

**A systematic review on oral complications in children following covid-19 infection**

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**Type of Publication:** Systematic Review

**Conflicts of Interest:** Nil

**Abstract**

**Background:** Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by a virus named SARS-CoV-2. Pediatric population affected with Covid-19 experience milder systemic symptoms due to increased expression of ACE-2 receptor that is required for viral binding. However, literature suggests that several kinds of intraoral lesions were a common finding in children which were non-specific and discrete.

**Purpose:** Covid-19 showed high Prevalence in children. Children who had covid-19 infection showed very mild symptoms. Most of the affected children had oral

manifestation of high degree. The purpose of this systematic review was to explore and document oral manifestations seen in children affected by covid-19.

**Methods:** Literature search was conducted on PubMed, EBSCO, Scopus, Embase and Google Scholar databases between 2019 to 2022 including the grey literature available. Initial search yielded 505 articles, after the application of predetermined eligibility criteria, title abstract screening, and removal of duplicates, 8 studies were selected for analysis. PRISMA guidelines were followed.

**Results:** Oral manifestation seen in children were ulcers, blisters, geographic tongue, oral pseudomembranous candidiasis, coated tongue, hyperaemic pharynx, taste alteration, xerostomia, anosmia, mucormycosis, aspergillosis, vesiculobullous lesions, oral ulcers. Among oral finding in affected children most commonly seen were ulcers (37.5%) followed by altered taste (25%) and mucormycosis. Other lesions like vesiculobullous lesions, blisters, geographic tongue etc. accounted about (1-5%).

**Conclusion:** COVID-19 in children, was observed to be associated with non-specific oral and cutaneous manifestations.

**Keywords:** Children, COVID-19, oral lesion, oral mucosa, taste.

### **Introduction**

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by a virus named SARS-CoV-2 (severe acute respiratory syndrome corona virus-2)<sup>1</sup>. The COVID-19 epidemic was first reported in December 2019 in Wuhan<sup>2</sup>.

The present Severe Acute Respiratory Syndrome Coronavirus-2 pandemic is a public health issue of global concern (SARS-CoV-2)<sup>2</sup>. It was the third coronavirus to affect human population and was preceded by the severe acute respiratory syndrome coronavirus (SARS-CoV) outbreak In 2002, Middle East Respiratory Syndrome 2012 had a coronavirus outbreak (MERS-CoV)<sup>3,4</sup>.

Although the prevalence of COVID-19 in children is diminished as expression of the ACE-2 receptor, which is required for viral binding but children at all age groups appeared susceptible to COVID-19, and there was no significant gender difference<sup>5</sup>. Also, clinical manifestations of COVID-19 in pediatric patients were

generally less severe than that in adults, young children, particularly infants, were vulnerable to infection<sup>6</sup>.

Precisely during the COVID-19 outbreak children who had COVID-19 infection frequently showed very mild symptoms, which had raised concerns about the virus's potential hidden role in transmission. How children spread the disease had been a major concern ever since the outbreak started. They may be blamed for it because of their humorous and conversational personality. According to the evidence, yelling and loud speech may cause the virus to spread through droplets. Similar to this, children frequently touch their faces, noses, and mouth when playing that may lead to transmission.<sup>7</sup>

The most common symptoms seen in children include runny nose and nasal congestion, anosmia, dysgeusia or hypogeusia, diarrhoea, nausea/vomiting, respiratory distress, fatigue, ocular symptoms and abdominal pain<sup>8</sup>. These systemic conditions are often accompanied by skin and mucosal lesions.

The intraoral findings in a child affected by the disease are usually non-specific which can be attributed to the mild form of COVID-19. Martin et al. (2020)<sup>9</sup> presented a case series on oral manifestations as ulcers and blisters in patients affected or suspected of the disease.

The oral cavity is recognised for harbouring a variety of respiratory viruses due to its abundance in saliva and the oral microbiota<sup>10</sup>. It has been discovered that saliva has a high viral output, pointing to the salivary glands being the virus active replicating locations. Furthermore, the malfunction of the salivary glands linked to COVID-19 might cause xerostomia and taste loss<sup>11</sup>.

### **Materials and methods**

**Study design and setting:** The present study is a systematic review that was prepared according to the Preferred Reporting Items for Systematic Reviews (PRISMA) statement.

**Eligibility criteria:** PICO outline was followed.

**Inclusion criteria:** All articles published as case studies, case series, cohorts or observational studies from December 2019 to 31<sup>st</sup> JULY 2022 using specific keywords in English that dealt with characteristics of COVID-19 infection in children. (TABLE 1)

**Exclusion criteria:** Articles published as letter to editor, or commentary. (Table 1)

### **Search strategy and protocol**

In this systematic review, a comprehensive search was conducted on medical databases including Cochrane Library, Embase, Pubmed, Google scholar using English including COVID-19, children, newborn, child, neonate, infant, adolescent, Corona virus 2019, 2019-CoV, SARS-CoV-2 using Boolean Logics including AND, OR, NOT.

#### **Search#1**

“Child” or “children “or “paediatric patients” or “paediatric patients” or “preschool” or “infant” or “toddler” or “pedo”

#### **Search#2**

“Covid-19” or “sars-cov-2” or “coronavirus” or “pandemic” or “corona” or “post covid” or “global pandemic”

#### **Search #3**

“Viral diseases” or “oral symptoms” or “oral complications” or “intraoral infections” or “oral lesions” or “oral manifestations” or “periodontal disease” or “oral conditions” or “herpex simplex” or “candidiasis” or “geographic tongue” or “aphthous-like ulcers” or “hemorrhagic ulcerations” or “necrotic ulcerations” or “reddish macules” or “petechiae” or “parotitis” or “dental pain” or “strawberry tongue” or “oral changes” or “oropharyngeal changes” or “ulcers” or “erosion” or “bullae” or “vesicles” or “pustule” or “fissured tongue” or “depapillated tongue” or “macule” or “papule” or “plaque” or “pigmentation” or “halitosis” or

“haemorrhagic crusts “ or “necrosis” or “petechiae” or “swelling” or “erythema” or “spontaneous bleeding”

#### **Search #4**

#1 and #2 and #3

### **Results**

#### **Study selection**

Initial search using these keywords yielded 505 articles that were assessed. After reviewing the titles and excluding duplicates, 36 relevant full-text articles remained. 28 of 36 articles were excluded due to lack of relevance to the purpose of the study, letter to editor or commentary. Finally, 8 full-text articles were included.

#### **Study characteristics**

The included articles studied children in the age group of 0-15 years. The characteristics of the 8 included studies in this systematic review are studied in detail and tabulated (Table 2). Among these articles 3 were systematic reviews, 2 were review articles, 2 were retrospective studies and 1 literature review. Children with COVID-19 showed non-specific or minimal symptoms or manifested oral lesions as part of multi-system disorders. This systematic review analyzed variables corresponding to the “lesion location,” “mean time to lesion’s manifestation”, “lesion mean duration” , “mean age of patients” and “patients’ gender” of each COVID-19 paediatrics oral manifestations. Oral manifestation seen in children were ulcers, blisters, geographic tongue, oral pseudomembranous candidiasis, coated tongue, hyperaemic pharynx, taste alteration, loss of taste, xerostomia, anosmia, Mucor mycosis, aspergillosis, vesiculobullous lesions, oral ulcers. Ulcers and alteration in taste accounted 37.5%, Oral candidiasis and geographic tongue was almost 25%, Xerostomia and Vesciculobullous lesions 10%, and other oral lesion accounted in the range of 1% to 5% in the children suffering from covid.

## Discussion

The present study surveyed the published literature on the clinical characteristics of COVID-19 in infants and children with emphasis on oral manifestations in the oral cavity. A literature review of studies demonstrated that children with COVID-19 can be completely asymptomatic or have mild to moderate symptoms that can result in not being diagnosed.

Lack of oral hygiene, opportunistic infections, stress, immune-suppression, vasculitis, and hyper-inflammatory response secondary to COVID-19 are the most important predisposing factors for onset of oral lesions in COVID-19 patients. Some other forms of lesions, such as lesions on the tongue, palate, and commissure were consistent with pseudo-membranous candidiasis and angular cheilitis.<sup>15</sup> With a frequency of 45%, gustatory or taste impairment was the most prevalent oral symptom. Oral mucosal lesions displayed a variety of clinical features, including erythematous and white plaques, petechiae, irregular ulcers, tiny blisters, and desquamative gingivitis<sup>15</sup>. The afflicted areas included were the lips, gingiva, and buccal mucosa. In mild cases, oral mucosal lesions appeared prior to or concurrently with the beginning of the first respiratory symptoms. However, in patients who needed treatment and hospitalisation, the lesions appeared seven to 24 days after the onset of symptoms<sup>15</sup>.

Recent studies demonstrated that the receptor angiotensin-converting enzyme 2 (ACE2) through which the coronavirus enters human cells. The study determined that vital organs, such as the lungs, are susceptible to infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)<sup>15</sup>. Therefore, cells with a high distribution of ACE2 receptors can act as host cells for the virus and trigger an inflammatory response in tissues and organs nearby, such as the

tongue mucosa and salivary glands<sup>15</sup>. Most common oral finding seen during COVID-19 infection was loss of taste sensation. One possible reason for this condition could be the interaction of SARS-CoV-2 with ACE2 receptors which may potentially reduce taste bud sensitivity and results in abnormal gustatory responses.

**Koticha PB et al. (2020)<sup>16</sup>** reviewed an article by **Martin et al. (2020)<sup>9</sup>** that presented a case series on oral manifestations as **ulcers and blisters** in patients affected or suspected of the disease. Three cases (two suspected and one confirmed) of patients with ulcers in the oral cavity was presented. It concluded that oral manifestations developed during the lock-down period between the last week of March and the first week of April 2020, and consisted of **pain, desquamative gingivitis, ulcers and blisters**. It also stated that there is no literature yet available that stated the intraoral findings in a COVID positive child and paediatric dentists should be vigilant while examining COVID positive children due to the paucity in information. It also addresses the treatment of COVID-19 in children with symptoms.

In a meta-analysis of 551 laboratory-confirmed cases **Zhang L et al. (2020)<sup>17</sup>** reviewed forty-six articles reporting in children (aged 1 day-17.5 years). The most common symptoms and signs were **fever, cough, and sore throat or pharyngeal erythema**. The less common symptoms and signs included tachypnea/dyspnea, nasal symptoms, diarrhea, vomiting, fatigue/weakness, and headache. All patients received symptomatic treatment.

**Bardellini E et al. (2021)<sup>18</sup>** conducted a retrospective study to analyse the prevalence and characteristics of oral and cutaneous lesions in 27 children age ranged from 3 months to 14 years of age showing a COVID-19 positive family history. The majority of the patients

displayed a body temperature over 38°C. Ten out of twenty-seven patients had febrile symptoms. Although difficulty in breathing was occasionally noted, the majority of the first clinical symptoms reported were cough and rhinorrhea. However, all patient's oxygen saturation levels consistently remained above 92 percent. Oral pseudomembranous candidiasis (7.4%), geographic tongue (3.7%), coated tongue (7.4%), and hyperaemic pharynx (37%) were the oral lesions that were noted. Three patients noticed taste changes (11.1%). Mucormycetes is what causes the deadly fungus known as mucormycosis also called as oral pseudomembranous candidiasis, which affects those with compromised immune systems. Children with COVID-19 had lumps, ulcers, edema, and tongue irritation. The top of the tongue in COVID patients was seen to be white and patchy or red and puffy. They had sores, tumours, or open spots on their tongue. Numerous COVID tongue patients also mention taste loss and a burning sensation in their mouth. There were cutaneous flat papular lesions in six cases (22.2%). In paediatric sample, six children presented cutaneous lesions i.e. non-itchy confluent flat papular lesions of the face and limbs, without any associated lesions in the inner part of the oral cavity. Based on results, it was speculated that there are no specific oral manifestations in children during a COVID-19 infection. It is instead possible to find lesions consistent with those typically found during a common influenza virus infection.

In a literature review conducted by **Moraes MF et al. (2021)**<sup>19</sup> cutaneous manifestations and taste disorders were found to be associated to COVID-19. It was identified that 17 patients under the age of 18 years showed oral manifestations, such as erythema and edema on the tongue, lips, oral mucosa, lingual papillae, and cleft lip. Gustatory dysfunction may be a patient's first

sign of COVID-19. Evidence from a previous study in SARS-CoV revealed that the cerebral Smell and taste dysfunctions in COVID-19 involvement of the virus might happen during the early and late phase of infection. Moreover, the impaired cranial nerves (VII, IX, X), gustatory system (N. glossopharyngeus, N. facialis, and N. vagus) and receptors cease the taste transportation and lead to gustatory dysfunction. Dysgeusia and ageusia were commonly seen in asymptomatic COVID-19 patients. It was seen that Kawasaki Disease was identified simultaneously or shortly after confirmation of Covid-19. It emphasized that the paediatric dentists involved in the screening procedure should guide patients if they notice any changes in the oral health.

Halepas S et al. (2021)<sup>20</sup> conducted a cross-sectional study of all patients with COVID-19 with multisystem inflammatory syndrome in children (MIS-C) hospitalized at the Morgan Stanley Children's Hospital of NewYork-Presbyterian (MSCHONY) in New York, from March 15 to June 1, 2020. All patients with mean age of 9, had a documented fever of prolonged duration, had inflammation, required hospitalization, had multi-organ involvement, and had a confirmed positive COVID RT-PCR or serology test results. Both the sexes were affected equally (51.1% male, 48.9% female). Many patients also experienced nonspecific constitutional symptoms such as diarrhea, vomiting, cough, irritability or rhinorrhea. Twenty-three patients had red or swollen lips, but only five had strawberry tongue. Strawberry tongue describes a hyperplastic appearance of the fungiform papilla set against either a white (white strawberry tongue) or erythematous (red strawberry tongue) background. Three patients had reported blisters or sores in their mouths. Overall, oral or oro-pharyngeal findings were identified in more than

one-half (55.3%) of patients. They also reported that a cursory examination in a small child could easily go undetected.

In a review article conducted by Bhattacharyya SG et al. (2021)<sup>21</sup> that aimed to investigate the oral and cutaneous manifestations in children stated that Oral manifestations of COVID-19 include ulcers, erosion, bullae, vesicles, pustule, fissured or depapillated tongue, macule, papule, plaque, pigmentation, halitosis, whitish areas, haemorrhagic crusts, necrosis, petechiae, swelling, erythema, and spontaneous bleeding. The most common sites of involvement in descending order are tongue (about 38%), labial mucosa (about 26%), and palate (about 22%). Oral lesions are nearly equally found in both genders (49% female and 51% male). Lack of oral hygiene, opportunistic infections, stress, immunosuppression, vasculitis, and hyper-inflammatory response secondary to COVID-19 are the most important predisposing factors for onset of oral lesions in COVID-19 patients. Other types of lesions are also found, like lesions on the tongue, palate, and commissure compatible with pseudomembranous candidiasis and angular cheilitis. In another study the literature stated that, gustatory or taste impairment was the most common oral manifestation, with a prevalence of 45%.<sup>22</sup> The pooled eligible data in this study, for different taste disorders were 38% for dysgeusia and 35% for hypogeusia, while ageusia had a prevalence of 24%. Oral mucosal lesions presented multiple clinical aspects, including white and erythematous plaques, irregular ulcers, small blisters, petechiae, and desquamative gingivitis. Tongue, palate, lips, gingiva, and buccal mucosa were affected. In mild cases, oral mucosal lesions developed before or at the same time as the initial respiratory symptoms; however, in those who required medication and hospitalization, the lesions

developed approximately seven to 24 days after onset of symptoms. Other lesions like irregular ulcers are also sometimes observed on dorsum of tongue in some patients commonly seen in vasculitis that occurs in COVID-19 infection.

In view of the rising documented cases of oral lesions of COVID-19, **Sharma P et al. (2022)**<sup>22</sup> conducted a systematic review aimed to assess the prevalence of oral manifestations in COVID-19 confirmed individuals. In a two-phase selection, 34 studies were included: 21 observational, 3 case-series and 10 case reports. These observational studies included approximately 14,003 patients from 10 countries and explored the most commonly oral and dental manifestations in COVID-19 and reported the loss of taste acuity, xerostomia and anosmia. **Olfactory and gustatory disorders** were found to be closely associated and were the most commonly reported oral manifestations, followed by vesiculo-bullous lesions and oral ulcers. **Oral pseudo-membranous candidiasis** was the most frequently observed oral presentation, followed by **geographic tongue and taste alteration**, in 27 COVID-19 positive children in a retrospective study conducted in Italy. These included primary manifestations probably caused directly by SARS-CoV-2 and secondary manifestations caused as a sequelae and treatment of COVID-19 infection. Infection like oral ulcers, angina bullosa hemorrhagica, burning mouth, erythematous macules, plaque-like changes in the tongue, masticatory muscle pain, acute infectious parotitis and secondary manifestations like facial palsy, enanthema resembling petechiae without erythema, Melkersson-Rosenthal syndrome, Bell's palsy, parotitis, Guillain-Barre syndrome, secondary herpetic gingivostomatitis, macroglossia, and trigeminal neuralgia. Pasquini NR et al. (2022)<sup>23</sup> conducted a systemic review in which 35

articles were selected for review, totalizing 369 patients. The most common COVID-19 cutaneous manifestations in children and adolescents were Chilblain-like lesions, presented in 67.5% of the cases, followed by erythema multiforme-like (31.7%) and varicella-like lesions (0.8%). The Chilblain-like lesions appeared 7.6 days (95%) after the viral infection and lasted for 17.5 days (95%), erythema multiforme like lesions appeared in 9.5 days and lasted for 10.3 days and varicella-like lesions appeared in 12.3 days and lasted for 7 days. The authors emphasize the importance of paediatric careful evaluation on cutaneous and oral manifestations as a possible first sign of COVID-19 disease. Pediatric population might present a hyper-inflammatory response due SARS-CoV-2 infection and early diagnosis may prevent possible complications such as Kawasaki disease, immune/idiopathic thrombocytopenic purpura, hemophagocytic lymph histiocytosis, and multisystemic inflammatory syndrome.

### Conclusion

In this systematic review, taste changes, xerostomia, and vesiculobullous lesions were the most often seen oral manifestation. Although more children experienced oral signs of COVID-19, but it is still unclear if these symptoms are directly related to the fatal infection or are merely secondary presentations that develop during treatment. More high-quality prevalence studies must be undertaken in the current COVID-19 virus environment in order to establish a link between oral symptoms and COVID-19. It's noteworthy that dentists can be crucial in the early detection of this viral infection.

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**Legends Figures and Tables**

<b>Criterion</b>	<b>Inclusion</b>	<b>Exclusion</b>
Population	children (0-15)	N/A
Setting	Any	N/A
Interventions	N/A	N/A
Study designs	Systemic review, retrospective study, literature review, review articles	N/A
Publication type	Peer review of original research	Opinion pieces, editorials, magazine articles
Outcomes	Articles that explore the self-perceived oral health impacts of COVID-19 pandemic  Articles that explore the barriers and enablers of achieving optimal oral health during the COVID-19 pandemic	Articles that explore the transmission of COVID-19 in oral healthcare settings  Articles that focus on prevention of COVID-19 at oral healthcare settings  Articles that explore the perspectives, experiences and attitudes of oral health service providers on COVID-19 pandemic  Articles that focus on challenges or enablers experienced by oral health service providers during the COVID-19 pandemic
Language	Articles written in English	Articles in language other than English
Availability	Full text available	Not full text available
Date	All articles from 2019 to July 2022	Anything outside of this range

Table 1: Table for exclusion and inclusion criteria

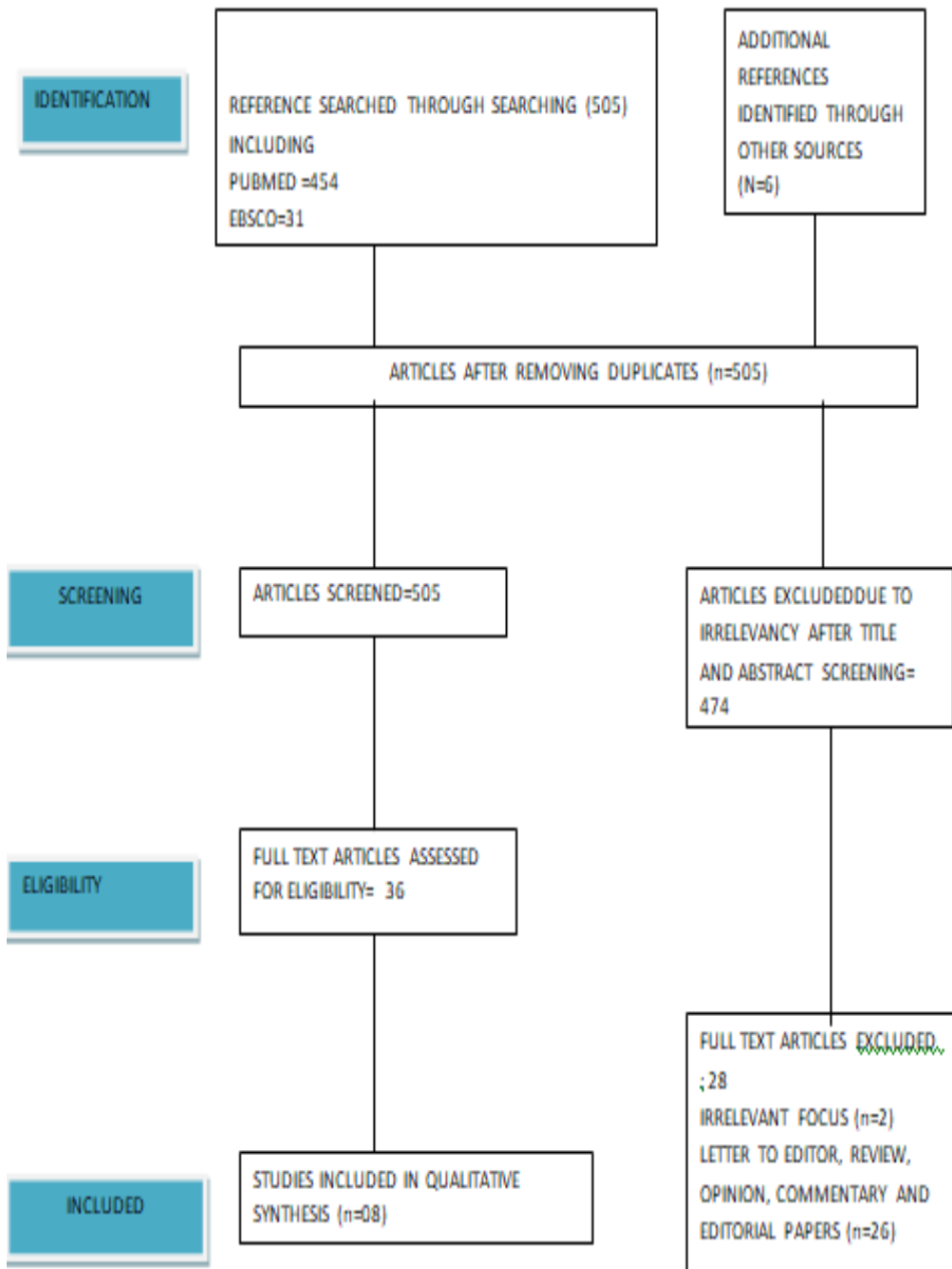


Figure 1. Flow diagram of literature search and selection criteria adapted from PRISMA

Table 2: Table for descriptive characteristics of included studies

Author	Title	Study Design	Sample	Age (Years)	Objectives / Methods	Oral Manifestations	Key Findings
PB Koticha, D Pradhan, F Katge, V Krishna, Bhanushali P , Patil D (2020) <sup>16</sup>	COVID-19 in Children: Its Impact on Oral Health and Paediatric Dentistry	Review article	-	-	Provide Urgent Care	Ulcers, Blisters, Cellulitis	Pediatric dentists during this pandemic should enact universal infection control protocols to the highest standards to limit the spread.
Zhang L, Peres TG, Silva MVF, Camargos P. (2020) <sup>17</sup>	What we know so far about Coronavirus Disease 2019 in children: A meta-analysis of 551 laboratory-confirmed cases	Systematic review	551 cases	1 day to 17.5 years	To summarize what we know so far about coronavirus disease in children.	sore throat, pharyngeal erythema	Children with COVID-19 and major underlying condition are more likely to have severe/critical disease and poor prognosis, even death.
Bardellini E, Bondioni MP, Amadori F, Veneri F, Lougaris V, Meini A, Plebani A, Majorana A. (2021) <sup>18</sup>	Non-specific oral and cutaneous manifestations of Coronavirus Disease 2019 in children	Retrospective cross-sectional study	27	(mean age 4,2 years + 1,7)	investigate the oral and cutaneous manifestations in children.	oral pseudomembranous candidiasis , geographic tongue , coated tongue ,hyperaemic pharynx , Taste alteration	COVID-19 resulted to be associated with non-specific oral and cutaneous manifestations.
MF Moraes, YR Natalino, AF Holanda, SOUZA Sobrinho HF, Sarmento LC, Gome APM, Sanglard LF (2021) <sup>19</sup>	Oral and cutaneous manifestations of covid-19 in pediatric patients	Literature review	-	18	oral manifestations, dysgeusia, ageusia and skin manifestations	taste dysfunction, erythematous eruption	oral and skin manifestations of COVID-19 in paediatric patients
Halepas S, Lee KC, Myers A, Yoon RK, Chung W, Peters SM. (2021) <sup>20</sup>	Oral manifestations of COVID-2019 related multisystem inflammatory syndrome in	Retrospective review	-	Mean age 9	oral and oropharyngeal manifestations	red or swollen lips strawberry tongue.	The presence of oral or oropharyngeal changes may be an early indicator of MIS-C

	children: a review of 47 paediatric patients						
Bhattacharyya SG, Bhattacharyya S (2021) <sup>21</sup>	Oral Manifestations of Covid-19 In Children and Adults	Review article	-		investigate the oral and cutaneous manifestations in children	ulcers, erosion, bullae, vesicles, pustule, fissured or depapillated tongue, macule, papule, plaque, pigmentation, halitosis, whitish areas, haemorrhagic crusts, necrosis, petechiae, swelling, erythema, and spontaneous bleeding	COVID-19 can cause many oral and mucosal lesions
Sharma P, Malik S, Wadhwan V, Appa S, Singh R. (2022) <sup>22</sup>	Prevalence of oral manifestations in COVID-19: A systematic review	systematic review	14,003 patients	-	aims to identify and bring together all the available evidence on the prevalence of oral manifestations of covid 19.	loss of taste , xerostomia, anosmia, mucormycosis, aspergillosis, vesiculobullous lesions, oral ulcers.	Immunosuppression and poor oral hygiene led to secondary manifestations like enanthematous lesions.
Pasquini Neto R, Mazzo FAT, Vieira FA, Bueno GS, Previdi JVC, Silva LRD, Silva NKBD, Jorizzo JL, Cerci FB. (2022) <sup>23</sup>	COVID-19 cutaneous manifestations in children and adolescents: a systematic review	systematic review	-	369 patients.	The aim of this study was to evaluate the coronavirus disease 2019 (COVID-19) cutaneous manifestations	Chilblain-like lesions, erythema multiforme- varicella-like lesions	Knowledge of the different skin manifestations in children and adolescents with COVID-19 is essential for an early diagnosis .