Review Article

Pathophysiology of oral lesions subsequent to SARS-CoV-2 vaccination: A systematic review

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Abstract

Amidst worldwide reports of adverse oral lesions subsequent to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination, the current systematic review planned to determine the prevalence of adverse oral events in adult individuals (≥18 years) after SARS-CoV-2 vaccination, emphasizing upon the type and dose of vaccine, time of onset, and underlying pathophysiology. The registered protocol (PROSPERO CRD42023421307), conforming with PRISMA guidelines, included an all-inclusive literature search through online databases, consisting of Scopus, PubMed/MEDLINE, Web of Science, Lilacs, Livivo, and PROSPERO, completed on 2 May 2023, followed by assessment of risk of bias by Joana Briggs Institute Evaluation Checklist. Due to the paucity of literature, case reports and case series were included. Self-reported lesions were excluded. Qualitative synthesis employing Microsoft Excel software 2019 revealed low prevalence (43 subjects) from 26 case reports and two case series. There were multiple erosive oral ulcers on gingiva, palate, burning pain in the mouth, xerostomia, tongue fissuring and glossitis, palatal petechiae, diffuse erythematous lesions and loss of smell (16.2%), primary herpetic gingivostomatitis (21%), oral lichen planus (16.2%), Stevens-Johnson syndrome (6.9%), Bell's palsy in four cases where two cases were Guillain-Barré syndrome (9.3%), erythema multiforme (11.6%), pemphigus (4.6%), idiopathic thrombocytopenic purpura (6.9%), unilateral hypoglossal nerve palsy (4.6%), and trigeminal neuralgia (2.3%). Maximum cases (22 subjects) presented oral lesions after Pfizer (BNT162b2) SARS-CoV-2 vaccine. No association was found between the vaccine type and dose with oral side effects. Dentists must be aware of the oral adverse effects after coronavirus disease 2019 vaccination to better understand the pathogenesis and the risk factors associated with such reactions.

Keywords: COVID-19, oral adverse effects, oral lesions, oral side effects, SARS-CoV-2 vaccination

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INTRODUCTION

Almost all the countries in the world witnessed the devastating Coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which called for extensive measures to be enforced. SARS-CoV-2 vaccines were administered on a colossal scale in almost all the countries, remarkably minimising the hazards of viral transmission and infection, impeding the severe forms of COVID-19, and reducing hospitalisation time and mortality.[1-3]

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Presently available vaccines are manufactured by utilising one of the technologies: mRNA-based vaccines, inactivated or whole virus vaccines, viral vector-based vaccines, and protein subunit vaccines.[4,5] However, the surge of COVID-19 cases in recent years, in almost all the countries, was an emergency condition and demanded mass vaccination of the general population. Therefore, many vaccines were authorised without standard measures or long-term research and investigation.[6,7] Thus, SARS-CoV-2 vaccine administration is not without risks and serious side effects, which must be detected and handled at the earliest to minimise possible harm.[8,9] Recently, a systematic review reported the prevalence of oral manifestations like altered taste, dry mouth, and vesiculobullous lesions during COVID-19 infection.[10] Adverse oral and facial manifestations post SARS-CoV-2 vaccination, specifically oral aphthous-like ulcers, burning sensation, xerostomia, taste alteration, palatal petechiae, pain on gingiva, tongue, lips, and facial paralysis have also been described.[11] Significantly, most of the oral manifestations have been reported to occur in congruence with cutaneous lesions.[12] Therefore, it has become significant for dermatologists, dental surgeons, and other healthcare workers to be well-versed with clinical scenarios supporting diagnoses of oro-facial adverse manifestations following SARS-CoV-2 vaccination and to understand the immune mechanisms underlying these adverse events and manage them rapidly to improve patient outcomes.

This systematic review was mainly aimed to evaluate the available data, comprising largely case reports and case series of patients (≥18 years old) diagnosed with oral adverse effects after administration of any dose of the World Health Organisation (WHO)-authorised and European Medicines Agency (EMA)-licensed vaccines.[13,14] Additionally, the objective of the study was to identify the most prevalent oral lesions post SARS-CoV-2 vaccination and to understand the underlying pathogenesis and immune mechanisms.

METHODS

The systematic review protocol was registered at the National Institute of Health Sciences (PROSPERO. International Prospective Register of Systematic reviews database) under registration number CRD42023421307. PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analyses) were followed while doing the literature search.[15,16]

The question under review focused on the oral lesions and adverse side effects in the adult population (≥18 years) who have received any dose of the SARS-CoV-2 vaccine, following the PECOS strategy.

Participants/population

Adult persons ≥18 years of age who were administered any dose of anti-SARS-CoV-2 vaccine.

Exposure/intervention

SARS-CoV-2 vaccination

Comparator/control: Not applicable.

Outcomes

Main outcome

To find out the global prevalence of oral mucosal lesions and adverse effects in the oral cavity following administration of any dose of SARS-CoV-2 vaccine.

Additional outcomes

a. To identify the most frequent oral lesions observed.
b. To understand the pathogenesis and immune mechanism associated with these adverse oral lesions.

Inclusion criteria

a. Data from cross-sectional and case-control studies, along with case reports and case series, describing oral adverse effects in the adult (≥18 years) population who received at least one dose of European Medicines Agency (EMA) licensed and WHO (World Health Organization)-approved COVID-19 vaccines.
b. Only English language articles published till 2 May 2023 were taken under purview for this systematic review.

Exclusion criteria

a. All narrative reviews, grey literature, abstract only, and systematic reviews were excluded.
b. Studies where the SARS-CoV-2-vaccinated subjects were <18 years of age.
c. SARS-CoV-2-positive patients with oral side effects were also not included in this analysis.

Information sources and search strategy

a. The online search included the PubMed/MEDLINE, Scopus, Web of Science, Livivo, and Lilacs databases as well as the PROSPERO register, applying various key words: 1. Vaccine OR Vaccination AND, 2. Oral manifestation OR Oral lesion AND, 3. SARS-CoV-2 OR COVID-19, 4. COVID-19 vaccine AND Oral adverse effects. There was no constraint regarding the date of publication, and the search was conducted through 2 May 2023 across these databases. After collecting all references, the duplicate articles were removed employing a software reference manager (Mendeley Desktop Version 1.19.8, Elsevier).

Study selection

In compliance of the inclusion and exclusion criteria, the study selection was accomplished individually by two authors in two phases. Employing Rayyan software in phase 1, two authors (PS and SM) independently segregated the abstracts and titles of all the references. The inter-reviewer agreement was assessed through Cohen's Kappa statistics. Articles complying with the inclusion criteria were shortlisted, and the rest of the articles were rejected. The finishing curation was done in discussion with the third author (VW). In phase 2, the same selection criteria were followed separately by both the authors and the publications which described the oral and facial manifestations following any dose of COVID-19 vaccination were chosen. After thorough critical appraisal of the selected articles by three authors (PM, SM, and VW), the most suitable ones were chosen for analysis. In case of disagreement in either of the phases, a unanimous decision was taken after a consensus among the three authors. In the end, only full-text articles were included for the current systematic review.

Data collection

Mainly, two independent reviewers (PS and SM) derived the data from the selected references, consulting the third reviewer (VW) if required. An exclusive extraction form was made, on which the following were listed: essential information on the authors, name of the country, year of study, funding, study design, number of subjects, mean age, gender, co-morbidities, history of COVID-19, SARS-CoV-2 vaccine, number of doses, chief complaints, oral side effects, manifestation time after administration, treatment and progression, and pathogenesis. Subsequently, the third reviewer (VW) corroborated the collected data and confirmed its veracity. Disagreements, if any, were resolved by mutual discussion among all the reviewers. All selected articles were full-text and freely available, so no efforts were made to contact with the authors.

Risk of bias within studies

Three reviewers (PS, SM, and VW) evaluated the bias risk of all the included studies one by one by employing a quality assessment checklist for case reports, case series, and prevalence studies adapted by the Joanna Briggs Institute's Critical Appraisal checklist (Munn *et al*. 2015 and Moola *et al*. 2017).[17,18] Each article was conclusively scored in consultation with all authors, and a study was categorised on the basis of the risk of bias: high risk of bias when the "yes" score was up to 49%, moderate when 50% to 69%, and low when >70%.[17,18] Any of the selected and shortlisted studies, which showed high risk of bias, were eliminated from the current review.

Summary measures/data synthesis

A narrative synthesis was carried out, emphasising on the analysed population, intervention, comparison, and outcome. Microsoft Excel software 2019 (Microsoft Corporation, Redmond, WA, USA) was used to qualitatively synthesise the descriptive data. The primary outcome was to find out the prevalence of oral adverse effects post COVID-19 vaccination. The additional outcomes were to identify the most frequent oral lesions observed and to understand the pathogenesis and immune mechanism associated with these adverse oral lesions.

RESULTS

Study selection and characteristics

Overall, 484 records were identified from databases, notably 285 from PubMed/MEDLINE, 31 from Web of Science, 112 from Scopus, 23 from Livivo, and 31 from Lilacs. The search in PROSPERO register showed two records. After removing 118 duplicate records, 366 references remained for abstract and title screening. After analysing all the records, the authors (PS and SM) screened 40 full-text articles for the second phase, excluding 12 articles in accordance with the set criteria. Initially, three studies seemed to fulfill the inclusion criteria but were finally excluded. Specifically, one questionnaire-based survey was eliminated[11] since the oral lesions were detected by clinical examination, and another study on a cohort of herpes zoster (shingles) was also precluded from synthesis as the age criterion of ≥18 years was not fulfilled.[19] A case-control study assessing only facial nerve palsy as an outcome in 21 subjects vaccinated by BNT162b2 vaccine was eliminated from the analysis because of high risk of bias.[20] Additionally, in one case series of four subjects of oral erythema multiforme, one of the patients was <18 years old; therefore, this particular subject was not included in synthesis.[21]

Finally, 28 studies were selected for synthesis, of which 26 were case reports and two were case series on oro-facial adverse effects following COVID-19 vaccination. A flow chart adhering PRISMA guidelines is depicted in Figure 1. Table 1 illustrate the detailed information retrieved from the included studies. Only those studies which were compliant with the inclusion/exclusion criteria were considered. Therefore, those describing subjects <18 years of age and where oral lesions were not detailed post SARS-CoV-2 vaccination were eliminated from the current review.

Though the oral mucosal lesions following COVID-19 vaccination have been reported from many countries, maximum reported cases were from Europe, predominantly Italy, Germany, Malta, Switzerland, and Poland, followed

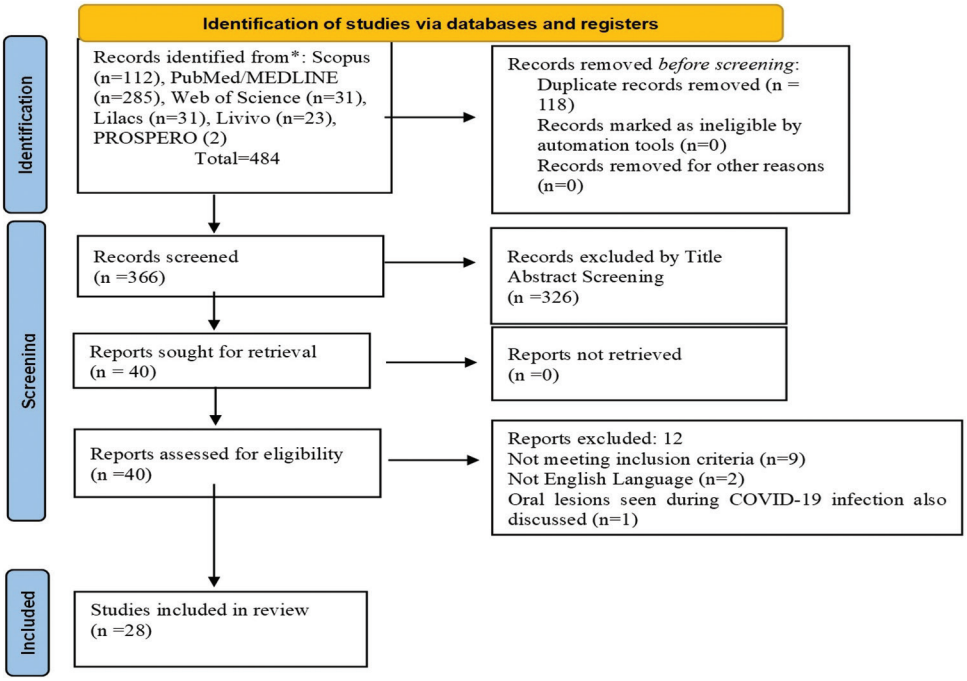

Figure 1: Flow diagram depicting selection criteria adapted from PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[16]

by India, China, Australia, Thailand, Iran, Egypt, Japan, Turkey, Israel, and USA. English language articles which were published through 2 May 2023 only were included.

Risk of bias within studies

All included studies were scrutinised for the bias risk by applying Joana Briggs Institute guidelines, after which the observations are summarised in Table 1 and details are presented in [Appendix Table 1(A) and (B)]. Case reports and case series were appraised against the checklist designated for each study design.[17,18] The observational studies, case series, and case reports showing high risk of bias were eliminated from this appraisal. All included case series (n = 2; 100%) and 25 case reports (96.1%) examined in the present review presented low risk of bias, while only one case report showed moderate risk of bias [Appendix Table 1(A)]. A single case-control study on facial nerve palsy subjects was precluded because of high risk of bias.[20]

Synthesis of studies

Overall, 28 studies, comprising two case series and 26 case reports, were included for analysis. The investigated population constituted 43 subjects in all case series and case reports, 30 females and 13 males between 18 and 88 years old, with a mean age of 37.56 years.

Table 1 present the distinctive features of the included studies describing the study design, type and dose of SARS-CoV-2 vaccination, oro-facial manifestations, progression, and immune mechanism behind the oral symptoms. Data were extracted and synthesised employing inclusion and exclusion criteria; thus, systemic adverse effects were not detailed.

Overall, the co-morbidities reported were hypertension, hyperlipidemia, Type I diabetes mellitus, recurrent cystitis, prostatic disease, osteoporosis, hyperthyroidism in a case series of nine subjects,[24] acquired hypothyroidism due to Hashimoto thyroiditis in one case,[22] Type II diabetes mellitus, hyperlipidemia and hypercholesterolemia in two subjects,[30,36] history of adverse drug reaction following metamizole and penicillin intake,[33] post-operative intestinal obstruction and hypopharyngeal cancer in one case,[35] Leiden factor V mutation in a 31-year old female,[28] anemia, hypothyroidism,[37] diabetes, and hypertension.[44] One subject was allergic to polysorbate 80 during allergy tests with skin reaction and reappearance of oral signs and symptoms,[48] mucous membrane pemphigoid in one subject and celiac disease, and spastic colon and lactose intolerance in another subject.[23] History of COVID-19 infection was not mentioned in 34 subjects.[22-32,34,35-37,39,42,43,45,46] Six subjects gave no history of COVID-19 infection,[35,37,38,44,45,47] and three participants tested negative.[23,33,49] One case was diagnosed positive for SARS-CoV-2 (after 10 days) between the first and second vaccine doses.[41]

Out of a total of 43 patients analysed in case series and case reports, 21 patients manifested oral adverse effects after the use of Pfizer-BioNTech vaccine[23-25,29,31,32,34-36,38,41,43,45,46,48], 4 patients after

Table 1: Data retrieved on oral side-effects following anti-SARS-CoV-2 vaccination (Case Report [CR] *n*=26); (Case Series [CS]=2)

Study Id, Funding and Design	Anti-SARS-CoV-2 Vaccine	Oral side-effects	Pathophysiology
CR- Andreozzi V *et al*., Italy, Neurol Sci 2022 [22]. No funding.	ChAdOx1- Vaxzevria™ (AstraZeneca). First dose	First patient: Complete facial diplegia with Bell's phenomenon. Second patient: Guillain-Barré syndrome (GBS)	Autoimmune mechanism because of molecular mimicry between the virus and human proteins
CR- Bechtold A and Owczarczyk-Saczonek A, Poland, Dermatol Ther 2022 [23]. No funding.	Ad26.COV2.S (Johnson & Johnson, Janssen). Not clear	Ulcerations on side of the tongue. Sweet syndrome	Elevated levels of interleukins and TNF-α and interferon- ϒ in neutrophilic diseases
CR- Elboraey MO and Essa EESF, Egypt, Oral Surg Oral Med Oral Pathol Oral Radiol 2021 [25]. No funding.	BNT162B2 (Pfizer BioNTech). Second dose	Stevens-Johnson syndrome	Possibility of acute hypersensitivity reaction
CR- Liu W, *et al*., China, Exp Ther Med 2022 [26]. Funding -Grant from the Gansu Province Innovation Base and Talent Plan (Gansu Province Leukemia Clinical Research Center; grant no. 21JR7RA015).	CoronaVac (Vero Cells, , Beijing Kexing Zhongwei Biotechnology Co., Ltd.). Second dose	Immune thrombocytopenic Purpura (ITP)	ITP may be induced by components of the vaccine, such as yeast proteins, adjuvants and preservatives or diluents.
CR- Maeda K, *et al*., Japan, J Stomatol Oral Maxillofac Surg 2022 [27]. No funding.	mRNA-1273 (Moderna). Second dose	Bilateral palatal mucosal ulcers with well-defined margins, in the molar region.	Increased levels of local and systemic T helper type 1 cytokine (e.g., interferon-γ) production
CR- Kaomongkolgit R and Sawangarun W, Oral Dis. 2022, Thailand [28]. No funding	BNT162b2 (Pfizer/BioNTech). Second dose	OLP	Autoimmune development triggered by epitope. Another possible mechanism is vaccine-associated hyper-viscosity
CR- Kaya A and Kaya SY, Turkey, J Neurovirol 2022 [29]. No funding.	BNT162b2(Pfizer/BioNTech). First dose	Trigeminal neuralgia	Immune-mediated inflammation
CR- Padniewski JJ *et al*., USA. Int J Dermatol 2022 [30]. No funding.	mRNA-1273 (Moderna). First dose	Stevens-Johnsons syndrome/ Toxic Epidermal necrolysis	Not explained
CR-Panholzer J *et al*., Austria, BMC Neurol 2022 [31]. No funding.	AZD1222 (AstraZeneca) and BNT162b2. (BioNTech/Pfizer). Second dose	Unilateral hypoglossal nerve palsy	Autoimmune reactions such as antibodies cross-reacting with peripheral myelin proteins
CR- Raccampo L *et al*., Italy. Oral Surg Oral Med Oral Pathol Oral Radiol 2022 [32]. No funding.	BNT162b2 (BioNTech/Pfizer). Second Dose	OLP	Cytokine production secondary to the Th1 (T-helper cell) response that triggers the vaccination may play a fundamental role in the Lichen planus outbreak
CR- Saibene AM *et al*., Italy, Clin Case Rep 2021 [33]. No funding.	mRNA-1273 (Moderna vaccine). Second dose	Erythema multiforme	Immune-mediated reaction
CR- Sayare B *et al*., India, Egyptian J of Otolaryngology 2021 [34]. No funding.	COVISHIELD (ChAdOx1), Serum Institute of India. First dose	Palatal petechiae	Not clear
CR- Shonai T *et al*., Japan, Intern Med 2022 [35]. No funding.	BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna vaccine). Second dose	Immune thrombocytopenia	Not clear
CR- Tan E and Salman S, Australia, Am J Case Rep 2022[36]. No funding.	BNT162B2 (Pfizer-BioNTech). Onset of symptoms after first dose, which worsened after second and booster doses.	Tongue swelling with new fissuring and xerostomia.	Strong temporal relationship between onset and exacerbation of symptoms following each vaccination.
CR- Thongprasom K, *et al*., Thailand, Oral Dis 2021 [37]. No funding.	AZD1222 (Astrazeneca). First dose	Generalized desquamative gingivitis, erythematous areas along the gingival, alveolar mucosa. Pemphigus	Not clear
CR- Woo CJ *et al*., Hong Kong, China, Postgraduate Medical Journal, 2022 [38]. No funding.	BNT162b2 (Pfizer-BioNTech). First dose	Grade 4 right facial nerve palsy of the lower motor neuron type with right sensorineural hearing loss. Ramsay Hunt Syndrome Type 2	Immunomodulation may be responsible. VZV -specific CD8 cells may be temporarily incapable of controlling the VZV after the massive shift of naive CD8+ cells to produce vaccine-targeting CD8+ cells.
CR- Collela G *et al*., Italy, J Neurol. 2021 [39]. No funding.	BNT162b2 (Pfizer-BioNTech). First dose	Bell's palsy	Causal relationship not established
CR- Azzi L *et al*., Italy, Oral Dis. 2021 [40]. No funding.	AZD 1222 (Astrazeneca). First dose	Diffuse, erythematous and swollen red lesions on buccal mucosa, tongue, gums and palate	Mucosal hypersensitivity may have been triggered by a specific adaptive immune response against the virus, producing neutralizing antibodies directed against SARS-CoV-2 Spike protein.

Contd...

Table 1: Contd...

Study Id, Funding and Design	Anti-SARS-CoV-2 Vaccine	Oral side-effects	Pathophysiology
CR- Babazadeh A *et al*., Iran, Clin. Case. Rep. 2022 [41]. No funding.	BBIBP-CorV Sinopharm, Beijing Institute of Biological Products. First and second dose	OLP	Vaccine triggers Th1 response, which in turn leads to the elevation of interleukin-2 (IL-2), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) levels.
CR- Caggiano M *et al*., Italy, Oral Dis. 2022 [42]. No funding.	BNT162b2 (Pfizer-BioNTech). Second dose	OLP	Cell-mediated reaction
CR- Borg L *et al*., Malta, J Eur Acad Dermatol Venereol 2022 [43]. No funding.	BNT162b2 (Pfizer-BioNTech). First dose	Erythema multiforme	Not Clear
CR- Dash S *et al*., India, Cin Exp Dermatol 2021[44]. No funding.	COVISHIELD (ChAdO×1), Serum Institute of India. First dose	Oral erosions and haemorrhagic crusting over the lips. SJS	Virotopes on the surface of keratinocytes leads to a CD8+ T-lymphocyte response against epidermal cells and causes apoptosis of keratinocytes and detachment at the dermo-epidermal junction, leading to SJS in genetically susceptible individuals.
CR- Sharda P *et al*, India, J Eur Acad Dermato IVenereol 2022 [45]. No funding.	N.M.	OLP	Exact mechanism not explained
CR- Troeltzsch M *et al*., Germany, Oral Dis. 2021[46]. No funding.	Ad26.COV2.5 (Janssen, Johnson & Johnson). Dose N.M.	OLP	Cytokine flare leading to manifestation of lichen planus.
CR- Calabria E *et al*., Italy, Pathol. Res. Pract. 2022 [47]. No funding.	BNT162b2 (Pfizer BioNTech). Second dose	Pemphigus vulgaris	Molecular mimicry mechanism
CR- Manfredi M *et al*., Italy, Oral Dis. 2021[48]. No funding.	BNT162b2 (Pfizer BioNTech). First dose	Multiple erosive oral ulcers	Polysorbate 80 is used to make the m-RNA fat-soluble and the patient showed reactivity to it. It causes a cross-link reaction with one of the components of the BNT162b2 vaccine.
CS- Petruzzi M *et al*., Switzerland, BMC Oral Health 2022 [21]. No funding	BNT 162b2 (Pfizer BioNTech). First and second dose	Bullous erythematous lesions on left buccal mucosa. Oral erythema multiforme	Expression of an antigen on keratinocyte, causing T-cell activation.
CS- Chun Y *et al*., Korea, BMC Oral Health 2022 [24]. No Funding	BNT162b2 (Pfizer BioNTech) in 4 subjects and AZD1222 (Astrazeneca) in 5 subjects. First and second dose	Primary herpetic gingivostomatitis. Multiple ulcerative lesions with surrounding erythema and slight swelling on posterior hard palate, ulceration of the palatal gingiva, whitish, dried and cracked lower lip mucosa, erythema with whitish lesion on right buccal mucosa and lower vestibule, fissured tongue.	Molecular mimicry resulting from the significant similarity between certain vaccine elements and human proteins.

COVID-19-Coronavirus disease 2019; SARS-CoV-2- Severe Acute Respiratory Syndrome Coronavirus 2; Y/F: Year-old female; Y/M: Year-old male; N.M.: Not mentioned; ITP (Immune Thrombocytopenic Purpura); VZV (Varicella Zoster Virus); Th1 (T-helper 1 cell); IFN-ϒ (Interferon-ϒ); TNF-α (Tumor Necrosis Factor-α); IL-2 (Interleukin-2); SJS (Stevens-Johnson Syndrome); OLP (Oral Lichen Planus)

vaccination with mRNA1273/Moderna vaccine,[28,30,33,35] 13 cases were described after AstraZeneca or ChAdox1 vaccine,[22,24,32,37,40,42,44] and 2 cases following the administration of Ad26.CoV2.S (Johnson and Johnson, Janssen,[25,39] 1 each after Sinopharm, Beijing[48] and Vero Cells, Beijing Kexing Zhongwei Biotechnology Co., Ltd.)[27] vaccination. In one case report, the name and dose of the vaccine were not mentioned[47] [Figure 2].

The minimum time of onset of oral symptoms post COVID-19 vaccination was 3 hours,[22] and the maximum time gap reported was 30 days.[26,42] The average time of onset was 7.03 days.

Oral aphthous-like ulcerations, multiple erosive oral ulcers on gingiva, palate, burning pain in mouth, xerostomia, tongue fissuring and glossitis, palatal petechiae, and diffuse erythematous lesions were reported subsequent to SARS-CoV-2 vaccination in seven patients (16.3%).[21,23,30,34,40,48] Specifically, herpetic gingivostomatitis in a case series (n = 9, 21%),[24] oral lichen planus in 7 cases (16.3%),[36,39,41,43,45,48] Stevens-Johnson syndrome in 3 cases (6.97%),[25,30,44] Bell's palsy in 4 cases where two cases were Guillain-Barré syndrome (GBS) (9.3%),[22,38,39] erythema multiforme in 5 subjects (11.6%),[21,33,43] pemphigus in 2 (4.62%),[29,46] immune thrombocytopenic purpura in 3 (6.97%),[27,34]

unilateral hypoglossal nerve palsy in 2 subjects (4.62%),[31] and trigeminal neuralgia in one case (2.32%) were reported.[29]

Oro-facial adverse effects were observed after the first dose of COVID-19 vaccine in 23 cases and after the second dose in 15 cases. In 3 subjects, the vaccine dose was not mentioned.[23,45,46] However, administration of the first dose of BNT162B2 (Pfizer) vaccine in a 60-year-old female resulted in tongue swelling, xerostomia, and fissuring, which progressively worsened after the second and booster doses of vaccination.[36] Acute appearance of oral lichen planus in a 52-year-old female was noticed after the first dose, which re-appeared subsequent to the second dose of Sinopharm (BBIBP-CorV) vaccine.[41]

Intravenous immunoglobulin for 5 days significantly decreased paresthesia after 8 days in two subjects of facial palsy following SARS-CoV-2 vaccination.[22] Oral and topical corticosteroids showed remarkable regression of oral mucosal ulcerations, lichen planus, erythema multiforme, Stevens-Johnson syndrome, and pemphigus vulgaris subsequent to COVID-19 vaccination in almost all the patients.

DISCUSSION

This systematic review was conducted to do a comprehensive qualitative analysis on oral mucosal adverse effects and facial manifestations among the adult (≥18 years old) SARS-CoV-2-vaccinated individuals, who were administered at least one dose of European Medicines Agency (EMA)-licensed vaccines and WHO-licensed vaccines[13,14]; therefore, cases or studies describing only systemic adverse effects after SARS-CoV-2 vaccination were not incorporated in the synthesis. Due to the lack of literature on oral adverse effects post COVID-19 vaccination, case series, case reports, and observational studies were considered and included for qualitative synthesis. Additionally, the review focussed on addressing the most commonly occurring oral lesions post SARS-CoV-2 vaccination, exploring any association with dose and type of SARS-CoV-2 vaccine, co-morbidities, and understanding the underlying pathogenesis and immune mechanism of such adverse reactions in the oral cavity.

Riad A *et al*.[49] assessed the European Union Drug Regulating Authorities Pharmacovigilance (EudraVigilance) database and Vaccine Adverse Event Reporting System (VAERS) data and found a low prevalence of oral side effects following COVID-19 vaccination, with altered taste (e.g., dysgeusia and ageusia), hypersensitivity reactions like glossitis, lip and mouth swelling, and sensory (e.g., oral paresthesia) adverse effects being the most frequent in Europe[49] and the US population.[50] Quite significantly, most of the oral adverse events following SARS-CoV-2 vaccination were described by the medical specialists and not oral medicine experts, thus focussing on the severe systemic reactions which required urgent attention. This might have led to under-reporting of oral mucosal lesions. Furthermore, oral mucosal involvement was often manifested with cutaneous manifestations, specifically in oral lichen planus, erythema multiforme, Stevens-Johnson syndrome, pemphigus vulgaris and Sweet syndrome, and Behcet's-like adverse events.[23,25,26,37,42-45,51] Nevertheless, oral mucous membrane pemphigoid manifesting as erythematous areas on the gingiva was reported in a 74-year-old female after 21 days subsequent to the administration of the first dose of mRNA vaccine (BNT162B2, Pfizer/BioNTech).[52] Regarding sex-specific prevalence, a higher proportion of oral lesions following SARS-CoV-2 vaccination were found in females (69.8%, 30 cases) than in males (30.2%, 13 cases). Simulating our findings, Di Spirito *et al*.[53] observed an increased prevalence of oral adverse effects following SARS-CoV-2 vaccination in females (68.8%) than in males (31.2%). Likewise, in a registry-based study of 414 cases by McMahon *et al*.,[54] 90% females presented cutaneous adverse reactions post Pfizer and Moderna COVID-19 vaccination. Analysis of EudraVigilance reports by Riad *et al*.[49] revealed that females had significantly higher prevalence of xerostomia, altered taste, oral ulcers, and toothache following viral vector-based vaccines than mRNA-based vaccines.[49] This may be explained by cumulative gender-specific differences in life style, psycho-social factors, behavioural differences, body mass index, and pharmacodynamics.[55]

Regarding the type of vaccine, a higher incidence of cases (48.83%, 21 out of 43 cases) were described subsequent to mRNA BNT162b2 Comirnaty (Pfizer-BioNTech) vaccine, followed by ChAdOX1 vaccine (Astrazeneca) (30.23%, 13 cases), mRNA-1273/Moderna vaccine (9.3%, 4 cases), Ad26.COV2.5 (Johnson and Johnson) (2 cases), and one case each of Sinopharm, Beijing and Vero cells. Concerning the dose, oral adverse effects occurred following the first dose in 24 cases and the second dose in 15 cases, while the dose number was not mentioned in 3 cases. Noteworthily, in a 60-year-old female, onset of glossitis and xerostomia occurred following the administration of the first dose of BNT162b2 vaccine, which worsened with appearance of fissuring after the second and booster doses.[36] Acute onset of symptoms of oral lichen planus was reported in a 52--year-old female subject after the

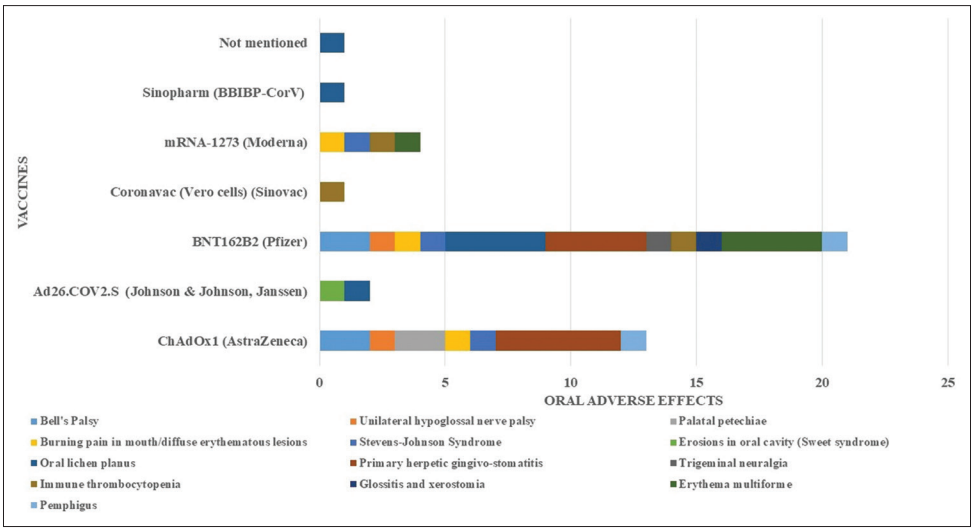

Figure 2: Oral adverse effects subsequent to COVID-19 vaccination

first dose, followed by re-appearance after the second dose of Sinopharm (BBIBP-CorV) COVID-19 vaccine.[41] However, in a questionnaire-based survey conducted in European countries, almost all the subjects received Pfizer-BioNTech vaccine; 3.1% showed oral aphthous-like ulcers, burning sensation, dysgeusia, xerostomia, pain, and tongue depapillation, while 5.4% manifested facial symptoms like facial paresis and changes in sensitivity. No significant correlation was observed between SARS-CoV-2 vaccine administration and oro-facial manifestations.[11]

Hatami P *et al*.[56] described mucocutaneous adverse events like swelling, erythema, and tenderness post SARS-CoV-2 vaccination and categorised them as acute (<24 hours) and delayed (>24 hours) reactions. The current review observed that the time period of onset of symptoms following SARS-CoV-2 vaccination ranged from acute primary herpetic gingivostomatitis (as early as 3 hours)[21] and emergence of palatal petechiae after 4 hours[34] to delayed manifestations (within 30 days). Our findings are in contrast with the systematic review by Spirito FD *et al.,* 2022,[53] where oral lesions were diagnosed within 1 to 30 days after vaccination.

Raised levels of tumor necrosis factor (TNF-α), interferon-γ, and interleukins in neutrophilic diseases may have resulted in oral ulcerations and acute febrile neutrophilic dermatosis or Sweet syndrome after 7 days of Ad26.COV2.S SARS-CoV-2 vaccination in a 44-year-old female.[23] Molecular mimicry because of marked similarity between certain vaccine components and human proteins and T-cell-specific response induced by AZD1222 vaccine may trigger immune cross-reactivity as reported by Chun Y *et al*.[24] in a case series (n = 9; BNT162B2 in 4 subjects and AZD1222 IN 5 subjects) of primary herpetic gingivostomatitis. Acute hypersensitivity reaction after 5 days of the second dose of Pfizer SARS-CoV-2 vaccination in a middle-aged female patient and 3 days post the first dose of mRNA 1273 SARS-CoV-2 vaccination in a 46-year-old female resulted in multiple large ulcers on buccal and labial mucosa, tongue and palate, oral discomfort, and erosions, diagnosed as Stevens-Johnson syndrome.[25,30] Also, following 3 days of the first dose of ChAdOx1CoV-19 (Covishield) vaccination in a 60-year-old male, oral erosions and haemorrhagic crusting occurred and histopathologic diagnosis confirmed Stevens-Johnson syndrome (SJS).[44] ChAdOx1 nCoV-19 vaccine-induced T-cell-specific response may have been produced, comprising mainly Th1 cells, due to which an immune response may have been triggered with consequent keratinocyte cell damage. Presentation of bilateral white reticular patterns on oral mucosa, confirmed as oral lichen planus histopathologically, which was seen post BNT162b2 Pfizer BioNTech and Ad26.COV2.S vaccination in 7 cases, may have been triggered by cytokine flare secondary to the Th1 (T-helper cell) response, which results in elevated levels of interleukin-2 (IL-2), tumor necrosis factor-α (TNF-α), and interferon-γ levels.[36,39,41,43,45,48] The Nocebo effect, that is, when the individual has a premonition that some adverse reaction may occur after vaccination, was hypothesised by Kalkur *et al*.,[57] who observed that there is association of lichen planus with stress and anxiety.[57] Immune thrombocytopenic purpura (ITP) presenting as oral bleeding may be prompted by the vaccine ingredients, like preservatives, adjuvants, diluents, and yeast proteins. Additionally, cross-reactivity, epitome spreading, and cryptic antigen expression may induce auto-immune reaction.[26,33]

In a case-control study, Shemer *et al*.[20] observed no association between acute-onset facial palsy in 21 subjects and vaccination with the BNT162B2 vaccine. The current analysis detailed four cases of facial nerve palsy,[24,38,39] where one subject was diagnosed as Ramsay Hunt Syndrome Type 2,[38] all manifesting after the first dose of Pfizer BioNTech (BNT162b2) vaccination. The plausible explanation is that the BNT162b2 vaccine might induce auto-immune mechanism as a result of molecular mimicry between the virus and human proteins.[49] Accordingly, cell-mediated immune failures due to the host's response to COVID-19 vaccination may cause Varicella zoster virus (VZV) reactivation, manifesting as herpes zoster (shingles) as suggested by Hertel M *et al*.,[19] who investigated an association between COVID-19 vaccination and a large cohort of herpes zoster patients extracting the data from the TriNetX Global Health Research database, USA. They observed that 2204 vaccinated subjects manifested herpes zoster within 60 days of COVID-19 vaccination. No causal relationship was established between a case series of nine subjects of Guillain-Barré Syndrome (GBS) variant known as Bilateral Facial Palsy with Paresthesia (BFP) presenting after SARS-CoV-2 vaccination (Sputnik V in 5 and AstraZeneca in 4 subjects) with an average time of onset being 17.4 days.[58,59] The most definitive association between COVID-19 vaccines and oral adverse effects has not been confirmed yet; however, the possible pathogenesis may comprise anaphylactic reactions, auto-immune imbalance, immune cross-reactivity, molecular mimicry, and allergy to vaccine components.[60]

Limitations

First, there is substantial documentation on systemic adverse effects post SARS-CoV-2 vaccination; however, there is still scarce literature on oral side effects following the COVID-19 administration. Second, we precluded the survey-based studies or self-reported oral lesions from the final synthesis; thus, this further reduced the number of included studies. The data were retrieved from case reports and case series only, which is not regarded to have high scientific evidence. Third, confirmatory diagnosis was largely based on clinical examination and histopathologic investigation was not executed in all the included case reports. Fourth, since many oral adverse effects or oral lesions occur concomitantly with serious systemic or cutaneous adverse reactions, the treatment of which may require urgent attention by the healthcare workers, the manifestations in the oral cavity may have been under-reported. Finally, since the retrieved data were heterogeneous, meta-analysis was not undertaken, thus precluding conclusive findings.

CONCLUSION

The current systematic review revealed an overall low prevalence of oral side effects following anti-SARS-CoV-2 vaccination, with non-specific aphthous-like oral ulcers, multiple ulcerative and erythematous lesions of primary herpetic gingivostomatitis erythema-multiforme like oral ulcers, oral lichen planus, and facial nerve palsy, being the most common. Pfizer-BioNTech vaccine (51.1%) and females (69.7%) were associated with higher prevalence of oral adverse effects. Adverse oral effects following a SARS-CoV-2 vaccination may be due to the immune-modulatory effect of the vaccine, activation of T and B cells causing elevated cytokines in auto-immune diseases like oral lichen planus and pemphigus vulgaris, and hypersensitivity reactions such as Stevens-Johnson syndrome. Further research is warranted to establish the causal relationship between a SARS-CoV-2 vaccination and presentation of oral side effects. Considering the constantly surfacing viral variants and the consistent advancement of commercially developed vaccines, the observations of this study may be constantly upgraded.

List of abbreviations

COVID-19	= Coronavirus disease 2019
SARS-CoV-2	= Severe Acute Respiratory Syndrome Coronavirus 2
PRISMA	= Preferred Reporting Items for Systematic Review and Meta-analysis
GBS	= Guillain-Barré syndrome
WHO	= World Health Organisation
EMA	= European Medicines Agency
VAERS	= Vaccine Adverse Event Reporting System
Th1	=T-helper cell
IL-2	=interleukin-2
IF-γ	=Interferon-γ
PRISMA	=Preferred Reporting Items for Systematic Reviews and Meta-analyses
HSV-1	= Herpes Simplex Virus-1
TNF-α	= Tumor necrosis factor-alpha
HZ	= Herpes Zoster
VZV	= Varicella Zoster Virus
ITP	= Immune Thrombocytopenic Purpura
BFP	= Bilateral Facial Palsy with Paresthesia.

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Conflicts of interest

There are no conflicts of interest.

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Appendix Table 1: Risk of Bias assessed by the Joanna Briggs Institute Critical Appraisal Tools (A) for case reports and (B) for case-series. Risk of bias was categorized as High when the study reaches up to 49% score "yes", Moderate when the study reached 50% to 69% score "yes", and Low when the study reached more than 70% score "yes"

A. Checklist for Case Reports

Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	%Yes/Risk
Andreozzi V *et al*., Italy, 2022	Y	Y	Y	Y	Y	Y	Y	Y	100%/L
Bechtold A and Owczarczyk-Saczonek A, Poland, 2022	N	Y	Y	Y	Y	Y	Y	Y	87.5%/L
Elboraey MO, *et al*., Egypt, 2021	N	Y	Y	Y	Y	Y	Y	Y	87.5%/L
Liu W, *et al*., China, 2022	Y	Y	Y	Y	Y	Y	Y	Y	100%/L
Maeda K, *et al*., Japan, 2022	Y	Y	Y	Y	Y	Y	Y	Y	100%/L
Kaomongkolgit R and Sawangarun W, Thailand, 2022	Y	Y	Y	Y	Y	Y	Y	Y	100%/L
Kaya A and Kaya SY, Turkey, 2022	N	Y	Y	Y	Y	Y	Y	Y	87.5%/L
Padniewski JJ *et al*., USA, 2022	Y	Y	Y	Y	Y	Y	Y	Y	100%/L
Panholzer J *et al*., Austria, 2022	N	Y	Y	Y	Y	Y	Y	Y	87.5%/L
Raccampo L *et al*., Italy, 2022	N	Y	Y	Y	Y	Y	Y	Y	87.5%/L
Saibene AM *et al*., Italy, 2021	N	Y	Y	Y	Y	Y	Y	Y	87.5%/L
Sayare B *et al*., India, 2021	N	Y	Y	Y	Y	Y	Y	Y	87.5%/L
Shonai T *et al*, Japan, 2022	N	Y	Y	Y	Y	Y	Y	Y	87.5%/L
Tan E and Salman S, Australia, 2022	Y	Y	Y	Y	Y	Y	Y	Y	100%/L
Thongprasom K, *et al*., Thailand, 2021	N	Y	Y	Y	Y	Y	Y	Y	87.5%/L
Woo CJ *et al*., Hong Kong, China, 2022	N	Y	N	Y	N	N	Y	Y	50%/M
Collela G *et al*., Italy, 2021	Y	Y	Y	N	Y	Y	Y	Y	87.5%/L
Azzi L *et al*., Italy, 2021	N	Y	Y	N	Y	Y	Y	Y	75%/L
Babazadeh A *et al*., Iran, 2022	N	Y	Y	Y	Y	Y	Y	Y	87.5%/L
Caggiano M *et al*., Italy, 2022	N	Y	Y	Y	N	N	Y	Y	62.5%/L
Borg L *et al*., Malta, 2022	N	Y	Y	Y	Y	Y	Y	Y	87.5%/L
Dash S eta al, India, 21	Y	Y	Y	Y	Y	Y	Y	Y	100%/L
Sharda P *et al*., India, 2022	N	Y	Y	Y	Y	Y	Y	Y	87.5%/L
Troeltzsch M *et al*., Germany, 2021	N	N	Y	Y	Y	Y	Y	Y	75%/L
Calabria E *et al*., Italy, 2022	Y	Y	Y	Y	Y	Y	Y	Y	100%/L
Manfredi M *et al*., Italy, 2021	Y	Y	Y	Y	Y	Y	Y	Y	100%/L

Q1. Were patient's demographic characteristics clearly described? Q2. Was the patient's history clearly described and presented as a timeline? Q3. Was the current clinical condition of the patient on presentation clearly described? Q4. Were diagnostic tests or assessment methods and the results clearly described? Q5. Was the intervention(s) or treatment procedure(s) clearly described? Q6. Was the post-intervention clinical condition clearly described? Q7. Were adverse events (harms) or unanticipated events identified and described? Q8. Does the case report provide takeaway lessons? Y - Yes; N - No; U – Unclear; NA – Not applicable; H – High, M – Moderate; L – Low

B. Checklist for case series

Authors	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	%Y/Risk
Chun Y *et al*., Korea, 2022	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	90%/L
Petruzzi M *et al*, Switzerland, 2022	Y	Y	Y	Unclear	N	Y	Y	Y	Y	Y	80%/L

Q1. Were there clear criteria for inclusion in the case series? Q2. Was the condition measured in a standard, reliable way for all participants included in the case series? Q3. Were valid methods used for identification of the condition for all participants included in the case series? Q4. Did the case series have consecutive inclusion of participants? Q5. Did the case series have complete inclusion of participants? Q6. Was there clear reporting of the demographics of the participants in the study? Q7. Was there clear reporting of clinical information of the participants? Q8. Were the outcomes or follow-up results of cases clearly reported? Q9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information? Q10. Was statistical analysis appropriate? Y - Yes; N - No; U – Unclear; NA – Not applicable; H – High, M – Moderate; L – Low