

Pharmacoeconomic Literature Review: Antibiotics As A Cost-Effective Treatment Of Typhoid Fever

Annastya Eka Agustin¹, Salman Salman²

^{1,2} Bagian Farmasi Fakultas Ilmu Kesehatan Universitas Singaperbangsa Karawang, Karawang, Indonesia

ARTICLE INFO

Keywords:

Cost-Effectiveness Analysis,
ACER,
Antibiotics,
Typhoid Fever

Email :

1910631210025@student.unsika.ac.id
Salman.kes@fikes.unsika.ac.id

ABSTRACT

Typhoid fever is a disease that we often encounter in people in Indonesia. With first-line treatment, namely antibiotics, to be precise, the chloramphenicol group. However, there are still many choices of antibiotic treatment therapy for typhoid fever such as cephalosporin, ampicillin, fluoroquinolone groups. With different groups, it is certain that they have different unit prices as well. This is what is done for inpatient typhoid fever patients by considering the cost-effectiveness side and desired therapeutic level. Effective cost can be determined through four categories. These four categories race against the results of ACER and ICER calculations.

Copyright © 2022 Jurnal Eduhealth.

All rights reserved.

is Licensed under a [Creative Commons Attribution-NonCommercial 4.0 International License \(CC BY-NC 4.0\)](https://creativecommons.org/licenses/by-nc/4.0/)

[NonCommercial 4.0 International License \(CC BY-NC 4.0\)](https://creativecommons.org/licenses/by-nc/4.0/)

1. INTRODUCTION

Pharmacoeconomics is the study of the cost-effectiveness required in treating a disease. Because each patient has their own economic level, taking into account the availability of existing drugs and the higher effectiveness desired by the patient. Pharmacoeconomics has four characteristic assessments including cost minimization analysis (AMiB), cost-effectiveness analysis (AEB), cost utility analysis (AUB), cost-benefit analysis (AMB). However, the analyzes that are commonly used are cost minimization analysis (AMiB) and cost-effectiveness analysis (AEB) because the interpretation results are easier to explain and use at every level of health facilities [5].

One of the diseases that needs to be studied pharmacoeconomics is typhoid fever. The definition of typhoid fever is a disease caused by the presence of *Salmonella typhi* bacteria through the feces or urine of flies sticking to food or drink. According to the Ministry of Health Number 364/MENKES/SK/V/2006, the targets to be infected by *Salmonella typhi* include the small intestine, spleen, and gallbladder. Which in turn, will release endotoxins as the body's response due to the presence of these bacteria, so that symptoms of fever will occur. Apart from fever, other symptoms experienced include discomfort in the digestive tract, enlarged liver, and excessive fatigue. With the emergence of clinical symptoms, it is more advisable for typhoid fever patients to undergo hospitalization.

This can be seen in the prevalence of typhoid fever hospitalization according to Indonesian health data for 2013 which ranks second with a total of approximately 81,116 (3.15%) people [6]. It was also strengthened according to WHO in 2013 typhoid fever was more common in endemic areas with a total of 75 – 80% cases [20]. Patients who experience typhoid fever the most are men, because most of them do activities outside the home more often than women [11]. In this treatment stage, antibiotics are the main drug to eliminate *Salmonella typhi* bacteria. Antibiotics have two mechanisms of action, namely, as a bactericidal or bacteriostatic. However, most of the antibiotics used are bactericidal or kill bacteria such as chloramphenicol,

It should be noted that the economic level in Indonesia is different. Therefore, in adjusting the use of antibiotics for typhoid fever one of the pharmacoeconomic analyzes is used, namely cost-effectiveness analysis (AEB). Before knowing AEB, first calculate the average cost - effectiveness ratio (ACER). From the results of ACER, it is possible to determine AEB through consideration of antibiotic

treatment therapy received by patients with costs incurred during hospitalization. Because the effectiveness of each drug has a different range in killing bacteria. When the results of the ACER and the effectiveness of the two drugs are balanced, it is necessary to calculate the incremental cost-effectiveness ratio (RIEB or ICER) to find out the price comparison if you want to change the treatment therapy [5].

From the background that has been presented, the author wants to analyze the cost-effectiveness of AEB related to typhoid fever. With the climate and conditions they face, they survive without thinking about whether the food or drink is free of bacteria or not. Likewise, looking at the economy and the poverty rate in Indonesia. Patients who are undergoing hospitalization have the right to get treatment with a good level of effectiveness and affordable costs.

2. METHOD

The method used in compiling this journal review is a literature review with sources taken from <https://scholar.google.com/> and <https://www.google.co.id/>. Journals, articles, and guidelines that are selected as references for a maximum of 10 years previously. While the statutory regulations used related to typhoid fever. In addition, other criteria use the keywords pharmacoeconomics, cost-effectiveness, typhoid fever, hospitalization, antibiotics, ACER, and ICER. After getting 20 journals that almost met these criteria, there were only 11 journals that really fit the topic and theme raised.

3. RESULTS AND DISCUSSION

The results that have been found from 11 journals, it can be observed that the most widely used antibiotic treatment therapy is the cephalosporin, fluoroquinolone, chloramphenicol, and penicillin classes. In addition, the majority of these antibiotics are bactericidal and have a broad spectrum. Broad spectrum means it can overcome gram negative bacteria and gram positive bacteria. However, because we are conducting a systematic review, we will discuss the reasons for pharmacological therapy and the factors considered in determining cost-effectiveness in typhoid fever.

Table 1. Data from the pharmacoeconomic literature review

Writer's name	Title	Antibiotics used and effectiveness of treatment (days or %)	ACER and ICER results	Information
(Jannah et al., 2019)	Cost Effectiveness of Using Ceftriaxone and Cefixime in Inpatient Typhoid Fever Patients at Anutapura Public Hospital Palu 2015-2017 Period	Ceftriaxone: 31.25 % Cefixime: 35.71 %	ACER: Ceftriaxone: Rp. 61,796.06 Cefixime: Rp. 60,781.97 ICER: IDR 53,676.45	Selection of antibiotics used cefixime. Because the effectiveness of the treatment was 35.71% and the ACER was lower.
(Rosyid et al., 2018)	Cost-Effectiveness Analysis of Treatment Using Cefotaxim and Ceftriaxone in Childhood	Cefotaxime: 4.93 days Ceftriaxone: 4.23 days	ACER: Cefotaxime: Rp. 298,810.00 Ceftriaxone: Rp. 314,973.00 ICER:-	In this study, choosing the drug cefotaxime was due to the ability of the majority of patients with a low ACER of IDR 298,810 and its

	Typhoid Fever Patients Hospitalized at Sultan Agung Islamic Hospital Semarang			effectiveness was slower for 4.93 days
(S Agatha et al., 2019)	Analysis of Cost Effectiveness in Pediatric Patients with Typhoid Fever at Bhayangkara Hospital Manado	Ceftriaxone: 4 days Cefotaxime: 5.6 days	ACER: Ceftriaxone: Rp. 526,609.00 Cefotaxim: Rp. 484,789.00 ICER: Rp. 340,582.00	Using the drug ceftriaxone with a faster treatment time, but the ACER is more expensive. If the patient wants to change treatment therapy from cefotaxime to ceftriaxone, an additional fee of Rp. 340,582.00
(Susono et al., 2014)	<i>Cost Effectiveness Analysis</i> Treatment of Pediatric Typhoid Fever Patients Using Cefotaxime and Chloramphenicol at the Inpatient Installation of Prof. Dr. Margono. Soekarjo	<i>Chloramphenicol</i> : 4.86 days <i>Cefotaxime</i> : 4.43 days	ACER: <i>Chloramphenicol</i> : IDR 299,098.00 <i>Cefotaxime</i> : Rp. 297,835.00 ICER: Rp. 312,104.00	This study used the drug Cefotaxime, which has a low ACER cost and high drug effectiveness.
(Magfirah, 2019)	Cost Effectiveness Analysis of Chloramphenicol and Ciprofloxacin in Typhoid Treatment at Datu Beru Hospital, Takengon City, Central Aceh	Chloramphenicol: 12.21 days Ciprofloxacin: 5.04 days	ACER: Chloramphenicol: Rp. 14,297.81 Ciprofloxacin: Rp. 647,2 ICER: Rp. 3,884.6	The most cost effective use of the ciprofloxacin antibiotic with a shorter length of treatment and lower ACER.
(Lorensia et al., 2018)	<i>Cost Effectiveness Analysis</i> Chloramphenicol and Ceftriaxone for the Treatment of Typhoid Fever in Adult Patients at Sanglah Hospital, Denpasar	Chloramphenicol: 10.22 days Ceftriaxone: 4.27 days	ACER: Chloramphenicol: Rp. 250,045.42 Ceftriaxone: Rp. 491,140.72 ICER:-	Ceftriaxone is considered more effective than chloramphenicol. Because the level of effectiveness is higher than the use of chloramphenicol.

(Haluang et al., 2015)	Cost Analysis of Using Antibiotics in Children with Typhoid Fever in the Inpatient Installation of Prof. Dr. RD Kandou Manado Period January 2013 – June 2014	General Patient Status:	ACER: General Patient Status:	Effective cost for the treatment of typhoid fever, namely chloramphenicol for general patient status and amoxicillin for patient status receiving JKN, with the lowest ACER value among the use of other antibiotics
		<i>Thiamfenicol</i> : 4 days	<i>Thiamfenicol</i> : Rp. 16,817.00	
		<i>Ceftriaxone</i> : 8.5 days	<i>Ceftriaxone</i> : Rp. 16016.00	
		<i>Cefixime</i> : 5 days	<i>Cefixime</i> : Rp. 24,546.00	
		<i>Chloramphenicol</i> : 4 days	<i>Chloramphenicol</i> : IDR 360.00	
		<i>Ciprofloxacin</i> : 4 days	<i>Ciprofloxacin</i> : IDR 872.00	
		<i>Ceftriaxone</i> - <i>Ampicillin</i> - <i>Ciprofloxacin</i> : 18 days	<i>Ceftriaxone</i> - <i>Ampicillin</i> - <i>Ciprofloxacin</i> : IDR 6261.00	
		<i>Amoxicillin</i> - <i>Chloramphenicol</i> : 8 days	<i>Amoxicillin</i> - <i>Chloramphenicol</i> : IDR 1841.00	
		JKN Patient Status:	JKN Patient Status:	
		<i>Thiamfenicol</i> : 4.7 days	<i>Thiamfenicol</i> : Rp. 4,996.00	
		<i>Ceftriaxone</i> : 5.8 days	<i>Ceftriaxone</i> : Rp. 7,821.00	
		<i>Cefixime</i> : 6.4 days	<i>Cefixime</i> : Rp. 12,962.00	
		<i>Chloramphenicol</i> : 11 days	<i>Chloramphenicol</i> : IDR 947.00	
		<i>Amoxicillin</i> : 5 days	<i>Amoxicillin</i> : IDR 762.00	
		<i>Ceftriaxone</i> - <i>Cefixime</i> : 7,4 days	<i>Ceftriaxone</i> - <i>Cefixime</i> : IDR 7,892	
		<i>Chloramphenicol</i> - <i>Cefixime</i> : 9.7 days	<i>Chloramphenicol</i> - <i>Cefixime</i> : IDR 5865.00	
		<i>Cefixime</i> - <i>Thiamfenicol</i> : 6,5	<i>Cefixime</i> - <i>Thiamfenicol</i> : IDR 20,969	
		<i>Chloramphenicol</i> - <i>Ceftriaxone</i> : 13 days	<i>Chloramphenicol</i> - <i>Ceftriaxone</i> : IDR 5,355	
		<i>Amoxicillin</i> - <i>Cefixim</i> : 9 days	<i>Amoxicillin</i> - <i>Cefixim</i> : IDR 5521.00	

ICER:-

(Beatrix et al., 2018)	Cost Effectiveness Analysis of Typhoid Fever Pediatric Treatment Using Cefixime and Cefotaxime at Pancaran Kasih General Hospital GMIM Manado	Cefixime: 4.35 days Cefotaxime: 4.38 days	ACER: Cefixime: Rp. 585,497.00 Cefotaxime: Rp. 592,917.00 ICER: Rp. 1,668,767	Using the antibiotic cefixime because of its high effectiveness and low ACER results.
(Rosyid et al., 2017)	Cost Effectiveness Analysis of Typhoid Fever Treatment in Children Using Chloramphenicol and Cefixime Antibiotics (Analytical Observational Study at Sultan Agung Islamic Hospital Semarang. Period January - December 2015.	Baitun Nisa Room 2: Chloramphenicol: 5 days Cefixime: 4.15 days Baitun Nisa Room 3: Chloramphenicol: 5.16 days Cefixime: 4.6 days	ACER: Baitun Room Nisa 2: Chloramphenicol: Rp. 376,775.00 Cefixime: Rp. 513,032.00 Baitun Nisa Room 3: Chloramphenicol: Rp. 296,980.00 Cefixime: Rp. 434,108.00 ICER:- ACER: Ceftriaxone: Rp. 1,303,603 Cefotaxime: Rp. 1,090,814 ICER:-	Using the antibiotic chloramphenicol, because the cost of the ACER is lower even though the effectiveness of the drug is low. However, on the one hand, there is no need to pay additional fees to change treatment therapy
(Tuloli, 2017)	<i>Cost-effectiveness Analysis</i> Ceftriaxone and Cefotaxime Antibiotic Therapy in Typhoid Patients at RSUD Dr. M.M Dunda Limboto	Ceftriaxone: 2.8 days Cefotaxime: 3.7 days	ACER: Ceftriaxone: Rp. 1,303,603 Cefotaxime: Rp. 1,090,814 ICER:-	This research decided to use ceftriaxone antibiotic considering its effectiveness and high ACER value.
(Nurmainah et al., 2017)	Cost Effectiveness of Using Ampicillin and Cefotaxime in Pediatric Typhoid Fever Patients	Ampicillin: 38% Cefotaxime: 76%	ACER: Ampicillin: Rp. 26,290.00 Cefotaxim: Rp. 15,710.00 ICER: Rp. 5.3777,71	Using Cefotaxime because the effectiveness of the treatment is higher.

In the cost-effectiveness analysis (AEB), the average cost-effectiveness ratio (ACER) and incremental cost-effectiveness ratio (ICER) are needed. The ACER formula is influenced by the

expenditure of funds needed during hospitalization divided by the effectiveness of drug therapy that has been prescribed in the form of percent or days. While the ICER is taken from the total cost of the two drugs compared divided by the therapeutic effectiveness of the two drugs used. The results from ACER and ICER will be presented in rupiah [4]. The following is the formula for ACER and ICER:

$$ACER = \frac{Biaya}{Efektivitas\ Terapi}$$

$$ICER = \frac{\Delta Total\ Biaya}{\Delta Efektivitas}$$

The biggest determining factor for AEB is the ACER calculation, because in the results there will be categories that need to calculate ICER or not. The ICER calculation aims to find out the cost comparison if the treatment therapy is replaced according to the effectiveness, the ability of the hospital, and the ability of the patient in terms of funds. There are four categories to determine, namely:

Table 2. Pharmacoeconomic group category in determining AEB

Effectiveness – cost	Lower cost	Same cost	Higher costs
Lower effectiveness	A (ICER calculation required)	B	C (dominated)
Same effectiveness	D	E	F
Higher effectiveness	G (Dominant)	H	I (ICER calculation required)

1. The ACER results of the two drugs obtained can be reviewed by considering high treatment effectiveness and the same expenditure (H) or the same treatment effectiveness, but lower expenditure (D), and higher treatment effectiveness with lower expenditure (G). If entered from one of the columns H, D, and G, there is no need to calculate the ICER. Because it is certain, including cost-effective analysis [5].
2. The ACER results of the two drugs obtained can be reviewed with consideration of lower effectiveness and the same expenditure (B), or the same drug effectiveness, but higher expenditure (F), and lower effectiveness, but higher expenditure (C). So, there is no need to assess it as an alternative because it is not considered as a cost-effective treatment for patients [5].
3. The ACER results of the two drugs obtained can be reviewed with the same considerations of effectiveness and cost (E). You can see other comparisons that can be chosen as the effectiveness of the treatment such as the ease of getting it, a better drug mechanism, according to management, and the availability of every level of existing health facilities [5].
4. The ACER results of the two drugs obtained can be reviewed with consideration of low effectiveness and cost (A) or high effectiveness and cost (I). Preferably, it is necessary to calculate the ICER first [5].

The AEB results that have been reviewed are included in columns G, C, A, and I. When columns G and C are compared, they prefer column G as their choice. Because the costs incurred are affordable, and the effectiveness of the treatment is fast. So that patients can save costs while undergoing hospitalization. Meanwhile, when A and I are compared, there is no ICER value.

In journals that get columns A and I, most of the journals that have been reviewed choose high effectiveness and high costs and vice versa. This is done by considering the condition of the patient and the hospital. When the availability of drugs is sufficient, the patient and the hospital agree. Thus, additional costs for drug procurement and therapy costs can be made. However, when the hospital agrees, but the patient is not willing because of limited funds, it can be discussed with the doctor and pharmacist.

In addition, the class of antibiotics used in the journal is chloramphenicol. Chloramphenicol is one of the first lines of typhoid fever with its mechanism of action by forming peptide bonds during protein synthesis [16]. However, the side effects are dangerous for children, namely aplastic anemia and inhibition of the formation of red blood cells in the spinal cord (myelodepression) [2]. In addition, resistance to chloramphenicol can occur through the bacterial enzyme *Salmonella typhi* in the form of chloramphenicolacetyl – transferase [16].

The second antibiotic used was ciprofloxacin in the fluoroquinolone group. The mechanism of action is carried out by penetrating *Salmonella typhi* into the tissue by interfering with the formation of nucleic acids. However, just like chloramphenicol, ciprofloxacin is dangerous to give to children because it can cause damage to the joints and stunt the child's growth. However, it can still be used at this time with doses that have been adjusted by doctors and pharmacists for typhoid fever patients [12].

Furthermore, the third antibiotic, namely amoxicillin and ampicillin which is a penicillin group. This antibiotic works by blocking the formation of bacterial cell walls, so that *Salmonella typhi* bacteria will not experience growth. The penicillin group can also develop bacterial resistance through the β lactamase enzyme process which will eliminate the effectiveness of the antibiotic [16].

The latter, namely, cephalosporin class antibiotics such as ceftriaxone, cefixime, and cefotaxime. It has the same mechanism of action as the penicillin group. The cephalosporin group is the second line after chloramphenicol for typhoid fever. Cephalosporins are also widely used because they have fairly good effectiveness, this can be seen in the results of Sunaryani et al, (2019). In the results of this study it is known that the protein that binds to cefotaxime is at least 36%. So that there are more and more free drugs in the body and can produce good treatment effectiveness.

So it can be seen that, cost-effectiveness analysis can use cephalosporins and fluoroquinolones. Because it has a fast level of effectiveness of treatment and costs that are still affordable. Although, the cephalosporin and fluoroquinolone groups are the second line of typhoid fever. However, it is unlikely that bacterial resistance will occur. And also, the side effects that occur in the cephalosporin class do not harm either the patient, especially for children.

4. CONCLUSION

The conclusion from the pharmacoeconomic study conducted regarding the Cost-Effectiveness Analysis (AEB) on typhoid fever is not only prioritizing costs. However, the effectiveness of treatment, side effects, and the possibility of resistance to *Salmonella typhi* bacteria. That way, doctors and pharmacists can provide the best treatment for typhoid fever patients. In addition, using the ACER and ICER values according to the guidelines to consider the economic capacity of people who are being hospitalized for typhoid fever.

REFERENCES

- [1] Beatrix, KMJ, Citraningtyas, G. and Sudewi, S. Cost-Effectiveness Analysis of Typhoid Fever Pediatric Treatment Using Cefixime and Cefotaxime at Pancaran Kasih General Hospital GMIM Manado. *Pharmacon*. 2018;7(2):17–27.
- [2] Gunawan, DO, Indriani, L. and Dewi, M. Evaluation of Antibiotic Administration in Typhoid Fever Patients at the Inpatient Installation of Azra Hospital, Bogor City. *Phytopharmaka Scientific Journal of Pharmacy*. 2020;10(1):54–64.
- [3] Haluang, O., Tjitrosantoso, H. and Kojong, NS Analysis of the Cost of Using Antibiotics in Children with Typhoid Fever in the Inpatient Installation of PROF Hospital. Dr. RD Kandou Manado Period January 2013 - June 2014. *Pharmacon*. 2015;7(2):17–27.
- [4] Jannah, N., Ihwan and Tandah, MR Cost Effectiveness of Using Ceftriaxone and Cefixime in Inpatient Typhoid Fever Patients at Anutapura General Hospital, Palu, 2015-2017 Period. *Medicamento Scientific Journal*. 2019;5(1):45–50.
- [5] Indonesian Ministry of Health. 2013. Guidelines for the Application of Pharmacoeconomic Studies. Directorate of Pharmaceutical Development and Medical Devices. Jakarta.
- [6] Indonesian Ministry of Health. 2013. Indonesia health profile 2013. Indonesian Ministry of Health. Jakarta.

- [7] Lorensia, A., Queljoe de, D. and Dwiwe, M. Cost-Effectiveness Analysis of Chloramphenicol and Ceftriaxone for the Treatment of Typhoid Fever in Adult Patients at Sanglah Hospital, Denpasar. *Media Pharmaceutica Indonesiana*. 2018;2(2):105–112.
- [8] Magfirah, A. Cost-Effectiveness Analysis of Chloramphenicol and Ciprofloxacin in Typhoid Treatment at Datu Beru Hospital, Takengon City, Central Aceh. *Serambi Saintia: Journal of Science and Applications*. 2019;7(2):84–91.
- [9] Minister of Health of the Republic of Indonesia, Decree of the Minister of Health of the Republic of Indonesia Number 364/MENKES/SK/V/2006 concerning Guidelines for Typhoid Fever Control, obtained through the internet site: <http://hukor.kemkes.go.id/hukor/0/2006/21>. Downloaded on 07 September 2022.
- [10] Nurmainah, N., Syabriyanti, S. and Susanti, R. Cost Effectiveness of Using Ampicillin and Cefotaxime in Pediatric Patients with Typhoid Fever. *Indonesian Public Health Media*. 2017;13(2):131–138.
- [11] Pramitasari. 2013. Risk Factors for Typhoid Fever in Patients Treated at the Ungaran Regional General Hospital. Thesis. Diponegoro University.
- [12] Pratiwi, I., Azis, S. and Kusumastuti, E. Rationality of the Use of Ciprofloxacin Antibiotics in Patients with Typhoid Fever. *Biomedical Journal of Indonesia: Biomedical Journal, Faculty of Medicine, Sriwijaya University*. 2018;4(2):46–51.
- [13] Rosyid, A., Santoso, A. and Andriani, IT Cost Effectiveness Analysis of Medication Using Cefotaxim and Ceftriaxone in Inpatient Child Typhoid Fever Patients at Sultan Agung Islamic Hospital Semarang. *Borneo Journal of Pharmascience*. 2018;2(1):31–39.
- [14] Rosyid, A., Timur, WW and Atikannafirin. Cost Effectiveness Analysis of Typhoid Fever Treatment in Children Using Chloramphenicol and Cefixime Antibiotics (Analytical Observational Study at Sultan Agung Islamic Hospital Semarang Period January - December 2015). *Indonesian Pharmaceutical Media*. 2017;12(2):1248–1258.
- [15] S Agatha, A., Citraningtyas, G. and Sudewi, S. Analysis of Cost-Effectiveness in Pediatric Patients with Typhoid Fever at Bhayangkara Hospital Manado. *Pharmacon*. 2019;8(2), 335–342.
- [16] Sandika, J. and Suwandi, JF Sensitivity of Salmonella thypi Causes Typhoid Fever to Several Antibiotics. *majority*. 2017;6(1):41–45.
- [17] Sunaryani, R., Mukaddas, A. and Tandah, RM Comparison of the Effectiveness of Third Generation Cephalosporin Antibiotics in Typhoid Fever Patients at Madani Regional Hospital, Central Sulawesi Province, 2017 Period. *Scientific Journal of Medicamento*. 2019;5(1):58–62.
- [18] Susono, RF, Sudarso and Galistiani, GF Cost Effectiveness Analysis Treatment of Pediatric Typhoid Fever Patients Using Cefotaxime and Chloramphenicol in the Inpatient Installation of Prof. Hospital. Dr. Margono Soekarjo. *Pharmacy*. 2014;11(1):86–97.
- [19] Tuloli, TS Cost-Effectiveness Analysis of Ceftriaxone and Cefotaxime Antibiotic Therapy in Typhoid Patients at RSUD Dr. MM Dunda Limboto. *Entropy Journal*. 2017;12(1):97–103.
- [20] WHO. 2013. Guidelines on the quality, safety and efficacy of typhoid conjugate vaccines, obtained from the internet site: <https://www.who.int/publications/m/item/tcv71-recommendations>. Downloaded on October 23, 2022.