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Antimicrobial mouthwashes (gargling) and nasal sprays administered to patients with suspected or confirmed COVID-19 infection to improve patient outcomes and to protect healthcare workers treating them (Review)

Burton MJ, Clarkson JE, Goulao B, Glenny AM, McBain AJ, Schilder AGM, Webster KE, Worthington HV

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[Intervention Review]

Antimicrobial mouthwashes (gargling) and nasal sprays administered to patients with suspected or confirmed COVID-19 infection to improve patient outcomes and to protect healthcare workers treating them

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ABSTRACT

Background

COVID-19 infection poses a serious risk to patients and – due to its contagious nature – to those healthcare workers (HCWs) treating them. If the mouth and nose of patients with infection are irrigated with antimicrobial solutions, this may help the patients by killing any coronavirus present at those sites. It may also reduce the risk of the active infection being passed to HCWs through droplet transmission or direct contact. However, the use of such antimicrobial solutions may be associated with harms related to the toxicity of the solutions themselves or alterations in the natural microbial flora of the mouth or nose.

Objectives

To assess the benefits and harms of antimicrobial mouthwashes and nasal sprays administered to patients with suspected or confirmed COVID-19 infection to both the patients and the HCWs caring for them.

Search methods

Information Specialists from Cochrane ENT and Cochrane Oral Health searched the Central Register of Controlled Trials (CENTRAL 2020, Issue 6); Ovid MEDLINE; Ovid Embase and additional sources for published and unpublished trials. The date of the search was 1 June 2020.

Selection criteria

This is a question that urgently requires evidence, however at the present time we did not anticipate finding many completed RCTs. We therefore planned to include the following types of studies: randomised controlled trials (RCTs); quasi-RCTs; non-randomised controlled trials; prospective cohort studies; retrospective cohort studies; cross-sectional studies; controlled before-and-after studies. We set no minimum duration for the studies.

We sought studies comparing antimicrobial mouthwash and/or nasal spray (alone or in combination) at any concentration, delivered with any frequency or dosage to suspected/confirmed COVID-19 patients.

Data collection and analysis

We used standard Cochrane methodological procedures. Our primary outcomes were: 1) RECOVERY* (www.recoverytrial.net) outcomes in patients **(**mortality; hospitalisation status; use of ventilation; use of renal dialysis or haemofiltration); 2) incidence of symptomatic or test-positive COVID-19 infection in HCWs; 3) significant adverse event: anosmia (or disturbance in sense of smell). Our secondary outcomes were: 4) change in COVID-19 viral load in patients; 5) COVID-19 viral content of aerosol (when present); 6) other adverse events: changes in microbiome in oral cavity, nasal cavity, oro- or nasopharynx; 7) other adverse events: allergy, irritation/burning of nasal, oral or oropharyngeal mucosa (e.g. erosions, ulcers, bleeding), long-term staining of mucous membranes or teeth, accidental ingestion. We planned to use GRADE to assess the certainty of the evidence for each outcome.

Main results

We found no completed studies to include in this review. We identified 16 ongoing studies (including 14 RCTs), which aim to enrol nearly 1250 participants. The interventions included in these trials are ArtemiC (artemisinin, curcumin, frankincense and vitamin C), Citrox (a bioflavonoid), cetylpyridinium chloride, chlorhexidine, chlorine dioxide, essential oils, hydrogen peroxide, hypertonic saline, Kerecis spray (omega 3 viruxide – containing neem oil and St John's wort), neem extract, nitric oxide releasing solution, povidone iodine and saline with baby shampoo.

Authors' conclusions

We identified no studies for inclusion in this review. This is not surprising given the relatively recent emergence of COVID-19 infection. It is promising that the question posed in this review is being addressed by a number of RCTs and other studies. We are concerned that few of the ongoing studies specifically state that they will evaluate adverse events such as changes in the sense of smell or to the oral and nasal microbiota, and any consequences thereof.

Very few interventions have large and dramatic effect sizes. If a positive treatment effect is demonstrated when studies are available for inclusion in this review, it may not be large. In these circumstances in particular it may be a challenge to weigh up the benefits against the harms if the latter are of uncertain frequency and severity.

PLAIN LANGUAGE SUMMARY

What are the benefits and risks of people with COVID-19 using antimicrobial mouthwashes or nasal sprays to improve their health and protect healthcare workers who treat them?

Why is this question important?

COVID-19 is an infectious disease caused by the SARS-CoV-2 virus. Most people infected with COVID-19 develop a mild to moderate respiratory illness, and some may have no symptoms (asymptomatic infection). Others experience severe symptoms and need specialist treatment and intensive care.

COVID-19 spreads from person to person primarily through droplets that are produced when an infected person coughs, sneezes or talks. A person can also become infected by touching a surface or object that has viral droplets on it, and then touching their own mouth or nose.

Administering antimicrobial mouthwash (to rinse the mouth) or nasal spray (sprayed into the nose) to people with COVID-19 might help them fight the infection and prevent them from infecting the healthcare workers who treat them. Antimicrobial mouthwash and nasal spray are liquids that kill or stop the growth of micro-organisms such as viruses or bacteria.

As with any medical treatment, antimicrobial mouthwash and nasal spray have potential risks as well as benefits. It is possible that using mouthwash or nasal spray could cause a variety of unwanted (adverse) effects, including irritation, allergic reactions or loss of smell. It may also remove micro-organisms from the mouth or nose that are useful for protecting the body against infection.

What did we aim to do?

To assess the benefits and risks for patients and healthcare workers of administering antimicrobial mouthwashes and nasal sprays to patients with COVID-19, we set out to review the research evidence. In particular, we wanted to investigate the effects of patient use of antimicrobial mouthwashes and nasal sprays on:

- patient deaths and healthcare needs – including the need for hospitalisation, artificial breathing support, dialysis or haemofiltration (treatments required when the kidneys do not work properly);

- new COVID-19 infections of healthcare workers;

- important adverse effects such as loss of smell;

- change in patients' COVID-19 viral load (the amount of virus in an infected person's blood); and

- the viral load of droplets produced by patients.

How did we search for evidence?

Our team of researchers searched the medical literature for studies that compared the effects of any antimicrobial mouthwash or nasal spray administered to patients with COVID-19 against no treatment, water or a salt solution.

What did we find?

We found no completed studies to include in this review.

We found 16 studies currently in progress that aim to enrol nearly 1250 participants. These studies are investigating a range of mouthwashes and nasal sprays.

Fourteen of the studies are randomised controlled trials (clinical, real-life studies where people are randomly put into one of two or more treatment groups). This type of study provides the most robust evidence about the effects of a treatment.

What does this mean?

There is currently no evidence relating to the benefits and risks of patients with COVID-19 using antimicrobial mouthwashes or nasal sprays.

Sixteen randomised controlled trials are underway. Once these studies are completed, we will be able to analyse them and include their findings in an updated version of this review.

It is important that future studies collect and analyse information about adverse events. Few of the ongoing studies we identified specifically state that they will investigate these. If future studies show a beneficial effect of mouthwashes and nasal sprays, it may not be a large effect (very few health interventions have large and dramatic effect sizes). It will only be possible to weigh up potentially small benefits against risks if any adverse events that occur are reported in studies.

How-up-to date is this review?

We last searched for evidence on 1 June 2020. This review covered research that was available up to that date, but did not consider any evidence that may have been produced since then.

SUMMARY OF FINDINGS

Summary of findings 1. Antimicrobial mouthwashes (gargling) and nasal sprays administered to patients with suspected or confirmed COVID-19 infection to improve patient outcomes and to protect healthcare workers treating them

Antimicrobial mouthwashes (gargling) and nasal sprays administered to patients with suspected or confirmed COVID-19 infection to improve patient outcomes and to protect healthcare workers treating them

Patient or population: patients with suspected or confirmed COVID-19 infection
Setting: any healthcare setting
Intervention: any antimicrobial mouthwash and/or nasal spray
Comparison: no treatment or saline or water

Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens
		Without nasal sprays and gargles	With nasal sprays and gargles	Difference		
RECOVERY trial outcomes	No data available (no included studies)					
Incidence of symptomatic or test-positive COVID-19 infection	No data available (no included studies)					
Anosmia	No data available (no included studies)					
Change in COVID-19 viral load in patients	No data available (no included studies)					
COVID-19 viral content of aerosol	No data available (no included studies)					
Changes in microbiome in oral cavity, nasal cavity, oro-or nasopharynx	No data available (no included studies)					
Other adverse events	No data available (no included studies)					

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

BACKGROUND

Description of the condition

The emergence of a novel coronavirus (SARS-CoV-2) in late 2019 has resulted in a global pandemic of an infectious condition - COVID-19. To date, almost 19.9 million people have been reported to be infected, with close to 732,000 deaths. Patients may be asymptomatic, or they may have an illness with symptoms varying from mild to very severe. Not all those who have the condition are tested for the presence of the virus. Multiple therapeutic interventions and vaccines are in development. The steroid dexamethasone has been shown to reduce the mortality rate of people requiring invasive ventilation for COVID-19 by a third (Horby 2020), and the antiviral drug remdesivir can reduce the time to recovery of patients in hospital (Beigel 2020). Prevention efforts have focused on measures of social distancing and isolation in many countries.

Healthcare workers are at the forefront of this crisis, with repeated exposure to individuals who are, or may be, infected, and are therefore at risk themselves. Access to and proper use of personal protective equipment (PPE) is a key intervention that should reduce the frequency of transmission of the infection to healthcare workers.

These workers may be especially at risk when undertaking 'aerosol-generating procedures' (AGPs). This is any medical, dental or patient-care procedure that results in the production of airborne particles (aerosols) from the upper aerodigestive tract (mouth, nose, throat, oesophagus) and lower respiratory tract where the virus is shedding. These can remain suspended in the air and travel over a distance. They may cause infection if they are inhaled. Such procedures therefore create the potential for airborne transmission of infection.

This review is one of a set of three which consider two measures that may protect healthcare workers and patients - both for their own benefit, and to reduce the frequency of onward transmission. These two measures are 1) the pre-procedural use of mouthwashes and nasal sprays by patients, to reduce the risk that any aerosol that they generate will infect healthcare workers, and 2) the use of mouthwashes and nasal sprays by healthcare workers pre- and post-exposure to patients with confirmed or suspected infection to reduce the risk of acquiring such infection through their mouth or nose. This particular review focuses on the use of antimicrobial mouthwashes and nasal sprays by patients with suspected or known COVID-19 infection. This intervention may be of benefit to the patients themselves - by reducing the severity of the infection. It may also be of benefit to healthcare workers who are treating the patients - by reducing the viral load in the oro-nasopharynx, and consequently reducing the transmission of COVID-19. It evaluates the use of mouthwashes and nasal sprays administered to patients alone (1) above) without any intervention to the HCWs (2) above). (The other two reviews will focus on a) the use of mouthwashes or nasal sprays by HCWs treating patients with suspected or confirmed COVID-19 infection (Burton 2020a) and b) the use of mouthwashes and nasal sprays by HCWs or patients during AGPs on patients who are not known to have, or suspected of having, COVID-19 infection (Burton 2020b)).

Description of the intervention

Mouthwashes are oral rinsing solutions: many are in common use to manage halitosis, prevent tooth decay and reduce plaque formation. In some countries they are recommended as a hygiene measure during the regular cold and flu season. Many mouthwashes with some antimicrobial activity can be purchased over the counter, and others are available on prescription. The antimicrobial agents and effectiveness vary and whilst most have some antibacterial properties a few are also antiviral.

Similar topical antimicrobial solutions may be administered via the nose using a nasal spray, or by direct irrigation or douching (administered by sniffing a solution through each nostril and spitting it out).

How the intervention might work

There has been considerable interest in the use of nasal irrigation or oral rinses to prevent transmission of upper respiratory tract infections (URTI) caused by viruses, or to alleviate their symptoms. Transmission of such disease occurs by the inhalation of small droplets containing viral particles, or by transfer (for example, from surfaces to hands, and then to the face, mouth and nose).

The use of mouthwashes and nasal sprays in individuals with known or suspected COVID-19 has the potential to reduce the viral load in the oro-nasopharynx. This may result in reduced severity of disease, or a more rapid recovery for the patient themselves. Furthermore, a reduced viral load may decrease the number of viral particles being shed by an infected individual. This has the potential to result in reduced transmission of disease from infected patients to the healthcare workers who are treating them.

Mouthwashes and sprays have previously been investigated to assess their use for both of these aims - to shorten the duration and severity of symptoms of upper respiratory tract disease, and also to limit the transmission of disease from one infected individual to their close contacts.

Gargles that have been investigated for their ability to reduce viral transmission include tea (or components of tea) (Ide 2016), water (Goodall 2014) and povidone iodine (Kitamura 2007; Satomura 2005). Other mouthwashes in common use, including hydrogen peroxide and chlorhexidine, may also have antiviral activity (Bernstein 1990).

Nasal irrigation with topical antimicrobial solutions similar to those used as mouthwashes has also been investigated. Carrageenan, a carbohydrate found in red seaweed, has been trialled as an antiviral nasal spray. Studies have identified a decrease in the nasal viral load from URTI, but results on symptomatic improvement have been mixed (Eccles 2010; Eccles 2015; Fazekas 2012; Ludwig 2013).

Given the new emergence of COVID-19, the efficacy of nasal or oral irrigation fluids against this disease is not yet known. However, activity against similar novel coronaviruses (such as those responsible for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS)) has been demonstrated for some preparations (Eggers 2015; Kariwa 2006). Gargle solutions of povidone iodine have been shown to be active against the coronaviruses causing both MERS and SARS in vitro (Eggers 2018; Kariwa 2006).

How the intervention might cause harm

Use of mouthwash or nasal irrigation has the potential to cause a variety of adverse effects. In common with many treatments, there is the possibility of irritation or allergic reaction to components of the product. A key concern for any agent used intranasally is the potential for long-term damage resulting in anosmia (loss of sense of smell). However, anosmia may also be a symptom of COVID-19 infection.

There is also a concern that local application of antimicrobials will disrupt the normal nasal and oral microbiota. The microbiome is increasingly recognised as playing a vital role in preventing colonisation with invading pathogens, supporting the host immune system and a variety of other functions (Kilian 2016; Man 2017). Alteration of this delicate environment by exposure to antimicrobial compounds could alter the composition and/or activities of the oral and nasal microbiotas. This may occur through reduced total microbial abundance and/or via the selective suppression of commensal micro-organisms with the greatest susceptibility to the treatment. Potential health problems resulting from this include an increased risk of infection due to the suppression of colonisation resistance, by which commensal micro-organisms inhibit extrinsic pathogens; the overgrowth of species within the microbiota with pathogenic potential, and interference with beneficial host-microbe interactions that prime the immune system.

Other potential harms are related to specific irrigation fluids. These include the risk of excess iodine ingestion from iodine-containing gargle solution or staining of teeth with chlorhexidine.

OBJECTIVES

To assess the benefits and harms of antimicrobial mouthwashes and nasal sprays administered to patients with suspected or confirmed COVID-19 infection in order to protect the healthcare workers (HCWs) caring for them.

To assess the benefits and harms of antimicrobial mouthwashes and nasal sprays in improving outcomes for patients with suspected or confirmed COVID-19 infection.

METHODS

Criteria for considering studies for this review

Types of studies

This is a question that urgently requires evidence, however at the present time we did not anticipate finding many completed RCTs. We therefore included the following types of studies:

- randomised controlled trials (RCTs);
- quasi-RCTs;
- non-randomised controlled trials;
- prospective cohort studies;
- retrospective cohort studies;
- cross-sectional studies;
- controlled before-and-after studies.

There was no minimum duration for the studies.

Types of participants

Patients with suspected or confirmed COVID-19 infection.

Setting

Any healthcare setting.

Types of interventions

Interventions

Any antimicrobial **mouthwash** and/or **nasal spray** (alone or in combination) at any concentration, delivered with any frequency or dosage to suspected/confirmed COVID-19 patients.

Comparator

No treatment or saline or water.

Types of outcome measures

We analysed the following outcomes in the review, but we did not use them as a basis for including or excluding studies.

We assessed the primary outcomes at a minimum of two weeks. For all other outcomes, there was no minimum follow-up.

For all outcomes we planned to accept the method of measurement used by the trialists but we would take a critical approach to the value of each measure.

Primary outcomes

- RECOVERY* outcomes in patients (www.recoverytrial.net):
  - mortality;
  - hospitalisation status;
  - use of ventilation;
  - use of renal dialysis or haemofiltration.
- Incidence of symptomatic or test-positive COVID-19 infection in HCWs.
- Significant adverse event: anosmia (or disturbance in sense of smell).

Secondary outcomes

- Change in COVID-19 viral load in patients.
- COVID-19 viral content of aerosol (when present).
- Other adverse events: changes in microbiome in oral cavity, nasal cavity, oro- or nasopharynx.
- Other adverse events: allergy, irritation/burning of nasal, oral or oropharyngeal mucosa (e.g. erosions, ulcers, bleeding), long-term staining of mucous membranes or teeth, accidental ingestion.

Search methods for identification of studies

The Cochrane ENT and Cochrane Oral Health Information Specialists conducted systematic searches for all human studies. There were no language, publication year or publication status restrictions. We contacted original authors for clarification and further data when trial reports were unclear and arranged translations of papers where possible. The date of the search was 1 June 2020.

Electronic searches

The Information Specialist searched:

- the Cochrane Central Register of Controlled Trials (CENTRAL 2020, Issue 6) (searched via the Cochrane Register of Studies);
- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to 1 June 2020);
- Ovid EMBASE (1974 to 1 June 2020);
- World Health Organization (WHO) COVID-19 Global literature on coronavirus disease https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov (searched to 1 June 2020);
- Cochrane COVID-19 Study Register https://covid-19.cochrane.org/ (search via the Cochrane Register of Studies to 1 June 2020).

The Information Specialist modelled subject strategies for databases on the search strategy designed for Ovid MEDLINE. Search strategies for major databases including CENTRAL are provided in Appendix 1.

Searching other resources

We did not perform a separate search for adverse effects. We planned to consider adverse effects described in the included studies only.

We did not perform a separate search for pre-print publications. We planned to identify and report as awaiting assessment any we identified from the sources above that met our inclusion criteria but we did not plan to extract the data until their publication in a peer-reviewed journal.

We planned to make efforts to identify full-text papers regardless of language of publication and to endeavour to seek help with translation; however, we did not plan to hold up the rapid review process. Any papers that we were unable to source quickly or were unable to get translated would be listed as awaiting assessment.

Data collection and analysis

Selection of studies

AMG, HW (and others) performed screening using Covidence.

Two review authors independently screened all titles and abstracts identified through the searching process. Discrepancies were discussed and, where necessary, a third review author was included. Where uncertainties remained, we retrieved the full text for clarification. Two review authors again screened the full text of potentially relevant articles, independently.

We documented and outlined in the final report all decisions regarding exclusion of studies, taken during screening with a list of excluded studies.

Data extraction and management

We planned that AMG, HW (and others) would perform data extraction using a predefined data extraction form (Word/Excel). Data were limited to a minimal set of required data items following input from content experts and methodologists.

A single review author would undertake data extraction and a second review author would check the completeness/accuracy of the data extraction. Discrepancies would be discussed and taken to a third review author as required.

We planned to contact study authors for missing outcome data, or where there were conflicting data reported across multiple sources for a single study.

Assessment of risk of bias in included studies

We planned to undertake 'Risk of bias' assessment at the same time as data extraction. We planned to use the Cochrane RCT 'Risk of bias' tool and the ROBINS-I tool for non-randomised studies. We planned to exclude studies judged to be at critical risk of bias from analysis.

As for data extraction, all judgements were to be checked by a second review author. Discrepancies would be discussed and taken to a third review author as required.

Measures of treatment effect

We planned to present dichotomous data as risk ratios (RR) with corresponding 95% confidence intervals (CIs). However, if we identified case-control studies relevant to the review questions, we would have considered the use of odds ratio as the appropriate estimate of effect.

We planned to present continuous data as mean differences (MD) with corresponding 95% CIs. Where necessary, we would have converted outcome data to the same unit of measurement.

Where data were extracted from non-RCTs, we planned to use adjusted effects where available. If multiple adjusted effects were reported, then we would have chosen the one judged to minimise the risk of bias due to confounding.

Unit of analysis issues

The unit of analysis was the participant. Any cluster-RCTs would need to have analysed results taking account of the clustering present in the data, otherwise we would have used the methods outlined in Section 16.3.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* in order to perform an approximately correct analysis (Higgins 2011). We planned to include studies with multiple treatment arms as appropriate, ensuring that there was no double counting of patients in any meta-analysis.

Dealing with missing data

We planned to contact study authors for missing outcome data. Where appropriate, we would have used the methods outlined in Section 7.7.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* in order to estimate missing standard deviations (Higgins 2011). We would not have used any further statistical methods or carried out any further imputation to account for missing data.

Assessment of heterogeneity

We planned to assess statistical heterogeneity initially through inspection of forest plots. We would use the Chi^2 for heterogeneity, with $P = 0.10$, to indicate substantial heterogeneity (acknowledging that this has low power if there is a small sample size or few studies).

We also planned to use the I^2 statistic, following the interpretation recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; 75% to 100% considerable heterogeneity) (Handbook 2019). We would be cautious in interpreting the I^2 value, as this may be uncertain when there are few studies.

We planned to explore potential sources of heterogeneity among study results. Sources may include: clinical setting and clinical procedure.

Assessment of reporting biases

Where there were 10 or more studies in a meta-analysis, we planned to assess possible publication bias by visually inspecting a funnel plot for asymmetry.

Data synthesis

We planned to make a judgement regarding the clinical and methodological heterogeneity; only where there was deemed to be reasonable homogeneity across studies would we consider statistical pooling of data. If appropriate, we would have conducted statistical pooling of data from RCTs, followed by data from non-RCTs. We would not have undertaken pooling across different types of study designs.

We planned to use a random-effects model.

Lastly, we planned to undertake a narrative synthesis, encompassing findings from both RCT and non-RCT studies.

Subgroup analysis and investigation of heterogeneity

Where data were available, we planned to conduct subgroup analyses, where possible, according to clinical procedure (AGP versus non-AGP) and clinical setting (e.g. inpatient, outpatient, dental, ENT).

Sensitivity analysis

We planned to undertake sensitivity analysis excluding studies at high risk of bias.

Summary of findings and assessment of the certainty of the evidence

We planned to use the GRADE approach and present 'Summary of findings' tables for all comparisons and all outcomes.

RESULTS

Description of studies

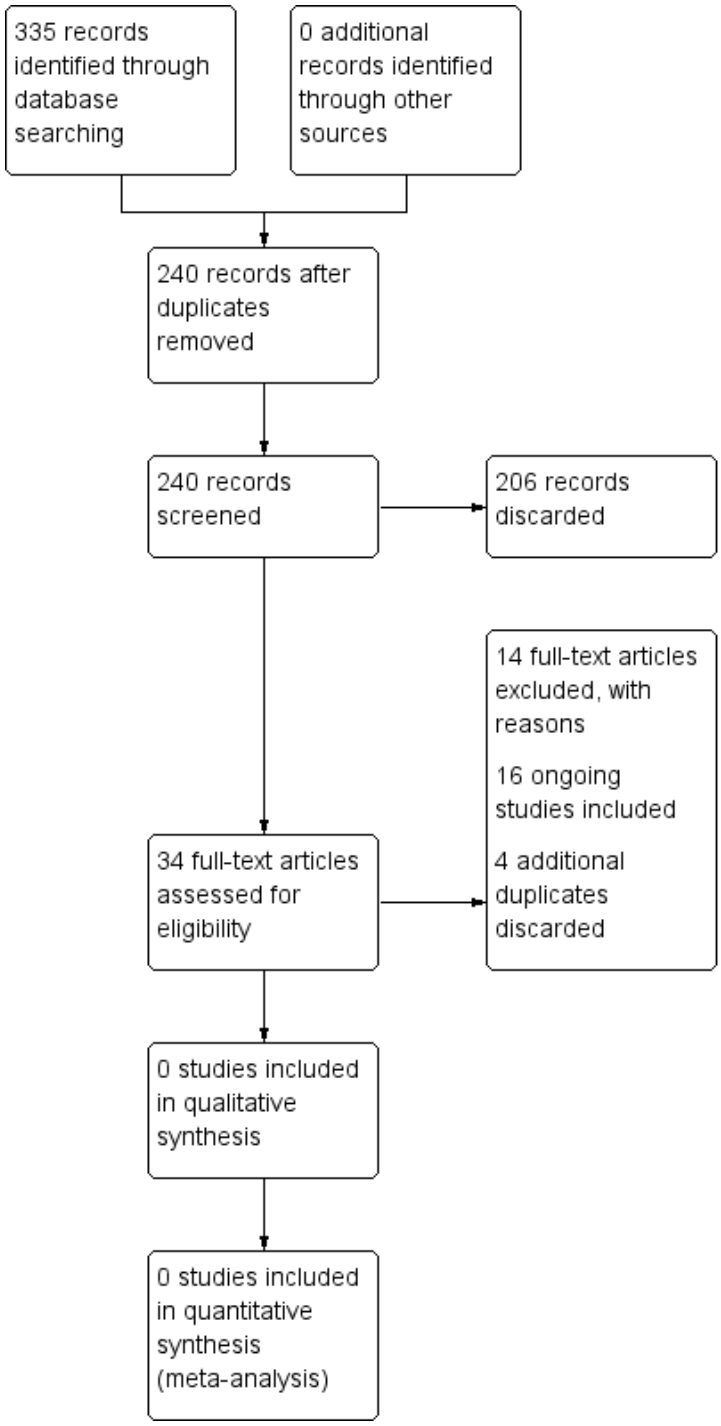
Results of the search

The searches retrieved a total of 335 references. This reduced to 240 after the removal of duplicates. We screened the title and abstracts of the remaining 240 references. We discarded 206 references and assessed 34 full-text articles. We identified four additional duplicates, which we discarded. We excluded 14 references with reasons recorded in the review (see Excluded studies).

We did not identify any completed studies that met the inclusion criteria for this review. We identified 16 references to 16 ongoing studies (ACTRN12620000470998p; AMPoL (NCT04409873); BBCovid (NCT04352959); ChiCTR2000030539; ELVIS-COVID-19 (NCT04382131); GARGLESa (NCT04341688); GARGLESb (NCT04410159); KILLER (NCT04371965); KONS-COVID-19 (NCT04357990); NCT04344236; NCT04347538; NCT04347954; NCT04382040; NOCOVID (NCT04337918); PICO (ISRCTN13447477); SINUS WASH (NCT04393792)). See Characteristics of ongoing studies for further details.

The PRISMA diagram in Figure 1 shows our study search and selection process.

Figure 1. Process for sifting search results and selecting studies for inclusion



Included studies

We did not include any studies.

Excluded studies

We excluded 14 references after reviewing the full text. Further details for the reasons for exclusion can be found in the Characteristics of excluded studies table. These are the main reasons for exclusion:

We excluded seven references that were narrative review articles, which did not report any data of relevance to this review (Carrouel 2020; Dexter 2020; Ham 2020; Hamid 2020; Henwood 2020; Leboulanger 2020; Parhar 2020).

We also excluded four references as they were letters to the editor of a journal, providing a comment rather than reporting on a study (Challacombe 2020; Loftus 2020; Mady 2020; Maguire 2020).

We excluded two studies as the intervention was used in an incorrect population - the trials considered the use of nasal sprays and gargles to protect healthcare workers from infection with COVID-19, rather than to treat individuals who have the virus (NCT04408183; PIIPPI (NCT04364802)).

Finally, we excluded one study as it was conducted in an incorrect population - although participants were infected with a coronavirus, this was not COVID-19 (Ramalingam 2020).

Ongoing studies

We identified 16 ongoing studies, aiming to enrol nearly 1250 participants, which may provide data for future versions of this review. It should be noted that not all of these studies have begun recruiting participants, or even identified funding for the trial, therefore they should be regarded as 'planned or ongoing studies'.

Fourteen of the ongoing studies are reported to be RCTs (AMPoL (NCT04409873); BBCovid (NCT04352959); ELVIS-COVID-19 (NCT04382131); GARGLESa (NCT04341688); GARGLESb (NCT04410159); KILLER (NCT04371965); KONS-COVID-19 (NCT04357990); NCT04344236; NCT04347538; NCT04347954; NCT04382040; NOCOVID (NCT04337918); PICO (ISRCTN13447477); SINUS WASH (NCT04393792)). One study appears to be an interventional 'before-and-after' study - it is not clear whether a comparator group will be included (ACTRN12620000470998p). Another study is described as a case-control study, but appears to be a non-randomised intervention study (ChiCTR2000030539).

The studies are evaluating the effectiveness of a range of interventions in differing strengths, often as both a gargle and a nasal spray. These include:

- ArtemiC (artemisinin, curcumin, frankincense and vitamin C);
- Citrox (a bioflavonoid);
- cetylpyridinium chloride (Crest Pro-Health Multi-Protection mouthwash);
- chlorhexidine (0.12%);
- chlorine dioxide (CloSYS mouthwash);
- essential oils (Listerine mouthwash);
- hydrogen peroxide (1%, 3% and Oral B Mouth Sore mouthwash);
- hypertonic saline (2%);
- Kerecis spray (omega 3 viruxide - containing neem oil and St John's wort);
- neem extract;
- nitric oxide releasing solution;
- povidone iodine (0.2%, 0.23%, 0.5%, 2% and 10%);
- saline with baby shampoo.

The studies evaluate a range of outcomes, including viral load, clinical symptoms, hospitalisation and mortality, but few mention looking for adverse effects or the impact on disease transmission to healthcare workers.

Risk of bias in included studies

No studies are included in the review.

Effects of interventions

See: **Summary of findings 1** Antimicrobial mouthwashes (gargling) and nasal sprays administered to patients with suspected or confirmed COVID-19 infection to improve patient outcomes and to protect healthcare workers treating them

No studies are included in the review. See Summary of findings 1.

DISCUSSION

Summary of main results

We identified no studies for inclusion in this review. This is not surprising given the relatively recent emergence of COVID-19 infection. It is, however, promising that the question posed in this review is being addressed by a number of RCTs and other studies.

Overall completeness and applicability of evidence

Although a number of ongoing studies were identified, we note that the proposed sample size for many studies is small (predominantly fewer than 50 participants). The varied interventions used in the different studies may also mean that meta-analysis will not be possible, further restricting our ability to identify interventions that may have significant benefits or harms. We are concerned that few of the ongoing studies specifically state that they will evaluate adverse events. Two specific issues are problematic and may remain so even if they are addressed in the studies - anosmia, and changes to the microbiome.

Anosmia

Anosmia may occur as an adverse effect of the intervention, rather than a consequence of the COVID-19 infection. Since temporary or permanent anosmia are now recognised features of the disease (Menni 2020), any small increase in prevalence occurring as an adverse effect will be difficult to identify without data from large numbers of trial participants. Moreover, trials must have been conducted over the required time period if both temporary and permanent anosmia are to be detected.

Microbiome changes and antimicrobial resistance

Changes to the oral and nasal microbiota induced by the application of antimicrobial substances into the oral and nasal cavities and the nasopharynx *may* have adverse consequences for participants. It is very difficult to be certain about the severity and likelihood of these adverse consequences, in particular in respect of nasal irrigation, which is much less commonly undertaken than oral irrigation. Good data are unlikely to come from any RCTs or other trials included in this review.

However, some indication of the likely frequency and severity of adverse events due to changes in the oral and nasal microbiota can be obtained from the current use of similar formulations. The use of oral rinses containing broad-spectrum antimicrobial compounds such as the bisbiguanide antiseptic chlorhexidine is common globally. Adverse effects specifically associated with changes in the composition of the oral or pharyngeal microbiota have generally not been reported (Tartaglia 2019).

Likewise, microbiome-associated adverse events have generally not been reported in clinical methicillin-resistant

Staphylococcus aureus (MRSA) decolonisation protocols involving the application of mupirocin (a broad-spectrum topical antibiotic) to the inner surface of the nostrils several times daily. Thus, in short-term applications, both types of adverse events can be considered to be very rare and most likely mild.

There is a potential risk of microbial adaptation to both mupirocin and chlorhexidine and there have been reports of correlations between biocide and antibiotic susceptibility in clinical isolates. As with the use of these compounds in MRSA decolonisation, the balance of risk (that may be difficult to quantify) versus benefit must be considered.

Balance of benefits versus harms

Very few interventions have large and dramatic effect sizes. If a positive treatment effect is demonstrated when studies are available for inclusion in this review, it may not be large. In these circumstances in particular it may be a challenge to weigh up the benefits against the harms if the latter are of uncertain frequency and severity. However, in the context of a global pandemic, even those interventions with a modest benefit have the potential to reduce the overall burden of disease considerably.

Transmission to healthcare providers and other individuals

Transmission of COVID-19 infection to healthcare workers is included in this review since this is a key concern within healthcare settings. Any intervention that has the potential to reduce the risk of viral transmission from an infected individual to others would be of huge importance. Whilst many of the ongoing studies aim to assess the impact of nasal sprays or gargles on oral or nasopharyngeal viral load, and this may provide *indirect* evidence of effects on viral transmission, they do not specifically aim directly to assess infection in HCWs.

Quality of the evidence

No studies are included in the review.

Potential biases in the review process

Given the recent emergence of COVID-19 infection, we aimed to design a protocol that would be inclusive, to encompass as much relevant information as possible.

The search strategy was designed and run by qualified Cochrane Information Specialists so any bias here should be minimal. The search was not limited to the English language. It is possible that suitable studies have been carried out and the results published elsewhere in another language; however, we feel that this is unlikely as all applicable studies are likely to have been registered with one of the central trial registries.

All studies that we discarded during our search and selection process were rejected based on a lack of relevant data (e.g. they were letter to the editor of a journal, or narrative review articles) or because they did not address the relevant population.

Agreements and disagreements with other studies or reviews

We are not aware of any other published reviews that address the use of antimicrobial mouthwashes and nasal sprays for the treatment of COVID-19, to either improve patient outcomes or reduce transmission to healthcare workers. We await the publication of the ongoing trials with interest.

Evidence for the activity of specific antimicrobials against SARS-CoV-2 is still developing. However, a number of the interventions identified in this review have been previously shown to have activity against coronaviruses. These include povidone iodine, chlorine dioxide and hydrogen peroxide (Dev Kumar 2020). There is some evidence that povidone iodine mouthwash has antiviral activity against SARS-CoV-2 in particular, although hydrogen peroxide oral rinse was not shown to be effective (Bidra 2020).

AUTHORS' CONCLUSIONS

Implications for practice

No studies are included in this review, therefore we are unable to ascertain the relative benefits and harms of the use of antimicrobial mouthwashes and nasal sprays by individuals with COVID-19.

Implications for research

It is promising that a number of ongoing studies were identified by the literature searches for this review. However, we note that a number of important issues may not be addressed by the trials that are currently ongoing - in particular the adverse effects of the interventions, and the impact on viral transmission to healthcare workers.

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Carrouel 2020	Review article, no relevant data.
Challacombe 2020	Letter to the editor - no relevant data.
Dexter 2020	Review article, no relevant data.
Ham 2020	Review article, no relevant data.
Hamid 2020	Review article, no relevant data.
Henwood 2020	Review article, no relevant data.
Leboulanger 2020	Review article, no relevant data.
Loftus 2020	Letter to the editor, no relevant data.
Mady 2020	Letter to the editor, no relevant data.
Maguire 2020	Letter to the editor, no relevant data.
NCT04408183	Incorrect population. This trial involves healthcare workers who are negative for COVID-19 using nasal spray/gargles to protect them from acquiring the virus, and is relevant for a different review in this suite (Use of antimicrobial mouthwashes (gargling) and nasal sprays by healthcare workers to protect them when treating patients with suspected or confirmed COVID-19 infection; Burton 2020a).
Parhar 2020	Review article, no relevant data.
PIIPPI (NCT04364802)	Incorrect population. This trial involves healthcare workers who are negative for COVID-19 using nasal spray/gargles to protect them from acquiring the virus, and is relevant for a different review in this suite (Use of antimicrobial mouthwashes (gargling) and nasal sprays by healthcare workers to protect them when treating patients with suspected or confirmed COVID-19 infection; Burton 2020a).
Ramalingam 2020	Incorrect population - participants did not have COVID-19.

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12620000470998p

Study name	'Virucidal pilot study of Nasodine antiseptic nasal spray (povidone iodine 0.5%) in people with COVID-19 and confirmed nasal shedding of SARS-CoV-virus'
Methods	Interventional, before-and-after study
Participants	Individuals with COVID-19 who are confirmed to have nasal shedding of the virus. Aged 18 to 65 years. **Inclusion criteria:** • Adults aged 18 years and over • Confirmed symptoms of COVID-19 • Symptom onset within past 5 days **Exclusion criteria:** • Known iodine sensitivity • Previously diagnosed thyroid disease • Previously diagnosed kidney disease • Known to be pregnant or currently breastfeeding **Planned sample size:** 20 participants
Interventions	**Intervention group:** • Single dose of aqueous solution of 0.5% povidone iodine **Comparator group:** • Not clear that a comparator group will be included for this trial **Use of additional interventions in both groups:** • Not reported
Outcomes	**Primary outcome:** • Reduction in virus concentration in nasal swab; time frame: 5 minutes after dosing **Secondary outcome:** • Reduction in virus concentration in nasal swab; time frame: 1 hour after dosing
Starting date	Estimated start date April 2020
Contact information	Professor Peter Friedland Email: peter.friedland@health.wa.gov.au
Notes	It is likely that this is an uncontrolled before-and-after study and therefore may not be eligible for inclusion in the review when the study results are reported. Trial registered in Australia Estimated completion date: June 2020

AMPoL (NCT04409873)

Study name	'Antiseptic mouthwash / pre-procedural rinse on SARS-CoV-2 load (COVID- 19) (AMPoL)'

AMPoL (NCT04409873) *(Continued)*

Methods	4-arm, parallel-group RCT
Participants	Participants with confirmed COVID-19 infection **Inclusion criteria:** • 18 years and over • Ability to gargle • Not having any condition that might worsen with gargling solutions • Not having an allergy to a study mouthwash ingredient • Not using another mouthwash/gargling solution • Not taking antimicrobial medications (antibacterial, antiviral, antibiotics including off-label FDA-approved medications such as hydroxychloroquine) • Anticipated ability to participate in the study for 4 weeks • Have a cell phone and agree to receive text messages for reminders to use mouthwash during the day and for follow-up visits **Exclusion criteria:** • People who because of their symptoms intend to receive antiviral medications that could potentially affect viral load in their saliva samples • Pregnant or lactating women due to potential aversions to mouthwash solution taste/smell **Planned sample size:** 120 participants
Interventions	**Intervention group A:** • Oral-B Mouth Sore mouthwash (hydrogen peroxide) rinse and gargle used 4 times daily for 15 seconds, for 4 weeks **Intervention group B:** • Crest Pro-Health Multi-Protection mouthwash (cetylpyridinium chloride) rinse and gargle used 4 times daily for 15 seconds, for 4 weeks **Intervention group C:** • CloSYS mouthwash (chlorine dioxide) rinse and gargle used 4 times daily for 15 seconds, for 4 weeks **Comparator:** • Distilled water rinse and gargle used 4 times daily for 15 seconds, for 4 weeks
Outcomes	**Primary outcome:** • Change in SARS-CoV-2 viral load (RT-PCR of saliva wash); time frame: 4 weeks **Secondary outcomes:** • Change in self-reported clinical symptom onset; time frame: 4 weeks • Change in healthcare utilisation and hospitalisation; time frame: 4 weeks **Other outcome measures:** • Change in SARS-CoV-2 viral toad in tobacco users, marijuana smokers or vapers; time frame: 4 weeks • Change in self-reported clinical symptom onset in tobacco users, marijuana smokers or vapers; time frame: 4 weeks • Change in healthcare utilisation and hospitalisation in tobacco users, marijuana smokers or vapers; time frame: 4 weeks

AMPoL (NCT04409873) *(Continued)*

Starting date	1 July 2020
Contact information	Stuart Gansky Email: stuart.gansky@ucsf.edu Sepideh Banava Email: sepideh.banava@ucsf.edu
Notes	Trial registered in USA Estimated completion date: 31 August 2021

BBCovid (NCT04352959)

Study name	'COVID-19: nasal and salivary detection of the SARS-CoV-2 virus after antiviral mouthrinses (BB-Covid)'
Methods	Triple-blinded, parallel-group randomised controlled trial
Participants	Individuals with a diagnosis of COVID-19, aged 18 to 70 years **Inclusion criteria:** • Clinical diagnosis of COVID-19 by the patient's general practitioner and hospital doctor (virological confirmation may exist, but is not necessary) • Clinical signs started less than 48 hours ago • Understanding and acceptance of the trial • Written agreement to participate **Exclusion criteria:** • Pregnancy • Breastfeeding • Inability to comply with protocol • Lack of written agreement **Planned sample size:** 178 participants
Interventions	**Intervention group:** • Mouthrinse with antiviral (beta-cyclodextrin and Citrox), 3 times daily for 7 days **Comparator group:** • Mouthrinse without antiviral, 3 times daily for 7 days **Use of additional interventions in both groups:** not reported
Outcomes	**Primary outcomes:** • Change from baseline amount of SARS-CoV-2 virus in salivary samples; time frame: 7 days **Secondary outcomes:** • Change from baseline amount of SARS-CoV-2 virus in nasal samples; time frame: 7 days

BBCovid (NCT04352959) *(Continued)*

Starting date	April 2020
Contact information	Carrouel Florence, Associate Professor, Claude Bernard University (no contact information reported)
Notes	Estimated completion date: June 2020 Trial registered in France

ChiCTR2000030539

Study name	'Study for the effect of 3% hydrogen peroxide gargle on the intraoral novel coronavirus of the patients with novel coronavirus pneumonia (COVID-19)'
Methods	Unclear Described as a "case control study" but register indicates this may be a non-randomised comparative study
Participants	Individuals with coronavirus pneumonia **Inclusion criteria:** • Pharyngeal swab identifying nucleic acid of the novel coronavirus, or high sequence homology to the novel coronavirus • Aged between 18 and 85 years of age • Able to consent to participation **Exclusion criteria:** • Participants who cannot co-operate with the study • Individuals judged by the researchers to be unsuitable for the study **Planned sample size:** 40 participants
Interventions	**Intervention group:** • 3% hydrogen peroxide gargle (no further details provided) **Comparator group:** • No intervention **Use of additional interventions in both groups:** not reported
Outcomes	**Primary outcome:** • Novel coronavirus nucleic acid **Secondary outcome:** none reported
Starting date	March 2020
Contact information	Fan Zhong Email: gz8hzf@126.com
Notes	Trial registered in China

ChiCTR2000030539 *(Continued)*	Estimated completion date: not reported

ELVIS-COVID-19 (NCT04382131)

Study name	'Hypertonic saline nasal irrigation and gargling in suspected or confirmed COVID-19 (ELVIS COVID-19)'
Methods	Open-label, parallel-group, 2-arm RCT

Participants	Participants with clinically suspected or confirmed COVID-19 being managed at home
	
	Inclusion criteria:
	
	• Adults (≥ 18 years) living in Scotland
	• Self-isolating at home within 48 hours of the start of the illness with:
	  * clinical symptoms suggestive of COVID-19 (i.e. those who have at least one of the following symptoms: recent onset of (i) new continuous cough and/or (ii) high temperature); OR
	  * virologically confirmed SARS-CoV-2 infection and clinical symptoms indicative of COVID-19 (as detailed above).
	
	Exclusion criteria:
	
	• Onset of illness > 48 hours
	• Inability to consent
	• Pregnancy
	• Immunosuppression
	• Inability to perform nasal irrigation
	• Those taking part in another interventional medical trial
	• Those without access to a supply of salt
	• Those who have had a negative COVID-19 swab result for the present symptoms
	• Those with suspected/confirmed COVID-19 in whom hospital admission is recommended
	• Those who do not have access to email/internet
	• Those living in a household with another person currently participating in this study
	
	Planned sample size: 405 participants

Interventions	**Intervention group:** • Hypertonic saline nasal irrigation and gargling with sodium chloride solution prepared by participants at home using water and salt. Used up to 12 times daily for a maximum of 14 days, or until feeling well. **Comparator group:** • No intervention **Use of additional interventions in both groups:** none reported
Outcomes	**Primary outcome:** • Time to resolution of symptoms; time frame: 14 days **Secondary outcomes:** • Severity of all symptoms; time frame: 14 days, or until feeling well • Length of time for individual symptoms to resolve; time frame: 14 days, or until feeling well • Severity of all individual symptoms; time frame: 14 days, or until feeling well

ELVIS-COVID-19 (NCT04382131) *(Continued)*

- Contact with healthcare providers (NHS 24, GP, out-of-hours care); time frame: 14 days, or until feeling well
- Need for GP appointments; time frame: 14 days, or until feeling well
- Participants attending hospital; time frame: 14 days, or until feeling well
- Length of stay in hospital; time frame: 14 days, or until feeling well
- Over-the-counter medication use; time frame: 14 days, or until feeling well
- Reduction in transmission to household contacts; time frame: 14 days, or until feeling well
- Number of participants reporting side effects of the intervention; time frame: 14 days, or until feeling well
- Types and severity of side effects reported; time frame: 14 days, or until feeling well
- Cost of over the counter medicine used; time frame: 14 days, or until feeling well

Starting date	May 2020
Contact information	Aziz Sheikh Email: aziz.sheikh@ed.ac.uk Emma Ward Email: ELVIS-COVID19@ed.ac.uk
Notes	Trial registered in UK Estimated completion date: July 2020

GARGLESa (NCT04341688)

Study name	'A quadruple blind, randomized controlled pilot trial of gargling agents in reducing intraoral viral load among laboratory confirmed COVID-19 patients: GARGLES STUDY'
Methods	Parallel-group, quadruple-blind, 6-arm study
Participants	Hospitalised individuals with COVID-19 **Inclusion criteria:** • 18 to 70 years old • Laboratory-confirmed COVID-19-positive • Admitted to hospital **Exclusion criteria:** • Edentulous patients (having no teeth) • Low Glasgow Coma Score • Intubated • Immunocompromised • History of radiotherapy or chemotherapy • Known pre-existing chronic mucosal lesions, such as lichen planus **Planned sample size:** 50 participants
Interventions	**Intervention group A:** • 0.2% povidone iodine gargle and nasal lavage 3 times daily for 6 days **Intervention group B:**

GARGLESa (NCT04341688) *(Continued)*

	• 1% hydrogen peroxide gargle and nasal lavage 3 times daily for 6 days **Intervention group C:** • Neem extract solution (*Azadirachta indica*) gargle and nasal lavage 3 times daily for 6 days **Intervention group D:** • 2% hypertonic saline gargle and nasal lavage 3 times daily for 6 days **Intervention group E:** • Distilled water gargle and nasal lavage 3 times daily for 6 days **Comparator:** • No intervention **Use of additional interventions in all treatment groups:** none reported
Outcomes	**Primary outcome:** • Intraoral viral load; time frame: day 5 **Secondary outcome:** • Salivary cytokine profile; time frame: day 5
Starting date	Estimated July 2020
Contact information	Farhan R Khan Email: farhan.raza@aku.edu
Notes	Estimated completion date: March 2021 Trial registered in Pakistan

GARGLESb (NCT04410159)

Study name	'Povidone-iodine vs essential oil vs tap water gargling for COVID-19 patients (GARGLES)'
Methods	Open-label, 4-arm, parallel-group RCT
Participants	Adults with recent onset COVID-19 **Inclusion criteria:** • Adults aged 18 years and above • Able to understand instructions • Stage 1 COVID-19 • < 5 days of illness or diagnosis **Exclusion criteria:** • Under 18 years old • Unable to understand instructions • Stage 2 and 3 COVID-19 • Respiratory symptoms or fever on admission • Abnormal chest radiograph or computed tomography (CT) findings on admission

GARGLESb (NCT04410159) *(Continued)*

	Planned sample size: 20 participants
Interventions	**Intervention group A:** • 10 mL povidone iodine gargle 3 times daily for 7 days **Intervention group B:** • 20 mL essential oils gargle (Listerine) 3 times daily for days **Intervention group C:** • Tap water gargle 3 times daily for 7 days **Comparator:** • No intervention **Use of additional interventions in all treatment groups:** none reported
Outcomes	**Primary outcome:** • Early viral clearance; time frame: 6 days **Secondary outcomes:** • Late viral clearance; time frame: 6 weeks • Symptom progression; time frame: 8 weeks • Disease progression (monitored by clinical data); time frame: 10 weeks • Disease progression (monitored by laboratory data); time frame: 12 weeks
Starting date	June 15 2020
Contact information	Nurul A Mohamed Email: drnurul@usim.edu.my Wan Shahida Wan Sulaiman Email: wanshahida@usim.edu.my
Notes	Discrepancy in trial register over intervention group C. Background information for trial states that this group will receive hydrogen peroxide gargle, but table of interventions indicates that this will be a tap water intervention. Study registered in Malaysia. Estimated completion date: 15 August 2020

KILLER (NCT04371965)

Study name	'Povidone iodine mouthwash, gargle, and nasal spray to reduce naso-pharyngeal viral load in patients with SARS-CoV-2 (KILLER)'
Methods	Open-label, parallel-group, randomised controlled trial
Participants	Individuals with positive nasopharyngeal SARS-CoV-2 carriage **Inclusion criteria:** • Adults aged over 18 of both sexes

KILLER (NCT04371965) *(Continued)*

	• Positive SARS-CoV-2 carriage by RT-PCR • Written consent **Exclusion criteria:** • Patients with low viral load (threshold cycle > 25 per RT-PCR) • Unable to perform oro-nasopharyngeal decolonisation • Known hypersensitivity to one of the constituents, particularly to povidone iodine • History of dysthyroidism • Known coagulopathy • Participating in another clinical trial aimed at reducing viral load in patients with SARS-CoV-2 • Pregnant or breastfeeding, or women of childbearing age without effective contraception • Not covered by a social security scheme • Patients with enhanced protection **Planned sample size:** 24 participants
Interventions	**Intervention group:** • 1% povidone iodine mouthwash, gargle and nasal spray and 10% nasal gel, 4 times per day for 5 days **Comparator group:** • No intervention **Use of additional intervention in both groups:** none reported
Outcomes	**Primary outcome:** • Change from baseline nasopharyngeal viral load; time frame: 7 days **Secondary outcomes:** • Time from inclusion to negative nasopharyngeal carriage of SARS-CoV-2; time frame: day 0, 1, 3, 5 and 7 • Time from inclusion to negative nasopharyngeal cell culture of SARS-CoV-2; time frame: day 0, 1, 3, 5 and 7 • Thyroid tests; time frame: day 0 and 7 • Patient satisfaction, using a numerical scale graded from 0 (no discomfort) to 10 (maximum possible discomfort); time frame: 7 days • Daily presence of clinical signs of COVID-19; time frame: day 0, 1, 3, 5 and 7 • Need for ward or intensive care hospitalisation; time frame: day 0, 1, 3, 5 and 7
Starting date	Estimated July 2020.
Contact information	Professor Olivier Mimoz olivier.mimoz@chu-poitiers.fr Sabrina Seguin sabrina.seguin@chu-poitiers.fr
Notes	Estimated completion date: August 2020

KONS-COVID-19 (NCT04357990)

Study name	'Kerecis oral and nasal spray for treating the symptoms of COVID-19 (KONS-COVID-19)'
Methods	3-arm, triple-blinded, parallel-group randomised controlled trial
Participants	Individuals positive for SARS-CoV-2 infection with symptoms of upper respiratory infection **Inclusion criteria:** • 18 years of age or older • Positive for SARS-CoV-2 infection • Symptoms of upper respiratory infection • Willing to participate in the trial, and gives consent • Not pregnant or trying to conceive **Exclusion criteria:** • Under 18 years of age • Negative for SARS-CoV-2 infection • Severe symptoms of infection • Symptoms involving the entire respiratory system, including pneumonia • Requires hospitalisation prior to study start • Asymptomatic • Pregnant, or trying to conceive • Other co-morbidities that would prevent administration of the device • Requirement to take regular medications administered by inhalation, or via the naso- and oropharyngeal route • Patients with known allergies to neem or hypericum oil • Patients with asthma **Planned sample size:** 81 participants
Interventions	**Intervention group A:** • Kerecis oral and nasal spray ('Omega3 Viruxide' containing neem oil and St. John's Wort) administered to the oral and nasal passages 3 times daily **Intervention group B:** • Kerecis oral and nasal spray ('Omega3 Viruxide' containing neem oil and St. John's Wort) administered to the oral passages only 3 times daily **Comparator group:** • Placebo (saline) spray, administered to the oral and nasal passages, 3 times daily **Use of additional interventions in both groups:** not reported
Outcomes	**Primary outcomes:** • Number of days until complete resolution of symptoms; time frame: 28 days • Need for hospital admission; time frame: 28 days **Secondary outcomes:** • Number of days until a reduction in symptoms; time frame: 28 days • Adverse events; time frame: 28 days
Starting date	May 2020

KONS-COVID-19 (NCT04357990) *(Continued)*

Contact information	Ragnar Freyr Ingvarsson Email: ragnari@landspitali.is
Notes	Estimated completion July 2020 Trial registered in Iceland

NCT04344236

Study name	'A phase II, randomized, open-label, single-institution study of the effects of povidone iodine oral gargles and nasal rinses on viral load in patients with COVID-19'
Methods	Open-label, parallel-group, 4-arm randomised controlled trial
Participants	Individuals diagnosed with COVID-19 **Inclusion criteria:** • Positive test for COVID-19 • Aged 18 to 79 years • Willing and able to perform oral gargles and nasal rinses 4 times per day **Exclusion criteria:** • Requiring mechanical ventilation • Unable or unwilling to perform oral gargles and nasal rinses 4 times per day • History of chronic upper respiratory tract disease • Known iodine allergy • History of thyroid disease **Planned sample size:** 48 participants
Interventions	**Intervention group A:** • Saline oral gargle and nasal rinse 4 times a day for 7 days **Intervention group B:** • 0.5% povidone iodine oral gargle and nasal rinse 4 times daily for 7 days **Intervention group C:** • 0.12% chlorhexidine oral gargle and nasal rinse 4 times daily for 7 days **Comparator group:** • No intervention **Use of additional interventions in all groups:** none reported
Outcomes	**Primary outcome:** • Viral load (and/or cycle time to PCR as a proxy for quantitative viral load) in the nasopharynx and oropharynx; time frame: 7 days **Secondary outcomes:** • Oxygen requirement of the patient; time frame: 7 days

NCT04344236 *(Continued)*

	• Oxygen saturation of the patient; time frame: 7 days
Starting date	April 2020
Contact information	Scott Rickert Email: scott.rickert@nyulangone.org Lindsey Moses Email: lindsey.moses@nyulangone.org
Notes	Estimated completion: May 2020 Trial registered in USA

NCT04347538

Study name	'Impact of nasal saline irrigations on viral load in patients with COVID-19'
Methods	3-arm, open-label, parallel-group RCT
Participants	Individuals diagnosed with COVID-19 **Inclusion criteria:** • Patients testing positive for COVID-19 at Vanderbilt University Medical Center or VUMC-associated testing centres • 18 years or over • Planning self-quarantine after infection in the greater Nashville area within a 30-mile radius of Vanderbilt University Medical Center **Exclusion criteria:** • Requiring hospitalisation (only outpatient COVID-19 cases are eligible) • Current use of nasal saline irrigations or other intranasal medications • Inability to perform saline irrigations/nasal swabs in separate bathroom away from household contacts **Planned sample size:** 90 participants
Interventions	**Intervention group A:** • Normal saline nasal irrigation, twice daily (duration of intervention not stated) **Intervention group B:** • Normal saline with 1/2 a teaspoon of baby shampoo nasal irrigation, twice daily (duration of intervention not stated) **Comparator group:** • No intervention **Use of additional interventions in all groups:** none reported
Outcomes	**Primary outcomes:** • Change in SARS-CoV-2 mucosal immune response in the nasopharynx; time frame: 21 days (viral RNA will be extracted using a standard Qiagen viral RNA isolation kit. An established, high-

NCT04347538 *(Continued)*

	throughput CoV genome sequencing pipeline will be used to perform overlapping long-range RT-PCR across the viral genome for each viral genome proposed in this project) • Change in microbial load in the nasopharynx; time frame: 21 days • Change in viral load in the nasopharynx over the course of COVID-19 infection; time frame: 21 days (qPCR analysis to asses viral copy number) **Secondary outcomes:** • Symptom assessment; time frame: 21 days • Temperature assessment; time frame: 21 days
Starting date	May 2020
Contact information	Kate Von Wahlde Email: kate.vonwahlde@vumc.org
Notes	Estimated completion: June 2022 Trial registered in USA

NCT04347954

Study name	'Effect of PVP-I nasal sprays vs normal saline nasal sprays on SARS-CoV-2 nasopharyngeal titers'
Methods	Parallel-group, double-blind randomised controlled trial
Participants	Individuals with positive test for COVID-19, aged 18 years or over **Inclusion criteria:** • Positive test for COVID-19 within 2 days of enrollment **Exclusion criteria:** • Allergy to iodine or shellfish • Receiving intranasal steroids **Planned sample size:** 45 participants
Interventions	**Intervention group A:** • 2% povidone iodine nasal spray, 2 sprays to each nostril, 4 times daily for 7 days **Intervention group B:** • 0.5% povidone iodine nasal spray, 2 sprays to each nostril, 4 times daily for 7 days **Comparator group:** • 0.9% isotonic saline, 2 sprays to each nostril, 4 times daily for 7 days **Use of additional interventions in both groups:** none reported
Outcomes	**Primary outcome:** • Mean change in viral titres of SARS-CoV-2; time frame: day 3, 6 and 9 **Secondary outcomes:**

NCT04347954 *(Continued)*

- Adverse events; time frame: up to 9 days. These include:
  - nasal burning/pain;
  - headaches;
  - ear pain;
  - sneezing;
  - nose bleeds.
- Frequency of symptoms related to SARS-CoV-2; time frame: up to 9 days. These include:
  - fever;
  - fatigue;
  - change in smell;
  - change in taste;
  - nasal obstruction.

Starting date	May 2020
Contact information	Neelaysh Vukkadala Email: nvukkada@stanford.edu
Notes	Estimated completion August 2020 Trial registered in the USA

NCT04382040

Study name	'A phase II, controlled clinical study designed to evaluate the effect of ArtemiC in patients diagnosed with COVID-19'
Methods	2-arm, parallel-group RCT
Participants	Adult patients with COVID-19 **Inclusion criteria:** • Confirmed SARS-CoV-2 infection • Hospitalised COVID-19 patient in stable moderate condition (i.e. not requiring ICU admission) • Under observation or admitted to a controlled facility or hospital (home quarantine is not sufficient) **Exclusion criteria:** • Tube feeding or parenteral nutrition • Patients who are symptomatic and require oxygen (Ordinal Scale for Clinical Improvement score > 3) at the time of screening • Respiratory decompensation requiring mechanical ventilation • Uncontrolled diabetes type 2 • Autoimmune disease • Pregnant or lactating women • Any condition which, in the opinion of the Principal Investigator, would prevent full participation in this trial or would interfere with the evaluation of the trial endpoints **Planned sample size:** 50 participants
Interventions	**Intervention group A:** • ArtemiC treatment, sprayed orally, twice daily for 2 days

NCT04382040 *(Continued)*

	Comparator group: • Placebo, sprayed orally, twice daily for 2 days **Use of additional interventions in both groups:** none reported
Outcomes	**Primary outcomes:** • Time to clinical improvement (national Early Warning Score 2 of less than or equal to 2 maintained for 24 hours); time frame: 24 hours • Definite or probable drug-related adverse events; time frame: 14 days **Secondary outcomes:** • Time to negative COVID-19 PCR; time frame: 14 days • Proportion of participants with normalisation of fever and oxygen saturation; time frame: 14 days • COVID-19 related survival; time frame: 14 days • Incidence and duration of mechanical ventilation; time frame: 14 days • Incidence of intensive care stay; time frame: 14 days • Duration of intensive care stay; time frame: 14 days • Duration of time on supplemental oxygen; time frame: 14 days
Starting date	2020 May 8
Contact information	Nadia Lisovoder Email: nadyal@galilee-cbr.com
Notes	Register states that "ArtemiC is a medical spray comprised of Artemisinin (6 mg/ml), Curcumin (20 mg/ml), Frankincense (Boswellia) (15 mg/ml) and vitamin C (60 mg/ml) in micellar formulation for spray administration." It is unclear whether this is intended as an antimicrobial oral wash. Trial registered in Israel Estimated completion data: 31 July 2020

NOCOVID (NCT04337918)

Study name	'Multi-center, randomized, controlled, phase II clinical efficacy study evaluating nitric oxide releasing solution treatment for the prevention and treatment of COVID-19 in healthcare workers and individuals at risk of infection'
Methods	Multicentre, parallel-group, single-blind randomised controlled trial
Participants	Healthcare workers and individuals at risk of infection with COVID-19, who are found to be positive for COVID-19 during screening **Inclusion criteria:** • Capacity to consent to participation • 19 years of age or older • English speaking • Willing to use adequate contraception for the duration of the trial • Positive COVID-19 test of presentation of clinical symptoms defined as fatigue with either fever [> 37.2°C] and/or a persistent cough **Exclusion criteria:**

NOCOVID (NCT04337918) *(Continued)*

	• Prior tracheostomy • Concomitant treatment of respiratory support (involving any form of oxygen therapy) • Any clinical contraindications, as judged by the attending physician • Pregnancy • Mentally or neurologically disabled participants who are not considered fit to consent to the study • Currently hospitalised for symptoms of COVID-19 **Planned sample size:** 10 participants
Interventions	**Intervention group:** • Daily self-administration of nitric oxide gargle every morning, nitric oxide nasopharyngeal irrigation every evening and nitric oxide nasal spray up to 5 times per day, for 14 days **Comparator group:** • No intervention **Use of additional interventions in both groups:** • Not reported

Outcomes	**Primary outcome:**
	
	• Measure the efficacy of nitric oxide releasing solution at reducing the progression of COVID-19; time frame: 21 days. Progression will be assessed by the following:
	  * need for hospitalisation for COVID-19/flu-like symptoms;
	  * requirement for oxygen therapy, BIPAP/CPAP, intubation and mechanical ventilation.
	
	Secondary outcomes:
	
	• Number of days to negative viral RT-PCR from nasopharyngeal swabs; time frame: 21 days
	• Time to clinical recovery (defined as discharge from hospital for those admitted, or normalisation of fever and respiratory rate); time frame: 21 days
	• Reduction in clinical symptoms of COVID-19 using the Modified Jackson Cold Score Diary; time frame: 21 days
	• Rate of positive sero-conversion for SARS-CoV-2; time frame: 21 days

Starting date	May 2020
Contact information	Chris Miller Email: chris@sanotize.com
Notes	This trial is a subsidiary trial of the use of nitric oxide releasing solutions for treatment of individuals with COVID-19. The main part of this study considers the use of nitric oxide releasing solution for prevention of infection in healthcare workers. Individuals who are screened for the prevention study but are found to be positive when tested for COVID-19 will be offered enrolment to the treatment trial. Trial registered in USA Estimated completion date: September 2020

PICO (ISRCTN13447477)

Study name	'A pilot study of the ability of povidone-iodine (PVP-I) 0.5% aqueous solution oral/nasal spray and mouthwash to kill the SARS-CoV-2 virus in people with COVID-19'

PICO (ISRCTN13447477) *(Continued)*

Methods	Non-randomised intervention study
Participants	Individuals who are hospitalised with COVID-19 **Inclusion criteria:** • Aged ≥ 18 years and ≤ 75 years • Confirmed COVID-19 symptoms and symptom onset within the past 10 days • Recently hospitalised with COVID-19 disease (within last 3 to 4 days) • COVID-19 disease proven by PCR testing for SARS-CoV-2 within the last 4 days • Capable of using a nasal spray device and the mouthwash required by the trial • Capacity and capability to give informed consent to take part in the trial **Exclusion criteria:** • Known sensitivity to PVP-I aqueous antiseptic solution or any of its listed excipients • Previously diagnosed thyroid disease • Chronic renal failure (stage ≥ 3 by eGFR MDRD) • Acute renal failure (KDIGO ≥ stage 2: creatinine ≥ 2x baseline) • Known pregnancy or currently breastfeeding • Current requirement for invasive or non-invasive ventilation or planned within next 6 hours • Undergoing or soon to undergo radioiodine treatment • Known dermatitis herpetiformis (Duhring's disease) • Current participation in research that is designed to, or is expected to, alter the COVID-19 disease course or viral load • Inability to communicate in English or read English **Planned sample size:** 25 participants
Interventions	**Intervention group:** • Use of a spray or mouthwash/gargle of 0.5% aqueous povidone iodine for 1 minute **Comparator group:** • The authors state that this will be a single-arm trial. However, the registration also reports that 5 of 25 participants will undergo mouthwash/gargling with water as a control. **Use of additional interventions in both groups:** • Not reported
Outcomes	**Primary outcome:** • Cultures of SARS-CoV-2 and quantitative PCR results of viral RNA in saliva and nasal samples at baseline and 5 further time points, up to 2 hours after administration **Secondary outcome:** • Salivary viral loads at baseline, 5 and 20 minutes
Starting date	15 March 2020
Contact information	Dr Justin Kirk-Bayley Email: pico@spacer.org.uk
Notes	Trial registered in the UK

PICO (ISRCTN13447477) *(Continued)*

	Estimated completion date: July 2020

SINUS WASH (NCT04393792)

Study name	'SINUS WASH pilot study in adults testing positive for COVID-19'
Methods	Open-label, parallel-group RCT
Participants	Healthcare staff and patients who have tested positive for COVID-19, and their household co-residents **Inclusion criteria:** • Healthcare worker OR patient on a general ward who has had a positive COVID-19 test OR a person who is co-residing with an affected staff member or patient who is now at home in self-isolation • Capable of giving informed consent • Able to self-administer the sinus rinses and mouthwashes • Able to have healthcare professional-led swabs OR self-administer the oral and nasopharyngeal swabs • Aged 18 years and over **Exclusion criteria:** • Not capable of giving informed consent • Unable to self-administer the sinus rinses and mouthwashes • Unable to have healthcare professional-led swabs OR self-administer the oral, nasal and/OR nasopharyngeal swabs • Unable to send swabs to the study team via the approved methods described in participant information leaflet and protocol • Under 18 years of age • Known hypersensitivity to iodine • At risk of aspiration due to an unsafe swallow • Hyperthyroidism or other manifest thyroid diseases • Herpetiform dermatitis (Duhring's disease) • Planned or undergoing radioiodine treatment • Pregnancy or breastfeeding
Interventions	**Intervention group:** • Povidone iodine 0.23% sinus rinse and mouthwash 3 times daily for 3 days **Comparator group:** • Normal saline sinus rinse and mouthwash 3 times daily for 3 days **Use of additional interventions in both groups:** • None reported
Outcomes	**Primary outcome:** • Change in viral load in the oral and nasopharyngeal cavity, as measured by real time PCR; time frame: to day 14 **Secondary outcome:** • Symptom severity in primary participants and co-residents; time frame: to day 14

SINUS WASH (NCT04393792) *(Continued)*

Starting date	May 2020
Contact information	Afroze Khan Email: Afroze.Khan@nhs.net Matthew Dryden Email: matthew.dryden@hhft.nhs.uk
Notes	Trial registered in the UK Estimated study completion: August 2020

BIPAP bilevel positive airway pressure; COVID-19 Coronavirus Disease 2019; CPAP continuous positive airway pressure; PVP-I povidone iodine; RT-PCR reverse transcriptase polymerase chain reaction; RCT: randomised controlled trial; SARS-CoV-2 Severe Acute Respiratory Syndrome-Coronavirus-2

APPENDICES

Appendix 1. Search strategies

CENTRAL	Ovid MEDLINE	Ovid Embase
1 ("2019 nCoV" or 2019nCoV or "COVID 19" or COVID19 or "new coronavirus" or "novel coronavirus" or "novel corona virus" or "SARS CoV-2" or "2019- novel CoV" or ncov19 or ncov-19) AND CENTRAL:TARGET 2 (Wuhan and (coronavirus or "corona virus")) AND CENTRAL:TARGET 3 ((coronavirus near3 2019) or ("corona virus" near3 2019)) AND CENTRAL:TARGET 4 ((wuhan near2 disease) or (wuhan near2 virus)) AND CENTRAL:TARGET 5 ("LAMP assay" or "COVID-19" or "COVID-19 drug treatment" or "COVID-19 diagnostic testing" or "COVID-19 serotherapy" or "COVID-19 vaccine" or "severe acute respiratory syndrome coronavirus 2" or "spike glycoprotein, COVID-19 virus") AND CENTRAL:TARGET 6 #1 OR #2 OR #3 OR #4 OR #5 7 MESH DESCRIPTOR Mouthwashes EXPLODE ALL AND CENTRAL:TARGET 8 MESH DESCRIPTOR Nasal Sprays EXPLODE ALL AND CENTRAL:TARGET 9 MESH DESCRIPTOR Nasal Lavage EXPLODE ALL AND CENTRAL:TARGET	1 ("2019 nCoV" or 2019nCoV or "COVID 19" or COVID19 or "new coronavirus" or "novel coronavirus" or "novel corona virus" or "SARS CoV-2" or "2019- novel CoV" or ncov19 or ncov-19).ab,ti. 2 (Wuhan and (coronavirus or "corona virus")).ab,ti. 3 ((coronavirus or "corona virus") adj3 "2019").ab,ti. 4 (wuhan adj2 (disease or virus)).ab,ti. 5 ("LAMP assay" or "COVID-19" or "COVID-19 drug treatment" or "COVID-19 diagnostic testing" or "COVID-19 serotherapy" or "COVID-19 vaccine" or "severe acute respiratory syndrome coronavirus 2" or "spike glycoprotein, COVID-19 virus").os. 6 1 or 2 or 3 or 4 or 5 7 exp Animals/ 8 exp Humans/ 9 7 not 8 10 (editorial or comment or letter or newspaper article).pt. 11 9 or 10 12 6 not 11 13 exp Mouthwashes/ 14 exp Nasal Sprays/	1. ("2019 nCoV" or 2019nCoV or "COVID 19" or COVID19 or "new coronavirus" or "novel coronavirus" or "novel corona virus" or "SARS CoV-2" or "2019- novel CoV" or ncov19 or ncov-19).ab,ti. 2. (Wuhan and (coronavirus or "corona virus")).ab,ti. 3. ((coronavirus or "corona virus") adj3 "2019").ab,ti. 4. (wuhan adj2 (disease or virus)).ab,ti. 5. ("LAMP assay" or "COVID-19" or "COVID-19 drug treatment" or "COVID-19 diagnostic testing" or "COVID-19 serotherapy" or "COVID-19 vaccine" or "severe acute respiratory syndrome coronavirus 2" or "spike glycoprotein, COVID-19 virus").ti,ab.

(Continued)

10 (mouthwash* or gargl* or mouthrins*) AND CENTRAL:TARGET

11 (oral near3 (spray* or douch* or irrigat* or lavag* or wash or rins* or decontaminat* or aerosol or mist or clean*)) AND CENTRAL:TARGET

12 (mouth near3 (spray* or douch* or irrigat* or lavag* or wash or rins* or decontaminat* or aerosol or mist or clean*)) AND CENTRAL:TARGET

13 (nasal near3 (spray* or douch* or irrigat* or lavag* or wash or rins* or decontaminat* or aerosol or mist or clean*)) AND CENTRAL:TARGET

14 (nose near3 (spray* or douch* or irrigat* or lavag* or wash or rins* or decontaminat* or aerosol or mist or clean*)) AND CENTRAL:TARGET

15 (nasopharyngeal near3 (spray* or douch* or irrigat* or lavag* or wash or rins* or decontaminat* or aerosol or mist or clean*)) AND CENTRAL:TARGET

16 (larynx* near3 (spray* or douch* or irrigat* or lavag* or wash or rins* or decontaminat* or aerosol or mist or clean*)) AND CENTRAL:TARGET

17 (pharynx* near3 (spray* or douch* or irrigat* or lavag* or wash or rins* or decontaminat* or aerosol or mist or clean*)) AND CENTRAL:TARGET

18 (intranasal near3 (spray* or douch* or irrigat* or lavag* or wash or rins* or decontaminat* or aerosol or mist or clean*)) AND CENTRAL:TARGET

19 MESH DESCRIPTOR Chlorhexidine EXPLODE ALL AND CENTRAL:TARGET

20 MESH DESCRIPTOR Povidone-Iodine EXPLODE ALL AND CENTRAL:TARGET

21 MESH DESCRIPTOR Cetylpyridinium EXPLODE ALL AND CENTRAL:TARGET

22 MESH DESCRIPTOR Hexetidine EXPLODE ALL AND CENTRAL:TARGET

23 MESH DESCRIPTOR Anti-Infective Agents, Local EXPLODE ALL AND CENTRAL:TARGET

24 MESH DESCRIPTOR Hydrogen Peroxide EXPLODE ALL AND CENTRAL:TARGET

25 MESH DESCRIPTOR Carbamide Peroxide EXPLODE ALL AND CENTRAL:TARGET

15 exp Nasal Lavage/

16 (mouthwash* or gargl* or mouthrins*).ab,ti.

17 ((oral or mouth or nasal or nose or nasopharyngeal or larynx* or pharynx* or intranasal) adj3 (spray* or douch* or irrigat* or lavag* or wash or rins* or decontaminat* or aerosol or mist or clean*)).ab,ti.

18 exp Chlorhexidine/

19 exp Povidone-Iodine/

20 exp Cetylpyridinium/

21 exp Hexetidine/

22 exp Anti-Infective Agents, Local/

23 exp Hydrogen Peroxide/

24 exp Carbamide Peroxide/

25 exp Triclosan/

26 exp Oils, volatile/

27 exp Plant oils/

28 Menthol/

29 Lavandula/

30 Thymus plant/

31 Mentha piperita/

32 Eugenol/

33 Cinnamomum verum/

34 Muramidase/

35 Lactoferrin/

36 Glucose oxidase/

37 Lactoperoxidase/

38 (povidone or chlorhexidine or CHX or PVP or Polyvinylpyrrolidone or Betadine* or Providine* or Disadine* or Isodine* or Pharmadine* or Alphadine* or Betaisodona or Tubulicid or Novalsan or Sebidin or MK-412A or MK412A).ab,ti.

39 (Chlorhexamed or Corsodyl or Curasept or Dyna-Hex or Eludril or Gibitan or Hexidine or Hibiclens or Hibident or Hibiscrub or Hibisol or Hibitane or Peridex or avagard).ab,ti.

40 (Hexadecylpyridinium or Cetylpyridium or Biosept or Ceepryn or Cetamium or Catamium or Sterogenol or Dobendan or Merocets or Pristacin or Pyrisept or Angifonil or Cetylyre).ab,ti.

6. or/1-5

7. mouthwash/

8. nose spray/

9. nasal lavage/

10. (mouthwash* or gargl* or mouthrins*).ab,ti.

11. ((oral or mouth or nasal or nose or nasopharyngeal or larynx* or pharynx* or intranasal) adj3 (spray* or douch* or irrigat* or lavag* or wash or rins* or decontaminat* or aerosol or mist or clean*)).ab,ti.

12. chlorhexidine/

13. povidone iodine/

14. cetylpyridinium salt/

15. hexetidine/

16. exp topical antiinfective agent/

17. hydrogen peroxide/

18. carbamide peroxide/

19. triclosan/

20. essential oil/

21. menthol/

22. lavender/

23. thymus extract/

24. Mentha piperita/

25. eugenol/

26. Cinnamomum zeylanicum/

27. lysozyme/

28. lactoferrin/

29. Glucose oxidase/

30. Lactoperoxidase/

(Continued)

26 MESH DESCRIPTOR Triclosan EXPLODE ALL AND CENTRAL:TARGET

27 MESH DESCRIPTOR Oils, Volatile EXPLODE ALL AND CENTRAL:TARGET

28 MESH DESCRIPTOR Plant Oils EXPLODE ALL AND CENTRAL:TARGET

29 MESH DESCRIPTOR Menthol AND CENTRAL:TARGET

30 MESH DESCRIPTOR Lavandula AND CENTRAL:TARGET

31 MESH DESCRIPTOR Thymus Plant AND CENTRAL:TARGET

32 MESH DESCRIPTOR Mentha piperita AND CENTRAL:TARGET

33 MESH DESCRIPTOR Cinnamomum zeylanicum AND CENTRAL:TARGET

34 MESH DESCRIPTOR Muramidase AND CENTRAL:TARGET

35 MESH DESCRIPTOR Lactoferrin AND CENTRAL:TARGET

36 MESH DESCRIPTOR Glucose Oxidase AND CENTRAL:TARGET

37 MESH DESCRIPTOR Lactoperoxidase AND CENTRAL:TARGET

38 (povidone or chlorhexidine or CHX or PVP or Polyvinylpyrrolidone or Betadine* or Providine* or Disadine* or Isodine* or Pharmadine* or Alphadine* or Betaisodona or Tubulicid or Novalsan or Sebidin or MK-412A or MK412A) AND CENTRAL:TARGET

39 (Chlorhexamed or Corsodyl or Curasept or Dyna-Hex or Eludril or Gibitan or Hexidine or Hibiclens or Hibident or Hibiscrub or Hibisol or Hibitane or Peridex or avagard) AND CENTRAL:TARGET

40 (Hexadecylpyridinium or Cetylpyridium or Biosept or Ceepryn or Cetamium or Catamium or Sterogenol or Dobendan or Merocets or Pristacin or Pyrisept or Angifonil or Cetylyre) AND CENTRAL:TARGET

41 (Vagi-Hex or Vagi Hex or VagiHex or Oraldene or Hexigel or Steri-sol or Steri sol or Hextril or Oraldine or Oralspray or Hexoral or Bactidol or Elsix or Duranil or Doreperol or Hexetidine) AND CENTRAL:TARGET

42 (Hydrogen Peroxide or H2O2 or Hydroperoxide or Superoxol or Oxydol or Perhydrol or Urea Peroxide or Perhydrol Urea) AND CENTRAL:TARGET

41 (Vagi-Hex or Vagi Hex or VagiHex or Oraldene or Hexigel or Steri-sol or Steri sol or Hextril or Oraldine or Oralspray or Hexoral or Bactidol or Elsix or Duranil or Doreperol or Hexetidine).ab,ti.

42 (Hydrogen Peroxide or H2O2 or Hydroperoxide or Superoxol or Oxydol or Perhydrol or Urea Peroxide or Perhydrol Urea).ab,ti.

43 (Methyl salicylate or methylsalicylate or Rheumabal or Metsal Liniment or Hewedolor or Linsal).ab,ti.

44 (Tricolsan or Hydroxydiphenyl or trichlorodiphenyl or Clearasil or Cliniclean or Irgasan or Trisan or Oxy Skin Wash or pHisoHex or Sapoderm or Tersaseptic or Aquasept or Ster-Zac or Manusept or Microshield).ab,ti.

45 ((Spray* or douch* or irrigat* or rins* or wash* or lavag* or intranasal* or topical) adj3 (antimicrobial or anti-microbial or disinfect* or antisept* or anti- infect*)).ab,ti.

46 ("essential oil$" or "plant oil$" or menthol or menthyl or (mint adj2 oil$) or lavender or thyme or peppermint or "mentha piperita" or eugenol o eucalyptus or "blue gum$" or cajeput or clove or cinnamon).ab,ti.

47 (muramidase or lysozyme$ or leftose or lactoferrin or lactotransferrin or "glucose oxidase" or lactoperoxidase or "saliva substitute").ab,ti.

48 (Listerine or Biotene).ab,ti.

49 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48

50 12 and 49

31. (povidone or chlorhexidine or CHX or PVP or Polyvinylpyrrolidone or Betadine* or Providine* or Disadine* or Isodine* or Pharmadine* or Alphadine* or Betaisodona or Tubulicid or Novalsan or Sebidin or MK-412A or MK412A).ab,ti.

32. (Chlorhexamed or Corsodyl or Curasept or Dyna-Hex or Eludril or Gibitan or Hexidine or Hibiclens or Hibident or Hibiscrub or Hibisol or Hibitane or Peridex or avagard).ab,ti.

33. (Hexadecylpyridinium or Cetylpyridium or Biosept or Ceepryn or Cetamium or Catamium or Sterogenol or Dobendan or Merocets or Pristacin or Pyrisept or Angifonil or Cetylyre).ab,ti.

34. (Vagi-Hex or Vagi Hex or VagiHex or Oraldene or Hexigel or Steri-sol or Steri sol or Hextril or Oraldine or Oralspray or Hexoral or Bactidol or Elsix or Duranil or Doreperol or Hexetidine).ab,ti.

35. (Hydrogen Peroxide or H2O2 or Hydroperoxide or Superoxol or Oxydol or Perhydrol or Urea Peroxide or Perhydrol Urea).ab,ti.

36. (Methyl salicylate or methylsalicylate or Rheumabal or Metsal Liniment or Hewedolor or Linsal).ab,ti.

37. ((spray* or douch* or irrigat* or rins* or wash* or lavag* or intranasal* or topical) adj3 (antimicrobial or anti-microbial or disin-

(Continued)

Peroxide or Perhydrol Urea) AND CENTRAL:TARGET 43 (Methyl salicylate or methylsalicylate or Rheumabal or Metsal Liniment or Hewedolor or Linsal) AND CENTRAL:TARGET 44 (Tricolsan or Hydroxydiphenyl or trichlorodiphenyl or Clearasil or Cliniclean or Irgasan or Trisan or Oxy Skin Wash or pHiso-Hex or Sapoderm or Tersaseptic or Aquasept or Ster-Zac or Manusept or Microshield) AND CENTRAL:TARGET 45 ((spray* or douch* or irrigat* or rins* or wash* or lavag* or intranasal* or topical) and (antimicrobial or anti-microbial or disinfect* or antisept* or anti-infect*)) AND CENTRAL:TARGET 46 ("essential oil*" or "plant oil*" or menthol or menthyl or (mint near2 oil*) or lavender or thyme or peppermint or "mentha piperita" or eugenol or eucalyptus or "blue gum*" or cajeput or clove or cinnamon) AND CENTRAL:TARGET 47 (muramidase or lysozyme* or leftose or lactoferrin or lactotransferrin or "glucose oxidase" or lactoperoxidase or "saliva substitute") AND CENTRAL:TARGET 48 (Listerine or Biotene) AND CENTRAL:TARGET 49 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 50 #49 AND #6		fect* or antisept* or anti- infect*)).ab,ti. 38. (Tricolsan or Hydroxydiphenyl or trichlorodiphenyl or Clearasil or Cliniclean or Irgasan or Trisan or Oxy Skin Wash or pHiso-Hex or Sapoderm or Tersaseptic or Aquasept or Ster-Zac or Manusept or Microshield).ab,ti. 39. ("essential oil$" or "plant oil$" or menthol or menthyl or (mint adj2 oil$) or lavender or thyme or peppermint or "mentha piperita" or eugenol or eucalyptus or "blue gum$" or cajeput or clove or cinnamon).ab,ti. 40. (muramidase or lysozyme$ or leftose or lactoferrin or lactotransferrin o "glucose oxidase" or lactoperoxidase or "saliva substitute").ab,ti. 41. (Listerine or Biotene).ab,ti. 42. or/7-41 43. 6 and 42
WHO COVID-19 Register	**Cochrane COVID-19 Register**	**—**
(tw:((oral or mouth or nasal or nose or nasopharyngeal or larynx* or pharynx* or intranasal))) AND (tw:(spray* or douch* or irrigat* or lavag* or wash or rins* or decontaminat* or aerosol or mist or clean*)) (tw:((mouthwash* or gargl* or mouthrins*))) (tw:((spray* or douch* or irrigat* or rins* or wash* or lavag* or intranasal* or topical))) AND (tw:((antimicrobial or anti-microbial or disinfect* or antisept* or anti-infect*))) (povidone or chlorhexidine or CHX or PVP or Polyvinylpyrrolidone or Betadine* or Providine* or Disadine* or Isodine* or Pharmadine* or Alphadine* or Betaisodona or Tubulicid or Novalsan or Sebidin or MK-412A or MK412A)	1 (mouthwash* or gargl* or mouthrins*) AND INREGISTER 2 (oral near3 (spray* or douch* or irrigat* or lavag* or wash or rins* or decontaminat* or aerosol or mist or clean*)) AND INREGISTER 3 (mouth near3 (spray* or douch* or irrigat* or lavag* or wash or rins* or decontaminat* or aerosol or mist or clean*)) AND INREGISTER 4 (nasal near3 (spray* or douch* or irrigat* or lavag* or wash or rins* or decontaminat* or aerosol or mist or clean*)) AND INREGISTER 5 (nose near3 (spray* or douch* or irrigat* or lavag* or wash or rins* or decontaminat* or aerosol or mist or clean*)) AND INREGISTER	—

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6 (nasopharyngeal near3 (spray* or douch* or irrigat* or lavag* or wash or rins* or decontaminat* or aerosol or mist or clean*)) AND INREGISTER

7 (larynx* near3 (spray* or douch* or irrigat* or lavag* or wash or rins* or decontaminat* or aerosol or mist or clean*)) AND INREGISTER

8 (pharynx* near3 (spray* or douch* or irrigat* or lavag* or wash or rins* or decontaminat* or aerosol or mist or clean*)) AND INREGISTER

9 (intranasal near3 (spray* or douch* or irrigat* or lavag* or wash or rins* or decontaminat* or aerosol or mist or clean*)) AND INREGISTER

10 (povidone or chlorhexidine or CHX or PVP or Polyvinylpyrrolidone or Betadine* or Providine* or Disadine* or Isodine* or Pharmadine* or Alphadine* or Betaisodona or Tubulicid or Novalsan or Sebidin or MK-412A or MK412A) AND INREGISTER

11 (Chlorhexamed or Corsodyl or Curasept or Dyna-Hex or Eludril or Gibitan or Hexidine or Hibiclens or Hibident or Hibiscrub or Hibisol or Hibitane or Peridex or avagard) AND INREGISTER

12 (Hexadecylpyridinium or Cetylpyridium or Biosept or Ceepryn or Cetamium or Catamium or Sterogenol or Dobendan or Merocets or Pristacin or Pyrisept or Angifonil or Cetylyre) AND INREGISTER

13 (Vagi-Hex or Vagi Hex or VagiHex or Oraldene or Hexigel or Steri-sol or Steri sol or Hextril or Oraldine or Oralspray or Hexoral or Bactidol or Elsix or Duranil or Doreperol or Hexetidine) AND INREGISTER

14 (Hydrogen Peroxide or H2O2 or Hydroperoxide or Superoxol or Oxydol or Perhydrol or Urea Peroxide or Perhydrol Urea) AND INREGISTER

15 (Methyl salicylate or methylsalicylate or Rheumabal or Metsal Liniment or Hewedolor or Linsal) AND INREGISTER

16 (Tricolsan or Hydroxydiphenyl or trichlorodiphenyl or Clearasil or Cliniclean or Irgasan or Trisan or Oxy Skin Wash or pHisoHex or Sapoderm or Tersaseptic or Aquasept or Ster-Zac or Manusept or Microshield) AND INREGISTER

17 ((Spray* or douch* or irrigat* or rins* or wash* or lavag* or intranasal* or topical) and (antimicrobial or anti-microbial or disinfect* or antisept* or anti infect*)) AND INREGISTER

18 ("essential oil*" or "plant oil*" or menthol or menthyl or (mint near2 oil*) or lavender or thyme or peppermint or "mentha piperita" or eugenol or eucalyptus or "blue gum*" or cajeput or clove or cinnamon) AND INREGISTER

(Continued)

	19 (muramidase or lysozyme* or leftose or lactoferrin or lactotransferrin or "glucose oxidase" or lactoperoxidase or "saliva substitute") AND INREGISTER
	20 (Listerine or Biotene) AND INREGISTER
	21 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20

HISTORY

Protocol first published: Issue 5, 2020
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CONTRIBUTIONS OF AUTHORS

The initial idea for these reviews was conceived by Janet Clarkson and Martin Burton. All authors were involved in the development of the protocols and reviews, responding to feedback and agreed the final drafts.

DECLARATIONS OF INTEREST

Martin J Burton: none known.
Janet E Clarkson: none known.
Beatriz Goulao: none known.
Anne-Marie Glenny: none known.
Andrew McBain: Andrew McBain conducts research and advises companies in the areas of antimicrobials, microbiome and microbial control.
Anne GM Schilder: in her roles of Director of NIHR UCLH BRC Hearing Theme and National Specialty Lead of NIHR CRN ENT, Professor Schilder advises companies in the hearing field about design and delivery of clinical trials. Her evidENT research team at UCL receives support from various funders, including NIHR, EU Horizon 2020 and Wellcome.
Katie E Webster: none known.
Helen V Worthington: none known.

Professors Martin Burton, Anne Schilder, Janet Clarkson and Anne-Marie Glenny are Co-ordinating Editors for Cochrane ENT and Cochrane Oral Health but had no role in the editorial sign-off process for these reviews.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are no differences between the published protocol and the review.