

Journal section: Oral Medicine and Pathology

Publication Types: Review

doi:10.4317/jced.60688

<https://doi.org/10.4317/jced.60688>

Systematic review of the oral manifestations produced by the SARS-CoV-2 vaccine

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López-Carriches C, Santana-Torres T, Bahram-Taheri R, Leco-Berrocal MA. Systematic review of the oral manifestations produced by the SARS-CoV-2 vaccine. J Clin Exp Dent. 2023;15(7):e578-83.

Received: 07/05/2023

Accepted: 22/06/2023

Article Number: 60688 <http://www.medicinaoral.com/odo/indice.htm>

© Medicina Oral S. L. C.I.F. B 96689336 - eISSN: 1989-5488

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Indexed in:

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Abstract

Background: To combat the coronavirus pandemic different vaccines have been developed. However, diverse adverse effects have been reported due to their use, including oral manifestations. Our objective is to review the existing bibliography to analyze what complications these vaccines have caused in the oral cavity.

Material and Methods: A bibliographic search was conducted by two independent reviewers (TS and CL), in parallel in 6 electronic databases (PubMed, Scopus, Cochrane, Google Scholar, LILACS, BioMed Central). A total of 22 articles were analyzed.

Results: The most frequent adverse effect was oral lichen planus, with a higher prevalence in women and after the Pfizer mRNA BNT162b2 vaccine.

Conclusions: These complications are minor and resolve with treatment, so the benefit of the use of vaccines outweigh the potential risks associated with these.

Key words: Covid-19 vaccine, oral lesions, oral manifestations, SARS-CoV-2 vaccine, oral symptoms.

Introduction

The pandemic produced by SARS-Cov-2 has been a challenge for the world population, largely mitigated by the appearance of vaccines which have significantly reduced the incidence.

Anti-SARS-CoV-2 vaccines approved by the FDA (United States Food and Drug Administration) and EMA (European Medicines Agency) are messenger RNA (mRNA) vaccines. The most used are BNT162b2 Comirnaty (Pfizer/BioNTech, New York, NY, USA) and

mRNA-1273 Spikevax (Moderna, Cambridge, MA, USA). The mRNA encoding the S protein is encapsulated in lipid nanoparticles. Nucleic acid vaccines introduce mRNA or DNA encoding the SARS-CoV-2 spike protein into cells, inducing them to produce antibodies (1).

In addition, viral vector vaccines are used. These vaccines use a chemically weakened virus (eg, adenovirus) to insert the code for SARS-CoV-2 antigens into cells. The two main viral vector vaccines are Jcovden Ad26.

COV2.S (Janssen, Johnson&Johnson New Brunswick, NJ, USA) which is produced with human adenovirus carrying protein S. VaxzevriaChAdOx1-S, and AstraZeneca (Cambridge, UK) which includes non-replicating chimpanzee adenovirus carrying protein S. Another vaccine used is Covilo/BBIBP-Corv (Sinopharm Beijing, China) (2).

In this context, and taking into account that all pharmacological treatments have risks of producing adverse effects, our objective is to review the existing bibliography and determine the appearance of oral manifestations caused by vaccines against SARS-Cov-2, classifying these oral adverse effects according to epidemiological data and clinical manifestations.

Material and Methods

A bibliographic search was conducted by two independent reviewers (TS and CL), in parallel in 6 electronic databases (PubMed, Scopus, Cochrane, Google Scholar, LILACS, BioMed Central). Publications in English and Spanish were reviewed using the following keywords: "Sars-cov-2 vaccine", "Covid-19 vaccination", "oral lesions" "oral complication", "oral manifestation". A total of 1236 articles were obtained from the different databases.

All identified articles were reviewed independently, including those that referred to the establishment of oral lesions after vaccination against SARS-CoV-2, including a total of 52 articles. For the management of bibliographic citations, ZOTERO program was used. A total of 42 articles were analyzed after deleting duplicates. After a qualitative review, 9 of the articles were not accessible in full format, 5 made exclusive reference to the oral manifestations produced by Covid-19 and not by the vaccine, 4 made no reference to oral manifestations and 5 were reviews of the literature, leaving us with a total of 22 articles.

As inclusion criteria, all patients were over 18 years of age, had received the COVID-19 vaccine and presented adverse oral manifestations after the administration of the vaccine. Literature reviews and clinical cases of oral manifestations caused by the disease and not by the vaccine were excluded.

Results

The 22 articles analyzed in this review (Table 1-1 cont.-1), include a total of 39 cases in which the oral lesions manifested by the patients could be directly related to the SARS-Cov-2 vaccine, since they did not present any other etiological agent.

Only one of the articles (4) reported neither age nor sex. We found that 71.05% are women (n:27) and the remaining 28.94% men (n:11). In this line, the age range in the male sex is between 15 and 81 years old, with an average of 48.25 years. The average age is slightly higher in the

female sex, reaching 56.7 years, with a minimum age of 20 and a maximum of 88. Therefore, the mean age of all cases is 52.66.

In relation to the type of vaccine, the one that produces more cases of oral manifestations is Pfizer's BNT162b2 with 20 (55.55%) followed by mRNA-1273 (Moderna) with 6 cases (16.66%), AZD1222 (Astrazeneca) with 5 cases (13.88%), ChAdOx1 (Jenner) with 3 cases (8.33%), Ad26.COV2.S (Janssen) with 2 cases (5.55%) and finally Corona-Vac (Sinovac) and BBIBP-CorV (Sinopharm) with 1 case each (2.77%). Regarding the dose, in 21 patients the adverse effects occurred after the first dose of the vaccine (55.26%); distributed as follows: BNT162b2 (PFIZER): 9, mRNA-1273 (MODERNA): 2, AZD1222 (Astrazeneca): 5, Ad26.COV2.S (JANSSEN): 2, ChAdOx1 (JENNER): 3, and in 17 patients occurred after receiving the second dose (44.73%); BNT162b2 (PFIZER): 11, mRNA-1273 (MODERNA): 4, BBIBP-CorV (sinopharm): 1, Corona-Vac (Sinovac): 1.

When classifying the lesions described, it is worth noting the appearance of lesions compatible with oral lichen planus; typical reticulated white plaques (Wickham's striae) next to areas of erosion in some presentations. These lesions were present in 16 cases, 8 of them confirmed with histopathological diagnosis by biopsy (3,5,7,9,11,15,17,19,22). We also found nonspecific manifestations such as erythematous lesions, glossitis, halitosis, fissured tongue, ulcers, petechiae, sensitive gums, and xerostomia. Other lesions were found with less prevalence: 3 cases of erythema multiforme minor (16,24), 2 cases of pemphigus (8,21), 1 of pemphigoid (16), 1 aphthous stomatitis (12), 1 case of acute neutrophilic dermatosis (6) and 1 hemangioma due to thrombocytopenia (23).

Discussion

The oral cavity is not exempt from complications after the COVID-19 vaccine. Riad *et al.* (25), studied the complications reported by drug agencies from different countries and found 128 oral adverse effects, 0.872% being oral paresthesia, followed by lip swelling (0.872%), ageusia (0.722%), hypesthesia (0.648%) and inflammation of the tongue (0.628%). These were more prevalent in older women. Also, it has been reported to be more prevalent after the first dose, especially vaccines based on messenger RNA. Adverse effects were more frequent than with the flu vaccine.

But the most frequently reported adverse effects are lichenoid lesions. Alharbi *et al.* (26), found that vaccinated patients had thousand times more odds of developing oral lichen planus compared to non-vaccinated patients.

On the other hand, Hertel *et al.* (27), carried out a retrospective analysis of patients vaccinated against Covid-19, to determine the risk of suffering from oral lichen planus

Table 1: Articles included.

Publication	Vaccine and dose	Sex	Age	Oral lesions	Evolution
Alabdulaaly <i>et al.</i> (3).	BNT162b2 (2nd dose)	F	56	Lichenoid striations, buccal mucosal erythema.	Resolution with topical corticosteroids
	mRNA-1273 (1st dose)	M	72	Erythema on the gum and upper lip.	Resolution with topical corticosteroids
	mRNA-1273 (2nd dose)	M	61	Exacerbation of lichen planus.	Resolution with topical corticosteroids
	BNT162b2 (2nd dose)	F	65	Lichen planus exacerbation, ulcerations	Resolution with topical corticosteroids
	BNT162b2 (2nd dose)	F	65	Lichen planus exacerbation, erythema and oral dryness.	Resolution with topical corticosteroids
	BNT162b2 (2nd dose)	M	51	Exacerbation of lichen planus, erosions, erythema.	Resolution with topical corticosteroids
Azzi <i>et al.</i> (4).	ChAdOx1 (1st dose)			Reddish, erythematous and diffuse lesions on oral mucosa, tongue, gums and palate	Resolution with topical corticosteroids
Babazadeh <i>et al.</i> (5).	BBIBP-CorV (2nd dose)	F	52	Lip desquamation together with lesions compatible with lichen planus.	Treatment with oral antihistamines and topical corticosteroids
Bechtold <i>et al.</i> (6).	Ad26.CO-V2.S (1st dose)	F	44	Case of acute neutrophilic dermatosis (Sweet syndrome). Erosions on the sides of the tongue and vestibule, the tongue had a yellowish covering.	Treatment with oral prednisone 0.6 mg/kg/d and intravenous doxycycline 200 mg/d
Caggiano <i>et al.</i> (7).	BNT162b2 (2nd dose)	M	40	Lesions compatible with lichen planus	-
Calabria <i>et al.</i> (8).	BNT162b2 (2nd dose)	F	60	Oropharyngeal pemphigus vulgar	Treatment with rituximab, after ineffective treatment with corticosteroids
Chun <i>et al.</i> (9).	BNT162b2 (1st dose)	M	79	Multiple ulcerative lesions with erythema and inflammation on the palate	Dexamethasone 0.1% topical solution, nystatin 100,000 U/ml 3v/d. Topical acyclovir 50mg/g
	BNT162b2 (1st dose)	F	81	Ulceration of the palatal gum, gingival recession	Dexamethasone in 0.1% solution 3 v/d, nystatin 1000,000 U/ml 3 v/d and rinses with chlorhexidine
	BNT162b2 (1st dose)	F	88	Pain in the mucosa of the lips and lower gingival tissue. Dry and flaking lips	Topical dexamethasone 1 mg/g 3 v/d, sodium hyaluronate 0.25 mg/g 2 v/d
	AZD1222 (1st dose)	M	61	Pain in the right preauricular region and lower right posterior gingival tissue Bilateral buccal mucosal pain, erythema with white lesions	Dexamethasone in 0.1% solution 3 v/d, nystatin 1000,000 U/ml 3 v/d and rinses with chlorhexidine
	AZD1222 (1st dose)	F	60	Pain in the right buccal mucosa, erythema and white pigmentation lesions	Topical dexamethasone 1 mg/g 3 v/d, sodium hyaluronate 0.25 mg/g 2 v/d
	AZD1222 (1st dose)	F	66	Pain in the right edge of the tongue (no lesions found)	Topical dexamethasone 1 mg/g 3 v/d, sodium hyaluronate 0.25 mg/g 2 v/d

Table 1 cont.: Articles included.

	AZD1222 (1st dose)	F	68	Pain in the right second molar area. Sore tongue, fissured tongue and covered.	Topical dexamethasone 1 mg/g 3 v/d, sodium hyaluronate 0.25 mg/g 2 v/d
Heboyan <i>et al.</i> (10)	mRNA-1273 (2nd dose)	M	34	Hypertrophic and sensitive gingival tissues, erosions in the oral mucosa and halitosis	Rinses with 0.12% chlorhexidine 2v/d
Kaomongkolgit <i>et al.</i> (11).	BNT162b2 (2nd dose)	F	28	Lesions compatible with lichen planus.	Topical corticosteroids (0.1% fluocinolone acetonide en orabase)
Kim <i>et al.</i> (12).	mRNA-1273 (2nd dose)	M	43	Extensive painless ulcer in the alveolar and buccal mucosa between the lower right first premolar and second molar (aphthous stomatitis)	Dexamethasone 0.05% topical solution
Maeda <i>et al.</i> (13).	mRNA-1273 (2nd dose)	F	58	Bilateral ulcers on the palate	Topical steroids, 4% lidocaine gel, and sodium sulfate rinse
Manfredi <i>et al.</i> (14).	BNT162b2 (1st dose)	F	34	Diffuse oral ulcers on the floor of the mouth with oral erythema on the ventral and anterior side of the tongue. Dry and inflamed labial mucosa, with signs of angular cheilitis	Topical antibacterials and lip moisturizer
Muradova <i>et al.</i> (15).	mRNA-1273 (1st dose)	F	33	White reticulate pigmentation next to erosion (lichen planus)	Topical clobetasol
Petruzzi <i>et al.</i> (16).	BNT162b2 (1st dose)	F	55	Painful oral lesions, combined with desquamative gingivitis (pemphigoid)	Prednisone 25 mg v/o daily plus 0.05% clobetasol propionate
	BNT162b2 (1st dose)	M	15	Oral erythema, erosions and pseudo-membranous lesions combined with pain and dysphagia (erythema multiforme minor)	Prednisone 25 mg v/o daily plus 0.05% clobetasol propionate
	BNT162b2 (2nd dose)	F	49	Erythematous and bullous lesions on the tongue and floor of the mouth (erythema multiforme minor)	Prednisone 25 mg v/o daily plus 0.05% clobetasol propionate
	BNT162b2 (1st dose)	F	20	Gingival erosions and lip mucosa, scaly lesions on the dermal tissue of the lip.	Prednisone 25 mg v/o daily plus 0.05% clobetasol propionate
Raccampo <i>et al.</i> (17).	BNT162b2 (2nd dose)	F	54	White bilateral reticular pattern in the oral mucosa, asymptomatic (lichen planus).	Treatment with topical corticosteroids
	BNT162b2 (2nd dose)	F	54	Erythematous lesion with erosive patterns on the gingiva, extending to the buccal mucosa (lichen planus)	Treatment with topical corticosteroids
Sayare <i>et al.</i> (18).	ChAdOx1 (1st dose)	M	21, 21	Petechiae on soft palate	No treatment was necessary
Sharda <i>et al.</i> (19).	BNT162b2 (1st dose)	F	35	White bilateral lesions with an erythematous base, some together with erosions on the oral mucosa and gingival tissues (lichen planus)	-
Tan <i>et al.</i> (20).	BNT162b2 (1st dose)	F	60	Glossitis and xerostomia	Treated with topical corticosteroids
Thongprasom <i>et al.</i> (21).	AZD1222 (1st dose)	F	38	Squamous and erythematous epithelium on the gingival margins and alveolar mucosa in the anteroinferior buccal area and floor of the mouth (pemphigus)	Triamcinolone acetonide 0.05%

Table 1 cont.-1: Articles included.

Troeltzsch <i>et al.</i> (22).	Ad26.CO-V2.S (1st dose)	F	49	Typical lesions of oral lichen planus	Treated with topical clobetasol 0.5 mg/ml
Vaira <i>et al.</i> (23).	BNT162b2 (2nd dose)	M	81	Blue lesion on the right buccal mucosa (due to thrombocytopenia)	Administration of platelet concentrate
Zhang <i>et al.</i> (24).	Corona Vac (2nd dose)	F	46	Multiple erosions on the lip and oral mucosa (erythema multiforme)	Treated with oral loratadine, chlorhexidine rinses, and topical corticosteroids

as a consequence of the vaccine, with the percentage of patients who develop it of 0.027%. Demonstrating that the risk of vaccination producing these lesions is very low. Joseph *et al.* (28), reviewed the treatments administered for oral manifestations after vaccination, evidencing that these cases were resolved by applying the conventional treatment with a good prognosis.

Conclusions

Dentists must be aware of the adverse effects that the COVID-19 vaccine can have on the oral cavity in order to treat the possible complications the patient may manifest. However, these complications do not outweigh the benefit of COVID-19 vaccines in the prevention of the disease.

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Source of funding

This research received no external funding.

Authors' contributions

C.L-C perform the study design, conceptualization, bibliographic search, correct and write original draft, supervision. T.S-T writing original draft, bibliographic search. R.B-T. bibliographic search and prepared the paper; and M.I.L-B, bibliographic search, contribute to interpretation of the data.

Conflicts of Interest

The authors declare no conflict of interest.

All authors have read and agreed to the published version of the manuscript.