

# Evaluation of Antibiotic Use in Children's Respiratory Tract Infections at Primary Health Center in Tabanan Bali

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#### **ABSTRACT**

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**Background**: Respiratory Tract Infections are among the most common health problems affecting children globally, with a particularly high prevalence in Southeast Asia, including Indonesia. Inappropriate antibiotic use in treating respiratory tract infections can lead to antibiotic resistance. This study evaluates the rationality of antibiotic use in pediatric respiratory tract infections cases and assesses prescribing patterns based on established guidelines. Method: A descriptive observational study with a cross-sectional approach was conducted using purposive sampling. Data collected from 130 medical records of pediatric patients with respiratory tract infections (from January to March 2024) at a primary health care center in Tabanan, Bali were analyzed. The Gyssens method evaluated antibiotic rationality based on dosage, duration, and clinical indications. Data were analyzed descriptively to determine antibiotic prescribing patterns and compared with national antibiotic use guidelines. Results: The results showed that 46.1% of antibiotic use was included in the rational category (Category 0), while 43.1% were included in the use without clear indications (Category V). Amoxicillin is the most widely prescribed antibiotic (90.8%). These findings indicate a tendency to use antibiotics not by clinical guidelines. Conclusion: The use of antibiotics in pediatric patients with respiratory tract infections is mostly suboptimal. Interventions are needed to improve compliance with rational antibiotic use guidelines, including education for healthcare workers and ongoing monitoring of antibiotic prescribing patterns.



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# Introduction

Respiratory tract infections (RTIs) are a significant health issue worldwide, particularly among children [1,2]. These infections encompass various conditions such as pharyngitis, tonsillitis, sinusitis, and the common cold. While predominantly caused by viruses, these conditions often present symptoms similar to bacterial infections, resulting in frequent prescriptions of antibiotics [3]. Focusing on antibiotic use in children with respiratory tract infections (RTIs) is essential because children are particularly vulnerable to the negative effects of antibiotics. Their developing immune systems make them more prone to complications such as allergic reactions, gastrointestinal disturbances, and long-term issues like altered gut microbiota, which can contribute to chronic conditions like asthma or obesity [4,5]. Inappropriate use of antibiotics is a critical problem, as it can result in the development of antibiotic-resistant bacteria, posing a significant public health threat [6–8]. These concerns are especially significant because children's bodies are more sensitive to disruptions caused by antibiotics compared to adults [9].

Globally, 17.1 billion incidents of RTIs were reported in 2017 [10]. Southeast Asia reports a high incidence, and Indonesia ranks among the nations with excessive antibiotic prescriptions [7,11]. In Indonesia, RTIs are one of the most common causes of health service visits in children [12]. Based on Basic Health Research (Riset Kesehatan Dasar) in 2018, the prevalence of RTIs in Indonesia reached 93%, which significantly affecting boys and girls, with a slightly higher figure in girls [13]. This prevalence, coupled with the routine use of antibiotics, raises concerns about the rationality of antibiotic prescribing, especially in primary health services such as community health centers, where access to diagnostic tools may be limited [14].

Irrational use of antibiotics is not only a local issue but has become a global issue. The World Health Organization (WHO) has repeatedly highlighted the dangers of antibiotic resistance if antibiotics are misused. Inappropriate use includes giving antibiotics for viral infections, inappropriate doses, and excessive duration of treatment. In many cases, healthcare providers may prescribe antibiotics as a precaution or because of pressure from the patient's family, even though clinical guidelines suggest otherwise [15]. The WHO Assembly (2017) recommended that each country have a strategy and plan to control antimicrobial resistance which is translated into the National Action Plan for Controlling Antimicrobial Resistance 2020-2024 [16].

To address this issue, the Indonesian Ministry of Health has established guidelines for the rational use of antibiotics. These guidelines recommend the use of antibiotics only when bacterial infection is confirmed or highly suspected, and the selection of appropriate antibiotics based on the sensitivity patterns of common pathogens [17]. However, despite these guidelines, previous studies showed that compliance is inconsistent, leading to high rates of irrational antibiotic use, especially in children [18]. The purpose of this study is to assess the appropriateness of prescribing antibiotics in pediatric RTI patients at a primary health care in Tabanan, Bali Province. Using the Gyssens technique, antibiotic prescriptions are categorized to assess their logic based on established criteria such as acceptable indications, dose, duration, and antibiotic choice. By measuring the degree of unconscionable antibiotic use, this study hopes to highlight areas where guidelines might be modified, helping efforts to combat antibiotic resistance and improve children's health outcomes.

#### **Materials and Method**

This study used a descriptive observational design with a cross-sectional approach to evaluate the rationality of antibiotic use in pediatric RTI patients at the Primary Health Center in Tabanan, Bali, a region where antibiotic use remains a significant concern.

A total of 130 medical records that met the inclusion criteria for the period January to March 2024 were selected purposively. The inclusion criteria for this study focused on pediatric patients diagnosed with RTIs. Only children who were prescribed antibiotics and whose medical records were complete (containing relevant details such as diagnosis, prescribed medications, dosage, and duration of antibiotic treatment) were selected. The exclusion criteria included non-pediatric

patients, incomplete or missing medical records, patients diagnosed with conditions other than URTIs, and any duplicate records.

Evaluation using the Gyssens method assesses the rationality of antibiotic use. The Gyssens method is an evaluation of antibiotic use to assess the appropriateness of antibiotic use, including appropriateness of indication, appropriateness of selection based on effectiveness, toxicity, price and spectrum, duration of administration, dose, interval, route, and time of administration. This method is a widely recognized tool for evaluating the quality of antibiotic prescriptions and involves classifying prescriptions into various categories based on certain criteria. The categories range from rational use (Category 0) to use of antibiotics without clear indications (Category V). The Gyssens method is very useful in identifying deviations from established guidelines and best practices, making it an appropriate choice for the purposes of this research [19].

The data is presented descriptively to summarize patterns of antibiotic use, including the most frequently prescribed antibiotics and common reasons for irrational use. This analysis allows researchers to identify trends and areas where antibiotic use can be optimized. These findings were then compared with the rational antibiotic use guidelines set by the Indonesian Ministry of Health, to determine levels of compliance and identify potential areas for intervention. The Bali International University Ethics Committee granted permission to conduct the research, ensuring the confidentiality of all data and the protection of patient privacy, with approval number 02/0432/UNBI/EC/VI/2024, dated June 6, 2024.

## Results

The study gathered 130 medical records of pediatric patients with RTIs Table 1 shows that most patients (34.6%) were aged 4-7 years. Additionally, the data indicates that most participants (53.1%) were male. The data collection period was concentrated in January, with 43.1%. These findings offer an initial overview of the demographics of the pediatric RTI patients under study.

Table 1. Characteristic of respondents (n=130)

Characteristics	Total	
	n	%
Age		
< 1	31	23.8
1-3	28	21.5
4-7	45	34.6
8-12	26	20.0
Gender		
Male	69	53.1
Female	61	46.9
Period		
January	56	43.1
February	34	26.2
March	40	30.8

Table 2. Antibiotics Therapy for RTI

Type of Antibiotics	Total	
	n	%
Amoxicillin	118	90.8
Cefadroxil	8	6.2
Azithromycin	3	2.3
Cotrimoxazole	1	0.8

Table 2 presents the types of antibiotics given to children with respiratory tract infections. Children with RTIs are prescribed different types of antibiotics, as seen in Table 2. A total of 118 prescriptions (90.8%) for Amoxicillin indicate that it is the most prescribed antibiotic. For the rest, the antibiotic that usually prescribed to the patients are Cefadroxil (6.2%), Azithromycin (2.3%), and Cotrimoxazole (0.8%).

**Table 3**. Antibiotic Use Based on Gyssens Method (n=130)

Category	Description	Number of cases	%
VI	Medical record data is incomplete and cannot be evaluated	0	0.0
V	There is no indication for the use of antibiotics	56	43.1
IVA	There are other antibiotics that are more effective	1	0.8
IVB	There are other antibiotics that are safer	0	0.0
IVC	There are other antibiotics that are cheaper	0	0.0
IVD	There are other antibiotics with a narrower spectrum	0	0.0
IIIA	Prolonged use of antibiotics	1	8.0
IIIB	Too short use of antibiotics	1	8.0
IIA	Inadequate dosage	11	8.4
IIB	Inappropriate use of antibiotics administration interval	0	0.0
IIC	Inappropriate route	0	0.0
I	Untimely use of antibiotics	0	0.0
0	Rational use of antibiotics	60	46.1

Table 3 presents a qualitative assessment of antibiotic use in pediatric RTI patients based on the Gyssens Method. A total of 130 medical records were obtained that met the inclusion criteria. It was found that 46.1% of the antibiotic usage was rational, while 53.9% of the patients prescribed irrational antibiotics. The irrational antibiotic use was categorized as follows: category V (43.1%), category IVA, III, IIIB (each 0.8%), and category IIA (8.4%). These findings highlight the critical requirement for additional oversight and education about antibiotic prescribing practices.

## Discussion

#### Characteristics

Most of the patients were classified within the 4-7 years age group, comprising 34.6% of the total cases. Given their increased exposure to social environments like schools and their still-developing immune systems, younger children, especially those in preschool and early school age - seem more vulnerable to RTIs, according to this age distribution [12,20]. This aligns with earlier studies indicating that toddlers in Indonesia experience coughs and colds approximately 3 to 6 times annually [12]. Previous studies indicate that antibiotic prescriptions should be limited in children under 2 years, except for confirmed bacterial infections [9]. However, in Indonesia, antibiotics are commonly prescribed for minor ailments, such as a cough in children, due to cultural beliefs [21]. Local wisdom and misconceptions play a role in excessive antibiotic use, necessitating educational campaigns.

The gender distribution among pediatric patients with RTI indicates a higher prevalence in males, accounting for 53.1% of cases. The RTI incidents can occur to anyone, regardless of social class, age, gender, race, or ethnicity. The WHO reports that there is generally no variation in the prevalence of RTIs by gender, with males experiencing it more commonly, particularly in children. This might be because boys' lung function is less developed than that of girls [22,23].

The proportion of children diagnosed with RTIs in January was 43.1%. Seasonal changes and uncontrolled air pollution cause an increase in RTI cases [24]. The immune system needs to work harder throughout the change of the seasons, which decreases the body's immunity. RTI symptoms often include fever, cough, runny nose, sneezing, and sore throat. Additionally, because of unhealthy habits, bacteria, and viruses can travel through the air and infect other people [25].

## **Accuracy of indication**

The high prevalence of antibiotic prescriptions without proper indications of 56 cases (43.1%) indicates a large gap between clinical practice and established guidelines. This irrational use, especially for conditions such as the common cold and acute nasopharyngitis mostly caused by viruses, underscores the need for better diagnostic protocols and education among healthcare providers. Overuse of antibiotics not only puts individual patients at risk but also increases the threat of antibiotic resistance to the general public's health [26].

Several clinical guidelines recommend amoxicillin as the first-line treatment for bacterial respiratory tract infections due to its broad-spectrum action and reasonable cost. This usage is consistent with the recommendation. For children with acute bacterial sinusitis, amoxicillinclavulanate (45 mg/kg/day) is the antibiotic of choice, recommended by the Infectious Diseases Society of America (IDSA) [27].

These data indicate a shift towards prescribing policies based on clinical judgment rather than based on evidence because antibiotics are still given even if there is no disease caused by bacteria. When the rationality of antibiotic prescriptions was evaluated using the Gyssens approach, only 46.1% of prescriptions were rational (Category 0). A significant percentage of prescriptions (43.1%) fell into Category V, indicating the use of antibiotics beyond their prescribed use. This group includes viral diseases that are usually treated without the need for antibiotics, such as the common cold and acute nasopharyngitis. These results are in line with previous research who reported that the use of antibiotics in RTI was not in accordance with clinical guidelines which require that antibiotic administration be preceded by clinical and microbiological examinations [28]. These results highlight critical areas requiring further development and underline the importance of following clinical recommendations to avoid the overuse of antibiotics.

## Accuracy of selection based on effectiveness

The accuracy of antibiotic selection based on efficacy showed that one case (0.8%) was classified as category IVA, related to the availability of alternative antibiotics with higher efficacy. Given that more efficacious alternative treatments were not utilized, this represents a deviation from best practice in prescribing treatment. This situation highlights the importance of adhering to evidence-based guidelines to ensure that the most appropriate antibiotic is selected, optimize treatment outcomes, and reduce the risk of antibiotic resistance [29].

Amoxicillin (90.8%) was the most prescribed antibiotic, aligning with first-line treatment recommendations but raising concerns about potential overused [17]. Cefadroxil (6.2%), Azithromycin (2.3%), and Cotrimoxazole (0.8%) were also prescribed, requiring further evaluation for guideline adherence. The age factor is crucial in prescribing, as guidelines specify appropriate dosages based on pediatric weight and metabolism [30].

### Accuracy of selection based on dose and duration of administration

For dose and duration, 11 cases (8.4%) fell into Category IIA, which indicates incorrect dosing, either too high or too low, which can lead to antibiotic resistance or therapy failure. Additionally, 1 case (0.8%) fell into Category IIIA, indicating the use of antibiotics for a longer time than recommended, increasing the risk of side effects and resistance [26]. These results highlight the importance of closely tracking therapy duration and dosage to optimize therapeutic effects.

One of the important factors driving irrational antibiotic use is the difficulty of differentiating between viral and bacterial infections based on clinical symptoms alone [31]. This diagnostic uncertainty often leads to empirical antibiotic prescription, a practice that is inconsistent with the principles of rational antibiotic use [32]. In primary healthcare settings where resources and access to diagnostic tools, such as rapid tests or culture facilities, are limited, empirical treatment is becoming more common. However, it is important to emphasize that empirical treatment should be based on clinical guidelines and local antibiograms to reduce the risk of resistance [33].

The inappropriate antibiotic dosing, which occurred in 8.4% of cases, highlights another important issue that needs attention. Dosing errors can lead to suboptimal therapeutic outcomes, including treatment failure and the development of resistance. In the pediatric population, the dose must be calculated based on body weight and the specific pharmacokinetics and

pharmacodynamics of the antibiotic. Overdosing can increase the risk of toxicity, while too low a dose may not effectively eliminate the pathogen, allowing resistant strains to emerge [34]. These findings indicate the need for ongoing training and implementation of standard dosing guidelines in clinical practice.

The study found that 0.8% of cases involved long-term antibiotic use (Category IIIA). Although this percentage may seem small, it can have significant implications. Long-term antibiotic use can increase the risk of side effects and disrupt the normal flora, leading to an environment conducive to resistant bacteria. On the other hand, a treatment period that is too short (Category IIIB) can result in incomplete eradication of the infection, thereby increasing resistance [6].

These findings underscore the importance of adhering to recommended treatment durations to optimize patient outcomes and minimize risks. Addressing this issue requires a multifaceted approach. First, there must be an emphasis on educating and training healthcare providers about the principles of rational antibiotic use and the potential consequences of misuse. Second, the development and dissemination of clear, evidence-based guidelines tailored to local contexts is critical. Third, increasing access to diagnostic tools that accurately differentiate between viral and bacterial infections will help reduce empirical prescribing. Finally, implementing antibiotic stewardship programs at the primary care level can help monitor and guide antibiotic use, ensuring that programs are consistent with best practices and guidelines [6,29].

In the treatment and prevention of respiratory diseases, one of the most popular natural health products purchased worldwide is Echinacea supplementation. Echinacea is an immuno-modulator that can reduce the severity and duration of RTI when consumed at the start of symptoms, by reducing pro-inflammatory cytokines [35,36]. However, the use of Echinacea in children needs to be considered with caution due to limited scientific evidence consistently supporting its safety in this age group.

Recommendations for improvement include ongoing training of health care providers on appropriate use of antibiotics; implementation of strict prescribing guidelines; and regular monitoring and evaluation of prescribing patterns. This research is limited to one primary health center and uses secondary data that may inaccurate.

# Conclusion

This study highlights the significant gap between clinical practice and antibiotic prescribing guidelines in pediatric RTI cases. The findings emphasize the need for stricter antibiotic stewardship, healthcare provider training, and public awareness campaigns to prevent unnecessary antibiotic use. Future research should expand to other healthcare centers to establish a comprehensive national antibiotic use profile.

# **Declaration**

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### References

- Koofy E, Koofy NM EI, Shabrawi MH EI, Abd BA, Zein MM, Badawi NE. Patterns of respiratory tract infections in children under 5 years of age in a low-middle-income country. J Egypt Public Health Assoc. 2022; 97(1):22. https://doi.org/10.1186/s42506-022-00118-0.
- 2. Methi F, Størdal K, Telle K, Larsen VB, Magnusson K. Hospital admissions for respiratory tract infections in children aged 0-5 years for 2017/2023. *Front Pediatr.* 2023; 9:1–8. https://doi.org/10.3389/fped.2021.822985.
- 3. Dadgostar P. Antimicrobial Resistance: Implications and Costs. *Infect Drug Resist.* 2019; 12:3903-3910. https://doi.org/10.2147/IDR.S234610.
- 4. Saturio S, Rey A, Samarra A, Collado MC, Suárez M, Mantecón L, et al. Old folks, bad boon: Antimicrobial resistance in the infant gut microbiome. *Microorganisms*. 2023; 11(8):1–21.

- https://doi.org/10.3390/microorganisms11081907.
- 5. Shekhar S, Petersen FC. The dark side of antibiotics: Adverse effects on the infant immune defense against infection. *Front Pediatr.* 2020; 8:1–7. https://doi.org/10.3389/fped.2020.544460.
- 6. Muteeb G, Rehman T, Shahwan M, Aatif M. Origin of antibiotics and antibiotic resistance, and their impacts on drug development: A narrative review. *Pharmaceuticals*. 2023; 16(11):1615. https://doi.org/10.3390/ph16111615.
- 7. Widowati IGAR, Budayanti NNS, Januraga PP, Duarsa DP. Self-medication and self-treatment with short-term antibiotics in Asian countries: A literature review. *Pharm Educ.* 2021; 21(2):152–162. https://doi.org/10.46542/pe.2021.212.152162.
- 8. Dewi NLPS, Widowati IGAR, Wirajaya MKM, Maharianingsih NM. Antimicrobial resistance: Knowledge, attitude, and awareness in the Bali locals community. *J Farm Indones*. 2024; 16(1):108–113. https://doi.org/https://doi.org/10.35617/jfionline.v16i1.161.
- 9. Romandini A, Pani A, Schenardi PA, Pattarino GAC, De Giacomo C, Scaglione F. Antibiotic resistance in pediatric infections: Global emerging threats, predicting the near future. *Antibiotics*. 2021; 10(4):1–12. https://doi.org/10.3390/antibiotics10040393.
- 10. WHO. The WHO AWaRe (Access, Watch, Reserve) antibiotic book. World Health Organization. 2022.
- 11. Limato R, Lazarus G, Dernison P, Mudia M, Alamanda M, Nelwan EJ, et al. Articles optimizing antibiotic use in Indonesia: A systematic review and evidence synthesis to inform opportunities for intervention. *Lancet Reg Heal Southeast Asia*. 2022; 2:100013. https://doi.org/10.1016/j.lansea.2022.05.002.
- 12. Windi R, Efendi F, Qona A, Estiningtyas Q, Adnani S, Ramadhan K, et al. Determinants of acute respiratory infection among children under-five years in Indonesia. *J Pediatr Nurs*. 2021; 60:e54-e59. https://doi.org/10.1016/j.pedn.2021.03.010.
- 13. Indonesian Ministry of Health. *Hasil Riset Kesehatan Dasar Tahun 2018*. Indonesian Ministry of Health. 2018.
- Sulis G, Adam P, Nafade V, Gore G, Daniels B, Daftary A, et al. Antibiotic prescription practices in primary care in low- and middle-income countries: A systematic review and metaanalysis. *Plos Med.* 2020; 17(6):e1003139. https://doi.org/10.1371/journal.pmed.1003139.
- 15. Kohut MR, Keller SC, Linder JA. The inconvincible patient: how clinicians perceive demand for antibiotics in the outpatient setting. *Fam Pract.* 2020; 37(2):276–282. https://doi.org/10.1093/fampra/cmz066.
- 16. Coordinating Minister for Human Development and Culture of The Republic of Indonesia. *National Action Plan fot Control of Antimicrobial Resistance 2020-2024*. Jakarta: 2024.
- 17. Indonesian Ministry of Health. *Peraturan Menteri Kesehatan Republik Indonesia Nomor* 28 *Tahun* 2021 *Tentang Pedoman Penggunaan Antibiotik*. Indonesian Ministry of Health. 2021.
- Kilpatrick M, Hons RN, Hutchinson A, Bpharm EM. Paediatric nurses', childrens' and parents' adherence to infection prevention and control and knowledge of antimicrobial stewardship:
   A systematic review. Am J Infect Control. 2021; 49(5):622–639. https://doi.org/10.1016/j.ajic.2020.11.025.
- 19. Gyssens IC. Antibiotic policy. *Int J Antimicrob Agents*. 2011; 38:11–20. https://doi.org/10.1016/j.ijantimicag.2011.09.002
- 20. Chiappini E, Santamaria F, Marseglia GL, Marchisio P, Galli L, Cutrera R, et al. Prevention of recurrent respiratory infections Inter-society Consensus. *Ital J Pediatr.* 2021; 47(211):1–17. https://doi.org/10.1186/s13052-021-01150-0.
- 21. Azmi M, Hassali A, Suryawati S, Ismahanisa W, Wiladatika A. Public practices towards antibiotics: A qualitative study. *Clin Epidemiol Glob Heal*. 2020; 8:1277–1281. https://doi.org/10.1016/j.cegh.2020.04.027.
- 22. Chowdhury NU, Guntur VP, Newcomb DC, Wechsler ME. Sex and gender in asthma. *Eur Respir Rev.* 2021; 30(165). https://doi.org/10.1183/16000617.0067-2021.
- 23. Silveyra P, Fuentes N, Bauza DR. Sex and gender differences in lung disease. Lung Inflamm. Heal. Dis., Springer International Publishing; 2021, p. 227–258. https://doi.org/10.1007/978-3-030-68748-9.
- 24. Larsen L, Wensaas K, Emberland KE, Rortveit G. Respiratory tract infections in Norwegian primary care 2006 2015: a registry-based study. *Scand J Prim Health Care*. 2022; 40(2):173–180. https://doi.org/10.1080/02813432.2022.2069711.
- 25. Zhang N, Chen W, Chan PJ. Close contact behavior in indoor environment and transmission of respiratory infection. *Indoor Air.* 2020; 30(4):645–661. https://doi.org/10.1111/ina.12673.
- 26. Amann S, Neef K, Kohl S. Antimicrobial resistance (AMR). Br J Biomed Sci. 2019; 26(3).

- https://doi.org/10.1136/ejhpharm-2018-001820.
- 27. Ghaderi M, Venkateswaramurthy N. Antibiotic choice for respiratory infection in pediatric. *Int J Health Sci (Qassim)*. 2022; 6(S8):5868–5873. https://doi.org/10.53730/ijhs.v6nS8.13616.
- 28. Anggraini AB, Wirasmi S. Treatment patterns of acute respiratory tract infection in children under-fives in Bogor, Indonesia. *Heal Sci J Indones*. 2020; 11(1):9–14. https://doi.org/10.22435/hsji.v11i1.2714.
- 29. Oliveira I, Rego C, Semedo G, Gomes D, Figueiras A, Roque F, Herdeiro MT. Systematic review on the impact of guidelines adherence on antibiotic prescription in respiratory infections. *Antibiotics*. 2020; 9(9):546. https://doi.org/10.3390/antibiotics9090546.
- 30. Khan D, Kirby D, Bryson S, Shah M, Mohammed AR. Paediatric specific dosage forms: Patient and formulation considerations. *Int J Pharm.* 2022; 616:121501. https://doi.org/10.1016/j.ijpharm.2022.121501.
- 31. Duan L, Liu C, Wang D, Lin R, Qian P. The vicious cycle of the public's irrational use of antibiotics for upper respiratory tract infections: A mixed methods systematic review. *Front Public Heal.* 2022; 10:985188. https://doi.org/doi: 10.3389/fpubh.2022.985188.
- 32. Kaprou GD, Bergšpica I, Alexa EA, Alvarez-ord A, Prieto M. Rapid methods for antimicrobial resistance diagnostics. *Antibiotics*. 2021; 10(2):1–30. https://doi.org/10.3390/antibiotics10020209.
- 33. Gajic I, Kabic J, Kekic D, Jovicevic M, Milenkovic M, Culafic DM, et al. Antimicrobial susceptibility testing: A comprehensive review of currently used methods. *Antibiotics*. 2022; 11(427):1–26. https://doi.org/https://doi.org/10.3390/antibiotics11040427.
- 34. Tu Q, Cotta M, Raman S, Graham N, Roberts JA. Individualized precision dosing approaches to optimize antimicrobial therapy in pediatric populations. *Expert Rev Clin Pharmacol*. 2021; 00(00):1–17. https://doi.org/10.1080/17512433.2021.1961578.
- 35. Aucoin M, Cooley K, Richard P, Carè J. The effect of Echinacea spp. on the prevention or treatment of COVID-19 and other respiratory tract infections in humans: A rapid review. *Adv Integr Med Jou*. 2020; 7(4):203–217. https://doi.org/10.1016/j.aimed.2020.07.004.
- 36. Kembuan GJ, Lie W, Tumimomor AH. Potensial usage of immune-modulating supplements of the Echinacea genus for COVID-19 infection. *Int J Med Rev Case Rep.* 2020; 4(9):13–17. https://doi.org/10.5455/IJMRCR.immune-modulating-supplements-Echinacea-genus-covid-19-infection.