

Entry

# COVID-19 and Dentistry

Hugh Devlin<sup>1</sup> and Parisa Soltani<sup>2,\*</sup> 

<sup>1</sup> Division of Dentistry, School of Medical Sciences, Faculty of Biology, Medicine & Health, The University of Manchester, Manchester M13 9PL, UK; hugh.devlin@manchester.ac.uk

<sup>2</sup> Department of Oral and Maxillofacial Radiology, Dental Implants Research Center, Dental Research Institute, School of Dentistry, Isfahan University of Medical Sciences, Isfahan 81746, Iran

\* Correspondence: p.soltani@dnt.mui.ac.ir

**Definition:** Dentistry is a healthcare profession requiring close contacts between the dental practitioner and the patient. In particular, many dental procedures generate aerosols and droplets which are proved to be the major transmission route for COVID-19.

**Keywords:** COVID-19; SARS-CoV-2; dentistry

## 1. A Global Perspective

According to the World Health Organization (WHO), the coronavirus disease 2019 (COVID-19) pandemic had, of April 2021, killed 2,850,521 people with most countries affected. The USA has accounted for nearly 20% of these deaths. There are many reasons for the wide disparity in death rates of different countries, such as the societal and political reactions to the infection, the clustering of infection in large cities, habitation in crowded multi-generation households as well as the underlying health and age profile of the population. Although the fatality rate is below 1% of the population, those infected can require mechanical ventilation and can suffer prolonged symptoms during their recovery phase. The most common of these post-infection symptoms include insomnia, fatigue and memory loss. About 2% of patients who have suffered COVID-19 go on to have these symptoms for more than 3 months.

The COVID-19 pandemic has ravaged Europe, India and the Americas, while countries such as China and South Korea have put in place containment measures quickly and thereby reduced the spread of the disease. Thailand and Vietnam are examples of countries that had minor outbreaks that were quickly controlled. New Zealand, Australia and China quickly contained the disease in their countries and then put in place strict border controls to prevent re-infections coming into the country. China, Hong Kong, Singapore, and Taiwan had previous experience with severe acute respiratory syndrome (SARS), a coronavirus outbreak in 2002–2003. Both SARS and COVID-19 are spread by droplet infection and can cause a severe respiratory illness. The Chinese government eradicated SARS by taking containment measures such as cancelling the 1 May national holiday, instituting school closures, etc. This demonstrated the value of lockdown measures.

With the present COVID-19 pandemic, those countries that were slow to put containment measures in place have seen the worst rise in deaths. Containment measures include prohibiting social gathering and instituting testing programmes, tracing those who test positive, and requiring them to self-isolate. With re-emergence of the infection in second and third waves, political leadership has been needed to combat public complacency. With continued spread of the virus, variants have arisen due to genetic drift (UK variant B117 variant; South African variant (B1351, 501Y, V2) and the Brazilian variant (P1 variant)). These variants are more transmissible.

At the peak of the pandemic, the health system in Italy was put under great pressure, which forced the Italian government to close all non-essential businesses and industries in March 2020. Governments have used the lockdown measures to protect their health



**Citation:** Devlin, H.; Soltani, P. COVID-19 and Dentistry. *Encyclopedia* **2021**, *1*, 496–504. <https://doi.org/10.3390/encyclopedia1020041>

Academic Editor: Stephen Bustin

Received: 20 May 2021  
Accepted: 17 June 2021  
Published: 21 June 2021

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Copyright:** © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

systems and prevent them from being overwhelmed. The pandemic has seen a general reorganisation of the healthcare workforce with volunteers and retired clinicians helping to fill gaps left by staff falling sick. Healthcare workers have suffered increases in stress-related illness due to changes in routine [1]. In most African countries (except South Africa) there have been comparatively fewer infections per head of the population. However, developing countries have limited resources to undertake mass testing and intensive care facilities are inadequate.

In those countries that have quickly rolled out an effective vaccination programme, such as USA and the United Kingdom, a reduced infection rate has resulted. There is a disparity between the vaccination rates of these wealthier countries that can afford the vaccines and that of developing countries which do not have the necessary resources to cope. COVAX is a programme coordinated by the World Health Organization that aims to ensure fairer vaccine access and it should result in a wider distribution of vaccines later in 2021.

## 2. Dentistry and Coronavirus Disease 2019 (COVID-19)

Patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may be asymptomatic or develop symptoms such as a cough, fever and a loss of smell. Some patients develop more severe symptoms such as difficulty in breathing that may require hospitalization, intubation and oxygen therapy. The disease spreads by droplet transmission, so it might reasonably be hypothesized that dentists would be among the professions with the highest death rate if they had continued treatment in the same way as pre-pandemic. For deaths in the England and Wales registered between March and December 2020, there is no evidence that dentists suffered a higher death rate due to COVID-19 [2]. However, any analysis by occupation is difficult as there are many other factors that cannot be quantified easily e.g., occupation of a partner, the use of personal protective equipment, the gender and age mix in a profession and other socio-economic factors which may be more important in predicting whether an individual becomes infected and dies. During the pandemic, dentists in the UK changed to providing a triage system involving remote consultations to assess the risk of transmission with treatment limited to advice, analgesia and antimicrobial treatment in the first instance. Those patients with confirmed COVID-19 were referred for face-to-face care at designated Urgent Dental Care Centres only. The low infection rate amongst dentists is due to these safety policies, measuring the temperature of patients and staff, the disinfection of surfaces and the wearing of personal protective equipment.

In a web survey of US dentists held in June 2020, 20 of the 2195 respondents (0.91%) reported that they had been infected with SARS-CoV-2, but only a relatively small minority of respondents had received a SARS-CoV-2 test (16.6%) to prove their infectivity [3]. A large proportion of individuals who become infected remain asymptomatic which is problematic in a self-completed questionnaire. The true figure of infected dentists may not be known.

When the pandemic struck, regulatory agencies across the European Union required dentists to limit the treatment provided to patients and provided financial relief to a varying extent.

## 3. Transmission of COVID-19

The spread of the virus SARS-CoV-2 is by droplet infection in the community. Spread occurs from those who are infected but also from asymptomatic individuals and those in the early stages of the disease who have not yet shown symptoms. Data from China has shown that asymptomatic and symptomatic patients have the same amount of viral load [4]. Asymptomatic individuals might unknowingly spread the disease, a difficult problem for authorities trying to control the viral spread. Up-to-date information about the spread of the virus is essential, especially where local “hot-spots” are present so that effective community containment measures can be put in place. Rapid testing of infected individuals allows those who test positive to self-isolate and prevent the spread of the

disease. Additionally, the contacts of those testing positive also need to be traced and asked to self-isolate. This requires considerable expenditure and use of resources, which are not readily available in poorer countries.

A false positive test happens when the test is positive but the reality is that no disease is present. A false negative occurs when the patient truly has the disease but the test says he does not. Brooks and Das [5] provide an online modelling calculator which allows the reader to calculate the risks and costs associated with COVID tests of different false positive and false negative results. They showed that when the prevalence of the disease is low, the cost of false positives is greater than that of true positives. As the prevalence of the disease declines, the significance of a false positive result becomes evident by the number of individuals that unnecessarily self-isolate [6]. This can have severe consequences for patient care if nurses and doctors are affected as they are then unable to care for patients.

A positive diagnosis of SARS-CoV-2 infection depends on the detection of viral RNA. The gold standard method uses an automated reverse transcription polymerase chain reaction (RT-PCR) method, which allows rapid testing of larger numbers of samples than manual methods [7]. Other antigen tests are available, but are less sensitive as they do not amplify the antigen. However, they may provide a cheaper and more affordable alternative to poorer countries.

The pathogenicity of the virus derives from the nucleocapsid protein inside the virus and an external spike glycoprotein [8]. In addition, changes in the spike protein may increase the viral infectivity [9]. It is the receptor-binding domain on the spike protein which binds to the respiratory cellular surface angiotensin convertase enzyme 2 (ACE2) receptor to gain entry into the cell. Many vaccines have been targeted at the spike protein in view of its essential role in viral transmission.

The RT-PCR test is unable to provide any information about whether an individual has had a past infection. That information is only available with the antibody test. IGG and IGM antibodies to SARS-CoV-2 only become detectable at one to three weeks after the onset of the infection. Although not known definitively, the presence of SARS-CoV-2 IgG does not indicate immunity to further infection. However, in experiments in macaque monkeys infected with SARS-CoV-2 it was shown that they had some immunity to re-infection for about one month [10]. However, this paper was in a pre-print form and, therefore, not peer-reviewed.

#### 4. Protection Mechanisms in the Dental Setting

Vaccination has provided an effective method of controlling the spread of COVID-19. By taking the vaccine, healthcare workers are, therefore, protecting themselves and their patients, but some people have legitimate reasons for not having the vaccine. Extremely rarely, some patients have reported blood clots with low levels of platelets (thrombocytopenia) after receiving the AstraZeneca COVID-19 vaccine. Those affected may complain of persistent headache or abdominal pain, or swelling of the legs for four or more days after the injection. For the older population, the risk to benefit ratio is heavily in favour of receiving the vaccine. At the other end of the age spectrum, deaths due to COVID-19 in children have been extremely rare [11].

Use of dental handpieces can generate aerosols in the dental office that have the potential to spread infection if inhaled. Advice on measures to protect dental staff and patients undertaking aerosol generating procedures is given by the Care Quality Commission as follows-

<https://www.cqc.org.uk/guidance-providers/dentists/dental-mythbuster-31-personal-protective-equipment-requirements-during> (Accessed on 19 April 2021).

This includes dental staff wearing “a long-sleeved disposable fluid repellent gown (covering the arms and body) or disposable fluid repellent coveralls, a filtering face piece class 3 (FFP3) respirator, a full-face shield or visor and gloves”. The fit of the respirator should be checked to ensure that all airborne particles are excluded.

A recent review examined whether providing antimicrobial mouthwashes prior to undertaking a dental procedure would be beneficial in preventing the spread of COVID-19 [12]. Although this found no completed randomized controlled trials, the issue requires investigation as it may provide benefits. On the other hand, the medicaments used may produce allergic reactions or staining of the teeth depending on which one is used.

Hand washing by all dental staff is important to prevent infection and should be undertaken before putting on and after removing the personal protective equipment. Patients should be given access to alcohol disinfection rubs and asked to avoid touching their eyes, nose and mouth. It is reassuring that due to widespread dissemination of public health measures, surveys of the general public show a good knowledge of the routes of transmission and adherence to personal protection procedures [13].

## 5. Oral Symptoms

Containment of this infection in any healthcare setting must involve reduction of saliva and droplet spread. The ribonucleic acid (RNA) of SARS-CoV-2 is present in saliva samples of patients [14] and salivary glands and can be a reservoir for SARS-CoV-2 in infected patients. In experiments involving infection of rhesus macaque monkeys with SARS-CoV-2, the epithelial cells of the salivary duct cells were infected early [15]. Indeed, expression of ACE2 receptors is shown to be higher in minor salivary glands compared with the lungs [16]. Case reports describe symptoms of inflammation of the parotid salivary gland in patients with confirmed COVID-19 [17,18]. Sialadenitis can lead to salivary retention and reduced salivary flow, which can contribute to xerostomia and altered taste sensation.

Loss of taste and smell are some of the earliest symptoms of SARS-COV-2 infection and could form an important early screening test in predicting the spread of the disease in the population. The aetiology of these symptoms is not known, but could involve damage to the receptors or nerves. SARS-COV-2 can cause direct neural invasion, spread via the blood stream or via infected leukocytes. The virus has been detected post mortem in the brain neural and capillary endothelial cells [19].

According to a recent systematic review, the most common oral manifestations of COVID-19 are taste disorders with an overall prevalence of 45%. Among different gustatory dysfunctions, dysgeusia, distorted taste perception, is more common, followed by hypogeusia, which is a decrease in taste sensitivity, and ageusia, lack of taste sensation [20]. However, prevalence of taste alterations varies between 11% to 88% in different studies [21]. The mean duration for gustatory disorders was reported to be 15 days [20]. A prospective case-control study with a 6-month follow-up showed that gustatory dysfunctions resolved partially or totally in 88% of the cases. Oral dyspnea and nasal obstruction were reported to be risk factors for poor gustatory recovery [22]. In addition, according to another study, subjects with severe loss of taste recovered later than those with mild loss [23]. Taste alteration significantly correlated with mild/moderate COVID-19 cases and was more prevalent in female patients [20]. Paderno et al. [23] hypothesize that gustatory dysfunction is secondary to high oral viral load, leading to neural damage. Therefore, virus-induced neural disturbance could last much longer than the presence of the virus itself [24]. Additionally, COVID-19-induced sialadenitis can result in changes in salivary flow rate and eventually cause altered taste sensation [25].

Oral mucosal lesions subsequent to COVID-19 infection can vary in location, size, appearance and quantity. The observed lesions are either ulcers, erosions, bullae, vesicles, pustules, or a fissured or depapillated tongue, macules, papules, plaques, pigmentation, whitish areas, hemorrhagic crusts, necrosis, petechiae, swelling, erythema, xerostomia and spontaneous bleeding [26,27]. Based on a systematic review of case reports, oral lesions were more common on the tongue, labial mucosa and palate [20]. Based on another review study, patients with oral mucosal lesions had symptoms such as burning sensation, pain, and pruritus in 68% of the cases. The time between onset of systemic symptoms of COVID-19 and oral mucosal lesions was from 4 days prior to 12 weeks after the systemic symptoms, although in some cases oral lesions preceded systemic symptoms [26]. In addition, these

lesions healed within 3–28 days after appearance by topical or systemic treatments, oral hygiene, or spontaneously [20,26]. A suggested differential diagnosis of the oral mucosal lesions includes aphthous stomatitis, herpetiform lesions, mucositis, drug-induced eruption, necrotizing periodontal disease, Kawasaki-like lesions, erythema-multiform-like lesions, angina bullosa-like lesions, angular cheilitis, atypical Sweet syndrome, and Melkersson–Rosenthal syndrome [26]. As mentioned, ACE2 receptors are abundantly expressed in the oral cavity cells. Interaction of this transmembrane receptor with the spike protein of SARS-CoV-2 allows for merging of the virus with the cell. Similar to other viral infections, the genetic material of the virus then uses the cell organelles for replication, ultimately ending in lysis of infected cells. This process can manifest as different oral lesions reported in the literature. However, other infectious, inflammatory, and autoimmune disorders, such as opportunistic infections, medication-related effects, and multi-system involvement can also play a role in the pathogenesis of oral mucosal lesions.

The presence of ACE2 and other receptors linked to COVID-19 infection have been demonstrated in human pulpal and periodontal cells and has prompted researchers to hypothesize links between COVID-19 infection and pulpitis and periodontitis [28–31]. However, these hypotheses still need to be backed by stronger evidence.

## 6. Role of Saliva as a Diagnostic Tool

The standard method for detection of SARS-CoV-2 is RT-PCR of samples from oropharyngeal or nasopharyngeal swabs. Saliva samples have also been considered as potential diagnostic specimens for detection of viral particles. In contrast to oropharyngeal or nasopharyngeal samples, collection of salivary samples does not require trained healthcare staff and can be self-administered. This option can be helpful in decreasing the exposure of public and healthcare personnel to infection with SARS-CoV-2 through reducing unnecessary visits of potentially infected people to medical laboratories. Moreover, alleviating the workload could reduce human-resource costs. In addition, collecting salivary samples is easier and more comfortable than pharyngeal or sputum specimens [32–34]. Several studies have attempted to compare the diagnostic value of salivary samples in detection of SARS-CoV-2 RNA with nasopharyngeal swabs. Hanege et al. compared the positivity rate of different body fluids in confirmed COVID-19 cases. They found that saliva has the highest positivity rate (76.3%), followed by tears (55.3%) and cerumen (39.5%) [35]. In another study, Nacher et al. reported a sensitivity of 77% and 24% for symptomatic and asymptomatic patients for salivary samples, respectively. Based on their findings, the sensitivity considerably decreases in patients who have no COVID-19 symptoms. Another interesting finding in their study was that about 6% of their enrolled cases had negative nasopharyngeal swabs, while their salivary specimen was positive for the presence of SARS-CoV-2 RNA [36]. This can be partly due to the difficulty of obtaining proper pharyngeal samples which can cause patient discomfort. A meta-analysis showed a sensitivity of 91% (confidence interval (CI) 80–99%) for saliva samples compared with 98% (CI 89–100%) for nasopharyngeal swabbing [37]. The specificity of saliva samples is also reported to be not higher than 42% [38]. Additionally, a systematic review of articles reported that saliva can be effectively used for short- and long-term monitoring of humoral immunity against SARS-CoV-2 through primary infection or vaccines [39].

Three conditions are required for optimal salivary testing of SARS-CoV-2: a standardized method for collecting saliva must be selected based on studies comparing different methods of salivary collection; an optimal transport and storage medium for saliva specimens must be introduced; and an appropriate RNA assay must be optimized for detection of viral RNA within saliva samples [40,41]. Accordingly, the Food and Drug Administration (FDA) has granted emergency use authorization to some saliva-based SARS-CoV-2 test kits [37]. Several rapid salivary testing kits are used for mass screening purposes. However, negative rapid testing in the presence of symptoms of COVID-19 infection might show the need for pharyngeal swabbing techniques.

## 7. Dental Education during the COVID-19 Pandemic

The COVID-19 pandemic situation has considerably affected higher education and dental education in particular. Dentistry is a scientific field which deals with hands-on practice as well as theoretical science. Dental education requires sufficient pre-clinical and clinical training in order to ensure that the future dental professionals are competent. It is probable that the most important challenge in dental education during the ongoing pandemic is trying to balance maintaining the health of students, faculty members, personnel, and patients with the continuity in dental educational programs in the dynamic and ever-changing setting of a health crisis. Although regional differences between the lockdown policies, outbreak severity, and availability of resources all influence the function of dental schools during the pandemic, the response of dental educational institutions to the COVID-19 pandemic has some similarities [42]. For instance, distance learning has come to the forefront of theoretical dental education in many institutions. While e-learning has been around for quite some time, it has flourished as a result of the COVID-19 pandemic. Synchronous online teaching methods can be employed when interaction with the participants is required. Asynchronous methods can also be used but the instructor must ensure that the educational content is delivered in the most efficient way. Different online platforms have been used by dental schools for organizing video conferences, journal clubs, and webinars [43]. However, access to a high-speed internet connection is an obstacle for many dental students and faculty members in different geographical locations, which can worsen the educational inequality within an institution or among different institutions.

While distance learning might be a commonly adopted strategy for higher education in different fields, a unique challenge for dental education is reliance on clinical experience requirements for achieving competency in performing dental treatments. As many of these dental procedures produce considerable amounts of aerosols and droplets, health authorities have recommended suspension of routine and elective dental treatments. Therefore, the practical training of novice dental students has been affected by the current pandemic state. Dental educators have innovatively responded to these challenges. For instance, virtual slides using full-slide images have yielded positive outcomes for oral pathology courses compared with conventional microscopic training [44]. Using virtual patients is another case-based teaching strategy to improve the students' diagnostic and clinical judgement skills. A foreseeable perspective in dental laboratory and pre-clinical education is using virtual reality systems [45]. With the ongoing pandemic, university administrations must look into different strategies to ensure sufficient competency of graduated dentists in clinical settings, namely extending the duration of clinical courses and planned patient recruitment, or revising clinical requirements for different practical courses.

## 8. What Is the Future Post-COVID-19?

The future patient experience of dentistry depends on any further mutations of the virus, which will govern its infectivity and virulence. Almost certainly, ongoing strict procedures to eliminate the spread of COVID-19 will be needed in dental surgeries, especially where aerosol-generating procedures are involved. This will involve wearing appropriate personal protective equipment, such as FFP2 or FFP3 masks, and regular swab testing of dental staff for infection. There was early enthusiasm that hydroxychloroquine or azithromycin would be effective treatments against COVID-19. Azithromycin is a safe, broad spectrum antibiotic that has been shown to have some *in vitro* action against the Zika virus and rhinovirus [46]. Hydroxychloroquine is already used to prevent and treat malaria. Clinical trials are ongoing to determine the effectiveness of both drugs but, at present, COVID-19 containment relies on public health measures and vaccination programmes.

There is a considerable backlog of dental need since lockdown began early in 2020, but the landscape is changing with many calls in different countries for a reorganisation of the provision of dentistry. Whether patients return to have routine care in the post-COVID era is unknown, but given the reluctance of many dentists to undertake aerosol-generating procedures, they will have a greater emphasis on minimally invasive dentistry

and preventive dentistry in their daily practice. Dental teachers are also re-thinking the way they provide education for dental students. The theoretical content of these courses can be shared online using video conferencing and webinar tools. This has required adaptation by teachers and students.

For many, the era of the daily commute to work has ended as they have found that it is more productive to work from home, but it has created a sense of isolation and an increased prevalence of mental stress and anxiety. The pandemic has given us a greater appreciation of the value of social contact and a deeper appreciation that what happens on the other side of the world can affect our daily lives.

**Author Contributions:** Conceptualization, H.D. and P.S.; validation, H.D. and P.S.; investigation, H.D. and P.S.; writing—original draft preparation, H.D. and P.S.; writing—review and editing, H.D.; supervision, H.D. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not Applicable.

**Informed Consent Statement:** Not Applicable.

**Data Availability Statement:** Not Applicable.

**Conflicts of Interest:** The authors declare no conflict of interest.

**Entry Link on the Encyclopedia Platform:** <https://encyclopedia.pub/12210>.

## References

- Mattila, E.; Peltokoski, J.; Neva, M.H.; Kaunonen, M.; Helminen, M.; Parkkila, A.-K. COVID-19: Anxiety among hospital staff and associated factors. *Ann. Med.* **2021**, *53*, 237–246. [[CrossRef](#)]
- Windsor-Shellard, B.; Nasir, R. Coronavirus (COVID-19) Related Deaths by Occupation, England and Wales: Deaths Registered between 9 March and 28 December 2020. Available online: [https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofdeath/bulletins/coronaviruscovid19relateddeathsbyoccupationenglandandwales/deathsregisteredbetween9marchand28december2020#:~:text=There%20were%207%2C961%20deaths%20involving,\(2%2C833%20deaths\)%20among%20women](https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofdeath/bulletins/coronaviruscovid19relateddeathsbyoccupationenglandandwales/deathsregisteredbetween9marchand28december2020#:~:text=There%20were%207%2C961%20deaths%20involving,(2%2C833%20deaths)%20among%20women) (accessed on 5 November 2020).
- Estrich, C.G.; Mikkelsen, M.; Morrissey, R.; Geisinger, M.L.; Ioannidou, E.; Vujicic, M.; Araujo, M.W. Estimating COVID-19 prevalence and infection control practices among US dentists. *J. Am. Dent. Assoc.* **2020**, *151*, 815–824. [[CrossRef](#)] [[PubMed](#)]
- Zou, L.; Ruan, F.; Huang, M.; Liang, L.; Huang, H.; Hong, Z.; Yu, J.; Kang, M.; Song, Y.; Xia, J. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *N. Engl. J. Med.* **2020**, *382*, 1177–1179. [[CrossRef](#)]
- Brooks, Z.C.; Das, S. COVID-19 Testing: Impact of Prevalence, Sensitivity, and Specificity on Patient Risk and Cost. *Am. J. Clin. Pathol.* **2020**, *154*, 575–584. [[CrossRef](#)] [[PubMed](#)]
- Surkova, E.; Nikolayevskyy, V.; Drobniowski, F. False-positive COVID-19 results: Hidden problems and costs. *Lancet Respir. Med.* **2020**, *8*, 1167–1168. [[CrossRef](#)]
- Pfefferle, S.; Reucher, S.; Nörz, D.; Lütgehetmann, M. Evaluation of a quantitative RT-PCR assay for the detection of the emerging coronavirus SARS-CoV-2 using a high throughput system. *Eurosurveillance* **2020**, *25*, 2000152. [[CrossRef](#)] [[PubMed](#)]
- Gussow, A.B.; Auslander, N.; Faure, G.; Wolf, Y.I.; Zhang, F.; Koonin, E.V. Genomic determinants of pathogenicity in SARS-CoV-2 and other human coronaviruses. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 15193–15199. [[CrossRef](#)] [[PubMed](#)]
- Yoshimoto, F.K. A Biochemical Perspective of the Nonstructural Proteins (NSPs) and the Spike Protein of SARS CoV-2. *Protein J.* **2021**, 1–36. [[CrossRef](#)]
- Bao, L.; Deng, W.; Gao, H.; Xiao, C.; Liu, J.; Xue, J.; Lv, Q.; Liu, J.; Yu, P.; Xu, Y. Reinfection could not occur in SARS-CoV-2 infected rhesus macaques. *BioRxiv* **2020**. [[CrossRef](#)]
- Ludvigsson, J.F. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr.* **2020**, *109*, 1088–1095. [[CrossRef](#)]
- Burton, M.J.; Clarkson, J.E.; Goulao, B.; Glenny, A.-M.; McBain, A.J.; Schilder, A.G.; Webster, K.E.; Worthington, H.V. 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. *Cochrane Database Syst. Rev.* **2020**, *9*, CD013627.
- Bazaid, A.S.; Aldarhami, A.; Binsaleh, N.K.; Sherwani, S.; Althomali, O.W. Knowledge and practice of personal protective measures during the COVID-19 pandemic: A cross-sectional study in Saudi Arabia. *PLoS ONE* **2020**, *15*, e0243695. [[CrossRef](#)] [[PubMed](#)]
- Pasomsub, E.; Watcharananan, S.P.; Boonyawat, K.; Janchompoo, P.; Wongtabtim, G.; Suksuwan, W.; Sungkanuparph, S.; Phuphuakrat, A. Saliva sample as a non-invasive specimen for the diagnosis of coronavirus disease 2019: A cross-sectional study. *Clin. Microbiol. Infect.* **2021**, *27*, e281–e285. [[CrossRef](#)]

15. Liu, L.; Wei, Q.; Alvarez, X.; Wang, H.; Du, Y.; Zhu, H.; Jiang, H.; Zhou, J.; Lam, P.; Zhang, L. Epithelial cells lining salivary gland ducts are early target cells of severe acute respiratory syndrome coronavirus infection in the upper respiratory tracts of rhesus macaques. *J. Virol.* **2011**, *85*, 4025–4030. [[CrossRef](#)] [[PubMed](#)]
16. Xu, J.; Li, Y.; Gan, F.; Du, Y.; Yao, Y. Salivary Glands: Potential Reservoirs for COVID-19 Asymptomatic Infection. *J. Dent. Res.* **2020**, *99*, 989. [[CrossRef](#)] [[PubMed](#)]
17. Lechien, J.R.; Chetrit, A.; Chekkoury-Idrissi, Y.; Distinguin, L.; Ciciu, M.; Saussez, S.; Berradja, N.; Edjlali, M.; Hans, S.; Carlier, R. Parotitis-Like Symptoms Associated with COVID-19, France, March–April 2020. *Emerg. Infect. Dis.* **2020**, *26*, 2270–2271. [[CrossRef](#)]
18. Fisher, J.; Monette, D.L.; Patel, K.R.; Kelley, B.P.; Kennedy, M. COVID-19 associated parotitis. *Am. J. Emerg. Med.* **2021**, *39*, e251–e254. [[CrossRef](#)]
19. Paniz-Mondolfi, A.; Bryce, C.; Grimes, Z.; Gordon, R.E.; Reidy, J.; Lednicky, J.; Sordillo, E.M.; Fowkes, M. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). *J. Med. Virol.* **2020**, *92*, 699–702. [[CrossRef](#)]
20. Amorim dos Santos, J.; Normando, A.; Carvalho da Silva, R.; Acevedo, A.; De Luca Canto, G.; Sugaya, N.; Santos-Silva, A.; Guerra, E. Oral manifestations in patients with COVID-19: A living systematic review. *J. Dent. Res.* **2021**, *100*, 141–154. [[CrossRef](#)]
21. Cirillo, N.; Bizzoca, M.E.; Lo Muzio, E.; Cazzolla, A.P.; Lo Muzio, L. Gustatory dysfunction in COVID-19 patients: A rapid systematic review on 27,687 cases. *Acta Odontol. Scand.* **2021**, 1–8. [[CrossRef](#)]
22. Riestra-Ayora, J.; Yanes-Diaz, J.; Esteban-Sanchez, J.; Vaduva, C.; Molina-Quiros, C.; Larran-Jimenez, A.; Martin-Sanz, E. Long-term follow-up of olfactory and gustatory dysfunction in COVID-19: 6 months case–control study of health workers. *Eur. Arch. OtoRhino Laryngol.* **2021**, 1–7. [[CrossRef](#)]
23. Rojas-Lechuga, M.J.; Izquierdo-Domínguez, A.; Chiesa-Estomba, C.; Calvo-Henríquez, C.; Villarreal, I.M.; Cuesta-Chasco, G.; Bernal-Sprekelsen, M.; Mullol, J.; Alobid, I. Chemosensory dysfunction in COVID-19 out-patients. *Eur. Arch. Oto Rhino Laryngol.* **2021**, *278*, 695–702. [[CrossRef](#)] [[PubMed](#)]
24. Paderno, A.; Mattavelli, D.; Piazza, C. Long-term Olfactory and Gustatory Dysfunction May Be Related to Neural Damage. *Otolaryngol. Head Neck Surg.* **2021**. [[CrossRef](#)] [[PubMed](#)]
25. Keyhan, S.O.; Fallahi, H.R.; Cheshmi, B. Dysosmia and dysgeusia due to the 2019 Novel Coronavirus; a hypothesis that needs further investigation. *Maxillofac. Plast. Reconstr. Surg.* **2020**, *42*, 9. [[CrossRef](#)]
26. Iranmanesh, B.; Khalili, M.; Amiri, R.; Zartab, H.; Aflatoonian, M. Oral manifestations of COVID-19 disease: A review article. *Dermatol. Ther.* **2021**, *34*, e14578. [[CrossRef](#)]
27. Brandini, D.A.; Takamiya, A.S.; Thakkar, P.; Schaller, S.; Rahat, R.; Naqvi, A.R. Covid-19 and oral diseases: Crosstalk, synergy or association? *Rev. Med. Virol.* **2021**. [[CrossRef](#)]
28. Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; Krüger, N.; Herrler, T.; Erichsen, S.; Schiergens, T.S.; Herrler, G.; Wu, N.-H.; Nitsche, A. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* **2020**, *181*, 271–280. [[CrossRef](#)]
29. Galicia, J.C.; Guzzi, P.H.; Giorgi, F.M.; Khan, A.A. Predicting the response of the dental pulp to SARS-CoV2 infection: A transcriptome-wide effect cross-analysis. *Genes Immun.* **2020**, *21*, 360–363. [[CrossRef](#)]
30. Patel, J.; Woolley, J. Necrotizing periodontal disease: Oral manifestation of COVID-19. *Oral Dis.* **2020**, *27* (Suppl. 3), 768–769. [[CrossRef](#)]
31. Sakaguchi, W.; Kubota, N.; Shimizu, T.; Saruta, J.; Fuchida, S.; Kawata, A.; Yamamoto, Y.; Sugimoto, M.; Yakeishi, M.; Tsukinoki, K. Existence of SARS-CoV-2 entry molecules in the oral cavity. *Int. J. Mol. Sci.* **2020**, *21*, 6000. [[CrossRef](#)]
32. Nasiri, K.; Dimitrova, A. Comparing saliva and nasopharyngeal swab specimens in the detection of COVID-19: A systematic review and meta-analysis. *J. Dent. Sci.* **2021**, *16*, 799–805. [[CrossRef](#)]
33. Kim, Y.-g.; Yun, S.G.; Kim, M.Y.; Park, K.; Cho, C.H.; Yoon, S.Y.; Nam, M.H.; Lee, C.K.; Cho, Y.-J.; Lim, C.S. Comparison between saliva and nasopharyngeal swab specimens for detection of respiratory viruses by multiplex reverse transcription-PCR. *J. Clin. Microbiol.* **2017**, *55*, 226–233. [[CrossRef](#)]
34. Li, H.; Liu, S.-M.; Yu, X.-H.; Tang, S.-L.; Tang, C.-K. Coronavirus disease 2019 (COVID-19): Current status and future perspectives. *Int. J. Antimicrob. Agents* **2020**, *55*, 105951. [[CrossRef](#)]
35. Hanege, F.M.; Kocoglu, E.; Kalcioğlu, M.T.; Celik, S.; Cag, Y.; Esen, F.; Bayindir, E.; Pence, S.; Alp Mese, E.; Agalar, C. SARS-CoV-2 Presence in the Saliva, Tears, and Cerumen of COVID-19 Patients. *Laryngoscope* **2021**, *131*, E1677–E1682. [[CrossRef](#)]
36. Nacher, M.; Mergeay-Fabre, M.; Blanchet, D.; Benoit, O.; Pozl, T.; Mespouhle, P.; Sainte-Rose, V.; Vialette, V.; Toulet, B.; Moua, A.; et al. Prospective Comparison of Saliva and Nasopharyngeal Swab Sampling for Mass Screening for COVID-19. *Front. Med.* **2021**, *8*. [[CrossRef](#)]
37. Czumbel, L.M.; Kiss, S.; Farkas, N.; Mandel, I.; Hegyi, A.; Nagy, Á.; Lohinai, Z.; Szakács, Z.; Hegyi, P.; Steward, M.C.; et al. Saliva as a Candidate for COVID-19 Diagnostic Testing: A Meta-Analysis. *Front. Med.* **2020**, *7*, 465. [[CrossRef](#)]
38. Azzi, L.; Baj, A.; Alberio, T.; Lualdi, M.; Veronesi, G.; Carcano, G.; Ageno, W.; Gambarini, C.; Maffioli, L.; Di Saverio, S. Rapid Salivary Test suitable for a mass screening program to detect SARS-CoV-2: A diagnostic accuracy study. *J. Infect.* **2020**, *81*, e75–e78. [[CrossRef](#)]
39. Sagredo-Olivares, K.; Morales-Gómez, C.; Aitken-Saavedra, J. Evaluation of saliva as a complementary technique to the diagnosis of COVID-19: A systematic review. *Med. Oral Patol. Oral Cir. Bucal* **2021**. [[CrossRef](#)]
40. Williams, E.; Bond, K.; Zhang, B.; Putland, M.; Williamson, D.A. Saliva as a non-invasive specimen for detection of SARS-CoV-2. *J. Clin. Microbiol.* **2020**, *58*, e00776–20. [[CrossRef](#)]

41. Han, M.S.; Seong, M.-W.; Heo, E.Y.; Park, J.H.; Kim, N.; Shin, S.; Cho, S.I.; Park, S.S.; Choi, E.H. Sequential analysis of viral load in a neonate and her mother infected with severe acute respiratory syndrome coronavirus 2. *Clin. Infect. Dis.* **2020**, *71*, 2236–2239. [[CrossRef](#)] [[PubMed](#)]
42. Iyer, P.; Aziz, K.; Ojcius, D.M. Impact of COVID-19 on dental education in the United States. *J. Dent. Educ.* **2020**, *84*, 718–722. [[CrossRef](#)] [[PubMed](#)]
43. Machado, R.A.; Bonan, P.R.F.; Perez, D.E.d.C.; Martelli Junior, H. COVID-19 pandemic and the impact on dental education: Discussing current and future perspectives. *Braz. Oral Res.* **2020**, *34*, e083. [[CrossRef](#)]
44. Fernandes, C.I.; Bonan, R.F.; Bonan, P.R.; Leonel, A.C.; Carvalho, E.J.; de Castro, J.F.; Perez, D.E. Dental students' perceptions and performance in use of conventional and virtual microscopy in oral pathology. *J. Dent. Educ.* **2018**, *82*, 883–890. [[CrossRef](#)]
45. Chang, T.-Y.; Hong, G.; Paganelli, C.; Phantumvanit, P.; Chang, W.-J.; Shieh, Y.-S.; Hsu, M.-L. Innovation of dental education during COVID-19 pandemic. *J. Dent. Sci.* **2021**, *16*, 15–20. [[CrossRef](#)]
46. Retallack, H.; Di Lullo, E.; Arias, C.; Knopp, K.A.; Laurie, M.T.; Sandoval-Espinosa, C.; Leon, W.R.M.; Krencik, R.; Ullian, E.M.; Spatazza, J. Zika virus cell tropism in the developing human brain and inhibition by azithromycin. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, 14408–14413. [[CrossRef](#)]