OPEN ACCESS

Saudi Journal of Oral and Dental Research

Abbreviated Key Title: Saudi J Oral Dent Res
ISSN 2518-1300 (Print) | ISSN 2518-1297 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article | **Oral and Maxillofacial Surgery**

Oro-Facial Manifestations of COVID-19 Vaccines: A Systematic Review

Dr. Simran Kaur[1*], Dr. Manisha Lakhanpal Sharma[2]

[1]MDS Student, Department of Oral Medicine and Radiology, ITS Dental College, Greater Noida, Uttar Pradesh, India
[2]Professor & Head, Department of Oral Medicine and Radiology, ITS Dental College, Greater Noida, Uttar Pradesh, India

DOI: 10.36348/sjodr.2023.v08i06.003 | **Received:** 11.05.2023 | **Accepted:** 25.06.2023 | **Published:** 28.06.2023

***Corresponding author:** Dr. Simran Kaur
MDS Student, Department of Oral Medicine and Radiology, ITS Dental College, Greater Noida, Uttar Pradesh, India

Abstract

Severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) emerged in Wuhan, China, in late 2019. This became a global health crisis which caused millions of deaths worldwide. The first official case reported in India on 27th January 2020 in Thrissur, Kerala. The vaccines developed, approved and in function are Covaxin (BBV152), Oxford-AstraZeneca (ChAdOx1nCoV-19), Covishield, PfizerBioNtech and Moderna. These vaccines are still under their respective phases of trials. Their adverse effects are under surveillance. In India these AEFIs are reported to Ministry of Health and Family welfare. The common systemic reactions observed were injection site pain, myalgia, fever, headache and shivering. The delayed and rare side effects reported include dyspnea, ischemia, thrombolysis, anaphylaxis, neuralgias, orofacial symptoms and death. The list of orofacial adverse effects based on the clinical trials include palatal petechiae, herpes zoster, angular cheilitis, mucositis, xerostomia, burning sensation in mouth, dysguesia, oral apthous ulcers, trigeminal neuralgia and facial nerve palsy. Reporting these oral lesions are under the onus of oral medicine experts and this article aims to provide a systematic review of the same.

Keywords: COVID-19 disease, systemic manifestations, orofacial manifestations, manifestations in oral cavity, vaccines, SARS CoV-2, MERS.

Copyright © 2023 The Author(s): This is an open-access article distributed under the terms of the Creative Commons Attribution **4.0 International License (CC BY-NC 4.0)** which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited.

INTRODUCTION

A highly contagious infectious disease emerged in December 2019 which created an upheaval across the seven continents and emerged as one of the most lethal global pandemics. WHO named it as the COVID-19 disease after the causative agent novel Coronavirus. The COVID-19 disease was discovered to be caused by a Coronavirus which was later named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [1]. The virus belongs to the β coronavirus family. SARS-CoV, MERS-CoV and SARS-CoV-2, are able to cause severe symptoms and even death with fatality rates of 10%, 37%, and 5% respectively [2]. Till date, there are no specifically approved treatment therapies for the same [3]. Following the COVID-19 virus epidemic, huge, coordinated global studies have resulted in the rapid development of effective vaccines. In early 2021, the primary vaccines had been brought to stop the pandemic. Additionally, approximately 68.2% of the sector's population has been fully vaccinated against this disease.

The anti-SARS-CoV-2 vaccines developed use four major techniques [4]:

a) Nucleic acid based vaccine (DNA–mRNA).
b) Viral vector (replication–non-replication).
c) Live inactivated (or attenuated) virus.
d) Protein (spike protein or its subunits).

An adverse drug reaction (ADR) can be defined as ‘an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product; adverse effects usually predict hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product’ [5]. Thus, ADRs are the serious complications of vaccines. In nucleic acid and adenovirus-based vaccines, fragments of the virus mRNA or genome enter human cells and set off the production of viral proteins [4]. These viral proteins are eventually diagnosed as antigens and stimulate antibody production. In vaccines containing inactive or protein viruses, virus debris and proteins, as antigens, trigger the immune mechanics [6]. As of November 2021, 11 candidate vaccines for

COVID-19 had been authorized with the aid of the world health organization for mass vaccination after leaving phase three of medical studies. But, on the way to prove the effectiveness of the vaccine in phrases of safety and aspect effects, the implementation of phase 4 of medical studies is essential. Because the outcomes of the phase 4 research are the proper standards for a way the vaccine works within the real world [7]. The common systemic reactions observed were injection site pain, myalgia, fever, headache and shivering. The delayed and rare side effects reported include dyspnea, ischemia, thrombolysis, anaphylaxis, neuralgias, orofacial symptoms and death. The list of orofacial adverse effects documented in literature based on the clinical trials include palatal petechiae, herpes zoster, angular cheilitis, mucositis, xerostomia, burning sensation in mouth, dysguesia, oral apthous ulcers, trigeminal neuralgia and facial nerve palsy.

This systematic review aims to provide a comprehensive record of all the reported oral adverse effects from the functional COVID-19 vaccines. This would further aid in accurate and timely diagnosis which would make it easier for the healthcare professionals to report them to the concerned authorities.

METHODOLOGY

The research was carried out by electronic searching of database records of the past 2.5 years with the following criteria:

Criteria of Inclusion

1. Letters to the editor,
2. Case reports and case series,
3. Observational Studies: Case control studies, Cohort studies, Cross sectional studies.

Criteria of Exclusion

1. Language other than English,
2. Studies where only abstract is given,
3. Unpublished data.

Focused PICO Question

1. **Population:** Patients who were administered with anti SARS-CoV-2 vaccines presenting with oro-facial manifestations.
2. **Intervention:** Not applicable for current study.
3. **Comparison:** Not applicable.
4. **Outcome:** To review the cases of oro-facial manifestations in patients who were administered with anti-SARS-CoV-2 vaccines and to investigate the association between COVID-19 vaccines and clinical presentation in oral cavity.
5. **Timeline:** December 2020 to May 2023.

Search Strategy

1. **Electronic Databases:** PubMed, Scopus, Google Scholar.
2. **Keywords:** COVID-19 disease, systemic manifestations, orofacial manifestations, manifestations in oral cavity, vaccines, SARS CoV-2, MERS.
3. **Timeline:** December 2020 to May 2023.

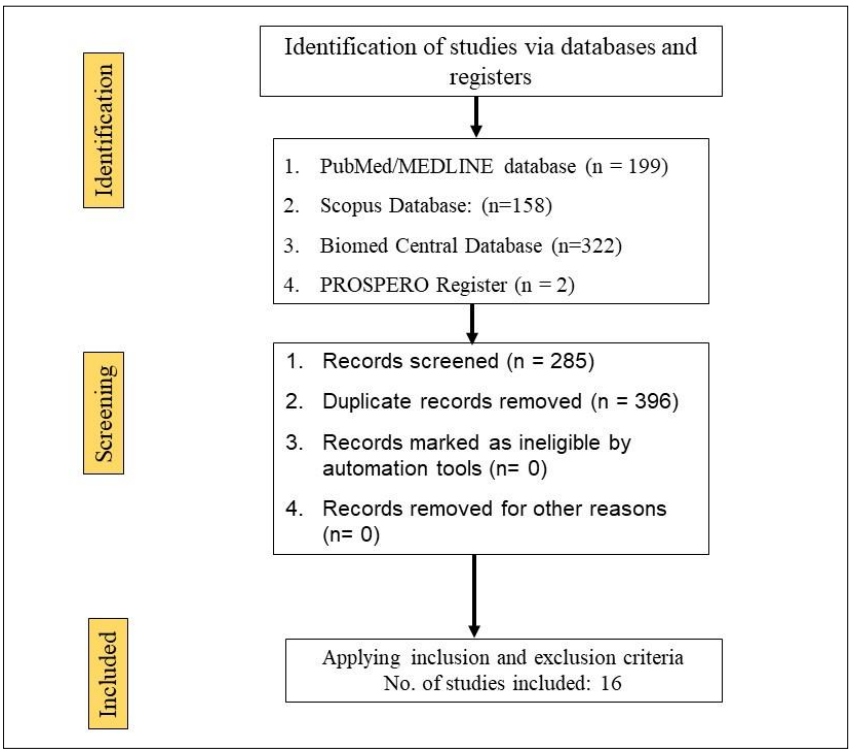

Figure 1: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart showing search strategy

RESULTS

Table 1: Summary of the oro-facial adverse effects and their possible mechanism of action

S. No	Authors	Type of study	Year	Results
1.	Mazur M Duś-Ilnicka I Jedliński M Ndokaj A	Survey	March 2021	223 participants completed out of 43,584 1. Change in sensitivity: 6 and 7 2. Burning sensation: 6 and 8 3. Aphthous: 4 and 6 4. Taste alterations: 3 and 8
2.	Sharda P Mohta A Ghiya BC Mehta RD.	Case report	Feb 2022	1. 35-year-old female with oral lichen planus. 2. Abrupt onset of severe burning sensation while eating spicy food for 2 days. 3. She gave a history of COVID vaccination 14 days ago. 4. She had lesions bilaterally over the buccal mucosa and the gingival mucosa sparing the tongue and the palate. 5. No relevant medical history was found. 6. The lesions had an erythematous base with white reticular streaks over them, some of them had erosions. 7. A punch biopsy was taken from the lesion which proved to have histopathological findings consistent with oral lichen planus
3	Bakir *et al.*,	Case Report	Aug 2021	US: Pfizer 49-year-old female one week after the first dose presented with Steven Johnson syndrome Extensive mucosal (oral, genitalia, and conjunctiva) involvement, vesiculobullous lesions and epidermal detachment over more than 30% of body surface area
4.	Dash *et al.*,	Case Report	June 2021	INDIA: AstraZeneca 60-year-old male 3 days after the first dose Mucosal involvement (oral and genital erosions and conjunctivitis), generalized skin rash
5.	Elboraey *et al.*,	Case Report	October 2021	SAUDI ARABIA: Pfizer Middle aged female 5 days after second dose experienced TEN Multiple large ulcers on the oral mucosa, no skin involvement
6.	Mansouri *et al.*,	Case Report	Nov 2021	IRAN: Sinopharm 49-year-old female 3 days after second dose experienced SJS Oral and genital erosions and *a blister* on the palm
7.	AzziLorenzo ToiaMarco StevanelloNicole Maggi Fabrizio Forlani Greta	Letter to the editor	April 2021	31-year-old female had first dose administration of the ChAdOx1 COVID-19 vaccine presence of diffuse, erythematous and swollen red lesions on her buccal mucosa, tongue, gums and palate
8.	Thongprasom K Pengpis N Phattarataratip E Samaranayake L	Letter to the editor	October 2021	A case of oral pemphigus lesion in a 38-year-oldThai female that was associated with the administration of the first dose of AZD1222 vaccine. The intraoral examination revealed generalized desquamative epithelium, erythematous areas along the marginal gingivae and alveolar mucosa. Pseudomembranes, and erosions and ulceration on the buccal gingiva subjacent to the maxillary and mandibular teeth, and the right lingual dorsum could be seen. Furthermore, generalized desquamative epithelium of the alveolar mucosa of the anterior mandibular teet has well as the right mandibular and left maxillary posterior molars extending to the mucobuccal folds were present. Erythematous areas also extended from the lingual

S. No	Authors	Type of study	Year	Results
				gingiva of anterior mandibular teeth onto the floor of mouth.
9.	Chun, Y. Jang, J. Jo J.H	Case series	March 2022	1. A 79-year-old male reported swelling and pain of the right posterior palatal area. The symptoms had occurred a day after his first BNT162b2 vaccination. Past medical history included hypertension and prostatic disease. There was no systemic fever nor any significant findings related to the chief complaint on panoramic radiography. Multiple ulcerative lesions with surrounding erythema and swelling were observed at the right posterior hard palate area. The initial diagnosis was primary herpetic gingivostomatitis. 2. An 81-year-old female reported pain on the palatal area of the left central incisor. The symptoms had occurred 3 h after her first BNT162b2 vaccination. The patient also complained of a burning sensation throughout the palate and pain of the tongue. Ulceration of the palatal gingiva accompanied by gingival recession and root exposure was observed on the hard palate posterior to both central incisors. The surrounding gingiva was erythematous and swollen. The tongue was fissured and had tongue coating on the dorsum. There were no pathologic findings related to the chief complaint on standard panoramic radiography. The initial diagnosis was necrotizing gingivitis. 3. An 88-year-old female reported pain on the mucosa of the upper and lower lip and lower gingiva. The symptoms had occurred about 3 days after her first BNT162b2 vaccination. Past medical history included hypertension, hyperlipidemia, recurrent cystitis, and cerebral infarction 5 years ago. 4. A 61-year-old male reported pain in the right preauricular and posterior lower gingival area. The symptoms had occurred 19 days after his first AZD1222 vaccination. Past medical history included hypertension. The quality of pain was electrical and the intensity was NRS 8. The pain occurred only when eating hot food and lasted for 30 s per episode. There were no specific findings related to the chief complaint on panoramic radiography and clinical examination. The patient was provisionally diagnosed with herpes zoster and trigeminal neuropathy. 5. A 60-year-old female reported pain on the right buccal mucosa. The symptom had occurred a day after the first AZD1222 vaccination. Past medical history included osteoporosis. The patient was diagnosed with lichen planus of the right buccal mucosa 6. A 66-year-old female reported pain on the right lateral border of the tongue. The symptom had occurred a day after her first AZD1222 vaccination. Past medical history included hypertension, osteoporosis, hyperthyroidism, and headache. The patient was diagnosed with burning mouth syndrome 7. A 68-year-old female reported aggravation of pre-existing pain on the right lower second molar. The

S. No	Authors	Type of study	Year	Results
				symptoms had occurred a day after her first AZD1222 vaccination. Past medical history included hypertension, type 1 diabetes mellitus, osteoarthritis, rhinitis, and gastritis. The patient had been diagnosed with neuropathic pain earlier based on the fact that there were no specific findings related to her initial chief complaint on panoramic radiography and clinical examination. 8. A 72-year-old woman reported pain on both buccal mucosae. The symptom had occurred a day after the first AZD1222 vaccination. Past medical history included diabetes mellitus. The patient was previously diagnosed with oral lichen planus 9 years ago. On clinical examination, the right buccal mucosa and lower buccal vestibule showed erythema with white striae, and the left buccal mucosa showed mild erythema. 9. An 85-year-old female complained of a significant increase in tongue pain that had occurred three days after the second BNT162b2 vaccination. Past medical history included hypertension, osteoporosis, hyperlipidemia, and stroke. The patient had been diagnosed with oral candidiasis and burning mouth syndrome 31 months ago which currently seem aggravated.
10.	Hertel M Schmidt-Westhausen A-M Wendy S Heiland M Nahles S Preissner R Preissner S	Comparative analysis	March 2022	Initial cohorts of 274,481 vaccinated and 9,429,892 not vaccinated patients were retrieved from the TriNetX database (TriNetX, Cambridge, Massachusetts, USA), and matched for age, gender and the frequency of use of non-steroidal anti-inflammatory drugs, beta blockers, and angiotensin-converting enzyme inhibitors. After matching each cohort, we accounted for 217,863 patients. Among cohort I, 146 individuals had developed OLL/OLP within 6 days after COVID-19 vaccination (88 and 58 subjects had received mRNA- and adenovirus vector-based vaccines) In cohort II, 59 patients were newly diagnosed with OLL/OLP within 6 days after having visited the clinic for any other reason.
11.	Petruzzi, M. Galleggiante S Messina, S. *et al.*,	Case series	2022	Report of four cases of oral erythema multiforme flare arising after BNT162b2 vaccination administration. All the patients denied previous erythema-like and herpetic manifestations history. Two of the reported cases (number 1 and 2) presented with both oral and cutaneous lesions, while cases 3 and 4 showed only oral manifestations. Three of the cases presented the erythema after the first vaccination dosage administration, only one case reported lesions after the second vaccination dosage administration.
13.	Keigo Maeda Daisuke Yamashita Toshihiko Takenobu	Case report	Feb 2022	A 58-year-old Japanese woman with no medical history presented with bilateral palatal mucosal ulcers. She received a second dose of the mRNA-1273 COVID-19 vaccine 20 d earlier. On the day after the second vaccination, she experienced transient mild fatigue and local pain at the injection site, and the symptoms resolved the following day. However, she experienced severe palatal mucosal pain 10 d after the second vaccination.
14	Luca Raccampo, Salvatore Sembronio Alessandro Tel	Case Report	April 2022	A 54-year-old woman presented with a bilateral white reticular pattern on the oral mucosa with no other reported skin or nail lesions. The lesions were

S. No	Authors	Type of study	Year	Results
	Veronica Cacitti Massimo Robiony			asymptomatic. She had received the second dose of the COVID-19 vaccine 10 days before the oral lesions appeared. A 56-year-old woman presented with a sudden onset of burning pain localized in the upper gingival mucosa, limiting normal daily activities, especially tooth brushing and swallowing. Clinical examination revealed an erythematous lesion with erosive aspects on the gingiva extending to the buccal vestibular mucosa. The week before, the patient had received the second dose of the COVID-19 vaccine.
15	Troeltzsch M Gogl M Berndt R Troeltzsch M	Letter to the editor	Nov 2022	A 49-year-old male patient presented with a 9-week history of oral mucosal discomfort, burning sensations, and desquamation that had developed six days after the COVID-19 vaccination with Ad26.COV2.S. The patient had suffered from flu-like symptoms for three days immediately following the vaccination. The clinical examination showed the classical image of OLP. The clinical diagnosis was confirmed by a surgical biopsy
16.	Sayare, B. BhardwajV.K SharmaD	Case report	September 2021	The twin subjects aged 21 years, otherwise systemically healthy with no history of anticoagulants, anti-platelets, or other drugs in take received the first dose of COVISHIELD (ChAdOx1-nCoV-19) vaccine in the morning hours on day 1. After 4 h, the subjects complained of shivering, fever (102 °F), pain and tenderness at the site of injection, dry mouth, loss of smell, loss of appetite, difficulty in swallowing, cough, and severe headache in the occipital region. The subjects did not have any previous history of allergy or any significant medical or dental condition. One of the twin subjects experienced petechiae at the site of injection and in the palatal region.
17.	Heboyan A Karobari MI Marya A	Case report	Dec 2022	A 34-year-old male patient presented to the university dental clinic with malaise, high fever, weakness, tender gums, gingival hypertrophy, rashes on the mucous membrane of the oral cavity and halitosis. The man had no previous history of oral conditions and it was noted that the symptoms occurred the day after receiving the second dose of the Modern a COVID vaccine. Objective examination revealed lesions on the boundary between the Vermilion border, the mucous membrane and the gingival area of teeth 34–35. The gingiva in the area of the anterior teeth was edematous. The teeth were covered with dental plaque, as the patient could not brush his teeth due to tender gingiva. The possible differential diagnosis for the lesion included drug-induced conditioned enlargement.
18.	Chaudhari PJ Chawda UB Bhad BJ Mevada AV Jha SG	Case report	Dec 2022	A 16 years old adolescent girl presented with chief complaints of left side deviation of mouth with difficulty in closing right eye after 29 days of receiving the first dose of Covaxin, which was finally diagnosed as a "Covaxin induced facial palsy"

DISCUSSION

Several reviews of literature reported the varied oro-facial manifestations of COVID-19 disease. For instance, maculopapular rash, urticaria, vesicles, ulceration, chilblain, petechiae, stomatitis, necrotizing periodontal disease, livedo reticularis and Erythema multiforme-like lesions are some of the clinical presentations that have been observed. The ability of the SARS-CoV-2 for interacting with or binding to different cells in the body other than just type 2 alveolar cells in the lungs explains the wide range of symptoms and multi-organ failure which can be caused by the virus. In contrast the triggered immune response following the COVID-19 vaccination is a justification

for causing the same lesions. The antibodies now accessible against SARS-CoV-2 are delivered utilizing one of the accompanying innovations: (a) vaccines based on mRNA; b) vaccines based on viral vectors; c) vaccines based on protein subunits; and d) vaccines based on inactivated or whole viruses. Pfizer/BioNTech's BNT162b2 and Moderna's mRNA1273 are both mRNA vaccines, while ChAdOx1 from Johnson & Johnson and Astra Zeneca are a type of viral vector vaccine. T-cell activation following the secretion of inflammatory cytokines can result in potential adverse effects, and both of the mentioned vaccine types trigger T-cell-mediated immunity.

Additionally, myeloid or plasmacytoid dendritic cells associated with hypersensitivity or autoimmunity may be triggered by mRNA vaccines. It was reported that the allergic reactions that occurred following the administration of the vaccine were linked to the other components of mRNA. Polysorbate 80 may be involved in the cross-link reaction with polyethylene glycol (PEG), the other component of mRNA-based vaccines that has been confirmed to enhance the immunogenicity and stability of vaccine particles [25]. Polysorbate 80 is added to mRNA-based vaccines as a constituent component to dissolve mRNA in lipid nanoparticles. In a case reported by Azzi *et al.*, [14], oral mucositis was observed following the administration of the first dose of the ChAdOx1 vaccine, this was cited as the cause. Additionally, vaccine- related adverse events are strongly correlated with genetic predisposition to particular disorders. Zermatten *et al.*, reported it [26] that the onset of oral mucositis following COVID-19 vaccination may be triggered by a heterozygous Factor V Leiden mutation, which is associated with an increased risk of thromboembolism.

Pemphigus vulgaris, an autoimmune condition reported following COVID-19 vaccination. Production of autoantibodies against desmosomal proteins localized in the lower epidermis of skin or mucosa called desmoglein (Dsg) 1 and 3, give rise to a damaging inflammatory response characterized by blistering and multiple erosions. Clinical manifestations of the disease appear in the form of painful, non-healing, and erosive lesions affecting oral mucosa. In a case reported by Solimani *et al.*, [27], oral lesions appeared 3 days after receiving the first dose of the BNT162b2 vaccine and 5 days after administration of the second dose. The histopathologic and direct immunofluorescence evaluation of the lesions with a view of honeycomb-like epidermal pattern of intercellular Immunoglobulin G (IgG) confirm the diagnosis of PV along with detection of anti-Dsg3 and Dsg1 autoantibodies in serum. Activation of T and B cells followed by BNT162b2 administration, and increased production of related cytokines including interleukin -2, IL-4, IL-17, and IL-21 is associated with the onset of PV.

Bullous pemphigoid (BP), autoimmune condition that is caused due to the production of autoantibodies against hemi-desmosomal proteins. A case of BP related to the SARS-CoV-2 mRNA vaccine (BNT162b2) was reported by Tomayko M. M *et al.*, [28], and a single ulcer appeared 2 weeks after the patient received the second dose of vaccine along with cutaneous blister. The case is not substantiated with exact mechanism of occurrence in literature.

Recently some cases have been reported characterized by oral herpes zoster (HZ) following COVID-19 vaccination. It is believed that the varicella-zoster virus (VZV) is latent in the spinal dorsal root ganglia (DRG) and trigeminal ganglia (TG). Previous studies have demonstrated that vaccines like hepatitis A, influenza, rabies and Japanese encephalitis vaccines can also cause HZ. In these cases, after COVID-19 vaccination, reactivation of the VZV caused oral HZ. The mechanism of re-activation is still unclear. However, some studies suggested the immune-modulatory effect of vaccines might lead to VZV reactivation. Oral HZ appears after the first or second dose of the BNT162b2, mRNA-1273, AZD1222 (AstraZeneca), mRNA COVID vaccines and inactivated SARS-CoV-2 vaccine [24]. It can happen from 2 to 38 days after the vaccine administration. Symptoms included a cluster of fluid-filled lesions on the face, multiple unilateral small ulcers in the mouth, and one-sided facial droop [24].

According to reports published in the VAERS database, COVID-19 vaccines have several local and systemic neurological complications that occur in different people, from mild to severe, depending on age, sex, history of the disease, and pre-existing immunity [29]. Complications usually appear within one day to 1 month after injection and are usually acute, transient, and self-limiting, but in severe cases lead to hospitalization and intensive care [30]. On the other hand, women have the highest incidence of neurological complications because they induce a stronger immune response against foreign antigens, which can lead to the targeting of self-antigens and lead to autoimmune disorders [31]. Adverse reactions after the second dose of the vaccine are reported more than in the first dose [6].

COVID-19 vaccination also affects the cranial and peripheral nerves and causes side effects such as Bell's palsy (facial nerve palsy—7 cranial nerve), abducens nerve palsy (lateral rectus ocular muscle nerve palsy—6 cranial nerve), impaired vision, olfactory, hearing, Guillain–Barre syndrome (GBS), small fiber neuropathy, Parsonage–Turner syndrome, and also herpes zoster. The proposed mechanism is the induction of autoimmunity by molecular mimicry. Bell's palsy and small fiber neuropathy are more commonly observed in mRNA-based vaccines. Herpes zoster is a disease that occurs as a result of the re-

activation of the varicella-zoster virus (VZV) after receiving the COVID-19 vaccine. mRNA-based vaccines can increase the risk of herpes zoster. A.Riad, in August 2022, reported a case of Ramsey Hunt Syndrome (RHS) after the Pfizer vaccination. RHS leads to facial nerve palsy, vestibulocochlear neuropathy, and glossopharyngeal nerve neuropathy, so it causes numbness of the face, tongue, and hearing loss.

Due to the activity of the immune system, after the injection of COVID-19 vaccines, especially adenovirus- based type, thrombocytopenia, cerebral venous sinus thrombosis, ischemic stroke and intracerebral hemorrhage, have also been reported [32]. Adenovirus-based vaccines are at the forefront of causing this complication due to the transfer of the nucleic acids encoding the viral spike (S) protein. Due to the leakage of these genetic materials and their binding to factor 4 platelet, autoimmunity develops [33]. Such a pathomechanism is proposed as a cause of neurological complications after defective immunization, with de-myelination of the central nervous system (CNS) reported [4]. One of the currently suggested patho-physiology of TN is local de-myelination within the CN V root [34]. This process is usually triggered by compression of the root of the nerve, such as in the case of neurovascular conflict.

Oral lichen planus (OLP) is an inflammatory, chronic, autoimmune and T cell-mediated disease. Tetanus- diphtheria–acellular pertussis (Tdap), hepatitis B vaccine, measles–mumps– rubella (MMR), rabies, and influenza vaccines have been reported to provoke OLP. The reported cases presented erythematous-based lesions with white reticular streaks over them, and some of them had erosions. Also, the patients presented desquamation of the lips. These lesions appeared 1 week to 2 weeks after the second dose administration of the BBIBPCorV (Sinopharm) and BNT162b2. The physiopathological mechanisms underlying the relationship between LP and vaccination for COVID-19 are still poorly understood, however, it has been shown that after such vaccines there can be a stimulation of the immune response of T helper lymphocytes type 1 (Th1), leading to the stimulation of the production of interleukin (IL)-12, tumor necrosis factor (TNF)a, and interferon (IFN)c, cytokines involved in the pathogenesis of LP. What emerges from the literature at present, is that COVID-19 vaccines can cause strong T-cell responses [9, 17, 20, 21].

Ten cases of erythema multiforme (EM) were reported with muco-cutaneous manifestations within 10 days after Pfzer/BioNTech COVID-19 vaccine administration were reported. None of the patients had history of EM, Stevens Johnson syndrome, or recurrent herpes simplex virus. Only one case of EM after BNT162b2 vaccination has been reported while 3 cases are known after other mRNA vaccines' first dose administration. Lavery *et al.,* reported a case of recurrence of EM after BNT162b2 vaccination in a female patient who was already affected by the disease in 2018, and who recurrently suffered from herpes labialis. Pathophysiological mechanisms behind the observed lesions were related to a lymphocyte cell-mediated hypersensitivity reaction leading to pro-infammatory cytokines production targeting SARS-COV- 2 antigens. The "cytokine storm", due to a hyper-immune response by the host. The vaccination could lead to the outbreak of EM due to the expression of an antigen on keratinocyte, causing T-cell activation; a mechanism already described for other vaccinations (tetanus and diphtheria, inactivated polio and Hemophilus b, smallpox, hepatitis B vaccine). EM could be also incidental to herpes simplex infection reactivation, which is a possible reaction to the BNT162b2 vaccine. Pathogenesis of herpes-associated EM is consistent with a delayed-type hypersensitivity reaction. Reactivation of HSV-1 can be related to a failure of CD8+T cell to maintain latency. On the other hand, vaccination stimulates the immune system and polarizes T cell. Sahin *et al.,* reported that the BNT162b2 vaccine induced a coordinated humoral and cellular adaptive immunity [35]. Seven days after the first dose, a strong cellular response with spike-specific CD8+T cell and T helper type 1 (T1) was noted. CD4+T cells were expanding with a production of interferon-γ (IFNγ). Protein spike (S1)-binding antibody present after the first dose, increased following the second dose; significant neutralizing antibodies (Nab) were only present after the second dose [10, 18, 35].

Steven-Johnsons syndrome (SJS) is a rare immune-mediated cutaneous reaction typically secondary to medications and less commonly to infections. Re-exposure to a culprit agent leads to a recurrence that is usually more severe than the first episode and can be life-threatening. COVID-19 vaccines have two components: virotopes and excipients. Generally, oral manifestations of SJS are described as polymorphic, erosive, annular and erythematous lesions. In the two cases oral manifestations were large, red-colored bullae at the retromolar area, whitish-yellow patches all over the tongue, dorsal surface and lips. Multiple large ulcers at the buccal mucosa, labial mucosa, tongue, palate with hemorrhagic crusting over the lips were observed. One of the cases showed the symptoms 5 days after the second dose of the BNT162b1 vaccine. Dash S. *et al.,* hypothesized that virotopes of the vaccine caused the SJS in the reported case. They believed in genetically predisposed individuals, the virotopes component induced CD8+ T-lymphocyte response against epidermal cells and the keratinocytes. Consequentially, apoptosis and dermo-epidermal junction detachment resulted in SJS [12, 13].

Other adverse effects associated with COVID-19 vaccination include: vesicles (2.7%), ulcers (1.7%),

paraesthesia (1.2%), recurrent aphthous stomatitis (0.7%), blisters (0.65%), burning sensation in mouth (0.4%) and angular cheilitis (0.05%).

CONCLUSION

Recently characterized COVID-19-associated syndromes characterized by a plethora of signs and symptoms, have raised the need to examine the impact and, prospectively, the potential causal role of SARS-CoV-2 infection and related vaccines on oral lesions in the pediatric population. Data from above studies describing oral lesions following viral infection and two records reporting oral lesions following vaccine administration were extracted and qualitatively synthesized, resulting in scarce, jeopardized, and incomplete findings. Since most of the rare lesions recorded were a part of broad-spectrum systemic disorders and syndromes, and were, thus, undetailed or nonspecific, further studies should assess the prevalence and macro-microscopic features of oral lesions following SARS-CoV-2 infection, estimating the degree of association and grading primary oral lesions based on COVID-19 forms in pediatric subjects, also considering novel viral variants. Future investigations should also evaluate the epidemiology, clinical appearance, and histopathology of oral lesions diagnosed among pediatric subjects who received at least one dose of the WHO Emergency Use Listing approved and EMA authorized COVID-19 vaccines in relation to cases' ages, genders, comorbidities, related treatments, and histories of COVID-19, and vaccine types and the number of doses administered, to point out those factors predisposing, or determining, such adverse reactions, especially considering newly introduced vaccines. A deeper insight into oral lesions potentially detectable in pediatric SARS-CoV-2 positive subjects and following COVID-19 vaccination may enhance clinicians' preparedness to improve inter-disciplinary pediatric oral and general healthcare, also introducing oral screening for early diagnosis and appropriate management.

REFERENCES

1. Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., Song, J., Zhao, X., Huang, B., Shi, W., Lu, R., Niu, P., Zhan, F., Ma, X., Wang, D., Xu, W., Wu, G., Gao, G. F., Tan, W., & China Novel Coronavirus Investigating and Research Team (2020). A Novel Coronavirus from Patients with Pneumonia in China, 2019. *The New England journal of medicine*, *382*(8), 727–733.
2. Lu, R., Zhao, X., Li, J., Niu, P., Yang, B., Wu, H., Wang, W., Song, H., Huang, B., Zhu, N., Bi, Y., Ma, X., Zhan, F., Wang, L., Hu, T., Zhou, H., Hu, Z., Zhou, W., Zhao, L., Chen, J., … & Tan, W. (2020). Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet (London, England)*, *395*(10224), 565–574.
3. Samieefar, N., Yari Boroujeni, R., Jamee, M., Lotfi, M., Golabchi, M., Afshar, A., Rezaei, N. (2021). Country Quarantine during COVID-19: Critical or Not? *Disaster Medicine and Public Health Preparedness*, *15*(4), E24-E25.
4. Nagy, A., & Alhatlani, B. (2021). An overview of current COVID-19 vaccine platforms. *Computational and structural biotechnology journal*, *19*, 2508–2517.
5. Aronson, J. K., & Ferner, R. E. (2005). Clarification of terminology in drug safety. *Drug safety*, *28*(10), 851–870.
6. Abraham, G., Bhalala, O. G., de Bakker, P. I., Ripatti, S., & Inouye, M. (2014). Towards a molecular systems model of coronary artery disease. *Current Cardiology Reports*, *16*, 1-10.
7. Al Khames Aga, Q. A., Alkhaffaf, W. H., Hatem, T. H., Nassir, K. F., Batineh, Y., Dahham, A. T., Shaban, D., Al Khames Aga, L. A., Agha, M. Y. R., & Traqchi, M. (2021). Safety of COVID-19 vaccines. *Journal of medical virology*, *93*(12), 6588–6594.
8. Mazur, M., Duś-Ilnicka, I., Jedliński, M., Ndokaj, A., Janiszewska-Olszowska, J., Ardan, R., Radwan-Oczko, M., Guerra, F., Luzzi, V., Vozza, I., Marasca, R., Ottolenghi, L., & Polimeni, A. (2021). Facial and Oral Manifestations Following COVID-19 Vaccination: A Survey-Based Study and a First Perspective. *International journal of environmental research and public health*, *18*(9), 4965.
9. Sharda, P., Mohta, A., Ghiya, B. C., & Mehta, R. D. (2022). Development of oral lichen planus after COVID-19 vaccination - a rare case report. *Journal of the European Academy of Dermatology and Venereology: JEADV*, *36*(2), e82–e83.
10. Bakir, M., Almeshal, H., Alturki, R., Obaid, S., &Almazroo, A. (2021). Toxic Epidermal Necrolysis Post COVID-19 Vaccination - First Reported Case. *Cureus*, *13*(8), e17215.
11. Dash, S., Sirka, C. S., Mishra, S., &Viswan, P. (2021). COVID-19 vaccine-induced Stevens-Johnson syndrome. *Clinical and experimental dermatology*, *46*(8), 1615–1617.
12. Elboraey, M. O., & Essa, E. E. S. F. (2021). Stevens-Johnson syndrome post second dose of Pfizer COVID-19 vaccine: a case report. *Oral surgery, oral medicine, oral pathology and oral radiology*, *132*(4), e139–e142
13. Mansouri, P., Chalangari, R., Martits-Chalangari, K., &Mozafari, N. (2021). Stevens - Johnson syndrome due to COVID-19 vaccination. *Clinical case reports*, *9*(11), e05099.
14. Azzi, L., Toia, M., Stevanello, N., Maggi, F., & Forlani, G. (2021). An episode of oral mucositis after the first administration of the ChAdOx1 COVID-19 vaccine. *Oral diseases*, *28 Suppl 2*, 2583–2585.
15. Thongprasom, K., Pengpis, N., Phattarataratip, E., & Samaranayake, L. (2021). Oral pemphigus after

COVID-19 vaccination. *Oral diseases*, *28 Suppl 2*, 2597–2598.
16. Chun, Y., Jang, J., Jo, J. H., & Park, J. W. (2022). Various painful oral adverse reactions following COVID-19 vaccination: a case series. *BMC oral health*, *22*(1), 64.
17. Hertel, M., Schmidt-Westhausen, A. M., Wendy, S., Heiland, M., Nahles, S., Preissner, R., &Preissner, S. (2022). Onset of Oral Lichenoid Lesions and Oral Lichen Planus Following COVID-19 Vaccination: A Retrospective Analysis of about 300,000 Vaccinated Patients. *Vaccines*, *10*(3), 480.
18. Petruzzi, M., Galleggiante, S., Messina, S., & Della Vella, F. (2022). Oral erythema multiforme after Pfizer-BioNTech COVID-19 vaccination: a report of four cases. *BMC oral health*, *22*(1), 90.
19. Maeda, K., Yamashita, D., &Takenobu, T. (2022). Ulcers on the bilateral palate mucosa following mRNA-based vaccination for coronavirus disease 2019 (COVID-19): A case report. *Journal of stomatology, oral and maxillofacial surgery*, *123*(3), 283–286.
20. Raccampo, L., Sembronio, S., Tel, A., Cacitti, V., &Robiony, M. (2022). Oral lichen planus arising after BNT162b2 mRNA COVID-19 vaccine: report of 2 cases. *Oral surgery, oral medicine, oral pathology and oral radiology*, *134*(3), e54–e57.
21. Troeltzsch, M., Gogl, M., Berndt, R., &Troeltzsch, M. (2022). Oral lichen planus following the administration of vector-based COVID-19 vaccine (Ad26.COV2.S). *Oral diseases*, *28 Suppl 2*, 2595–2596.
22. Sayare, B., Bhardwaj, V. K., & Sharma, D. (2021). Palatal petechiae: an uncommon oral adverse effect of COVID-19 vaccine. *Egypt J Otolaryngol*, *37*, 99.
23. Heboyan, A., Karobari, M. I., & **Marya, A.** (2022). Possible oral manifestation after vaccination against COVID-19: a case report. *Oxford Medical Case Reports*, *2022*(12), omac136.
24. Chaudhari, P. J., Chawda, U. B., Bhad, B. J., Mevada, A. V., & Jha, S. G. (2023). Facial Palsy Induced by Covaxin in Adolescent Female - A Rare Case Report. *Current drug safety*, *18*(4), 603–605.
25. Lee, S., Tong, X., & Yang, F. (2016). Effects of the poly (ethylene glycol) hydrogel crosslinking mechanism on protein release. *Biomaterials science*, *4*(3), 405–411.
26. Zermatten, M. G., Bertaggia Calderara, D., Aliotta, A., & Alberio, L. (2020). Thrombin generation in a woman with heterozygous factor V Leiden and combined oral contraceptives: A case report. *Research and practice in thrombosis and haemostasis*, *4*(3), 429–432.
27. Solimani, F., Mansour, Y., Didona, D., Dilling, A., Ghoreschi, K., & Meier, K. (2021). Development of severe pemphigus vulgaris following SARS-CoV-2 vaccination with BNT162b2. *Journal of the European Academy of Dermatology and Venereology: JEADV*, *35*(10), e649–e651.
28. Tomayko, M. M., Damsky, W., Fathy, R., McMahon, D. E., Turner, N., Valentin, M. N., Rallis, T., Aivaz, O., Fox, L. P., & Freeman, E. E. (2021). Subepidermal blistering eruptions, including bullous pemphigoid, following COVID-19 vaccination. *The Journal of allergy and clinical immunology*, *148*(3), 750–751.
29. Paul, S., Abbas, M. S., Nassar, S. T., Tasha, T., Desai, A., Bajgain, A., Ali, A., Dutta, C., Pasha, K., & Khan, S. (2022). Correlation of Anxiety and Depression to the Development of Gastroesophageal Disease in the Younger Population. *Cureus*, *14*(12), e32712.
30. Finsterer J. (2022). Neurological side effects of SARS-CoV-2 vaccinations. *Acta neurologica Scandinavica*, *145*(1), 5–9.
31. Ismail, I. I., & Salama, S. (2022). A systematic review of cases of CNS demyelination following COVID-19 vaccination. *Journal of neuroimmunology*, *362*, 577765.
32. Ercoli, T., Lutzoni, L., Orofino, G., Muroni, A., & Defazio, G. (2021). Functional neurological disorder after COVID-19 vaccination. *Neurological sciences: official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *42*(10), 3989–3990.
33. McGonagle, D., De Marco, G., & Bridgewood, C. (2021). Mechanisms of Immunothrombosis in Vaccine-Induced Thrombotic Thrombocytopenia (VITT) Compared to Natural SARS-CoV-2 Infection. *Journal of autoimmunity*, *121*, 102662.
34. Kadyrova, I., Yegorov, S., Negmetzhanov, B., Kolesnikova, Y., Kolesnichenko, S., Korshukov, I., Baiken, Y., Matkarimov, B., Miller, M. S., & Hortelano, G. H. (2022). Sputnik-V reactogenicity and immunogenicity in the blood and mucosa: a prospective cohort study. *medRxiv*.
35. Sahin, U., Derhovanessian, E., Miller, M., Kloke, B. P., Simon, P., Löwer, M., Bukur, V., Tadmor, A. D., Luxemburger, U., Schrörs, B., Omokoko, T., Vormehr, M., Albrecht, C., Paruzynski, A., Kuhn, A. N., Buck, J., Heesch, S., Schreeb, K. H., Müller, F., Ortseifer, I., & Türeci, Ö. (2017). Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. *Nature*, *547*(7662), 222–226.