REVIEW ARTICLE

The Potential Benefit of Mouthwashes in Reducing COVID-19 Viral Load: A Mini Review

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Abstract

Scientists throughout the world are searching for a lasting solution in the form of a vaccine or a drug that could be used to combat COVID-19 infections. A number of studies have proposed the antiviral efficacy of mouthwashes across a different population. Research has shown over the years that active ingredients present in commercially available mouthwash are potent enough to damage viruses, particularly those with the lipid envelope, rendering them harmless. This paper reviews the effect of mouthwashes on few viruses, including those possibly linked to SARS-COV-2. The aim is to provide evidence on the potential benefit of mouthwashes in reducing viral load and pool together the impact of various mouthwashes in managing individuals diagnosed with viral infections. We searched academic, English-scripted paper published between 1995 and June 2020 on PubMed, MEDLINE, ScienceDirect, EMBASE, WHO and the Cochrane Library databases. Two review authors independently assessed the eligibility and quality of the retrieved papers using the Jadad scale. Result showed there were evidences indicating that the benefits of mouthwashes to viral infections might be transferrable to COVID-19. However, future trials are recommended to establish the benefits of mouthwashes in reducing the burden of COVID-19.

Key words: *Covid-19, SARS-CoV-2, Mouthwashes.*

BACKGROUND

Coronaviruses (CoVs) are a group of viruses, which belong to the family of *Coronaviridae*, the largest family in the order of *Nidovirales* (Pal et al., 2020). Coronaviruses are positive-stranded RNA which depends on the fusion of their envelope with the host cell membrane (Belouzard et al., 2010). Coronaviruses were first isolated in animals; first in chickens in 1931 known as infectious bronchitis virus (Shalk, 1931) and then mouse hepatitis virus was isolated in mouse in 1940 (Cecílio, 2000). In subsequent years, other coronaviruses such as transmissible gastroenteritis virus (TGEV) and Porcine epidemic diarrhoea virus (PEDV) causing severe gastro and respiratory disease in pigs, cows, dogs, cats and chickens (Liu & Gerdts, 2019; Paules et al., 2020) were identified. The animal coronavirus mostly leads to enteric infection and the ability to infect the nervous system, causing encephalitis and vomiting, leading to significant morbidity and mortality (Paules et al., 2020).

Human coronaviruses were first discovered in the 1960s after it was isolated in the UK at the common cold unit of the British Medical Research Council from a boy with common cold

symptoms (Kendall et al., 1962). The virus was uncultivable using standard techniques, until serially passed through an organ culture of the human embryonic trachea (Tyrell & Bynoe, 1965). Initially, there were six human coronaviruses with varying levels of severity, which are all capable of producing potentially severe symptoms (Pal et al., 2020). The first is 229E, a coronavirus species responsible for the common cold; second is NL63, associated with mild to moderate upper respiratory tract infections and severe lower respiratory tract infection. The third is OC43, which is a coronavirus responsible for the common cold; the fourth is HKU1, responsible for the upper respiratory tract. The fifth human coronavirus in the Middle East respiratory syndrome-related coronavirus (MERS-CoV), which is the cause of the MERS disease. Severe acute respiratory syndrome coronavirus (SARS-CoV) is the sixth human coronavirus, first identified in Shunde, China (Pal et al., 2020).

In December 2019, a novel coronavirus genetically, related to SARS-CoV was isolated in Wuhan, China, becoming the seventh human coronavirus (Sohrabi et al., 2020). This new virus has since spread to most parts of the world, causing massive number of deaths which has led to an ongoing pandemic. In January 2020, the World Health Organisation (WHO) recommended that the interim name of the disease caused by this coronavirus should be "2019-nCoV acute respiratory disease" (where 'n' is for a novel, and 'CoV' is for coronavirus).

The new strain of the coronavirus was eventually named as SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV) on the 11th February 2020. On the same day, following previously developed guidelines with the World Organisation for Animal Health (OIE) and the Food and Agriculture Organisation of the United Nations (FAO), the WHO announced and confirmed the new name for the disease caused by SARS-CoV-2 as "COVID-19" (WHO, 2020). The WHO concluded that the SARS-CoV-2 is transmissible from humans to humans through the inhalation of respiratory droplets from coughs and sneezes (6 feet) as well as via indirect contact through contaminated surfaces (Morawska & Cao, 2020). Common symptoms include fever, cough, shortness of breath, loss of smell and taste, while complications could result in pneumonia, acute respiratory distress syndrome, kidney failure, viral sepsis and cytokine release syndrome (Paules et al., 2020).

The emergence of this novel human coronavirus has become a global health concern which has led to a worldwide pandemic, disrupting global health security and economy. As of 14th June 2020, there were more than 7.5 million cases and approximately half a million death worldwide (WHO, 2020). Till now, there is neither a vaccine to stop the transmission of the SARS-CoV-2 virus nor effective antiviral drugs to cure and combat the COVID-19 disease (Paules et al., 2020). Given that there is no cure for COVID-19, it is imperative to explore other options to contain the propagation of the infection, especially about its transmission. The oral cavity is a significant point of entry for pathogenic agents, which is linked to the elocutionary process of SARS-CoV-2 especially in the inhalation of ambient particles in the air and the expectorations, considering that SARS-CoV-2 is abundantly present in nasopharyngeal and salivary sections of affected patients (Morawska & Cao, 2020; WHO, 2020).

Mouthwashes contain a wide variety of active ingredients which have been proven to modify the oral microbiota as well as reduce the viral load presence in the mouth. In particular, the efficacy of mouthwashes in inhibiting viruses such as Herpes Simplex Virus (HSV), Human Immunodeficiency Virus (HIV), Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Modified Vaccinia Virus Ankara (MVA) have been reported (Baqui, 2001 & Eggers, et al., 2015). The objective of this paper is to review the available evidence

surrounding the efficacy of mouthwash in reducing viral load of viral infections which could be beneficial in the case of COVID-19.

Materials and Method

We searched academic, English-scripted papers published between December 2019 and May 2020 on PubMed, MEDLINE, ScienceDirect, EMBASE, www.clinicaltrials.gov, WHO and the Cochrane Library databases. We searched for journals published between December 2019 and May 2020 and reviewed the reference lists of the included studies.

Search Strategy and Selection Criteria

The search phrases used included (mouthwash AND viral infection), (mouthwash trials AND COVID-19) and (Adults with respiratory viral infections on toothpaste). The keywords used were checked with the Medical Subject Headings (MESH) database. We used the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) flow chart (See Figure 1) to shows the flow chart of the articles included.

The titles and abstracts of all these articles were reviewed and a total of 98 studies excluded in addition to the removal of duplicate items identified through multiple database sources. The remaining articles were screened for quality by excluding the studies in which the subject matter was not directly addressed or evaluated. 35 records were excluded thereafter, while the remaining 44 articles were assessed for eligibility by a full text review. At the end of the review, five studies were entered into the final evaluation process. Details of the search strategy are given in the PRISMA diagram. All the results shown were evaluated and the articles that directly evaluated the subject matter were included in the final review (N = 5).

Inclusion criteria

We included all papers that relates to the subject matter as restriction were not placed on language and date of publication or articles in the resources found. This was due to the paucity of relevant studies relating to the subject matter.

Exclusion criteria

We excluded adults diagnosed with bacterial infections and people with underlying health conditions who had mouthwashes interventions. This is because such individuals are often placed on a different anti-microbial treatment plan, which might interfere with the study on the anti-viral efficacy of mouthwashes. Children and people with mental health conditions were excluded for us to conduct a more focused review.

Data collection and data analysis

Two review authors independently assessed the eligibility and quality of the retrieved papers using the Jadad scale. We were unable to conduct a meta-analysis of study outcomes, given the small number of included studies and their heterogeneity nature. Consequently, we did a narrative review to report on various types of mouthwashes trialed for reducing viral infections in people across multiple populations. We used the Population, Intervention/Indicator, Comparison, Outcome (PICO) to analyse the data retrieved. We provided a tabular summary of research findings on the efficacy of mouthwashes in reducing viral infections within the specified population.

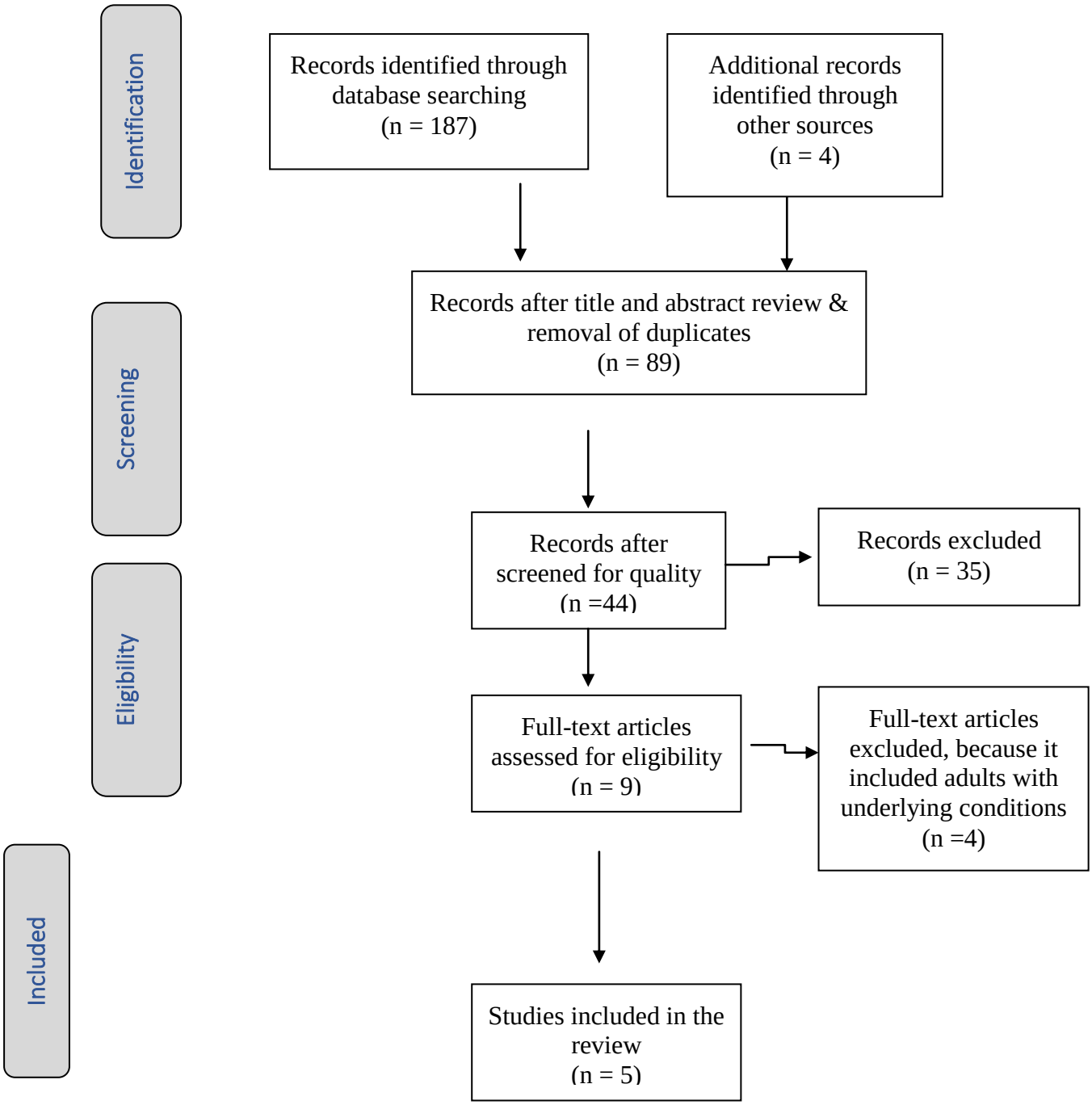

Figure 1: PRISMA Flow Diagram

Results

Tabular presentation of findings

Authors & Year	Study Design	Type of Mouthwash and constituents	Virus Tested	Experimentation	Outcome
Satomura et al (2005)	Randomised Trial	Water gargling, povidone-iodine gargling, and usual care (control). Participants were followed for 60 days.	Upper Respiratory Tract Infection (Influenza).	Subjects in the two gargling groups were requested to gargle with water or diluted povidone-iodine at least three times a day.	A Cox regression (proportional hazard model) revealed the efficacy of water gargling (hazard ratio=0.60, 95% CI=0.39-0.95).
Eggers et al. (2018)	Experimental (in-vitro)	Povidone-iodine (PVP-I) 7%	Severe Acute Respiratory Syndrome Middle East respiratory syndrome Rotavirus strain Influenza virus subtype H1N1	PVP-I 7% mouthwash was diluted 1:30 with water to a concentration of 0.23%.	PVP-I 7% gargle/mouthwash showed rapid viricidal efficacy in vitro at a concentration of 0.23% PVP-I. This suggests that the ingredient could provide a protective oropharyngeal hygienic measure during this pandemic.
Meiller, T. et al. (2005)	In-vivo (40 participants age 18 - 65)	Listerine	*Herpes simplex* virus	Participants asked to rinse for the 30s with $20cm^3$ of Listerine mouthwash or $20cm^3$ of sterile distilled waste for control patients	A significant difference ($p < 0.05$) was found between the control group and the experimental group at 30 min post rinse.
Dennison, D. et al. (1995)	Direct Exposure	Listerine	Herpes simplex type 1 and 2 Influenza A Rotavirus Adenovirus	Each virus was missed with an equal volume of Listerine for 30 seconds to 5 minutes, and the residual infectivity of the virus was assessed.	Exposure to Listerine for 30 seconds had an antiviral effect against herpes simplex type 1 and 2 (96.3 and 100% respectively), Influenza A (100%). At 5 minutes exposure, Listerine resulted in a 21.5% and 33.4% reduction in Rotavirus and Adenovirus respectively
(Yamanaka et al. 1994)	Direct Exposure	Listerine	MRSA & HIV	The viruses were exposed to Listerine for 30 seconds and the viral load measured afterwards	60% of HIV was inactivated by a 30 second exposure to 50% Listerine, while exposure for 30 seconds to Listerine killed MRSA completely

Narrative and Analytical Description of Result

The first reviewed paper, (Satomura et al., 2005) conducted a randomised trial, water gargling, povidone-iodine gargling, and usual care (control) on upper respiratory tract infection. Participants were followed for 60 days. Subjects in the two gargling groups were requested to rinse with water or diluted povidone-iodine at least three times a day. A Cox regression (proportional hazard model) revealed the efficacy of water gargling (hazard ratio=0.60, 95% CI=0.39-0.95).

The second reviewed paper, (Eggers et al., 2018) conducted an experimental study using Povidone-iodine (PVP-I) 7% in Severe Acute Respiratory Syndrome Middle East respiratory syndrome Rotavirus strain Influenza virus subtype (H1N1). PVP-I 7% mouthwash was diluted 1:30 with water to a concentration of 0.23%. PVP-I 7% gargle/mouthwash showed rapid viricidal efficacy *in vitro* at a level of 0.23% PVP-I. This finding suggests that the active ingredient (PVP-I) present in the mouthwash could provide a protective oropharyngeal hygienic measure during this pandemic.

The third reviewed paper (Meiller, T. et al. 2005) randomly assigned 40 patients to two treatment groups; mouthwash active ingredient (Listerine) and sterile control water. The efficacy of these two treatment groups (Listerine and Water) was tested in reducing the presence of viral contamination in oral fluids for at least 30 minutes after oral rinse. The paper suggested that the risk of viral cross contamination generated from these oral fluids in person to person contact is significantly reduced using Listerine.

The fourth and fifth reviewed papers, (Yamanaka et al., 1994; Dennison, et al., 2005) assessed the efficacy of Listerine antiviral effect in the mouth. This active mouthwash ingredient (Listerine) was tested against a number of viruses such as Herpes simplex type 1 and 2, Influenza A Rotavirus, Adenovirus, MRSA and HIV. The result concluded that exposure of the virus to Listerine for 30 seconds had an antiviral effect, which caused a 60-100% inactivation.

Discussion

It is not surprising that simple water gargling was inadequate to minimise cross-infection of COVID-19 as water has no antiviral properties and as such gargling with water will definitely not produce such effect. In addition, given the aggressiveness of COVID-19, it is less likely that simple water gargling will be adequate to minimise cross-infection of COVID-19. However, gargling with mouthwash ingredients such as povidone-iodine seems to be a measure that could be effective in reducing COVID-19 viral load. This is due to its established and published potent effect on viruses of the upper respiratory tract as corroborated by Meister et al., (2020). The authors (Meister et al., 2020) concluded that gargling with mouthwash cannot inhibit the production of viruses in the cells, however it could reduce viral load in the short term. This can be particularly useful and related to COVID-19 infection where the greatest potential for infection comes from the oral cavity and throat.

Another reviewed article, (Eggers et al., 2018), concluded that the active ingredient (PVP-I) present in the mouthwash could provide a protective oropharyngeal hygienic measure during this pandemic. The use of Povidone-iodine (PVP-I) 7% in Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), Rotavirus strain, Influenza virus subtype (H1N1) showed rapid viricidal efficacy. The efficacy of (PVP-I) in showing rapid viricidal effect when tested against MERS and SARS, is encouraging and promising, considering the fact that they are both closely related to SARS-CoV-2.

Moreover, the three experimental studies (Dennison, D. et al., 1995; Meiller, T. et al., 2015 and Yamanaka et al., 2020) trialed Listerine mouthwashes in three different viral infections with promising outcomes in patients infected with HIV, Adenovirus and Rotavirus. Given that the characteristics of these viruses differ from COVID-19 features, we cannot expressly indicate that Listerine will be efficacious in minimizing cross-transmission of COVID-19 until proven by a future study, however its potent effect on viruses is encouraging and worthy of further research.

The five papers reviewed showed that mouthwash is effective in reducing the viral load of the viruses tested against it. To buttress this point, a recent paper (Carrouel et al., 2020) suggested that active ingredients present in mouthwashes could provide valuable adjunctive treatment to reduce the viral load of saliva and nasopharyngeal microbiota, including potential SARS-CoV-2 carriage.

Recently, (Farzan & Firoozi, 2020) assessed the appropriate mouthwash to eliminate coronaviruses for pre-procedural rinsing in dental practice. The paper concluded that PVP-I is a promising substance to eliminate coronaviruses such as SARS-CoV, MERS-CoV and few other viruses. To this effect, PVP-I mouthwash is an approved mouthwash for pre-procedural rinsing in dental practices to eliminate coronaviruses. More randomised controlled trials are currently underway explicitly studying the effect of mouthwashes on SARS CoV-2.

CONCLUSION

In the absence of vaccines or medicines that have unfortunately arrived too late for many dead patients, it is vital that we explore simple day-to-day activities that can be optimised in combating this present COVID-19 pandemic. While we do not confirm that mouthwashes currently on the market could be used as a panacea for SARS CoV-2, nonetheless, our findings provide valuable information on mouthwashes that could possibly be beneficial in reducing the viral load of this killer micro-organism.

This review buttresses the evidence that certain commercially available mouthwashes can inactivate SAR-Cov-2 virus or reduce the viral load in the throat and mouth. However, the mouthwashes are not suitable for treating COVID-19 patients and do not serve as a protective mechanism against the virus. There is need for further clinical studies to determine the efficacy of mouthwashes on SARS-CoV-2. This could be done in-vitro using cell culture experiments and in-vivo experiments which compares the viral loads in the oral cavity and throat of COVID-19 patients before and after mouthwash use.

References

Baqui A., Kelley J., Jabra-Rizk M., DePaola L., Falkler W., & Meiller T. (2001). In vitro effect of oral antiseptics on human immunodeficiency virus-1 and herpes simplex virus type 1. Journal of Clinical Periodontology. 28(7): 610-616.

Belouzard S., Millet J., Licitra B., & Whittaker, G. (2012). Mechanisms of Coronavirus Cell Entry Mediated by the Viral Spike Protein. Viruses, 4(6): 1011-1033.

Cecílio A., Cândido A., Resende M., Bontempo E., & Martins A. (2000). Detection of mouse hepatitis virus in mouse colonies using the nested polymerase chain reaction. ArquivoBrasileiro de MedicinaVeterinária e Zootecnia. 52(4): 307-312.

Carrouel F., Conte M., Fisher J., Gonçalves L., Dussart C., Llodra J., & Bourgeois D. (2020). COVID-19: A Recommendation to Examine the Effect of Mouth rinses with β-Cyclodextrin

Combined with Citrox in Preventing Infection and Progression. Journal of Clinical Medicine. 9(4): 1126.

Dennison D., Meredith G., Shillitoe E., & Caffesse R. (1995). The antiviral spectrum of Listerine antiseptic. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology: 79(4): 442-448.

Eggers M., Eickmann M., & Zorn J., (2015). Rapid and Effective Virucidal Activity of Povidone-Iodine Products Against Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Modified Vaccinia Virus Ankara (MVA). Infectious Diseases and Therapy. 4(4): 491-501.

Eggers M., Koburger-Janssen, T., Eickmann M., & Zorn J. (2018). In Vitro Bactericidal and Virucidal Efficacy of Povidone-Iodine Gargle/Mouthwash Against Respiratory and Oral Tract Pathogens. Infectious Diseases and Therapy. 7(2): 249-259.

Kendall E, Bynoe M, & Tyrrell D., (1962). Virus Isolations from Common Colds Occurring in a Residential School. BMJ, 2(5297): 82-86.

Liu Q., & Gerdts V (2019). Transmissible Gastroenteritis Virus of Pigs and Porcine Epidemic Diarrhoea Virus in Module in Life Sciences (Elsevier B.V) https://www.sciencedirect.com/science/article/pii/B978012809633820928X Accessed 14 June 2020.

Keep S M., Bickerton E., & Britton P (2015) in Coronaviruses: Methods and Protocols, (New York, Springer Verlag), pp 115 -134.

Meister T., Brüggemann Y., Todt, D., Conzelmann, C., Müller, J., & Groß, R. et al. (2020). Virucidal Efficacy of Different Oral Rinses Against Severe Acute Respiratory Syndrome Coronavirus 2. The Journal of Infectious Diseases.

Meiller T., Silva A., Ferreira S., Jabra-Rizk M., Kelley J.,& DePaola L., (2005). Efficacy of Listerine Antiseptic in reducing viral contamination of saliva. Journal of Clinical Periodontology. 32(4): 341-346.

Morawska L., & Cao J., (2020). Airborne transmission of SARS-CoV-2: The world should face the reality. Environment International. 139(1): 105730.

PalM., Berhanu G., Desalegn C., & Kandi V (2020). Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2): An Update. Cureus, 12(3): 7423.

Paules C., Marston H., & Fauci A (2020). Coronavirus Infections - More Than Just the Common Cold. JAMA. 323(8): 707.

Satomura K., Kitamura T., Kawamura T., Shimbo T, Watanabe M., Kamei M., Takano Y& Tamakoshi A (2005). Prevention of Upper Respiratory Tract Infections by Gargling: A Randomized Trial. American Journal of Preventive Medicine. 29(4): 302-307.

Schalk A (1931). An apparently new respiratory disease of baby chicks. J Am Vet Med Assoc. 78(19): 413 - 422.

Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, Iosifidis C, & Agha R, (2020). World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). International Journal of Surgery. 76(1): 71-76.

Tyrrell D, & Bynoe M (1965). Cultivation of a Novel Type of Common-cold Virus in Organ Cultures. BMJ. 1(5448): 1467-1470.

WHO (2020). Naming the Coronavirus Disease (COVID-19) And the Virus That Causes It. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it Accessed 14 June 2020.

WHO (2020). Coronavirus. https://www.who.int/emergencies/diseases/novel-coronavirus-2019 Accessed 14 June 2020.

WHO (2020). Coronavirus Disease (COVID-19) Situation Report–143. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200611-covid-19-sitrep-143.pdf?sfvrsn=2adbe568_4 Accessed 2 June 2020.

Wood A, & Payne D, (1998). The action of three antiseptics/disinfectants against enveloped and non-enveloped viruses. Journal of Hospital Infection. 38(4): 283-295.

Yamanaka A, Hirai K, Kato T, Naito Y, Okuda K, Toda, S. & Okuda K (1994). Efficacy of Listerine antiseptic against MRSA, Candida albicans and HIV. Bulletin of Tokyo Dental College. 35(1): 23-6.