respiratory Syndrome Coronavirus 2" in All Text AND Intravenous Immunoglobulin OR IVIG OR Immunoglobulin in Title Abstract Keyword AND children OR child OR pediatrics OR pedia OR adolescent OR infant OR neonate OR newborn in Title Abstract Keyword - (Word variations have been searched)	1/4/22 8 PM	33	Adults
COVID-NMA Initiative		1/4/22 9:30 PM	7	Adults
ClinicalTrials.gov		1/4/22 11PM	568	26 (24 on adults)
WHO database COVID-19 studies		1/4/22	0	0
China Registry		1/5/22	0	0
MedRxiv.org		1/5/22 8AM	217	1 (MIS-C)
BioRxiv.org		1/5/22	24	0
ChinaRxiv.org		1/5/22	0	0
Google Scholar		1/5/22	967	4 (MIS-C)
EU Clinical Trials Register		1/5/22		0
Republic of Korea - Clinical Research Information Service		1/5/22	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search		1/5/22	0	0

Appendix 2. Characteristics of Included Studies

Study ID	Design	Sample Size	Participants	Comparisons		Outcomes
Treatment of Multisystem Inflammatory Syndrome in Children McArdle et al 2021 (UK)	Observational (cohort)	N=420	pedia patients who met the World Health Organization (WHO) criteria for MIS-C	1.IVIG (dose not specified) 2. IVIG (dose not specified) + Glucocorticoids	Glucocorticoids	Composite of inotropic support or mechanical ventilation (invasive or noninvasive) by day 2 or later or death. The reduction in disease severity on a seven-point ordinal scale between day 0 and day 2.
ADULT STUDIES						
Gharebaghi et al 2020	RCT	59	adult patients with severe COVID-19 who did not respond to initial treatments, ARDS	4 vials of 5g IVIg x 3 days	placebo	In-hospital mortality
Tabarsi et al 2020	RCT	84	Severely ill COVID-19 adult patients	400 mg/Kg daily for three doses	Standard of care	invasive mechanical ventilation and oxygenation, the need for admission to the Intensive Care Unit (ICU), and the mortality rate
Sakoulas et al 2020	RCT, open label	33	Adult patients with Moderate to severe COVID-19	500 mg/kg daily for 3 days	Standard of care	Need for mechanical ventilation, length of hospital stay, length of ICU stay
Raman et al 2021	RCT open label	100	Adult patients with Moderate COVID-19	400 mg/kg daily for 5 days	Standard of care	Number of days hospitalized, time to clinical improvement, duration of mechanical ventilation, 28-day mortality, proportion of patients with negative RT PCR (day 14, 28)
Marezaud et al 2021 (new)	RCT double blind	146	Adult patients with COVID-19 associated Moderate	2 g/kg over 4 days or 0.5g/kg per day for 4 days	Placebo	The primary outcome was the number of ventilator-free days at day 28, defined as the number of days

			to severe ARDS			between the last extubation day and day 28 The key secondary outcomes were the sequential organ failure assessment score at day 14 and day 28; the occurrence of grade 3 or 4 adverse events or serious adverse events attributed to IVIG; the time to intensive care unit or hospital discharge; the clinical status at day 28 and day 90 as assessed by the seven-category ordinal scale; 90-day mortality; and lung injury score at day 28.
Parikh, D. et al 2021 (preprint) (new)	RCT open label	60	Admitted patients with moderate to critical COVID 19 infection	C-IVIG 30 ml IV on day 1 and 2	Standard of Care	Mean change from Day 1 to Day 8 in an 8-point ordinal scale
Ali et al 2021 (new)	RCT open label	50	Patients with confirmed with COVID 19 (moderate to severe) admitted to a center in Pakistan	C-IVIG 0.15-0.3g/kg IV x 1 dose	Standard of Care	Mortality at D28, WHO Score of 7 and above at D28, Clinical improvement at D28, Adverse events

Appendix 3A. Study Appraisal

Newcastle Ottawa Scale

McArdle et al. 2021		
Domain	**Assessment**	**Score**
Selection		
1) Representativeness of the exposed cohort	Truly representative (one star)	*
2) Selection of the non-exposed cohort	Drawn from the same community as the exposed cohort (one star)	*
3) Ascertainment of exposure	Secure record (one star)	*
4) Demonstration that outcome of interest was not present at start of study	Yes (one star)	*
TOTAL		4 STARS
Comparability		
Comparability of cohorts on the basis of the design or analysis controlled for confounders	Cohorts are not comparable on the basis of the design or analysis controlled for confounders	-
TOTAL		0 STAR
Outcome		
1) Assessment of outcome	Record linkage (one star)	*
2) Was follow-up long enough for outcomes to occur	Yes (one star)	-
3) Adequacy of follow-up of cohorts	Complete follow up- all subject accounted for (one star) 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)	*
TOTAL		2 STARS **=POOR**

OVERALL TOTAL	6 STARS

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, andpoor)**: Poor (Since it failed or zero star in the comparability domain)**

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Appendix 3B. Philippine Adult Living Clinical Practice Guidelines Phase II AGREE Assessment

AGREE II

A critical group appraisal of: Philippine COVID-19 Living Clinical Practice Guidelines using the AGREE II Instrument

Created with the AGREE II Online Guideline Appraisal Tool.

No endorsement of the content of this document by the AGREE Research Trust should be implied.

Co-ordinator:

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URL of this appraisal: http://www.agreetrust.org/group-appraisal/16554

Guideline URL:
https://drive.google.com/file/d/1bRloJGUGOkcmK8PTiPo9P7iO7U3TLXbN/view?usp=sharin

Comments

Domain 1. Scope and Purpose

Item 1

- Appraiser 3: Benefits for local end-user and other stakeholders for the contextualized recommendations clearly and concisely written.
  Clearly state expected health benefits from the guideline for the patient population/society

Domain 2. Stakeholder Involvement

Item 4

- Appraiser 3: List the institution and geographical location (to show distribution within the Philippines) of the members of CPG development groups which will contribute to the aim of the CPG to contextualize the evidence to the local setting.

Item 5

- Appraiser 4: Representation of target population perspectives not clear
- Appraiser 3: Steering committee and in Consensus Panel composition it is not clearly stated who represented the patients\' perspective. Although it is stated that the members who had experienced COVID-19 could represent the patients. If patients\' perspective through literature review, clearly state this also in the methodology.

Domain 3. Rigour of Development

Item 7

- Appraiser 4: Comprehensive search strategy in summary. Individual search strategies for clinical specific clinical questions may not have been exhaustive (e.g. vitamin c)
- Appraiser 3: General descriptions are detailed and comprehensive. Show search strategy used per clinical question

Item 10

- Appraiser 4: Elaborate on voting process
- Appraiser 3: Provide description of the recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered and outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique.

Item 13

- Appraiser 4: Include other methods in external review such as rating or assessment scales from relevant stakeholders.
- Appraiser 3: The process of external review relies on feedback from users and

members of the webpage. The process/method of the external review (rating scale, open-ended questions) of DOH and PCHRD, number of reviewers, outcomes gathered (i.e. summary of findings) should also be described.

Domain 4. Clarity of Presentation

Item 17

- Appraiser 3: Key recommendations are tabulated. Also they are boxed for each clinical question.

Domain 5. Applicability

Item 19

- Appraiser 4: May provide more information on guideline application or implementation (e.g. algorithms)
- Appraiser 3: The CPG is a reference for the unified COVID-19 algorithms on testing and management which is published in the PSMID website.

Item 20

- Appraiser 4: Provide more detail on cost information and methods by which this was sought, relevance to recommendations
- Appraiser 3: Include health economist or PhilHealth representative in the SC or CP.

Item 21

- Appraiser 3: Results of CPG downloads were described as part of monitoring and auditing. Suggest to describe in more detail the process for auditing/monitoring and use of the guideline taking into consideration possible process measures, behavioral measures, clinical or health outcome measures.

Domain 6. Editorial Independence

Item 23

- Appraiser 3: Oversight committee to assess for COI of CPG group members is present.

Created online at www.agreetrust.org 18 January 2022

AGREE II

A critical group appraisal of: Philippine COVID-19 Living Clinical Practice Guidelines using the AGREE II Instrument

Created with the AGREE II Online Guideline Appraisal Tool.

No endorsement of the content of this document by the AGREE Research Trust should be implied.

Co-ordinator:

Date: 18 January 2022

Email: pattiorduna@gmail.com

URL of this appraisal: http://www.agreetrust.org/group-appraisal/16554

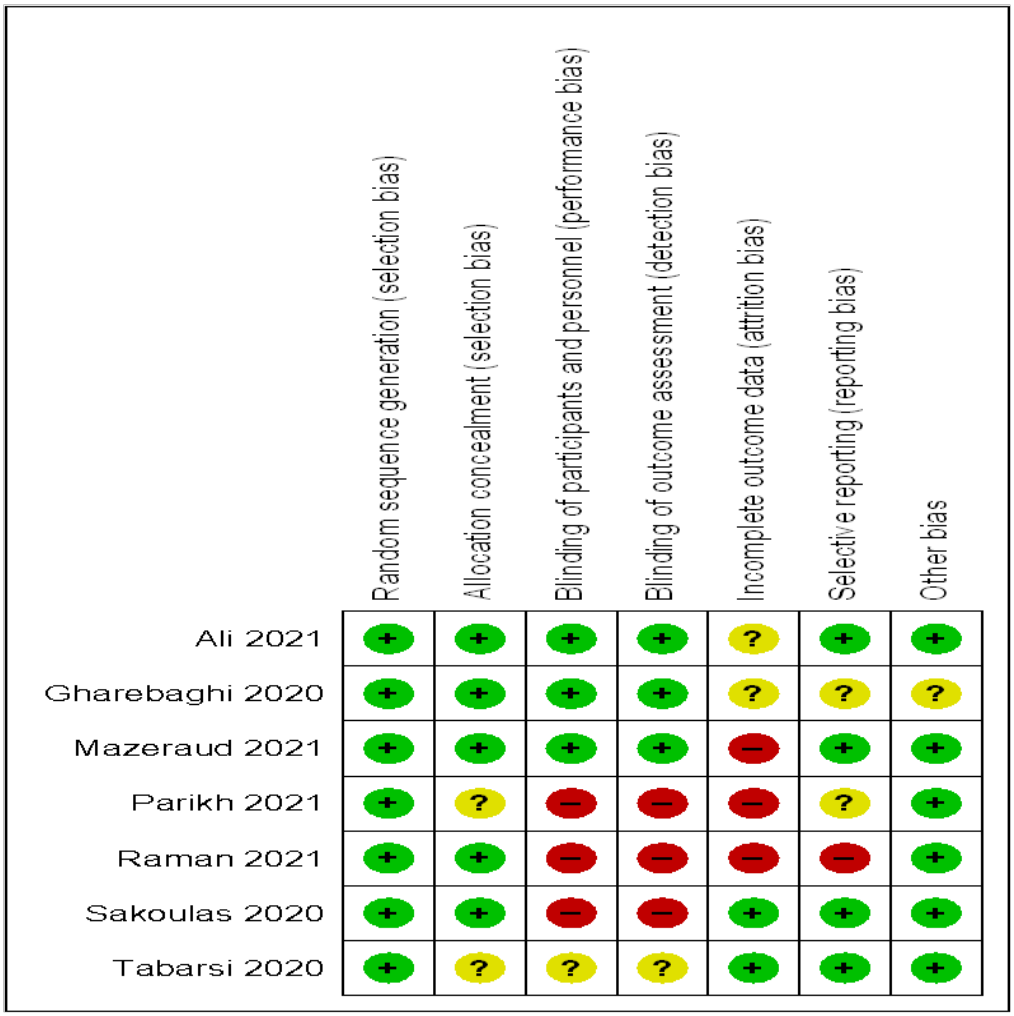
Guideline URL: https://drive.google.com/file/d/1bRloJGUGOkcmK8PTiPo9P7iO7U3TLXbN/view?usp=sharing

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	OA 1	OA 2
89%	83%	88%	98%	85%	100%	83%	Yes - 1, Yes with modifications - 2, No - 0

Domain 1. Scope and Purpose			
	Appraiser 2	Appraiser 4	Appraiser 3
Item 1	6	6	6
Item 2	5	7	7
Item 3	6	7	7
Domain 2. Stakeholder Involvement			
	Appraiser 2	Appraiser 4	Appraiser 3
Item 4	6	6	6
Item 5	5	5	5
Item 6	7	7	7
Domain 3. Rigour of Development			
	Appraiser 2	Appraiser 4	Appraiser 3
Item 7	6	6	6
Item 8	6	7	7
Item 9	6	7	7
Item 10	7	6	5
Item 11	6	7	7
Item 12	6	7	7
Item 13	5	5	5
Item 14	6	7	7
Domain 4. Clarity of Presentation			
	Appraiser 2	Appraiser 4	Appraiser 3
Item 15	6	7	7
Item 16	7	7	7
Item 17	7	7	7
Domain 5. Applicability			
	Appraiser 2	Appraiser 4	Appraiser 3
Item 18	7	7	7
Item 19	5	5	7
Item 20	5	5	6
Item 21	6	7	6
Domain 6. Editorial Independence			
	Appraiser 2	Appraiser 4	Appraiser 3
Item 22	7	7	7
Item 23	7	7	7
Overall Assessment			
	Appraiser 2	Appraiser 4	Appraiser 3
OA1	6	6	6

Created online at www.agreetrust.org 18 January 2022

Appendix 3C. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Appendix 4A: GRADE Evidence Summary: IVIG vs. Glucocorticoids for MIS-C

Author(s): Liza Bejemino, MD, Maria Theresa Tolosa, MD, Ma. Lucila Perez, MD
Reference(s): Mcardle AJ, et al..Treatment of Multisystem Inflammatory Syndrome in Children. N Engl J Med 2021;385:11-22.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Glucocorticoids	IVIG	Relative (95% CI)	Absolute (95% CI)		
Use of inotropic support or mechanical ventilation on or after day 2 or death												
1 (N=237)	observational studies	very serious[a]	not serious	not serious	serious[b]	none	12/68 (17.6%)	40/169 (23.7%)	**RR 0.75** (0.42 to 1.33)	**59 fewer per 1,000** (from 137 fewer to 78 more)	⊕◯◯◯ Very low	
Reduction in the score for disease severity on the ordinal scale by day 2												
1 (N= 212)	observational studies	very serious[a]	not serious	not serious	serious[b]	none	16/60 (26.7%)	43/152 (28.3%)	**RR 0.94** (0.58 to 1.54)	**17 fewer per 1,000** (from 119 fewer to 153 more)	⊕◯◯◯ Very low	

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

Explanations
a. Failed to meet the criteria for the comparability domain of the Newcastle-Ottawa Scale
b. Wide confidence interval

Appendix 4B: GRADE Evidence Summary: IVIG + glucocorticoids vs. Glucocorticoids for MIS-C

Author(s): Liza Bejemino, MD, Maria Theresa Tolosa, MD, Ma. Lucila Perez, MD
Reference(s): Mcardle AJ, et al..Treatment of Multisystem Inflammatory Syndrome in Children. N Engl J Med 2021;385:11-22.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IVIG + Glucocorticoids	Glucocorticoids	Relative (95% CI)	Absolute (95% CI)		
Composite: Use of inotropic support or mechanical ventilation on or after day 2 or death												
1 (N=237)	observational studies	very serious[a]	not serious	not serious	not serious	none	54/162 (33.3%)	12/68 (17.6%)	**RR 1.89** (1.08 to 3.30)	**157 more per 1,000** (from 14 more to 406 more)	⊕◯◯◯ Very low	Critical
Reduction in the score for disease severity on the ordinal scale by day 2												
1 (N=212)	observational studies	very serious[a]	not serious	not serious	serious[b]	none	52/152 (34.2%)	16/60 (26.7%)	**RR 1.28** (0.80 to 2.06)	**75 more per 1,000** (from 53 fewer to 283 more)	⊕◯◯◯ Very low	Important

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

Explanations
a. Failed to meet the criteria for the comparability domain of the Newcastle-Ottawa Scale.
b. Wide confidence interval

Appendix 4C: GRADE Evidence Summary: IVIG vs. SOC or placebo for COVID-19 infection

Author(s): Gharebaghi, et. al. 2020, Tabarsi, et. al. 2020, Sakoulas, et. al. 2020, Raman, et. al. 2021, Marezaud, et. al. 2021, Parikh, D. 2021, Ali, et. al. 2021
Reference(s): PHILIPPINE COVID-19 LIVING CLINICAL PRACTICE GUIDELINES. Updated June 30, 2021; Intravenous immunoglobulins in patients with COVID-19-associated moderate-to-severe acute respiratory distress syndrome (ICAR): multicentre, double-blind, placebocontrolled, phase 3 trial. Lancet Respir Med 2021; Safety and efficacy of COVID-19 hyperimmune globulin (HIG) solution in the treatment of active COVID-19 infection-Findings from a Prospective, Randomized, Controlled, MultiCentric Trial. 2021; Hyperimmune anti-COVID-19 IVIG (C-IVIG) treatment in severe and critical COVID-19 patients: A phase I/II randomized control trial. EClinicalMedicine 36 (2021).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IVIG	SOC or Placebo	Relative (95% CI)	Absolute (95% CI)		
Mortality												
7 (N=533)	randomised trials	not serious	not serious	serious[a]	serious[b]	none	66/288 (22.9%)	59/245 (24.1%)	**RR 0.73** (0.45 to 1.19)	**65 fewer per 1,000** (from 132 fewer to 46 more)	⊕⊕◯◯ Low	Critical
Clinical Improvement D28												
3 (N=230)	randomised trials	not serious	not serious	serious[a]	serious[b]	none	61/126 (48.4%)	33/104 (31.7%)	**RR 1.35** (0.93 to 1.95)	**111 more per 1,000** (from 22 fewer to 301 more)	⊕⊕◯◯ Low	Critical
Clinical improvement D7												
1 (N=50)	randomised trials	not serious	not serious	serious[a]	very serious[c]	none	15/40 (37.5%)	0/10 (0.0%)	**RR 8.32** (0.54 to 128.34)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕◯◯◯ Very low	Critical
Clinical Deterioration or WHO progression level 7 or above at D28												
2 (N=84)	randomised trials	not serious	not serious	serious[a]	not serious	none	11/57 (19.3%)	10/27 (37.0%)	**RR 0.39** (0.20 to 0.79)	**226 fewer per 1,000** (from 296 fewer to 78 fewer)	⊕⊕⊕◯ Moderate	Important
Viral Clearance D3												
1(n=60)	randomised trials	not serious	not serious	serious[a]	serious[b]	none	14/30 (46.7%)	11/30 (36.7%)	**RR 1.27** (0.69 to 2.33)	**99 more per 1,000** (from 114 fewer to 488 more)	⊕⊕◯◯ Low	Important
Viral Clearance D14												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IVIG	SOC or Placebo	Relative (95% CI)	Absolute (95% CI)		
2(n=160)	randomised trials	not serious	serious[d]	serious[a]	serious[c]	none	69/80 (86.3%)	36/80 (45.0%)	**RR 1.89** (0.37 to 9.73)	**400 more per 1,000** (from 284 fewer to 1,000 more)	⊕◯◯◯ Very low	Importatny
Adverse Events												
4(n=356	randomised trials	not serious	not serious	serious[a]	not serious	none	97/189 (51.3%)	75/167 (44.9%)	**RR 1.06** (0.89 to 1.27)	**27 more per 1,000** (from 49 fewer to 121 more)	⊕⊕⊕◯ Moderate	Critical
Serious Adverse Events												
4(n=340	randomised trials	not serious	not serious	serious[a]	serious[b]	none	24/166 (14.5%)	20/174 (11.5%)	**RR 1.39** (0.82 to 2.38)	**45 more per 1,000** (from 21 fewer to 159 more)	⊕⊕◯◯ Low	Critical
Need for Mechanical Ventilation												
3(n=264	randomised trials	not serious	not serious	serious[a]	serious[b]	none	38/138 (27.5%)	37/126 (29.4%)	**RR 0.85** (0.46 to 1.59)	**44 fewer per 1,000** (from 159 fewer to 173 more)	⊕⊕◯◯ Low	Critical
Duration of Hospitalization												
1(n=100)	randomised trials	not serious	not serious	serious[a]	not serious	none	50	50	-	MD **9.8 lower** (11.38 lower to 8.22 lower)	⊕⊕⊕◯ Moderate	Critical
Duration of ICU Admission												
1(n=100)	randomised trials	not serious	not serious	serious[a]	not serious	none	50	50	-	MD **1 lower** (1.92 lower to 0.08 lower)	⊕⊕⊕◯ Moderate	Critical
Need for ICU Admission												
1(n=84)	randomised trials	not serious	not serious	serious[a]	not serious	none	39/52 (75.0%)	27/32 (84.4%)	**RR 0.89** (0.72 to 1.10)	**93 fewer per 1,000** (from 236 fewer to 84 more)	⊕⊕⊕◯ Moderate	Critical

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. The subjects in the included studies are not children but adults.
b. Wide Confidence Interval
c. Very wide confidence interval
d. High heterogeneity

Appendix 5. Forest Plots

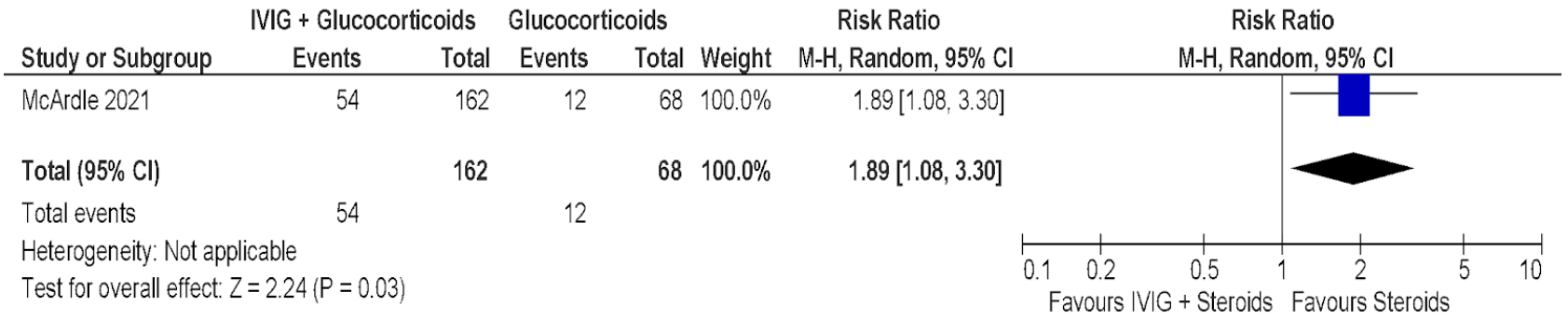


Figure 1. IVIG + Glucocorticoids vs Glucocorticoids in pediatric patients: Use of inotropic support or mechanical ventilation on or after day 2 or death.

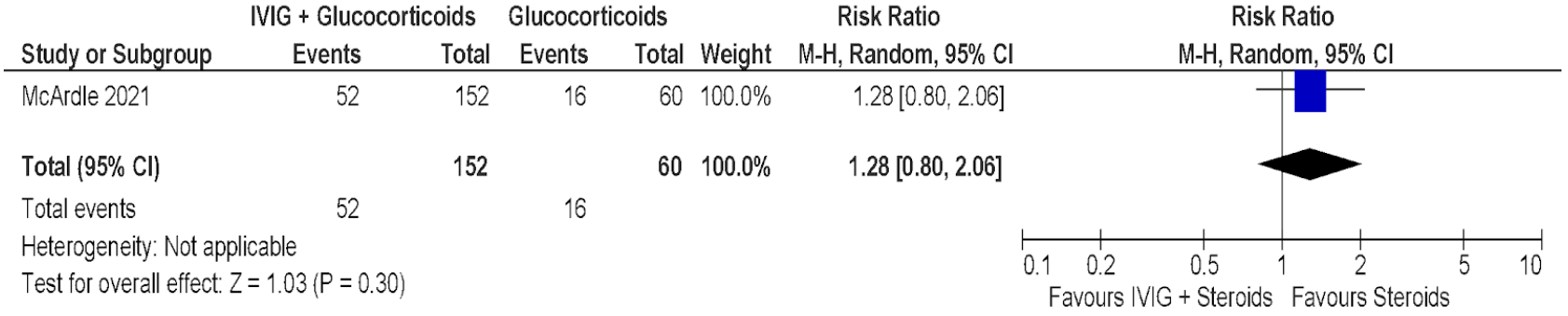


Figure 2. IVIG + Glucocorticoids in pediatric patients: Reduction in the score for disease severity on the ordinal scale by day 2.

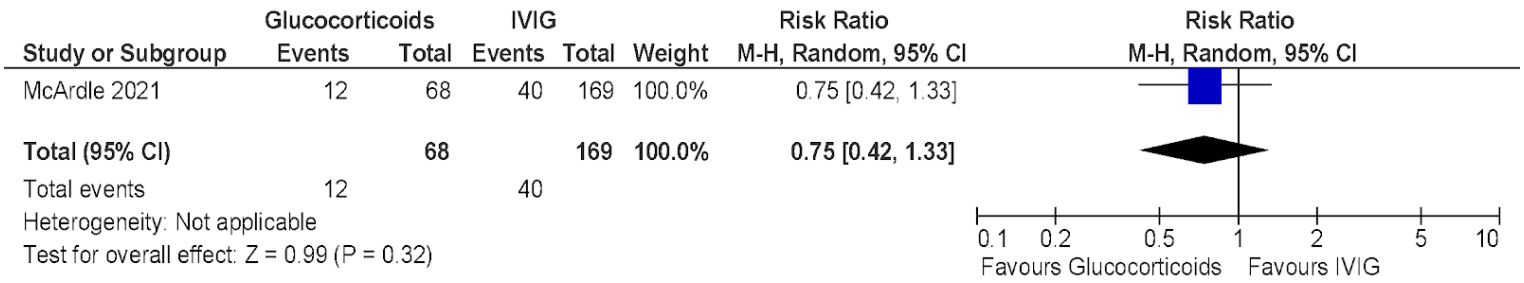


Figure 3. IVIG vs. Glucocorticoids in pediatric patients: Use of inotropic support or mechanical ventilation on or after day 2 or death.

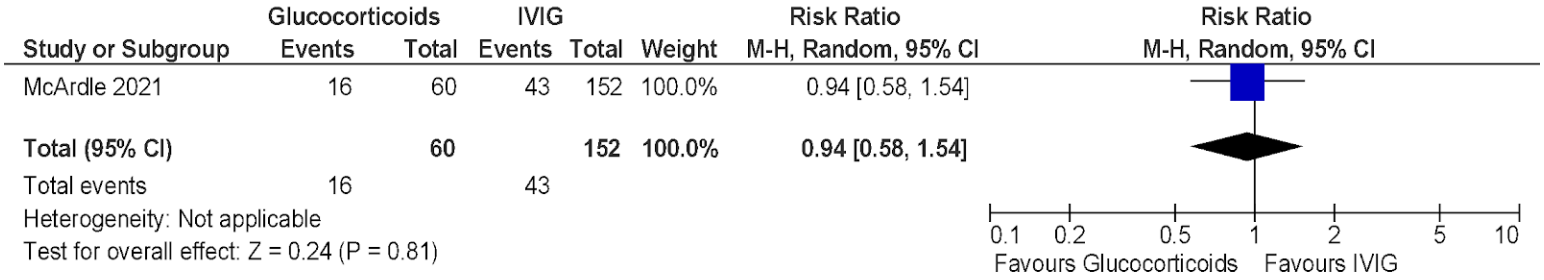


Figure 4. IVIG vs. Glucocorticoids in pediatric patients: Reduction in the score for disease severity on the ordinal scale by day 2.

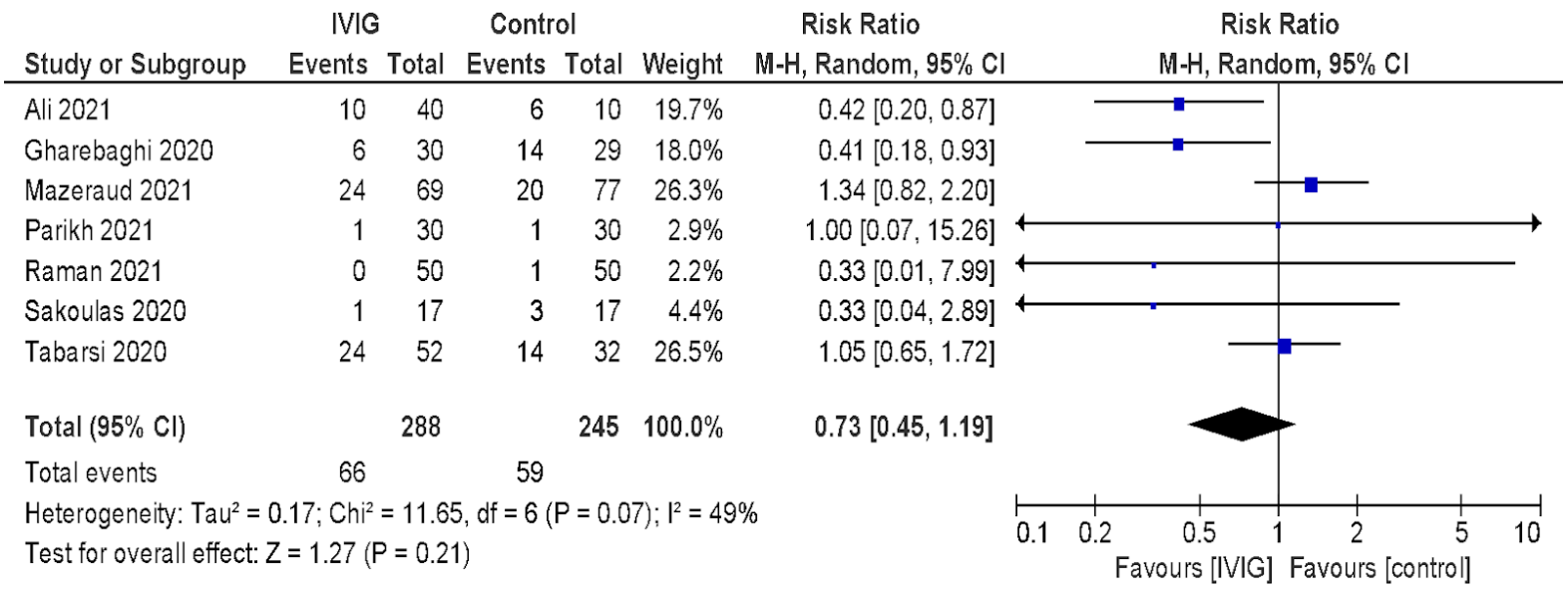


Figure 5. IVIG vs SOC or Placebo in adults: Mortality.

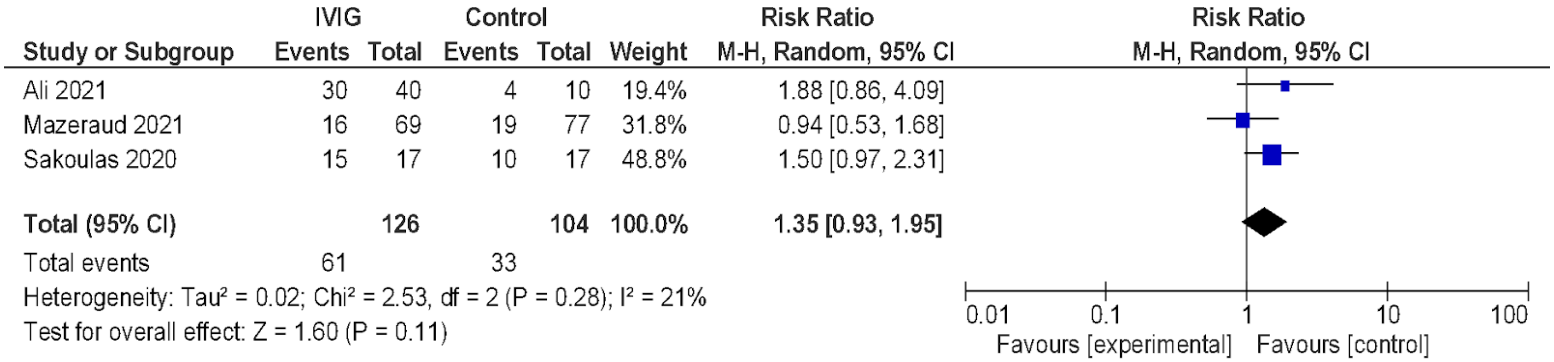


Figure 6. IVIG vs SOC or Placebo in adults: Clinical Improvement D28.

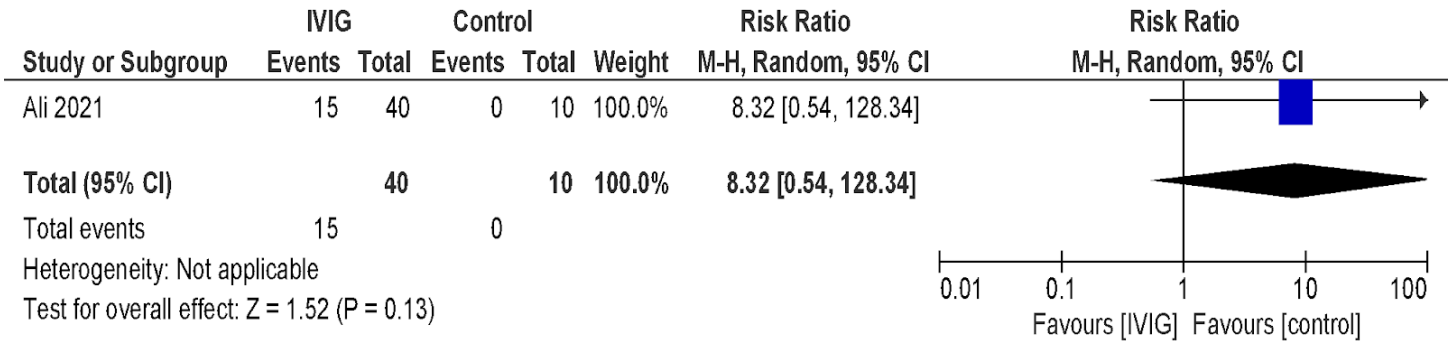


Figure 7. IVIG vs SOC or Placebo in adults: Clinical improvement D7.

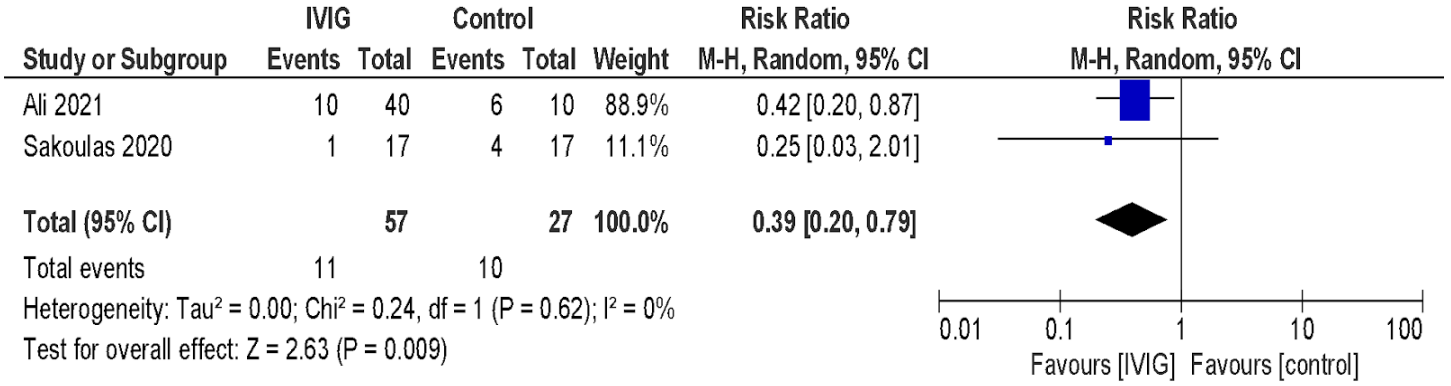


Figure 8. IVIG vs SOC or Placebo in adults: Clinical Deterioration or WHO progression level 7 or above at D28.

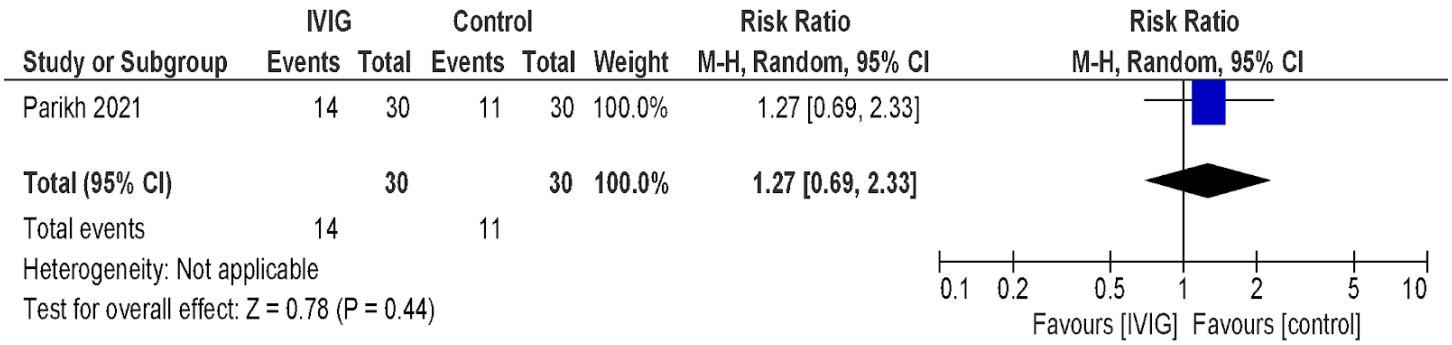


Figure 9. IVIG vs SOC or Placebo in adults: Viral Clearance D3.

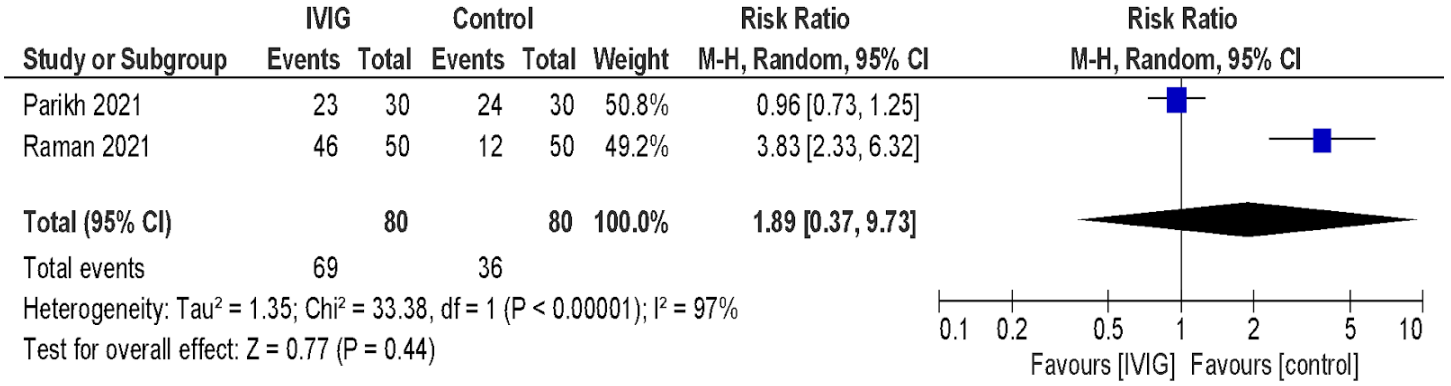


Figure 10. IVIG vs SOC or Placebo in adults: Viral Clearance D14.

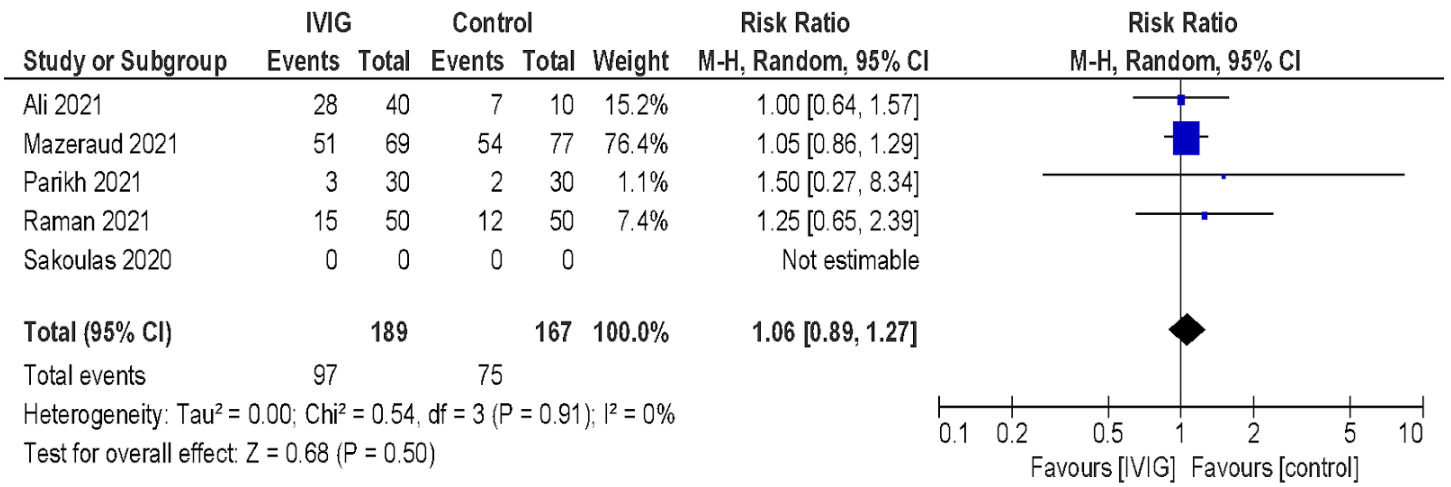


Figure 11. IVIG vs SOC or Placebo in adults: Adverse Events

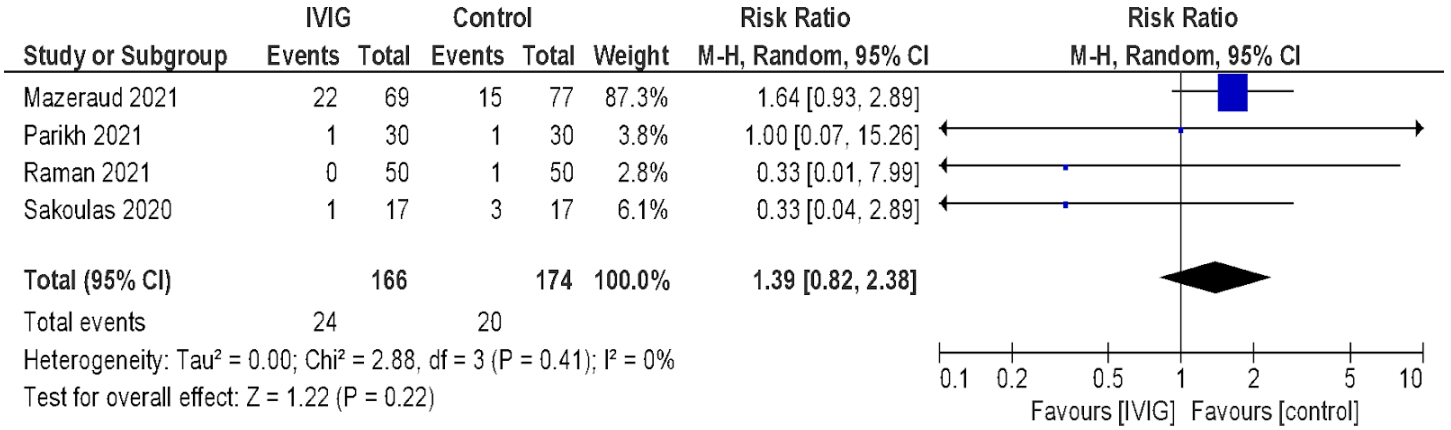


Figure 12. IVIG vs SOC or Placebo in adults: Serious Adverse Events.

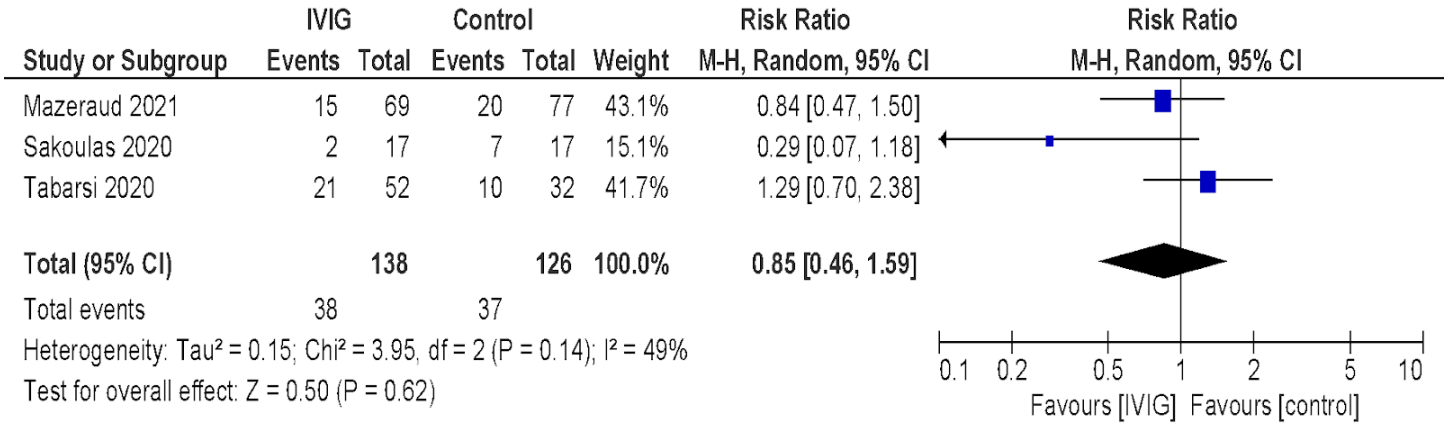


Figure 13. IVIG vs SOC or Placebo in adults: Need for Mechanical Ventilation.

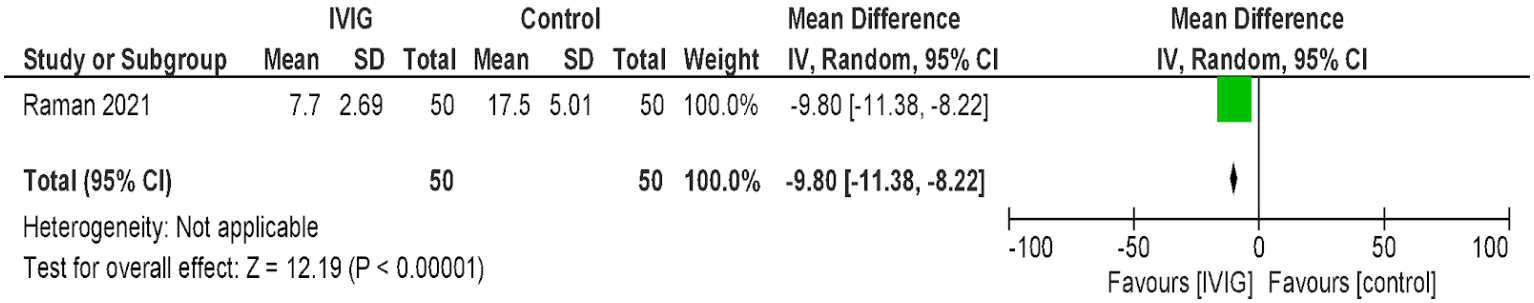


Figure 14. IVIG vs SOC or Placebo in adults: Duration of Hospitalization.

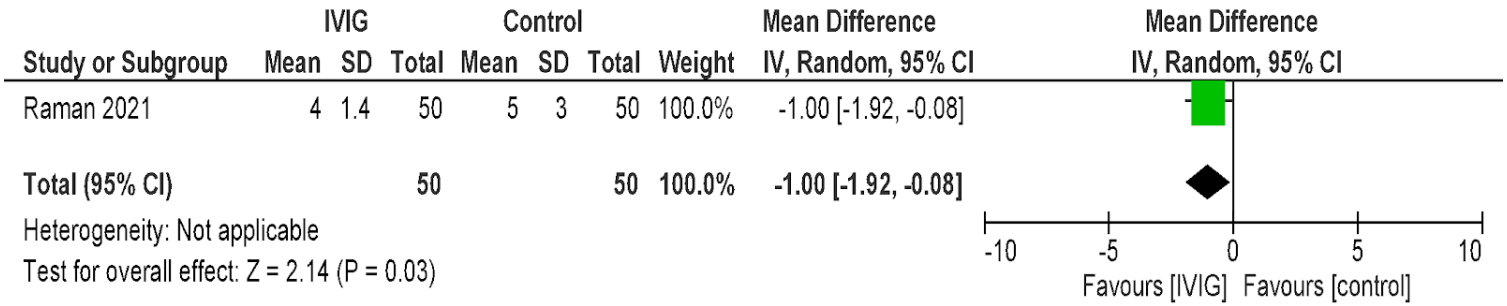


Figure 15. IVIG vs SOC or Placebo in adults: Duration of ICU Admission.

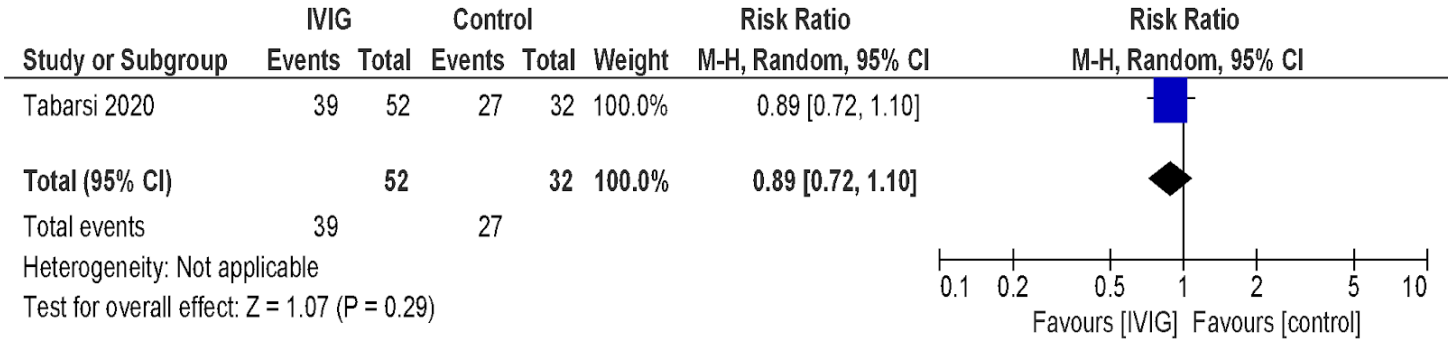


Figure 16. IVIG vs SOC or Placebo in adults: Need for ICU Admission.

Appendix 6. Summary of Recommendations from Other Groups

CPGs/ Expert Group	Recommendation	CPGs/ Expert Group
Interim Guidelines on the Screening, Classification, and Management Of Pediatric Patients With Suspected Or Confirmed Coronavirus Disease 2019 (Covid-19) Version 5, PPS, PIDSP	Recommend intravenous immunoglobulin (IVIG) with corticosteroids for the treatment of MIS-C at a dose of 2 g/kg over 8-12 hours (max 100 g)*	08 January 2022
	*Assess cardiac function and fluid status before giving IVIG; should only be administered when cardiac function is restored	
Australian Guidelines	The Taskforce is currently developing recommendations in children and adolescents with COVID-19*. The Australian Living Guidelines for adults allow the of use IVIG for the treatment of COVID-19, only in the context of clinical trials	17 December 2021
	*Do not use combination of immunoglobulin plus methylprednisolone to treat COVID-19 in children and adolescents unless they are eligible to be enrolled in trials.	
Us NIH Guidelines	There is currently insufficient evidence for the Panel to recommend either for or against any specific therapeutic strategy for the management of MIS-C.	21 April 2021
Philippine Covid-19 Living Clinical Practice Guidelines (Adult)	Suggest against the use of IVIG as treatment for moderate to severe COVID-19 (Conditional, Very low)	30 June 2021
Surviving Sepsis Guideline (Adult)	Suggest against the routine use of standard IV immunoglobulin in critically-ill adults with COVID-19	March 2021
WHO	No recommendation for children and adults	
IDSA		
American Thoracic Society		
European Respiratory Society		

Appendix 7. Characteristics of Ongoing Studies

	Title	Population	Interventions	Characteristics	Outcome Measures
1	Randomised Evaluation of COVID-19 Therapy (RECOVERY) in Children With PIMS-TS in Switzerland (SWISSPEDRECOVERY)	Age: 44 Weeks to 18 Years (Child, Adult)	•Drug: Methylprednisolone sodium succinate 10 mg/ kg intravenously •Biological: Human normal immunoglobulin (IVIg) •Drug: Methylprednisolone sodium succinate 2 mg/ kg	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Outcome Measures: •Hospital length of stay •All-cause mortality amongpatients •Composite endpoint of death orneed for mechanical ventilationor extracorporeal membrane oxygenation (ECMO)
2	Human COVID-19 immunoglobulin (COVID HIG) Therapy for COVID 19 Patients	18 Years to 65 Years (Adult, Older Adult)	•Biological: Human COVID-19 immunoglobulin (pH4) for intravenous injection •Drug: Placebo	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) •Primary Purpose: Treatment	Outcome Measures: •Time to clinical improvement •Changes of 7-point ordinalscale for COVID-19 clinical improvement •COVID-19-Related Symptoms •Discharge Status •Length of hospital stay •All-cause Mortality •Negativization rate of SARSCoV-2 nucleic acid •Changes of leukocyte count,lymphocyte count, C-reactive protein, IL-6 and SARS-CoV-2nucleic acid (quantitative) •Treatment in ICU •SARS-CoV-2 NeutralizingAntibody Level •and 3 more
3	A COVID-19 Study to Evaluate Safety and PK of COVID-HIG Administered Through IM, SC, or IV Routes as a Single Dose Regimen to SARS-CoV-2 Uninfected Adults	Age: 18 Years to 59 Years (Adult)	•Biological: COVID-HIG	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Outcome Measures: •Adverse events within 72 hourspost-dosing •Adverse events leading todiscontinuation or temporary suspension of study treatmentadministration •Adverse events up to 85 dayspost-administration of a singledose •Serious adverse events up to85 days post-administration of asingle dose •Pharmacokinetic parameter ofarea under the concentrationtime curve (AUC) from time 0 toinfinity •Pharmacokinetic parameterof maximum observed concentration after dosing(Cmax) •Pharmacokinetic parameterof time at (Tmax) which Cmax occurs after dosing

					•Pharmacokinetic parameterof observed or estimated concentration at 28 days (C28d)after dosing •Pharmacokinetic parameter ofAUC0-inf ratios (bioavailability)compared between routes forcomparable dose levels •Pharmacokinetic parameter ofAUC0-last after COVID-HIG Dosing•and 6 more
4	Outpatient Treatment With AntiCoronavirus Immunoglobulin	Age: 18 Years and older (Adult, Older Adult)	•Biological: Hyperimmune Immunoglobulin to SARSCoV-2 (hIVIG) •Other: Placebo	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) •Primary Purpose: Treatment	Outcome Measures: •Clinical Status •All-cause hospitalization or deaththrough 28 days. •All-cause mortality through 28days. •Significant Disease Progression •Ordinal Scale Distribution •Disease Progression Through 7Days •Significant Disease ProgressionThrough 7 Days •Disease Progression at Followup •Activity Limitations at Follow-up •Change in Viral Burden fromSerum Antigen •and 6 more
5	MISC COVID-19 Study in Pediatric Population	Age: 1 Year to 15 Years (Child)		Study Design: •Observational Model: CaseControl •Time Perspective: CrossSectiona	Outcome Measures: Characterization of immuneresponses
6	Clinical Study in the Treatment of Patients With Moderate Course of COVID-19	Age: 18 Years to 65 Years (Adult, Older Adult)	•Drug: COVID-globulin •Drug: Placebo	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Double (Participant, Investigator) •Primary Purpose: Treatment	Outcome Measures: •The proportion of subjects inthe study groups in whom, during the first 7 days afterdrug administration, one of the following events developed according to the laboratoryinstrumental methods or on the basis of a clinical presentation •All-cause mortality •The elimination time of theSARS-CoV-2 virus •The median time to clinicalimprovement on the WHO Ordinal Scale for ClinicalImprovement •The incidence of severe andextremely severe COVID-19 disease •The need for respiratory support

					•The need for invasivemechanical ventilation of the lungs, ECMO •Time to cancellation of oxygensupport •The need to stay at the intensivecare unit •Duration of fever (# 380C), days •and 3 more
7	A COVID-19 Study to Evaluate Safety and Pharmacokinetics of COVID-HIGIV Administered in Healthy Adults	Age: 18 Years to 60 Years (Adult)	•Biological: COVID-HIGIV •Other: Placebo (saline)	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) •Primary Purpose: Treatment	•Outcome Measures: •Number of Subjects with Adverse Events (AEs) postdosing •Number of Subjects withAdverse Events that Led to Discontinuation or TemporarySuspension of IV Infusion •Number of Subjects with AEsafter IV Infusion •Number of Subjects with SAEsafter IV Infusion •Pharmacokinetics parameter ofarea under the concentrationtime curve (AUC) from time0 to the last quantifiableconcentration (AUC0-t) of SARSCoV-2 antibodies after dose of COVID-HIGIV •Pharmacokinetics parameter ofarea under the concentrationtime (AUC) from time 0 to thelast quantifiable concentration(AUC0-t) of SARS-CoV-2antibodies plus the additionalarea extrapolated to infinity(AUC0-inf) after dose of COVIDHIGIV •Pharmacokinetics parameter ofarea under the concentrationtime curve (AUC) from time 0 to14 days (AUC0-14d) after doseof COVID-HIGIV •Pharmacokinetics parameter ofarea under the concentrationtime curve (AUC) from time 0 to28 days (AUC0-28d) after doseof COVID-HIGIV •Pharmacokinetics parameterof maximum observed concentration (Cmax) of SARSCoV-2 antibodies observed afterdose of COVID-HIGIV •Pharmacokinetics parameter of time at which Cmax occurs afterdose of COVID-HIGIV •and 5 more
8	IVIG in Patients With Severe COVID-19	Age:	•Drug: IVIG	Study Design: •Allocation: N/A	Outcome Measures: •Hospital length of stay

	Requiring Mechanical Ventilation	18 Years and older (Adult, Older Adult)		•Intervention Model: Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	•Human metabolome andproteome
9	TREATMENT WITH ANTI-SARS-COV-2 IMMUNOGLOBULIN IN PATIENTS WITH COVID-19	Age: 18 Years to 75 Years (Adult, Older Adult)	•Biological: Anti-SARSCoV-2 immunoglobulin	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Outcome Measures: •Rate of adverse events related tothe infusion of anti-SARS-CoV-2immunoglobulin through CTCAEv4.0. •Clearence of viral RNAevaluated by RT-PCR •Reduction of viral load evaluatedby area under the curve of RTPCR values •Length of hospital stay •Orotracheal Intubation Rate •Infusional reaction rate •Mortality rate •Assessment of adverse events •Evaluation of clinical status •Modulation of serum and cellularinflammatory marker
10	COVIDIG (COVID-19 HyperImmunoGlobulin	Age: 19 Years and older (Adult, Older Adult)	•Biological: GC5131 •Other: Placebo	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Outcome Measures: •Ordinal scale outcome •Viral negative •Change in NEWS2 (NationalEarly Warning Score 2) •mortality
11	Intravenous Immunoglobulins for the Treatment of Covid-19 Patients: a Clinical Trial	Age: 18 Years to 90 Years (Adult, Older Adult)	•Biological: intravenous immunoglobulin therapy	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Double (Investigator, Outcomes Assessor) •Primary Purpose: Treatment	Outcome Measures: •In hospital days •14 day mortality •D-dimers •C-reactive protein •Oxygen saturation •TNF alpha •IL-6 •Ferritin •Number of participants withtreatment-related adverse eventsas assessed by CTCAE v4.0
12	Inpatient Treatment of COVID-19 With Anti-Coronavirus Immunoglobulin (ITAC)	Age: 18 Years and older (Adult, Older Adult)	•Biological: Hyperimmune immunoglobulin to SARSCoV-2 (hIVIG) •Other: Placebo •Drug: Remdesivir	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)	Outcome Measures: •Ordinal Outcome Scale - Day 7 •All-cause mortality through Day28 •Ordinal Outcome Scale •Change in National EarlyWarning Score (NEWS) •Time to Worsening •Discharge Status •Days Alive Outside the Hospital •Pulmonary-only Components ofthe Primary Ordinal Outcome

				•Primary Purpose: Treatment	•Thrombotic Components of thePrimary Ordinal Outcome •Time to recovery •and 6 more
13	SARS-CoV-2 Antibodies Based IVIG Therapy for COVID-19 Patients	Age: 18 Years and older (Adult, Older Adult)	•Biological: SARS-CoV-2 antibody based IVIG therapy	Study Design: •Allocation: Randomized •Intervention Model: Sequential Assignment •Masking: Single (Participant) •Primary Purpose: Treatment	Outcome Measures: •28 Days mortality •Requirement of supplementaloxygen support •Number of days on assistedventilation •Days to step down •Days to Hospital Discharge •Adverse events during hospitalstay •Change in C-Reactive Protein(CRP) levels •Change in neutrophil lymphocyteratio •Change in Ferritin levels •Change in lactatedehydrogenase (LDH) levels •and 8 more
14	Intravenous Immunoglobulin (IVIG, Bioven) Efficacy Assess for COVID-19 / SARS-CoV-2 Severe Pneumonia Complex Treatmen	Age: 18 Years and older (Adult, Older Adult)	•Drug: IVIG	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Outcome Measures: •Period duration (in days) toclinical improvement •O2 saturation (SPO2percentage), with self-breathing •Respiratory movements rate(amount per minute), with selfbreathing •Body temperature withoutantipyretics use •Lymphocyte count •Time from the onset of thedisease to discharge, in days •Duration of the need forventilatory support, in days •Duration of the need for intensivecare, in days •Duration of need for oxygenationin days (SPO2 # 93% with selfbreathing) •The C-reactive protein (CRPlevel •and 10 more
15	Study to Evaluate the Safety and Efficacy of High Dose Intravenous Immune Globulin (IVIG) Plus Standard Medical Treatment (SMT) Versus SMT Alone in Participants in Intensive Care Unit (ICU) With Coronavirus Disease (COVID-19)	Age: 18 Years and older (Adult, Older Adult)	•Biological: GAMUNEX-C •Drug: Standard Medical Treatmen	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Outcome Measures: •All-Cause Mortality RateThrough Day 29 •Time to Actual ICU Discharge •Duration of MechanicalVentilation •Time to Actual HospitalDischarge •Duration of Any Oxygen Use •Mean Change from Baseline inOrdinal Scale •Absolute Value Change fromBaseline in Ordinal Scale •Percentage of Participants inEach Severity Category of the 7-Point Ordinal Scale

					•Overall Number of Participantswho Develop Acute RespiratoryDistress Syndrome (ARDS) •Number of Participants whoDevelop ARDS Distributed by Severity •and 3 more
16	Study to Evaluate the Safety and Efficacy of High Dose IVIG in Hospitalized Participants With Coronavirus Disease (COVID-19)	Age: 18 Years and older (Adult, Older Adult)	•Biological: Intravenous Immune Globulin •Drug: Standard Medical Treatment	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Outcome Measures: •Percentage of Participants Dyingor Requiring ICU Admission •Percentage of Participants Whoare Dependent on High Flow Oxygen Devices or InvasiveMechanical Ventilation •Change from Baseline inNational Early Warning Score (NEWS) •Time to Clinical Responseas Assessed by: NEWS # 2 Maintained for 24 hours •Time to Hospital Discharge •Duration of ICU Stay •Duration of Any Oxygen Use •Duration of MechanicalVentilation •Mean Change from Baseline inOrdinal Scale •Absolute Value Change fromBaseline in Ordinal Scale •and 5 more
17	Convalescent Antibodies Infusion in COVID 19 Patients	Age: 18 Years and older (Adult, Older Adult)	•Biological: Anticoronavirus antibodies (immunoglobulins) obtained with DFPP form convalescent patients	Study Design: •Allocation: N/A •Intervention Model: Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Outcome Measures: •Time to weaning of oxygensupport •Chest XR or CT scan evaluation •Survival, •Viral titer •Anti COVID 19 IgG antibodies •Anti COVID 19 IgM antibodies •C5a concentration •C3a concentration •Serum C5b-9 concentrationMarker of complement activation •Serum IL-6 levels •and 7 more
18	Study of SOC Plus IVIG Compared to SOC Alone in the Treatment of COVID-19	Age: 18 Years and older (Adult, Older Adult)	•Drug: Octagam	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatmen	Outcome Measures: •Mechanical Ventilation •Oxygen Therapy •Length of Stay
19	NORMAL HUMAN IMMUNOGLOBULINS	Age: 75 Years and older (Older	•Drug: IgIV	Study Design: •Allocation: N/A	Outcome Measures: •Mortality

	(IVIG) IN PATIENTS AGED 75 YEARS AND OVER, COVID-19 WITH SEVERE ACUTE RESPIRATORY FAILURE	Adult)		•Intervention Model: Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	•Total number of days of fullhospitalization •Duration of oxygen therapy •Ferritin level in the blood •CRP level in the blood •LDH level in the blood •Lymphocyte level in the blood •PNN level in the blood •platelet level in the blood •WHO performance index •and 4 more
20	Octagam 10% Therapy in COVID-19 Patients With Severe Disease Progression	Age: 18 Years and older (Adult, Older Adult)	•Biological: Octagam 10% •Other: Placebo	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) •Primary Purpose: Prevention	Outcome Measures: •Stabilization or Improvement inClinical Status •Descriptive Clinical StatusAnalysis •Clinical Status Assessment •Time to death •Mechanical Ventilation Initiation •Mechanical Ventilation Duration •SARS-CoV-2 Test Result •Incidence of all AEs •Incidence of AEs consideredrelated to the IMP •Incidence of serious adverseevents (SAEs) •and 45 more
21	Convalescent Plasma (PC) and Human Intravenous Anti-COVID-19 Immunoglobulin (IV Anti COVID-19 IgG) in Patients Hospitalized for COVID-19.	Age: 18 Years and older (Adult, Older Adult)	•Biological: COVID-19 convalescent plasma •Biological: Anti-COVID-19 human immunoglobulin •Drug: Standard (specific) therapy for COVID-19	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Outcome Measures: •Admission to ICU and/ormechanical ventilation •Length of hospital stay •Neutralizing antibody (IgG) titersagainst COVID-19 •Safety - Adverse events •Death
22	Clinical Study for Efficacy of AntiCorona VS2 Immunoglobulins Prepared From COVID19 Convalescent Plasma Prepared by VIPS Mini-Pool IVIG Medical Devices in Prevention of SARS-CoV-2 Infection in High Risk Groups as Well as Treatment of Early Cases of COVID19 Patients	Age: 21 Years to 50 Years (Adult)	•Other: hyper immunoglobulins containing anti-Corona VS2 immunoglobulin	Study Design: •Allocation: N/A •Intervention Model: Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Outcome Measures: •Efficacy of COVID19 hyperimmunoglobulins for patients •Efficacy of COVID19 hyperimmunoglobulins for high risk groups •Safety of anti-SARS-CoV-2hyper immunoglobulins assessed by percentage ofadverse events
23	Convalescent Plasma vs Human Immunoglobulin to Treat COVID-19 Pneumonia	Age: 16 Years to 90 Years (Child, Adult, Older Adult)	•Drug: Plasma from COVID-19 convalescent patient •Drug: Human immunoglobulin	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Double (Participant,	Outcome Measures: •Mean hospitalization time •Mean Oxigenation index evolution •Rate of severe ARDS •Rate and time to dead •Mean time with invasivemechanical ventilation

				Outcomes Assessor) •Primary Purpose: Treatment	•Time to Viral PCR Negativization
24	Polyvalent Immunoglobulin in COVID-19 Related ARds	Age: 18 Years and older (Adult, Older Adult)	•Drug: Human immunoglobulin •Drug: Placebo	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: Double (Participant, Care Provider) •Primary Purpose: Treatment	Outcome Measures: •Ventilator-free days •Mortality •Sequential Organ Failure Assessment Score •P/F ratio •Lung compliance •Radiological score •Biological efficacy endpoints - Creactive protein •Biological efficacy endpoints - Procalcitonin •Immunological profile •Number of patients using othertreatments for COVID-19 relatedARDS •and 6 more
25	Treatment of Acute Severe 2019-nCoV Pneumonia With Immunoglobulin From Cured Patients	Age: 18 Years and older (Adult, Older Adult)	•Drug: Immunoglobulin of cured patients •Drug: #-Globulin	Study Design: •Allocation: Non-Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Outcome Measures: •Time to Clinical Improvement(TTCI) •Clinical status assessed by theordinal scale •The differences in oxygen intakemethods •Duration (days) of supplementaloxygenation •Duration (days) of mechanicalventilation •The mean PaO2/FiO2 •The lesions of the pulmonarysegment numbers involved in pulmonary CT [every 7 days] •Time to 2019-nCoV RT-PCRnegativity in respiratory tract specimens [every 3 days] •Dynamic changes of 2019-nCoVantibody titer in blood •Length of hospital stay (days) •All cause mortality
26	The Efficacy of Intravenous Immunoglobulin Therapy for Severe 2019-nCoV Infected Pneumonia	Age: 18 Years and older (Adult, Older Adult)	•Drug: Intravenous Immunoglobulin •Other: Standard care	Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment	Outcome Measures: •Clinical improvement based onthe 7-point scale •Lower Murray lung injury score •28-day mortality •Duration of mechanicalventilation •Duration of hospitalization •Proportion of patients withnegative RT-PCR results •Proportion of patients in eachcategory of the 7-point scale •Proportion of patients withnormalized inflammation factors •Frequency of Adverse DrugEvents

					•Frequency of Serious AdverseDrug Events

Appendix 8. 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 (1)	Moderate (2)	Small (2)	Trivial	Varies (1)	Uncertain (5)			• Pedia studies: Inconclusive for inotropic support, use of mechanical ventilators • Indirect evidence from adult studies: benefit for clinical deterioration, duration of hospital stay, ICU admission; no significant effect for all-cause mortality
Harm	Large (1)	Moderate (1)	Small (5)	Trivial	Varies	Uncertain (4)			• No significant adverse events
Certainty of evidence	High	Moderate		Low (2)		Very low (9)			• Rated very low due to very serious risk of bias, indirectness and imprecision
Balance of effects	Favors drug (1)	Probably favors drug (1)	Does not favor drug or no drug	Probably favors no drug	Favors no drug (1)	Varies	Uncertain (8)		
Values	Important uncertainty or variability (3)	Possibly important uncertainty or variability (3)		Probably no important uncertainty or variability (4)		No important uncertainty or variability (1)			
Resources required	Uncertain	Varies	Large costs (10)	Moderate costs (1)	Negligible costs or savings	Moderate savings	Large savings		• Dose 2gkg; max dose: 100g • 1 vial IVIG: Php 9650.00 • 1 course IVIG: Php 33,841.31 to Php 322,985.00
Certainty of evidence of resources required	No included studies (8)		Very low	Low (1)	Moderate (6)	High			
Cost-effectiveness	No included studies (8)	Varies	Favors the comparison	Probably favors the comparison	Does not favor the comparison or the intervention	Probably favors the intervention (3)	Favors the intervention		
Equity	Uncertain (7)	Varies (1)	Reduced (1)	Probably reduced	Probably no impact (3)	Probably increased (1)	Increased		
Acceptability	Uncertain (5)	Varies (2)	No	Probably no (1)	Probably yes (2)	Yes (1)			
Feasibility	Uncertain (4)	Varies (2)	No (2)	Probably no	Probably yes (3)	Yes (1)			

Additional Comments

- The drug is costly.
- There is questionable accessibility and availability in far-flung areas.