Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Systematic review

Do hydrogen peroxide mouthwashes have a virucidal effect? A systematic review

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SUMMARY

Background: The presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in saliva has alerted health professionals to the possibility of contamination by aerosols generated in a number of procedures. The indication of preoperative mouthwash containing 1% hydrogen peroxide for reducing the viral load of SARS-CoV-2 in saliva prior to oral procedures has been significantly disseminated through several citations and influenced various dental associations in the elaboration of dental care protocols during this pandemic period, including patients admitted to hospital wards and intensive care units.
Aim: To Our aim was to perform a systematic review to answer the following question: does hydrogen peroxide mouthwash (at any concentration) have a virucidal effect?
Methods: The Cochrane, LILACS, PubMed, Scopus, and Embase databases were searched by using the following key-words: 'hydrogen peroxide', 'mouthwash', 'mouth rinse', 'rinse', 'oral rinse', 'mouth bath', 'mouth wash', and 'mouth washes'. Reviews, letters to the editor, personal opinions, book chapters, case reports, congress abstracts, studies with animals and studies on mouthwash containing other compounds other than hydrogen peroxide were excluded.
Findings: During the initial search 1342 articles were identified on the five electronic databases. After excluding some duplicates, 976 articles remained. Only studies assessing the virucidal effect of hydrogen peroxide mouthwash were selected, regardless of publication date.
Conclusion: After reading titles and abstracts, no article met the eligibility criteria. In conclusion, there is no scientific evidence supporting the indication of hydrogen peroxide mouthwash for control of the viral load regarding SARS-CoV-2 or any other viruses in saliva.

Introduction

Coronaviruses have been responsible for three major respiratory diseases in recent decades. The third one began in

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December 2019 in Wuhan, China, giving rise to a pandemic caused by a new virus termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. SARS-CoV-2 is mainly transmitted by direct contact with infected people through respiratory or salivary droplets, and to a lesser extent by indirect contact with contaminated surfaces [3]. The virus has tropism for cells whose membrane contains a specific receptor — the angiotensin converting enzyme-2 (ACE2), which is present in many human tissues other than the lung, which is the main target organ for the virus infection [4,5]. The identification of ACE2 in the oral mucosal epithelial cells, particularly the dorsum of the tongue, and the description of SARS-CoV-2 oral shedding has brought more fear to health professionals, especially those working in close contact with patients and who are exposed to aerosols [6—13].

In an attempt to prevent patient-to-practitioner transmission by means of contaminated saliva, opinions on how to proceed with patients began to emerge in the literature in order to reduce the risk of cross-infection through aerosol generation [14—17]. One of the presented solutions is the use of antiseptic mouthwashes. But it is important to understand that antisepsis (i.e. to destruct or to inhibit micro-organisms in a living tissue) is not the same as disinfection (i.e. to destruct or to inhibit micro-organisms on inanimate objects) [18]. These two processes require types of chemical compounds that must be tested in different ways for approval by the competent agencies according to regulatory norms.

According to Saddik and Pappan, mouthwashes are considered cosmetics in Europe whereas in the USA they can also be registered as drugs, depending on their therapeutic properties (or their intended use declared by the manufacturer) [19]. In the latter case, they should be submitted to a drug approval process involving pre-clinical studies (*in vitro* with cultured cells and *in vivo* with laboratory animals) and clinical trials. The last one involves four phases: phase 1: involving fewer than 100 healthy or diseased volunteers; phase 2: several hundreds of volunteers with the majority being patients with the disease; phase 3: with several thousand volunteers, this requires at least a few years for completion; phase 4: post-market phase in which the drug is actively monitored by the consumers [19].

Although it is easier to put a cosmetic product on the European market, those products are also subjected to regulations placed by the local law of all the member countries of the EU. After being made available in the European market, those products are subject to efficiency evaluation in official laboratories [19].

The International Organization for Standardization (ISO) specifies the chemical and physical properties and test methods for oral rinses, but the instructions for microbiological examination are about bacteria, mould, and yeast. There are no instructions about virus (ISO 16408:2015 (en) Dentistry — Oral care products — Oral rinses).

There are some standard tests to determine virucidal activity, but almost all are for surface disinfection and a few are aimed at antiseptic capacity for external surfaces (e.g. skin), which invariably do not have viral replication. None demonstrate how to verify virucidal effect in non-standardized samples from nasopharyngeal or oral cavity [20].

The use of mouthwash containing 1% hydrogen peroxide has been proposed to reduce viral load of SARS-CoV-2 in saliva [18]. This relationship seems to be demonstrated by studies assessing the use of mouthwash for reduction of oral microbiota, especially bacteria, meaning that the oxidative properties of hydrogen peroxide would also enable the degradation of viral particles. Nevertheless, there is no citation of a study supporting such an approach [21].

Because of the increasing number of publications replicating this information (Appendix A) and many institutions in several countries (EU, UK, New Zealand, India, Spain, Portugal, Brazil, Italy) recommending the use of hydrogen peroxide mouthwash as part of a dental care protocol during the coronavirus disease 2019 (COVID-19) pandemic, including patients admitted to hospital wards and intensive care units, the objective of this systematic review was to answer the following question: does hydrogen peroxide mouthwash have a virucidal effect? [22—28].

Methods

This systematic review was performed based on the items of the Systematic Reviews and Meta-Analyses (PRISMA) Checklist. The systematic review protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) according to number CRD42020189431.

Eligibility criteria

Inclusion criteria

Only studies assessing the virucidal effect of hydrogen peroxide mouthwash were selected. In order to reduce the publication bias, these studies were included regardless of publication date restrictions.

Exclusion criteria

Reviews, letters to the editor, personal opinions, book chapters, case reports, congress abstracts, studies with animals and studies on mouthwash containing compounds other than hydrogen peroxide were excluded.

Information sources

Individual search strategies were developed for Cochrane, LILACS, PubMed, Scopus and Embase databases. The following keywords were used in the search: 'hydrogen peroxide', 'mouthwash', 'mouth rinse', 'rinse', 'oral rinse', 'mouth bath', 'mouth wash' and 'mouth washes' (further information is provided in Appendix B). Additionally, the grey literature was also searched by using ProQuest, Open Grey, and Google Scholar, in which the last was limited to the first 120 articles published. The lists of references on this theme were also searched. The above-mentioned databases, including the grey literature, were searched on May 30th, 2020.

Study selection

The studies were selected in two phases. The first phase was conducted by using reference manager software (EndNote® X7; Thomson Reuters, Philadelphia, PA, USA) to collect references and exclude duplicates [29]. In the second phase, two reviewers evaluated independently the titles and abstracts of the articles selected from the search results. Also, in this

phase, articles clearly not meeting the inclusion criteria or meeting some of the exclusion criteria were excluded. In case of doubt, a third reviewer was consulted for a final decision.

Results

Study selection

During the initial search, a total of 1342 articles were identified on the five electronic databases (i.e. Cochrane, LILACS, PubMed, Scopus, and Embase) and 976 remained after eliminating duplicate studies. Nevertheless, no article met the eligibility criteria after reading the titles and abstracts. Likewise, no study was found in the grey literature (i.e. Pro Quest, Open Grey, Google Scholar) within the same parameters (Figure 1).

Discussion

With the recent emergence of the COVID-19 pandemic, the information that mouthwash with 1% hydrogen peroxide would be capable of reducing the viral load of SARS-CoV-2 in the saliva has been disseminated based on this compound's biological action on bacteria or opinions based on its efficacy on surfaces [30,31]. The authors of these publications believed that the reduction of viral load in the saliva would decrease

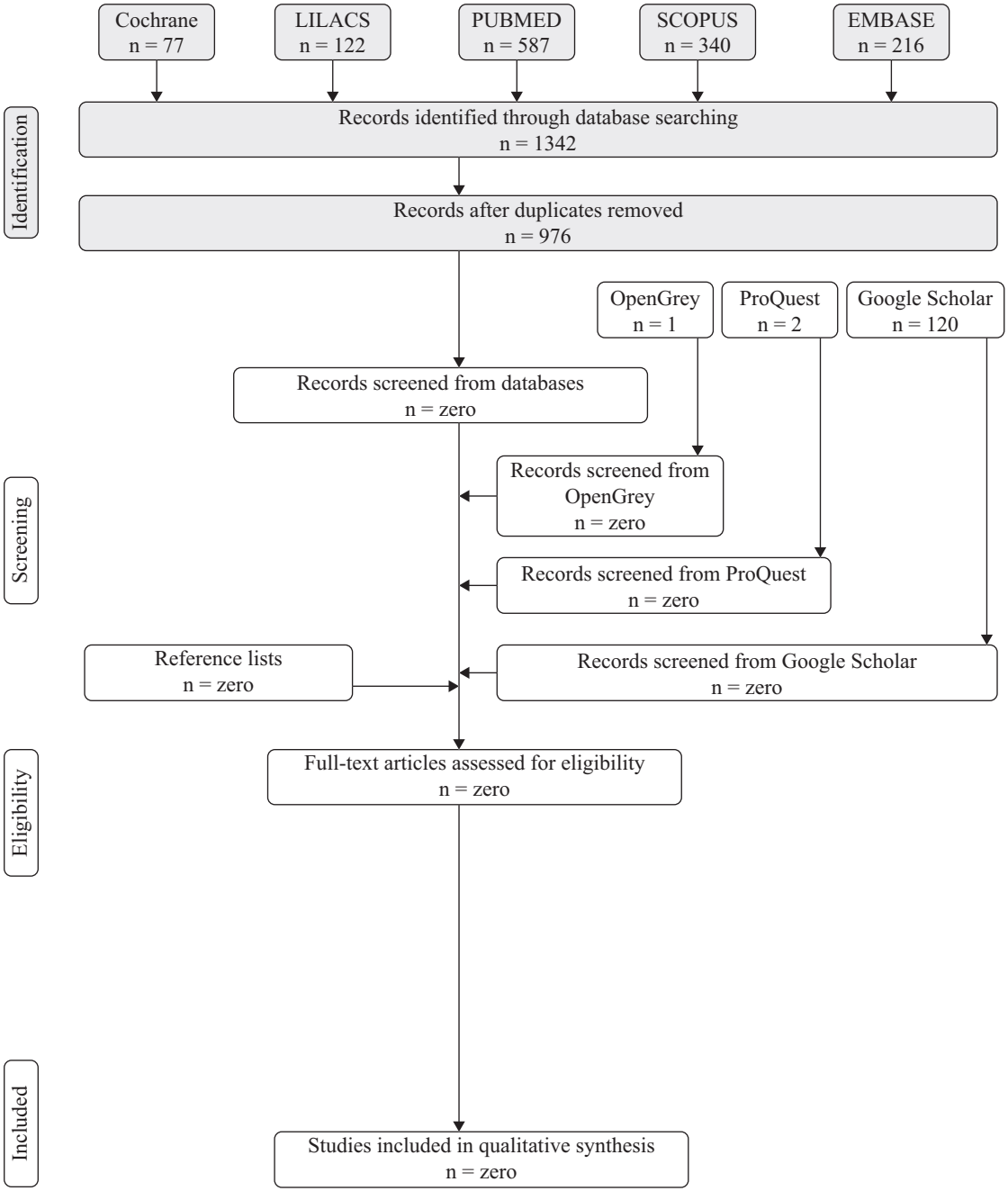

Figure 1. Procedure for searching references and selection criteria.

contamination of the dental office environment through aerosol following treatment of an infected patient, or even shorten the patient's hospitalization [30,31].

The routine use of mouthwash prior to dental procedures is aimed at decreasing the formation of biofilm, minimizing transient bacteraemia in the patient undergoing invasive procedures and preventing ventilator-associated pneumonia [32]. The dental practitioner would also benefit from the decreased bacterial load during aerosol generation. However, despite being a well-established routine, there is little scientific evidence on the effectiveness of preoperative mouthwash for control of bacteraemia and contamination through aerosols [33—35]. These analyses considered the action of these products on bacteria only, since nothing is mentioned about viruses.

There are some in-vitro studies demonstrating the virucidal action of Listerine® and chlorhexidine on human immunodeficiency virus and herpes simplex type 1 (HSV-1) [36,37]. Only one in-vivo study assessed the efficacy of Listerine in decreasing HSV-1 in the saliva of patients with active lip lesions, thus evidencing an effective control for 30 min [38]. It is important to remember that this effect may be related to the replication cycle of the virus itself and/or to the mechanical removal of viral particles with the use of mouthwash, rather than to an alleged virucidal effect of the active principle. A recent publication shows a variable viral load of SARS-CoV-2 in saliva depending on the period of the day analysed [39].

Other in-vitro studies, showing antiviral efficacy by analysing viral titres in cell culture, reported positive results for the efficacy of Listerine against respiratory viruses (e.g. influenza A and rotavirus) and of povidone iodine against influenza H1N1 virus and coronavirus (SARS-CoV, Middle East respiratory syndrome coronavirus, SARS-CoV-2) [20,40—42]. Nevertheless, there is no clinical study demonstrating these findings *in vivo*.

A limited clinical study with no placebo controls or in-vitro antiviral efficacy data using saline mouthwashes has recently been reported [43].

The small number of published studies on virucidal effect of mouthwashes may be related to different regulations for this product observed worldwide [19]. The current scenario of a pandemic, where transmission also results from contaminated saliva particles, highlights that the classification of mouthwashes as a therapeutic agent is the more appropriate and could provide more robust clinical studies for market registration purposes. Moreover, it is worth pointing out that none of these studies assessed the action of hydrogen peroxide mouthwashes [38,40,43].

Hydrogen peroxide is a substance which is degraded into oxygen and water when in contact with catalase — an enzyme present in almost all living beings, including micro-organisms within the oral microbiota — and this oxidative process would be capable of eliminating bacteria and fungi [44]. Peng *et al.* assumed that this process of oxidation might also be effective against SARS-CoV-2 by alleging that this virus would be sensitive to oxidation [30]. The work in question has been cited frequently in the literature since its publication (Appendix A), becoming a source of information and basis for attitudes during the COVID-10 pandemic in several dental specialties [30].

Taking into consideration the chemical reaction on which the antimicrobial properties of hydrogen peroxide are based, this degradation occurring almost instantaneously would not be capable of impeding an immediate recontamination of the oral cavity, since the particles of a virus (e.g. SARS-CoV-2) can potentially come from various sources such as respiratory secretions, oropharynx, salivary glands and gingival crevicular fluid [6,10,11,45—47]. Therefore, it would be necessary that any substance to be used as preoperative mouthwash had a high substantivity, that is, the capacity to interact with structures of the oral cavity to allow a slow release of this agent, thus increasing the duration of its virucidal effect.

A systematic review demonstrated that effect of hydrogen peroxide mouthwash in preventing formation of oral biofilm was poor as well as brief, thus showing its low substantivity [48]. Most of the studies included in this review were published between the 1970s and 1990s, which reflects the discontinuation in the indication of hydrogen peroxide as an effective mouthwash for controlling oral microbiota, precisely because of the lack of substantivity [48].

In conclusion, since there is a lack of scientific evidence supporting any virucidal activity of hydrogen peroxide mouthwash, associated with its lack of substantivity, its indication in dental care protocols during the COVID-19 pandemic should be revised.

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Conflict of interest statement
None declared.

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Appendix C. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2020.10.003.

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