

REVIEW ARTICLE

Adverse Drug Reactions Post Vaccination of COVID-19 in Oral Cavity

Pratiwi Soesilawati¹, Annisa Anggie Tjahyaning Negri², Melza Nur Ramadhania², Yuliati¹, Masfueh bt Razali³

¹ Department of Biology Oral, Faculty of Dental Medicine, Universitas Airlangga, 60132 Surabaya, Indonesia

² Faculty of Dental Medicine, Universitas Airlangga, 60132 Surabaya, Indonesia

³ Department of Restorative Dentistry, Faculty of Dentistry, Universitas Kebangsaan Malaysia, 50300, Kuala Lumpur, Malaysia

ABSTRACT

The global outbreak of the COVID-19 pandemic, identified as the 2019 Novel Coronavirus (2019-nCoV), has precipitated profound consequences worldwide since its emergence in early 2020. Addressing this unprecedented crisis necessitates the implementation of a comprehensive strategy, encompassing pharmacological interventions and widespread vaccination efforts. The development of COVID-19 vaccines involves the utilization of diverse components, including nucleic acids (DNA and RNA), virus-like particles, peptides, viral vectors (both replicating and non-replicating), recombinant proteins, live attenuated vaccines, and inactivated vaccines. However, akin to conventional pharmaceutical agents, COVID-19 vaccines may elicit unintended adverse reactions (ADRs). Within the context of oral health, reported adverse reactions post-COVID-19 vaccination encompass manifestations such as oral ulceration, oral paraesthesia, and lip swelling. This review endeavours to consolidate existing literature pertaining to adverse reactions after COVID-19 vaccination, with particular attention to the etiological hypotheses underpinning these reactions within the oral cavity.

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Corresponding Author:

Pratiwi Soesilawati, PhD

Email: pratiwi-s@fkg.unair.ac.id

Tel :+62 81703968754

INTRODUCTION

The virus known as SARS-CoV-2, responsible for severe acute respiratory syndrome, originated in Wuhan, China, towards the end of 2019 (1). This paper provided the first genetic sequence of the virus obtained from a cluster of patients with pneumonia of unknown cause, and outlined preliminary information about the clinical characteristics of the disease. Initially termed the 2019 Novel Coronavirus (2019-nCoV), it is now universally recognized as Coronavirus Disease 2019 (COVID-19). This novel pathogen was characterized as zoonotic due to its initial transmission among animals, particularly birds and mammals (2).

COVID-19 presents a wide clinical spectrum, encompassing general symptoms such as fatigue, myalgia, fever, and dry cough, as well as involvement

of multiple organ systems, including the respiratory tract (manifesting as shortness of breath, cough, sore throat, chest pain, and haemoptysis), gastrointestinal system (marked by nausea, vomiting, and diarrhoea), and even neurological symptoms (such as headaches and confusion) (1, 3). Several studies have reported diverse clinical manifestations of COVID-19 within the oral cavity, including paraesthesia, ulcers, and salivary gland disorders ((4-8). The airborne nature of the virus leads to declaration of COVID-19 as global pandemic by the World Health Organization (WHO) in early 2020.

The rapid dissemination of the COVID-19 virus triggered various parties to undertake various efforts. The World Health Organization (WHO) released several priority strategies that governments were advised to implement, including the deployment of health workers and the establishment of quarantine protocols (9, 10). However, upon evaluation, it became evident that additional efforts were needed to contain the spread of COVID-19. Consequently, intensive research was underway to develop vaccines and drugs capable of combating the COVID-19 pandemic (4, 11). In several studies,

the COVID-19 vaccine was developed using various biotechnological methods, such as nucleic acids (RNA and DNA), peptides, virus-like particles, viral vectors (both non-replicating and replicating), inactivated vaccines, recombinant proteins, and live attenuated vaccines (12-14).

It is widely accepted in the scientific community that vaccination has significant benefits in preventing infectious diseases. Vaccines have been instrumental in reducing morbidity and mortality from various infectious diseases, potentially preventing millions of deaths each year (15). Like any medical intervention, vaccines can cause adverse reactions in some individuals. The mentioned symptoms such as pain (16), fever (17), headache (18), fatigue (19) and chills (20) are commonly reported after vaccination, especially with some COVID-19 vaccines.

Research has indeed shown potential links between COVID-19 vaccination and oral adverse effects (OAEs) (8, 21-23). Riad et al. (24) indicates a correlation between ADRs affecting the oral cavity and the COVID-19 vaccine. Therefore, it is crucial to promptly identify and manage any adverse reactions to the COVID-19 vaccine to mitigate the risk of more severe outcomes including those in the oral cavity. Consequently, this article aims to examine adverse reactions linked to COVID-19 vaccination in the oral cavity and propose potential mechanisms underlying vaccine-related pathogenicity in this area.

DISCUSSION

Coronavirus Disease-2019 (COVID-19)

The COVID-19 disease is caused by a type of coronavirus called the novel coronavirus or 2019-nCoV. Zoonotic viruses such as MERS-CoV, SARS-CoV, and 2019-nCoV can lead to severe infections in humans (2). SARS-CoV-2 is classified as a pathogenic coronavirus within the Coronaviridae family. There are four different types of Coronaviridae: alpha-CoV, delta-CoV, gamma-CoV, and beta-CoV. Beta-CoV and alpha-CoV have the potential to cause disease in humans, whereas delta-CoV and gamma-CoV are primarily pathogenic to poultry, such as birds (3). In Fig. 1 showing the genome structure of the coronavirus.

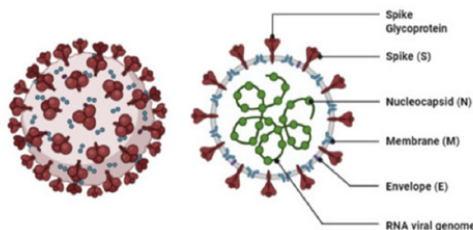


Fig. 1: Genome structure of coronavirus. Adapted and reproduced with permission (27)

The viral RNA genome is housed within a membrane alongside the nucleocapsid, comprising four structural proteins: the spike protein (S), nucleocapsid protein (N), membrane protein (M), and envelope protein (E). Upon the virus entering host cells, it triggers fusion and uncoating of the viral membrane. Subsequently, mRNA transcription and translation occur, facilitating viral assembly crucial for infectivity. Glycoproteins on the spike surface facilitate the virus's attachment and entry into host cells (25). This entry of viral particles into other cells prompts an immune response, leading to antibody production. Overall, the structural knowledge of SARS-CoV-2 proteins provides critical insights into the development of vaccines by guiding the antigen selection and vaccine design as well as efficacy testing. This understanding has been instrumental in the rapid development of vaccines against COVID-19 (26).

COVID-19 Vaccines

The COVID-19 vaccine utilizes various mediums, including nucleic acids (RNA and DNA), inactivated viruses, viral vectors (non-replicating and replicating), peptides, virus-like particles, live attenuated virus approaches, and recombinant proteins (28, 29). DNA vaccines consist of plasmid DNA molecules encoding one or more antigens. Unlike DNA vaccines, which operate by entering the nucleus, mRNA vaccines achieve the expression of the target antigen by entering the cytoplasm. The mRNA vaccine contains molecules encoding protein antigens. Encapsulation of mRNA molecules within lipid nanoparticles is necessary to prevent instability (30). These nanoparticle carriers serve as adjuvants to elicit immune responses from follicular helper B and T cells. One example of mRNA-based vaccine production currently in use is Moderna and Pfizer-BioNTech.

Non-replicating viral vector vaccines are mainly based on adenovirus, a virus causing the common cold with a genome consisting of double-stranded DNA (31). A viral vector vaccine option currently used is Oxford/AstraZeneca and CanSino. Inactivated vaccines, or vaccines derived from inactivated viruses, are traditionally obtained from cells infected with viruses. Conventional vaccine development methods use whole inactivated virus (WIV), such as Sinopharm from China and Bharat Biotech's Covaxin® from India.

Live attenuated vaccines utilize a weakened version of the virus within the body. When it enters the body, this virus grows and replicates in the body. However, it cannot cause disease symptoms in individuals (27, 32). Subunit vaccines comprise purified recombinant proteins and are widely regarded as the safest vaccine type. These vaccines use certain parts of virus-like antigens, fragments, protein parts or polysaccharides that cannot produce any infection in the body. Sanofi-

GSK, Novova, and Dynavax are vaccines that use this mechanism.

Adverse Drug Reactions (ADRS)

The definition of ADR, according to WHO, is a response to a dangerous and undesirable drug that occurs at doses typically used in humans. Adverse drug reactions (ADRs) are typically categorized into Type A and Type B. Type A (augmented) responses depend on the drug's mechanism of action and are often predictable, dose-dependent, and have low mortality rates (32). This type is caused by an increase in the pharmacological effects of administered drugs. Type B responses, on the other hand, are unpredictable, uncommon, and have a high mortality rate. Moreover, Type B responses are not related to the drug's mechanism of action.

Oral Adverse Effects (OAEs)

Numerous reports have been published regarding the adverse effects of COVID-19 vaccines, demonstrating that each vaccine possesses a distinct safety and effectiveness profile (Table I). These reports vary depending on the vaccine types and populations studied (17, 19, 33, 34). Individual reports published suggest the occurrence of oral adverse effects (OAEs) following COVID-19 vaccination (18, 33, 35). In a retrospective analysis of 690,853 individuals who had received the COVID-19 vaccine residing in the United States, Riad and co-workers (36) found that oral paraesthesia (tingling in the mouth) (0.872%), lip swelling (0.844%), oral hypoesthesia (0.648%), ageusia (0.722%), dysgeusia (0.617%), and swollen tongue (0.628%) were the most frequently reported adverse events (AEs). To the contrary, the European study by the same principal author found that dysgeusia emerged as the most frequently noted oral adverse event (AE), with a reported incidence of 0.381 cases per 100 received reports (24). Following dysgeusia were oral paraesthesia (0.315%), ageusia (0.296%), lip swelling (0.243%), dry mouth (0.215%), oral hypoesthesia (0.210%), swollen tongue (0.207%), and taste disorder (0.173%). These figures were less than half of what reported in the United States of America.

Meanwhile, study conducted in Slovakia on healthcare workers who received mRNA-based vaccinations found that 9.6% of all participants reported experiencing OAEs (19). The most common side effect reported was burning or bleeding gingiva (3.3%), followed by ulcers (1.9%), blisters (2.1%), and vesicles (1.5%). Notably, this study did not identify any instances of taste disorders or oral paraesthesia. The most common locations for ulcers, vesicles, and blisters were the labial and buccal mucosa (46.7%), followed by the tongue (26.7%) and gingiva (33.3%). Meanwhile, the most common locations for red and white plaques were the tongue (57.1%). Approximately 20.4% of oral side effects occurred within

Table I Summary of the Prevalence of Oral Adverse Effects After the COVID-19 Vaccine

Author	Side effect(s)	Prevalence	Participant(s) receiving vaccines	
Abanoub Riad	Oral parasthesia	0,872%	All ages in all US states	
	Ageusia	0,737%		
Ave Pold	Oral hypoesthesia	0,722%		
Elham Kateeb		0,648%		
Sameh Attia (2022)	Dysgeusia	0,617%		
	Lip swelling	0,617%		
	Swollen tongue	0,628%		
Abanoub Riad, et al. (2021)	Bleeding or Burning Gingiva	3,3%		522 participants among healthcare workers in Slovakia
	Blisters	2,1%		
	Ulcers	1,9%		
	Vesicles	1,5%		
	Bleeding or sove gingiva	4,76%		
Abanoub Riad, et al. (2021)	Ulcer, resicles, bister (UVB)	4,46%	878 participants among healthcare workers in Turkey	
	Halitosis	2,1%		
	Dysgeusia	0,9%		
	Oral parasthesia	0,3%		

1-3 days after vaccination, and another fifth (20.4%) appeared within the first, second, and third weeks.

Moreover, when healthcare workers in Turkey were examined by employing a cross-sectional method, they revealed OAEs after administering the CoronaVac vaccine, including oral ulceration (4.4%), oral paraesthesia (0.3%), and dysgeusia (0.9%) (34). However, OAEs are rarely reported, and COVID-19 patients have previously reported some of these oral conditions and mucocutaneous lesions. Most reported side effects are mild symptoms lasting about one to three days (8).

Several studies have found the prevalence of oral side effects in different types of Covid-19 vaccines (Table II). Klugar et al. (20) has observed that mRNA-based vaccines tend to elicit more local side effects compared to viral vector-based vaccines (78.3% vs. 70.4%). It was reported the viral vector-based vaccines were associated with systemic side effects more frequent (87.2% vs. 61%). Additionally, research by Riad et al. (34) on healthcare workers in Turkey noted a higher prevalence of side effects with mRNA-based vaccines compared to inactivated vaccines. The use of inactivated vaccines, such as CoronaVac, was associated with lower systemic side effects (40.6%) and local side effects (42.2%) compared to mRNA-based vaccines like Pfizer-BioNTech, which exhibited systemic side effects (77.4%) and local side effects (84.7%).

Table II Summary of the Prevalence of Oral Adverse Effects Associated with Different Types of COVID-19 Vaccines

Side effect(s)	Vaccines type	Prevalence	Author
Local side effects	mRNA	78,3%	Miloslav Klugar, et al. (2021)
	Viral vector-based vaccine	70,4%	
	mRNA	84,7%	Abanoub Riad, et al. (2021)
	Inactivated vaccines	42,2%	
Systemic side effects	mRNA	87,2%	Miloslav Klugar, et al. (2021)
	Viral vector-based vaccine	61%	
	mRNA	77,4%	Abanoub Riad, et al. (2021)
	Inactivated vaccines	40,6%	

Furthermore, multiple systematic reviews (21, 37) reported the occurrences of oral lichen planus, pemphigus vulgaris, varicella-zoster, and Stevens-Johnson syndrome with mRNA-based vaccines such as BNT162b2 and mRNA-1273. These observations suggest a potential immunomodulatory effect of the vaccine, which could explain these occurrences (22). Diseases like oral lichen planus and pemphigus vulgaris may be linked to increased cytokine production following B and T cell activation post-vaccination (38-40).

Possible pathogenic oral adverse effects post vaccination of COVID-19

The pathophysiology of oral adverse events following COVID-19 vaccination is currently uncertain, but several hypotheses have been proposed. These include the possibility of direct infiltration of the SARS-CoV-2 virus into the epithelial lining of the oral cavity, where angiotensin-converting enzyme two (ACE2) receptors are frequently found, as well as secondary infections and an inflammatory response (6, 19, 41).

Another hypothesis suggests that a direct immune response to the lipid nanoparticles in the mRNA vaccine may trigger a hypersensitivity reaction. The administration of BNT162b2 (42), for example, activates T and B lymphocytes, and autoimmune diseases have been associated with certain interleukins (IL-2, IL-17, IL-4, and IL-21). The mRNA vaccine could potentially trigger plasmacytoid dendritic cells or myeloid cells, which are known to be involved in autoimmune reactions or hypersensitivity, leading to the development of oral lesions (23).

Furthermore, the mRNA vaccine contains polysorbate 80 as an essential element to dissolve the mRNA into lipid nanoparticles. This component may potentially trigger allergic reactions due to its possibility of cross-linking with polyethylene glycol (PEG) (22). Oral adverse events such as mucositis (43, 44) and oral ulceration (16, 45,

46) could also be caused by infections occurring during vaccination.

The angiotensin-converting enzyme 2 (ACE2) receptor, crucial for enabling host cell entry, is widely distributed throughout the body and exhibits particularly high expression levels in the epithelial cells of the tongue and salivary glands. However, it is currently unclear whether mRNA-based vaccines or adenovirus vaccines can directly infect host cells, and the potential transmission route through the oral mucosa remains uncertain (6). Various pathogenic hypotheses mentioned in the literature may underlie the occurrence of adverse events from the COVID-19 vaccine, some of which are related to viral infections.

However, it's important to note that the presence of adverse effects, including those in the oral cavity, doesn't necessarily diminish the overall benefits of vaccination. Vaccination remains one of the most effective public health measures for preventing the spread of infectious diseases and reducing their impact on society. Additionally, it's crucial to interpret scientific findings within the broader context of peer-reviewed research and to consider the limitations of individual studies. A review of adverse reactions associated with COVID-19 vaccination, including those in the oral cavity, can provide valuable insights into vaccine safety and potential mechanisms of action. Yet, further research is often needed to confirm associations and understand underlying mechanisms fully.

CONCLUSION

Overall, the most commonly reported adverse side effects in the oral cavity include oral paraesthesia, ulcers, dysgeusia, vesiculobullous lesions, and even gingival bleeding. Among the reported vaccines, mRNA-based vaccines are most frequently associated with these local side effects. Specifically, mRNA-based vaccines have been linked to the development of conditions such as oral lichen planus and pemphigus vulgaris, which are believed to be immune system-related.

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