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Oral adverse events following COVID-19 and influenza vaccination in Australia

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ABSTRACT

Vaccine hesitancy, spurred by misinterpretation of Adverse Events (AEs), threatens public health. Despite sporadic reports of oral AEs post-COVID-19 vaccination, systematic analysis is scarce. This study evaluates these AEs using the Australian Database of Adverse Event Notifications (DAEN). A secondary analysis of DAEN data was conducted, with the analysis period commencing from the start of the COVID-19 vaccination rollout in February 2021 and the inception of the influenza vaccine database in 1971, both through until December 2022. The focus of the analysis was on oral AEs related to COVID-19 and influenza vaccines. Reports were extracted according to a predefined schema and then stratified by vaccine type, sex, and age. Oral paresthesia was the most common oral AE after COVID-19 vaccination (75.28 per 10,000 reports), followed by dysgeusia (73.96), swollen tongue (51.55), lip swelling (49.43), taste disorder (27.32), ageusia (25.85), dry mouth (24.75), mouth ulceration (18.97), oral hypoaesthesia (15.60), and oral herpes (12.74). While COVID-19 and influenza vaccines shared most oral AEs, taste-related AEs, dry mouth, and oral herpes were significantly more common after COVID-19 vaccination. mRNA vaccines yielded more oral AEs than other types. Females had higher oral AE incidence. Most oral AEs did not differ significantly between COVID-19 and influenza vaccination. However, specific oral AEs, particularly taste-related, dry mouth, and oral herpes, were more prevalent after COVID-19 vaccination compared with seasonal influenza, especially in females and mRNA vaccine recipients.

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Introduction

Promoting vaccine confidence is a vital public health goal to control vaccine-preventable diseases and their associated sequelae.[1,2] Despite this, our today's societies face a rising tide of vaccine hesitancy, fueled in part by the organized efforts of groups known as the "anti-vaccination movement."[2,3] While rigorous standards of drug production and clinical trials strive to guarantee the efficacy and safety of newly developed vaccines before authorization, and despite meticulous strategies for tracking real-world effectiveness and safety, anti-vaccination proponents persist in their campaigns challenging the safety and effectiveness of vaccines.[1,4,5] An exemplary case is the European Medicines Agency's (EMA) decision to suspend Vaxzveria due to thrombotic events reports in March 2021, which led to an increased hesitancy that turned into a public aversion to this particular vaccine.[6,7]

The unsolicited adverse events (AEs) of vaccines are frequently misinterpreted by anti-vaxxers to spread fear and undermine vaccine coverage; therefore, Joyce et al. 2022 attempted to understand AEs incidence and severity among a vaccine-hesitant community by providing a space for the respondents to add unsolicited AEs.[8] Sporadic reports of oral AEs following COVID-19 vaccination began to emerge since the early months of vaccines rollout.[9–13] These reports were not surprising for oral medicine specialists and researchers, as the oral cavity is known to reflect an array of AEs following various vaccines, e.g. hepatitis, polio, and diphtheria.[14–16] For instance, a middle-aged male patient suffered from oral lichen planus after receiving the Vaxzevria vaccine.[17] Likewise, Caggiano et al. 2022 documented another case of an Italian male patient who developed oral lichen planus following BNT162b2 vaccination.[13] In response to this growing number of case reports/series, independent post-marketing studies (active surveillance) were designed and conducted to evaluate oral AEs following COVID-19 vaccination among healthcare workers.[18,19] These studies found a larger incidence rate of oral AEs, e.g., 13% and 9.6% of Comirnaty recipients in the Czech Republic and Slovakia reported at least one oral AE.[20,21]

Passive surveillance systems like VAERS (US), EudraVigilance (Europe), and DAEN (Australia) play a critical role in evaluating vaccine safety by collecting and analyzing spontaneous reports of Adverse Events post-vaccination, thereby providing invaluable data for ongoing safety monitoring.[22] A comprehensive analysis of VAERS database revealed that oral paresthesia, lip swelling, ageusia, oral hypoesthesia, and swollen tongue were the most

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commonly reported oral AEs following COVID-19 vaccination in the American population.[23] Another population-level evidence on oral AEs had been driven from the EudraVigilance database, which agreed that taste-related AEs (e.g., dysgeusia, ageusia, and taste disorder), anaphylactic AEs (e.g., lip swelling and swollen tongue) and other sensory AEs (e.g., oral paresthesia and oral hypoesthesia) were the most common oral AEs in Europe.[24] Both American and European analyses indicated females and mRNA-vaccines association with a higher reported incidence of oral AEs, as well as the general similarity between COVID-19 and influenza vaccines, except for a few AEs such as taste-related ones.[23,24]

Given the wealth of information provided by the Australian database of passive surveillance reports (DAEN) and the lack of systematic analysis for oral AEs following COVID-19 vaccination in the Australian population, the present study aimed to explore these AEs.[25] In this study, the influenza vaccination was chosen as a control group. Like the COVID-19 vaccine, it is recommended for all sexes and ages. Both COVID-19 and influenza are respiratory infections with somewhat similar clinical manifestations. The long history of influenza vaccine use in Australia provides a comparative basis for evaluating the oral AEs of the newer COVID-19 vaccine. The primary objective was to estimate the prevalence of oral AEs following COVID-19 vs influenza vaccination, while the secondary objective was to evaluate oral AEs of COVID-19 vaccines according to vaccine type, sex, and age group.

Materials and methods

Design

In January 2023, secondary data analysis was initiated using the Database of Adverse Event Notifications (DAEN) from the Therapeutic Goods Administration (TGA) in Australia. The primary objective was to examine the reported Adverse Events (AEs) in Australians associated with two vaccines: COVID-19, with data starting from its rollout in February 2021, and seasonal influenza, with data available since the inception of its database in 1971. This analysis covered the period up until December 31st, 2022.[25]

Data sources

The Australian TGA oversees the safety of authorized therapeutic products, including medicines, vaccines, biological therapies, and medical devices. It operates a passive surveillance system that collects reports of possible AEs, thus aiding in the identification of unusual patterns with post-authorization safety.[25] These reports, which can be submitted by any individual, including health professionals, the general public, or pharmaceutical companies, are collated and disseminated via the "DAEN – medicines" and "DAEN – medical devices" online platforms which were utilized in this study.[25]

Population

As of December 31st, 2022, the DAEN had suspected AEs reports of four COVID-19 vaccines; Pfizer-BioNTech (Comirnaty), Moderna (Spikevax), AstraZeneca (Vaxzervria), and Novavax (Nuvaxovid). In addition, there were 41 influenza vaccines, e.g., Fluad, Fluarix, Fluvax, Influvac and Xflu included in the DAEN database to date.[25]

The current analysis encompassed all AEs reports associated with COVID-19 and influenza vaccines. This data was extracted as summary figures and stratified by two principal demographics: sex (distinguished as female and male) and age group (segregated into under 18 years, between 18 and 64 years, and 64 years and above).[25]

Variables

DAEN employs the Medical Dictionary for Regulatory Activities (MedDRA) framework for the arrangement and presentation of suspected AEs.[26] The MedDRA system is hierarchical with five tiers, ranging from the "System Organ Class" level, such as gastrointestinal disorders, down to the most specific "Lowest Level Term" level, like aphthous stomatitis.[26]

To initiate our study, we constructed an anatomo-physiological scheme aimed at identifying and extracting all potential AEs associated with oral cavity structures and functions within the MedDRA framework.[23] This schema, detailed in a prior publication, essentially divided the oral cavity into six primary regions: a) oral mucosa, b) tongue, c) lips, d) palate, e) salivary glands, and f) dentition, and it also defined two functions: a) taste and b) other sensory disorders.[23]

Subsequently, a comprehensive list of 310 potential oral AEs was compiled according to our unique schema. This list was then scrutinized and refined by a panel of oral surgery specialists. In total, 182 potential AEs were eventually dismissed for reasons including duplication ($n = 43$), congenital origins ($n = 16$), traumatic injuries ($n = 20$), iatrogenic causes ($n = 42$), chronic or oncologic conditions ($n = 52$), or biological irrelevance ($n = 9$).[23]

The study thus utilized a final list of 128 plausible oral AEs.

Analyses

The statistical analysis process began by calculating the absolute frequencies and relative proportions of each suspected AE. These were then cross-tabulated, accounting for variables such as vaccine group (influenza *vs.* COVID-19), COVID-19 vaccine type (e.g., Comirnaty *vs.* Spikevax), sex, and age category. For subsequent analyses, the age classifications were restructured into three distinct groups: minors (0–17 years old), adults (18–64 years old), and seniors (>64 years old). Reports with either sex or age data missing were discarded from the dataset. The total frequencies of AE reports for each vaccine group and demographic category served as the denominator for these calculations.

Inferential tests, including the Chi-squared test (χ^2) and Fisher's exact test, were employed to identify significant differences between vaccine groups, sex, and age categories. These tests were performed assuming that the significance level (*Sig.*) should be ≤ 0.05. All statistical tests were executed using R,

version 4.1.1 (The R Foundation for Statistical Computing, Vienna, Austria, 2022).[27]

Results

Demographic characteristics

A total of 136,555 and 26,798 AEs reports were received following COVID-19 and influenza vaccines, respectively. Among COVID-19 vaccines, Comirnaty had the highest frequency of reported AEs ($n = 80,957$), followed by Vaxzervria ($n = 48,048$), Spikevax ($n = 7,351$), and Novavax ($n = 964$).

Females (65.14%) had a significantly (*Sig.* <0.001) higher frequency of reported AEs than males (32%). Vaxzervria had the highest frequency of AEs among the (≥65 years old) group (33.83%), while Novavax had the highest frequency among the (18–64 years old) group Table 1.

Oral AEs of COVID-19 vs. influenza vaccines

Oral paresthesia was the most commonly reported oral AE after COVID-19 vaccination (75.28 cases per 10,000 reports), followed by dysgeusia (73.96), swollen tongue (51.55), lip swelling (49.43), taste disorder (27.32), ageusia (25.85), dry mouth (24.75), mouth ulceration (18.97), oral hypoaesthesia (15.60), and oral herpes (12.74). Similarly, oral paresthesia was the most commonly reported oral AE after influenza vaccination (71.65 cases per 10,000 reports), followed by lip swelling (57.84), swollen tongue (41.79), dysgeusia (32.09), mouth ulceration (14.93), oral hypoaesthesia (14.18), dry mouth (13.06), taste disorder (7.46), mouth swelling (5.22), and salivary hypersecretion (4.85) Table 2.

COVID-19 vaccines were significantly associated with a higher reported frequency of taste-related AEs than influenza vaccines, including ageusia (25.85 *vs*. 3.73 cases per 10,000 reports; *Sig.* <0.001), dysgeusia (73.96 *vs*. 32.09; *Sig.* <0.001), and taste disorder (27.32 *vs*. 7.46; *Sig.* <0.001). While swollen tongue (51.55 *vs*. 41.79; *Sig.* = 0.043), dry mouth (24.75 *vs*. 13.06; *Sig.* <0.001), oral herpes (12.74 *vs*. 2.61; *Sig.* <0.001), and oral pain (3.88 *vs*. 0.75; *Sig.* = 0.018) were more common after COVID-19 vaccines, tongue edema (0.29 *vs*. 4.48; *Sig.* <0.001), and lip edema (0.29 *vs*. 1.49; *Sig.* = 0.037) were less common after COVID-19 vaccines as compared with influenza vaccines. The majority of oral AEs did not differ statistically significantly between COVID-19 and influenza vaccines Table 2.

Oral AEs of Comirnaty vs. Spikevax

The most common oral AE after Comirnaty was oral paresthesia (87.47 cases per 10,000 reports), followed by dysgeusia (82.63), swollen tongue (60.78), lip swelling (56.58), and taste disorder (27.05). Likewise, dysgeusia (70.74) was the most common oral AE after Spikevax, followed by swollen tongue (58.50), lip swelling (44.89), taste disorder (42.17) and oral paresthesia (32.65) Table 3.

On comparing the two mRNA-based vaccines, Comirnaty was significantly associated with a higher frequency of oral paresthesia (87.47 *vs*. 32.65 cases per 10,000 reports; *Sig.* <0.001) and oral hypoaesthesia (17.74 *vs*. 0; *Sig.* = 0.001). On the other hand, Spikevax was associated with a higher frequency of taste disorder (42.17 *vs*. 27.05; *Sig.* = 0.026) and toothache (24.49 *vs*. 5.71; *Sig.* <0.001) Table 3.

Oral AEs of mRNA vs. viral vector vs. protein subunit COVID-19 vaccines

The most common oral AE after mRNA-based vaccines was oral paresthesia (82.89 cases per 10,000 reports), followed by dysgeusia (81.64), swollen tongue (60.04), lip swelling (55.60), and taste disorder (28.31). Similarly, oral paresthesia (60.98) was the most commonly reported oral AE after viral vector vaccines, followed by dysgeusia (57.86), lip swelling (39.34), swollen tongue (36.01), and taste disorder (31.22). Dysgeusia was the most common oral AE after protein subunit vaccines (165.98), followed by oral paresthesia (72.61), taste disorder (41.49), dry mouth (31.12) and ageusia (31.12) Table 4.

On comparing mRNA *vs* viral vector vaccines, dysgeusia (81.64 *vs*. 57.86 cases per 10,000 reports; *Sig.* <0.001), swollen tongue (60.04 *vs*. 36.01; *Sig.* <0.001), lip swelling (55.60 *vs*. 39.34; *Sig.* <0.001), oral paresthesia (82.89 *vs*. 60.98; *Sig.* <0.001), and oral hypoaesthesia (16.26 *vs*. 0.416; *Sig.* <0.001) were more common after mRNA vaccines. Contrarily, ageusia was more common after viral vector vaccines (31.22 *vs*. 22.97; *Sig.* = 0.005) Table 4.

On comparing mRNA *vs* protein subunit vaccines, dysgeusia (165.98 *vs*. 81.64; *Sig.* = 0.007), salivary gland pain (10.37 *vs*. 0.34; *Sig.* = 0.027), and tongue blistering (20.75 *vs*. 0.57; *Sig.* <0.001) were more common after protein subunit vaccines. Contrarily, swollen tongue (60.04 *vs*. 0; *Sig.* = 0.028) and lip swelling (55.60 *vs*. 0; *Sig.* = 0.035) were more common after mRNA vaccines Table 4.

Table 1. Demographic characteristics of COVID-19 vaccines recipients in Australia who experienced post-vaccination adverse events until December 31st, 2022 (database of adverse event notifications "DAEN").

Variable	Outcome	Comirnaty	Spikevax	Vaxzevria	Novavax	Total	*Sig.*
Sex	Female	53,033 (65.8%)	4,778 (64.998%)	30,775 (64.051%)	626 (64.938%)	89,212 (65.137%)	**<0.001 (Significant)**
	Male	25,323 (31.419%)	2,448 (33.302%)	15,739 (32.757%)	321 (33.299%)	43,831 (32.003%)	
Age Group	<5 years	70 (0.087%)	3 (0.041%)	12 (0.025%)	0 (0%)	85 (0.062%)	**<0.001 (Significant)**
	5–11 years	1,512 (1.876%)	24 (0.326%)	4 (0.008%)	1 (0.104%)	1,541 (1.125%)	
	12–17 years	3,369 (4.18%)	488 (6.639%)	206 (0.429%)	14 (1.452%)	4,077 (2.977%)	
	18–64 years	57,805 (71.721%)	5,371 (73.065%)	24,016 (49.983%)	788 (81.743%)	87,980 (64.238%)	
	≥65 years	4,009 (4.974%)	684 (9.305%)	16,254 (33.829%)	72 (7.469%)	21,019 (15.347%)	

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

Table 2. Oral adverse events reported following COVID-19 *vs*. Influenza vaccines in Australia until December 31st, 2022 (database of adverse event notifications "DAEN").

Group	Preferred Term (MedDRA Code)	COVID-19 (*per 10,000 reports*)	Influenza (*per 10,000 reports*)	*Sig.*
Dentition-related AE[a]	Dental Discomfort (10054217)	7 (0.513)	0 (0)	0.508 (Not Significant)
	Dental Paraesthesia (10078276)	1 (0.073)	0 (0)	1.000 (Not Significant)
	Hyperaesthesia Teeth (10082426)	13 (0.952)	0 (0)	0.221 (Not Significant)
	Toothache (10044055)	95 (6.957)	4 (1.493)	**0.001 (Significant)**
Taste-related AE[b]	Ageusia (10001480)	353 (25.85)	10 (3.732)	**<0.001 (Significant)**
	Dysgeusia (10013911)	1010 (73.963)	86 (32.092)	**<0.001 (Significant)**
	Hypogeusia (10020989)	8 (0.586)	1 (0.373)	1.000 (Not Significant)
	Taste Disorder (10082490)	373 (27.315)	20 (7.463)	**<0.001 (Significant)**
Salivary glands-related AE[c]	Dry Mouth (10013781)	338 (24.752)	35 (13.061)	**<0.001 (Significant)**
	Aptyalism (10003068)	4 (0.293)	0 (0)	0.833 (Not Significant)
	Saliva Altered (10039379)	2 (0.146)	0 (0)	1.000 (Not Significant)
	Noninfective Sialoadenitis (10075243)	1 (0.073)	0 (0)	1.000 (Not Significant)
	Salivary Gland Disorder (10061935)	1 (0.073)	0 (0)	1.000 (Not Significant)
	Salivary Gland Enlargement (10039408)	5 (0.366)	2 (0.746)	0.72 (Not Significant)
	Salivary Gland Pain (10039421)	4 (0.293)	1 (0.373)	1.000 (Not Significant)
	Salivary Hypersecretion (10039424)	42 (3.076)	13 (4.851)	0.205 (Not Significant)
	Sialoadenitis (10040628)	5 (0.366)	0 (0)	0.699 (Not Significant)
	Salivary Duct Obstruction (10039386)	1 (0.073)	0 (0)	1.000 (Not Significant)
Tongue-related AE[d]	Glossitis (10018386)	14 (1.025)	2 (0.746)	0.933 (Not Significant)
	Glossodynia (10018388)	40 (2.929)	2 (0.746)	0.067 (Not Significant)
	Hypertrophy of Tongue Papillae (10020893)	1 (0.073)	0 (0)	1.000 (Not Significant)
	Plicated Tongue (10035630)	5 (0.366)	0 (0)	0.699 (Not Significant)
	Strawberry Tongue (10051495)	0 (0)	1 (0.373)	0.364 (Not Significant)
	Swollen Tongue (10042727)	704 (51.554)	112 (41.794)	**0.043 (Significant)**
	Tongue Blistering (10043942)	7 (0.513)	1 (0.373)	1.000 (Not Significant)
	Tongue Discolouration (10043949)	16 (1.172)	2 (0.746)	0.773 (Not Significant)
	Tongue Discomfort (10077855)	46 (3.369)	3 (1.119)	0.08 (Not Significant)
	Tongue Disorder (10043951)	18 (1.318)	7 (2.612)	0.195 (Not Significant)
	Tongue Dry (10049713)	5 (0.366)	1 (0.373)	1.000 (Not Significant)
	Tongue Eruption (10052002)	0 (0)	1 (0.373)	0.364 (Not Significant)
	Tongue Erythema (10079075)	6 (0.439)	1 (0.373)	1.000 (Not Significant)
	Tongue Movement Disturbance (10043963)	1 (0.073)	4 (1.493)	**0.001 (Significant)**
	Tongue Oedema (10043967)	4 (0.293)	12 (4.478)	**<0.001 (Significant)**
	Tongue Paralysis (10043972)	2 (0.146)	0 (0)	1.000 (Not Significant)
	Tongue Pruritus (10070072)	17 (1.245)	0 (0)	0.134 (Not Significant)
	Tongue Rough (10043977)	1 (0.073)	0 (0)	1.000 (Not Significant)
	Tongue Spasm (10043981)	1 (0.073)	0 (0)	1.000 (Not Significant)
	Tongue Thrust (10082545)	1 (0.073)	0 (0)	1.000 (Not Significant)
	Tongue Ulceration (10043991)	18 (1.318)	2 (0.746)	0.637 (Not Significant)
	Trichoglossia (10080276)	2 (0.146)	0 (0)	1.000 (Not Significant)
	Ankyloglossia Acquired (10049243)	1 (0.073)	0 (0)	1.000 (Not Significant)
Lip-related AE[e]	Cheilitis (10008417)	9 (0.659)	0 (0)	0.379 (Not Significant)
	Chapped Lips (10049047)	7 (0.513)	5 (1.866)	**0.048 (Significant)**
	Lip Blister (10049307)	15 (1.098)	3 (1.119)	1.000 (Not Significant)
	Lip Discolouration (10024549)	6 (0.439)	0 (0)	0.593 (Not Significant)
	Lip Disorder (10048470)	3 (0.22)	0 (0)	1.000 (Not Significant)
	Lip Dry (10024552)	14 (1.025)	1 (0.373)	0.503 (Not Significant)
	Lip Erythema (10080124)	2 (0.146)	2 (0.746)	0.255 (Not Significant)
	Lip Exfoliation (10064482)	2 (0.146)	0 (0)	1.000 (Not Significant)
	Lip Oedema (10024558)	4 (0.293)	4 (1.493)	**0.037 (Significant)**
	Lip Pain (10024561)	8 (0.586)	2 (0.746)	1.000 (Not Significant)
	Lip Pruritus (10070721)	12 (0.879)	1 (0.373)	0.636 (Not Significant)
	Lip Swelling (10024570)	675 (49.431)	155 (57.84)	0.085 (Not Significant)
	Lip Ulceration (10024572)	9 (0.659)	1 (0.373)	0.905 (Not Significant)
Palate-related AE[f]	Palatal Disorder (10052453)	1 (0.073)	0 (0)	1.000 (Not Significant)
	Palatal Swelling (10074403)	2 (0.146)	1 (0.373)	0.99 (Not Significant)
Other Sensory AE[g]	Burning Mouth Syndrome (10068065)	3 (0.22)	0 (0)	1.000 (Not Significant)
	Oral Dysaesthesia (10050820)	1 (0.073)	0 (0)	1.000 (Not Significant)
	Anaesthesia Oral (10082548)	10 (0.732)	0 (0)	0.33 (Not Significant)
	Hypoaesthesia Oral (10057371)	213 (15.598)	38 (14.18)	0.648 (Not Significant)
	Paraesthesia Oral (10057372)	1028 (75.281)	192 (71.647)	0.553 (Not Significant)
Oral Mucosa-related AE[h]	Aphthous Ulcer (10002959)	38 (2.783)	2 (0.746)	0.083 (Not Significant)
	Circumoral Oedema (10052250)	4 (0.293)	1 (0.373)	1.000 (Not Significant)
	Circumoral Swelling (10081703)	6 (0.439)	0 (0)	0.593 (Not Significant)
	Coating in Mouth (10075366)	2 (0.146)	0 (0)	1.000 (Not Significant)
	Mouth Swelling (10075203)	73 (5.346)	14 (5.224)	1.000 (Not Significant)
	Oedema Mouth (10030110)	1 (0.073)	2 (0.746)	0.116 (Not Significant)
	Oral Blood Blister (10076590)	1 (0.073)	1 (0.373)	0.743 (Not Significant)
	Oral Candidiasis (10030963)	28 (2.05)	3 (1.119)	0.442 (Not Significant)
	Oral Discomfort (10030973)	56 (4.101)	4 (1.493)	0.062 (Not Significant)
	Oral Disorder (10067621)	8 (0.586)	3 (1.119)	0.571 (Not Significant)
	Oral Herpes (10067152)	174 (12.742)	7 (2.612)	**<0.001 (Significant)**

(*Continued*)

Table 2. (Continued).

Group	Preferred Term (MedDRA Code)	COVID-19 (*per 10,000 reports*)	Influenza (*per 10,000 reports*)	*Sig.*
	Oral Lichen Planus (10030983)	3 (0.22)	1 (0.373)	1.000 (Not Significant)
	Oral Mucosal Blistering (10030995)	27 (1.977)	6 (2.239)	0.968 (Not Significant)
	Oral Mucosal Discolouration (10030996)	1 (0.073)	1 (0.373)	0.743 (Not Significant)
	Oral Mucosal Eruption (10030997)	4 (0.293)	11 (4.105)	**<0.001 (Significant)**
	Oral Mucosal Exfoliation (10064487)	3 (0.22)	1 (0.373)	1.000 (Not Significant)
	Oral Pain (10031009)	53 (3.881)	2 (0.746)	**0.018 (Significant)**
	Oral Pruritus (10052894)	20 (1.465)	5 (1.866)	0.829 (Not Significant)
	Oral Pustule (10056674)	1 (0.073)	0 (0)	1.000 (Not Significant)
	Perioral Dermatitis (10034541)	5 (0.366)	0 (0)	0.699 (Not Significant)
	Stomatitis (10042128)	27 (1.977)	4 (1.493)	0.776 (Not Significant)
	Mouth Ulceration (10028034)	259 (18.967)	40 (14.926)	0.181 (Not Significant)
	Oral Papule (10031010)	1 (0.073)	0 (0)	1.000 (Not Significant)

Chi-squared test (χ^2) and Fisher's exact test were used with a significance level *Sig.* ≤0.05.
[a]Hypoaesthesia Teeth (10051780) and Sensitivity of Teeth (10040012) had no reports in COVID-19 or Influenza groups.
[b]Hypergeusia (10029205) had no reports in COVID-19 or Influenza groups.
[c]Saliva Discolouration (10049069), Salivary Duct Stenosis (10039388), Salivary Gland Calculus (10039394), Salivary Gland Mass (10057002), Salivary Duct Inflammation (10056681) and Salivary Gland Induration (10071363) had no reports in COVID-19 or Influenza groups.
[d]Atrophic Glossitis (10069085), Macroglossia (10025391), Stiff Tongue (10081491), Tongue Coated (10043945), Tongue Exfoliation (10064488), Tongue Fungal Infection (10075845), Tongue Induration (10084548), Tongue Pigmentation (10069164), Acquired Macroglossia (10058835), Atrophic Glossitis (10003712) and Tongue Black Hairy (10043941) had no reports in COVID-19 or Influenza groups.
[e]Angular Cheilitis (10002509), Lip Scab (10082767) and Lip Erosion (10051992) had no reports in COVID-19 or Influenza groups.
[f]Palatal Oedema (10056998), Palatal Ulcer (10077519) and Palatal Palsy (10072012) had no reports in COVID-19 or Influenza groups.
[g]Burn Oral Cavity (10075532) had no reports in COVID-19 or Influenza groups.
[h]Leukoplakia Oral (10024396, Oral Fungal Infection (10061324), Oral Lichenoid Reaction (10083833), Oral Mucosa Erosion (10064594), Oral Mucosal Erythema (10067418), Oral Mucosal Roughening (10084009), Oral Pigmentation (10077552), Oral Purpura (10083533), Oral Viral Infection (10065234), Oropharyngeal Blistering (10067950), Oropharyngeal Plaque (10067721), Aphthous Stomatitis (10002958), Buccal Mucosal Roughening (10048479), Mouth Plaque (10028032), Oral Soft Tissue Disorder (10061326), Oral Mucosal Hypertrophy (10062956), Oral Mucosal Petechiae (10030998) and Oral Mucosal Scab (10082769) had no reports in COVID-19 or Influenza groups.

Sex-specific incidence of oral AEs

Overall, females had a higher reported incidence of oral AEs following COVID-19 vaccines compared to males, e.g., oral paresthesia (96.74 *vs*. 28.98 cases per 10,000 reports; *Sig*. <0.001), dysgeusia (87.54 *vs*. 46.77; *Sig*. <0.001), swollen tongue (61.88 *vs*. 29.89; *Sig*. <0.001), lip swelling (56.16 *vs*. 35.59; *Sig*. <0.001), and taste disorder (34.75 *vs*. 18.25; *Sig*. <0.001) Table 5.

Among Comirnaty recipients, all the top 10 oral AEs were more commonly reported by females than males, e.g., oral paresthesia (111.06 *vs*. 33.96; *Sig*. <0.001), dysgeusia (97.86 *vs*. 50.94; *Sig*. <0.001) and swollen tongue (73.92 *vs*. 31.20; *Sig*. <0.001), and lip swelling (65.43 *vs*. 37.52; *Sig*. <0.001). Similarly, among Spikevax recipients, all the top 10 oral AEs were more commonly reported by females than males, e.g., oral paresthesia (46.04 *vs*. 8.18; *Sig*. = 0.015), dysgeusia (90 *vs*. 36.80; *Sig*. = 0.017), and mouth ulceration (39.77 *vs*. 4.09; *Sig*. = 0.013) Table 5.

For viral vector vaccines, females had a higher reported frequency of the top 10 oral AEs, including oral paresthesia (80.26 *vs*. 24.14; *Sig*. <0.001), dysgeusia (67.26 *vs*. 40.03; *Sig*. <0.001), swollen tongue (41.92 *vs*. 25.42; *Sig*. = 0.007), and taste disorder (38.34 *vs*. 17.16; *Sig*. <0.001) Table 5.

Age-specific incidence of oral AEs

In the pediatric group (0–17 years old), lip swelling was the most commonly reported oral AE (59.62 cases per 10,000 reports), followed by swollen tongue (33.32) and oral paresthesia (19.29). In the adult group (18–64 years old), oral paresthesia (96.04) was the most common AE, followed by dysgeusia (93.09), swollen tongue (61.04), lip swelling (57.63), taste disorder (32.62), and ageusia (28.64). Similarly, oral paresthesia (55.66) was the most common oral AE in the senior group (>64 years old), followed by dysgeusia (46.62), swollen tongue (39.01), and lip swelling (33.78) Table 6.

Spikevax and Comirnaty were associated with most oral AEs in the pediatric group (0–17 years old), except for dysgeusia which was most common in the Vaxzervria group (90.09 cases per 10,000 reports). In the adult group (18–64 years old), oral paresthesia was the most common in the Comirnaty group (107.95), dysgeusia in the Spikevax group (78.20), oral paresthesia in the Vaxzervria group (88.83), and dysgeusia in the Novavax group (139.59). In the senior group (>64 years old), oral paresthesia was the most common in the Comirnaty group (79.82), swollen tongue in the Spikevax group (102.34), and oral paresthesia in the Vaxzervria group (52.29) Figure 1.

Discussion

The present analysis aimed to evaluate oral AEs linked to COVID-19 vaccines, compared with influenza vaccines, utilizing data from the DAEN database of Australian TGA. Employing a rigorous anatomo-physiological framework capable of capturing all plausible oral AEs, we scrutinized reports related to four COVID-19 vaccines authorized in Australia: mRNA-based (Comrinaty and Spikevax), viral vector (Vaxzervria) and protein subunit vaccines (Novavax). Our study revealed several findings, including the concordance between COVID-19 and influenza vaccines and the increased susceptibility among females.

Table 3. Oral adverse events reported following Comirnaty *vs*. Spikevax in Australia until December 31st, 2022 (database of adverse event notifications "DAEN").

Group	Preferred Term (MedDRA Code)	Comirnaty (*per 10,000 reports*)	Spikevax (*per 10,000 reports*)	*Sig.*
Dentition-related AE[a]	Dental Discomfort (10054217)	3 (0.372)	1 (1.36)	0.765 (Not Significant)
	Dental Paraesthesia (10078276)	1 (0.124)	0 (0)	1.000 (Not Significant)
	Hyperaesthesia Teeth (10082426)	6 (0.744)	0 (0)	0.998 (Not Significant)
	Toothache (10044055)	46 (5.707)	18 (24.486)	**<0.001 (Significant)**
Taste-related AE[b]	Ageusia (10001480)	181 (22.457)	21 (28.568)	0.357 (Not Significant)
	Dysgeusia (10013911)	666 (82.633)	52 (70.739)	0.309 (Not Significant)
	Hypogeusia (10020989)	4 (0.496)	1 (1.36)	0.894 (Not Significant)
	Taste Disorder (10082490)	218 (27.048)	31 (42.171)	**0.026 (Significant)**
Salivary glands-related AE[c]	Dry Mouth (10013781)	201 (24.939)	18 (24.486)	1.000 (Not Significant)
	Aptyalism (10003068)	3 (0.372)	1 (1.36)	0.765 (Not Significant)
	Saliva Altered (10039379)	2 (0.248)	0 (0)	1.000 (Not Significant)
	Noninfective Sialoadenitis (10075243)	1 (0.124)	0 (0)	1.000 (Not Significant)
	Salivary Gland Disorder (10061935)	1 (0.124)	0 (0)	1.000 (Not Significant)
	Salivary Gland Enlargement (10039408)	5 (0.62)	0 (0)	1.000 (Not Significant)
	Salivary Gland Pain (10039421)	2 (0.248)	1 (1.36)	0.603 (Not Significant)
	Salivary Hypersecretion (10039424)	25 (3.102)	0 (0)	0.251 (Not Significant)
	Sialoadenitis (10040628)	4 (0.496)	0 (0)	1.000 (Not Significant)
Tongue-related AE[d]	Glossitis (10018386)	6 (0.744)	2 (2.721)	0.288 (Not Significant)
	Glossodynia (10018388)	22 (2.73)	5 (6.802)	0.119 (Not Significant)
	Hypertrophy of Tongue Papillae (10020893)	1 (0.124)	0 (0)	1.000 (Not Significant)
	Plicated Tongue (10035630)	4 (0.496)	0 (0)	1.000 (Not Significant)
	Swollen Tongue (10042727)	485 (60.176)	43 (58.495)	0.921 (Not Significant)
	Tongue Blistering (10043942)	5 (0.62)	0 (0)	1.000 (Not Significant)
	Tongue Discolouration (10043949)	10 (1.241)	1 (1.36)	1.000 (Not Significant)
	Tongue Discomfort (10077855)	31 (3.846)	3 (4.081)	1.000 (Not Significant)
	Tongue Disorder (10043951)	13 (1.613)	2 (2.721)	0.818 (Not Significant)
	Tongue Dry (10049713)	5 (0.62)	0 (0)	1.000 (Not Significant)
	Tongue Erythema (10079075)	3 (0.372)	2 (2.721)	0.080 (Not Significant)
	Tongue Movement Disturbance (10043963)	1 (0.124)	0 (0)	1.000 (Not Significant)
	Tongue Oedema (10043967)	2 (0.248)	0 (0)	1.000 (Not Significant)
	Tongue Paralysis (10043972)	2 (0.248)	0 (0)	1.000 (Not Significant)
	Tongue Pruritus (10070072)	15 (1.861)	0 (0)	0.482 (Not Significant)
	Tongue Rough (10043977)	1 (0.124)	0 (0)	1.000 (Not Significant)
	Tongue Spasm (10043981)	1 (0.124)	0 (0)	1.000 (Not Significant)
	Tongue Thrust (10082545)	1 (0.124)	0 (0)	1.000 (Not Significant)
	Tongue Ulceration (10043991)	11 (1.365)	0 (0)	0.648 (Not Significant)
	Trichoglossia (10080276)	2 (0.248)	0 (0)	1.000 (Not Significant)
Lip-related AE[e]	Cheilitis (10008417)	6 (0.744)	1 (1.36)	1.000 (Not Significant)
	Chapped Lips (10049047)	5 (0.62)	0 (0)	1.000 (Not Significant)
	Lip Blister (10049307)	9 (1.117)	2 (2.721)	0.527 (Not Significant)
	Lip Discolouration (10024549)	4 (0.496)	0 (0)	1.000 (Not Significant)
	Lip Disorder (10048470)	2 (0.248)	1 (1.36)	0.603 (Not Significant)
	Lip Dry (10024552)	8 (0.993)	0 (0)	0.829 (Not Significant)
	Lip Erythema (10080124)	1 (0.124)	1 (1.36)	0.395 (Not Significant)
	Lip Exfoliation (10064482)	2 (0.248)	0 (0)	1.000 (Not Significant)
	Lip Oedema (10024558)	3 (0.372)	0 (0)	1.000 (Not Significant)
	Lip Pain (10024561)	3 (0.372)	0 (0)	1.000 (Not Significant)
	Lip Pruritus (10070721)	10 (1.241)	0 (0)	0.701 (Not Significant)
	Lip Swelling (10024570)	456 (56.578)	33 (44.892)	0.227 (Not Significant)
	Lip Ulceration (10024572)	6 (0.744)	0 (0)	0.998 (Not Significant)
Palate-related AE[f]	Palatal Disorder (10052453)	1 (0.124)	0 (0)	1.000 (Not Significant)
	Palatal Swelling (10074403)	1 (0.124)	1 (1.36)	0.395 (Not Significant)
Other Sensory AE[g]	Oral Dysaesthesia (10050820)	1 (0.124)	0 (0)	1.000 (Not Significant)
	Anaesthesia Oral (10082548)	10 (1.241)	0 (0)	0.701 (Not Significant)
	Hypoaesthesia Oral (10057371)	143 (17.743)	0 (0)	**0.001 (Significant)**
	Paraesthesia Oral (10057372)	705 (87.472)	24 (32.649)	**<0.001 (Significant)**
Oral Mucosa-related AE[h]	Aphthous Ulcer (10002959)	29 (3.598)	2 (2.721)	0.953 (Not Significant)
	Circumoral Oedema (10052250)	3 (0.372)	0 (0)	1.000 (Not Significant)
	Circumoral Swelling (10081703)	6 (0.744)	0 (0)	0.998 (Not Significant)
	Coating in Mouth (10075366)	2 (0.248)	0 (0)	1.000 (Not Significant)
	Mouth Swelling (10075203)	49 (6.08)	2 (2.721)	0.372 (Not Significant)
	Oral Candidiasis (10030963)	17 (2.109)	2 (2.721)	1.000 (Not Significant)
	Oral Discomfort (10030973)	43 (5.335)	1 (1.36)	0.235 (Not Significant)
	Oral Disorder (10067621)	7 (0.869)	1 (1.36)	1.000 (Not Significant)
	Oral Herpes (10067152)	107 (13.276)	10 (13.604)	1.000 (Not Significant)
	Oral Lichen Planus (10030983)	2 (0.248)	0 (0)	1.000 (Not Significant)
	Oral Mucosal Blistering (10030995)	11 (1.365)	2 (2.721)	0.679 (Not Significant)
	Oral Mucosal Discolouration (10030996)	1 (0.124)	0 (0)	1.000 (Not Significant)
	Oral Mucosal Eruption (10030997)	2 (0.248)	0 (0)	1.000 (Not Significant)
	Oral Mucosal Exfoliation (10064487)	2 (0.248)	0 (0)	1.000 (Not Significant)
	Oral Pain (10031009)	31 (3.846)	3 (4.081)	1.000 (Not Significant)
	Oral Pruritus (10052894)	16 (1.985)	0 (0)	0.449 (Not Significant)
	Oral Pustule (10056674)	1 (0.124)	0 (0)	1.000 (Not Significant)

(*Continued*)

Table 3. (Continued).

Group	Preferred Term (MedDRA Code)	Comirnaty (*per 10,000 reports*)	Spikevax (*per 10,000 reports*)	*Sig.*
	Perioral Dermatitis (10034541)	3 (0.372)	0 (0)	1.000 (Not Significant)
	Stomatitis (10042128)	17 (2.109)	0 (0)	0.420 (Not Significant)
	Mouth Ulceration (10028034)	152 (18.859)	20 (27.207)	0.158 (Not Significant)
	Oral Papule (10031010)	1 (0.124)	0 (0)	1.000 (Not Significant)

Chi-squared test (χ^2) and Fisher's exact test were used with a significance level *Sig.* ≤0.05.
[a]Hypoaesthesia Teeth (10051780) and Sensitivity of Teeth (10040012) had no reports in Comirnaty or Spikevax groups.
[b]Hypergeusia (10029205) had no reports in Comirnaty or Spikevax groups.
[c]Saliva Discolouration (10049069), Salivary Duct Stenosis (10039388), Salivary Gland Calculus (10039394), Salivary Gland Mass (10057002), Salivary Duct Inflammation (10056681), Salivary Gland Induration (10071363) and Salivary Duct Obstruction (10039386) had no reports in Comirnaty or Spikevax groups.
[d]Atrophic Glossitis (10069085), Macroglossia (10025391), Stiff Tongue (10081491), Tongue Coated (10043945), Tongue Exfoliation (10064488), Tongue Fungal Infection (10075845), Tongue Induration (10084548), Tongue Pigmentation (10069164), Acquired Macroglossia (10058835), Atrophic Glossitis (10003712), Strawberry Tongue (10051495), Tongue Eruption (10052002), Ankyloglossia Acquired (10049243) and Tongue Black Hairy (10043941) had no reports in Comirnaty or Spikevax groups.
[e]Angular Cheilitis (10002509), Lip Scab (10082767) and Lip Erosion (10051992) had no reports in Comirnaty or Spikevax groups.
[f]Palatal Oedema (10056998), Palatal Ulcer (10077519) and Palatal Palsy (10072012) had no reports in Comirnaty or Spikevax groups.
[g]Burn Oral Cavity (10075532) and Burning Mouth Syndrome (10068065) had no reports in Comirnaty or Spikevax groups.
[h]Leukoplakia Oral (10024396, Oral Fungal Infection (10061324), Oral Lichenoid Reaction (10083833), Oral Mucosa Erosion (10064594), Oral Mucosal Erythema (10067418), Oral Mucosal Roughening (10084009), Oral Pigmentation (10077552), Oral Purpura (10083533), Oral Viral Infection (10065234), Oropharyngeal Blistering (10067950), Oropharyngeal Plaque (10067721), Aphthous Stomatitis (10002958), Buccal Mucosal Roughening (10048479), Mouth Plaque (10028032), Oral Soft Tissue Disorder (10061326), Oral Mucosal Hypertrophy (10062956), Oral Mucosal Petechiae (10030998), Oedema Mouth (10030110), Oral Blood Blister (10076590) and Oral Mucosal Scab (10082769) had no reports in Comirnaty or Spikevax groups.

The most commonly reported oral AE of COVID-19 vaccination in the Australian population was oral paresthesia (75.3 cases per 10,000 reports), followed by dysgeusia (74), swollen tongue (51.6), lip swelling (49.4), taste disorder (27.3), ageusia (25.9), dry mouth (24.8), mouth ulceration (19), and oral hypoaesthesia (15.6). These findings resonate with what was found earlier in the European Union Drug Regulating Authorities Pharmacovigilance (EudraVigilance) database of the European Medicines Agency (EMA), where dysgeusia was the most common oral AE of COVID-19 vaccines among Europeans (38.1), followed by oral paresthesia (31.5), ageusia (29.6), lip swelling (24.3), dry mouth (21.5), oral hypoaesthesia (21), swollen tongue (20.7), and taste disorder (17.3).[24] Similarly, oral paresthesia (87.2) was the most common oral AE in the Vaccine Adverse Event Reporting System (VAERS) database of the US Food and Drug Administration (FDA), followed by lip swelling (84.4), ageusia (72.2), oral hypoesthesia (64.8), swollen tongue (62.8), dysgeusia (61.7), taste disorder (31.7), and dry mouth (30.1).[23] Table 7 displays the ten most frequently reported oral AEs subsequent to COVID-19 vaccination in Australia (DAEN), Europe (EudraVigilance), and the United States (VAERS), thereby underscoring the noticeable concordance in oral AEs patterns across these population reports.

Broadly speaking, the oral AEs associated with COVID-19 vaccines paralleled those linked with influenza vaccines. In Australian DAEN, only 13 out of the 129 solicited oral AEs (10.1%) exhibited statistically significant differences between the two vaccine groups. Likewise, only 9 solicited oral AEs (7%) in the American VAERS were significantly different.[23] Maltezou et al. 2022 revealed that anaphylactic events following COVID-19 vaccination are comparable with other vaccines, including seasonal influenza vaccines in both American VAERS and European EudraVigilance databases.[28] Nevertheless, other secondary data analyses demonstrated that the reported AEs incidence following COVID-19 vaccination was multiple folds higher than seasonal influenza vaccination, e.g., anxiety-related AEs, including syncope, were 164 times more common after Janssen COVID-19 vaccination.[29]

On comparing COVID-19 with influenza vaccines, taste-related AEs were found to be more common significantly after COVID-19 vaccination, e.g. ageusia (25.9 *vs*. 3.7 per 10,000 reports; *Sig*. <0.001), dysgeusia (74 *vs*. 32.1; *Sig*. <0.001), and taste disorder (27.3 *vs*. 7.5; *Sig*. <0.001). Likewise, taste-related AEs were more significantly associated with COVID-19 vaccines than seasonal influenza vaccines in American VAERS, e.g. ageusia (72.2 *vs*. 14.3; *Sig*. <0.001), dysgeusia (61.7 *vs*. 24.4; *Sig*. <0.001), and taste disorder (31.7 *vs*. 11.5; *Sig*. <0.001).[23] Riad et al. 2022 found that in American VAERS, there was a significant increase in reports of taste-related Adverse Events during the COVID-19 pandemic (January 2020–December 2021) compared to the pre-pandemic period (January 2010–December 2019) for all vaccines potentially due to the increased public awareness of taste dysfunction as a symptom of COVID-19, despite negative PCR tests ruling out infection in some vaccinated individuals experiencing these symptoms.[23,30–32]

Additionally, dry mouth was significantly associated with COVID-19 vaccines than influenza vaccines in both Australian DAEN (24.8 *vs*. 13.1; *Sig*. <0.001) and American VAERS (30.1 *vs*. 4.3; *Sig*. <0.001).[23] Similarly, oral herpes and swollen tongue were more significantly associated with COVID-19 vaccination in both Australian DAEN (12.7 and 51.6 *vs*. 2.6 and 41.8; *Sig*. <0.001 and = 0.043, respectively) and American VAERS (18.9 and 62.8 *vs*. 8.6 and 37.3; *Sig*. = 0.050 and = 0.007, respectively).[23] Avasarala et al. 2022 found that the reported incidence of injection site pain was significantly higher following COVID-19 than seasonal influenza vaccines (119.7 *vs*. 2.4 cases per 10,000 vaccine doses). Likewise, headache (936.7 *vs*. 10.2) and seizures (31.9 *vs*. 0.9) were more commonly reported after COVID-19 vaccination.[33] Avasarala posited that the heightened incidence AEs following COVID-19 vaccination could be attributed to amplified reporting during the pandemic, making these Adverse Events seem more

Table 4. Oral adverse events reported following mRNA-based vs. Vaxzevria (viral vector-based) vs. Novavax (protein subunit-based) vaccines in Australia until December 31st, 2022 (database of adverse event notifications "DAEN").

Group	Preferred Term (MedDRA Code)	mRNA-based (*per 10,000 reports*)	Viral Vector (*per 10,000 reports*)	*Sig.* (mRNA vs. Viral Vector)	Protein Subunit (*per 10,000 reports*)	*Sig.* (mRNA vs. Protein Sub)
Dentition-related AE[a]	Dental Discomfort (10054217)	4 (0.455)	3 (0.624)	0.983 (Not Significant)	0 (0)	1.000 (Not Significant)
	Dental Paraesthesia (10078276)	1 (0.114)	0 (0)	1.000 (Not Significant)	0 (0)	1.000 (Not Significant)
	Hyperaesthesia Teeth (10082426)	6 (0.682)	7 (1.457)	0.268 (Not Significant)	0 (0)	1.000 (Not Significant)
	Toothache (10044055)	64 (7.277)	31 (6.452)	0.658 (Not Significant)	2 (20.747)	0.351 (Not Significant)
Taste-related AE[b]	Ageusia (10001480)	202 (22.968)	150 (31.219)	**0.005 (Significant)**	3 (31.12)	0.851 (Not Significant)
	Dysgeusia (10013911)	718 (81.639)	278 (57.859)	**<0.001 (Significant)**	16 (165.975)	**0.007 (Significant)**
	Hypogeusia (10020989)	5 (0.569)	4 (0.833)	0.823 (Not Significant)	0 (0)	1.000 (Not Significant)
	Taste Disorder (10082490)	249 (28.312)	150 (31.219)	0.371 (Not Significant)	4 (41.494)	0.645 (Not Significant)
Salivary glands-related AE[c]	Dry Mouth (10013781)	219 (24.901)	118 (24.559)	0.949 (Not Significant)	3 (31.12)	0.952 (Not Significant)
	Aptyalism (10003068)	4 (0.455)	0 (0)	0.339 (Not Significant)	0 (0)	1.000 (Not Significant)
	Saliva Altered (10039379)	2 (0.227)	0 (0)	0.760 (Not Significant)	0 (0)	1.000 (Not Significant)
	Noninfective Sialoadenitis (10075243)	1 (0.114)	0 (0)	1.000 (Not Significant)	0 (0)	1.000 (Not Significant)
	Salivary Gland Disorder (10061935)	1 (0.114)	0 (0)	1.000 (Not Significant)	0 (0)	1.000 (Not Significant)
	Salivary Gland Enlargement (10039408)	5 (0.569)	0 (0)	0.236 (Not Significant)	0 (0)	1.000 (Not Significant)
	Salivary Gland Pain (10039421)	3 (0.341)	0 (0)	0.499 (Not Significant)	1 (10.373)	**0.027 (Significant)**
	Salivary Hypersecretion (10039424)	25 (2.843)	16 (3.33)	0.740 (Not Significant)	1 (10.373)	0.68 (Not Significant)
	Sialoadenitis (10040628)	4 (0.455)	1 (0.208)	0.803 (Not Significant)	0 (0)	1.000 (Not Significant)
	Salivary Duct Obstruction (10039386)	0 (0)	1 (0.208)	0.759 (Not Significant)	0 (0)	NA (NA)
Tongue-related AE[d]	Glossitis (10018386)	8 (0.91)	6 (1.249)	0.757 (Not Significant)	0 (0)	1.000 (Not Significant)
	Glossodynia (10018388)	27 (3.07)	14 (2.914)	1.000 (Not Significant)	0 (0)	1.000 (Not Significant)
	Hypertrophy of Tongue Papillae (10020893)	1 (0.114)	0 (0)	1.000 (Not Significant)	0 (0)	1.000 (Not Significant)
	Plicated Tongue (10035630)	4 (0.455)	1 (0.208)	0.803 (Not Significant)	0 (0)	1.000 (Not Significant)
	Swollen Tongue (10042727)	528 (60.035)	173 (36.006)	**<0.001 (Significant)**	0 (0)	**0.028 (Significant)**
	Tongue Blistering (10043942)	5 (0.569)	0 (0)	0.236 (Not Significant)	2 (20.747)	**<0.001 (Significant)**
	Tongue Discolouration (10043949)	11 (1.251)	5 (1.041)	0.936 (Not Significant)	0 (0)	1.000 (Not Significant)
	Tongue Discomfort (10077855)	34 (3.866)	13 (2.706)	0.343 (Not Significant)	0 (0)	1.000 (Not Significant)
	Tongue Disorder (10043951)	15 (1.706)	3 (0.624)	0.159 (Not Significant)	0 (0)	1.000 (Not Significant)
	Tongue Dry (10049713)	5 (0.569)	0 (0)	0.236 (Not Significant)	0 (0)	1.000 (Not Significant)
	Tongue Erythema (10079075)	5 (0.569)	3 (0.624)	1.000 (Not Significant)	0 (0)	1.000 (Not Significant)
	Tongue Movement Disturbance (10043963)	1 (0.114)	0 (0)	1.000 (Not Significant)	0 (0)	1.000 (Not Significant)
	Tongue Oedema (10043967)	2 (0.227)	2 (0.416)	0.928 (Not Significant)	0 (0)	1.000 (Not Significant)
	Tongue Paralysis (10043972)	2 (0.227)	0 (0)	0.76 (Not Significant)	0 (0)	1.000 (Not Significant)
	Tongue Pruritus (10070072)	15 (1.706)	2 (0.416)	0.075 (Not Significant)	0 (0)	1.000 (Not Significant)
	Tongue Rough (10043977)	1 (0.114)	0 (0)	1.000 (Not Significant)	0 (0)	1.000 (Not Significant)
	Tongue Spasm (10043981)	1 (0.114)	0 (0)	1.000 (Not Significant)	0 (0)	1.000 (Not Significant)
	Tongue Thrust (10082545)	1 (0.114)	0 (0)	1.000 (Not Significant)	0 (0)	1.000 (Not Significant)
	Tongue Ulceration (10043991)	11 (1.251)	7 (1.457)	0.945 (Not Significant)	0 (0)	1.000 (Not Significant)
	Trichoglossia (10080276)	2 (0.227)	0 (0)	0.760 (Not Significant)	0 (0)	1.000 (Not Significant)
	Ankyloglossia Acquired (10049243)	0 (0)	1 (0.208)	0.759 (Not Significant)	0 (0)	NA (NA)
Lip-related AE[e]	Cheilitis (10008417)	7 (0.796)	2 (0.416)	0.635 (Not Significant)	0 (0)	1.000 (Not Significant)
	Chapped Lips (10049047)	5 (0.569)	2 (0.416)	1.000 (Not Significant)	0 (0)	1.000 (Not Significant)
	Lip Blister (10049307)	11 (1.251)	4 (0.833)	0.666 (Not Significant)	0 (0)	1.000 (Not Significant)
	Lip Discolouration (10024549)	4 (0.455)	1 (0.208)	0.803 (Not Significant)	1 (10.373)	0.054 (Not Significant)
	Lip Disorder (10048470)	3 (0.341)	0 (0)	0.499 (Not Significant)	0 (0)	1.000 (Not Significant)
	Lip Dry (10024552)	8 (0.91)	6 (1.249)	0.757 (Not Significant)	0 (0)	1.000 (Not Significant)
	Lip Erythema (10080124)	2 (0.227)	0 (0)	0.76 (Not Significant)	0 (0)	1.000 (Not Significant)
	Lip Exfoliation (10064482)	2 (0.227)	0 (0)	0.76 (Not Significant)	0 (0)	1.000 (Not Significant)
	Lip Oedema (10024558)	3 (0.341)	1 (0.208)	1.000 (Not Significant)	0 (0)	1.000 (Not Significant)
	Lip Pain (10024561)	3 (0.341)	5 (1.041)	0.216 (Not Significant)	0 (0)	1.000 (Not Significant)
	Lip Pruritus (10070721)	10 (1.137)	2 (0.416)	0.293 (Not Significant)	0 (0)	1.000 (Not Significant)
	Lip Swelling (10024570)	489 (55.601)	189 (39.336)	**<0.001 (Significant)**	0 (0)	**0.035 (Significant)**
	Lip Ulceration (10024572)	6 (0.682)	3 (0.624)	1.000 (Not Significant)	0 (0)	1.000 (Not Significant)
Palate-related AE[f]	Palatal Disorder (10052453)	1 (0.114)	0 (0)	1.000 (Not Significant)	0 (0)	1.000 (Not Significant)
	Palatal Swelling (10074403)	2 (0.227)	0 (0)	0.760 (Not Significant)	0 (0)	1.000 (Not Significant)
Other Sensory AE[g]	Burning Mouth Syndrome (10068065)	0 (0)	3 (0.624)	**0.044 (Significant)**	0 (0)	NA (NA)
	Oral Dysaesthesia (10050820)	1 (0.114)	0 (0)	1.000 (Not Significant)	0 (0)	1.000 (Not Significant)
	Anaesthesia Oral (10082548)	10 (1.137)	0 (0)	**0.045 (Significant)**	0 (0)	1.000 (Not Significant)
	Hypoaesthesia Oral (10057371)	143 (16.26)	2 (0.416)	**<0.001 (Significant)**	0 (0)	0.396 (Not Significant)
	Paraesthesia Oral (10057372)	729 (82.89)	293 (60.981)	**<0.001 (Significant)**	7 (72.614)	0.864 (Not Significant)
Oral Mucosa-related AE[h]	Aphthous Ulcer (10002959)	31 (3.525)	7 (1.457)	**0.044 (Significant)**	0 (0)	1.000 (Not Significant)
	Circumoral Oedema (10052250)	3 (0.341)	1 (0.208)	1.000 (Not Significant)	0 (0)	1.000 (Not Significant)
	Circumoral Swelling (10081703)	6 (0.682)	0 (0)	0.167 (Not Significant)	0 (0)	1.000 (Not Significant)

(*Continued*)

Table 4. (Continued).

Group	Preferred Term (MedDRA Code)	mRNA-based (*per 10,000 reports*)	Viral Vector (*per 10,000 reports*)	*Sig.* (mRNA vs. Viral Vector)	Protein Subunit (*per 10,000 reports*)	*Sig.* (mRNA vs. Protein Sub)
	Coating in Mouth (10075366)	2 (0.227)	0 (0)	0.760 (Not Significant)	0 (0)	1.000 (Not Significant)
	Mouth Swelling (10075203)	51 (5.799)	22 (4.579)	0.420 (Not Significant)	0 (0)	0.943 (Not Significant)
	Oedema Mouth (10030110)	0 (0)	1 (0.208)	0.759 (Not Significant)	0 (0)	NA (NA)
	Oral Blood Blister (10076590)	0 (0)	1 (0.208)	0.759 (Not Significant)	0 (0)	NA (NA)
	Oral Candidiasis (10030963)	19 (2.16)	10 (2.081)	1.000 (Not Significant)	0 (0)	1.000 (Not Significant)
	Oral Discomfort (10030973)	44 (5.003)	12 (2.498)	**0.042 (Significant)**	0 (0)	1.000 (Not Significant)
	Oral Disorder (10067621)	8 (0.91)	1 (0.208)	0.241 (Not Significant)	0 (0)	1.000 (Not Significant)
	Oral Herpes (10067152)	117 (13.303)	56 (11.655)	0.462 (Not Significant)	0 (0)	0.492 (Not Significant)
	Oral Lichen Planus (10030983)	2 (0.227)	1 (0.208)	1.000 (Not Significant)	0 (0)	1.000 (Not Significant)
	Oral Mucosal Blistering (10030995)	13 (1.478)	0 (0)	**0.018 (Significant)**	1 (10.373)	0.369 (Not Significant)
	Oral Mucosal Discolouration (10030996)	1 (0.114)	0 (0)	1.000 (Not Significant)	0 (0)	1.000 (Not Significant)
	Oral Mucosal Eruption (10030997)	2 (0.227)	1 (0.208)	1.000 (Not Significant)	1 (10.373)	**0.009 (Significant)**
	Oral Mucosal Exfoliation (10064487)	2 (0.227)	1 (0.208)	1.000 (Not Significant)	0 (0)	1.000 (Not Significant)
	Oral Pain (10031009)	34 (3.866)	20 (4.163)	0.904 (Not Significant)	0 (0)	1.000 (Not Significant)
	Oral Pruritus (10052894)	16 (1.819)	3 (0.624)	0.123 (Not Significant)	1 (10.373)	0.46 (Not Significant)
	Oral Pustule (10056674)	1 (0.114)	0 (0)	1.000 (Not Significant)	0 (0)	1.000 (Not Significant)
	Perioral Dermatitis (10034541)	3 (0.341)	2 (0.416)	1.000 (Not Significant)	0 (0)	1.000 (Not Significant)
	Stomatitis (10042128)	17 (1.933)	9 (1.873)	1.000 (Not Significant)	1 (10.373)	0.488 (Not Significant)
	Mouth Ulceration (10028034)	172 (19.557)	88 (18.315)	0.663 (Not Significant)	2 (20.747)	1.000 (Not Significant)
	Oral Papule (10031010)	1 (0.114)	0 (0)	1.000 (Not Significant)	0 (0)	1.000 (Not Significant)

Chi-squared test (χ^2) and Fisher's exact test were used with a significance level *Sig.* ≤ 0.05.

[a]Hypoaesthesia Teeth (10051780) and Sensitivity of Teeth (10040012) had no reports in mRNA, viral vector or protein subunit groups.

[b]Hypergeusia (10029205) had no reports in mRNA, viral vector or protein subunit groups.

[c]Saliva Discolouration (10049069), Salivary Duct Stenosis (10039388), Salivary Gland Calculus (10039394), Salivary Gland Mass (10057002), Salivary Duct Inflammation (10056681) and Salivary Gland Induration (10071363) had no reports in mRNA, viral vector or protein subunit groups.

[d]Atrophic Glossitis (10069085), Macroglossia (10025391), Stiff Tongue (10081491), Tongue Coated (10043945), Tongue Exfoliation (10064488), Tongue Fungal Infection (10075845), Tongue Induration (10084548), Tongue Pigmentation (10069164), Acquired Macroglossia (10058835), Atrophic Glossitis (10003712), Strawberry Tongue (10051495), Tongue Eruption (10052002) and Tongue Black Hairy (10043941) had no reports in mRNA, viral vector or protein subunit groups.

[e]Angular Cheilitis (10002509), Lip Scab (10082767) and Lip Erosion (10051992) had no reports in mRNA, viral vector or protein subunit groups.

[f]Palatal Oedema (10056998), Palatal Ulcer (10077519) and Palatal Palsy (10072012) had no reports in mRNA, viral vector or protein subunit groups.

[g]Burn Oral Cavity (10075532) had no reports in mRNA, viral vector or protein subunit groups.

[h]Leukoplakia Oral (10024396, Oral Fungal Infection (10061324), Oral Lichenoid Reaction (10083833), Oral Mucosa Erosion (10064594), Oral Mucosal Erythema (10067418), Oral Mucosal Roughening (10084009), Oral Pigmentation (10077552), Oral Purpura (10083533), Oral Viral Infection (10065234), Oropharyngeal Blistering (10067950), Oropharyngeal Plaque (10067721), Aphthous Stomatitis (10002958), Buccal Mucosal Roughening (10048479), Mouth Plaque (10028032), Oral Soft Tissue Disorder (10061326), Oral Mucosal Hypertrophy (10062956), Oral Mucosal Petechiae (10030998), and Oral Mucosal Scab (10082769) had no reports in mRNA, viral vector or protein subunit groups.

pronounced when juxtaposed with the minimal adverse reactions associated with influenza vaccines.[33]

The mRNA-based vaccines were the most administered in Australia,[34] Europe,[35] and the United States;[36] therefore, their AEs were expected to be the most frequently reported. In our analysis, Comirnaty was associated with the highest number of reported AEs. Moreover, Comrinaty had a higher frequency of oral paresthesia (87.5 *vs*. 32.7 cases per 10,000 reports; *Sig*. <0.001) and oral hypoaesthesia (17.7 *vs*. 0; *Sig*. = 0.001) than Spikevax. In the American VAERS, Comirnaty had a higher reported incidence of all most common oral AEs, except for oral herpes and oral pain.[23] According to Shimabukuro et al. 2021, the reported incidence of anaphylactic AEs following Comirnaty was 4.7 cases per million vaccine doses, while Spikevax had only 2.5 cases per million vaccine doses.[37] Bell's palsy, myocarditis/pericarditis and lymphadenopathy were significantly more common after Comirnaty than Spikevax.[38] Contrarily, a contemporary analysis of American VAERS revealed that the reported incidence of common (31.3 *vs*. 15.2 cases per 100,000 vaccine doses) and severe (1 *vs*. 0.8) AEs was higher in Spikevax than Comirnaty.[38] Lassanova et al. 2023 analyzed the AEs received by the Slovak State Institute for Drug Control (SIDC) between January and May 2021 and found that there was no significant difference between Spikevax and Comirnaty in serious AEs.[39]

In the comparison between mRNA-based and viral vector vaccines, we found that dysgeusia (81.6 *vs*. 57.9 cases per 10,000 reports; *Sig*. <0.001), swollen tongue (60 *vs*. 36; *Sig*. <0.001), lip swelling (55.6 *vs*. 39.3; *Sig*. <0.001), oral paresthesia (82.9 *vs*. 61; *Sig*. <0.001), and oral hypoaesthesia (16.3 *vs*. 0.4; *Sig*. <0.001) were more significantly common after mRNA-based vaccines. In line with these findings, mRNA-based vaccines had a significantly higher frequency of swollen tongue (59.6 *vs*. 44.7; *Sig*. <0.001), lip swelling (70.6 *vs*. 52.5; *Sig*. <0.001) and oral paresthesia (83.8 *vs*. 58.2; *Sig*. <0.001) according to the American VAERS.[23] Additionally, oral paresthesia, oral hypoesthesia, and swollen tongue were significantly more frequent after mRNA-based than viral vector vaccines, according to the European EudraVigilance.[24] While viral vector vaccines had fewer inflammation-related AEs, they had a higher reported incidence of coagulation disorders.[38] Klugar et al. found that local AEs were more associated with mRNA-based vaccines, as reported by German healthcare workers, while systemic AEs were more common in the viral vector vaccine group.[40]

Table 5. Top 10 oral adverse events of COVID-19 vaccines reported until December 31st, 2022, stratified by sex (database of adverse event notifications "DAEN").

	Comirnaty (*per 10,000 reports*)			Spikevax (*per 10,000 reports*)		
Preferred Term (MedDRA Code)	Female	Male	*Sig.*	Female	Male	*Sig.*
Paraesthesia Oral (10057372)	589 (111.063)	86 (33.961)	**<0.001 (Significant)**	22 (46.044)	2 (8.177)	**0.015 (Significant)**
Dysgeusia (10013911)	519 (97.864)	129 (50.942)	**<0.001 (Significant)**	43 (89.996)	9 (36.795)	**0.017 (Significant)**
Swollen Tongue (10042727)	392 (73.916)	79 (31.197)	**<0.001 (Significant)**	31 (64.881)	12 (49.06)	0.506 (Not Significant)
Lip Swelling (10024570)	347 (65.431)	95 (37.515)	**<0.001 (Significant)**	24 (50.23)	9 (36.795)	0.537 (Not Significant)
Taste Disorder (10082490)	166 (31.301)	45 (17.77)	**0.001 (Significant)**	25 (52.323)	5 (20.442)	0.072 (Not Significant)
Ageusia (10001480)	123 (23.193)	53 (20.93)	0.586 (Not Significant)	15 (31.394)	6 (24.53)	0.778 (Not Significant)
Dry Mouth (10013781)	155 (29.227)	37 (14.611)	**<0.001 (Significant)**	13 (27.208)	4 (16.353)	0.519 (Not Significant)
Mouth Ulceration (10028034)	107 (20.176)	38 (15.006)	0.137 (Not Significant)	19 (39.766)	1 (4.088)	**0.013 (Significant)**
Hypoaesthesia Oral (10057371)	106 (19.988)	32 (12.637)	**0.028 (Significant)**	0 (0)	0 (0)	NA (NA)
Oral Herpes (10067152)	85 (16.028)	22 (8.688)	**0.012 (Significant)**	9 (18.836)	1 (4.088)	0.207 (Not Significant)
	Vaxzevria (*per 10,000 reports*)			Novavax (*per 10,000 reports*)		
	Female	Male	*Sig.*	Female	Male	*Sig.*
Paraesthesia Oral (10057372)	247 (80.26)	38 (24.144)	**<0.001 (Significant)**	5 (79.872)	1 (31.153)	0.670 (Not Significant)
Dysgeusia (10013911)	207 (67.262)	63 (40.028)	**<0.001 (Significant)**	12 (191.693)	4 (124.611)	0.560 (Not Significant)
Swollen Tongue (10042727)	129 (41.917)	40 (25.415)	**0.007 (Significant)**	0 (0)	0 (0)	NA (NA)
Lip Swelling (10024570)	130 (42.242)	52 (33.039)	0.154 (Not Significant)	0 (0)	0 (0)	NA (NA)
Taste Disorder (10082490)	118 (38.343)	27 (17.155)	**<0.001 (Significant)**	1 (15.974)	3 (93.458)	0.116 (Not Significant)
Ageusia (10001480)	95 (30.869)	48 (30.497)	1.000 (Not Significant)	3 (47.923)	0 (0)	0.555 (Not Significant)
Dry Mouth (10013781)	73 (23.721)	35 (22.238)	0.832 (Not Significant)	2 (31.949)	1 (31.153)	1.000 (Not Significant)
Mouth Ulceration (10028034)	65 (21.121)	21 (13.343)	0.083 (Not Significant)	2 (31.949)	0 (0)	0.551 (Not Significant)
Hypoaesthesia Oral (10057371)	2 (0.65)	0 (0)	0.792 (Not Significant)	0 (0)	0 (0)	NA (NA)
Oral Herpes (10067152)	43 (13.972)	12 (7.624)	0.081 (Not Significant)	0 (0)	0 (0)	NA (NA)
	Total (*per 10,000 reports*)					
	Female	Male	*Sig.*			
Paraesthesia Oral (10057372)	863 (96.736)	127 (28.976)	**<0.001 (Significant)**			
Dysgeusia (10013911)	781 (87.544)	205 (46.773)	**<0.001 (Significant)**			
Swollen Tongue (10042727)	552 (61.875)	131 (29.889)	**<0.001 (Significant)**			
Lip Swelling (10024570)	501 (56.158)	156 (35.593)	**<0.001 (Significant)**			
Taste Disorder (10082490)	310 (34.749)	80 (18.253)	**<0.001 (Significant)**			
Ageusia (10001480)	236 (26.454)	107 (24.413)	0.527 (Not Significant)			
Dry Mouth (10013781)	243 (27.238)	77 (17.568)	**0.001 (Significant)**			
Mouth Ulceration (10028034)	193 (21.634)	60 (13.69)	**0.002 (Significant)**			
Hypoaesthesia Oral (10057371)	108 (12.106)	32 (7.301)	**0.014 (Significant)**			
Oral Herpes (10067152)	137 (15.357)	35 (7.986)	**0.001 (Significant)**			

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

Table 6. Top 10 Oral adverse events of COVID-19 vaccines reported until December 31st, 2022, stratified by age group (database of adverse event notifications "DAEN").

Preferred Term (MedDRA Code)	Pediatric Group (0–17 years old)	Adult Group (18–64 years old)	Senior Group (> 64 years old)
Paraesthesia Oral (10057372)	11 (19.288)	845 (96.045)	117 (55.664)
Dysgeusia (10013911)	7 (12.274)	819 (93.089)	98 (46.624)
Swollen Tongue (10042727)	19 (33.316)	537 (61.037)	82 (39.012)
Lip Swelling (10024570)	34 (59.618)	507 (57.627)	71 (33.779)
Taste Disorder (10082490)	7 (12.274)	287 (32.621)	57 (27.118)
Ageusia (10001480)	2 (3.507)	252 (28.643)	59 (28.070)
Dry Mouth (10013781)	5 (8.767)	253 (28.757)	57 (27.118)
Mouth Ulceration (10028034)	7 (12.274)	183 (2.800)	35 (16.652)
Hypoaesthesia Oral (10057371)	2 (3.507)	130 (14.776)	3 (1.427)
Oral Herpes (10067152)	6 (1.521)	115 (13.0712)	25 (11.894)

Females had a higher reported incidence of oral AEs compared to males in our study, including oral paresthesia (96.7 *vs.* 29; *Sig.* <0.001), dysgeusia (87.5 *vs.* 46.8; *Sig.* <0.001), swollen tongue (61.8 *vs.* 29.9; *Sig.* <0.001), lip swelling (56.2 *vs.* 35.6; *Sig.* <0.001), and taste disorder (34.8 *vs.* 18.3; *Sig.* <0.001). The American VAERS analysis revealed that all the top 20 oral AEs were more significantly common among females, except for ageusia.[23] Similarly, the European EudraVigilance analysis demonstrated increased females' susceptibility for oral AEs in all top 20 AEs except for salivary hypersecretion.[24] Active surveillance studies for short-term AEs of COVID-19 vaccines confirmed the females' susceptibility across various population groups, e.g. Czech,[20] Slovak,[21] Turkish,[41] and German healthcare workers.[40] One of the hypotheses to explain the increased frequency and intensity of post-vaccination AEs among females is related to the simultaneous production of type-I interferon (INF-I) during the early stages of the immune response.[42]

Oral herpes was reported 174 times after COVID-19 vaccination (12.7 cases per 10,000 reports) in Australia, which was significantly (*Sig.* <0.001) higher than influenza vaccination (2.6). There was no significant difference between Comirnaty and Spikevax (13.3 *vs.* 13.6; *Sig.* = 1.000) or between mRNA-based and viral vector vaccines (13.3 *vs.* 11.7; *Sig.* = 0.462). Females had a significantly higher prevalence of oral herpes than males (15.4 *vs.* 8; *Sig.* = 0.001). The same findings were reported in the American VAERS, where COVID-19 *vs.* seasonal influenza vaccination was (18.9 *vs.* 8.6; *Sig.* = 0.050), Comirnaty *vs.* Spikevax (17.9 *vs.* 17.9; *Sig.* = 0.977), mRNA-based *vs.* viral vector vaccines (17.9 *vs.* 18.5; *Sig.* = 0.702), and females *vs.* males (22.4 *vs.* 8.8; *Sig.* <0.001).[23]

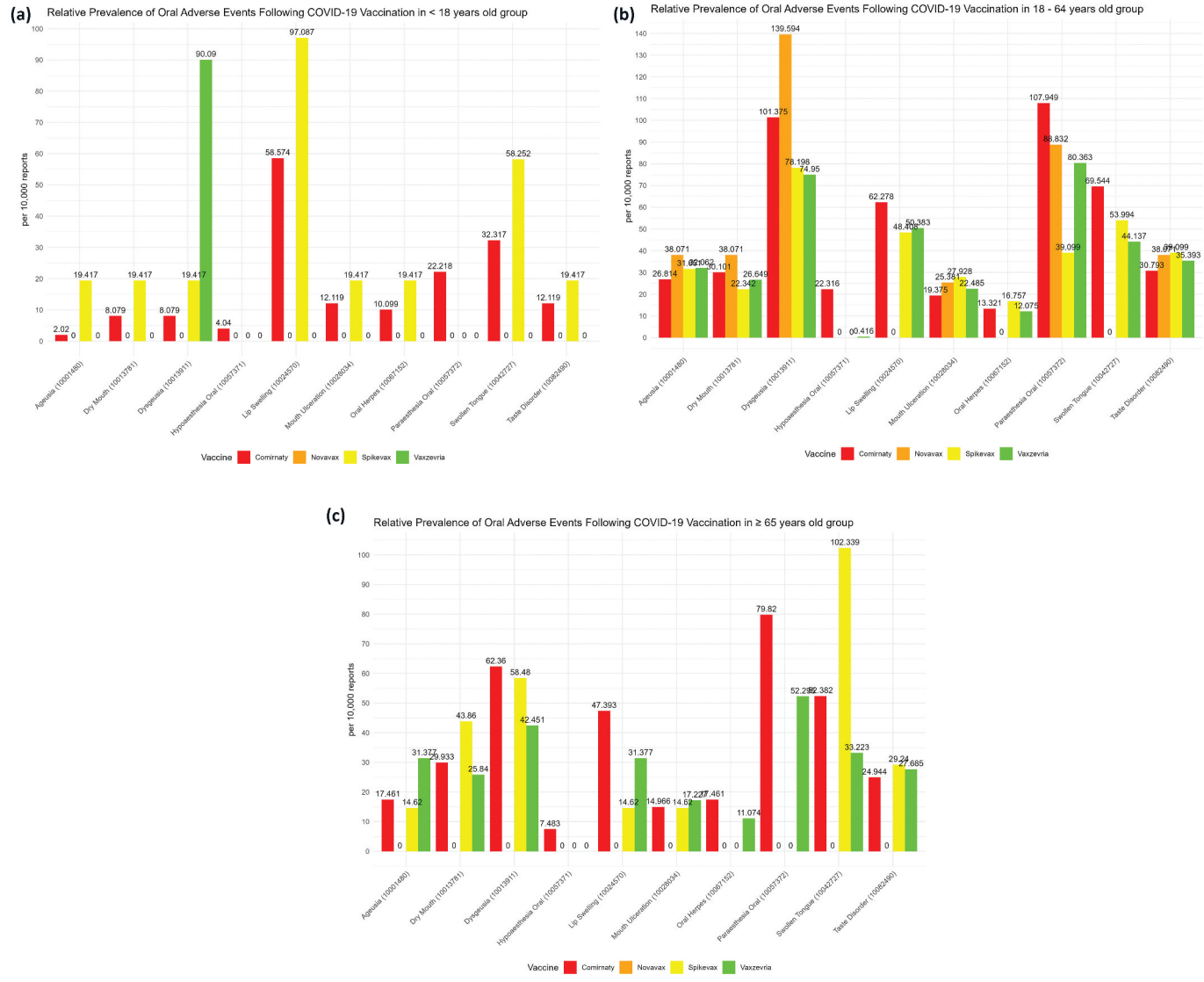

Figure 1. Top 10 oral adverse events of COVID-19 vaccines reported until December 31st, 2022, stratified by age group (database of adverse event notifications "DAEN").

Table 7. Top 10 oral adverse events of COVID-19 vaccines reported in Australia, Europe, and the United States (2020–2022).

Rank	Australia: DAEN (no. of cases per 10,000 reports)	Europe: EudraVigilance (no. of cases per 10,000 reports)	United States: VAERS (no. of cases per 10,000 reports)
First	Oral Paraesthesia (75.3)	Dysgeusia (38.1)	Oral Paraesthesia (87.2)
Second	Dysgeusia (74)	Oral Paraesthesia (31.5)	Lip Swelling (84.4)
Third	Swollen Tongue (51.6)	Ageusia (29.6)	Ageusia (72.2)
Fourth	Lip Swelling (49.4)	Lip Swelling (24.3)	Oral Hypoesthesia (64.8)
Fifth	Taste Disorder (27.3)	Dry Mouth (21.5)	Swollen Tongue (62.8)
Sixth	Ageusia (25.9)	Oral Hypoesthesia (21)	Dysgeusia (61.7)
Seventh	Dry Mouth (24.8)	Swollen Tongue (2.7)	Taste Disorder (31.7)
Eighth	Mouth Ulceration (19)	Taste Disorder (17.3)	Dry Mouth (3.1)
Nineth	Oral Hypoaesthesia (15.6)	Toothache (1.4)	Oral Herpes (18.9)
Tenth	Oral Herpes (12.7)	Mouth Ulceration (6.1)	Toothache (14.2)

Oral herpes zoster was reported after several vaccines, including rabies, Japanese encephalitis, and hepatitis A vaccines, due to activation of the varicella-zoster virus (VZV), which is latent in the spinal dorsal root ganglia and trigeminal ganglia.[43] Brosh-Nissimov et al. 2021 compared the herpesviruses oral shedding before COVID-19 vaccination versus one week after vaccination.[44] However, their results were negative; the study had several methodological limitations that can not rule out the hypothesis of vaccine-induced VZV

reactivation.[44] One of the limitations of Brosh-Nissimov et al. 2021 work was the investigation interval which was 7 days post-vaccination, despite the fact that latency of VZV can range between 1 and 24 days.[45] Given the consistency of increased oral herpes incidence following COVID-19 than influenza vaccination in both Australian and American population-wide databases, the self-controlled cases series methodology is strongly suggested to resolve the questionable causality between COVID-19 vaccination and VZV reactivation.[46]

Strengths

Replacing the MedDRA framework with the oral AEs anatomo-physiological scheme of Riad et al. was found to be effective for managing a substantial volume of disorganized data and excluding symptoms not related to vaccination that could appear as post-vaccine effects.[23] By adopting the methodology of two previous studies on American VAERS and European EudraVigilance, this study amassed a vast amount of population-wide data on oral AEs of COVID-19 vaccines, enriching the scope for comparison across populations.[23,24] Utilizing a national database like DAEN, which is systematically categorized according to vaccine type, sex, and age group, facilitated sub-group analysis which is beneficial for clinical practitioners.

Limitations

This study is subject to inherent limitations, predominantly originating from the constraints of passive surveillance systems, including reporting biases. Underreporting may be an issue as the denominator for this analysis is the number of AEs reports, not the number of vaccine doses administered. Overreporting, particularly for taste disorders, could also distort results, given the increased public awareness of COVID-19 symptoms. Selective reporting by physicians and patients could further introduce bias. Consequently, the incidence rates of oral AEs should be regarded as indicative rather than definitive. The accuracy of reporting is largely dependent on the reporter's knowledge, skills, and situational context. Furthermore, the study offers a limited set of factors for sub-group analysis, such as sex and age group, despite the considerable influence of other demographic and anamnestic risk factors in post-vaccination AEs.

Implications

This study highlights the overlooked, yet critical area of non-serious AEs following COVID-19 vaccination. These AEs, although minor, can be exploited by anti-vaccination campaigns to erode public trust. Our findings, consistent across Australian, European, and American populations, underline the need for detailed investigations into certain oral AEs such as oral herpes. On the other hand, the extremely low incidence of some oral AEs, coupled with their resemblance between COVID-19 and seasonal influenza vaccinations, undermines the possibility of being causally linked to the COVID-19 vaccine and the need for subsequent research.

Conclusion

This study underscores the largely similar oral AEs following COVID-19 and influenza vaccinations; however, taste-related AEs, dry mouth and oral herpes were significantly more common after COVID-19 vaccination. Females and mRNA-based vaccines, especially Comirnaty, were associated with a higher incidence of oral AEs than males and viral vector vaccines, respectively. Future studies should prioritize understanding the cause-effect relationship for prevalent oral AEs such as oral herpes and examine the factors leading to higher susceptibility among females.

Author contributions

Conceptualization, AR; methodology, AR and SA; validation, AR and JI; formal analysis, AR; investigation, JI; writing – original draft preparation, AR; writing – review and editing, JI, SA, LD, and MK; supervision, MK; project administration, AR; funding acquisition, SA and LD. All authors have read and agreed to the published version of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data that support the findings of this study are available at: https://apps.tga.gov.au/PROD/DAEN/daen-entry.aspx.

Institutional review board statement

This study does not require ethical approval because no primary data was collected or analyzed.

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