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Use of antimicrobial mouthwashes (gargling) and nasal sprays by healthcare workers to protect them when treating patients with suspected or confirmed COVID-19 infection (Review)

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

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[Intervention Review]

Use of antimicrobial mouthwashes (gargling) and nasal sprays by healthcare workers to protect them when treating patients with suspected or confirmed COVID-19 infection

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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 HCWs are irrigated with antimicrobial solutions, this may help reduce the risk of active infection being passed from infected patients 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. Understanding these possible side effects is particularly important when the HCWs are otherwise fit and well.

Objectives

To assess the benefits and harms of antimicrobial mouthwashes and nasal sprays used by healthcare workers (HCWs) to protect themselves when treating patients with suspected or confirmed COVID-19 infection.

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of Controlled Trials (CENTRAL 2020, Issue 6); Ovid MEDLINE; Ovid Embase and additional sources for published and unpublished trials.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 randomised controlled trials (RCTs). We therefore planned to include the following types of studies: 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 any antimicrobial mouthwash and/or nasal spray (alone or in combination) at any concentration, delivered to HCWs, with or without the same intervention being given to the patients with COVID-19.

Data collection and analysis

We used standard Cochrane methodological procedures. Our primary outcomes were: 1) incidence of symptomatic or test-positive COVID-19 infection in HCWs; 2) significant adverse event: anosmia (or disturbance in sense of smell). Our secondary outcomes were: 3) viral content of aerosol, when present (if intervention administered to patients); 4) other adverse events: changes in microbiome in oral cavity, nasal cavity, oro- or nasopharynx; 5) 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 three ongoing studies (including two RCTs), which aim to enrol nearly 700 participants. The interventions included in these trials are povidone iodine, nitric oxide and GLS-1200 oral spray (the constituent of this spray is unclear and may not be antimicrobial in nature).

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 two RCTs and a non-randomised study. We are concerned that only one of the ongoing studies specifically states that it will evaluate adverse events and it is not clear if this will include 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, where those receiving the intervention are otherwise fit and well, 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 healthcare workers using antimicrobial mouthwashes or nasal sprays to protect themselves when they treat people with COVID-19?

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.

Healthcare workers who treat people with COVID-19 are at risk of becoming infected themselves. Self-administered use of an antimicrobial mouthwash (to rinse the mouth) or nasal spray (sprayed into the nose) might help healthcare workers to protect themselves against infection. Antimicrobial mouthwashes and nasal sprays are liquids that kill or stop the growth of micro-organisms such as viruses or bacteria.

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

To assess the benefits and risks of self-administered antimicrobial mouthwashes and nasal sprays for healthcare workers treating patients with COVID-19, we set out to review the research evidence.

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 used by healthcare workers against no treatment, water or a salt solution.

What did we find?

We found no completed studies to include in this review.

We found three studies currently in progress that aim to enrol nearly 700 participants. These studies are investigating the effects of povidone iodine (as a mouthwash and nasal spray), nitric oxide (as a mouthwash and nasal spray) and GLS-1200 nasal spray (though the content of this spray is unclear, and it may not turn out to include an antimicrobial agent).

Two 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. The third study is a non-randomised clinical study.

Only one of the ongoing studies specifically states that it will investigate adverse events. It is not clear whether this will include changes in the sense of smell or to the mix of micro-organisms that are present in the mouth or nose, and the consequences of these changes.

What does this mean?

There is currently no evidence relating to the benefits and risks of healthcare workers' use of antimicrobial mouthwashes or nasal sprays to protect themselves when they treat people with COVID-19.

Two randomised controlled trials and one non-randomised study 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. Only one of the ongoing studies we identified specifically states that it 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. Nasal sprays and gargles compared to no intervention for protecting healthcare workers when treating patients with suspected COVID-19

Use of antimicrobial mouthwashes (gargling) and nasal sprays by healthcare workers to protect them when treating patients with suspected or confirmed COVID-19 infection

Patient or population: healthcare workers (HCWs) treating 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		
Incidence of symptomatic or test-positive COVID-19 infection in HCWs	No data available (no included studies)					
Anosmia	No data available (no included studies)					
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; **OR:** odds 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 over 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 **protection of HCWs** treating patients with suspected or confirmed COVID-19 infection. It evaluates the use of mouthwashes and nasal sprays by those HCWs (2) above) with or without the addition of similar interventions by the patients (1) above). (The other two reviews will focus on a) the use of antimicrobial mouthwashes and nasal sprays in the treatment of patients with suspected or confirmed COVID-19 infection (Burton 2020a) and b) the protection of HCWs when they are undertaking 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). Rinsing the mouth and/or nose may eradicate viral particles completely - preventing transmission to that individual - or reduce the viral load that the individual is exposed to. This may prevent the disease developing in that individual or reduce the severity of it. 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 used by healthcare workers (HCWs) to protect themselves when treating patients with suspected or confirmed COVID-19 infection.

The review also sought to address whether there is a difference if the intervention is used solely by the HCWs or both the HCWs and the patients they are caring for.

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

Healthcare workers (HCWs) treating 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 the HCWs, with or without the same intervention being given to the 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

- Incidence of symptomatic or test-positive COVID-19 infection in HCWs.
- Significant adverse event: anosmia (or disturbance in sense of smell).

Secondary outcomes

- Viral content of aerosol, when present (if intervention administered to patients).
- 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 would not 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 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 difference (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

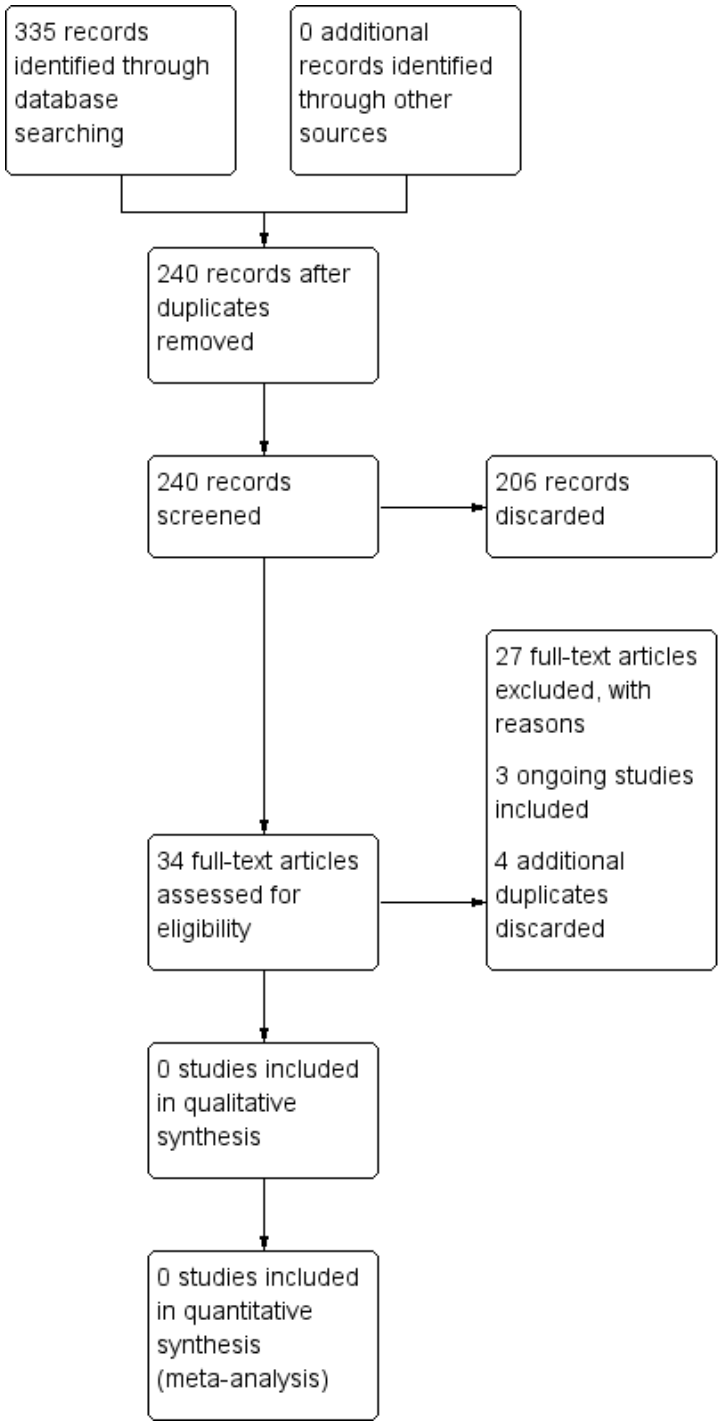
Results of the search

The searches retrieved a total of 335 references. This reduced to 240 after the removal of duplicates. We screened the titles 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 27 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 three ongoing studies (NCT04408183; NOCOVID (NCT04337918); PIIPPI (NCT04364802)). 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 28 papers 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 15 studies as the intervention was used in an incorrect population - the trial considered the use of nasal sprays and gargles to treat individuals who have the virus, rather than as prophylaxis to prevent transmission of the virus (ACTRN12620000470998p; AMPoL (NCT04409873); BBCovid (NCT04352959); ChiCTR2000030539; ELVIS-COVID-19 (NCT04382131); GARGLES (NCT04341688); GARGLESb (NCT04410159) KILLER (NCT04371965); KONS-COVID-19 (NCT04357990); NCT04344236; NCT04347954; NCT04382040; NCT04347538; PICO (ISRCTN13447477); SINUS WASH (NCT04393792)).

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 three ongoing studies, aiming to enrol 675 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, therefore they should be regarded as 'planned or ongoing studies'.

Two of the studies are reported to be RCTs (NCT04408183; NOCOVID (NCT04337918)), and the third study is reported as a non-randomised intervention study (PIIPPI (NCT04364802)). They evaluate the effectiveness of different interventions, including povidone iodine (as a nasal spray and gargle), nitric oxide (as a gargle, nasopharyngeal rinse and nasal spray) and GLS-1200 oral spray (the constituent of this spray is unclear and may not be antimicrobial in nature).

The studies all consider the incidence of COVID-19 as an outcome, and some consider the severity of the disease. Adverse events are considered by only one trial, although the remaining trials do look at tolerability of use for the intervention.

Risk of bias in included studies

No studies are included in the review.

Effects of interventions

See: **Summary of findings 1** Nasal sprays and gargles compared to no intervention for protecting healthcare workers when treating patients with suspected COVID-19

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, good that the question posed in this review is being addressed by ongoing studies.

Overall completeness and applicability of evidence

We are concerned that only one of the ongoing studies specifically states that it will consider adverse events. A number of specific issues are problematic and some may remain so even if they are addressed in the studies.

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.

Duration of treatment

The duration of treatment in the ongoing trials is relatively short, as is the follow-up period. If interventions are shown to be of benefit in reducing viral transmission then it is likely that healthcare workers would need to use them for extended periods, and at least for as long as they interact with individuals who are known to have COVID-19. An extended period of use may result in an increase in adverse events, or reduced tolerability of the interventions, which may not be evident from short-term studies.

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.

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 to protect healthcare workers when treating patients with suspected or confirmed COVID-19 infection. We await the publication of the ongoing trials with interest.

Evidence for activity of specific antimicrobials against SARS-CoV-2 is still developing. However, povidone iodine mouthwash has previously been shown to have antiviral activity against coronaviruses, and new data suggest that it may also be effective against SARS-CoV-2 in particular (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 healthcare workers who are treating patients with COVID-19.

Implications for research

It is promising that a small number of ongoing studies were identified by the literature searches for this review. However, we note that some important issues may not be addressed by the trials that are currently ongoing – in particular the adverse effects from both short- and longer-term use of the interventions.

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CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
ACTRN12620000470998p	Incorrect population. This trial considers the use of nasal sprays/gargles by individuals who are diagnosed with COVID-19, and is relevant for another review in this suite (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; Burton 2020a).
AMPoL (NCT04409873)	Incorrect population. This trial considers the use of nasal sprays/gargles by individuals who are diagnosed with COVID-19, and is relevant for another review in this suite (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; Burton 2020a).
BBCovid (NCT04352959)	Incorrect population. This trial considers the use of nasal sprays/gargles by individuals who are diagnosed with COVID-19, and is relevant for another review in this suite (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; Burton 2020b).
Carrouel 2020	Review article, no relevant data.
Challacombe 2020	Letter to the editor, no relevant data.
ChiCTR2000030539	Incorrect population. This trial considers the use of nasal sprays/gargles by individuals who are diagnosed with COVID-19, and is relevant for another review in this suite (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; Burton 2020a).
Dexter 2020	Review article, no relevant data.
ELVIS-COVID-19 (NCT04382131)	Incorrect population. This trial considers the use of nasal sprays/gargles by individuals who are diagnosed with COVID-19, and is relevant for another review in this suite (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; Burton 2020a).
GARGLES (NCT04341688)	Incorrect population. This trial considers the use of nasal sprays/gargles by individuals who are diagnosed with COVID-19, and is relevant for another review in this suite (Antimicrobial mouthwashes (gargling) and nasal sprays administered to patients with suspected or confirmed COVID-19

Study	Reason for exclusion
	infection to improve patient outcomes and to protect healthcare workers treating them; Burton 2020a).
GARGLESb (NCT04410159)	Incorrect population. This trial considers the use of nasal sprays/gargles by individuals who are diagnosed with COVID-19, and is relevant for another review in this suite (Antimicrobial mouth-washes (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; Burton 2020a).
Ham 2020	Review article, no relevant data.
Hamid 2020	Review article, no relevant data.
Henwood 2020	Review article, no relevant data.
KILLER (NCT04371965)	Incorrect population. This trial considers the use of nasal sprays/gargles by individuals who are diagnosed with COVID-19, and is relevant for another review in this suite (Antimicrobial mouth-washes (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; Burton 2020a).
KONS-COVID-19 (NCT04357990)	Incorrect population. This trial considers the use of nasal sprays/gargles by individuals who are diagnosed with COVID-19, and is relevant for another review in this suite (Antimicrobial mouth-washes (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; Burton 2020a).
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.
NCT04344236	Incorrect population. This trial considers the use of nasal sprays/gargles by individuals who are diagnosed with COVID-19, and is relevant for another review in this suite (Antimicrobial mouth-washes (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; Burton 2020a).
NCT04347538	Incorrect population. This trial considers the use of nasal sprays/gargles by individuals who are diagnosed with COVID-19, and is relevant for another review in this suite (Antimicrobial mouth-washes (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; Burton 2020a).
NCT04347954	Incorrect population. This trial considers the use of nasal sprays/gargles by individuals who are diagnosed with COVID-19, and is relevant for another review in this suite (Antimicrobial mouth-washes (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; Burton 2020a).
NCT04382040	Incorrect population. This trial considers the use of nasal sprays/gargles by individuals who are diagnosed with COVID-19, and is relevant for another review in this suite (Antimicrobial mouth-washes (gargling) and nasal sprays administered to patients with suspected or confirmed COVID-19

Study	Reason for exclusion
	infection to improve patient outcomes and to protect healthcare workers treating them; Burton 2020a).
Parhar 2020	Review article, no relevant data.
PICO (ISRCTN13447477)	Incorrect population. This trial considers the use of nasal sprays/gargles by individuals who are diagnosed with COVID-19, and is relevant for another review in this suite (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; Burton 2020a).
Ramalingam 2020	Incorrect population. Although participants were infected with a coronavirus, this was not COVID-19.
SINUS WASH (NCT04393792)	Incorrect population. This trial considers the use of nasal sprays/gargles by individuals who are diagnosed with COVID-19, and is relevant for another review in this suite (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; Burton 2020a).

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

NCT04408183

Study name	'GLS-1200 topical nasal spray to prevent SARS-CoV-2 infection (COVID-19) in health care personnel'
Methods	2-arm, parallel-group RCT
Participants	Adult healthcare professionals **Inclusion criteria:** • Aged 18 or over • Able to provide informed consent • Able and willing to comply with study procedures • Adult healthcare professional **Exclusion criteria:** • Known allergy to quinine, quinidine or mefloquine • Confirmed prior positive test for SARS-CoV-2 • Treatment within the past 2 weeks with chloroquine, hydroxychloroquine or remdesivir **Planned sample size:** 225 participants
Interventions	**Intervention group:** • 1 mL of GLS-1200 per nostril, 3 times daily via atomiser (duration not stated) **Comparator group:** • 1 mL of 0.9% saline per nostril, 3 times daily via atomiser (duration not stated) **Use of additional interventions in both groups:** • None reported
Outcomes	**Primary outcomes:**

NCT04408183 *(Continued)*

	• Number of GLS-1200 topical nasal spray adverse events; time frame: 4 weeks • Incidence of SARS-CoV-2 infection, confirmed by PCR; time frame: 4 weeks **Secondary outcomes:** • Symptom score of documented SARS-CoV-2 infection; time frame: 4 weeks
Starting date	May 2020
Contact information	Email: jmaslow@geneonels-us.com; cremigio@geneonels-us.com
Notes	Trial registered in USA Estimated completion date: November 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 who are negative for COVID-19 during screening, aged 19 years and over **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 • Symptom free at screening/baseline • Working/living in contact with COVID-19 infected patients, or scheduled to work in a setting with high likelihood of exposure to COVID-19 infected patients **Exclusion criteria:** • Prior tracheostomy • Concomitant treatment of respiratory support (involving any form of oxygen therapy) • Any clinical contraindications, as judged by the attending physician • Any symptoms consistent with COVID-19 • Pregnancy • Mentally or neurologically disabled participants who are not considered fit to consent to the study • Prior COVID-19 infection **Planned sample size:** 200 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:**

NOCOVID (NCT04337918) *(Continued)*

	• All participants will receive standard institutional precautions
Outcomes	**Primary outcome:** • Proportion of healthcare workers with either positive COVID-19 or presentation of clinical symptoms (fatigue with either fever (> 37.2°C) and/or a persistent cough); time frame: 21 days following randomisation **Secondary outcomes:** • Proportion of participants requiring hospitalisation for COVID-19/flu-like symptoms and/or needing oxygen therapy, BIPAP/CPAP, intubation and mechanical ventilation following enrolment; time frame: 21 days following randomisation • Tolerability of nitric oxide releasing solution (NORS) treatment; time frame: 21 days following randomisation
Starting date	8 May 2020
Contact information	Chris Miller Email: chris@sanotize.com
Notes	Primarily a prevention study, but has a second arm to the trial that considers the use of the same interventions in individuals who have COVID-19 (relevant for another review in this suite). Trial registered in the USA Estimated completion date: September 2020

PIIPPI (NCT04364802)

Study name	'COVID-19: povidone-iodine intranasal prophylaxis in front-line healthcare personnel and inpatients (PIIPPI)'
Methods	Non-randomised clinical trial
Participants	Frontline healthcare workers who are negative for COVID-19 or hospital inpatients (who have a hospitalisation of more than 7 days, or who are set to undergo a significant surgical procedure), aged 18 to 99 years **Inclusion criteria:** • Healthcare worker OR patient with expected hospital stay of 7+ days OR patient admitted for major surgery • COVID-19 negative by nasal swab test • Asymptomatic for COVID-19 • Able to consent to participation **Exclusion criteria:** • Positive for COVID-19 by nasal swab • Symptomatic for COVID-19 • Unable to consent **Planned sample size:** 250 participants
Interventions	**Intervention group:**

PIIPPI (NCT04364802) *(Continued)*	• For healthcare workers: povidone-iodine nasal spray and gargle (10% diluted 1:30) will be used at the beginning of their shift, in the middle and at the end of their shift • For hospital inpatients: povidone-iodine nasal spray and gargle (10% diluted 1:30) for patient participants to use shortly after admission or pre-operatively (no further details provided) **Comparator group:** • No intervention **Use of additional interventions for both study groups:** • Standard PPE and a pre- and post-study test for COVID-19
Outcomes	**Primary outcomes:** • Percentage of healthcare workers testing positive for COVID-19; time frame: 3 weeks • Percentage of patients testing positive for COVID-19; time frame: 2 weeks **Secondary outcomes:** • PVP-I ease of use; time frame: 3 weeks • PVP-I comfort; time frame: 3 weeks • Adherence to treatment protocol; time frame: 3 weeks
Starting date	May 2020
Contact information	Alexandra Kejner Email: alexandra.kejner@uky.edu
Notes	Trial registered in USA Estimated completion date: May 2021

BIPAP: bilevel positive airway pressure; COVID-19 coronavirus disease 2019; CPAP: continuous positive airway pressure; PCR: polymerase chain reaction; PPE: personal protective equipment; PVP-I povidone iodine; 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	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"	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.

(Continued)

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

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

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/

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/

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.

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/

(Continued)

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

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

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.

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

22. lavender/

23. thymus extract/

24. Mentha piperita/

25. eugenol/

26. Cinnamomum zeylanicum/

27. lysozyme/

28. lactoferrin/

29. Glucose oxidase/

30. Lactoperoxidase/

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

(Continued)

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

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 pHisoHex 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

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 disinfect* 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 pHisoHex 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

(Continued)

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 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	—

(Continued)

	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
	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
Review first published: Issue 9, 2020

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.