Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
Funded by the DOH AHEAD Program through the PCHRD

EVIDENCE SUMMARY

Should nasal sprays be used in the prevention and treatment of COVID-19 infection?

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RECOMMENDATION

We suggest against the use of nasal spray as an adjunct to treatment of COVID-19 infection. *(Low certainty of evidence; Weak recommendation)*

There was no consensus on the use of nasal spray in addition to other preventive interventions such as vaccination, proper use of personal protective equipment, and adherence to quarantine and isolation protocols to prevent COVID-19 infection.

Consensus Issues

The statement suggesting against the use of nasal spray as an adjunct to treatment was unanimously approved by the panel members due to the high certainty of the risk of adverse events and the uncertain benefits from the use of glycerol- and hydrogen-peroxide-based nasal sprays. For the panel, the statement warranted a weak recommendation because (1) it is not a primary intervention and (2) despite the risk of harm, it may not necessarily result in overuse, unlike other drugs such as antibiotics.

The decision regarding the statement on the use of nasal spray as an adjunctive to other preventive interventions reached an impasse. The panel members who were inclined towards its use despite possible added costs based their arguments on the risk reduction of developing COVID-19, its availability in the local market, and its authorization from the Philippine Food and Drug Administration as a medical device intended for short-term use. They also claimed that it could be a weak recommendation and that it would not be a replacement for any existing recommended intervention. However, other panel members who voted against its use placed a greater value on the benefit of vaccinations. A panel member also voiced opposition because the word “suggest” implied a strong recommendation for use despite the fact that only two small trials demonstrated benefit and several clinical trials are still underway. Another posited that glycerol-based sprays, which can be oily, might obstruct breathing when used with masks.

Key Findings

As an adjunct to prevention, two randomized controlled trials on healthy asymptomatic healthcare workers providing direct care to COVID-19 patients showed that the use of iota-carrageenan or dimethylsulfoxide ethanol nasal spray provided significant benefit in reducing the risk of COVID-19 infection compared to routine care with or without saline placebo. The risk of adverse events and discontinuation of the intervention due to intolerance, comparing treatment and control groups, was inconclusive. Nasal sprays in these trials were used as an adjunct to proper personal protective equipment and universal precautions. Overall certainty of evidence was low.

As an adjunct to treatment, nine randomized controlled trials on patients with mild and moderate COVID-19 showed that the use of nasal sprays containing different active agents (one study each for glycerol, hydrogen peroxide, nitric oxide, ivermectin, momethasone and triamcinolone; povidone iodine in three studies) did not result in significant benefit in terms of viral clearance and showed inconsistent benefit in terms of symptomatic relief. Furthermore, the risk for adverse events (mostly minor, such as sensation of nasal and throat burning, frequent sneezing, altered taste sensation, and minor epistaxis) was significantly higher in the nasal spray arm compared to placebo. Overall certainty of evidence was low.

Introduction

As the primary sites of infection and replication of SARS-CoV-2 are through the nasal cavity, it has been theorized that early and targeted treatment of the nasal mucosa may block viral entry and interfere locally with the cascade of viral replication and host infection.[1] In vitro and pre-clinical studies have shown that the effectiveness of various active compounds in nasal sprays against SARS-CoV-2 is mainly based on the creation of a film barrier [1] and the general vulnerability of SARS-CoV-2 to osmotic [2,3], chemical [4], cytokine-regulated [5,6], free-radical membrane [7] disruption, and oxidative damage [8,9]. However, safety and tolerability concerns that arise from potential irritation of nasal mucosa, and allergic reactions to components of the products are major concerns. This systematic review aimed to estimate the effectiveness of nasal sprays as an adjunctive intervention in the prevention and treatment of COVID-19.

Review Methods

The Pubmed for Medline database, ClinicalTrials.gov, and WHO International Clinical Trials Registry Platform were searched on 18 November 2021 using the search terms “nasal spray” and “COVID-19” or “SARS-COV-2.” The medRxiv and bioRxiv databases were also searched for pre-publication articles. Full texts were reviewed to determine which studies would be included in the final analysis. When randomized controlled trials were available, we excluded brief communications, reviews, cohort studies, case-control studies, case series, and case reports in the final screening of studies.

Results

As Adjunct to Treatment of COVID-19 Infection

A total of nine randomized controlled trials [3, 7, 9-15] were reviewed and analyzed to determine the efficacy of nasal sprays as an adjunct to the routine treatment of mild to moderate COVID-19. The trials investigated nasal sprays containing seven different ingredients namely glycerol [3] nitric oxide [7], povidone iodine [9,11,12], hydrogen peroxide [10], ivermectin [13], momethasone [14], and triamcinolone [15]. Nasal sprays together with routine care were compared to routine care with placebo. Clinically important outcomes were viral clearance, forward transmission of SARS-CoV-2 to household contacts, symptomatic relief of COVID-19 symptoms, and adverse events. Characteristics of studies included in this review are shown in Appendix 3A.

Outcome: Viral Clearance

Two studies [11,13] on two different active agents provided data on viral clearance, which was defined as a negative SARS-CoV-2 RT-PCR after the use of nasal spray. The first study, which utilized a povidone iodine-based nasal spray, showed statistically significant viral clearance (RR 10.00, 95% CI 2.61-38.31; Low Certainty) after only one application of the nasal spray [11]. Another study, which utilized ivermectin-based nasal spray, also showed statistically significant viral clearance (RR 1.26, 95% CI 1.07-1.47; Low Certainty) [13]. In the latter study, viral clearance

was defined as two consecutive negative SARS-CoV-2 RT-PCR. Certainty of evidence in both studies were low due to very serious risk of bias. Both studies had unclear to high risk of bias in terms of participant and outcome assessor blinding, and allocation concealment. An attempt to do pooled analysis further downgraded the certainty of evidence to very low due to very serious risk of bias, highly significant heterogeneity resulting in very serious inconsistency, and overall imprecision (RR 3.40, 95% CI 0.13-91.80; I^2=88.9%; Very Low Certainty).

Outcome: Forward Transmission
One study, which utilized hydrogen peroxide-based nasal spray, investigated the incidence of forward transmission of SARS-CoV-2 among family members of 106 study participants. In this study, the risk for forward transmission of SARS-CoV-2 between intervention and placebo groups was inconclusive (RR 0.69, 95% CI 0.24-1.95; Moderate Certainty).[10] Certainty of evidence was downgraded to moderate due to imprecision of risk estimates.

Outcome: Symptomatic Relief of COVID-19 Symptoms
Relief of COVID-19 symptoms was reported in three trials which utilized three different types of nasal sprays. The trial on glycerol-based nasal spray [3] reported statistically significant benefits in the relief of sore throat (RR 2.50, 95% CI 1.24-5.05; High Certainty), fever (RR 1.12, 95% CI 1.04-1.20; High Certainty), and ageusia (RR 3.50, 1.92-6.27; High Certainty) but inconclusive benefit on the relief of headache (RR 1.24, 95% CI 1.00-1.54; Moderate Certainty). Length of follow-up for relief of symptoms ranged from 7 to 14 days. Certainty of evidence on relief of loss of headache was downgraded to moderate certainty due to imprecision of risk interval estimates.

In another trial which compared hydrogen peroxide-based nasal spray versus control [10], there were inconclusive results for the relief of cough (RR 1.23, 95% 0.50-3.02; Moderate Certainty), ageusia (RR 2.50, 95% 0.78-7.97; Moderate Certainty), anosmia (RR 1.73, 95% 0.62-4.82; Moderate Certainty), dyspnea (RR 2.50, 95% CI 0.57-11.05; Moderate Certainty), and sore throat (RR 0.51, 95% 0.10-2.51; Moderate Certainty). Length of follow-up for relief of symptoms ranged from 4 to 6 days. Certainty of evidence were all downgraded to moderate certainty due to the imprecision of risk interval estimates. One small trial, which utilized a povidone iodine-based nasal spray [12], also reported inconclusive effect in terms of relief of the loss of sense of smell (RR 3.25, 95% 0.93-11.40; Moderate Certainty) between the intervention and the placebo. This finding was in agreement with the results from the study which used hydrogen peroxide-based nasal spray.[10] Certainty of evidence was downgraded to moderate due to imprecision of risk interval estimates.

Outcome: Adverse Events
The risk of developing adverse events associated with the use of nasal sprays was reported in four trials that utilized three different types of nasal sprays, and the pooled risk was found to be significantly higher in the nasal spray arm compared to control (RR 6.18, 95%CI 1.79-21.37). The nasal spray with highest risk for developing adverse events when compared to placebo was found in the glycerol-based nasal spray (RR 81.70, 95% CI 5.10-1309.53; High Certainty) [3] followed by the hydrogen peroxide-based nasal spray (RR 5.87, 95% CI 2.53-13.61; High Certainty) [10], and lastly in the povidone iodine-based nasal sprays (RR 2.91, 95% CI 0.88-9.63; I^2=0%; Moderate Certainty).[11,12] All reported adverse events were considered minor. Most common adverse events observed were burning sensation in the nose and throat, frequent sneezing, altered sense of taste, altered tongue sensation, and minor epistaxis. No life-threatening adverse events were observed in all four trials. Certainty of evidence was downgraded to moderate certainty because of the serious risk of bias from the lack of blinding in one of the trials that utilized povidone iodine-based nasal sprays.[11,12]

As Adjunct to Prevention of COVID-19 Infection

We found two randomized controlled trials that enrolled a total of 626 healthcare workers providing direct care to COVID-19 patients from Argentina [1] and Iran [4]. Healthcare workers included in these studies were healthy physicians, nurses, kinesiologists and other medical professionals providing direct care to COVID-19 patients. Study participants were asymptomatic [1,4] and IgG and IgM seronegative [4] at the beginning of the study to confirm that they were not infected with COVID-19. In both studies, participants in treatment and control groups had similar baseline characteristics. Only the Argentine study specified that study participants were still unvaccinated during the trial implementation. The study further specified that the trial was carried out during the time when Argentina was experiencing sustained community transmission of SARS-CoV-2. Thus, even though the study participants were healthcare workers, there was still significant participant community exposure. Two different active interventions were analyzed in this evidence review. The Argentine study used iota-carrageenan (IC) 1 puff per nostril (delivering 0.17mg of IC) compared to routine care with saline solution placebo. Meanwhile, the Iranian study used dimethylsulfoxide ethanol (3% dimethylsulfoxide with 20% ethanol; DMSO-ethanol) 1 puff per nostril every 8 hours compared to routine care without placebo. Clinically important outcomes measured in the studies were incidence of COVID-19 infection in 21-28 days, development of adverse events, and discontinuation of the intervention due to intolerance. Characteristics of studies included in this review are shown in Appendix 3B.

Outcome: Risk of Developing COVID-19

The use of IC-based nasal spray [1] as an additional preventive measure significantly reduced the risk of developing COVID-19 among healthcare workers within 21 days (RR 0.20, 95% CI 0.04-0.91; Moderate Certainty). No death or hospitalization for any cause was observed in either the intervention and control groups. Likewise, the use of DMSO-ethanol-based nasal spray [2] significantly reduced the risk of developing COVID-19 among healthcare workers within 28 days (RR 0.13, 95% CI 0.02-0.98; Moderate Certainty). Certainty of evidence in this outcome was downgraded to moderate certainty due incomplete outcome assessment [1] and lack of participant blinding.[4]

Outcome: Adverse Events

The risk of adverse events (RR 1.14, 95% CI 0.73-1.79; Low Certainty) and discontinuation of the intervention due to intolerance (RR 0.67, 95% CI 0.11-3.99; Low Certainty), comparing treatment with IC spray and control groups, was inconclusive. No significant difference was found in the occurrence of commonly observed adverse events, namely, headache (RR 1.32, 95% CI 0.66-2.65) and rhinorrhea (RR 0.50, 95% CI 0.13-1.99) between the use of IC-based nasal spray compared to placebo [1]. No data on adverse events were provided in the DMSO-ethanol-based nasal spray study. Certainty of evidence in this outcome was downgraded to low certainty due to incomplete outcome assessment and imprecision of risk estimates.

Evidence to Decision

Presently, at least ten different [1-10] active agents are being investigated as potential prophylactic and treatment interventions against COVID-19 infection. However, current studies providing moderate to high certainty of evidence are still very limited. Among the active agents presented in this evidence base, IC- and glycerol-based nasal sprays are currently available commercially with regulatory approval for use for prevention and symptomatic relief of common viral respiratory infections but not yet for COVID-19. Certain limitations of currently available data should be taken into careful consideration. In both analyses, the studies had relatively short lengths of follow up ranging from 21 to 28 days for prevention studies and 14 to 60 days for

symptomatic treatment studies. Thus, long-term effectiveness and adverse events in prolonged use could not be established at this time. Most importantly, clinical effectiveness of nasal sprays was intended as an adjunct to vaccination, proper use of personal protective equipment like masking, hand hygiene, physical distancing, and adherence to quarantine and isolation protocols for the prevention and as an adjunct to routine treatment of COVID-19.

Currently, no cost-effectiveness study on nasal sprays in the prevention of COVID-19 is available for review. The price of nasal spray in local market ranges from Php 297 (20 mL with each mL containing 1.2 mg of Carrageenan) to Php 1,050 (COVISPRAY).

Recommendations from Other Groups

Currently, there are no published recommendations from the World Health Organization, US National Institutes of Health, and the Centers of Disease Control regarding the use of nasal sprays in preventing COVID-19 infection.

In September 2021, the Philippine Food and Drug Administration released FDA Advisory No. 2021-2289 to notify the public that nasal spray products have been authorized as medical devices with non-specific effect against pathogens. The advisory further emphasized that nasal sprays should not be used as substitutes to vaccines and interventions to prevent or treat SARS-CoV-2 infection.[16]

IC-based nasal sprays have been approved in USA (FDA Medical Devices Databases Establishment Registration & Device & Listing D 441354)[1], Latin America [1], Europe [1], France [3], Asia[1], and Australia [1] as over-the-counter products for common cold and related diseases.

Research Gaps

Despite the significant reduction in the risk of COVID-19 infection, findings in these trials should be replicated with longer follow-up periods to ascertain long term effectiveness, safety, and tolerability. Furthermore, effect of nasal sprays on viral clearance and symptomatic relief should still be established. At present, seven randomized controlled trials are investigating iota-carrageenan (2 studies), ivermectin + carrageenan (1 study), GLS-1200 which is a quinine-based agent (1 study), hypochlorous acid (1 study), and nitrous oxide (2 studies) as prophylactic and therapeutic nasal spray against COVID-19 infection.

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgments prior to the actual panel meeting (n = 5)

FACTORS	JUDGMENT					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS FROM PANEL MEMBERS
Problem	No	Yes (5)				• Especially in instances when an individual is not yet fully protected by vaccine immunity and in instances when personal protective equipment like masks are temporarily being removed. [1,4]
Benefits	Large (1)	Moderate (4)	Small	Uncertain		• As an adjunct to prevention, two randomized controlled trials on healthy asymptomatic healthcare workers providing direct care to COVID-19 patients showed that the use of iota-carrageenan or dimethylsulfoxide ethanol nasal spray provided significant benefit in reducing the risk of COVID-19 infection compared to routine care with or without saline placebo. Nasal sprays in these trials were used as adjunct to proper personal protective equipment and universal precautions. Overall certainty of evidence was low. • As an adjunct to treatment, nine randomized controlled trials on patients with mild and moderate COVID-19 showed that the use of nasal sprays containing different active agents (one study each for glycerol, hydrogen peroxide, nitric oxide, ivermectin, momethasone and triamcinolone; povidone iodine in three studies) did not result in significant benefit in terms of viral clearance and showed inconsistent benefit in terms of symptomatic relief.
Harm	Large	Small (4)	Uncertain (1)	Varies		• The risk of adverse events and discontinuation due to intolerance, comparing adjunctive treatment to prevention and control groups, was inconclusive. • As adjunct to treatment, the risk for adverse events (mostly minor, such as sensation of nasal and throat burning, frequent sneezing, altered taste sensation, and minor epistaxis) was significantly higher in the nasal spray arm compared to placebo.

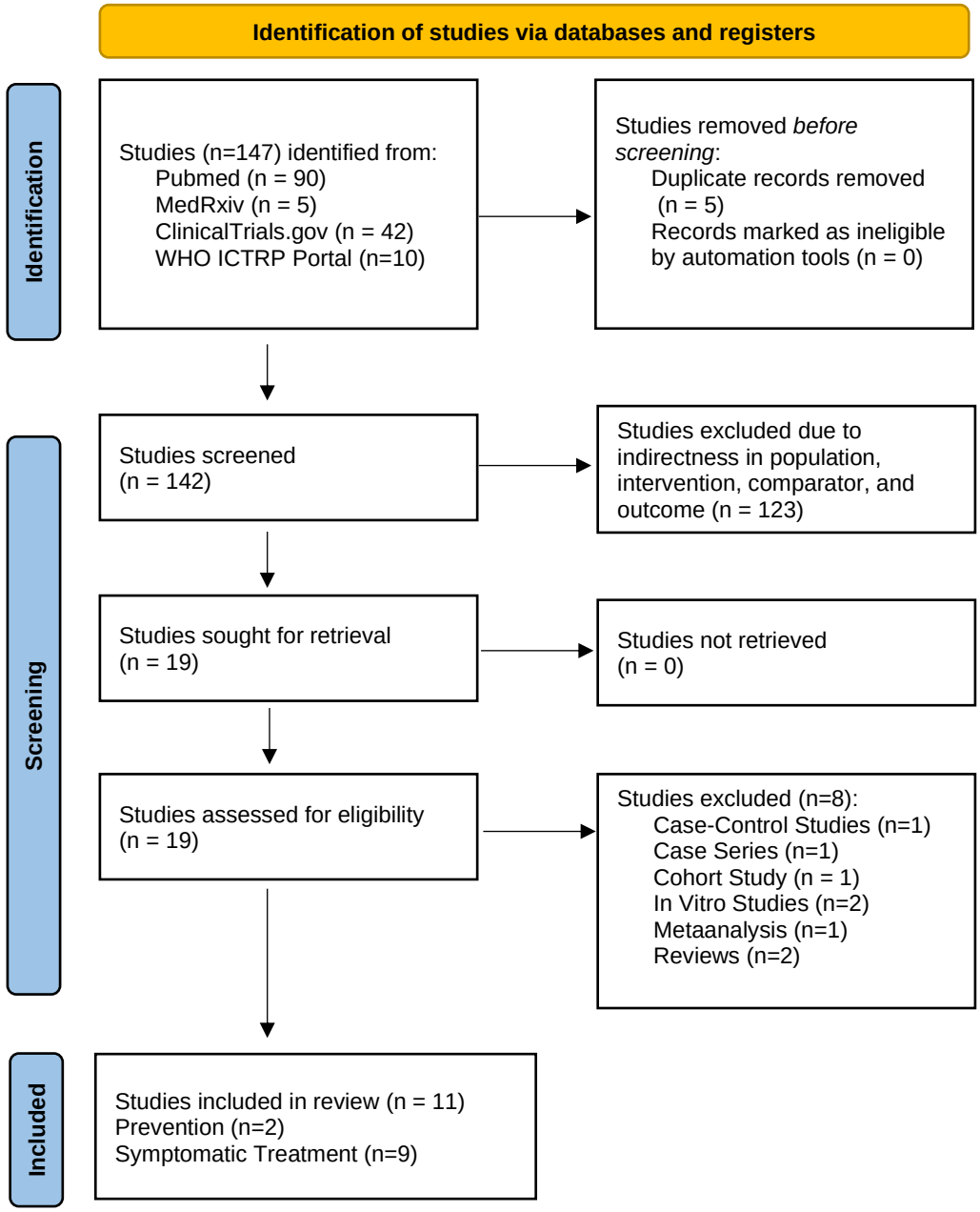
FACTORS	JUDGMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS FROM PANEL MEMBERS
Certainty of Evidence	High	Moderate	Low (5)	Very low			• Overall certainty of evidence for nasal spray as adjunct to prevention and treatment was low due to serious risk of bias and imprecision.
Balance of effects	Favors nasal spray (4)	Does not favor nasal spray	Uncertain (1)	Varies			• As an adjunct to prevention, two randomized controlled trials on healthy asymptomatic healthcare workers providing direct care to COVID-19 patients showed that the use of iota-carrageenan or dimethylsulfoxide ethanol nasal spray provided significant benefit in reducing the risk of COVID-19 infection compared to routine care with or without saline placebo. As an adjunct to treatment, nine randomized controlled trials on patients with mild and moderate COVID-19 showed that the use of nasal sprays containing different active agents (one study each for glycerol, hydrogen peroxide, nitric oxide, ivermectin, momethasone and triamcinolone; povidone iodine in three studies) did not result in significant benefit in terms of viral clearance and showed inconsistent benefit in terms of symptomatic relief. • The risk of adverse events and discontinuation due to intolerance, comparing adjunctive treatment to prevention and control groups, was inconclusive. As adjunct to treatment, the risk for adverse events (mostly minor, such as sensation of nasal and throat burning, frequent sneezing, altered taste sensation, and minor epistaxis) was significantly higher in the nasal spray arm compared to placebo
Values	Important uncertainty or variability	Possibly important uncertainty or variability (4)	Possibly NO important uncertainty or variability (1)	No important uncertainty or variability			• Lack of studies investigating long-term effectiveness, safety, and tolerability
Resources Required	Uncertain (4)	Large cost	Moderate Costs	Negligible costs or savings	Moderate savings (1)	Large savings	• Currently, no cost-effectiveness study on nasal sprays in the prevention of COVID-19 is available for review.

FACTORS	JUDGMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS FROM PANEL MEMBERS
							• The price of nasal spray in local market ranges from Php 297[1] (each mL with 1.2 mg of Carrageenan) to Php 1050[2] (COVISPRAY) (without shipping fee).
Certainty of evidence of required resources	No included studies (4)	Very low (1)	Low	Moderate	High		• Currently, no cost-effectiveness study on nasal sprays in the prevention of COVID-19 is available for review.
Cost effectiveness	No included studies (5)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention			• Currently, no cost-effectiveness study on nasal sprays in the prevention of COVID-19 is available for review. • *Cost is probably one of the important considerations. However, if the spray will indeed prevent many infections, the intervention will likely be deemed extremely cost-effective. (n = 1)*
Equity	Uncertain (2)	Reduced	Probably no impact (2)	Increased (1)			• No research evidence found.
Acceptability	Uncertain (1)	No	Yes (4)	Varies			• Nasal sprays have been authorized as medical devices by the FDA of the Philippines. (FDA Advisory 2021-2289)
Feasibility	Uncertain (1)	No	Yes (4)	Varies			• Nasal sprays are available in local drugstores.

[1] https://www.mims.com/philippines/company/info/mono%20chem-pharm

[2] https://www.lazada.com.ph/products/preventia-covispray-i2448793605.html

Appendix 2. Search Yield and Results



Appendix 3A. Table of Included Studies for Nasal Spray as Adjunct to Treatment of COVID-19

Study Characteristics of Included Studies

Study ID Title Author	Study Design	Setting/ Country	Total number of Patients Included	Population	Intervention	Comparator/ Control	Outcomes
Aref et. Al., 2021 [13] Clinical, Biochemical and Molecular Evaluations of Ivermectin Mucoadhesive Nanosuspension Nasal Spray in Reducing Upper Respiratory Symptoms of Mild COVID-19	Randomized Controlled Trial	Egypt	114	Mild COVID-19	Ivermectin Nanosuspension Nasal Spray + Routine Care (n=57)	Routine Care included paracetamol 500 mg IV every 6 hours, hydroxychloroquine 500 mg every 12 hours, azithromycin 1g on day 1 then 500 mg per 3 days or clarithromycin 500 mg every 12 h for 7-14 days, oseltamivir 150 mg every 12 hours for 5 days, ascorbic acid 500 mg every 12 hours 1(n=57)	Viral Clearance defined as 2 consecutive negative RT-PCR (54/57 vs 43/57; p=0.004) Symptom duration: fever, cough, dyspnea, anosmia, GIT*, PCR conversion *NS Duration taken for nasopharyngeal swab to be negative Improvement of the abnormal routine laboratory parameters 7 days after treatment: NLR, CRP, d-dimer, ferritin
Arefin, et. Al, 2021 [11] Virucidal effect of povidone iodine on COVID-19 in the nasopharynx: an open-label randomized clinical trial	Randomized Controlled Trial	Iran	81	Mild, Moderate, Severe COVID-19	Povidone Iodine 0.5%, 0.6% Nasal Spray (n=54)	Normal Saline (n=27)	Viral clearance after one application Number of adverse events
DiDomenico et. Al., 2021 [10] Hydrogen peroxide as an auxiliary treatment for COVID-19 in Brazil: a randomized double-blind clinical trial	Randomized Controlled Trial	Brazil	106	Mild and Moderate COVID-19	Hydrogen peroxide 0.5%, 1.0% Nasal Wash (n=63)	Deionized water with Mint Essence + Routine Care (n=43)	Forward transmission Improvement Adverse Events

Study ID Title Author	Study Design	Setting/ Country	Total number of Patients Included	Population	Intervention	Comparator/ Control	Outcomes
Guenezan et. Al., 2021 [19] Povidone Iodine Mouthwash, Gargle, and Nasal Spray to Reduce Nasopharyngeal Viral Load in Patients With COVID-19: A Randomized Clinical Trial	Randomized Controlled Trial	9842	24	Mild COVID-19 in the Outpatient	Povidone Iodine 1% Mouthwash + Gargle + Nasal Spray (n=12)	Routine Care (n=12)	Mean Difference in Viral Titer at Day 0
Kasiri et al., 2021 [14] Mometasone furoate nasal spray in the treatment of patients with COVID-19 olfactory dysfunction: A randomized, double blind clinical trial	Randomized Controlled Trial Prospective double-blind trial	Iran	77	Mild and Moderate COIVD-19	Mometasone furoate 0.05% nasal spray BID for four weeks (n=39)	Saline spray + Routine Care (n=38)	Olfactory dysfunction
Shrivastava et. Al., 2021 [3] Clinical Efficacy of an Osmotic, Antiviral and Anti-Inflammatory Polymeric Nasal Film to Treat Covid-19 Early-Phase Respiratory Symptoms	Randomized Controlled Trial	France	200	Mild and Moderate COVID-19	Glycerol (COVISPRAY) + Symptomatic Treatment (n=98)	Symptomatic Treatment (n=102)	Overall Clinical Improvement Adverse Events
Winchester et. Al., 2021 [7] Clinical efficacy of nitric oxide nasal spray (NONS) for the treatment of mild COVID-19 infection	Randomized Controlled Trial	United Kingdom	80	Mild COVID-19	Nitric oxide Nasal Spray (NONS) 5-6x/day, two s[rays per nostril per dose, 120-140 microliter of solution per spray) for 9 days (n=20)	Placebo (n=20)	Overall Clinical Improvement Adverse Events
Yildiz et. Al., 2021 [15] Comparison of the Healing Effect of Nasal Saline Irrigation with Triamcinolone Acetonide Versus Nasal Saline Irrigation alone in COVID-19 Related Olfactory Dysfunction: A Randomized Controlled Study	Randomized Controlled Trial	India	100	Mild COVID-19 Olfactory Dysfunction	Triamcinolone acetonide nasal spray + Nasal irrigation (n=50)	Nasal Irrigation (n=50)	Self-rating Olfactory Score Duration of Olfactory Dysfunction NI: 12.2 ± 2.2 NS+NI: 5.6 ± 3.2 MD -6.6 days; 95% CI -7.68, -5.52

Study ID Title Author	Study Design	Setting/ Country	Total number of Patients Included	Population	Intervention	Comparator/ Control	Outcomes
Zarabanda et. Al., 2021 [12] The Effect of Povidone-Iodine Nasal Spray on Nasopharyngeal SARSCoV-2 Viral Load: A Randomized Control Trial	Randomized Controlled Trial	USA	35	Mild COVID-19	Povidone Iodine 0.5%, 2% in water (n=24)	Saline Solution (n=11)	Mean Cycle Threshold value: Conversion to RT-PCR Negative From Detectable Minus-strand SARS-CoV- Overall Clinical Improvement Adverse Event

References:

[3] Shrivastava R, Vijay M, Maneby N, Shrivastava R. Clinical Efficacy of an Osmotic, Antiviral and Anti-inflammatory Polymeric Nasal Film to Treat Covid-19 Early-Phase Respiratory Symptoms. Open Access J. Clin. Trials. 2021 May 18;13:11-20. Doi: 10.2147/OAJCT.S307144

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[9] Guenezan J, Garcia M, Strasters D, Jousselin C, Lévêque N, Frasca D, Mimoz O. Povidone Iodine Mouthwash, Gargle, and Nasal Spray to Reduce Nasopharyngeal Viral Load in Patients With COVID-19: A Randomized Clinical Trial. JAMA Otolaryngol Head Neck Surg. 2021 Apr 1;147(4):400-401. Doi: 10.1001/jamaoto.2020.5490. PMID: 33538761; PMCID: PMC7863011.

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[11] Arefin MK. Povidone Iodine (PVP-I) Oro-Nasal Spray: An Effective Shield for COVID-19 Protection for Health Care Worker (HCW), for all. Indian J Otolaryngol Head Neck Surg. 2021 Apr 8:1-6. Doi: 10.1007/s12070-021-02525-9. Epub ahead of print. PMID: 33846691; PMCID: PMC8026810.

[12] Zarabanda D, Vukkadala N, Phillips KM, Qian ZJ, Mfuh KO, Hatter MJ, Lee IT, Rao VK, Hwang PH, Domb G, Patel ZM, Pinsky BA, Nayak JV. The Effect of Povidone-Iodine Nasal Spray on Nasopharyngeal SARS-CoV-2 Viral Load: A Randomized Control Trial. Laryngoscope. 2021 Nov 1. Doi: 10.1002/lary.29935. Epub ahead of print. PMID: 34724213.

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[15] Yildiz E, Koca Yildiz S, Kuzu S, Günebakan Ç, Bucak A, Kahveci OK. Comparison of the Healing Effect of Nasal Saline Irrigation with Triamcinolone Acetonide Versus Nasal Saline Irrigation alone in COVID-19 Related Olfactory Dysfunction: A Randomized Controlled Study. Indian J Otolaryngol Head Neck Surg. 2021 Jul 10:1-6. Doi: 10.1007/s12070-021-02749-9. Epub ahead of print. PMID: 34277384; PMCID: PMC8272442.

Appendix 3B. Table of Included Studies for Nasal Spray as Adjunct to Prevention of COVID-19

Study Characteristics of Included Studies

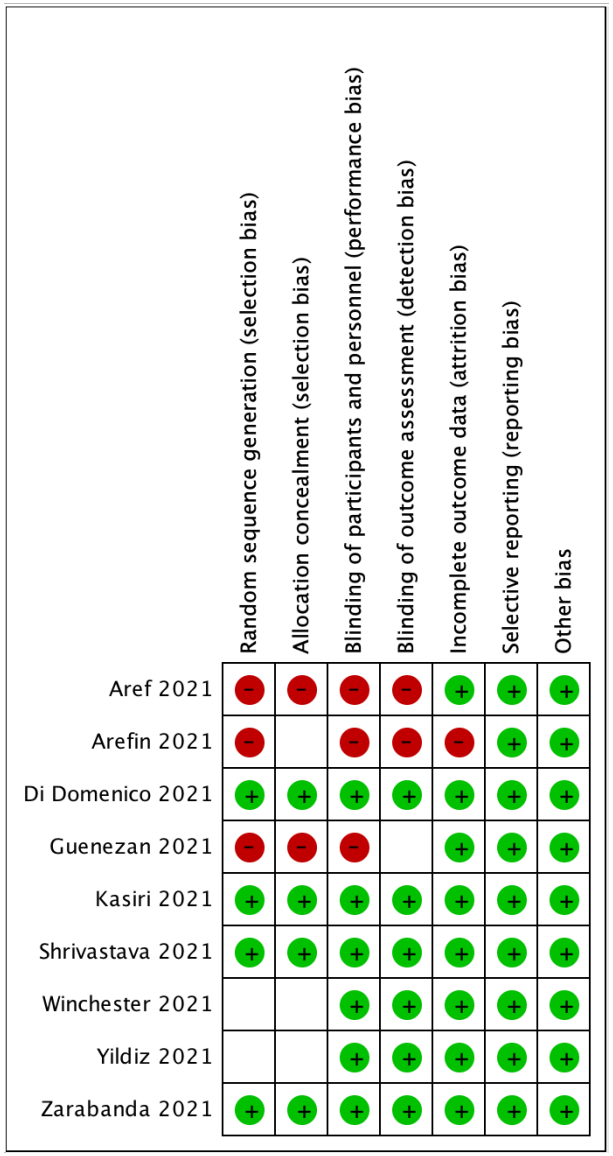
Study ID Title Author	Study Design	Setting/ Country	Total number of Patients Included	Population	Intervention	Comparator/ Control	Outcomes
Figueroa and the CARR-CoV-2 Trial, 2021 Efficacy of a nasal spray containing Iota-Carrageenan in the prophylaxis of COVID-19 in hospital personnel dedicated to patients care with COVID-19 disease.	Randomized Controlled Trial	Argentina	394	Healthcare Workers handling COVID-19 Patients	Iota-carrageenan 0.10 mL (0.17 mg) per puff 4 times a day (n=196)	Routine care with saline solution as placebo (n=198)	Incidence of SARS-CoV-2 Infection in 28 days Symptomatic SARS-CoV-2 Negative Infection Any Adverse Events Discontinuation due to Intolerance
Hosseinzadeh et al., 2021 (Pre-print) Application of nasal spray containing dimethyl sufoxide (DMSO) and ethanol during the COVID-19 pandemic may protect healthcare workers: A randomized controlled trial.	Randomized Controlled Trial	Iran	232	Healthcare Workers handling COVID-19 Patients	Dimethylsulfoxide ethanol 1 puff every 8 hours (n=116)	Routine care without placebo (n=116)	Incidence of SARS-CoV-2 Infection in 21 days

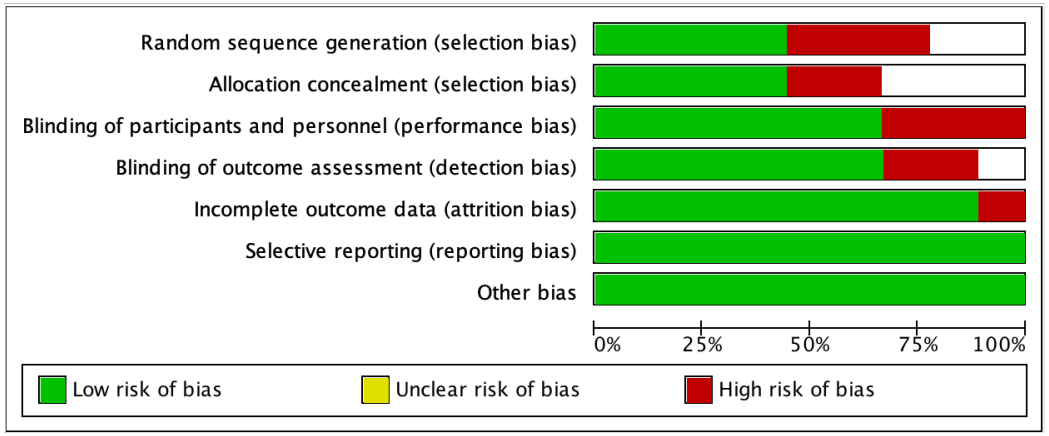
References:

[1] Figueroa JM, Lombardo ME, Dogliotti A, Flynn LP, Giugliano R, Simonelli G, Valentini R, Ramos A, Romano P, Marcote M, Michelini A, Salvado A, Sykora E, Kniz C, Kobelinsky M, Salzberg DM, Jerusalinsky D, Uchitel O. Efficacy of a Nasal Spray Containing Iota-Carrageenan in the Postexposure Prophylaxis of COVID-19 in Hospital Personnel Dedicated to Patients Care with COVID-19 Disease. Int J Gen Med. 2021 Oct 1;14:6277-6286. Doi: 10.2147/IJGM.S328486. PMID: 34629893; PMCID: PMC8493111.

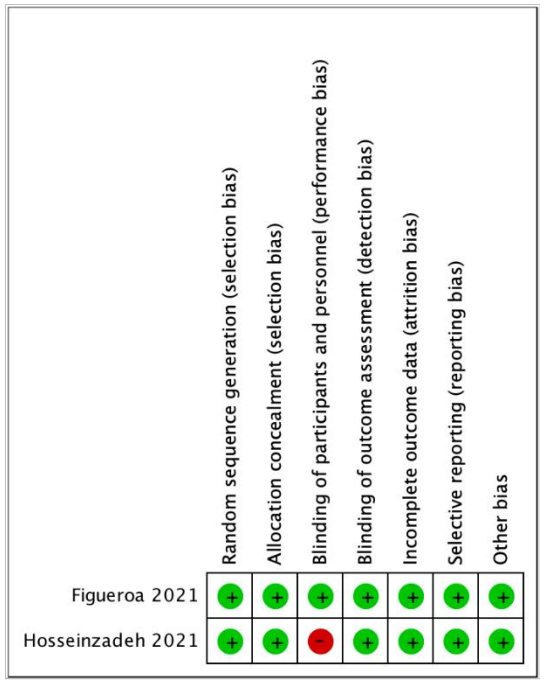
[4] Hosseinzadeh A, Tavakolian A, Kia V, Ebrahimi H, Sheibani H, Binesh E, Jafari R, Mirrezaie SM, Jafarisani M, Emamian MH. Application of nasal spray containing dimethyl sufoxide (DMSO) and ethanol during the COVID-19 pandemic may protect healthcare workers: A randomized controlled trial. Available online https://www.medrxiv.org/content/10.1101/2021.07.06.21259749v2.

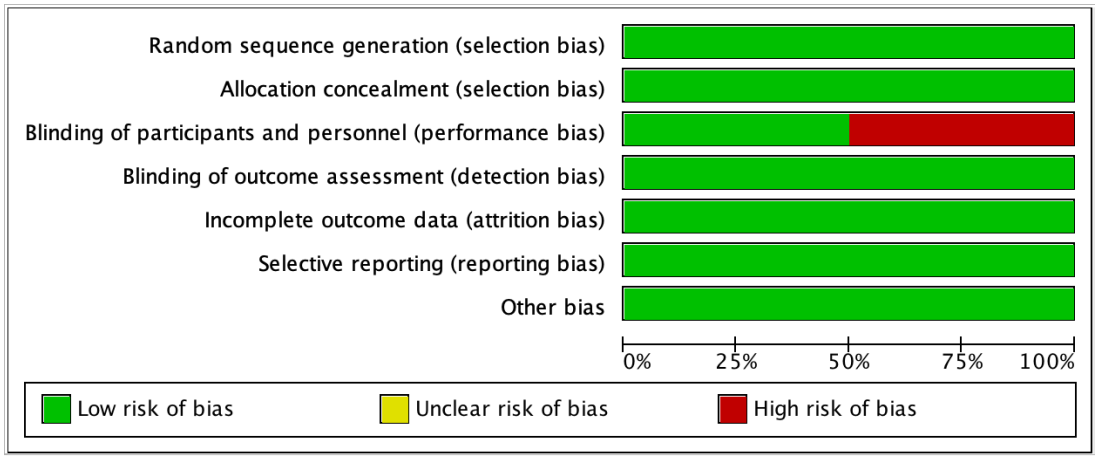
Appendix 4A. Risk of Bias Summary and Risk of Bias Graph of Studies for Nasal Sprays as Adjunct to Treatment of COVID-19 Infection





Appendix 4B. Risk of Bias Summary and Risk of Bias Graph of Studies for Nasal Sprays as Adjunct to Prevention of COVID-19 Infection





Appendix 5A. Forest Plots for Nasal Spray As Adjunct to Treatment of COVID-19

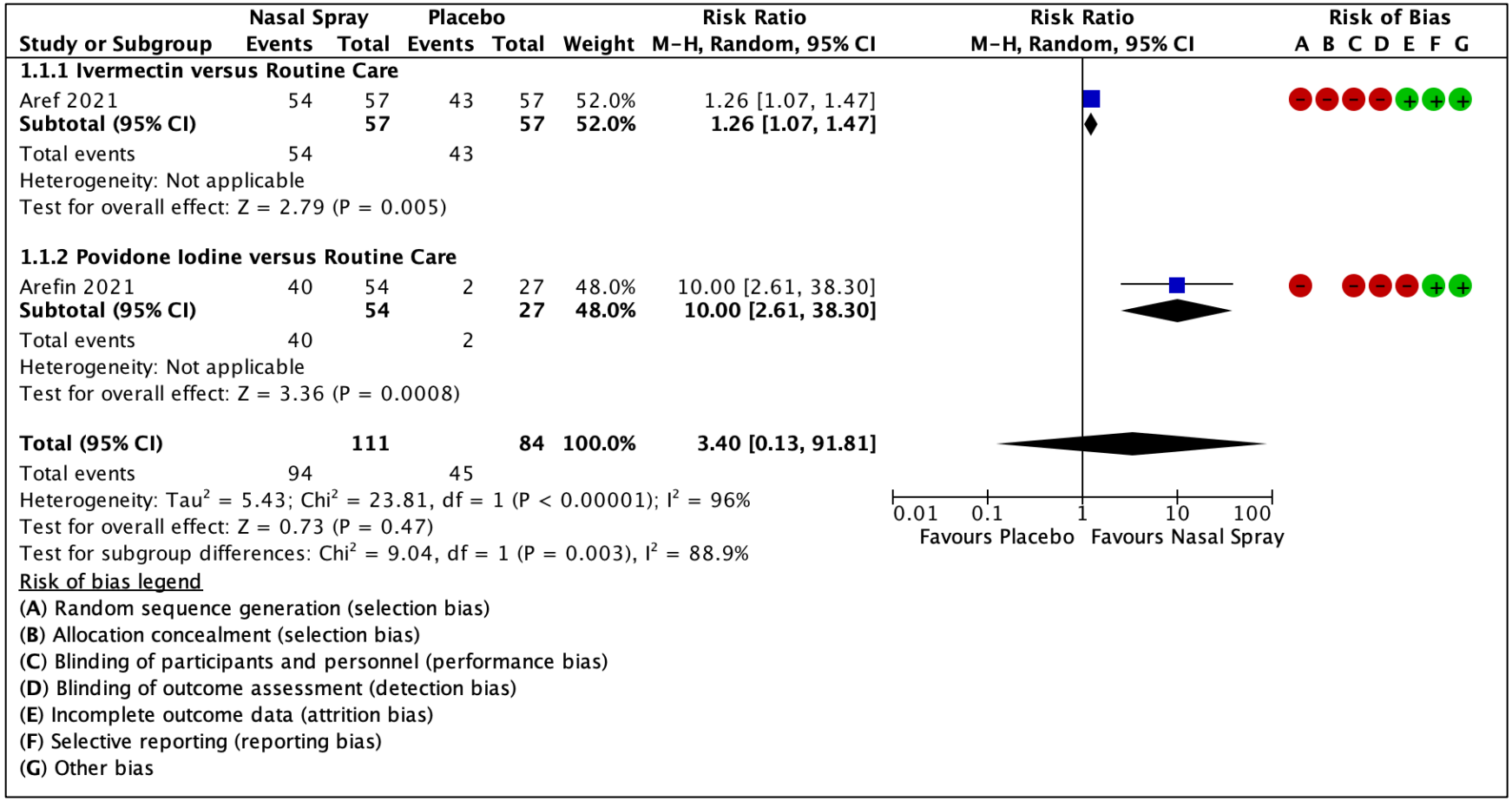


Figure 5A-1. Forest Plot for viral clearance

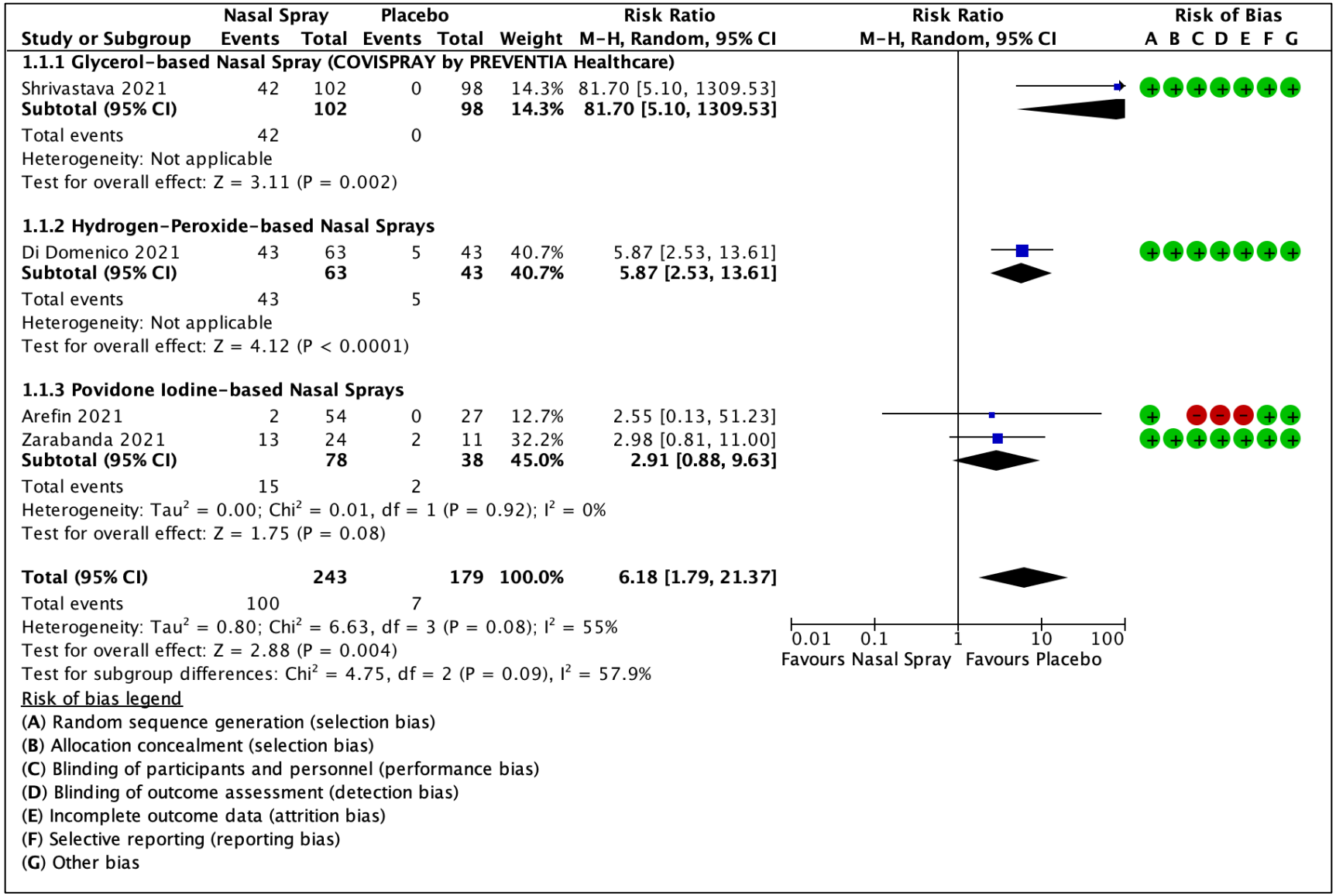


Figure 5A-2 Forest Plot for Adverse Events

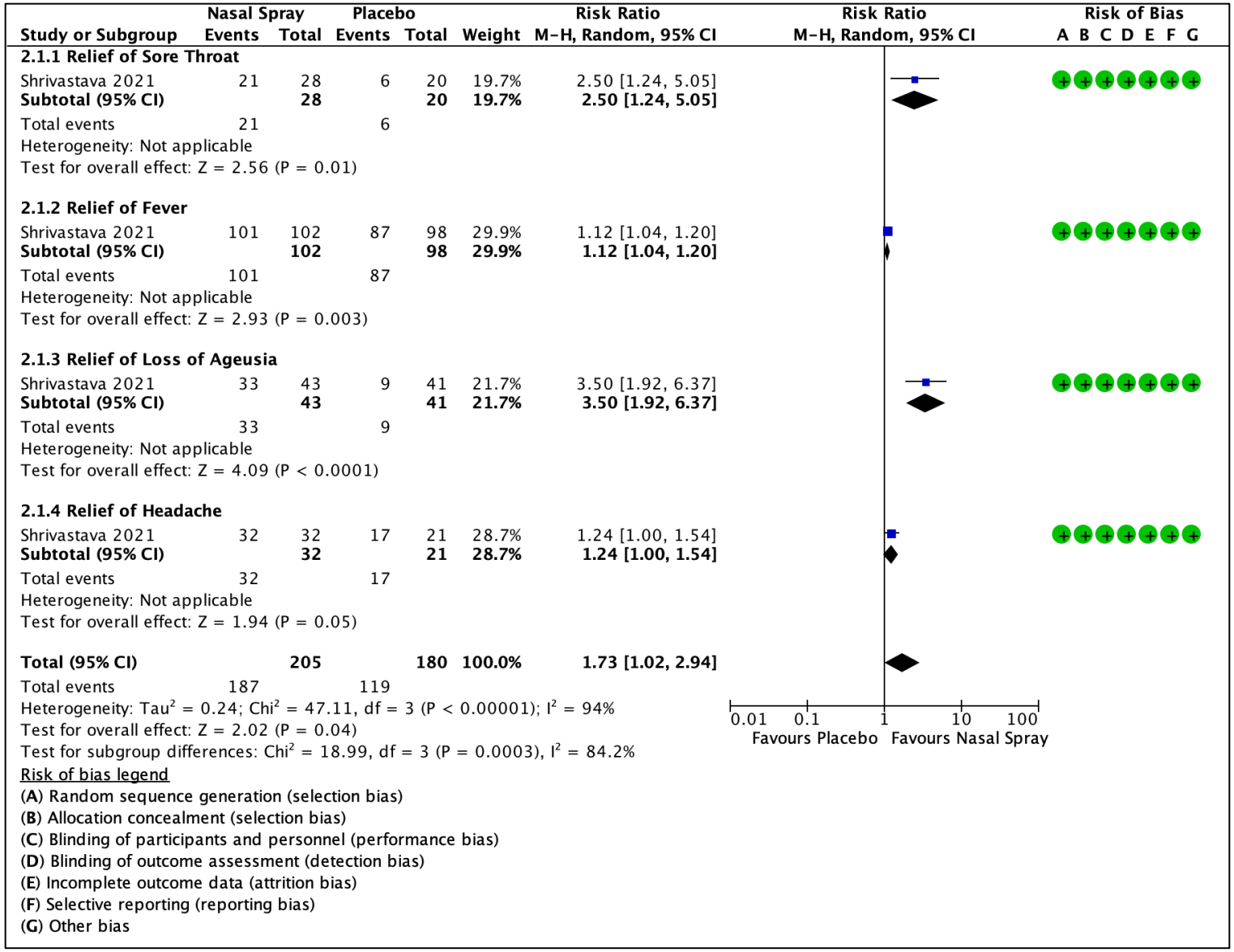


Figure 5A-3. Forest Plot for relief of COVID-19 symptoms as reported in Shrivastava et. Al., 2021

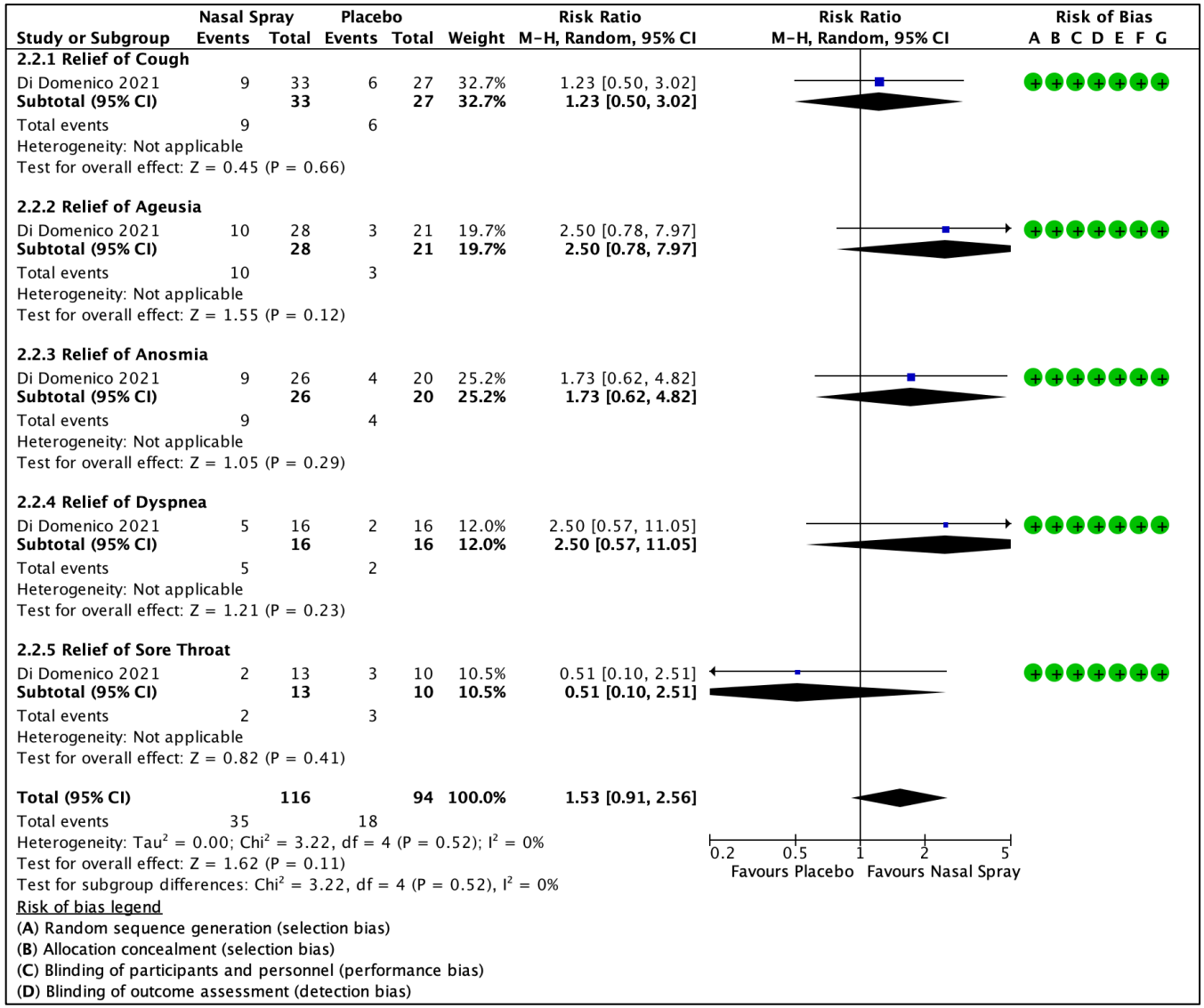


Figure 5A-4. Forest Plot for relief of COVID-19 symptoms at 4-6 days as reported in Di Domenico et. Al., 2021

Appendix 5B. Forest Plot for Nasal Spray as Adjunct to Prevention of COVID-19

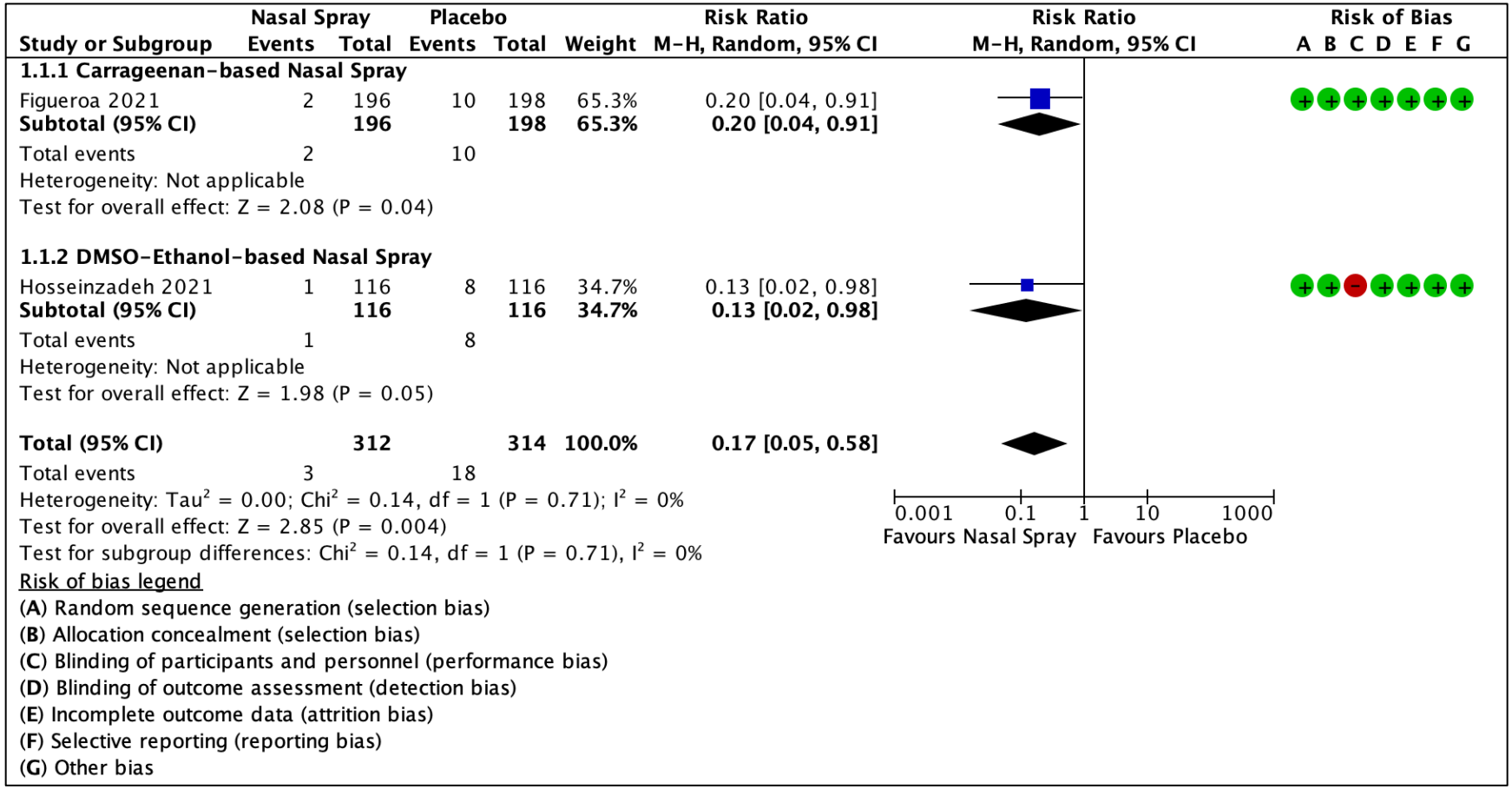


Figure 5B. Forest plot for the risk of developing COVID-19

Appendix 6A. GRADE Evidence Profile – Nasal spray as Adjunctive Treatment for COVID-19

Author(s): Christopher G. Manalo, MD
Question: Nasal spray compared to placebo for treatment of COVID-19 infection
Setting: Mild and Moderate COVID-19 in the General Population
Bibliography

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	nasal sprays	placebo	Relative (95% CI)	Absolute (95% CI)		
SARS-CoV-2 Clearance in Ivermectin-based Nasal Spray												
1	55dministra trials	very serious[a]	not serious	not serious	not serious	none	54/57 (94.7%)	43/57 (75.4%)	**RR 1.26** (1.07 to 1.47)	**196 more per 1,000** (from 53 more to 355 more)	⨁⨁◯◯ Low	CRITICAL
SARS-CoV-2 Clearance in Povidone Iodine-based Nasal Spray												
1	55dministra trials	very serious[a]	not serious	not serious	not serious	none	40/54 (74.1%)	2/27 (7.4%)	**RR 10.00** (2.61 to 38.30)	**667 more per 1,000** (from 119 more to 1,000 more)	⨁⨁◯◯ Low	CRITICAL
Forward Transmission												
1	55dministra trials	serious[a]	not serious	not serious	serious[b]	none	6/51 (11.76%)	6/35 (17.14%)	**RR 0.6863** (0.2400 to 1.9500)	**260 fewer per 1,000** (from 630 fewer to 787 more)	⨁⨁◯◯ Low	CRITICAL

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

Explanations

a. Unclear to high risk of bias due to lack of allocation concealment and blinding
b. Risk interval estimates cross the line of no effect

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	nasal sprays	placebo	Relative (95% CI)	Absolute (95% CI)		
Relief of Sore Throat Reported in Shrivastava et. Al., 2021												
1	56dministra trials	not serious	not serious	not serious	not serious	none	21/28 (75.0%)	6/20 (30.0%)	**RR 2.50** (1.24 to 5.05)	**450 more per 1,000** (from 72 more to 1,000 more)	⨁⨁⨁⨁ High	CRITICAL
Relief of Fever Reported in Shrivastava et. Al., 2021												
1	56dministra trials	not serious	not serious	not serious	not serious	none	101/102 (99.0%)	87/98 (88.8%)	**RR 1.12** (1.04 to 1.20)	**107 more per 1,000** (from 36 more to 178 more)	⨁⨁⨁⨁ High	CRITICAL
Relief of Ageusia in Shrivastava et. Al., 2021												
1	56dministra trials	not serious	not serious	not serious	not serious	none	33/43 (76.7%)	9/41 (22.0%)	**RR 3.50** (1.92 to 6.37)	**549 more per 1,000** (from 202 more to 1,000 more)	⨁⨁⨁⨁ High	CRITICAL
Relief of Headache Reported in Shrivastava et. Al., 2021												
1	56dministra trials	not serious	not serious	not serious	serious[a]	none	32/32 (100.0%)	17/21 (81.0%)	**RR 1.24** (1.00 to 1.54)	**194 more per 1,000** (from 0 fewer to 437 more)	⨁⨁⨁◯ Moderate	CRITICAL

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

Explanations

a. Unclear to high risk of bias due to lack of allocation concealment and blinding
b. Risk interval estimates cross the line of no effect

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	nasal sprays	placebo	Relative (95% CI)	Absolute (95% CI)		
Relief of Cough Reported Di Domenico et. Al., 2021												
1	57dministra trials	not serious	not serious	not serious	serious[c]	none	9/33 (27.3%)	6/27 (22.2%)	**RR 1.23** (0.50 to 3.02)	**51 more per 1,000** (from 111 fewer to 449 more)	⨁⨁⨁◯ Moderate	CRITICAL
Relief of Ageusia Reported in Di Domenico et. Al., 2021												
1	57dministra trials	not serious	not serious	not serious	serious[c]	none	10/28 (35.7%)	3/21 (14.3%)	**RR 2.50** (0.78 to 7.97)	**214 more per 1,000** (from 31 fewer to 996 more)	⨁⨁⨁◯ Moderate	CRITICAL
Relief of Anosmia Reported in Di Domenico et. Al.. 2021												
1	57dministra trials	not serious	not serious	not serious	serious[c]	none	9/26 (34.6%)	4/20 (20.0%)	**RR 1.73** (0.62 to 4.82)	**146 more per 1,000** (from 76 fewer to 764 more)	⨁⨁⨁◯ Moderate	CRITICAL
Relief of Dyspnea Reported in Di Domenico et. Al., 2021												
1	57dministra trials	not serious	not serious	not serious	serious[c]	none	5/16 (31.3%)	2/16 (12.5%)	**RR 2.50** (0.57 to 11.05)	**188 more per 1,000** (from 54 fewer to 1,000 more)	⨁⨁⨁◯ Moderate	CRITICAL
Relief of Loss of Sore Throat Reported in Di Domenico et. Al., 2021												
1	57dministra trials	not serious	not serious	not serious	serious[c]	none	2/13 (15.4%)	3/10 (30.0%)	**RR 0.51** (0.10 to 2.50)	**147 fewer per 1,000** (from 270 fewer to 450 more)	⨁⨁⨁◯ Moderate	CRITICAL
Adverse Events												
5	57dministra trials	serious[a]	not serious	not serious	not serious	none	114/261 (43.7%)	13/196 (6.6%)	**RR 4.59** (1.56 to 13.53)	**238 more per 1,000** (from 37 more to 831 more)	⨁⨁⨁◯ Moderate	CRITICAL

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

Explanations

a. Unclear to high risk of bias due to lack of allocation concealment and blinding
b. Risk ratio crosses line of no effect
c. Risk interval estimates cross the line of no effect

Appendix 6B. GRADE Evidence Profile – Nasal Spray for Prevention

Author(s): Christopher G. Manalo, MD
Question: Nasal spray compared to placebo for prevention of COVID-19 infection
Setting: Healthcare Workers
Bibliography:

[1] Figueroa JM, Lombardo ME, Dogliotti A, Flynn LP, Giugliano R, Simonelli G, Valentini R, Ramos A, Romano P, Marcote M, Michelini A, Salvado A, Sykora E, Kniz C, Kobelinsky M, Salzberg DM, Jerusalinsky D, Uchitel O. Efficacy of a Nasal Spray Containing Iota-Carrageenan in the Postexposure Prophylaxis of COVID-19 in Hospital Personnel Dedicated to Patients Care with COVID-19 Disease. Int J Gen Med. 2021 Oct 1;14:6277-6286. Doi: 10.2147/IJGM.S328486. PMID: 34629893; PMCID: PMC8493111.
[4] Hosseinzadeh A, Tavakolian A, Kia V, Ebrahimi H, Sheibani H, Binesh E, Jafari R, Mirrezaie SM, Jafarisani M, Emamian MH. Application of nasal spray containing dimethyl sufoxide (DMSO) and ethanol during the COVID-19 pandemic may protect healthcare workers: A randomized controlled trial. Available online https://www.medrxiv.org/content/10.1101/2021.07.06.21259749v2.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	nasal spray	placebo	Relative (95% CI)	Absolute (95% CI)		
Incidence of COVID-19 Infection in IC-based Nasal Spray												
1	58dministra trial	serious[a]	not serious	not serious	not serious	none	2/196 (1.0%)	10/198 (5.1%)	**RR 0.20** (0.04 to 0.91)	**40 fewer per 1,000** (from 48 fewer to 5 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Incidence of COVID-19 Infection in DMSO-Ethanol-based Nasal Spray												
1	58dministra trial	serious[b]	not serious	not serious	not serious	none	1/116 (0.9%)	8/116 (6.9%)	**RR 0.13** (0.02 to 0.98)	**60 fewer per 1,000** (from 68 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Development of Adverse Events in IC-based Nasal Spray												
1	58dministra trial	serious[a]	not serious	not serious	serious[c]	none	34/196 (17.3%)	30/198 (15.2%)	**RR 1.14** (0.73 to 1.79)	**21 more per 1,000** (from 41 fewer to 120 more)	⨁⨁◯◯ Low	IMPORTANT
Discontinuation Due to Intolerance												
1	58dministra trials	serious[a]	not serious	not serious	serious[c]	none	2/196 (1.0%)	3/198 (1.5%)	**RR 0.67** (0.11 to 3.99)	**5 fewer per 1,000** (from 13 fewer to 45 more)	⨁⨁◯◯ Low	IMPORTANT

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

Explanations

a. Incomplete outcome assessment (Figueroa et al., 2021)
b. Lack of patient blinding and lack of placebo in one of the trials (Hosseinzadeh et al., 2021)
c. Confidence interval of risk estimates cross the line of no effect

Appendix 7. Table of Ongoing Studies

Study Characteristics of Ongoing Studies (7)

Title **Identifier** **Expected Completion Date**	**Intervention**	**Comparator/** **Control**	**Patients/** **Population Recruited**	**Outcomes**
Nitric Oxide Nasal Spray (NONS) as Prevention for Treatment of Individuals at Risk of Exposure to COVID-19 Infection NCT05109611 ECD: 31 May 2022	The Sponsor designed a dual chamber nasal spray bottle for NORS administration. Components are mixed from two chambers to create the final NO-producing formulation. The liquid contains NO at 0.11 ppm*hour, which acts as a viricidal agent. Instructions for storing, preparing, and administering the study treatment will be provided to participants. Other Name: Nasal spray	The Sponsor designed a dual chamber nasal spray bottle for NORS administration. The bottle will be filled with normal saline before being provided to the participant. Other Name: Normal saline, 0.9% saline	Inclusion Criteria: Each participant must meet the following criteria to be enrolled in this study. 1. At least aged 18 years old at the time of consent. 2. If female, be surgically sterile or post-menopausal (no menses for at least 12 months), or if of child-bearing potential, must be using an acceptable method of contraception (other than a combination estrogen/progestin hormonal contraceptive) for at least 1 month prior to Day 1, such as an intrauterine device (IUD), implant, or two forms of the following: diaphragm, cervical cap, patch, condom, spermicide, or sponge. In addition, females of child-bearing potential must agree to continue to use their method of birth control for the duration of the study and 12 weeks following discharge from the study. 3. If male, be surgically sterile, or agree to use	Primary Outcome Measures : 1. To assess the efficacy of NONS in the reduction of risk of COVID-19 infection. [Time Frame: 28 days] Confirmed positive COVID-19 test (Both antigen and SARS-CoV-2 RT-PCR acceptable) by Day 28. Secondary Outcome Measures : 1. To assess the efficacy of NONS in prevention of severe COVID-19. [Time Frame: 28 days] Hospitalization or ER/ED visits for COVID-19/flu-like symptoms by Day 28. 2. Assess tolerability of NONS in participants with all participants including those with COVID-19. [Time Frame: 28 days] Aes and discontinuation of treatment.

			appropriate contraception (latex condom with spermicide) when engaging in sexual activity and agree to not donate sperm for the duration of the study and 12 weeks following discharge from the study. 4. Be in good health (ie, no acute illnesses or hospitalizations within 30 days of the study start, no planned procedures during study participation, and no newly diagnosed chronic illnesses that are not deemed stable by the participant's primary care physician), in the opinion of the Investigator, based on medical history (ie, absence of any clinically relevant abnormality) during Screening. 5. Be able to understand and provide written, informed consent. 6. Must have access to the internet and a device that reliability connects to the internet and is able to dial into Telehealth checkups and study related assessments. 7. Must be able to receive study product shipments directly to their home (ie, no Post Office Boxes). Exclusion Criteria:	

			Participants who meet any of the following criteria will be excluded from the study. 1. Participants with any respiratory infection, flu-like symptoms, or unexplained fever or chills during the week prior to Screening. 2. Participants with any prior history of SARS-CoV-2 infection. 3. Participants who have received any dose of SARS-CoV-2 vaccine. 4. Participants who use intranasally dosed drugs, prescriptions or over-the-counter medications such as fluticasone. 5. Participants who underwent a previous tracheostomy. 6. Participants who are receiving concomitant treatment of respiratory support (involving any form of oxygen therapy). 7. Females who are breastfeeding, pregnant, or attempting to become pregnant. 8. Participants who have any other condition that, in the opinion of the Investigator, would interfere with a participant's ability to adhere to the protocol (eg, participants whom are mentally or neurologically disabled and whom are considered not fit to their participation in the study), interfere with assessment of the	

			investigational product, or compromise the safety of the participant or the quality of the data.	
Title **Identifier** **Expected Completion Date**	**Intervention**	**Comparator/** **Control**	**Patients/** **Population Recruited**	**Outcomes**
GLS-1200 Topical Nasal Spray to Prevent SARS-CoV-2 Infection (COVID-19) NCT04408183 ECD: December 2022	GLS-1200 is given as a nasal spray using an atomizer	Placebo is given as nasal spray using an atomizer	Inclusion Criteria: • Age 18 or older • Able to provide informed consent • Able and willing to comply with study procedures • Able and willing to utilize an approved form of pregnancy prevention for women of child bearing potential through to the end of treatment Exclusion Criteria: • Know allergy to quinine, quinidine, or mefloquine • Confirmed prior positive test for SARS-CoV-2 • Treatment within the past 2 weeks with chloroquine, hydroxychloroquine, or remdesivir • Pregnancy or documentation of pregnancy by pre-treatment urine test or breast feeding or plans to become pregnant during the course of the study	Primary Outcome Measures : 1. Evaluate the number of GLS-1200 topical nasal spray adverse events as assessed by CTCAE v5.0 [Time Frame: 4 weeks of treatment] 2. Incidence of SARS-CoV-2 infection, confirmed by PCR relative to treatment group [Time Frame: 4 weeks of treatment] Secondary Outcome Measures : 1. Symptom score of documented SARS-CoV-2 infection relative to treatment group with a higher score being a worse outcome. [Time Frame: 4 weeks of treatment]

Title Identifier Expected Completion Date	Intervention	Comparator/ Control	Patients/ Population Recruited	Outcomes
Carrageenan Nasal Spray for COVID-19 Prophylaxis NCT04590365 ECD: December 2021	Iota-carrageenan nasal and throat spray (verum *Coldamaris* plus i.e. Iota-Carrageenan 0.12% plus 0.04% Kappa-Carrageenan in 0.5% saline)	Saline nasal and throat spray (placebo *Coldamaris sine* i.e. 0.5% saline)	Inclusion Criteria: • Age ≥18 years; • Study participants who have given informed consent, and received a copy of signed consent form prior to any study related procedures; • Healthcare professionals (nurses, doctors, allied health professionals, health care assistants, operating department practitioners) working in Swansea Bay University Health Board initially as well as any other volunteers >18 years who have not previously tested positive for COVID19 or been vaccinated. • Subjects agree to refrain from taking over the counter products intended to prevent, intervene in, or treat colds/flu, starting at study entry and continuing through week 10 of the study. Exclusion Criteria: Capacity, consent and conflicts of interest: • The person lacks capacity; • The subject is related to any study personnel or has any other close ties or conflicts of interest with the research team or the study sponsor;	Primary Outcome Measures : 1. Rate of COVID-19 infection [Time Frame: 9-12 months] Acquisition of COVID-19 infection as confirmed by positive PCR swab taken at the time of symptom onset or positive serology measured 2 weeks after symptom onset or seroconversion at the end of the trial (via trial entry and exit serology) to detect asymptomatic infection during the study period Secondary Outcome Measures : 1. Duration of COVID-19 infection [Time Frame: 9-12 months] Time taken for all symptoms to resolve (days) 2. Hospitalisation due to COVD-19 infection [Time Frame: 9-12 months] Length of hospital and intensive care stay (days) 3. Severity of COVID-19 infection [Time Frame: 9-12 months] Morality rate 4. Quality of life of nasal spray use

			• The subject has received any investigational drug or participated in a clinical trial within 4 weeks of entry to this study. • Unable to complete the daily symptom tracker • Unable to communicate in English or Welsh Comorbidities: • Known hypersensitivity or allergy to any component of the test product; • Severe cardiovascular, endocrinological, neurological, respiratory, gastrointestinal disease, immune deficiency, autoimmune disease or a history or any current disease that is considered by the investigator as a reason for exclusion; • Severe nasal septal deviation, nasal polyps or other non-infectious condition that could cause nasal obstruction; • A history of any nasal or sinus surgery in the past that in the opinion of the investigator may influence the symptoms or spray administration; • An unrelated infection that in the opinion of the investigator may influence symptoms	[Time Frame: 9-12 months] Usability of spray and effect on cost and quality adjusted life years

			(gastrointestinal infection, other viral diseases such as measles, mumps); COVID-19 Status: • Participants with proven COVID-19 infection (previous positive serology and/or viral PCR swab) • Participants that have already received their vaccination or already booked in for their vaccination Medications: • Recent treatment of common cold that in the opinion of the investigator may influence symptoms (see Table 2) • Participants taking any of the medications outlined in Table 2 during the trial period will be excluded	
Title **Identifier** **Expected Completion Date**	**Intervention**	**Comparator/** **Control**	**Patients/** **Population Recruited**	**Outcomes**
Prophylactic Treatment With Carragelose Nasal Spray to Prevent SARS-CoV-2, COVID-19 Infections in Health Care Workers NCT04681001 ECD: January 2021	• 1 puff of Coldamaris pro. Nasal spray into each nostril (1.2 mg/ml; 140 µl per puff) and • 3 puffs of Coldamaris pro. Nasal spray into mouth Weekly sampling for testing of SARS-CoV-2 and respiratory virus panel (Influenza A, Human Metapneumovirus, Influenza A – subtype H1 Adenovirus,	• Placebo Comparator: Coldamaris sine • One puff per nostril three puffs into mouth	Inclusion Criteria: • Age ≥18 years • Study participants that have given informed consent before any study related procedures are performed, and received a copy of signed consent form • Healthcare workers (nurses, doctors) employed and working at Gesundheitsverbund	Primary Outcome Measures : 1. Presence of COVID-19 symptoms including symptoms of respiratory viral infection documented in a diary [Time Frame: 84 days] daily assessment of subjective COVID-19 symptom score Secondary Outcome Measures : 1. Nasal swabs for analysis of viruses by

	Influenza A – subtype H3 Parainfluenza 1, Influenza A – subtype 2009 H1N1, Parainfluenza 2, Influenza B Parainfluenza 3, SARS-CoV-2 Parainfluenza 4, Coronavirus HKU1 Respiratory Syncytial Virus A, Coronavirus N63L, Respiratory Syncytial Virus B, Coronavirus OC43, Rhinovirus/Enterovirus , Coronavirus 229E, Human Bocavirus) At begin and end of trial blood samples will be taken for differential blood count and for serology. The primary end point of the is the presence of COVID-19 symptoms including symptoms of respiratory viral infection. The primary hypothesis is a reduction of symptom days caused by SARS-CoV-2 and/or respiratory viral infection in health care workers treated with Coldamaris pro. Nasal spray compared to placebo treated ones		• Healthcare workers looking after confirmed COVID-19 positive patients in a secondary care setting such as Accident and Emergency departments, wards, operating theatres, outpatient departments, High Dependency Unit or Intensive Care Units Exclusion Criteria: • The subject is related to any study personnel or has any other close ties or conflicts of interest with the study sponsor. • The subject has received any investigational drug or participated in a clinical trial within 4 weeks of entry to this study • Known hypersensitivity or allergy to any component of the test product • Severe cardiovascular, endocrinological, neurological, respiratory, gastrointestinal disease or a history or any current disease that is considered by the investigator as a reason for exclusion. • The subject has a clinically significant disease that could interfere with participation in the study, with the intervention being studied, or with the	PCR [Time Frame: 84 days] weekly assessment of SARS-CoV-2, Influenza A, Human Metapneumovirus, Influenza A – subtype H1, Adenovirus, Influenza A – subtype H3, Parainfluenza 1, Influenza A – subtype 2009 H1N1, Parainfluenza 2, Influenza B, Parainfluenza 3, Parainfluenza 4, Coronavirus HKU1, Respiratory Syncytial Virus A, Coronavirus N63L, Respiratory Syncytial Virus B, Coronavirus OC43, Rhinovirus/Enterovirus , Coronavirus 229E, Human Bocavirus, Chlamydophila pneumoniae, Mycoplasma pneumoniae, Legionella pneumophila 2. Serology of antibodies against SARS-CoV-2 [Time Frame: 84 days] 66dmin and end of trial 3. Number of viral co-infections dedected by PCR [Time Frame: 84 days] weekly **nasal** swabs for analysis of viruses

			evaluation of symptoms. Specific exclusions include immune deficiency, autoimmune disease, substantive cardiovascular, endocrinological, neurological, respiratory, or gastrointestinal disease. • Asymptomatic disease such as elevated blood pressure or cholesterol will not be a reason for exclusion. Those with well-controlled mental illness (e.g. depression, anxiety) will be eligible. The enrolling physician will be empowered to exclude potential subjects that s/he deems unreliable. • Pregnant women at the time of recruitment will be excluded from the study • Current medication other than oral contraception, that is considered by the investigator as a reason for exclusion e.g. intranasal medication • Participation in another antiviral clinical trial	

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Prophylaxis in COVID-19 Healthcare Agents by Intensive Treatment With Ivermectin and Iota-carrageenan NCT04701710 ECD: 23 February 2021	The EG received Ivermectin orally 2 drops of 6 mg = 12 mg every 7 days, and Iota-Carrageenan 6 sprays per day for 4 weeks. Standard biosecurity care	No Intervention: Control Group Standard biosecurity care	Inclusion Criteria: • Personnel who perform patient care and administrative tasks: ○ medical personnel, ○ nurses, ○ kinesiologists, ○ orderlies, ○ 68dministrative, ○ cleaning personnel. Exclusion Criteria: • People under 18 years of age, • Pregnant or actively breastfeeding women, • Presenting symptoms related to COVID-19 disease, • Concurrent autoimmune or chronic disease, • Immunosuppression, • Active infectious diseases, • History of previous SARSCoV-2 infection confirmed by RT-PCR or rapid test.	Primary Outcome Measures : 1. Pearson's Chi-square and proportion test. [Time Frame: 4 week] Number of subjects who were diagnosed with COVID-19 in EG and CG. Secondary Outcome Measures : 1. Odd Ratio, probabilistic test [Time Frame: 4 week] Contagion risk. Severity and progression of symptoms. 2. Logistic regression test [Time Frame: 4 week] Prophylactic effect associated with patient's preexisting comorbidity.

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Use of Hypochlorous Acid as Prophylaxis in Health Personnel at High Risk of Infection by SARS-CoV-2 (COVID-19) NCT04684550 ECD: 28 December 2020	Application of 2 puffs and gargles every 8 hours of a solution with low concentrations of S-HCLO (3-5 ppm).	Application of 2 puffs and gargles every 8 hours of a solution with low concentrations of S-HCLO (3-5 ppm).	**Criteria** Inclusion Criteria: • Specialist physicians, resident physicians, medical students, and nursing personnel who work at the San Ignacio University Hospital. • Subjects of any sex over 18 years of age who work as health care personnel, in care services that care for patients with a suspected or confirmed diagnosis of COVID-19 and who are active during the study recruitment. • That they have not presented general symptoms such as malaise, fever, cough, dyspnea or muscle pain during the last 7 days. • Subjects negative to the antigen test for COVID-19. Exclusion Criteria: • Subjects considered as a resolved case of COVID-19 infection, according to guidelines from the Colombian National Institute of Health. • Health personnel with social distancing due to close contact without personal protective equipment with patients confirmed to be infected or taking any medication as a possible prophylaxis for COVID-19 (example: chloroquine, hydroxychloroquine, azithromycin) • Health workers who have permits or temporary withdrawal from their hospital work for more than one week during the month of the study.	Primary Outcome Measures : 1. Prevention of infection by COVID19 [Time Frame: Through study completion, an average of 6 months] Number of participants who get COVID19 infection during the application of S-HclO Secondary Outcome Measures : 1. Adverse drug reaction (ADR) [Time Frame: Through study completion, an average of 6 months] Determine the occurrence of ADR by the use of S-HclO 2. Seroconversion [Time Frame: Through study completion, an average of 6 months] Determine the frequency of seroconversion due to COVID 19 3. Hospitalization [Time Frame: Through study completion, an average of 6 months] Number of participants who fell ill from COVID-19 and was not hospitalized 4. ICU [Time Frame: Through study completion, an average of 6 months] Number of participants who fell ill from COVID-19 and was hospitalized in ICU

			• Some type of allergy to chlorinated agents or hypersensitivity to HclO • Known diagnosis of upper airway respiratory disease where COVID-19 such as the common cold, sinusitis, pharyngitis, laryngotracheitis and epiglottitis or lower such as bronchiolitis, pneumonia, and mixed conditions have been ruled out. • Previous COVID19 infection determined by positive PCR or positive serum antibody titers. • Any condition that in the principal investigator's discretion renders the subject ineligible to participate in the study.	
Title **Identifier** **Expected Completion Date**	**Intervention**	**Comparator/** **Control**	**Patients/** **Population Recruited**	**Outcomes**
Nitric Oxide Releasing Solutions to Prevent and Treat Mild/Moderate COVID-19 Infection NCT04337918 ECD: 10 February 2021	NORS treatment will consist of daily self-administration of three routes; Nitric Oxide Gargle (NOG) every morning, Nitric Oxide Nasopharyngeal Irrigation (NONI) every evening, and Nitric Oxide Nasal Spray (NONS) up to 5 times per day. Other Name: NOG, NONI, NONS	Standard Precautions	Prevention Study Inclusion Criteria: 1. Capable of understanding and providing signed informed consent and ability to adhere to the requirements and restrictions of this protocol; 2. Men and Women ≥ 19 years of age unless local laws dictate otherwise; 3. English speaking; 4. Must be willing to use an adequate form of contraception (or abstinence) from the time of the first dose with the IMP until after the last dose of IMP. 5. Be symptom-free at screening/baseline. 6. Work/live in contact with COVID-19 infected patients or scheduled to work in a setting with high likelihood of contact with COVID-19 infected patients.	Primary Outcome Measures : 1. Prevention Study: Measure the effect of NORS on the prevention of COVID-19 infection among health care professionals at risk of exposure to COVID-19 [Time Frame: 14 days] Measure the proportion of subjects with either swab positive COVID-19 or presentation of clinical symptoms as measured by fatigue with either fever >37.2 (oral)and/or a persistent cough. 2. Treatment Sub Study: Measure the efficacy of NORS at reducing the progression of COVID- 19 [Time Frame: 21 days] Measure the proportion of participants requiring requiring hospitalization for COVID-19/flu-like symptoms and/or needing

			Prevention Study Exclusion Criteria: 1. Prior Tracheostomy; 2. Concomitant treatment of respiratory support (involving any form of oxygen therapy); 3. Any clinical contraindications, as judged by the attending physician; 4. Any symptoms consistent with COVID-19; 5. Pregnant; 6. Mentally or neurologically disabled patients who are considered not fit to consent to their participation in the study; 7. Prior COVID-19 infection. Treatment Sub study Inclusion Criteria: 1. Capable of understanding and providing signed informed consent and ability to adhere to the requirements and restrictions of this protocol; 2. Men and Women ≥ 19 years of age unless local laws dictate otherwise; 3. English speaking; 4. Must be willing to use an adequate form of contraception (or abstinence) from the time of the first dose with the IMP until after the last dose of IMP; 5. Positive COVID-19 test or presentation of clinical symptoms defined as fatigue with either fever >37.2 (oral) and/or a persistent cough. Treatment Sub Study Exclusion Criteria: 1. Prior Tracheostomy; 2. Concomitant treatment of respiratory support (involving any form of oxygen therapy); Any clinical contraindications, as judged by the attending physician; 3. Mentally or neurologically disabled patients who are considered not fit to	oxygen therapy, BIPAP/CPAP, intubation and mechanical ventilation following enrollment. Secondary Outcome Measures : 1. Prevention Study: Measure the effect of NORS on the prevention of progression of COVID-19 [Time Frame: 21 days] Measure the proportion of participants requiring requiring hospitalization for COVID-19/flu-like symptoms and/or needing oxygen therapy, BIPAP/CPAP, intubation and mechanical ventilation following enrollment. 2. Prevention Study: Measure the tolerability of NORS treatments [Time Frame: 21 days] Measure the tolerability of the NORS treatments as determined by number of adverse events, pain, discomfort or discontinuations of treatment. 3. Treatment Sub Study: Measure the virucidal effect of NORS Treatments [Time Frame: 21 days] Measure the median number of days to negative conversion of SARS-CoV-2 RT-PCR from a nasopharyngeal swabs. 4. Treatment Sub Study: Determine effect of NORS on the speed of clinical recovery [Time Frame: 21 days] Determine the time to clinical recovery in participants with COVID-19 by measuring the

			consent to their participation in the study; 4. Pregnant; 5. Currently hospitalized for symptoms of COVID-19.	median number of days from enrollment to discharge (if admitted), or to normalization of fever (defined as <36.6°C from axillary site, or < 37.2°C from oral site or < 37.8°C from rectal or tympanic site), respiratory rate (< 24 bpm while breathing room air). 5. Treatment Sub Study: Determine the reduction in clinical symptoms [Time Frame: 21 days] Measure the reduction clinical symptoms in participants with COVID-19 by the magnitude of the change in Modified Jackson Cold Score Diary Score (5-unit change is a substantial clinical benefit). 6. Treatment & Sub Study: Determine positive sero-conversion for SARS-CoV-2 [Time Frame: 21 days] Measure the proportion of participants that have a positive sero-conversion for SARS-CoV-2

ECD = Expected date of Completion