



Oral Adverse Events Following COVID-19 Vaccination: Analysis of VAERS Reports

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Background: Oral adverse events (AEs) following COVID-19 vaccination have been sporadically reported during the previous months, warranting further investigation for their prevalence and suspected relationship with vaccine-elicited immune response.

Methods: A retrospective analysis using the Vaccine Adverse Event Reporting System (VAERS) data was conducted to evaluate AEs within the oral cavity (mucosa, tongue, lips, palate, dentition, salivary glands) and AEs involving taste and other sensations. Oral AEs reported after receiving COVID-19 vaccination (test group) and seasonal influenza vaccination (control group) were extracted and cross-tabulated to assess their relative prevalence.

Results: Among the 128 solicited (suspected) oral AEs, oral paresthesia (0.872%) was most reported after receiving COVID-19 vaccines, followed by the swelling of lips (0.844%), ageusia (0.722%), oral hypoesthesia (0.648%), swollen tongue (0.628%), and dysgeusia (0.617%). The reported prevalence of oral AEs was higher in the COVID-19 vaccine group than in the seasonal influenza group. The distribution pattern of the most reported oral AEs was similar for both COVID-19 and seasonal influenza vaccines. Female sex, older age (>39 years old), primer doses, and mRNA-based COVID-19 vaccines exhibited a higher reported prevalence of oral AEs.

Conclusion: Within the limitations of this study, COVID-19 vaccines were found to be associated with rare oral AEs that are predominantly similar to those emerging following seasonal influenza vaccines. The most commonly reported oral AEs were oral paraesthesia (mouth-tingling), lip swelling, and ageusia, representing various pathophysiologic pathways that remain unclear. Taste-related AEs should be acknowledged in the context of the COVID-19 pandemic and the public should be adequately informed about a potential taste dysfunction after receiving the COVID-19 vaccination. Dentists and dental teams need to be aware of the prevalence, severity, and prognosis of oral AEs to inform their patients and increase public confidence in vaccines.

Keywords: anaphylaxis, COVID-19 vaccines, drug-related side effects and adverse reactions, oral manifestations, pharmacovigilance oral adverse events following COVID-19 vaccination 2

INTRODUCTION

A wide array of clinical manifestations associated with coronavirus disease (COVID-19) have been reported within the oral cavity, including taste dysfunction, oral mucosal lesions, and salivary gland disorders (1). Therefore, dentists and dental team members encountered additional challenges in providing their services amid the pandemic while attempting to protect their patients and colleagues from cross-infection (2).

Fortunately, a strong global collaboration between pharmaceutical companies enabled the rapidly developing vaccines against this novel respiratory disease leading to certain vaccines receiving emergency authorization by the end of the first year of the pandemic. As vaccines offer the best solution to control this pandemic by establishing herd immunity, it is essential to achieve substantial vaccine uptake levels across the global community (3). To ensure a high vaccine uptake and prevent vaccine hesitancy, it is necessary to manage with its key triggers including the fear of potential post-vaccination side effects (3).

Individual reports were published sporadically during the previous months about oral adverse events (AEs) that emerged after receiving various COVID-19 vaccines, thus, warranting further investigation by epidemiologic researchers and careful attention by dental practitioners (4). The overarching aim of this study was to evaluate the oral AEs reported within the United States (US) population following COVID-19 vaccination, their prevalence and demographic risk factors, and compare them against oral AEs of seasonal influenza.

MATERIALS AND METHODS

Design

A retrospective analysis for the Vaccine Adverse Event Reporting System (VAERS), an open-access database co-managed by the US Food and Drug Administration (FDA) and the Centers for Diseases Control and Prevention (CDC), was conducted in April 2022 (5). VAERS reports had been accessed through the CDC Wide-ranging Online Data for Epidemiologic Research (WONDER) tool, which provides summarized frequencies of reported symptoms based on the Medical Dictionary for Regulatory Activities (MedDRA) scheme (5, 6).

Population

All VAERS reports of the individuals who received COVID-19 vaccination from January 1st to December 31st, 2021, were accessed through the WONDER tool and used as a “test group.” To select an appropriate “control group,” VAERS reports of all vaccines administered during 2021 were thoroughly examined. The decision to use seasonal influenza vaccines as a “control group” was made based on the following reasons: (a) seasonal influenza and COVID-19 vaccines are recommended/administered to all age groups and sexes in all US states and territories indiscriminately, (b) the frequency of seasonal influenza vaccine-related AEs reported during 2021 came second after the frequency of

COVID-19 vaccine-related AEs, (c) both vaccines are primarily administered through intramuscular injection, and (d) both vaccines target respiratory infections that can spread similarly and synergistically in the community leading to similar clinical complications (7).

Variables

MedDRA uses a logical classification hierarchy consisting of five levels starting from the “System Organ Class” level e.g., (gastrointestinal disorders) until the “Preferred Term” and the “Lowest Level Term” e.g., (aphthous stomatitis) and (aphthous ulcer), respectively (6). Oral AEs are scattered across various levels of the MedDRA hierarchy; therefore, we developed an anatomo-physiological scheme to extract all potential AEs related to oral cavity structures and functions. Our *de novo* scheme divided the oral cavity into six regions, including oral mucosa (e.g., oral herpes), tongue (e.g., swollen tongue), lips (e.g., lip swelling), palate (e.g., palatal oedema), salivary glands (e.g., dry mouth), and dentition (e.g., hyperaesthesia teeth), and two functions, including taste (e.g., dysgeusia) and other sensory disorders (e.g., oral paraesthesia) (**Figure 1**).

An exhaustive list of potential oral AEs ($n = 310$) was extracted based on our proposed scheme, and two oral surgery specialists reviewed it for further validation and filtration (**Supplementary Table S1**). A total of 182 preferred terms / lowest level terms (PT/LLT) had been excluded from the original list due to de-duplication ($n = 43$), being of congenital or developmental nature e.g., ankyloglossia congenital ($n = 16$), behavioral and traumatic injuries e.g., tooth fracture ($n = 20$), clinical dental procedures e.g., x-ray dental ($n = 42$), chronic conditions e.g., salivary gland cancer ($n = 52$) and irrelevant to oral cavity e.g., oral contraception ($n = 9$). A final list of 128 potential oral AEs was used in the downstream analyses.

Analyses

The primary outcome was the proportion of oral AEs within all VAERS reports of the same vaccine group, e.g., [(number of ageusia reports related to COVID-19 vaccines)/(total reports related to COVID-19 vaccines)] * 100. The secondary outcome was the prevalence of reported AEs per 100,000 administered vaccine doses. Given the median age of the US population which is 38.5 years old, the age of 39 years was used as a cut-off point for the age-specific analysis of oral AEs prevalence (8). Chi-squared test (χ^2) and Fisher’s exact test were used to compare percentages and rates of oral AEs between COVID-19 vs. seasonal influenza vaccines, females vs. males, and ≤ 39 years old vs. > 39 years old. Crosstabulation tests also compared oral AEs across various COVID-19 vaccine brands and doses. Moreover, taste-related AEs were compared between the pre-COVID-19 pandemic period (January 2010–December 2019) vs. the pandemic period (January 2020–December 2021). All analytical tests were performed using GraphPad Prism version 9.3.1 (GraphPad Software Inc. San Diego, CA, USA, 2021) and following the assumptions of confidence interval (CI) 95% and significance level (Sig.) ≤ 0.05 .

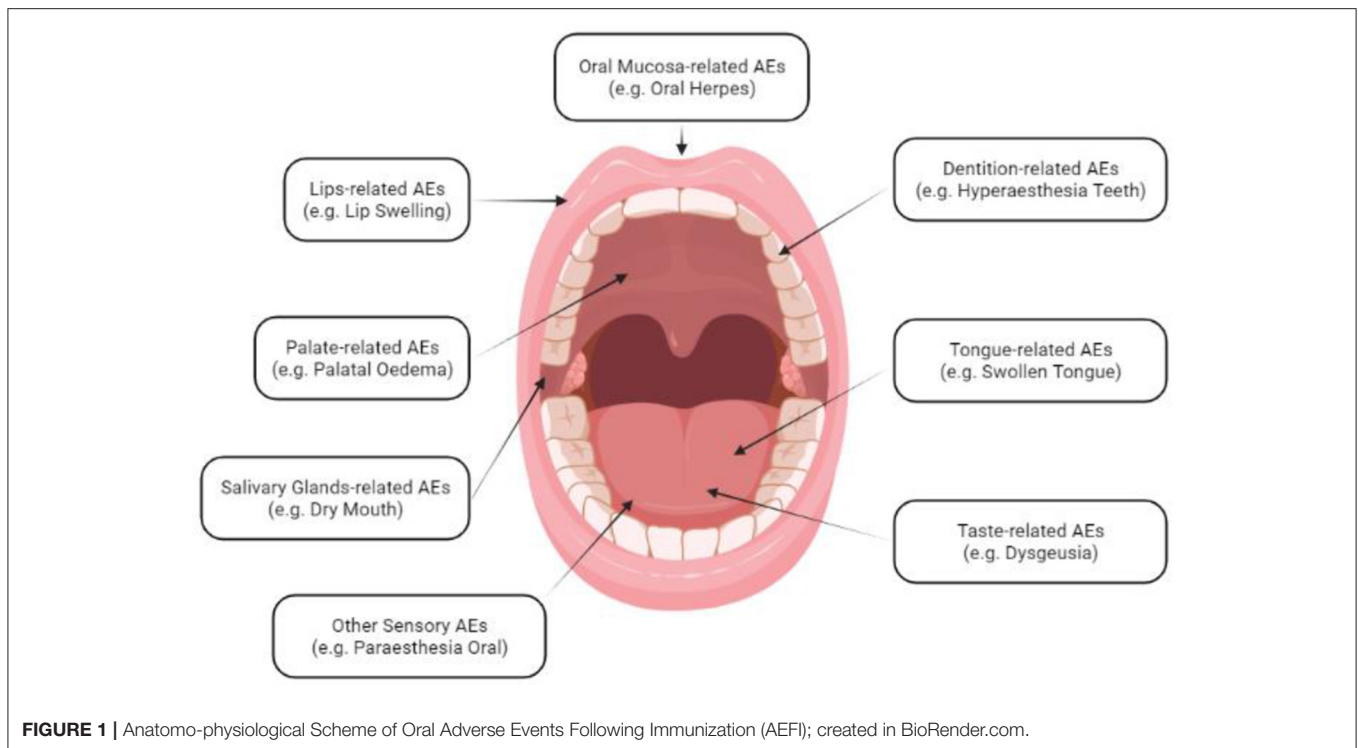


FIGURE 1 | Anato-mo-physiological Scheme of Oral Adverse Events Following Immunization (AEFI); created in BioRender.com.

TABLE 1 | Demographic characteristics of COVID-19 and seasonal influenza vaccines recipients in the United States, January–December 2021 (CDC; VAERS-WONDER).

Variable	Outcome	COVID-19 vaccine (n = 507 M)	Seasonal influenza vaccine (n = 173.3 M)	Sig.
Received reports [†]	N (rate)	690,853 (136.3 per 100,000 doses)	6,970 (4.0 per 100,000 doses)	<0.001
[†] Sex	Female	466,323 (67.5%)	4,587 (65.8%)	0.003
	Male	211,597 (30.6%)	2,189 (31.4%)	0.162
	Unknown	12,933 (1.9%)	194 (2.8%)	<0.001
[†] Age group	<6 years	1,000 (0.1%)	439 (6.3%)	<0.001
	6–17 years	33,817 (4.9%)	734 (10.5%)	<0.001
	18–29 years	76,243 (11.0%)	625 (9.0%)	<0.001
	30–39 years	103,093 (14.9%)	789 (11.3%)	<0.001
	40–49 years	104,505 (15.1%)	655 (9.4%)	<0.001
	50–59 years	111,229 (16.1%)	877 (12.6%)	<0.001
	60–64 years	55,859 (8.1%)	596 (8.6%)	0.158
	65–79 years	133,504 (19.3%)	1,620 (23.2%)	<0.001
	80+ years	36,135 (5.2%)	370 (5.3%)	0.766
	Unknown	35,468 (5.1%)	265 (3.8%)	<0.001

Chi-squared test (χ^2) and Fisher's exact test had been used with a significance level (Sig.) < 0.05.

Bold values represents significant values.

[†] Total number of received reports.

RESULTS

Demographic Characteristics

In total, 690,853 and 6,970 reports were received for COVID-19 and seasonal influenza vaccines, respectively, from individuals who were vaccinated in 2021, thus, constituting the denominator of the primary outcome in each vaccine group. Most reports in both COVID-19 (67.5%) and seasonal influenza (65.8%) groups were from females. The 65–79 years

old was the most reporting age group in both COVID-19 (19.3%) and seasonal influenza (23.2%) groups, while the least reporting age group for COVID-19 vaccines was <6 years old, and for seasonal influenza vaccine was ≥80 years old (Table 1).

It is worth noting that the overall rate of reported AEs is significantly (Sig. < 0.001) higher in the COVID-19 group (136.3 reports per 100,000 administered doses) than in the seasonal influenza group (4 reports per 100,000 administered doses).

Overall Prevalence of Oral AEs

In the domain of oral mucosa-related AEs, oral herpes was the most commonly reported AE in both COVID-19 and seasonal influenza vaccine groups (0.189 vs. 0.086%; *Sig.* = 0.050), followed by stomatitis and aphthous ulcer (0.168 vs. 0.158%; *Sig.* = 0.829), mouth swelling (0.131 vs. 0.115%; *Sig.* = 0.868), oral discomfort (0.108 vs. 0.072%; *Sig.* = 0.463), oral pain (0.103 vs. 0.086%; *Sig.* = 0.851), oral pruritus (0.065 vs. 0.014%; *Sig.* = 0.147), and oral mucosal blistering (0.057 vs. 0.043%; *Sig.* = 1.000). Despite the lack of statistically significant differences between vaccine groups in terms of the primary outcome (proportion of oral AEs to all reported AEs in VAERS), differences between vaccine groups in terms of the secondary outcome (proportion of oral AEs to all administered vaccine doses) were all statistically significant (*Sig.* < 0.001; **Table 2**).

Swollen tongue (0.628% vs. 0.072%; *Sig.* = 0.007) was the most common tongue-related AE in both COVID-19 and seasonal influenza groups, followed by tongue discomfort (0.083 vs. 0%), tongue disorder (0.075 vs. 0.057%; *Sig.* = 0.598), and tongue pruritus (0.070 vs. 0.057%; *Sig.* = 0.694). Lip swelling (0.737 vs. 0.588%; *Sig.* = 0.148) and lip pruritus (0.050 vs. 0.029%; *Sig.* = 0.424) were the most common lip-related AEs in both vaccine groups. Dry mouth (0.301 vs. 0.043%; *Sig.* < 0.001) was the most common salivary glands-related AE, while toothache (0.142 vs. 0.043%; *Sig.* = 0.023) was the most common dentition-related AE in both vaccine groups (**Supplementary Figure S2**).

Ageusia (0.722 vs. 0.143%; *Sig.* < 0.001) was the most common taste-related AE in both vaccine groups, followed by dysgeusia (0.617 vs. 0.244%; *Sig.* < 0.001) and taste disorder (0.317 vs. 0.115%; *Sig.* < 0.001). Oral paraesthesia (0.872 vs. 0.473%; *Sig.* < 0.001) and oral hypoesthesia (0.648 vs. 0.430%; *Sig.* < 0.001) were the most frequently reported sensory AEs in both vaccine groups (**Figure 2**).

Sex- and Age-Specific Prevalence

In the COVID-19 group, analysis of the top twenty oral AEs sex-specific prevalence revealed that females had a significantly (*Sig.* < 0.001) higher prevalence than males in all solicited AEs except for ageusia. The prevalence of ageusia was similar among females (0.683%) and males (0.708%), *Sig.* = 0.238. Likewise, females reported more oral AEs than males in the seasonal influenza group except for oral herpes, toothache, and tongue discomfort which were almost equally prevalent across sexes (**Figure 3**).

Interestingly, in the COVID-19 group, the older age group (>39 years old) had significantly (*Sig.* < 0.001) higher prevalence of oral AEs compared to the younger age group (≤39 years old) except for lip swelling, tongue pruritus, and oral pruritus. Similarly, the older age group reported oral AEs more frequently than the younger age group following seasonal influenza vaccination, except for dysgeusia, oral herpes and tongue pruritus (**Table 3**).

Dose- and Vaccine Brand-Related Prevalence

The first dose of COVID-19 vaccination was significantly (*Sig.* < 0.001) associated with more oral AEs than the second dose, except for ageusia, stomatitis and aphthous ulcer, oral herpes, and

toothache where the second dose was associated more frequent oral AEs. On comparing the primer doses (first dose and second dose) with the booster doses (third dose), the primer doses were significantly associated with a higher prevalence of all solicited AEs compared to the booster doses (*Sig.* < 0.001; **Figure 4**).

Pfizer-BioNTech COVID-19 vaccine (BNT162b2) was associated with more frequently reported oral AEs than Moderna COVID-19 vaccine (mRNA-1273), except for oral herpes and oral pain. Overall, mRNA-based vaccines (BNT162b2 and mRNA-1273) had a significantly higher prevalence of oral paraesthesia (0.838 vs. 0.582%; *Sig.* < 0.001), lip swelling (0.706 vs. 0.525%; *Sig.* < 0.001), swollen tongue (0.599 vs. 0.447%; *Sig.* < 0.001), mouth swelling (0.127 vs. 0.090%; *Sig.* = 0.021), oral discomfort (0.106 vs. 0.058%; *Sig.* = 0.001), tongue disorder (0.072 vs. 0.038%; *Sig.* = 0.004), tongue pruritus (0.068 vs. 0.038%; *Sig.* = 0.011), and oral pruritus (0.063 vs. 0.040%; *Sig.* = 0.040; **Tables 4, 5**).

Longitudinal Analysis of Taste-Related AEs

On comparing the overall percentage of taste-related AEs before (January 2010–December 2019) and during (January 2020–December 2021) the COVID-19 pandemic, ageusia was significantly more commonly reported during the pandemic (0.622 vs. 0.035%; *Sig.* < 0.001) than before the pandemic interval. Likewise, dysgeusia (0.581 vs. 0.182%; *Sig.* < 0.001), taste disorder (0.279 vs. 0.006%; *Sig.* < 0.001), and hypogeusia (0.019 vs. 0.006%; *Sig.* < 0.001) were significantly more common during the pandemic interval (**Table 6**).

DISCUSSION

The present analysis aimed to synthesize population-based evidence about oral adverse events (AEs) after COVID-19 vaccination utilizing a national surveillance database. Comparison between COVID-19 and seasonal influenza vaccines revealed a remarkable similarity in the distribution of the most reported oral AEs. Among the top twenty oral AEs, oral paresthesia was most reported after COVID-19 and seasonal influenza vaccination (14 and 16%, respectively), followed by lip swelling (12 and 20%), ageusia (12 and 5%), oral hypoesthesia (11 and 14%), swollen tongue (10 and 7%), dysgeusia (10 and 8%), taste disorder (5 and 4%), dry mouth (5 and 1%), and oral herpes (3 and 3%). Cohen et al. found that constitutional AEs such as headache, fatigue, and pyrexia had a significantly higher prevalence following COVID-19 than seasonal influenza and hepatitis B vaccines in the VAERS database (9). Likewise, a recent comprehensive analysis of the US and European Union surveillance systems indicated that the largest absolute risks following COVID-19 vaccines were constitutional, dermatological, neurological and gastrointestinal AEs (10). Given the nature of passive surveillance systems, including VAERS, which are inclined toward under-reporting than over-reporting, the higher prevalence of oral AEs following COVID-19 vaccines as compared with seasonal influenza vaccines can be attributed to reporting bias that might be triggered by public anxiety due to the novelty of COVID-19 vaccines (10, 11).

TABLE 2 | Oral adverse events reported after receiving COVID-19 and seasonal influenza vaccines in the United States, January–December 2021 (CDC; VAERS-WONDER).

Preferred term	COVID-19 vaccine		Seasonal influenza vaccine		Sig.		Group
	% of Total AE (n = 690,853)	Rate per 100,000 doses	% of total AE (n = 6,970)	Rate per 100,000 doses	% of total AE	Rate per 100K D	
Dental discomfort (10054217)	57 (0.008%)	0.011	1 (0.014%)	0.001	0.441	0.006	Dentition-Related AE ^a
Dental paraesthesia (10078276)	22 (0.003%)	0.004	0 (0%)	N/A	N/A	N/A	
Hyperaesthesia teeth (10082426)	159 (0.023%)	0.031	0 (0%)	N/A	N/A	N/A	
Hypoesthesia teeth (10051780)	15 (0.002%)	0.003	0 (0%)	N/A	N/A	N/A	
Toothache (10044055)	981 (0.142%)	0.193	3 (0.043%)	0.002	0.023	<0.001	Taste-Related AE
Ageusia (10001480)	4,985 (0.722%)	0.983	10 (0.143%)	0.006	<0.001	<0.001	
Dysgeusia (10013911)	4,263 (0.617%)	0.841	17 (0.244%)	0.010	<0.001	<0.001	
Hypogeusia (10020989)	141 (0.020%)	0.028	1 (0.014%)	0.001	1.000	<0.001	
Taste disorder (10082490)	2,193 (0.317%)	0.433	8 (0.115%)	0.005	0.001	<0.001	Salivary glands and saliva-related AE ^b
Salivary duct stenosis (10039388)	1 (<0.001%)	<0.001	0 (0%)	N/A	N/A	N/A	
Salivary gland pain (10039421)	19 (0.003%)	0.004	0 (0%)	N/A	N/A	N/A	
Salivary gland enlargement (10039408)	41 (0.006%)	0.008	0 (0%)	N/A	N/A	N/A	
Salivary gland calculus (10039394)	3 (<0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Salivary gland mass (10057002)	8 (0.001%)	0.002	0 (0%)	N/A	N/A	N/A	
Salivary gland disorder (10061935)	11 (0.002%)	0.002	0 (0%)	N/A	N/A	N/A	
Salivary hypersecretion (10039424)	259 (0.037%)	0.051	1 (0.014%)	0.001	0.529	<0.001	
Dry mouth (10013781)	2,080 (0.301%)	0.410	3 (0.043%)	0.002	<0.001	<0.001	
Aptyalism (10003068)	32 (0.005%)	0.006	0 (0%)	N/A	N/A	N/A	
Saliva discoloration (10049069)	4 (0.001%)	0.001	0 (0%)	N/A	N/A	N/A	Tongue-Related AE ^c
Saliva altered (10039379)	16 (0.002%)	0.003	1 (0.014%)	0.001	0.157	0.625	
Sialoadenitis (10040628)	31 (0.004%)	0.006	0 (0%)	N/A	N/A	N/A	
Non-infective sialoadenitis (10075243)	10 (0.001%)	0.002	0 (0%)	N/A	N/A	N/A	
Atrophic glossitis (10069085)	3 (<0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Hypertrophy of tongue papillae (10020893)	10 (0.001%)	0.002	0 (0%)	N/A	N/A	N/A	
Glossitis (10018386)	148 (0.021%)	0.029	0 (0%)	N/A	N/A	N/A	
Glossodynia (10018388)	564 (0.082%)	0.111	5 (0.072%)	0.003	0.773	<0.001	
Macroglossia (10025391)	2 (<0.001%)	<0.001	0 (0%)	N/A	N/A	N/A	
Plicated tongue (10035630)	9 (0.001%)	0.002	0 (0%)	N/A	N/A	N/A	
Swollen tongue (10042727)	4,340 (0.628%)	0.856	26 (0.373%)	0.015	0.007	<0.001	
Tongue oedema (10043967)	31 (0.004%)	0.006	0 (0%)	N/A	N/A	N/A	
Tongue blistering (10043942)	155 (0.022%)	0.031	3 (0.043%)	0.002	0.255	<0.001	
Tongue ulceration (10043991)	126 (0.018%)	0.025	0 (0%)	N/A	N/A	N/A	
Tongue coated (10043945)	39 (0.006%)	0.008	0 (0%)	N/A	N/A	N/A	
Tongue discoloration (10043949)	188 (0.027%)	0.037	1 (0.014%)	0.001	0.516	<0.001	
Trichoglossia (10080276)	7 (0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Tongue pigmentation (10069164)	4 (0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Tongue erythema (10079075)	138 (0.020%)	0.027	1 (0.014%)	0.001	0.740	<0.001	
Strawberry tongue (10051495)	4 (0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Tongue eruption (10052002)	66 (0.010%)	0.013	0 (0%)	N/A	N/A	N/A	
Tongue movement disturbance (10043963)	49 (0.007%)	0.010	0 (0%)	N/A	N/A	N/A	
Stiff tongue (10081491)	10 (0.001%)	0.002	0 (0%)	N/A	N/A	N/A	
Tongue paralysis (10043972)	24 (0.003%)	0.005	0 (0%)	N/A	N/A	N/A	
Tongue discomfort (10077855)	573 (0.083%)	0.113	0 (0%)	N/A	N/A	N/A	
Tongue disorder (10043951)	516 (0.075%)	0.102	4 (0.057%)	0.002	0.598	<0.001	
Tongue exfoliation (10064488)	12 (0.002%)	0.002	0 (0%)	N/A	N/A	N/A	
Tongue induration (10084548)	1 (<0.001%)	<0.001	0 (0%)	N/A	N/A	N/A	

(Continued)

TABLE 2 | Continued

Preferred term	COVID-19 vaccine		Seasonal influenza vaccine		Sig.		Group
	% of Total AE (n = 690,853)	Rate per 100,000 doses	% of total AE (n = 6,970)	Rate per 100,000 doses	% of total AE	Rate per 100K D	
Tongue dry (10049713)	75 (0.011%)	0.015	0 (0%)	N/A	N/A	N/A	
Tongue pruritus (10070072)	483 (0.070%)	0.095	4 (0.057%)	0.002	0.694	<0.001	
Tongue rough (10043977)	12 (0.002%)	0.002	0 (0%)	N/A	N/A	N/A	
Tongue spasm (10043981)	14 (0.002%)	0.003	0 (0%)	N/A	N/A	N/A	
Tongue fungal infection (10075845)	1 (<0.001%)	<0.001	0 (0%)	N/A	N/A	N/A	
Tongue thrust (10082545)	2 (<0.001%)	<0.001	0 (0%)	N/A	N/A	N/A	
Angular cheilitis (10002509)	14 (0.002%)	0.003	0 (0%)	N/A	N/A	N/A	Lip-Related AE ^d
Cheilitis (10008417)	303 (0.044%)	0.060	2 (0.029%)	0.001	0.547	<0.001	
Chapped lips (10049047)	210 (0.030%)	0.041	1 (0.014%)	0.001	0.443	<0.001	
Lip blister (10049307)	283 (0.041%)	0.056	4 (0.057%)	0.002	0.501	<0.001	
Lip discolouration (10024549)	102 (0.015%)	0.020	2 (0.029%)	0.001	0.343	<0.001	
Lip disorder (10048470)	125 (0.018%)	0.025	2 (0.029%)	0.001	0.514	<0.001	
Lip dry (10024552)	189 (0.027%)	0.037	3 (0.043%)	0.002	0.432	<0.001	
Lip erythema (10080124)	145 (0.021%)	0.029	1 (0.014%)	0.001	0.703	<0.001	
Lip exfoliation (10064482)	63 (0.009%)	0.012	2 (0.029%)	0.001	0.092	0.003	
Lip oedema (10024558)	60 (0.009%)	0.012	1 (0.014%)	0.001	0.615	0.003	
Lip pain (10024561)	266 (0.039%)	0.052	5 (0.072%)	0.003	0.161	<0.001	
Lip pruritus (10070721)	347 (0.050%)	0.068	2 (0.029%)	0.001	0.424	<0.001	
Lip scab (10082767)	7 (0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Lip swelling (10024570)	5,092 (0.737%)	1.000	41 (0.588%)	0.024	0.148	<0.001	
Lip ulceration (10024572)	24 (0.003%)	0.005	1 (0.014%)	0.001	0.131	0.219	
Palatal disorder (10052453)	18 (0.003%)	0.004	0 (0%)	N/A	N/A	N/A	Palate-Related AE ^e
Palatal oedema (10056998)	13 (0.002%)	0.003	0 (0%)	N/A	N/A	N/A	
Palatal swelling (10074403)	74 (0.011%)	0.015	2 (0.029%)	0.001	0.176	0.001	
Palatal ulcer (10077519)	5 (0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Anesthesia oral (10082548)	20 (0.003%)	0.004	0 (0%)	N/A	N/A	N/A	Other sensory AE
Paraesthesia oral (10057372)	6,024 (0.872%)	1.188	33 (0.473%)	0.019	<0.001	<0.001	
Hypoaesthesia oral (10057371)	4,477 (0.648%)	0.883	30 (0.430%)	0.017	0.024	<0.001	
Burn oral cavity (10075532)	9 (0.001%)	0.002	0 (0%)	N/A	N/A	N/A	
Burning mouth syndrome (10068065)	31 (0.004%)	0.006	0 (0%)	N/A	N/A	N/A	
Oral dysaesthesia (10050820)	4 (0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Aphthous ulcer (10002959)	340 (0.049%)	0.067	0 (0%)	N/A	N/A	N/A	Oral mucosa-related AE ^f
Circumoral oedema (10052250)	8 (0.001%)	0.002	0 (0%)	N/A	N/A	N/A	
Circumoral swelling (10081703)	44 (0.006%)	0.009	0 (0%)	N/A	N/A	N/A	
Coating in mouth (10075366)	21 (0.003%)	0.004	0 (0%)	N/A	N/A	N/A	
Leukoplakia oral (10024396)	5 (0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Mouth swelling (10075203)	908 (0.131%)	0.179	8 (0.115%)	0.005	0.868	<0.001	
Oedema mouth (10030110)	9 (0.001%)	0.002	1 (0.014%)	0.001	0.096	1.000	
Oral blood blister (10076590)	46 (0.007%)	0.009	1 (0.014%)	0.001	0.376	0.022	
Oral candidiasis (10030963)	108 (0.016%)	0.021	0 (0%)	N/A	N/A	N/A	
Oral discomfort (10030973)	747 (0.108%)	0.147	5 (0.072%)	0.003	0.463	<0.001	
Oral disorder (10067621)	191 (0.028%)	0.038	2 (0.029%)	0.001	0.720	<0.001	
Oral fungal infection (10061324)	14 (0.002%)	0.003	0 (0%)	N/A	N/A	N/A	
Oral herpes (10067152)	1,309 (0.189%)	0.258	6 (0.086%)	0.003	0.050	<0.001	
Oral lichen planus (10030983)	39 (0.006%)	0.008	1 (0.014%)	0.001	0.331	0.039	
Oral lichenoid reaction (10083833)	2 (<0.001%)	<0.001	0 (0%)	N/A	N/A	N/A	
Oral mucosa erosion (10064594)	1 (<0.001%)	<0.001	0 (0%)	N/A	N/A	N/A	
Oral Mucosal Blistering (10030995)	394 (0.057%)	0.078	3 (0.043%)	0.002	1.000	<0.001	

(Continued)

TABLE 2 | Continued

Preferred term	COVID-19 vaccine		Seasonal influenza vaccine		Sig.		Group
	% of Total AE (n = 690,853)	Rate per 100,000 doses	% of total AE (n = 6,970)	Rate per 100,000 doses	% of total AE	Rate per 100K D	
Oral mucosal discolouration (10030996)	6 (0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Oral mucosal eruption (10030997)	175 (0.025%)	0.035	4 (0.057%)	0.002	0.106	<0.001	
Oral mucosal erythema (10067418)	78 (0.011%)	0.015	0 (0%)	N/A	N/A	N/A	
Oral mucosal exfoliation (10064487)	32 (0.005%)	0.006	0 (0%)	N/A	N/A	N/A	
Oral mucosal roughening (10084009)	10 (0.001%)	0.002	0 (0%)	N/A	N/A	N/A	
Oral pain (10031009)	715 (0.103%)	0.141	6 (0.086%)	0.003	0.851	<0.001	
Oral pigmentation (10077552)	1 (<0.001%)	<0.001	0 (0%)	N/A	N/A	N/A	
Oral pruritus (10052894)	452 (0.065%)	0.089	1 (0.014%)	0.001	0.147	<0.001	
Oral purpura (10083533)	4 (0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Oral pustule (10056674)	12 (0.002%)	0.002	0 (0%)	N/A	N/A	N/A	
Oral viral infection (10065234)	2 (<0.001%)	<0.001	0 (0%)	N/A	N/A	N/A	
Oropharyngeal blistering (10067950)	46 (0.007%)	0.009	0 (0%)	N/A	N/A	N/A	
Oropharyngeal plaque (10067721)	6 (0.001%)	0.001	0 (0%)	N/A	N/A	N/A	
Perioral dermatitis (10034541)	8 (0.001%)	0.002	0 (0%)	N/A	N/A	N/A	
Stomatitis (10042128)	824 (0.119%)	0.163	11 (0.158%)	0.006	0.379	<0.001	

Chi-squared test (χ^2) and Fisher's exact test had been used with a significance level (Sig.) < 0.05.

^aThe preferred term Sensitivity of Teeth (10040012) was not reported in any vaccine groups.

^bThe preferred terms Salivary Duct Obstruction (10039386), Salivary Duct Inflammation (10056681) and Salivary Gland Induration (10071363) were not reported in any vaccine groups.

^cThe preferred terms Acquired Macroglossia (10058835), Ankyloglossia Acquired (10049243), Atrophy of Tongue Papillae (10003712), and Tongue Black Hairy (10043941) were not reported in any vaccine groups.

^dThe preferred term Lip Erosion (10051992) was not reported in any vaccine groups.

^eThe preferred term Palatal Palsy (10072012) was not reported in any vaccine groups.

^fThe preferred terms Aphthous Stomatitis (10002958), Buccal Mucosal Roughening (10048479), Mouth Plaque (10028032), Mouth Ulceration (10028034), Oral Soft Tissue Disorder (10061326), Oral Mucosal Hypertrophy (10062956), Oral Mucosal Petechiae (10030998), Oral Mucosal Scab (10082769), and Oral Papule (10031010) were not reported in any vaccine groups.

Bold values represents significant values.

Taste disorders, including complete (ageusia) and partial (hypogeusia) loss of taste and disturbed taste (dysgeusia) had been among the most reported oral AEs following COVID-19 vaccination per our analysis. Taste dysfunction was depicted as one of the characteristic symptoms of COVID-19 infection due to its high prevalence, estimated to be 39.2% (CI 95%: 35.34–43.12%) according to latest meta-analyses (12–14). Therefore, public health authorities had broadly used taste dysfunction in case finding protocols and triage recommendations (15). Lechien et al. reported a series of six cases with new-onset taste disorders following COVID-19 vaccination with repeated negative PCR results for SARS-CoV-2. Thus ruling out the possibility of COVID-19 infection as the etiology of taste disorders in this particular case series; however it does not rule it out in the VAERS reports (16). On reviewing random VAERS reports manually, we found out that breakthrough infection was commonly reported in association with taste disorders. One of the hypotheses we suggest for the remarkably higher prevalence of ageusia (0.722 vs. 0.143%; Sig. < 0.001), dysgeusia (0.617 vs. 0.244%; Sig. < 0.001), and taste disorder (0.317 vs. 0.115%; Sig. < 0.001) among COVID-19 vaccinees is the increased public awareness of taste dysfunction as one of the characteristic symptoms of COVID-19 infection (17, 18). Our hypothesis can be supported by the overall reporting prevalence of taste disorders during the COVID-19 pandemic period compared to the pre-pandemic years.

Xerostomia, or dry mouth, was among the common oral AEs following COVID-19 vaccination with female and older age predominance and without a preference for a particular vaccine brand. Active surveillance through the cross-sectional studies of self-reported COVID-19 vaccines side effects revealed varying prevalence of xerostomia that ranged between 0.4 and 2.7% (19–21). It remains unclear whether the humoral immune response triggered by COVID-19 vaccination and manifested in salivary secretions has any link with salivary gland-AEs, including xerostomia (22, 23).

Anaphylactic symptoms e.g., lip swelling (MedDRA ID: 10024570), swollen tongue (10042727) and tongue pruritus (10070072) were more common among COVID-19 vaccinees and females as compared to seasonal influenza vaccinees and males. Interestingly, Maltezou et al. concluded that anaphylactic reactions rates are the lowest after COVID-19 vaccines (10.67 cases per one million doses) as compared with rabies, tick-borne encephalitis, measles-mumps-rubella-varicella, and human papillomavirus vaccines (70.77, 20, 19.8, and 13.65 cases per one million doses, respectively) (24). Earlier VAERS-based analyses indicated that anaphylactic rates were higher following BNT162b2 than mRNA-1273 vaccine, which is consistent with our findings (25, 26). Female predominance for post-vaccination allergic reactions was attributed to polyethylene glycol

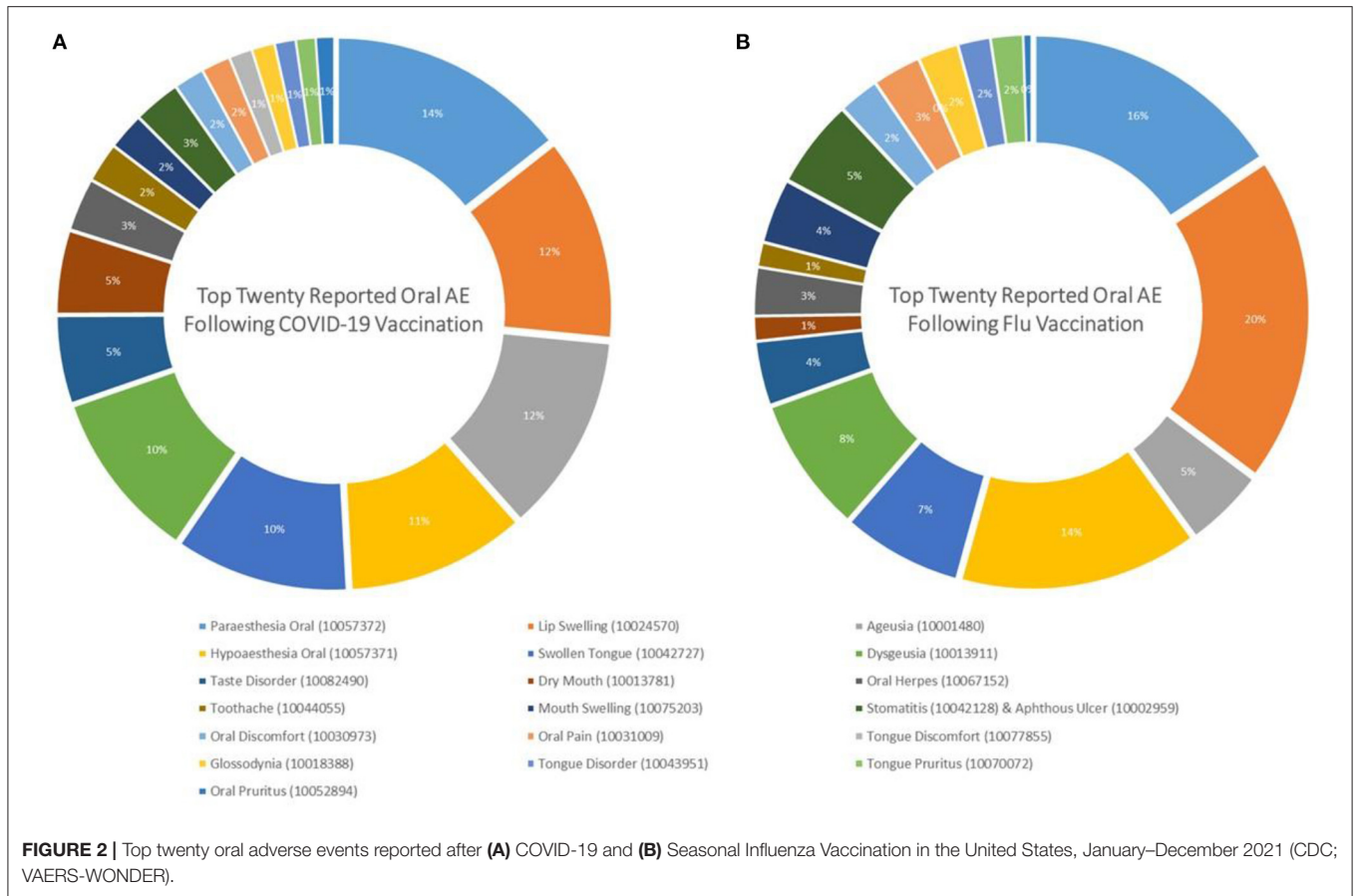


FIGURE 2 | Top twenty oral adverse events reported after (A) COVID-19 and (B) Seasonal Influenza Vaccination in the United States, January–December 2021 (CDC; VAERS-WONDER).

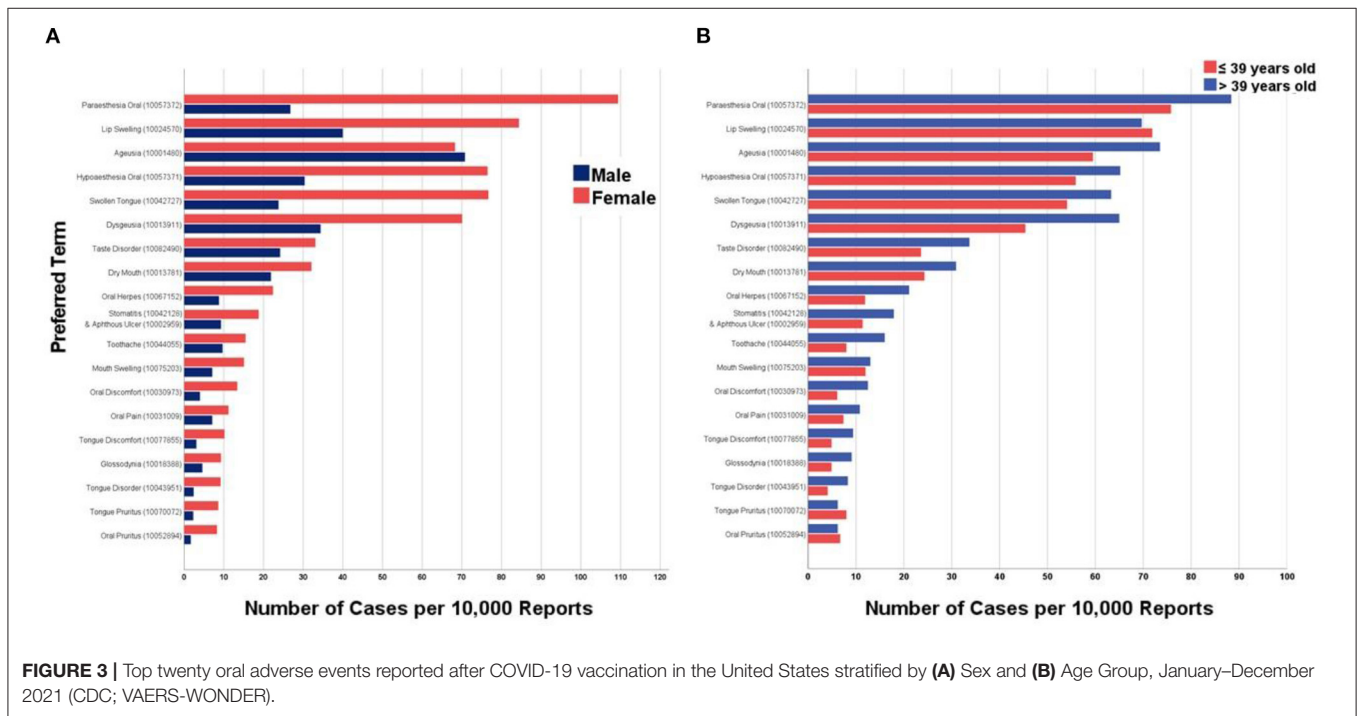


FIGURE 3 | Top twenty oral adverse events reported after COVID-19 vaccination in the United States stratified by (A) Sex and (B) Age Group, January–December 2021 (CDC; VAERS-WONDER).

TABLE 3 | Top twenty oral adverse events reported after COVID-19 and seasonal influenza vaccines in the United States stratified by sex and age group, January–December 2021 (CDC; VAERS-WONDER).

#	Preferred term	COVID-19			Seasonal flu		
		Female (n = 489,571)	Male (n = 226,792)	Sig.	Female (n = 4,629)	Male (n = 2,210)	Sig.
1	Paraesthesia oral (10057372)	5,355 (1.094%)	608 (0.268%)	<0.001	26 (0.562%)	7 (0.317%)	0.195
2	Lip swelling (10024570)	4,132 (0.844%)	907 (0.400%)	<0.001	35 (0.756%)	6 (0.271%)	0.018
3	Ageusia (10001480)	3,342 (0.683%)	1,605 (0.708%)	0.238	8 (0.173%)	2 (0.090%)	0.516
4	Hypoaesthesia oral (10057371)	3,743 (0.765%)	689 (0.304%)	<0.001	25 (0.540%)	5 (0.226%)	0.078
5	Swollen tongue (10042727)	3,749 (0.767%)	540 (0.238%)	<0.001	23 (0.497%)	3 (0.136%)	0.021
6	Dysgeusia (10013911)	3,431 (0.701%)	781 (0.344%)	<0.001	16 (0.346%)	1 (0.045%)	0.018
7	Taste disorder (10082490)	1,619 (0.331%)	549 (0.242%)	<0.001	6 (0.130%)	2 (0.090%)	1.000
8	Dry mouth (10013781)	1,573 (0.321%)	497 (0.219%)	<0.001	3 (0.065%)	0 (0%)	N/A
9	Oral herpes (10067152)	1,097 (0.224%)	200 (0.088%)	<0.001	4 (0.086%)	2 (0.090%)	1.000
10 & 11	Stomatitis (10042128) & Aphthous ulcer (10002959)	919 (0.188%)	211 (0.093%)	<0.001	8 (0.173%)	3 (0.136%)	1.000
12	Toothache (10044055)	758 (0.155%)	219 (0.097%)	<0.001	1 (0.022%)	2 (0.090%)	0.246
13	Mouth swelling (10075203)	738 (0.151%)	162 (0.071%)	<0.001	6 (0.130%)	2 (0.090%)	1.000
14	Oral discomfort (10030973)	654 (0.134%)	91 (0.040%)	<0.001	5 (0.108%)	0 (0%)	N/A
15	Oral pain (10031009)	547 (0.112%)	161 (0.071%)	<0.001	6 (0.130%)	0 (0%)	N/A
16	Tongue discomfort (10077855)	500 (0.102%)	71 (0.031%)	<0.001	0 (0%)	0 (0%)	N/A
17	Glossodynia (10018388)	457 (0.093%)	104 (0.046%)	<0.001	5 (0.108%)	0 (0%)	N/A
18	Tongue disorder (10043951)	448 (0.092%)	55 (0.024%)	<0.001	3 (0.065%)	1 (0.045%)	1.000
19	Tongue pruritus (10070072)	422 (0.086%)	53 (0.023%)	<0.001	4 (0.086%)	0 (0%)	N/A
20	Oral pruritus (10052894)	406 (0.083%)	39 (0.017%)	<0.001	1 (0.022%)	0 (0%)	N/A

#	Preferred Term	COVID-19			Seasonal flu		
		≤39 years old (n = 223,053)	>39 years old (n = 471,468)	Sig.	≤39 years old (n = 2,606)	>39 years old (n = 4,099)	Sig.
1	Paraesthesia oral (10057372)	1,691 (0.758%)	4,168 (0.884%)	<0.001	10 (0.384%)	23 (0.561%)	0.373
2	Lip swelling (10024570)	1,604 (0.719%)	3,288 (0.697%)	0.312	13 (0.499%)	27 (0.659%)	0.516
3	Ageusia (10001480)	1,327 (0.595%)	3,467 (0.735%)	<0.001	1 (0.038%)	10 (0.244%)	0.060
4	Hypoaesthesia oral (10057371)	1,246 (0.559%)	3,075 (0.652%)	<0.001	8 (0.307%)	23 (0.561%)	0.144
5	Swollen tongue (10042727)	1,206 (0.541%)	2,984 (0.633%)	<0.001	6 (0.230%)	18 (0.439%)	0.209
6	Dysgeusia (10013911)	1,013 (0.454%)	3,063 (0.650%)	<0.001	8 (0.307%)	9 (0.220%)	0.619
7	Taste disorder (10082490)	526 (0.236%)	1,589 (0.337%)	<0.001	2 (0.077%)	6 (0.146%)	0.496
8	Dry mouth (10013781)	542 (0.243%)	1,458 (0.309%)	<0.001	1 (0.038%)	2 (0.049%)	1.000
9	Oral herpes (10067152)	265 (0.119%)	996 (0.211%)	<0.001	3 (0.115%)	3 (0.073%)	0.683
10 & 11	Stomatitis (10042128) & Aphthous ulcer (10002959)	255 (0.114%)	845 (0.179%)	<0.001	2 (0.077%)	9 (0.220%)	0.220
12	Toothache (10044055)	178 (0.080%)	755 (0.160%)	<0.001	2 (0.077%)	1 (0.024%)	0.564
13	Mouth swelling (10075203)	268 (0.120%)	614 (0.130%)	0.271	2 (0.077%)	5 (0.122%)	0.713
14	Oral discomfort (10030973)	137 (0.061%)	587 (0.125%)	<0.001	1 (0.038%)	4 (0.098%)	0.655
15	Oral pain (10031009)	165 (0.074%)	510 (0.108%)	<0.001	0 (0%)	6 (0.146%)	N/A
16	Tongue discomfort (10077855)	109 (0.049%)	443 (0.094%)	<0.001	0 (0%)	0 (0%)	N/A
17	Glossodynia (10018388)	110 (0.049%)	428 (0.091%)	<0.001	0 (%)	2 (0.049%)	N/A
18	Tongue disorder (10043951)	91 (0.041%)	392 (0.083%)	<0.001	0 (0%)	4 (0.098%)	N/A
19	Tongue pruritus (10070072)	179 (0.080%)	292 (0.062%)	0.006	2 (0.077%)	2 (0.049%)	0.645
20	Oral pruritus (10052894)	149 (0.067%)	293 (0.062%)	0.473	0 (0%)	1 (0.024%)	N/A

Chi-squared test (χ^2) and Fisher's exact test had been used with a significance level (Sig.) < 0.05. Bold values represents significant values.

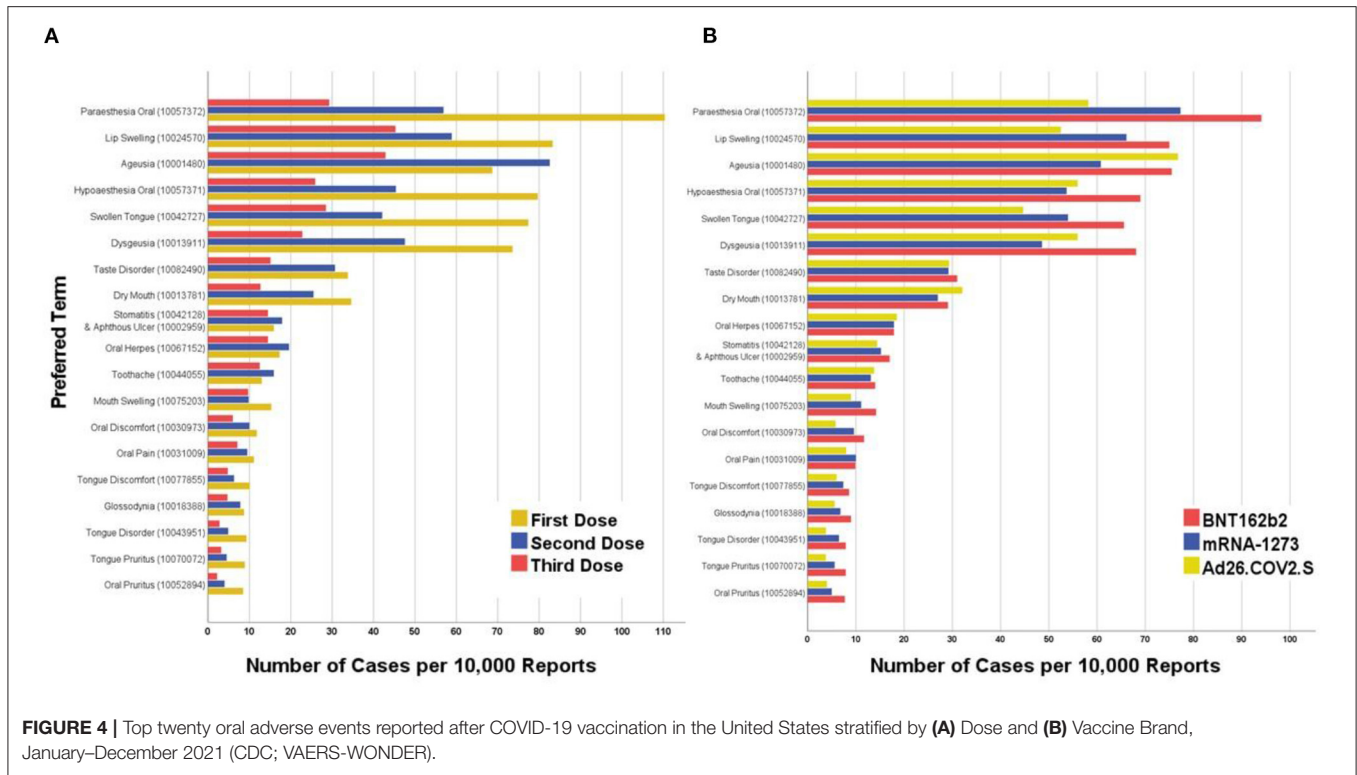


TABLE 4 | Top twenty oral adverse events reported after COVID-19 vaccines in the United States stratified by dose, January–December 2021 (CDC; VAERS-WONDER).

Order	Preferred term	First dose (n = 350,247)	Second dose (n = 227,377)	Third dose (n = 53,620)	Sig.	
					1st vs. 2nd	(1st & 2nd) vs. 3rd
1	Paraesthesia oral (10057372)	3,868 (1.104%)	1,294 (0.569%)	157 (0.293%)	<0.001	<0.001
2	Lip swelling (10024570)	2,918 (0.833%)	1,339 (0.589%)	243 (0.453%)	<0.001	<0.001
3	Ageusia (10001480)	2,406 (0.687%)	1,877 (0.826%)	230 (0.429%)	<0.001	<0.001
4	Hypoaesthesia oral (10057371)	2,793 (0.797%)	1,033 (0.454%)	139 (0.259%)	<0.001	<0.001
5	Swollen tongue (10042727)	2,710 (0.774%)	958 (0.421%)	153 (0.285%)	<0.001	<0.001
6	Dysgeusia (10013911)	2,577 (0.736%)	1,082 (0.476%)	122 (0.228%)	<0.001	<0.001
7	Taste disorder (10082490)	1,183 (0.338%)	697 (0.307%)	81 (0.151%)	0.042	<0.001
8	Dry mouth (10013781)	1,212 (0.346%)	580 (0.255%)	68 (0.127%)	<0.001	<0.001
9	Oral herpes (10067152)	606 (0.173%)	445 (0.196%)	78 (0.145%)	0.050	0.061
10 & 11	Stomatitis (10042128) & Aphthous ulcer (10002959)	557 (0.159%)	406 (0.179%)	78 (0.145%)	0.080	0.266
12	Toothache (10044055)	455 (0.130%)	361 (0.159%)	67 (0.125%)	0.005	0.365
13	Mouth swelling (10075203)	536 (0.153%)	222 (0.098%)	52 (0.097%)	<0.001	0.032
14	Oral discomfort (10030973)	413 (0.118%)	227 (0.100%)	32 (0.060%)	0.047	<0.001
15	Oral pain (10031009)	389 (0.111%)	217 (0.095%)	38 (0.071%)	0.074	0.016
16	Tongue discomfort (10077855)	355 (0.101%)	144 (0.063%)	26 (0.048%)	<0.001	0.003
17	Glossodynia (10018388)	304 (0.087%)	178 (0.078%)	25 (0.047%)	0.284	0.003
18	Tongue disorder (10043951)	324 (0.093%)	112 (0.049%)	15 (0.028%)	<0.001	<0.001
19	Tongue pruritus (10070072)	313 (0.089%)	103 (0.045%)	17 (0.032%)	<0.001	<0.001
20	Oral pruritus (10052894)	299 (0.085%)	91 (0.040%)	12 (0.022%)	<0.001	<0.001

Chi-squared test (χ^2) and Fisher's exact test had been used with a significance level (Sig.) < 0.05. Bold values represents significant values.

TABLE 5 | Top twenty oral adverse events reported after COVID-19 vaccines in the United States stratified by vaccine type, January–December 2021 (CDC; VAERS-WONDER).

Order	Preferred term	BNT162b2 (n = 341,389)	mRNA-1273 (n = 337,518)	Ad26.COV2.S (n = 50,138)	Sig.	
					Pfizer vs. Moderna	mRNA vs. Vector
1	Paraesthesia oral (10057372)	3,212 (0.941%)	2,475 (0.773%)	292 (0.582%)	<0.001	<0.001
2	Lip swelling (10024570)	2,562 (0.750%)	2,232 (0.661%)	263 (0.525%)	<0.001	<0.001
3	Ageusia (10001480)	2,578 (0.755%)	2,053 (0.608%)	385 (0.768%)	<0.001	0.027
4	Hypoaesthesia oral (10057371)	2,354 (0.690%)	1,812 (0.537%)	281 (0.560%)	<0.001	0.145
5	Swollen tongue (10042727)	2,241 (0.656%)	1,823 (0.540%)	224 (0.447%)	<0.001	<0.001
6	Dysgeusia (10013911)	2,324 (0.681%)	1,639 (0.486%)	281 (0.560%)	<0.001	0.523
7	Taste disorder (10082490)	1,057 (0.310%)	986 (0.292%)	147 (0.293%)	0.191	0.800
8	Dry mouth (10013781)	992 (0.291%)	912 (0.270%)	161 (0.321%)	0.113	0.098
9	Oral herpes (10067152)	611 (0.179%)	603 (0.179%)	93 (0.185%)	0.977	0.702
10 & 11	Stomatitis (10042128) & Aphthous ulcer (10002959)	580 (0.170%)	512 (0.152%)	72 (0.144%)	0.065	0.385
12	Toothache (10044055)	477 (0.140%)	442 (0.131%)	69 (0.138%)	0.338	0.900
13	Mouth swelling (10075203)	485 (0.142%)	375 (0.111%)	45 (0.090%)	<0.001	0.021
14	Oral discomfort (10030973)	399 (0.117%)	324 (0.096%)	29 (0.058%)	0.009	0.001
15	Oral pain (10031009)	338 (0.099%)	336 (0.100%)	40 (0.080%)	0.969	0.208
16	Tongue discomfort (10077855)	295 (0.086%)	249 (0.074%)	30 (0.060%)	0.072	0.137
17	Glossodynia (10018388)	306 (0.090%)	229 (0.068%)	28 (0.056%)	0.002	0.080
18	Tongue disorder (10043951)	270 (0.079%)	219 (0.065%)	19 (0.038%)	0.030	0.004
19	Tongue pruritus (10070072)	271 (0.079%)	188 (0.056%)	19 (0.038%)	<0.001	0.011
20	Oral pruritus (10052894)	262 (0.077%)	169 (0.050%)	20 (0.040%)	<0.001	0.040

Chi-squared test (χ^2) and Fisher's exact test had been used with a significance level (Sig.) < 0.05. Bold values represents significant values.

TABLE 6 | Taste-related adverse events reported after all vaccines in the United States, January 2010–December 2021 (CDC; VAERS-WONDER).

Preferred term	Before COVID-19 pandemic; January 2010–December 2019 (n = 311,941)	During COVID-19 Pandemic; January 2020–December 2021 (n = 786,047)	Sig.
Ageusia (10001480)	109 (0.035%)	4,893 (0.622%)	<0.001
Dysgeusia (10013911)	567 (0.182%)	4,566 (0.581%)	<0.001
Taste disorder (10082490)	20 (0.006%)	2,193 (0.279%)	<0.001
Hypogeusia (10020989)	18 (0.006%)	146 (0.019%)	<0.001

Fisher's exact test had been used with a significance level (Sig.) < 0.05. Bold values represents significant values.

hypersensitivity which was found to be higher among females than males (27, 28).

Other allergic AEs such as oral paraesthesia and oral hypoaesthesia were commonly reported among COVID-19 vaccinees and females. In the product assessment report of the mRNA-1273 vaccine published by the European Medicines Agency (EMA), oral paraesthesia was mentioned among the rare AEs (29). Likewise, mouth-tingling was enlisted as a rare

allergic AE by regulators and professional societies in other countries (30).

Sporadic case reports/series for oral mucosa-related AEs following COVID-19 vaccination had been published during the previous months, calling for further investigation about the potential link between those AEs and the vaccine-elicited immune response (4). Oral lichen planus (OLP) was diagnosed in recently vaccinated individuals who received mRNA-(BNT162b2) and viral vector-based vaccines (Ad26.COV2.S) and whose medical anamneses and serological investigations ruled out suspected infections and allergens (31–33). Therefore, Hertel et al. performed a retrospective analysis for COVID-19 vaccinated vs. non-vaccinated cohorts of normal and overweight individuals and figured out that OLP incidence was higher in the vaccinated group (0.067 vs. 0.027%; Sig. < 0.001) (34). Contrarily, our current analysis found that OLP prevalence was lower among COVID-19 than among seasonal influenza vaccinees (0.006 vs. 0.014%; Sig. = 0.331). A recent meta-analysis of OLP point prevalence exhibited remarkably higher levels (0.89% for general populations and 0.98% for clinical patients) than reported after vaccination (35).

Oral herpes zoster (OHZ) is one of the suggested mucosa-related AEs empirically diagnosed in vaccinees with an irrelevant underlying anamnesis who received BNT162b2 (36). However,

the pathophysiologic pathway remained unclear for how COVID-19 vaccines can trigger OHZ reactivation and the investigators warned the clinical and scientific communities from misdiagnosing OHZ as oral herpes (37). Prevalence of oral herpes (MedDRA ID: 10067152) that may include both herpes simplex and herpes zoster infections was significantly higher in the COVID-19 (0.189 vs. 0.086%; *Sig.* = 0.050) than seasonal influenza group. Within the COVID-19 group, prevalence of oral herpes was significantly higher among females (0.224 vs. 0.088%; *Sig.* < 0.001) and older age group (0.211 vs. 0.119%; *Sig.* < 0.001), and it was not significantly different between primer vs. booster doses (0.182 vs. 0.145%; *Sig.* = 0.061) or among vaccine brands. Female sex and older age predominance correspond with the current US demographics of oral herpes infection (38).

Aphthous stomatitis was suspected to be linked with recent COVID-19 vaccination in a few reported cases where patients presented with non-specific oral ulcers (39, 40). Unlike oral herpes, the prevalence of aphthous stomatitis was not significantly higher among COVID-19 vaccinees (0.168 vs. 0.158%; *Sig.* = 0.829); even though it resembled oral herpes in female and older age predominance and lack of preference for a particular dose or vaccine brand.

Limitations

Several limitations should be taken into consideration while reading our analysis. Firstly, it is based on a passive surveillance database which is usually biased toward the less common moderate-to-severe AEs rather than the common mild AEs. Secondly, passive surveillance systems do not provide accurate epidemiologic estimates such as prevalence or incidence of the reported AEs; instead, they are used as an early alerting tool. Thirdly, most oral conditions, including neurological and mucosal AEs do not have background estimates that would have enabled us to perform the conventional observed-to-expected (O:E) analysis; therefore, we had to compare COVID-19 rates with another preemptively similar vaccine, i.e., seasonal influenza. Fourthly, the reported AEs were not systematically classified according to their exact onset, i.e., the interval between injection and AE emergence, by the VAERS database. Therefore, it is imperative that future research on oral AEs should record their onset to help determine the required resources for their management.

Strengths

Heretofore, this analysis is the first to provide population-based evidence for COVID-19 AEs that might affect oral cavity structures and functions. It also suggests a *de novo* methodology that can be used for evaluating oral AEs of other vaccines e.g., H1N1, human papillomavirus and herpes zoster vaccines.

Implications

By reading the findings of our analysis, dentists and dental team members can become more knowledgeable about the prevalence, severity, and prognosis of oral AEs that might arise after vaccination. Dentists are seen as trustworthy information sources

by their patients and their knowledge and attitudes toward vaccine effectiveness and safety play a crucial role in enhancing the public uptake of vaccines. Moreover, oral health specialists should be actively engaged in the pharmacovigilance process as pragmatic point-of-care diagnostic schemes are urgently needed to improve the reporting quality of oral AEs—the Brighton Collaboration scheme for anaphylaxis diagnosis can be taken as an example. Finally, the general public should be reassured that the present analysis found that most COVID-19 oral AEs greatly resemble those of seasonal influenza vaccines and may not require particular attention except for those emerging immediately after the shot as they can be anaphylactic reactions.

CONCLUSION

Within the limitations of this study, COVID-19 vaccines were found to be associated with rare oral AEs that were predominantly similar to those emerging following seasonal influenza vaccines. The most reported oral AEs were oral paresthesia (mouth-tingling), lip swelling, and ageusia, representing various pathophysiologic pathways that remain unclear. Taste-related AEs should be acknowledged in the context of the COVID-19 pandemic and the public should be adequately informed about a potential taste dysfunction after receiving the COVID-19 vaccination. Dentists and dental teams need to be aware of the prevalence, severity, and prognosis of oral AEs to inform their patients and increase public confidence in vaccines.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: <https://wonder.cdc.gov/vaers.html>.

AUTHOR CONTRIBUTIONS

AR: conceptualization, methodology, formal analysis, and project administration. AR and SA: validation. AR, AP, and EK: writing—original draft preparation. SA: writing—review and editing and funding acquisition. All authors have read and agreed to the published version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpubh.2022.952781/full#supplementary-material>

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