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An exploratory study of children with caries and its relationship to SARS-CoV-2

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Abstract: This exploratory study investigated whether children with dental decay were more likely to have COVID-19 than those without caries. The children underwent dental inspection and blood collection for detection of SARS-CoV-2 antibodies. Fifty-four children aged 6 to 9 years participated in the survey, which was conducted between March and June 2020 in the municipality of Ipojuca, Pernambuco, Brazil. The diagnosis of caries was performed using the dmft and DMFT indices. Parents reported signs and symptoms of sickness in their children during this period. The serology test aimed to verify the immune response of the children to coronavirus by detecting IgM/IgG antibodies. Statistical analyses were performed at $P < 0.05$. The majority of the children presented caries (68.5%). Of the nine children who tested positive for COVID-19 (16.7%), eight presented IgG antibodies to the virus, and only one had IgG and IgM antibodies to SARS-CoV2. Children who tested positive for SARS-CoV-2 had a higher percentage of caries lesions than those who tested negative for SARS-CoV-2 (77.8% vs 65.9%), but this difference was not statistically significant.

Keywords: Dental Caries; Child; COVID-19; Immunity; Serology.

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak that began in late 2019 in Wuhan, China, spread quickly and posed an immediate threat to global public health.[1] The pandemic started in Brazil in the first quarter of 2020, and with only approximately 3% of the global population, accounts for 10% of all cases and deaths worldwide. The disease poses a greater threat to those with underlying chronic diseases and immunosuppression.[2]

Caries shares similar risk factors to other chronic/systemic diseases, which provides opportunities for developing common prevention strategies and promoting health equity through action on the social determinants of health.[3] Poor oral health, as well as other oral disorders, can increase the risk of developing systemic conditions like diabetes, obesity, chronic kidney disease, and liver disease.[4,5] According to some studies, cytokines or microbial products released systemically in response to oral infection can cause inflammation in other parts of the human body, resulting in an array of systemic diseases.[6] Since the mouth is a controlled pathogen reservoir, improving oral hygiene can lower the risk of oropharyngeal colonization and pulmonary complications.[7]

Antibody testing assesses the presence (qualitative testing) or the amount of an antibody (quantitative testing) in a sample (usually blood, serum, or plasma).[8] Antibodies are large proteins produced by the immune system to identify and neutralize a disease-causing agent (such as bacteria or viruses). During the process, immune cells are also activated.[9] The ability of the immune system to respond to new pathogens can be affected by age.[10,11] Children have better antibody responses than adults and are better equipped to deal with novel viruses.[11]

According to studies, most children are asymptomatic for COVID-19, and when present, symptoms are relatively milder in children than in adults.[12] According to a systematic review, children account for less than 5% of COVID-19 diagnoses and typically have milder forms of the disease.[13]

In addition to assessing the patient's immune response, coronavirus antibody testing helps tracing viral circulation and estimate the extent of exposure in the population. Nevertheless, for the results to be valid, the test must be performed at the correct time and interpreted correctly.[14] Antibodies in the blood are measured by serological tests. Antibodies appear seven days after the onset of symptoms in COVID-19. IgM antibodies appear sooner than IgG antibodies, which appear about two weeks after infection.[15]

IgG (immunoglobulin G) and IgM (immunoglobulin M) are the two most common antibodies identified in serological tests. A positive IgM result indicates that the person has already been exposed and is in the active phase of COVID-19, with the possibility that the microorganism is circulating in the patient at the time.[16] A positive IgG result may indicate that the person is in the chronic convalescent stages of the disease, or that they have had contact with COVID-19 at some point in their life.[17]

PCR is a molecular biology method that amplifies and identifies the genetic material of the virus. The purpose of this methodology is to exponentially multiply genetic material. That is, it will detect the presence or absence of RNA from the virus under study. If it is positive, coronavirus infection is confirmed (in the acute phase of the disease).[8] To test for the disease, a sample of nasal, oropharyngeal (throat), or sputum secretion is used.[18] The test can be positive in the first days after the onset of symptoms, but it tends to be negative after more than seven days.

The relationship between oral health and COVID-19 infection remains unknown. Children with poor health, particularly those with substantially reduced immunity, may be at higher risk.[19] Dental caries is the most common chronic disease in childhood,[20] and recent evidence confirms that individuals with comorbidities, such as chronic diseases, have reduced immune response to viral diseases.[21] Therefore, this study aimed to investigate the relationship between caries and virus exposure in a population of children from the Brazilian city of Ipojuca, in the state of Pernambuco. Parents reported signs and symptoms of the illness of their children during the lockdown period. The purpose of this exploratory study was to investigate whether children with dental decay were more likely to have COVID-19 than those without caries.

Methodology

This study followed Resolution 466/2012 of the National Council for Research in Humans and approved by the ethics committee of the Universidade de Pernambuco, under nº: 4.203.296. The free and informed consent form was signed by the parents of the examined children.

This was an exploratory study conducted at the only two community health centers in Ipojuca, Pernambuco, Brazil, that were open for dental emergencies during the pandemic.

Ipojuca is a municipality located 60 kilometers from the state capital. It has a population of approximately 80,637 inhabitants (IBGE), with 5% of children aged 6 to 9 years. Since this was an exploratory study, an intentional sampling was used selecting 54 boys and girls aged 6 to 9 years. Intentional sampling methods are non-probabilistic procedures in which a group of individuals is selected for a sample to meet specific prescribed criteria.[22]

Children with syndromes that made the exam extremely difficult to perform and children who used orthodontic appliances were excluded from the study. The Kappa test for consistency was employed to calibrate the dentists in dental caries evaluation (0.76). Fifty-four children underwent dental exams using the Decayed, Missing, and Filled Teeth (dmft and DMFT) indices. A blood sample was taken for immunology testing at the health clinics and processed at the health provider laboratory. The dental exam and blood collection were performed in the same session. Guardians or parents responded questions regarding their children's health during the months of lockdown. The dentists followed biosafety protocols such as wearing personal protective equipment and using sterile instruments while performing exams in a dental chair.

Fisher's exact test was used to assess the association between two categorical variables. The margin of error was of 5%. Data was entered in an EXCEL spreadsheet and the statistical calculations were done in IMB SPSS version 25.

Results

Table 1 shows that most participants were aged six (31.5%) and seven (38.9%) years; 30 (55.6%) were female. As reported above, this population accounts for 5.0% of the total population.

Nine children (16.7%) tested positive for COVID-19, eight tested positive for IgG, and only one tested positive for both immunoglobulins (IgM and IgG). In one case, IgM was undetermined (Table 2).

The majority of the patients in the sample – 37 (68.5%) – had caries, while 17 (31.5%) were caries-free (Table 3). Children who tested positive on the serological test for SARS-CoV-2 and for immunoglobulin had more dental caries than children who tested negative. Seven (77.8%) of the nine children with a positive serological test result had dental decay and two (22.2%) were free of caries ($p > 0.05$) (Table 4).

Runny nose, headache, and sneezing were the most common signs and symptoms reported by parents, both in children who tested positive for COVID-19 and in those who tested negative. The most common symptoms in positive patients were runny nose (55.6%), fever (44.4%), headache (44.4%), cough (33.3%), sneezing (44.4%), and sore throat (33.3%) (Table 5).

Table 1. Sociodemographic characteristics of the study participants.

Variable	n (%)
Age (years)	
6	17 (31.5)
7	21 (38.9)
8	9 (16.7)
9	7 (13.0)
Gender	
Male	24 (44.4)
Female	30 (55.6)
Family income (minimum wages)	
< 1	19 (35.2)
1	22 (40.7)
2–3	13 (24.1)

Discussion

During the pandemic, only a limited number of national population-based studies have examined the presence of antibodies against SARS-CoV-2 in children.[23] For instance, a study conducted in Spain by Póllan et al.[24] revealed lower rates of antibody positivity for the infection among children under the age of ten. According to a study by Costa et al.,[25] the available data indicate a low incidence of COVID-19 among children. A meta-analysis

Table 2. Results of the serological immunoglobulin test.

Variable	n (%)
COVID 19 (by serological test)	
Positive	9 (16.7)
Negative	44 (81.5)
Indeterminate	1 (1.8)
Result of the immunoglobulin test	
Absent	44 (81.5)
IgG present	8 (14.8)
IgG and IgM present	1 (1.8)

Table 3. Results of the intraoral examination.

Variable	Result
dmft and components	
Decayed primary teeth: mean ± SD (median)	1.74 ± 1.94 (1.00)
Filled primary teeth: mean ± SD (median)	0.63 ± 1.15 (0.00)
Primary teeth with extraction indicated due to caries): mean ± SD (median)	0.20 ± 0.48 (0.0)
ceo-d	2.57 ± 2.31 (2.00)
DMFT and components	
Permanent decayed teeth: mean ± SD (median)	0.11 ± 0.42 (0.00)
Permanent filled teeth: mean ± SD (median)	0.04 ± 0.27 (0.00)
Permanent teeth lost due to caries: mean ± SD; median (P25; P75)	0.02 ± 0.14 (0.00)
DMFT	0.17 ± 0.50 (0.00)
Early tooth loss: n (%)	
Yes	9 (16.7)
No	45 (83.3)
Presence of caries: n (%)	
Yes	37 (68.5)
No	17(31.5)

Table 4. Caries according to the result of the COVID-19 test.

Variable	Positive (n = 9)	Negative (n = 44)	Total (n = 53)	p-value	OR (95%CI)
	n (%)	n (%)	n (%)		
Presence of caries				0.475*	
Yes	7 (77.8)	29 (65.9)	36 (67.9)		1.8 (0.3-9.8)
No	2 (22.2)	15 (34.1)	17 (32.1)		1.0

*Fisher's exact test.

Table 5. Most common clinical characteristics in children with and without IgG / IgM.

Total (n = 53)	Laboratory results	Most common clinical characteristics (%)	Presence of caries (%)	Caries experience (%)	Early loss (%)
Group 1 (n = 9)	IgG/IgM present (16.7%)	Runny nose (55.6) Fever (44.4) Headache (44.4) Cough (33.3) Sneezing (44.4) Sore throat (33.3)	77.8	88.9	22.2
Group 2 (n = 44)	IgG/IgM absent (81.5%)	Headache (38.6) Runny nose (36.4) Sneezing (34.1) Cough (29.5) Sore throat (22.7) Fever (15.9)	65.9	75.0	15.9

conducted to evaluate different serological methods for detecting SARS-CoV-2 infection suggested that utilizing combined IgG and IgM tests, as done in this study, provides better sensitivity than evaluating only a single antibody.[15]

In this study, the time between illness and blood sampling might be associated with a higher prevalence of IgG antibodies compared to IgM. Only one child had both types of immunoglobulins. According to Moraes et al.,[26] (2020), positive IgM and negative IgG antibodies indicates recent infection. In turn, negative IgM and positive IgG indicates that an infection occurred three weeks previously. Parents were unsure when their children became ill at the time of the survey, but all children had the same signs and symptoms of the disease, even though the majority tested negative.

Upon reflection, we agree with Savitz et al.[27] when they emphasize the importance of making a considered judgment rather than automatically dismissing a study based on the uncertainty of the timing of exposure. Judgment must be made as whether the estimated exposure accurately reflects the relevant period in the past that is causally linked to the disease. Additionally, the authors suggest that when relying on fallible, self-reported exposures, recall bias may arise due to reverse causality, wherein the presence of the disease influences either the actual exposure or the measured/reported exposure.

According to Long et al.,[28] the reduction in IgG levels and neutralizing antibodies in the early stages of convalescence may have implications for immunity. In their study, the individuals infected with SARS-CoV-2 presented immune responses specific to IgG; the virus-specific IgG levels in the asymptomatic group were significantly lower ($p = 0.005$) compared to the symptomatic group in the acute phase. When compared to symptomatic patients, asymptomatic individuals had a greater reduction in IgG and neutralizing antibody levels during the early convalescent phase.

Based on the relationship between antibody titers and disease severity, Zhao et al.[29] found that critically ill patients had significantly higher antibody titers compared to non-critical patients two weeks after symptom onset. Méndez-Echevarría et al.[30] reported that children infected with SARS-CoV-2 who required hospital admission remained seropositive. On the other hand, one out of five children with mild or asymptomatic infections, as well as those with low antibody titers, had no antibodies. Some of the children in this study, whether asymptomatic or mildly symptomatic, may have become infected despite initially showing a negative result, making antibody detection difficult. After infection, some asymptomatic children may exhibit low antibody titers, often experiencing a decline in IgG titer,[26] which could have occurred to the children included in this study. Furthermore, evidence suggests that immune protection against other human coronaviruses is not long-lasting.[31]

Most studies on COVID-19 primarily focus on adults because of their high infection rates. However, Dong et al.[32] conducted an evaluation of 728 pediatric patients with confirmed COVID-19. Over 90% were asymptomatic or experienced mild to moderate disease. Similar findings were reported by Guner et al.,[33] who studied 251 pediatric patients, of which 48 (19.1%) patients were asymptomatic and 183 (72.9%) had mild symptoms.

In the present study, children exhibited a low prevalence of dental caries, which is in line with a global trend observed over the past decade. This finding is consistent with the last National Oral Health Survey (SB Brazil 2010), which reported that Brazilian children, on average, have 2.43 carious teeth by the age of five.[34]

Based on the findings of Méndez-Echevarra et al.,[30] it is important to consider the potential lack of precision in parents' reporting of the duration of their children's illness. In such case, some of the children who tested negative in the study may have either lost their immunoglobulins over time, especially considering the three-month lockdown, or had mild cases of the disease. As noted by Savitz et al.,[27] the exposure status measured at the time of disease ascertainment may not accurately reflect the relevant exposure period from an etiological standpoint. Furthermore, the presence of the disease can potentially affect the measurement of exposure, which is akin to the biological counterpart of recall bias, where the presence of disease distorts self-reported exposure.

It is important to highlight that the target population resides in communities with high population density, such as favelas. This implies that children were highly likely to have regular contact with infected individuals during the lockdown. Therefore, considering the circumstances, the parents' lack of memory regarding their children's health may not be a genuine weakness of this report,

The sample size of our study was small due the methodological aspects already explained. This may explain the lack of sensitivity of statistical tests to prove the research hypothesis. With small samples, it is often not possible to obtain a statistically significant difference or association.[35]

As the pandemic progresses and more studies are developed, there is evidence of a lower incidence of the disease in children.[36] There is enough evidence that the new coronavirus has a unique mechanism of interaction with the host. More studies are essential to fill the knowledge gap about children's immune response to SARS-CoV-2 and to better understand the relationship between chronic diseases, such as caries, and the new coronavirus.

Conclusion

Children who tested positive for SARS-CoV-2 had a higher percentage of caries lesions than the children who tested negative, but the difference was not statistically significant.

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References

1. Acter T, Uddin N, Das J, Akhter A, Choudhury TR, Kim S. Evolution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as coronavirus disease 2019 (COVID-19) pandemic: a global health emergency. Sci Total Environ. 2020 Aug;730:138996. https://doi.org/10.1016/j.scitotenv.2020.138996
2. Mesenburg MA, Hallal PC, Menezes AM, Barros AJ, Horta BL, Barros FC, et al. Chronic non-communicable diseases and Covid-19: Epicovid-19 Brazil results. Rev Saude Publica. 2021 Jun;55:38. https://doi.org/10.11606/s1518-8787.2021055003673
3. Pitts NB, Twetman S, Fisher J, Marsh PD. Understanding dental caries as a non-communicable disease. Br Dent J. 2021 Dec;231(12):749-53. https://doi.org/10.1038/s41415-021-3775-4
4. Bui FQ, Almeida-da-Silva CL, Huynh B, Trinh A, Liu J, Woodward J, et al. Association between periodontal pathogens and systemic disease. Biomed J. 2019 Feb;42(1):27-35. https://doi.org/10.1016/j.bj.2018.12.001
5. Sabella FM, Feiria SN, Ribeiro AA, Theodoro LH, Höfling JF, Parisotto TM, et al. Exploring the interplay between oral diseases, microbiome, and chronic diseases driven by metabolic dysfunction in childhood. Front Dent Med. 2021;2:718441. https://doi.org/10.3389/fdmed.2021.718441
6. Sudhakara P, Gupta A, Bhardwaj A, Wilson A. Oral dysbiotic communities and their implications in systemic diseases. Dent J. 2018 Apr;6(2):10. https://doi.org/10.3390/dj6020010
7. Botros N, Iyer P, Ojcius DM. Is there an association between oral health and severity of COVID-19 complications? Biomed J. 2020 Aug;43(4):325-7. https://doi.org/10.1016/j.bj.2020.05.016
8. Fundação Osvaldo Cruz. Instituto de Tecnologia em Imunobiológicos Bio-Manguinhos. O que é IgG e IgM? 2022 July 20 [citado 2023 Feb 20]. Available from: https://www.bio.fiocruz.br/index.php/en/noticias/1739-o-que-e-igg-e-igmHowever,accessed
9. Jacofsky D, Jacofsky EM, Jacofsky M. Understanding antibody testing for COVID-19. J Arthroplasty. 2020 Jul;35(7 7S):S74-81. https://doi.org/10.1016/j.arth.2020.04.055
10. Shen K, Yang Y, Wang T, Zhao D, Jiang Y, Jin R, et al.; China National Clinical Research Center for Respiratory Diseases; National Center for Children's Health, Beijing, China; Group of Respirology, Chinese Pediatric Society, Chinese Medical Association; Chinese Medical Doctor Association Committee on Respirology Pediatrics; China Medicine Education Association Committee on Pediatrics; Chinese Research Hospital Association Committee on Pediatrics; Chinese Non-government Medical Institutions Association Committee on Pediatrics; China Association of Traditional Chinese Medicine, Committee on Children's Health and Medicine Research; China News of Drug Information Association, Committee on Children's Safety Medication; Global Pediatric Pulmonology Alliance. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. World J Pediatr. 2020 Jun;16(3):223-31. https://doi.org/10.1007/s12519-020-00343-7

11. Carsetti R, Quintarelli C, Quinti I, Piano Mortari E, Zumla A, Ippolito G, et al. The immune system of children: the key to understanding SARS-CoV-2 susceptibility? Lancet Child Adolesc Health. 2020 Jun;4(6):414-6. https://doi.org/10.1016/S2352-4642(20)30135-8
12. Selva KJ, Sandt CE, Lemke MM, Lee CY, Shoffner SK, Chua BY, et al. Systems serology detects functionally distinct coronavirus antibody features in children and elderly. Nat Commun. 2021 Apr;12(1):2037. https://doi.org/10.1038/s41467-021-22236-7
13. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr. 2020 Jun;109(6):1088-95. https://doi.org/10.1111/apa.15270
14. Vogl T, Leviatan S, Segal E. SARS-CoV-2 antibody testing for estimating COVID-19 prevalence in the population. Cell Rep Med. 2021 Feb;2(2):100191. https://doi.org/10.1016/j.xcrm.2021.100191
15. Kontou PI, Braliou GG, Dimou NL, Nikolopoulos G, Bagos PG. Antibody tests in detecting SARS-CoV-2 infection: a meta-analysis. Diagnostics (Basel). 2020 May;10(5):319. https://doi.org/10.3390/diagnostics10050319
16. Long QX, Liu BZ, Deng HJ, Wu GC, Deng K, Chen YK, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nat Med. 2020 Jun;26(6):845-8. https://doi.org/10.1038/s41591-020-0897-1
17. Li K, Huang B, Wu M, Zhong A, Li L, Cai Y, et al. Dynamic changes in anti-SARS-CoV-2 antibodies during SARS-CoV-2 infection and recovery from COVID-19. Nat Commun. 2020 Nov;11(1):6044. https://doi.org/10.1038/s41467-020-19943-y
18. Calvet G, Ogrzewalska M, Tassinari W, Guaraldo L, Resende P, Fuller T, et al. Accuracy of saliva for SARS-CoV-2 detection in outpatients and their household contacts during the circulation of the Omicron variant of concern. BMC Infect Dis. 2023 May;23(1):295. https://doi.org/10.1186/s12879-023-08271-3
19. Antunes BS, Kinalski DD, Schneider V, Silva AF, Motta MD. COVID-19 and children with chronic diseases: scope review. Research. Soc Dev. 2020;9(12):e5391210748-e5391210748. https://doi.org/10.33448/rsd-v9i12.10748
20. Olatosi OO, Alade AA, Naicker T, Busch T, Oyapero A, Li M, et al. Dental caries severity and nutritional status of Nigerian preschool children. JDR Clin Trans Res. 2022 Apr;7(2):154-62. https://doi.org/10.1177/23800844211002108
21. Feitoza TM, Chaves AM, Muniz GT, da Cruz MC, Junior ID, Comorbidades E. Covid-19. Revista Interfaces: saúde. Humanas e Tecnologia. 2020;8(3):711-23. https://doi.org/10.16891/2317-434X
22. Lauretto MD, Nakano F, Pereira CA, Stern JM. Intentional sampling by goal optimization with decoupling by stochastic perturbation. Conference Proceedings. American Institute of Physics. 2012; 1490(1): 189-201. https://doi.org/10.1063/1.4759603
23. Hallal PC, Hartwig FP, Horta BL, Silveira MF, Struchiner CJ, Vidaletti LP, et al. SARS-CoV-2 antibody prevalence in Brazil: results from two successive nationwide serological household surveys. Lancet Glob Health. 2020 Nov;8(11):e1390-8. https://doi.org/10.1016/S2214-109X(20)30387-9
24. Pollán M, Pérez-Gómez B, Pastor-Barriuso R, Oteo J, Hernán MA, Pérez-Olmeda M, et al. Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. Lancet. 2020 Aug;396(10250):535-44. https://doi.org/10.1016/S0140-6736(20)31483-5
25. Costa A, Almeida H, Moniz M, Alves C. COVID-19 screening in a Portuguese pediatric population. Enferm Infecc Microbiol Clin (Engl Ed). 2022 Jan;40(1):28-31. https://doi.org/10.1016/j.eimce.2020.09.006
26. Moraes EN, Viana LG, Resende LM, Vasconcellos LS, Moura AS, Menezes A, et al. COVID-19 in long-term care facilities for the elderly: laboratory screening and disease dissemination prevention strategies. Cien Saude Colet. 2020 Sep;25(9):3445-58. https://doi.org/10.1590/1413-81232020259.20382020
27. Savitz DA, Wellenius GA. Can cross-sectional studies contribute to causal inference? It Depends. Am J Epidemiol. 2023 Apr;192(4):514-6. https://doi.org/10.1093/aje/kwac037
28. Long QX, Tang XJ, Shi QL, Li Q, Deng HJ, Yuan J, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med. 2020 Aug;26(8):1200-4. https://doi.org/10.1038/s41591-020-0965-6
29. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease. Clin Infect Dis. 2020 Nov;71(16):2027-34. https://doi.org/10.1093/cid/ciaa344
30. Méndez-Echevarría A, Sainz T, Falces-Romero I, Felipe B, Escolano L, Alcolea S, et al. Long-term persistence of Anti-SARS-CoV-2 antibodies in a pediatric population. Pathogens. 2021 Jun;10(6):700. https://doi.org/10.3390/pathogens10060700
31. Callow KA, Parry HF, Sergeant M, Tyrrell DA. The time course of the immune response to experimental coronavirus infection of man. Epidemiol Infect. 1990 Oct;105(2):435-46. https://doi.org/10.1017/S0950268800048019
32. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 among children in China. Pediatrics. 2020 Jun;145(6):e20200702. https://doi.org/10.1542/peds.2020-0702
33. Guner Ozenen G, Sahbudak Bal Z, Umit Z, Bilen NM, Yildirim Arslan S, Yurtseven A, et al. Demographic, clinical, and laboratory features of COVID-19 in children: the role of mean platelet volume in predicting hospitalization and severity. J Med Virol. 2021 May;93(5):3227-37. https://doi.org/10.1002/jmv.26902
34. Ministério da Saúde (BR). Secretaria de Atenção à Saúde. Secretaria de Vigilância em Sapude. Pesquisa nacional de saúde buccal: resultados principais. Brasília, DF: Ministério da Saúde; 201 [cited 2022 Nov 20, 2022]. Avaliable from: https://bvsms.saude.gov.br/bvs/publicacoes/pesquisa_nacional_saude_bucal.pdf

35. Leppink J, Winston K, O'Sullivan P. Statistical significance does not imply a real effect. Perspect Med Educ. 2016; 5(2):122-124. https://doi.org/10.1007/S40037-016-0256-6
36. Dunay GA, Barroso M, Woidy M, Danecka MK, Engels G, Hermann K. et al. Long-term antibody response to SARS-CoV-2 in children. J Clin Immunol. 2022 Sep;43:46-56. https://doi.org/10.1101/2022.02.11.22270611