Use of Meglumine acridone acetate (MA) for treating patients with COVID-19

RAPID REVIEW

Service Line	Rapid Review
Version	1
Publication date	7 April 2020
Report Length	36 pages
Prepared by	Policy, Planning and Evaluation Team - Health Technology Assessment Unit, DOH Health Regulation Team
Presented to	Health Technology Assessment Council

1. CONTEXT AND POLICY ISSUES

In early 2020, the World Health Organization (WHO) declared severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which causes coronavirus disease 2019 (COVID-19) as a global pandemic affecting more than 160 countries and regions with at least 350,000 cases and 15,000 deaths worldwide as of 23 March 2020 (*Dong, Du & Gardner, 2020*). In the Philippines, there has been 3,660 confirmed COVID-19 cases with 163 deaths as of 6 April 2020 (*DOH, 2020*). The local mortality rate of 4.45% is within the global mortality rate (3%-6%). Note that the rates do not fully account for the asymptomatic cases (*Dong, Du & Gardner, 2020; Department of Health, 2020a*).

In response to the increasing number of COVID-19 cases, the World Health Organization has announced the SOLIDARITY trial, a global testing of effective treatments across several countries (World Health Organization, 2020a). Furthermore, separate studies and trials using existing drugs in the market have been launched to find a treatment targeting SARS-CoV-2. In the Philippines, the Department of Health endorses the use of The Philippine Society of Microbiology and Infectious Disease (PSMID) treatment guidelines for COVID-19 through its issuance of Department Memorandum No. 2020-0108. The latest PSMID guideline (issued March 31, 2020) has listed several drugs that may be considered for use in hospitalized, probable or confirmed COVID-19 cases with moderate to high-risk pneumonia:

- off-label use of hydroxychloroquine, chloroquine, lopinavir/ritonavir, tocilizumab, and;
- compassionate use of remdesivir.

Recently, a Russian pharmaceutical company has expressed its intent to donate Cycloferon®, also known as meglumine acridone acetate or MA (ATC L03AX Other Immunostimulants), to the Philippines as part of the clinical management of COVID-19 cases. Cycloferon® is used in Russia as treatment of influenza and other acute respiratory viral infections. Based on the provided dossier, Cycloferon® is a 'low molecular weight inducer of alpha-beta-interferon with a wide range of biological activities (antiviral, immunomodulating, anti-inflammatory, etc.)'. It is available as 12.5% solution for injection and as 0.015g enteric-coated tablet, with the following provided indications:

(1) In adults, recommended during combined therapy of: influenza and acute viral infections; herpes infections; HIV infections (stages 2A-3B); neural infections; chronic viral hepatitis A, B, C, D; and, acute enteric infections
(2) In children over 4 years old, recommended during combined therapy of: influenza and acute viral infections; herpes infections; viral hepatitis A, B, C, D; and, HIV infections

As of writing, there is no conclusive guidance on the use of MA (Cycloferon®) for management of COVID-19; hence, evidence is needed to support its use for such. For this reason, **a rapid review** was conducted to search and synthesize **information on the market approval of MA** in different settings**, existing COVID-19 treatment guidelines (TGs) or clinical practice guidelines (CPGs)** recommending its use, as well as existing **evidence on its clinical efficacy, safety and cost-effectiveness.**

As our search did not find any published study on the clinical efficacy and safety of MA, we eventually ***expanded our review to explore its evidence on influenza***. Drugs for influenza, among others, are also currently being investigated as potential treatments for COVID-19. The Pan American Health Organization (2020) noted that COVID-19 has been compared with influenza because both can cause respiratory disease (ranging from asymptomatic to severe), and the known mode of transmission is through contact or droplets. These may have been some of the reasons why drugs for influenza have been gaining interest

as study drugs. In addition, a study by Wang et. al. (2020) has successfully demonstrated the inhibitory effects of another influenza drug "favipiravir" on SARS-CoV-2 in Vero E6 cell line (ATCC-1586).

2. POLICY AND RESEARCH QUESTIONS

2.1. Policy question

Should the Philippine government accept the donation and introduce MA as an add-on to the DOH-PSMID-recommended treatment regimens for patients with COVID-19 ***versus the DOH-PSMID recommended guidelines as of March 31***?

2.2 Research questions

1. What is the market entry status of MA across different countries? What are the current country TGs or CPGs which recommend the use of MA in treating patients with COVID-19?

2. What is the clinical efficacy/ effectiveness and safety of MA as an add-on to the DOH-PSMID-recommended treatment regimens for patients with COVID-19 *versus the DOH-PSMID recommended guidelines as of March 31*? [primary] What is the clinical efficacy/ effectiveness and safety of MA as an add-on to supportive treatment for patients with influenza *versus the DOH-PSMID recommended guidelines as of March 31*? [secondary]

3. Does MA as an add-on to the DOH-PSMID-recommended treatment regimens represent value for money for patients with COVID-19 *versus the DOH-PSMID recommended guidelines as of March 31*?

3. KEY FINDINGS

To date, MA is neither used in any of the TGs or CPGs, nor registered yet in all the reviewed countries for the treatment of COVID-19, even in its source country Russia. Further, there are no ongoing clinical trials testing the clinical efficacy and safety of MA for COVID-19, to date. Considering other indications, our review showed that it is registered in Russia only, specifically for cases of immunocompromised patients, neuroinfection, HIV, viral hepatitis, herpes, and cytomegalovirus infection. The submitted dossier stated that MA has been presented in the Republic of Belarus, Georgia, Moldova, Kazakhstan, Kyrgyzstan, Uzbekistan, Mongolia, Tajikistan, Laos, Armenia, Turkmenistan, Azerbaijan; however, we are unable to verify the claimed registration status due to limitations in accessing databases of international drug regulatory bodies. The countries where this is supposedly being marketed are all in the global south (developing countries), and there was no mention of it being marketed in the global north (e.g., US, Singapore) where health systems are more robust.

As with existing evidence on the clinical efficacy and safety of MA for COVID-19, no relevant studies were found. The evidence attachment on the dossier submitted by Polysan, Ltd. was a clinical trial using Cycloferon® on influenza and acute respiratory tract viral infections, particularly type A (H1N1)

verified and type A (H3N2) *by Sologub et. al. (2009)*, but no mention of its use on COVID-19. Incidentally, this study was detected and included in the expanded search for influenza use; hence shall be discussed in the next section.

Regarding its existing clinical efficacy and safety evidence for influenza, three of the five studies were successfully retrieved upon contact with the main author and were translated from Russian to English language (using Google® Translate). The following summarizes the evidence found and our appraisal results:

- The study by *Romantsov et. al. (2010)* studied the effect of Cycloferon® on patients with acute respiratory tract viral infection who all received the intervention. The primary outcome was the normalization of temperature per day (until 5th day). The results demonstrated that Cycloferon® was able to normalize the body temperature of high fever on the 4th day of acute viral respiratory infection or influenza.
- The multicenter randomized trials by *Romantsov et. al. (2009)* explored the possibility of improving the natural resistance of children on acute respiratory tract viral infection using Cycloferon® as compared with placebo. The results demonstrated that using Cycloferon® in children 4-16 years old had marked reduction of symptoms of intoxication, duration of catarrhal episodes of the upper respiratory tract, and the absence of adverse drug reactions.
- The multicentre randomized controlled comparative trial by *Sologub et. al. (2009)* had two sub-studies, wherein both used Cycloferon® as therapy and prophylaxis for influenza and acute respiratory tract viral infections:
    - In sub-study 1, they compared Cycloferon® with symptomatic basic treatment. The reported outcomes [i.e., temperature intensity and duration of fever (average duration ranging from 1.8 to 3.0 days versus 5 days), lesser duration (in mean days) of catarrhal events and symptoms in influenza patients (on average, 2-2.5 days lesser than the control), and lesser number of adverse events] favored Cycloferon®.
    - In sub-study 2, the population was stratified into three subgroups (with unclear rationale). All of the subgroups compared Cycloferon® with multivitamins. While the reported outcome "incidence of illness" favored Cycloferon®, the interpretations and clinical impact for the reported outcomes "efficiency index" and "safety index" were unclear as their definitions were not mentioned in the report.
- All studies had low internal validity. The study of *Romantsov et. al., (2010)* had no control group; hence, relative treatment effects cannot be established. Both the studies of *Romantsov et. al., (2009)* and *Sologub et. al., (2009)* used Cycloferon® for the prevention of influenza / SARS like illnesses. *Romantsov et. al., (2009)* involved children while that of *Sologub et. al., (2009)* involved adults. The studies of *Romantsov et. al. (2009 and 2010)* failed to report allocation concealment, blinding, intention to treat and complete follow up. None of the studies documented baseline characteristics. The studies of *Sologub et. al., (2009)* mentioned the use of envelopes for randomization and the use of table of random numbers. There was, however, limited discussion on the methods and the lack of completeness of presented data on the outcomes. None of the studies reported mortalities or other clinically relevant outcomes for influenza such as clinical recovery and length of hospital stay. Hence, while they all reported favorable outcomes on the use of Cycloferon® for influenza, the overall low internal validity of the studies cannot support such claim.

Lastly, in terms of cost-effectiveness, no relevant studies were found.

As evidence on the different facets of COVID-19 is on-going and rapidly evolving, regular scoping for evidence and updating of recommendations are advised.

4. METHODS

4.1 Literature Search Methods

Three reviewers for the clinical studies, and three reviewers for the market entry status, TG or CPG recommendations and economic evaluations performed a limited literature search for relevant studies published from inception to 24 March 2020 via different scientific databases, select HTA agencies, and Google® Search. Evidence pertaining to its market entry status and COVID-19 TGs or CPGs recommending MA were searched through individual country websites as provided and linked by UpToDate®. Ongoing trials for MA were searched on Center for Evidence-Based Medicine (CEBM) database.

For studies on the clinical efficacy and safety for COVID-19, PubMed, Cochrane Library, and Google Scholar were used to search for scientific articles. Documentary submissions by the proponent were also reviewed for any relevant scientific evidence. Moreover, in recognition that this is a potential novel indication for an existing treatment, general searches on Google® Search were also performed to retrieve any relevant scientific or news articles. For economic evaluations, LitCovid and publications of select HTA agencies were also reviewed, in addition to the previously mentioned databases. Search terms used were MeSH terms for nCov-19 and MeSH terms for Cycloferon®. No filters/restrictions on study type, language and publication date were applied in these databases, except on Google Scholar, where filter on publication date was applied to view publications from year 2019 onwards.

As for the expanded search to explore its clinical efficacy and safety for influenza, we quickly searched and screened through PubMed using the MeSH terms for Cycloferon® and human influenza.

4.2 Selection Criteria and Methods

Three reviewers for the clinical efficacy and safety studies, and three reviewers for the TG or CPG recommendations and economic evaluations screened the total citations and selected the studies with supervision. The full text of potentially eligible studies with relevant abstracts and titles were retrieved and evaluated for eligibility using the set inclusion and exclusion criteria.

Table 1: Inclusion Criteria	
Population	patients with confirmed or probable COVID-19 who are referred for treatment [primary search]; patients with influenza [secondary search]
Intervention	meglumine acridone acetate as an add-on to the DOH-PSMID-recommended treatment regimens (regardless of the dosage form and strength)
Comparator	DOH-PSMID- recommended treatment regimens

Outcomes	Clinical efficacy/ effectiveness: cure rate, cure time, clinical improvement time, ratio of normal progression to severe disease, time to heavy progression, survival rate and mortality Safety: incidence of adverse outcomes Cost-effectiveness: cost per life year saved, cost per case averted, cost per QALY, cost per DALY (Note: Such as but not limited to the outcome measures listed above)
Study Designs	Health technology assessments, systematic reviews (SRs), meta-analyses, TGs, CPGs, primary clinical studies, economic evaluations

Exclusion Criteria
Articles were excluded if they did not meet the selection criteria outlined in Table 1 or they were duplicate publications.

4.3 Data Extraction and Critical Appraisal of included studies

Three reviewers for the clinical efficacy and safety studies, and three reviewers for the TGs, CPGs and economic evaluations extracted and summarized the key data domains using a standard data extraction tool. Prior to data extraction and appraisal, non-English manuscripts of the citations included in the review were translated to English language using Google® Translate. The following appraisal tools were intended to applied to evaluate the overall quality and validity of the included clinical and cost-effectiveness studies:

- Clinical studies: Evaluation of Articles on Therapy tool by *Dans et. al. (2017)*
- Economic evaluations: *Drummond et. al., (1996)* tool

5. SUMMARY OF EVIDENCE

5.1 Market Availability and COVID-19 Guideline Recommendations on MA

According to the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), and the U.S. Food and Drug Administration (FDA), there are currently no medications or vaccines that have been proven to be effective for the treatment or prevention of COVID-19, to date (*WHO, 2020b; CDC, 2020; U.S. FDA, 2020*). In the absence of recognized treatment regimen, several countries, through their Ministries of Health, Infectious Disease Societies, and other relevant agencies, have come up with their own guidelines allowing off-label or compassionate use of certain treatments for COVID-19.

In our review of TGs or CPGs across different countries included in this review (i.e., China, Canada, United Kingdom, United States, Australia, Japan, Russia, Singapore, South Korea, Taiwan and Thailand), there was no mention of MA in any of these guidelines, to date.

Across all these countries reviewed, the drug has not been registered yet for the treatment of COVID-19 or for other indication/s except in Russia where it is indicated for immunocompromised patients, neuroinfection, HIV, Viral Hepatitis, Herpes, and Cytomegalovirus infection. Further, the drug was not considered as a possible treatment option yet, whether off-label or compassionate use, in any of the reviewed countries. Interestingly, even from its source country, our review did not find any supporting evidence that MA is registered and recommended for COVID-19 treatment in Russia. The submitted dossier stated that MA (Cycloferon®) has been presented in the following countries: Republic of Belarus, Georgia, Moldova, Kazakhstan, Kyrgyzstan, Uzbekistan, Mongolia, Tajikistan, Laos, Armenia, Turkmenistan, Azerbaijan. We are unable to verify the registration status of this drug for other indications due to limitations in accessing databases of international drug regulatory bodies. The countries where this is supposedly being marketed are all in the global south (developing countries) and there was no mention of it being marketed in the global north (e.g., US, Singapore) where health systems are more robust.

In addition, our search in the database of COVID-19 registered trials by the Center for Evidence-Based Medicine (CEBM) - University of Oxford showed that there are no ongoing clinical trials for the efficacy or safety of MA.

A summary of MA market registration status and current COVID-19 treatment guidelines of the countries included in this review can be found in Appendix 1.

5.2 Clinical Efficacy and Safety of MA

5.2.1 COVID-19 (primary review)

Literature search from PubMed and Cochrane Library yielded no evidence regarding the efficacy and safety of MA (see Appendix 2 for actual search results). On the other hand, using a more general search strategy of the intervention terminologies and “coronavirus”, our search yielded eight results in total Google Scholar. There was one duplicate report, one was in Russian, two mentioned Cycloferon® in the references only, one study was focused on synthesis of a different compound along with mentioning endogenous inducers of interferon, one study used Cycloferon® as control drug, one study was an in vitro experiment about a wound healing chemical with mention of Cycloferon®, and one mentioned Cycloferon® as a potential treatment but focused on tilorone. The study focused on tilorone, a broad spectrum antiviral and other potential treatment options for COVID-19 along with arbidol, triazavirin, Cycloferon® and Kagocel without mentions of relevant clinical trials (*Ekins et al., 2020*).

The same strategy was also used on a broader and more general search engine, Google. However, the only statement found relevant on the clinical efficacy of Cycloferon® was from the article published by CNN Philippines wherein the drug which will be donated to the country reportedly has been effective in curing the symptoms of those infected with the viral illness in Russia and China (*CNN Philippines, 2020*). Aside from the non-inclusion of Cycloferon® in the potential treatment options published by *Smith et al. (2020)*, no other scientific articles were retrieved aside from the repeated mentions of the intent to donate Cycloferon® to the country as a potential treatment for COVID-19. Lastly, in the dossier submitted by Polysan, Ltd., the primary

scientific evidence used for clinical efficacy was the clinical trial [(*Sologub et. al., (2009*)] of Cycloferon® conducted in Russia for influenza and acute respiratory tract viral infections, particularly type A (H1N1) verified and type A (H3N2), along with a statement from Russian experts consulted by the company. The said clinical trial was found in our exploratory search for its evidence on influenza and was successfully retrieved and translated. The details of the study will be discussed in the next subsection. The dossier submitted to the Secretary of Health detailed that the basis for its possible management of COVID-19 is due to the use of intravenous solution Cycloferon® during the SARS-CoV epidemic in 2003. The drug, which was donated to the Institute of Tropical Medicine in Hanoi, claimed to have proven effective in the treatment and prevention of the disease at that time.

As no reference study/ studies were found in our primary independent search nor provided in the dossier for its treatment effect on COVID-19, critical appraisal of evidence was not done. Therefore, no evidence summary to support its clinical efficacy and safety for the treatment of COVID-19 can be provided to establish its recommendation.

5.2.1 Influenza (secondary/ exploratory review)

5.2.1.1 Quantity and characteristics of studies

Literature search from PubMed yielded five relevant citations which were all requested to the main authors for full-text access. Of these, only three were available in full-text and were all in Russian language; hence, were translated to English (using Google® Translate) for the critical appraisal.

These three studies included in this review were two studies by *Romantsov et. al. (2009* and *2010)*, and one study by *Sologub et. al., (2009)* that had data from two populations of patients. Two of the studies [*Romantsov et. al., (2009)*, *Sologub et. al., (2009)]* were multicenter randomized trials while one [*Romantsov et. al., (2010)]* was a descriptive study. Two of the studies included adult patients specifically those with influenza and acute respiratory viral infection [*Romantsov et. al., (2010)*], and with influenza or SARS [*Romantsov et. al., (2009)*]; while one [*Sologub et. al., (2009)*] included pediatric patients aged 4 to 16 years old but with unclear patient inclusion criteria. As for their comparator, *Romantsov et. al., (2010)* had no comparator/ control group; *Romantsov et. al., (2009)* compared to placebo; and, *Sologub et. al., (2009)* separately compared Cycloferon® to symptomatic basic treatment and multivitamins. Their outcome measures were also varied. These study characteristics are detailed in Appendix 2.

5.2.1.2 Summary of Findings

Romantsov et. al. (2010)

The results demonstrated that Cycloferon® was able to normalize the body temperature of high fever on the 4th day of acute viral respiratory infection or influenza. However, there was no control group mentioned in the study.

Romantsov et. al. (2009)

The results demonstrated that using Cycloferon® in children 4-16 years old had marked reduction of symptoms of intoxication, duration of catarrhal episodes of the upper respiratory tract, had marked reduction of symptoms of intoxication, duration of catarrhal episodes of the upper respiratory tract, and the absence of adverse drug reactions.

Sologub et. al. (2009)

Sub-study 1

The reported outcomes [i.e., temperature intensity and duration of fever (average duration ranging from 1.8 to 3.0 days versus 5 days), lesser duration (in mean days) of catarrhal events and symptoms in influenza patients (on average, 2-2.5 days lesser than the control), and lesser number of adverse events] favored Cycloferon®.

Sub-study 2

Among those observed in the first subgroup, 15.5% (50 out of 320) of people who were treated with Cycloferon® fell ill. In those who were given with multivitamins, 84.3% (166 out of 197) of the people fell ill. The reported efficiency index was 5.4 and the reported safety index was 82.0%. In the second subgroup, 26.7% (203 out of 760) of people were treated with Cycloferon® fell ill. In those who were given with multivitamins, 68.6% (508 out of 740) of the peple fell ill. The reported efficiency index was 2.6 and the reported safety index was 61.0%. The third subgroup consisted of 400 people, of whom 300 received Cycloferon® and 100 people received multivitamin. The incidence of illness was not reported. The reported efficiency index was 2.7 and the reported safety index was 62.9%. The reported overall efficiency index was 3.6 percent and the safety index was 68.6%. However, interpretations and clinical impact for the reported outcomes “efficiency index” and “safety index” were unclear as their definitions were not mentioned in the report.

5.2.1.3 Critical Appraisal

All studies had low internal validity. The study of *Romantsov et. al., (2010)* had no control group; hence, relative treatment effects cannot be established. Both the studies of *Romantsov et. al., (2009)* and *Sologub et. al., (2009)* used Cycloferon® for the prevention of influenza / SARS like illnesses. *Romantsov et. al., (2009)* involved children while that of *Sologub et. al., (2009)* involved adults. The studies of *Romantsov et. al. (2009 and 2010)* failed to report allocation concealment, blinding, intention to treat and complete follow up. None of the studies documented baseline characteristics. The studies of *Sologub et. al., (2009)* mentioned the use of envelopes for randomization and the use of table of random numbers. There was, however, limited discussion on the methods and the lack of completeness of presented data on the outcomes. None of the studies reported mortalities or other clinically relevant outcomes for influenza (as identified on influenza studies by *Lee et. al., 2010; Tamma et. al., 2010; Shiley et. al., 2010; Lynfield et. al., 2014; Wang, Y. et. al., 2019*) such as clinical recovery and length of hospital stay. Table 2 provides a comparative summary of the critical appraisal while Appendix 3 provides details of the critical appraisal for each study.

Table 2. Comparative summary of critical appraisal of included studies									
Author and year	**Patients**	**Treatment**	**Control**	**Randomization**	**Allocation concealment**	**Blinding**	**Intention to treat**	**Follow-up complete**	**Outcomes**
Romantsov et. al. (2010)	Adults 18-21 years old	Cycloferon® 600 mg once daily	None	Not randomized	No	No	Not applicable	Not applicable	Normalization of temperature per day (until 5th day)
Romantsov et. al. (2009) #	Children 10-16 years old	Cycloferon® (n=9,299)	Placebo (n=6,852)	Randomized through "envelopes" method	Envelopes	Not mentioned	Not mentioned	Cannot be determined	Incidence of acute respiratory viral infections
	Children 7-10 years old	Cycloferon® (n=524)	Placebo (n=731)						
Sologub et. al (2009) *[Sub-study 1]*	Adults 18-20 years old	Cycloferon® (10mg/kg) (n=266)	Symptomatic therapy (n=256)	Randomized through "envelopes" method	Envelopes	Not mentioned	Not done	Yes	Temperature intensity, duration of fever, duration of catarrhal events and symptoms, adverse events
Sologub et. al (2009) *[Sub-study 2]*	Adults 18-25 years old	Cycloferon® (10mg/kg) (n=2,080)	Multivitamins (n=1,637)	Random numbers	Not mentioned	Not mentioned	Not done	No	Incidence of illness, efficiency and safety index

#Note: No outcomes were reported for age group 4-7; hence, was removed from this summary table. See Appendix 3 for the full critical appraisal.

5.3 Cost-effectiveness of MA

Literature search from PubMed, LitCovid, Cochrane, and select HTA agencies yielded no evidence on the cost-effectiveness of MA; therefore, no evidence summary to support its cost-effectiveness can be provided to establish its recommendation.

6. LIMITATIONS

This review recognizes the following limitations: First, as this is a rapid review, certain steps of a systematic review were abbreviated. Second, the review is solely dependent on the provided dossier and published study search. The possibility of missing unpublished evidence to support their claims still remains. Third, the translation of the Russian references in our exploratory search were not professionally done. It is likely that the translated versions are not highly accurate; hence, some important items and keywords in the original articles might have been missed. Lastly, as evidence on the different facets of COVID-19 is on-going and rapidly evolving, the evidence presented here can rapidly change as well.

7. CONCLUSION

Summing all the information at hand, our rapid review did not find existing evidence on the clinical efficacy, safety and value for money on the use of MA for the treatment of patients with COVID-19. As for its treatment effect on influenza, our review showed limited evidence to support its claim. In the reviewed countries, the drug is currently neither registered nor recommended in the reviewed COVID-19 TGs or CPGs, to date, even from its source country Russia.

Generation of further evidence is needed to establish its claim on clinical efficacy and safety for COVID-19 that will allow for appraisal and validation as the basis for its recommendation.

Finally, as evidence on the different facets of COVID-19 is ongoing and rapidly evolving, regular scoping for evidence and updating of recommendations are strongly advised.

8. DECLARATION OF CONFLICT OF INTERESTS

The reviewers have no relevant affiliations or financial involvement with any organization or entity with a financial interest or in financial conflict with the subject matter or materials discussed in the review report.

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APPENDIX

Appendix 1. Market Availability and COVID-19 Treatment Guideline Recommendation on MA

Country	Is there off-label use* or compassionate use** of meglumine acridone acetate (MA) in the country?	Is Cycloferon ® registered? (Indication if possible)	List of medications used in the management	References
WHO	None	N/A	No antivirals recommended currently Investigational: ● Remdesivir ● Chloroquine and Hydroxychloroquine ● Ritonavir/ Lopinavir ● Ritonavir/ Lopinavir and Interferon-beta	World Health Organization. (2020b). Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Retrieved 25 March 2020 from https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected Kupferschmidt, K & Cohen, J. (2020). WHO launches global megatrial of the four most promising coronavirus treatments. Retrieved 25 March 2020 from https://www.sciencemag.org/news/2020/03/who-launches-global-megatrial-four-most-promising-coronavirus-treatments
Russia	None	Yes Indicated for immunocompromised patients, neuroinfection, HIV,	No specific recommendation on anti-virals ● Ribavirin ● Lopinavir/ Ritonavir ● Combined with empirical antibiotics for pneumonia	Russia Ministry of Health. (2020). Temporary Guidelines for the prevention, diagnosis, and treatment of the new 2019-coronavirus infection. Retrieved 25 March 2020 from https://www.rosminzdrav.ru/news/20

Country	Is there off-label use* or compassionate use** of meglumine acridone acetate (MA) in the country?	Is Cycloferon ® registered? (Indication if possible)	List of medications used in the management	References
		Viral Hepatitis, Herpes, and Cytomegalovirus infection	• Aprotinin • Glucocorticoids Cycloferon® not mentioned in the guidelines.	20/01/30/13236-vremennye-metodicheskie-rekomendatsii-po-profilaktike-diagnostike-i-lecheniyu-novoy-koronavirusnoy-infektsii-2019-ncov Biomedservice. (2001). Cyclopheron 12.5% 2 mL. No. 5 RR D/ V/ M AMP./ polysan. Retrieved 25 March 2020 from http://www.biomedservice.ru/price/goods/1/1132
Australia	None	No	Off-label use: • Lopinavir / Ritonavir +/- Hydroxychloroquine Investigational: • REMAP-CAP: ICU patients. Arms: Lopinavir / Ritonavir, Hydroxychloroquine, both or none • ASID: ward patients. Arms: Lopinavir / Ritonavir, Hydroxychloroquine, both or none	New South Wales Ministry of Health. (2020). Interim Guidance on use of antiviral therapy in COVID-19. Retrieved 25 March 2020 from https://www.health.nsw.gov.au/Infectious/diseases/Pages/covid-19-antiviral-therapy-interim-guidance.aspx
Canada	None	No	• Remdesivir (patient to patient basis)	Canada Ministry of Health. (2020). Coronavirus disease (COVID-19): For health professionals. Retrieved last 25

Country	Is there off-label use* or compassionate use** of meglumine acridone acetate (MA) in the country?	Is Cycloferon ® registered? (Indication if possible)	List of medications used in the management	References
				March 2020 from https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/health-professionals.html
China	None	No	• Interferon x • Lopinavir/Ritonavir x • Arbidol x • Ribavirin x • Chloroquine phosphate x • Tocilizumab • Corticosteroids	China National Health Commission. (2020). Chinese clinical guidance for COVID-19 pneumonia diagnosis and treatment (7th ed.) Retrieved last 25 March 020 from http://kjfy.meetingchina.org/msite/news/show/cn/3337.html Dong, L., Hu, S., & Gao, J. (2020). Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug discoveries & therapeutics, 14(1), 58–60. https://doi.org/10.5582/ddt.2020.01012
China - Zhejiang Univ. School of Medicine	None	No	• Lopinavir/Ritonavir • Arbidol • Nebulized Interferon • Darunavir/ Cobicistat • Favipiravir • Chloroquine • Corticosteroids	First Affiliated Hospital, University of Zhejiang University, School of Medicine. (2020). Handbook of COVID-19 Prevention and treatment. Retrieved March 25 2020 from https://covid-19.alibabacloud.com/

Country	Is there off-label use* or compassionate use** of meglumine acridone acetate (MA) in the country?	Is Cycloferon ® registered? (Indication if possible)	List of medications used in the management	References
Japan	None	No	Listed in Concept of treatment with antiviral drugs for COVID-19: ● Favipiravir ● Lopinavir and Ritonavir ● Ciclesonide	Tokyo Metropolitan Infectious Disease Surveillance Center. (2020). Guide to the treatment of new coronavirus infectious diseases (first edition). Retrieved March 25 2020 from http://idsc.tokyo-eiken.go.jp/assets/diseases/respiratory/ncov/treatmentguid.pdf Bryner, J. (2020). Flu drug used in Japan shows promise in treating COVID-19. Retrieved last March 25 2020 from https://www.livescience.com/flu-drug-could-treat-coronavirus.html
Singapore	None	No	Investigational: ● Remdesivir ● Lopinavir and Ritonavir ● Chloroquine	Saw Swee Hock School of Public Health. (2020). COVID-19 Science Report: Therapeutics. Retrieved 25 March 2020 from https://sph.nus.edu.sg/wp-content/uploads/2020/03/COVID-19-Science-Report-Therapeutics-23-Mar.pdf
South Korea	None	No	● Lopinavir/ Ritonavir ● Chloroquine or Hydroxychloroquine ● Ribavirin ● Interferon-alpha	Physicians work out treatment guidelines for coronavirus. (2020, February 13). Retrieved from http://www.koreabiomed.com/news/articleView.html?idxno=7428

Country	Is there off-label use* or compassionate use** of meglumine acridone acetate (MA) in the country?	Is Cycloferon ® registered? (Indication if possible)	List of medications used in the management	References
Taiwan	None	No	Investigational: ● Remdesivir	Taiwan Centers for Disease Control. (2020). Coronavirus disease 2019 (COVID-19). Retrieved last March 25 2020 from https://www.cdc.gov.tw/En/Category/ListContent/bg0g_VU_Ysrgkes_KRUDgQ?uaid=0nAzwpXdBNIAPOvJhwrGoQ
Thailand	None	No	Investigational (through WHO's Solidarity Trial): ● Remedesivir ● Lopinavir and Ritonavir ● Lopinavir and Ritonavir plus Interferon beta ● Chloroquine	World Health Organization Thailand. (2020). Coronavirus disease 2019 (COVID-19) WHO Thailand Situation Report – 23 March 2020. Retrieved 25 March 2020 from https://www.who.int/docs/default-source/searo/thailand/2020-03-23-tha-sitrep-30-covid19-final.pdf?sfvrsn=6d9f54f4_0
United Kingdom	None	No	Investigational: ● Lopinavir / Ritonavir and dexamethasone	NHS Clinical Management of COVID-19. (2020). Last accessed on March 25 2020 https://www.england.nhs.uk/coronavirus/secondary-care/management-confirmed-coronavirus-covid-19/clinical-medical-management/ Rigby, S. (2020, March 24). Coronavirus: UK patients to test existing drugs as COVID-19 treatments. Retrieved from https://www.sciencefocus.com/news/

Country	Is there off-label use* or compassionate use** of meglumine acridone acetate (MA) in the country?	Is Cycloferon ® registered? (Indication if possible)	List of medications used in the management	References
				coronavirus-uk-patients-to-test-existing-drugs-as-covid-19-treatments/
United States	None	No	Investigational: ● Remdesivir	United States Centers for Disease Control and Prevention. (2020). Retrieved March 25 2020 from https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html

* An off-label refers to the use of a licensed medicinal product prescribed for an indication, or to a patient for which the product is not specifically licensed

** A compassionate use refers to the use of the medicinal product not licensed and not used as a treatment for any disease

Appendix 2. Selection of included studies

All information is directly translated from Russian to English language using Google® Translate.

Author, Year, Title	Study design	Country	PICO	Main Findings and Conclusion	Reference
Romantsov, M.G. & Golofeevsky, S.V. (2010) Cycloferon Efficacy in the Treatment of Acute Respiratory Tract Viral Infection and Influenza During the Morbidity Outbreak in 2009—2010	Clinical trial	Russia	P: Adult patients ARVI and influenza using the drug Cycloferon®, in November-December 2009 in Belgorod I: Cycloferon® C: *Control group not specified* O: Primary - Normalization of temperature per day (until 5th day)	The patients were randomized by their body temperature on the day of the medical advise seeking. The clinical manifestation of the respiratory tract infection was characterized by the increase of the body temperature stated in 31.8% of the patients. Normalization of the temperature was obtained on the 4th or 5th day of the observation. The catarrhal and intoxication syndromes (including chills, headache with localization in the frontal region and temples, aching muscles, joints, pain with movement by eyeballs or when pressed on them, photophobia, lacrimation, weak bones and fatigue, lethargy) were observed for no more than 5 days. When the treatment was started in time (on the day of the medical advise seeking), Cycloferon® provided minimization of the intoxication and catarrhal syndromes and normalization of the body temperature on the 4th day of the therapy without the use of antibacterial agents.	https://drive.google.com/open?id=1mZns_Fxqm-Ej3bQjkYg0JHsC4s6DTSeO

Author, Year, Title	Study design	Country	PICO	Main Findings and Conclusion	Reference
Romantsov, M.G, Selkova, E.P., Garashchenko, M.V., Semenenko, T.A., Shuldyakov, A.A., Kondratyeva, E.I., Tyuteva, E.Y., & Kovalenko, A.L. (2009) Improvement of natural resistance in children for prophylaxis of influenza and acute respiratory tract viral infections (results of multicenter randomized trials)	Randomized Controlled Clinical Trial	Russia	P: School children of 4-16 years old I: Cycloferon® C: Placebo O: Incidence of Acute Respiratory Viral Infections (ARVI)	The prophylactic effect of the drug (2.9—7.2-fold decrease of the morbidity) with respect to the respiratory tract mono- and mixed infections was shown. The marked cytoprotective effect, evident from lower destruction of the epithelial cells and increased activity of the local nonspecific resistance factors (lysozyme, secretory immunoglobulin A) was observed.	https://drive.google.com/open?id=1LCL2ZEGfu1YcLkxx72Q33RnABHAh3cTK
Sologub, T.V., Shuldyakov, A.A., Romancova, M.G., Yekalov, A.N., Petlenco, S.V., Yerofeeva, M.K., Maksakova, V.L., Isakov, V.A., Sarubayev, V.V., Gasan, V.V., &	Randomized control - comparative study	Russia	[Sub-study 1] P: adults aged 18-20 years old with the presence of a verified diagnosis of influenza and/or SARS I: Cycloferon® C: symptomatic basic treatment O: temperature intensity; duration of fever of temperature reaction; duration	[Sub-study 1] In patients receiving Cycloferon®, the temperature intensity and duration of fever was stopped faster, their average duration ranged from 1.8 to 3 days, against 5 days in the comparison group (symptomatic therapy). The improvement in the condition was observed from the 2nd day in patients who received Cycloferon®. Complications of influenza, in the form of pneumonia, were noted in	https://drive.google.com/open?id=1CkpKnaKcjvN8t5Cjj67NHHJiFZ26Un1f

Author, Year, Title	Study design	Country	PICO	Main Findings and Conclusion	Reference
Kovalenko, A.L. (2009). Cycloferon, as an agent in the therapy and urgent prophylaxis of influenza and acute respiratory tract viral infection (multicentre randomized controlled comparative study)			of symptoms (headache, general malaise); dynamics of catarrhal symptoms (cough, runny nose, sore throat); presence and frequency of flu complications [Sub-study 2] P: adults aged 18-25 years old with the presence of a verified diagnosis of influenza and/or SARS, subdivided into three groups with undefined/ unclear basis of subgrouping I: Cycloferon® C: multivitamins O: incidence of illness, efficiency index, safety index	2.2% of cases in patients treated with Cycloferon®, and in 21.4% of cases (bronchitis, pneumonia, angina) in patients receiving symptomatic therapy. [Sub-study 2] The 1st subgroup was 517 people, of which 320 people received Cycloferon®, 197 - multivitamin. Among those observed in this group, 15.5% of people who received the drug fell ill, and among those receiving multivitamins - 84.3%. The efficiency index was 5.4 and the safetyindex was 82.0%. The 2nd subgroup consisted of 1,500 people. The pre-attack was received by 760 people, multivitamin - 740 people. Among young people who received cicloferon, 26.7% fell ill, while in the group of collapse - 68.6%. The efficiency index was 2.6 and the safety index was 61.0%. The third subgroup consisted of 400 people, of whom 300 received Cycloferon® and 100 people received multivitamin. Among these observed, the efficiency index was 2.7 and the safety index was 62.9%. Overall, the efficiency index was 3.6 percent and the safety index was 68.6%.	

Appendix 3. Critical appraisal of included studies using Evaluation of Articles on Therapy tool by *Dans et. al. (2017)*

Cycloferon efficacy in the treatment of acute respiratory tract viral infection and influenza during the morbidity outbreak in 2009-2010

Author: Romantsov et al, 2010

CRITICAL APPRAISAL

Reference: https://drive.google.com/open?id=1mZns_Fxqm-Ej3bQjkYg0JHsC4s6DTSeO

1. DIRECTNESS

Research Question	
P	*Adult patients ARVI and influenza using the drug Cycloferon® , in November-December 2009 in Belgorod* *In connection with the above, in November-December 2009 in Belgorod we have treated patients ARVI and influenza using the drug Cycloferon® [13]…"* *"Under the supervision were 150 men in age from 18 to 21 years (average age is pitchfork 20.0 ± 1.3 years) division of the Belgorod garrison, organizing bath in October-November 2009."*
I	*Cycloferon®* *"To everyone patients were prescribed treatment on the day of treatment Cycloferon® in a dose of 600 mg (4 tablets - Ki) 1 time per day with an interval of 24 hours. Cycloferon® is included in the federal treatment standard patients with influenza (order of the Ministry of Health and Social Development Russia No. 460 dated June 7, 2006) and to the list (under Kaz No. 116 dated 09/01/09) recommended by the Management Rospotrebnadzor in Moscow ny means for carrying out nonspecific prevention and treatment of acute respiratory viral infections and influenza."*
C	*No control*
O	Primary outcome : Normalization of temperature per day (until 5th day) *"Depending on the temperature reaction in patients are randomized on admission distributed into 3 groups. Group A included patients with fluctuations in temperature set from 38.7 to 39.1 ° C, the average level of set 38.9 ± 0.2 ° C. In patients assigned to group C, the temperature did not exceed subfeb- level, and in patients of group B the temperature The temperature ranged from 37.9 to 38.7 ° C (Table 2)."*

Table 2. The distribution of patients (n = 150) in groups on the day of admission, depending on temperature reactions

Best practices, especially if you are	Work (° °)) â ∈ ä Remain
Group A, *n* = 64	38.9 ± 0.2 (39.138.7)
Group C, *n* = 66	37.6 ± 0.2 (37.837.4)
Group B, *n* = 20	38.3 ± 0.4 (38.737.9)

Table 3. Dynamics of the temperature reaction in the observed patients

REVIEW	Group A, *n* = 64	Group C, *n* = 66
1st	38.9 ± 0.2 (39.138.7)	37.6 ± 0.2 (37.837.4)
2nd	37.6 ± 0.4 (38.037.2)	37.3 ± 0.3 (37.637.0)
3rd	36.6 ± 0.1 (36,736.5)	36.8 ± 0.3 (37.136.5)
4th	36.6 ± 0.2 (36.836.4)	36.9 ± 0.4 (37.336.5)
5th	36.5 ± 0.08 (36,436.6)	36.6 ± 0.3 (36.636.3)

Table 4. Normalization of the temperature reaction in patients of groups A and C

For further information	General Information Part A, *n* = 64	Group C, *n* = 66
1st	-	-
2nd	8 / 12.5	-
3rd	13 / 20.3	26 / 39.4
4th	59 / 92.2	44 / 66.7
5th	61 / 95.3	62 / 93.9

Table 5. The second peak of the temperature reaction in patients of group C

For further information	× Generally (complete / exclusive / optional)
2nd	4 / 6.1
3rd	8 / 12.1
4th	4 / 6.1
5th	3 / 4,5
7th	2 / 3.0
Total for the group (in%)	21 / 31.8

2. APPRAISAL OF VALIDITY

2.1. Were the patients randomly assigned to treatment groups? (Randomization)

No

In this study, all patients who have acute viral respiratory infections and influenza were given the same intervention as there was no control group

2.2. Was allocation concealed? (Allocation Concealment)

No

Since all patients who have acute viral respiratory infections and influenza were given the same intervention, no allocation concealment happened.

2.3. Were baseline characteristics similar at the start of the trial?

No

There was no control, therefore, no comparisons can be made. However, the patients who all received Cycloferon® were stratified based on their temperature on the day of the treatment as shown in Table 2.

Table 2. The distribution of patients (n = 150) in groups on the day of admission, depending on temperature reactions

Best practices, especially if you are	Work (° °)) â ∈ ä Remain
Group A, *n* = 64	38.9 ± 0.2 (39.138.7)
Group C, *n* = 66	37.6 ± 0.2 (37.837.4)
Group B, *n* = 20	38.3 ± 0.4 (38.737.9)

2.4. Were patients blinded to treatment assignment?

No

"To everyone patients were prescribed treatment on the day of treatment Cycloferon® in a dose of 600 mg (4 tablets - Ki) 1 time per day with an interval of 24 hours. Cycloferon® is included in the federal treatment standard patients with influenza (order of the Ministry of Health and Social Development Russia No. 460 dated June 7, 2006) and to the list (under Kaz No. 116 dated 09/01/09) recommended by the Management Rospotrebnadzor in Moscow ny means for carrying out nonspecific prevention and treatment of acute respiratory viral infections and influenza."

2.5. Were caregivers blinded to treatment assignments?

No

"To everyone patients were prescribed treatment on the day of treatment Cycloferon® in a dose of 600 mg (4 tablets - Ki) 1 time per day with an interval of 24 hours. Cycloferon® is included in the federal treatment standard patients with influenza (order of the Ministry of Health and Social Development Russia No. 460 dated June 7, 2006) and to the list (under Kaz No. 116 dated 09/01/09) recommended by the Management Rospotrebnadzor in Moscow ny means for carrying out nonspecific prevention and treatment of acute respiratory viral infections and influenza."

2.6. Were outcome assessors blinded to treatment assignment?

No

The English-translated manuscript of the study did not mention blinding of assessor/s.

2.7. Were all patients analyzed in the groups to which they were originally randomized?

Not applicable

There was no control group in the study. All patients enrolled received the same intervention.

2.8. Was follow-up rate adequate?

Not applicable

3. APPRAISING THE RESULTS

3.1. How large is the effect treatment?

Normalization of temperature among Group A was largely achieved in the 4th day of infection (59/64, 92.2%). For group C, only 66.7% of the patients had normalization of temperature and 93.9% normalization of temperature on the 5th day of infection. Group C had a much lower baseline temperature compared to Group A patients.

Primary clinical efficacy outcome:

Day	Mean temperature of Group A (ºC) n=64	Number of normalized temperature among Group A n=66	Mean temperature of Group C	Number of normalized temperature among Group C
1st	38.9±0.2	-	37.6±0.2	-
2nd	37.6+0.4	8 (12.5%)	37.3±0.3	-
3rd	36.6±0.1	13 (20.3%)	36.8±0.3	26 (39.4%)
4th	36.6±0.2	59 (92.2%	36.9±0.4	44 (66.7%)

5th	36.5±0.08	61 (95.3%	36.6±0.3	62 (93.9%)

4. APPLICABILITY

In terms of age and sex of the patients in the study, participants are not comparable to the Filipino population. (men, age from 18 to 21 years (average age is pitchfork 20.0 ± 1.3 years). The population involved must be of all ages, preferable of the older population. Also, there was no way to determine the causes of the acute viral respiratory infections, whether they were COVID-19 cases or not. It was found in the study that Cycloferon® is able to normalize the body temperature of high fever on the 4th day of acute viral respiratory infection or influenza. Since no control group was used in the study and was performed on a narrow age range, results may only be applicable to other acute viral respiratory infections or influenza among ages 18-21. There is no conclusive evidence to say that the study can also be applicable to severe cases of patients diagnosed with COVID-19 in the Philippines.

5. CONCLUSION

Based on the reported results, Cycloferon® is able to normalize the body temperature of high fever on the 4th day of acute viral respiratory infection or influenza. The major flaw of the study is in its design where there was no control group. Without a control group, relative treatment effects cannot be established. Hence, we deem that the study has low validity.

Improvement of natural resistance in children for prophylaxis of influenza and acute respiratory tract viral infections (results of multicenter randomized trials)

Author: Romantsov et al, 2009

CRITICAL APPRAISAL

Reference: https://drive.google.com/open?id=1LCL2ZEGfu1YcLkxx72Q33RnABHAh3cTK

1. DIRECTNESS

Research Question	
P	Schoolchildren of 10-16 years old, *subdivided into 3 groups:* *10-16 yo = 16,151* *7-10 yo = 1.255* *4 to 7 yo = 114* **Inclusion and exclusion criteria were not indicated* "A multicenter randomized controlled study in schoolchildren of 10-16 years old, the sample consisted of 16,151 people. Of this number, 9,299 children received treatment, and 6,852 people were receiving placebo. In addition, 1255 children, aged 7 to 10 years, were under observation. Experimental group consisted of 524 children, receiving the drug Cycloferon®, the control group amounted to 731 people who did not receive Cycloferon®. The group of children from 4 to 7 years old was 114 people."
I	Cycloferon® **Dose, timing, and duration of treatment was not indicated*
C	Placebo
O	Incidence of Acute Respiratory Viral Infections (ARVI) *Method of diagnosing the infections were not indicated

2. APPRAISAL OF VALIDITY

2.1. Were the questions randomly assigned to treatment groups? (Randomization)

Yes. The treatment groups were randomized according to "envelopes".

2.2. Was allocation concealed? (Allocation Concealment)

Not mentioned

While they reported using the envelope method, the paper did not mention whether it was effective (ie, use of sealed and opaque envelopes).

"Randomization study was conducted using the method of 'envelopes'."

2.3. Were baseline characteristics similar at the start of the trial?

No.

Baseline characteristics were not reported in the study.

2.4. Were patients blinded to treatment assignment?

Not mentioned

The paper did not mention the blinding of the patients to treatment assignments.

2.5. Were caregivers blinded to treatment assignments?

Not mentioned

The paper did not mention the blinding of the caregivers to treatment assignments.

2.6. Were outcome assessors blinded to treatment assignment?

Not mentioned

The paper did not mention the blinding of the outcome assessors to treatment assignments.

2.7. Were all patients analyzed in the groups to which they were originally randomized?

No.

The patient assignment to each group in the 4 to 7 age group and their outcome reporting were not presented and accounted for.

2.8. Was follow-up rate adequate?

No/ Cannot be determined

The patient assignment to each group and their outcome reporting were not presented and accounted for. It did not mention if there were drop-outs.

3. APPRAISING THE RESULTS

3.1. How large is the effect treatment?

Primary clinical efficacy outcome: Incidence of Acute Respiratory Viral Infections (ARVI)

Population group	RR (95%CI)
4 to 7 years old	No data provided
7 to 10 years old	0.14 (0.1 to 0.2)
10 to 16 years old	0.34 (0.3 to 0.38)

4. APPLICABILITY

The age group generally affected by acute viral respiratory illnesses are generally similar to the Philippines, although the seasons and temperature changes in Russia and the Philippines differ drastically.

5. CONCLUSION

The study has multiple gaps which includes failure to report, effective allocation concealment, baseline characteristics, blinding, and accounting of patient assignment to outcome reporting. The outcomes for age group 4-7 was not provided. Hence, there is high risk of selection bias, performance bias and detection bias; as well as selective reporting. This results in low internal validity of the study.

Cycloferon, as an agent in the therapy and urgent prophylaxis of influenza and acute respiratory tract viral infection (multicentre randomized controlled comparative study) [Sub-study 1]

Author: Sologub et al, 2009

CRITICAL APPRAISAL

Reference: https://drive.google.com/open?id=1CkpKnaKcjvN8t5Cjj67NHHJiFZ26Un1f

1. DIRECTNESS

Research Question	
P	adults aged 18-20 years old with the presence of a verified diagnosis of influenza and/or SARS *The observed age is 18-20 years. A total of 522 people were monitored, 266 of them received Cycloferon® for early treatment, 256 people made up a comparison group, they received symptomatic basic treatment."* Page 32
I	*Cycloferon® (10 mg/kg)* *"Emergency prevention of influenza and SARS was carried out by Cycloferon®, which was prescribed from the calculation of 10 mg/kg of body weight, according to the instructions on the medical use of the drug."* *"The schemes and doses of use corresponded to the instructions for medical use."Page 32*
C	*symptomatic basic treatment* *Page 32*
O	Temperature intensity; duration of fever; duration of symptoms (headache, general malaise); dynamics of catarrhal symptoms (cough, runny nose, sore throat); presence and frequency of flu complications *"Evaluation of the clinical effectiveness of the drug was carried out on the duration and intensity of temperature reaction; duration of symptoms (headache, general malaise); dynamics of catarrhal symptoms (cough, runny nose, sore throat); presence and frequency of flu complications."*

2. APPRAISAL OF VALIDITY

2.1. Were the patients randomly assigned to treatment groups? (Randomization)

Yes

"Randomization method using random number tables formed 'experienced and control' groups..."

2.2. Was allocation concealed? (Allocation Concealment)

No.

While they reported using the envelope method, the paper did not mention whether it was effective (i.e., use of sealed and opaque envelopes).

"Randomization of the groups was carried out using the method of "envelopes"..."

2.3. Were baseline characteristics similar at the start of the trial?

No.

Baseline characteristics were not reported in the study.

2.4. Were patients blinded to treatment assignment?

Not mentioned

The paper did not mention the blinding of the patients to treatment assignments.

2.5. Were caregivers blinded to treatment assignments?

Not mentioned

The paper did not mention the blinding of the caregivers to treatment assignments.

2.6. Were outcome assessors blinded to treatment assignment?

Not mentioned

The paper did not mention the blinding of the outcome assessors to treatment assignments.

2.7. Were all patients analyzed in the groups to which they were originally randomized?

Yes.

The number of patients assigned in the treatment groups were the same number reflected in the analysis/ outcome reporting.

2.8. Was follow-up rate adequate?

Yes.

While it did not present a detailed accounting of patients, we can assume that there were no drop-outs since the number of patients assigned in the treatment groups were the same number reflected in the analysis/ outcome reporting.

3. APPRAISING THE RESULTS

3.1. How large is the effect treatment?

Primary clinical efficacy outcome: Temperature intensity in patients with influenza

Temperature	Cycloferon® (N=266)	Symptomatic therapy (N=256)
37.6-38.0 deg C	103	24
38.1-38.5 deg C	103	87
38.6-38.9 deg C	30	48
39 deg C	30	97

Based on the presented table of temperature intensity, no insights can be drawn to support evidence on the benefits of Cycloferon® as antiviral treatment against influenza and SARS. Given that symptomatic therapy was limited to administering multivitamins to patients, rationale on its usage was not specified in the study.

Primary clinical efficacy outcome: Duration of fever in patients with influenza

Duration	Cycloferon® (N=266)	Symptomatic therapy (N=256)	RR	NNT
Day 1 With Without	 11 255	 0 256	 22.14 (1.31-373.76)	 24.32
Day 2 With Without	 29 237	 63 193	 0.44 (0.30-0.66)	 3.94
Day 3 With Without	 15 251	 54 202	 0.27 (0.15-0.46)	 4.74
Day 4 With Without	 8 258	 69 187	 0.11 (0.05-0.23)	 4.18
Day 5 With Without	 5 261	 46 210	 0.10 (0.04-0.26)	 6.22
Day 6 With Without	 0 266	 16 240	 0.29 (0.002-0.48)	 16.04
Day 7 With Without	 0 266	 8 248	 0.06 (0.003-0.98)	 32.05

Primary clinical efficacy outcome: Duration (in mean days) of catarrhal events and symptoms in influenza patients who took and did not take Cycloferon® during the flu epidemic

Clinical symptoms	Cycloferon® (N=266)	Symptomatic therapy (N=256)	Mean difference
Total malaise	2.1	4.8	2.7
Headache	1.8	4.2	2.4
Nasal congestion	1.8	4.0	2.2
Runny nose	2.5	4.6	2.1
Cough	2.7	4.9	2.2
Pharyngeal hyperemia	3.0	4.6	1.6
Shortness of breath	2.3	4.8	2.5

The presence of dry and wet wheezing during auscultation	-	3.8	3.8

Clinical safety outcome: Adverse events

Adverse Event	Cycloferon® (N=266)	Symptomatic therapy (N=256)	RR
Complicated flu course With Without	 6 260	 55 206	0.11 (0.05-0.24)
Acute bronchitis With Without	 0 266	 24 232	0.02 (0.001-0.32)
Angina With Without	 0 266	 6 250	0.07 (0.004-1.31)
Pneumonia With Without	 6 260	 18 238	0.32 (0.13-0.80)
Repeated diseases With Without	 0 266	 6 250	0.07 (0.004-1.31)

4. APPLICABILITY

Sex distribution of the participants in the study was not discussed in the study. In terms of age, only adult patients aged 18-25 were included. Comorbidities of the patients were not disclosed. Due to the very limited discussion on methods and baseline characteristics of study participants, applicability of the study to the Philippines cannot be inferred.

5. CONCLUSION

Based on temperature intensity and duration of fever, no insights can be drawn to support evidence on the benefits of Cycloferon® as antiviral treatment against influenza and SARS. Given that symptomatic therapy was limited to administering multivitamins to patients, rationale on its usage was not specified in the study. In terms of safety outcomes, more treatment-related adverse events were reported on the symptomatic therapy arm than in the experimental (Cycloferon®) arm on the basis of absolute numbers.

In summary, due to the limited discussion on the methods and the lack of completeness of presented data on the outcomes, this study may not be fit for use as evidence in reviewing the efficacy and safety of Cycloferon® as a potential antiviral agent against influenza and SARS.

The study has multiple gaps which includes failure to report effective allocation concealment, baseline characteristics and blinding. Hence, there is high risk of selection bias, performance bias and detection bias. This results in low internal validity of the study.

Cycloferon, as an agent in the therapy and urgent prophylaxis of influenza and acute respiratory tract viral infection (multicentre randomized controlled comparative study) [Sub-study 2]

Author: Sologub et al, 2009

CRITICAL APPRAISAL

Reference: https://drive.google.com/open?id=1CkpKnaKcjvN8t5Cjj67NHHJiFZ26Un1f

1. DIRECTNESS

Research Question	
P	adults aged 18-25 years old with the presence of a verified diagnosis of influenza and/or SARS, subdivided into three groups with undefined/ unclear basis of subgrouping *"There were 3,117 people between the ages of 18 and 25 under surveillance. Cycloferon® was received by 2,080 people ("experienced" group) and 1,637 people received multivitamins."* *Page 32* *"The group of persons receiving Cycloferon® included 3 subgroups:"* *"the 1st subgroup was 517 people, of which 320 people received Cycloferon®, 197 - multivitamin."* *"The 2nd subgroup consisted of 1,500 people. The pre-attack was received by 760 people, multivitamin - 740 people."* *"The third subgroup consisted of 400 people, of whom 300 received Cycloferon® and 100 people received multivitamin."* *Page 35*
I	*Cycloferon® (10 mg/kg)* *"Emergency prevention of influenza and SARS was carried out by Cycloferon®, which was prescribed from the calculation of 10 mg/kg of body weight, according to the instructions on the medical use of the drug."* *"The schemes and doses of use corresponded to the instructions for medical use."* *Page 32*
C	Multivitamins *"Cycloferon® was received by 2,080 people (experimental group) and 1,637 people received multivitamins."* *Page 32*
O	Incidence of illness Efficiency index Safety index ****Outcomes undefined*

2. APPRAISAL OF VALIDITY

2.1. Were the patients randomly assigned to treatment groups? (Randomization)

Yes

"Randomization method using random number tables formed 'experienced and control' groups..."

2.2. Was allocation concealed? (Allocation Concealment)

Not mentioned

2.3. Were baseline characteristics similar at the start of the trial?

No.

Baseline characteristics were not reported in the study.

2.4. Were patients blinded to treatment assignment?

Not mentioned

The paper did not mention the blinding of the patients to treatment assignments.

2.5. Were caregivers blinded to treatment assignments?

Not mentioned

The paper did not mention the blinding of the caregivers to treatment assignments.

2.6. Were outcome assessors blinded to treatment assignment?

Not mentioned

The paper did not mention the blinding of the outcome assessors to treatment assignments.

2.7. Were all patients analyzed in the groups to which they were originally randomized?

No.

Patient flow from treatment assignment and outcome reporting was not presented.

2.8. Was follow-up rate adequate?

No.

Patient flow from treatment assignment and outcome reporting was not presented.

3. APPRAISING THE RESULTS

3.1. How large is the effect treatment?

Primary clinical efficacy outcome: Incidence of illness

We calculated the relative risks (RRs) based on the reported data in the paper. We note, however, that the reported number of patients in the treatment assignment and those in the outcome reporting do not match.

Outcome	Cycloferon®	Multivitamins	RR	NNT
Group 1 Ill Well	(N=320) 50 (15.5%) 270 (84.5%)	(N=197) 166 (84.3%) 31 (15.7%)	0.185 (0.1427 to 0.2409)	1.46
Group 2 Ill Well	(N=760) 203 (26.7%) 557 (73.3%)	(N=740) 508 (68.6%) 232 (31.4%)	0.39 (0.3425-0.4420)	2.38
Group 3 Ill Well	(N=300) No reported data	(N=100) No reported data	-	-

In terms of incidence of illness, RRs for both Groups 1 and 2 indicate that Cycloferon® reduces the risk of influenza by 81.5% and 61%, respectively.

Primary clinical efficacy and safety outcomes: Efficiency index and safety index

Index	Group 1 Cycloferon® (N=320) + Multivitamins (N=197)	Group 2 Cycloferon® (N=760) + Multivitamins(N=740)	Group 3 Cycloferon® (N=300) + Multivitamins (N=100)
Efficiency Index	5.4	2.6	3.6
Safety Index	82.0%	61.0%	68.6%

As these measured outcomes were not defined, it is difficult to validate and interpret the clinical value of the reported results.

4. APPLICABILITY

Sex distribution of the participants in the study was not discussed in the study. In terms of age, only adult patients aged 18-25 were included. Comorbidities of the patients were not disclosed. Due to the very limited discussion on methods and baseline characteristics of study participants, applicability of the study to the Philippines cannot be inferred.

5. CONCLUSION

Based on incidence of illness and efficiency and safety indices, no insights can be drawn to support evidence on the benefits of Cycloferon® as antiviral treatment against influenza and SARS. Given that symptomatic therapy was limited to administering multivitamins to patients, rationale on its usage was not specified in the study. In terms of safety outcomes, more treatment-related adverse events were reported on the symptomatic therapy arm than in the experimental (Cycloferon®) arm on the basis of absolute numbers.

In summary, due to the limited discussion on the methods and the lack of completeness of presented data on the outcomes, this study may not be fit for use as evidence in reviewing the efficacy and safety of Cycloferon® as a potential antiviral agent against influenza and SARS.

The study has multiple gaps which includes failure to report allocation concealment, baseline characteristics, blinding and patient flow diagram. The measured outcomes were also not defined; hence, it is difficult to validate and interpret the clinical value of the reported results. Hence, there is high risk of selection bias, performance bias and detection bias; as well as selected reporting. This results in low internal validity of the study.