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[Intervention Protocol]

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

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

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 spray in improving outcomes for patients with suspected or confirmed COVID-19 infection.

BACKGROUND

Description of the condition

The emergence of a novel coronavirus in late 2019 has resulted in a global pandemic of an infectious condition - COVID-19. To date, almost five million people have been reported to be infected, with close to 300,000 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. No vaccine has been developed nor have any therapeutic agents been shown to be effective. Management options are largely supportive. Many efforts have focused on prevention, using measures of social distancing and isolation.

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

These workers are 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 **treatment of patients** with suspected or confirmed COVID-19 infection *and* the **protection of HCWs** treating them. 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 protection of HCWs treating 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 that 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 direct 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 possible 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 could result in significant health problems.

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 spray 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 do not anticipate finding many completed RCTs. We will therefore include 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 is 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 will analyse the following outcomes in the review, but we will not use them as a basis for including or excluding studies.

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

For all outcomes we will accept the method of measurement used by the triallists but will 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 Oral Health Information Specialists will conduct systematic searches for all human studies. There will be no language, publication year or publication status restrictions. We may contact original authors for clarification and further data if trial reports are unclear and we will arrange translations of papers where possible.

Electronic searches

Published, unpublished and ongoing studies will be identified by searching the following databases from their inception:

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

The subject strategies for databases will be modelled on the search strategy designed for Ovid MEDLINE (Appendix 1).

Searching other resources

We will not perform a separate search for adverse effects. We will consider adverse effects described in included studies only.

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

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

Data collection and analysis

Selection of studies

AMG, HW (and others) will perform screening using Covidence.

All titles and abstracts identified through the searching will be screened independently by two review authors. Discrepancies will be discussed and, where necessary, a third review author will be included. Where uncertainties remain, we will retrieve the full text for clarification. The full text of potentially relevant articles will again be screened by two review authors, independently.

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

Data extraction and management

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

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

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

Assessment of risk of bias in included studies

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

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

Measures of treatment effect

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

We will present continuous data as mean difference (MD) with corresponding 95% CIs. Where necessary, we will convert outcome data to the same unit of measurement.

Where data are extracted from non-RCTs, we will use adjusted effects where available. If multiple adjusted effects are reported, then we will choose the one judged to minimise the risk of bias due to confounding.

Unit of analysis issues

The unit of analysis will be the participant. Any cluster-RCTs would need to have analysed results taking account of the clustering present in the data, otherwise we will use 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 will include studies with multiple treatment arms as appropriate, ensuring that there is no double counting of patients in any meta-analysis.

Dealing with missing data

We will contact study authors for missing outcome data. Where appropriate, we will use 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 will not use any further statistical methods or carry out any further imputation to account for missing data.

Assessment of heterogeneity

We will assess statistical heterogeneity initially through inspection of forest plots. We will 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 will also 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 will be cautious in interpreting the I^2 value, as this may be uncertain when there are few studies.

We will explore potential sources of heterogeneity among study results. Sources may include: clinical setting, clinical procedure.

Assessment of reporting biases

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

Data synthesis

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

We will use a random-effects model.

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

Subgroup analysis and investigation of heterogeneity

Where data are available, we will 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 will undertake sensitivity analysis excluding studies at high risk of bias.

Summary of findings and assessment of the certainty of the evidence

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

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Burton MJ, Clarkson JE, Gaulao B, , McBain A, Schilder AGM, et al. Use of antimicrobial mouthwashes (gargling) and nasal sprays by healthcare workers to protect them when treating patients with suspected or confirmed COVID-19 infection. *Cochrane Database of Systematic Reviews* 2020, Issue 5. [DOI: 10.1002/14651858.CD013626]

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Man 2017

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Satomura 2005

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APPENDICES

Appendix 1. Search strategy

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.	8083
2	(Wuhan and (coronavirus or "corona virus")).ab,ti.	656
3	((coronavirus or "corona virus") adj3 "2019").ab,ti.	1474
4	(wuhan adj2 (disease or virus)).ab,ti.	34
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.	981
6	1 or 2 or 3 or 4 or 5	8284
7	exp Animals/	23104204
8	exp Humans/	18413197
9	7 not 8	4691007
10	(editorial or comment or letter or newspaper article).pt.	1847573
11	9 or 10	6471247
12	6 not 11	5782
13	exp Mouthwashes/	14306
14	exp Nasal Sprays/	501
15	exp Nasal Lavage/	1356
16	(Mouthwash* or gargl* or mouthrins*).ab,ti.	4510
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.	10846
18	exp Chlorhexidine/	8260
19	exp Povidone-Iodine/	2816
20	exp Cetylpyridinium/	939
21	exp Hexetidine/	148
22	exp Anti-Infective Agents, Local/	230412

(Continued)

23	exp Hydrogen Peroxide/	57593
24	exp Carbamide Peroxide/	1055
25	exp Triclosan/	2807
26	exp Oils, volatile/	14097
27	exp Plant oils/	36092
28	Menthol/	1915
29	Lavandula/	461
30	Thymus plant/	1410
31	Mentha piperita/	378
32	Eugenol/	2260
33	Cinnamomum verum/	776
34	Muramidase/	22670
35	Lactoferrin/	5996
36	Glucose oxidase/	5060
37	Lactoperoxidase/	1333
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.	24280
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.	403
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.	154
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.	141
42	(Hydrogen Peroxide or H2O2 or Hydroperoxide or Superoxol or Oxydol or Perhydrol or Urea Peroxide or Perhydrol Urea).ab,ti.	91131
43	(Methyl salicylate or methylsalicylate or Rheumabal or Metsal Liniment or Hewedolor or Linsal).ab,ti.	1103
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.	333
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.	2880

(Continued)

46	("essential oil$" or "plant oil$" or menthol or menthyl or (mint adj2 oil$) or lavender or thyme or peppermint or "mentha piperita" or eugenol or eucalyptus or "blue gum$" or cajeput or clove or cinnamon).ab,ti.	30191
47	(muramidase or lysozyme$ or leftose or lactoferrin or lactotransferrin or "glucose oxidase" or lactoperoxidase or "saliva substitute").ab,ti.	42128
48	(Listerine or Biotene).ab,ti.	361
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	422052
50	12 and 49	14

HISTORY

Protocol first published: Issue 5, 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 responding to feedback, and have 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: as the head of a biofilm and microbiome research group, Professor McBain advises companies and conducts research 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 protocols.

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