Arch Clin Infect Dis. 2025 February; 20(1): e144402 https://doi.org/10.5812/archcid-144402

Published Online: 2024 December 28 **Research Article**

Study of Outpatient Children in Five Waves of COVID-19: Comparing Clinical Manifestations, Need for Hospitalization, and Antibiotic Prescription

Ali Hosseininasab [1,*], Katayoun Alidousti [2], Maedeh Jafari [3,4], Maryam Ebrahimpour [3], Mehrdad Farrokhnia [5]

[1] The Infectious and Tropical Research Center, Kerman University of Medical Sciences, Kerman, Iran
[2] Razi Nursing and Midwifery Faculty, Kerman University of Medical Sciences, Kerman, Iran
[3] Department of Pediatrics, School of Medicine, Kerman University of Medical Sciences, Kerman, Iran
[4] Clinical Research Development Unit, Afzalipour Hospital, Kerman University of Medical Sciences, Kerman, Iran
[5] Department of Internal Medicine, Kerman University of Medical Sciences, Kerman, Iran

[*] ***Corresponding Author:*** The Infectious and Tropical Research Center, Kerman University of Medical Sciences, Kerman, Iran. Email: ali4221@gmail.com

Received: 26 December, 2023; **Revised:** 17 November, 2024; **Accepted:** 12 December, 2024

Abstract

Background: The SARS-CoV-2 virus has shown various subtypes with unique characteristics, but the recurrence of COVID-19 in children and the use of antibiotics for secondary bacterial infections have not been thoroughly investigated.

Objectives: This study aimed to analyze the frequency of COVID-19 infections in children and the prescription of antibiotics for secondary bacterial infections in pediatric outpatient cases.

Methods: This cross-sectional study was conducted at three outpatient centers from February 2020 to August 2022. It included children under 15 years old with complete medical records related to SARS-CoV-2 infection. The study assessed clinical symptoms, hospitalization needs, antibiotic prescriptions, and the number of COVID-19 episodes.

Results: Out of 2,448 children diagnosed with COVID-19, 65% were male. A total of 192 children (7.84%) had two episodes, 35 (1.43%) had three episodes, 7 (0.29%) had four episodes, and 2 (0.14%) had five episodes. 143 children (5.84%) required hospitalization. Antibiotics were prescribed in 17.73% of cases (n = 434), primarily for acute bacterial sinusitis (12.21%) and middle ear infections (8.52%). Common antibiotics included Azithromycin, Amoxicillin, Cefuroxime, and Co-trimoxazole.

Conclusions: Different subtypes of SARS-CoV-2 display distinct clinical behaviors in the pediatric population. Children can contract COVID-19 multiple times; however, antibiotic use in outpatient settings is relatively low and mainly associated with specific conditions, such as acute sinusitis and middle ear infections.

Keywords: COVID-19, Antibiotics, Reinfection, Pediatrics

1. Background

A few months after the first description of COVID-19 in China, evidence emerged that the situation was escalating worldwide and threatening to become a pandemi (1). Many studies have been published globally on the impact of SARS-CoV-2 infection in children (2). Generally, the disease presents mild symptoms in children; however, patients with complex medical conditions or those from certain racial and ethnic minority groups require more attention due to their increased risk of severe illness (3).

COVID-19 is primarily a viral infection that usually leads to mild symptoms in children. Secondary bacterial infections following COVID-19 are uncommon, especially among outpatients, and children with this infection would not typically be expected to receive antibiotics (4). This concern became more pronounced when it was found that Azithromycin, initially proposed as a drug with potential antiviral properties and reported to have

high consumption rates, did not significantly affect the treatment of the disease (5).

Given that severe and acute manifestations may resemble toxic shock syndrome in hospitalized children, existing consensus documents suggest that empirical broad-spectrum antibiotic treatment is appropriate if bacterial infections cannot be ruled out (6, 7). However, there are growing concerns about the potential negative impacts of the pandemic on children's health and education, particularly regarding the overuse of antibiotics. While this issue is especially contentious for adults with COVID-19, Velasco-Arnaiz et al. reported preliminary data suggesting that the pandemic could significantly impact the use of antimicrobial drugs in the pediatric inpatient population (8). They evaluated antibiotic prescriptions during and before the epidemic but did not assess the direct use of antibiotics and their determinants in children, particularly in outpatient COVID-19 cases (9).

As multiple cases continue to be reported worldwide, SARS-CoV-2 is expected to circulate for an extended period. Therefore, the appropriate management of children with COVID-19 remains a priority. The pandemic has not only directly affected children but has also raised concerns about inappropriate prescriptions that could exacerbate the critical issue of antibiotic overuse and antimicrobial resistance (10).

Many countries have experienced multiple waves of coronavirus outbreaks. Empirical data indicate that characteristics varied between waves in terms of clinical symptoms, complications, hospitalization needs, mortality rates, and transmission rates. Governments and health authorities, including the World Health Organization, have continued to educate the public about preventive measures to reduce virus spread, including quarantine protocols (11).

According to recent reports on COVID-19 in Iran, children infected with the virus range from less than four months to 15 years old, with most reported cases being male. Mortality within this age group is rare. Secondary infections and antibiotic use are not mentioned in this study (12). Bacterial co-infections or secondary infections have been reported in only 7 - 8% of patients with COVID-19. However, antibiotic prescribing rates across various studies were estimated at 56.6% to 74.6%, although these rates are lower in children than in adults (38.5% vs. 83.4%) (13). The overuse of antibiotics among hospitalized patients with COVID-19 has been evident due to disease severity and confusion with bacterial infections (14).

To date, no longitudinal studies have focused on the frequency of COVID-19 infections or on antibiotic use due to secondary bacterial infections in pediatric outpatients.

2. Objectives

Given the gap in existing studies, we conducted a longitudinal study in an area with relatively high antibiotic use to primarily evaluate ambulatory antibiotic use in children with COVID-19 and understand the determinants of its use (15).

3. Methods

We conducted a prospective cohort study on patients aged < 15 years visiting health centers in Kerman province, located in southeastern Iran. From February 2020 to August 2022, children diagnosed with SARS-CoV-2 infection by polymerase chain reaction (PCR) and/or the presence of clinical symptoms of COVID-19, along with one or more family members in the same condition, were included in the study. This study was carried out at three outpatient centers for pediatric infectious diseases affiliated with Kerman University of Medical Sciences in southeastern Iran.

To estimate the sample size for this study, we considered several key factors. We reviewed existing literature to determine the expected prevalence of COVID-19 among children in the target population. A confidence level of 95% was chosen to ensure reliable results, and a margin of error of 5% was accepted, which is standard in clinical studies. Using these parameters, we calculated the minimum sample size required to achieve statistical significance. The final sample included all eligible patients who consented to participate during the study period.

The treatment provided was supportive, including antipyretics, antitussives, and vitamin D or other supplements. The need for hospitalization was determined based on the patient's condition, considering the criteria for moderate to severe disease. The prescription of antibiotics during each visit was based on the suspected secondary bacterial infections, such as acute sinusitis and middle ear infections,

diagnosed using clinical criteria by a pediatrician or a pediatric infectious disease subspecialist. Data on the number of times a child was diagnosed with COVID-19 were obtained from electronic records.

Additionally, children's symptoms during the five waves of COVID-19 in Iran were investigated for each peak, with the dominant strain identified through a reference laboratory. All clinical characteristics at the time of referral—such as type of treatment, antibiotic administration, and need for hospitalization—were compared across different peaks of the disease. Parents were provided with a brief description of the study and informed that all responses were voluntary, anonymous, and confidential. The Kerman University of Medical Sciences ethics committee reviewed the study's draft and approved it under code IR.KMU.AH.REC.1400.384.

During the study period, data collection forms were completed for children whose parents signed consent forms to participate in the research. Study variables included age, gender, reason for referral, clinical signs and symptoms, duration of symptoms, number of COVID-19 infections, antibiotic use and its cause, and need for hospitalization. Unclear data items at the time of the child's visit were later extracted from electronic files or obtained by contacting parents directly. At the end of the study, the collected data were entered into SPSS 22 for statistical analysis. Descriptive findings were summarized as frequencies and percentages. Median and interquartile ranges were used for continuous variables. Pearson chi-Square tests were used to compare variables across different waves. In all comparative cases, a P-value < 0.05 indicated statistical significance.

4. Results

Study Population and Infections: A total of 2,448 children diagnosed with COVID-19 between February 2020 and August 2022 were included in this study. Figure 1 illustrates the monthly distribution of patients, with 1,590 (65%) being male. During the study period, 192 (7.84%) children experienced multiple COVID-19 infections: 35 (1.43%) had three infections, 7 (0.29%) had four infections, and 2 (0.14%) had five infections. Notably, no significant differences were found in underlying diseases, age, gender, or kindergarten attendance between children with single and multiple infections ($P = 0.982$).

Infection Sources and Hospitalization Rates: Parents were identified as the most frequent source of infection, accounting for 716 cases (29.25%). Among the total study population, 143 children (5.84%) required hospitalization based on clinical assessment, with notably higher rates during the third wave, which coincided with the delta strain ($P = 0.007$).

Antibiotic Use and Prescribing Patterns: Antibiotics were prescribed to 17.73% (n = 434) of patients, and the rationale for the prescription was unknown in 79.26% of cases. Acute bacterial sinusitis (12.21%) and middle ear infections (8.52%) were the most common reasons for antibiotic prescriptions. Azithromycin (47.70%) and Amoxicillin (29.03%) were the most frequently prescribed antibiotics, followed by Cefuroxime (17.28%) and Co-trimoxazole (5.99%). Notably, the use of Azithromycin significantly declined in subsequent waves compared to the first wave ($P = 0.001$).

Demographic Characteristics and Symptoms: Table 1 illustrates the demographic characteristics of the children included in the study, while Figure 2 shows the age distribution, indicating an average age of 44.07 ± 34.46 months, with a range from 6 days to 15 years. The most commonly reported symptoms were fever (69.2%) and a decreased sense of smell (0.24%). On average, patients sought medical attention and received diagnoses approximately 3.45 ± 1.72 days after symptom onset, with a range of 1 to 10 days. Table 2 outlines the frequency of clinical signs and symptoms. Although certain gastrointestinal symptoms were more prevalent during the delta wave and laryngitis and hoarseness were more common during the Omicron wave, these variations were not statistically significant ($P = 0.266$).

5. Discussion

This study involved 2,448 children diagnosed with COVID-19 over 30 months, coinciding with various disease waves in adults (13). Interestingly, the disease peaks did not correlate with specific seasonal patterns. Although the number of patients referred during the third wave, coinciding with the delta strain, was higher, the difference was not statistically significant. It is worth noting that other studies have also reported an increased impact of the delta and Omicron variants on children (13). The delta strain, in particular, led to more infections and subsequent complications, resulting in higher hospitalization rates for children. This may be

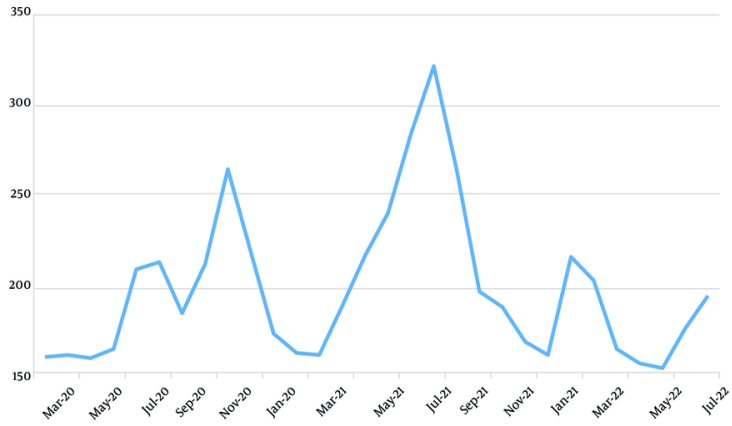

Figure 1. Frequency distribution of patients by month and year across different waves

Table 1. Demographic Characteristics of Patients [a]

Variables	Wave 1 (n = 337)	Wave 2 (n = 612)	Wave 3 (n = 918)	Wave 4 (n = 367)	Wave 5 (n = 214)	P-Value [b]
Index case						0.982
Parents	99 (29.37)	179 (29.24)	268 (29.19)	107 (29.15)	63 (29.43)	
Other families	16 (4.74)	30 (4.90)	45 (4.90)	18 (4.90)	0 (4.67)	
Kindergarten	32 (9.49)	58 (9.47)	86 (9.36)	35 (9.53)	20 (9.34)	
Unknown	190 (56.37)	346 (56.53)	518 (56.42)	207 (56.40)	121 (56.54)	
Management						0.007
Outpatient	325 (96.43)	584 (95.42)	844 (91.93)	348 (94.82)	204 (95.32)	
Hospitalization	12 (3.56)	28 (4.57)	74 (8.06)	19 (5.17)	10 (4.67)	
Antibiotics						
Azithromycin						0.001
Yes	37 (10.98)	49 (8)	75 (8.16)	29 (7.90)	0	
No	300 (89.02)	563 (91.99)	843 (91.83)	338 (92.09)	214 (100)	
Co-cotrimoxazole						0.964
Yes	5 (1.48)	6 (0.98)	10 (1.08)	4 (1.08)	2 (0.93)	
No	332 (98.51)	606 (99.01)	917 (99.89)	363 (98.91)	212 (99.06)	
Amoxicillin						0.982
Yes	17 (5.04)	32 (5.22)	47 (5.11)	19 (5.17)	11 (5.14)	
No	320 (94.95)	580 (94.77)	871 (94.88)	348 (94.82)	203 (94.85)	
Cefuroxime						0.903
Yes	10 (2.96)	19 (3.10)	28 (3.05)	11 (2.99)	6 (2.80)	
No	327 (97.03)	593 (96.89)	890 (96.94)	356 (97)	208 (97.19)	

[a] Values are expressed as No. (%).

[b] $P < 0.05$ was considered statistically significant.

attributed to the unique characteristics of the delta variant and increased adherence to preventive measures, immunity from prior infection, and/or vaccination in adults (13).

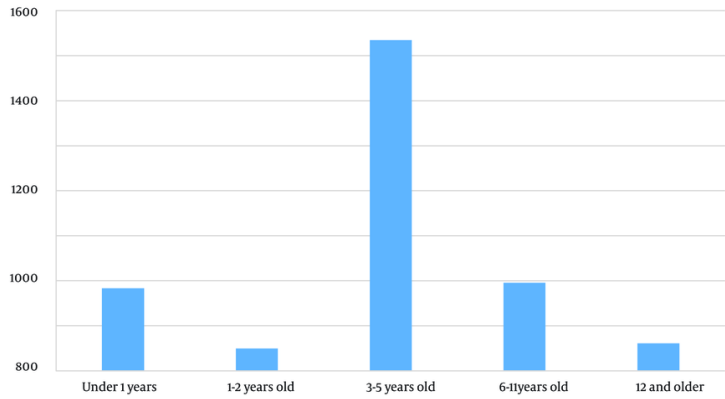

Figure 2. Age groups of patients

In terms of gender distribution, 65% of the patients were male, which aligns with previous research conducted in similar regions (14). This gender disparity in favor of boys was also observed in other surveys in Iran and various parts of the world (15). Approximately 8% of children experienced multiple infections, although this usually correlated with underlying conditions or specific causes. It is noteworthy that similar studies examining the frequency of COVID-19 infections in children have not been conducted. While some studies have reported multiple COVID-19 infections in adults, specific reasons for this phenomenon were generally not provided (16).

Parents and family members were the most commonly identified sources of children's infections (17). In many instances, the source of infection remained unclear, but it was highly likely that the initial case came from an adult family member. These adults, while potentially asymptomatic due to vaccination-induced immunity, could still transmit the virus to children (17). The need for hospitalization and the occurrence of severe side effects were notably higher during the third wave, coinciding with the delta strain. During this wave, more children were hospitalized due to complications such as severe diarrhea, vomiting, food intolerance, and uncontrollable fevers. Similar results were observed in other studies (18). Despite the increase in hospitalization cases during this wave, the rates of severe and fatal complications, such as lung involvement, did not significantly differ from those during other peaks.

In total, 434 patients (17.73%) received antibiotics during the study (19-22). In the majority of cases (79.26%), the reasons for prescribing antibiotics were unclear, raising concerns about the potentially irrational use of antibiotics during the COVID-19 pandemic. While antibiotics may be necessary for managing suspected or confirmed bacterial infections in COVID-19 patients, they appear to have been unnecessary in most cases. Interestingly, at the outset of the pandemic, antibiotics were prescribed more frequently to patients. Azithromycin was the most commonly prescribed antibiotic during the early stages of the pandemic, possibly due to its perceived anti-inflammatory, antibacterial, and antiviral properties. However, clinical data later refuted its effectiveness in treating COVID-19 (19-22). The high rate of azithromycin prescriptions in this study was likely due to limited information about its ineffectiveness at the time. The most common reasons for antibiotic use were acute bacterial sinusitis and middle ear infections.

The study found that fever was the most commonly reported symptom, consistent with numerous studies worldwide (23). On average, patients sought medical attention 3.45 days after the onset of symptoms, often driven by high fever and concerns about fever-induced seizures, although no cases of seizures due to fever were reported as the reason for clinic visits. Cases involving seizures or severe, sudden complications were typically taken to the hospital by family members or emergency services. The frequency of other clinical symptoms,

Table 2. Frequency of Clinical Signs and Symptoms of Patients [a]

Variables	Wave 1 (n = 337)	Wave 2 (n = 612)	Wave 3 (n = 918)	Wave 4 (n = 367)	Wave 5 (n = 214)	P-Value
Fever						0.87
Yes	223 (66.17)	424 (69.28)	635 (69.17)	254 (69.20)	148 (69.15)	
No	114 (34.13)	188 (30.71)	283 (30.82)	113 (30.79)	66 (30.84)	
Sore throat						0.978
Yes	35 (10.38)	63 (10.29)	94 (10.23)	38 (10.35)	22 (10.28)	
No	302 (89.61)	549 (89.7)	824 (89.76)	329 (89.64)	192 (89.71)	
Coryza						0.976
Yes	74 (21.95)	134 (21.89)	200 (21.78)	80 (21.79)	47 (21.69)	
No	263 (78.04)	478 (78.1)	718 (78.21)	287 (78.2)	167 (78.03)	
Cough						0.996
Yes	129 (38.27)	235 (38.39)	351 (38.23)	141 (38.41)	82 (38.31)	
No	208 (61.72)	377 (61.6)	567 (61.76)	226 (61.58)	132 (61.68)	
Diarrhea						0.995
Yes	27 (8.01)	50 (8.16)	75 (8.16)	30 (8.17)	17 (7.94)	
No	310 (91.98)	562 (91.83)	843 (91.83)	337 (91.82)	197 (92.05)	
Nausea and vomiting						0.99
Yes	34 (10.08)	61 (9.96)	95 (10.34)	37 (10.08)	21 (9.81)	
No	303 (89.91)	551 (90.03)	823 (89.65)	330 (89.91)	193 (90.18)	
Headache						0.943
Yes	15 (4.45)	28 (4.57)	41 (4.46)	16 (4.35)	10 (4.67)	
No	322 (95.54)	584 (95.42)	877 (95.53)	351 (95.64)	213 (99.53)	
Weakness						0.997
Yes	4 (1.18)	7 (1.14)	12 (1.30)	5 (1.36)	3 (1.40)	
No	333 (98.81)	605 (98.85)	906 (98.69)	362 (98.63)	211 (98.59)	
Anorexia						0.959
Yes	6 (1.78)	11 (1.79)	16 (1.74)	6 (1.63)	4 (1.86)	
No	331 (98.21)	601 (98.2)	902 (98.25)	361 (98.36)	210 (98.13)	
Vertigo						0.996
Yes	1 (0.29)	2 (0.32)	3 (0.32)	1 (0.27)	1 (0.46)	
No	336 (99.7)	610 (99.67)	915 (99.67)	366 (99.72)	213 (99.53)	
Skin rash						0.999
Yes	5 (1.48)	8 (1.30)	12 (1.30)	5 (1.36)	3 (1.40)	
No	332 (98.51)	604 (98.69)	906 (98.69)	362 (98.63)	211 (98.59)	
Body ache						0.982
Yes	17 (5.04)	30 (4.90)	45 (4.90)	18 (4.90)	11 (5.14)	
No	320 (94.95)	582 (95.09)	873 (95.09)	349 (95.09)	203 (94.85)	
Abdominal pain						0.993
Yes	37 (10.97)	68 (11.11)	101 (11)	40 (10.89)	24 (11.21)	
No	300 (89.02)	544 (88.88)	817 (88.99)	327 (89.1)	190 (88.78)	
Tonsil exudate						0.83
Yes	1 (0.29)	1 (1.16)	2 (0.21)	0	0	
No	336 (99.7)	611 (99.83)	916 (99.78)	367 (100)	214 (100)	
Chills						0.865
Yes	13 (3.85)	25 (4.08)	37 (4.03)	15 (4.08)	9 (4.20)	
No	324 (96.14)	587 (95.91)	881 (95.96)	352 (95.91)	205 (95.79)	
Loss of smell						0.954
Yes	1 (0.29)	1 (1.16)	2 (0.21)	1 (0.27)	1 (0.46)	
No	336 (99.7)	611 (99.83)	916 (99.78)	366 (99.72)	213 (99.53)	
Hoarseness						0.266
Yes	15 (4.45)	26 (4.24)	40 (4.35)	24 (6.53)	7 (3.27)	
No	322 (95.54)	586 (95.75)	878 (95.64)	343 (93.46)	207 (96.72)	

[a] Values are expressed as No. (%).

including diarrhea, vomiting, coryza, hoarseness, and skin rashes, varied across different waves. Changes in the sense of smell and taste could not be adequately assessed in very young children. Similarly, as in other studies, gastrointestinal symptoms were more prevalent in the delta wave, and laryngitis was more common in the Omicron wave. In other cases, there were no significant differences in the frequency of clinical symptoms across different waves (24).

Indeed, various subtypes of SARS-CoV-2 exhibit distinct clinical behaviors in the pediatric population. Severe complications and hospitalization rates are particularly associated with the Delta and Omicron strains. Additionally, it is noteworthy that individuals, including children, can be infected with COVID-19 multiple times.

In the case of outpatient treatment, antibiotics may not be a useful intervention due to the viral nature of the disease and the absence of clinical evidence supporting the presence of secondary bacterial infections. Their use appears to be limited to specific cases, highlighting the importance of judicious antibiotic prescribing to prevent overuse and the development of antimicrobial resistance.

Acknowledgements

The authors appreciate all the vulnerable parents who kindly participated in this study.

Footnotes

Authors' Contribution: A. H. and K. A. contributed to conceiving and designing the research. The data were collected, analyzed, and interpreted by A. H., M. J., and M. E. All authors contributed equally to writing and revising the manuscript and approved the final manuscript.

Conflict of Interests Statement: The authors declare that they have no competing interests.

Data Availability: The dataset presented in the study is available on request from the corresponding author during submission or after publication.

Ethical Approval: IR.KMU.AH.REC.1400.384 .

Funding/Support: This study did not receive any specific funding from any community funding organization, or commercial or non-profit sectors.

Informed Consent: Written informed consent was obtained from the parents of the children for publication.

References

1. Molteni E, Absoud M, Duncan EL. Assessing the impact of the pandemic in children and adolescents: SARS-CoV-2 infection and beyond. *Lancet Child Adolesc Health*. 2022;**6**(4):216-7. [PubMed ID: 35143769]. [PubMed Central ID: PMC8820956]. https://doi.org/10.1016/S2352-4642(22)00035-9.
2. Rajapakse N, Dixit D. Human and novel coronavirus infections in children: a review. *Paediatr Int Child Health*. 2021;**41**(1):36-55. [PubMed ID: 32584199]. https://doi.org/10.1080/20469047.2020.1781356.
3. Langford BJ, So M, Raybardhan S, Leung V, Soucy JR, Westwood D, et al. Antibiotic prescribing in patients with COVID-19: rapid review and meta-analysis. *Clin Microbiol Infect*. 2021;**27**(4):520-31. [PubMed ID: 33418017]. [PubMed Central ID: PMC7785281]. https://doi.org/10.1016/j.cmi.2020.12.018.
4. Echeverria-Esnal D, Martin-Ontiyuelo C, Navarrete-Rouco ME, De-Antonio Cusco M, Ferrandez O, Horcajada JP, et al. Azithromycin in the treatment of COVID-19: a review. *Expert Rev Anti Infect Ther*. 2021;**19**(2):147-63. [PubMed ID: 32853038]. https://doi.org/10.1080/14787210.2020.1813024.
5. Yock-Corrales A, Lenzi J, Ulloa-Gutierrez R, Gomez-Vargas J, Antunez-Montes OY, Rios Aida JA, et al. High rates of antibiotic prescriptions in children with COVID-19 or multisystem inflammatory syndrome: A multinational experience in 990 cases from Latin America. *Acta Paediatr*. 2021;**110**(6):1902-10. [PubMed ID: 33742466]. [PubMed Central ID: PMC8251202]. https://doi.org/10.1111/apa.15847.
6. Buonsenso D, Riitano F, Valentini P. Pediatric Inflammatory Multisystem Syndrome Temporally Related With SARS-CoV-2: Immunological Similarities With Acute Rheumatic Fever and Toxic Shock Syndrome. *Front Pediatr*. 2020;**8**:574. [PubMed ID: 33042918]. [PubMed Central ID: PMC7516715]. https://doi.org/10.3389/fped.2020.00574.
7. Aguilera-Alonso D, Epalza C, Sanz-Santaeufemia FJ, Grasa C, Villanueva-Medina S, Melendo Perez S, et al. Antibiotic Prescribing in Children Hospitalized With COVID-19 and Multisystem Inflammatory Syndrome in Spain: Prevalence, Trends, and Associated Factors. *J Pediatric Infect Dis Soc*. 2022;**11**(5):225-8. [PubMed ID: 35188190]. [PubMed Central ID: PMC8903467]. https://doi.org/10.1093/jpids/piac003.
8. Velasco-Arnaiz E, Lopez-Ramos MG, Simo-Nebot S, Jordan I, Rios-Barnes M, Urrea-Ayala M, et al. Pediatric antimicrobial stewardship in the COVID-19 outbreak. *Infect Control Hosp Epidemiol*. 2021;**42**(5):642-4. [PubMed ID: 32576298]. [PubMed Central ID: PMC7338437]. https://doi.org/10.1017/ice.2020.312.
9. World Health Organization. *Advice for the public: Coronavirus disease (COVID-19). 2021*. 2022. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public.
10. Viesy S, Beikmohammadi H, Shadpirouz M, Afrashteh S. Evaluation of the COVID-19 Pandemic in Iranian Children: A Narrative Review Study. *Journal of Environmental Treatment Techniques*. 2022;**10**(3):216-23.
11. Damle B, Vourvahis M, Wang E, Leaney J, Corrigan B. Clinical Pharmacology Perspectives on the Antiviral Activity of Azithromycin and Use in COVID-19. *Clin Pharmacol Ther*. 2020;**108**(2):201-11. [PubMed ID: 32302411]. [PubMed Central ID: PMC7262099]. https://doi.org/10.1002/cpt.1857.
12. Sharma B, Sreenivasan P, Biswal M, Mahajan V, Suri V, Singh Sehgal I, et al. Bacterial coinfections and secondary infections in COVID-19 patients from a tertiary care hospital of northern India: Time to adhere to culture-based practices. *Qatar Med J*. 2021;**2021**(3):62. [PubMed ID: 34745914]. [PubMed Central ID: PMC8555674]. https://doi.org/10.5339/qmj.2021.62.
13. Saito S, Shahbaz S, Sligl W, Osman M, Tyrrell DL, Elahi S. Differential Impact of SARS-CoV-2 Isolates, Namely, the Wuhan Strain, Delta, and Omicron Variants on Erythropoiesis. *Microbiol Spectr*. 2022;**10**(4). e0173022. [PubMed ID: 35943266]. [PubMed Central ID: PMC9430111]. https://doi.org/10.1128/spectrum.01730-22.
14. Hosseninasab A, Shafiei Bafti M, Ebrahimi S, Anjomshoaa A, Sadeghi Zerandi F, Jafari M, et al. Coronavirus Disease 2019 in Children with Acute Respiratory Infection: A Study From Southeastern Iran. *Shiraz E-Medical Journal*. 2020;**21**(12). https://doi.org/10.5812/semj.108377.
15. Mehraeen E, Najafi Z, Hayati B, Javaherian M, Rahimi S, Dadras O, et al. Current Treatments and Therapeutic Options for COVID-19 Patients: A Systematic Review. *Infect Disord Drug Targets*. 2022;**22**(1). e260721194968. [PubMed ID: 34313204]. https://doi.org/10.2174/1871526521666210726150435.
16. Viner RM, Mytton OT, Bonell C, Melendez-Torres GJ, Ward J, Hudson L, et al. Susceptibility to SARS-CoV-2 Infection Among Children and Adolescents Compared With Adults: A Systematic Review and Meta-analysis. *JAMA Pediatr*. 2021;**175**(2):143-56. [PubMed ID: 32975552]. [PubMed Central ID: PMC7519436]. https://doi.org/10.1001/jamapediatrics.2020.4573.

17. Mistry P, Barmania F, Mellet J, Peta K, Strydom A, Viljoen IM, et al. SARS-CoV-2 Variants, Vaccines, and Host Immunity. *Front Immunol*. 2021;**12**:809244. [PubMed ID: 35046961]. [PubMed Central ID: PMC8761766]. https://doi.org/10.3389/fimmu.2021.809244.
18. Rana R, Tripathi A, Kumar N, Ganguly NK. A Comprehensive Overview on COVID-19: Future Perspectives. *Front Cell Infect Microbiol*. 2021;**11**:744903. [PubMed ID: 34595136]. [PubMed Central ID: PMC8476999]. https://doi.org/10.3389/fcimb.2021.744903.
19. Hinks TSC, Cureton L, Knight R, Wang A, Cane JL, Barber VS, et al. Azithromycin versus standard care in patients with mild-to-moderate COVID-19 (ATOMIC2): an open-label, randomised trial. *Lancet Respir Med*. 2021;**9**(10):1130-40. [PubMed ID: 34252378]. [PubMed Central ID: PMC8270523]. https://doi.org/10.1016/S2213-2600(21)00263-0.
20. Salehi M, Khalili H, Seifi A, Davoudi H, Darazam IA, Jahangard-Rafsanjani Z, et al. Antibiotic use during the first 6 months of COVID-19 pandemic in Iran: A large-scale multi-centre study. *J Clin Pharm Ther*. 2022;**47**(12):2140-51. [PubMed ID: 36054303]. [PubMed Central ID: PMC9538430]. https://doi.org/10.1111/jcpt.13761.
21. Marom T, Pitaro J, Shah UK, Torretta S, Marchisio P, Kumar AT, et al. Otitis Media Practice During the COVID-19 Pandemic. *Front Cell Infect Microbiol*. 2021;**11**:749911. [PubMed ID: 35071032]. [PubMed Central ID: PMC8777025]. https://doi.org/10.3389/fcimb.2021.749911.
22. King LM, Lovegrove MC, Shehab N, Tsay S, Budnitz DS, Geller AI, et al. Trends in US Outpatient Antibiotic Prescriptions During the Coronavirus Disease 2019 Pandemic. *Clin Infect Dis*. 2021;**73**(3):e652-60. [PubMed ID: 33373435]. [PubMed Central ID: PMC7799289]. https://doi.org/10.1093/cid/ciaa1896.
23. Struyf T, Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Leeflang MM, et al. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19. *Cochrane Database Syst Rev*. 2022;**5**(5). CD013665. [PubMed ID: 35593186]. [PubMed Central ID: PMC9121352]. https://doi.org/10.1002/14651858.CD013665.pub3.
24. Iijima H, Kubota M, Ogimi C. Clinical characteristics of pediatric patients with COVID-19 between Omicron era vs. pre-Omicron era. *J Infect Chemother*. 2022;**28**(11):1501-5. [PubMed ID: 35933077]. [PubMed Central ID: PMC9349025]. https://doi.org/10.1016/j.jiac.2022.07.016.