Jurnal Farmasi dan Ilmu Kefarmasian Indonesia
Pharmacy and Pharmaceutical Sciences Journal
Published by Faculty of Pharmacy Universitas Airlangga
OPEN ACCESS
E-ISSN 2580-8303
P-ISSN 2406-9388

Jurnal Farmasi dan Ilmu Kefarmasian Indonesia Vol. 10 No. 3 December 2023, 360-368
DOI: 10.20473/jfiki.v10i32023.360-368
Available online at https://e-journal.unair.ac.id/JFIKI/

Five Years Outpatients Antibiotics Consumption at Public Tertiary Hospital in Bengkulu According to Access, Watch and Reserve Classification

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Submitted: 5 October 2023
Revised: 6 December 2023
Accepted: 13 December 2023

Abstract

***Background**: Access, Watch, and Reserve (AWaRe) antibiotics classification was released in 2019 by the World Health Organization (WHO) to enhance antimicrobial stewardship programs in all healthcare facilities. As a result, WHO advises global action to increase the availability of antibiotics from the Access group by more than 60%.**Objective**: to determine antibiotics consumption for outpatients at a public tertiary hospital in Bengkulu, Sumatera-Indonesia, from 2018 to 2022, focusing on antibiotics from Access class according to the AWaRe classification from WHO and Ministry of Health Republic of Indonesia (MoHRI). **Methods**: This is a cross-sectional survey analyzing aggregate data on antibiotics use for outpatients at the hospital during the study period. Data on antibiotics were collected from the hospital pharmacy department, while data on patient visits were collected from the medical records department. The quantity of antibiotics used was calculated using the ATC/DDD method and expressed in DDD/1000 patient-day (PD), which was then converted into a percentage. **Results**: During the study period, 50-60% and 65-73% out of 14-19 antibiotic agents are from Access class according to WHO and MoHRI AWaRe classification, respectively. Quantitatively, according to the WHO and MoHRI AWaRe classification, the consumption of antibiotics from the Access class was 25-50% and 33-71% of total consumption, respectively. In addition, the segment of drug utilization 90% (DU90%) of antibiotics was dominated by antibiotics from Watch class. **Conclusion**: The hospital has not yet met the WHO target for antibiotic consumption from the Access class, highlighting the need for some effective efforts from Watch class to limit the usage of antibiotics.*

***Keywords**: antibiotics consumption, antibiotics resistance, ATC/DDD, AWaRe classification 2*

How to cite this article:
Amrulloh, L. S. W. F., Harmastuti, N., Prasetiyo, A. & Herowati, R. (2023). Analysis of Molecular Docking and Dynamics Simulation of Mahogany (*Swietenia macrophylla* King) Compounds Against the PLpro Enzyme SARS-COV-2. *Jurnal Farmasi dan Ilmu Kefarmasian Indonesia*, 10(3), 360-368. http://doi.org/10.20473/jfiki.v10i32023.360-368

P-ISSN: 2406-9388
E-ISSN: 2580-8303

INTRODUCTION

The prevalence of antimicrobial resistance (AMR) has become a significant threat to global public health (Nwobodo *et al*., 2022; Xiao, 2023), and it was estimated that the number of AMR-related fatalities in 2019 was 4.95 million globally (Daneman *et al*., 2023; Wilson *et al*., 2022). Ranjbar *et al*. (2022) listed *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, and *Acinetobacter baumannii* as the six most lethal pathogens associated with antibiotic resistance. The overuse of antibiotics and high prescription of broad-spectrum antibiotics have been known to be the development of AMR (Dadgostar, 2019). Nationally, in Indonesia, high empirical use of broad-spectrum antibiotics and inadequate adherence to recommendations have been reported from a survey investigating antibiotics in six hospitals (Limato *et al*., 2021).

Responding to the threat of AMR requires regulations to control antibiotic use; in 2021 The Ministry of Health Republic of Indonesia (MoHRI) released a National Guideline on antibiotic use to strengthen and emphasize the implementation of antibiotics stewardship strategy. This guideline aims to improve patient outcomes through a coordinated program related to antibiotic use one important recommended strategy is to categorize antibiotics into AWaRe (Access, Watch, Reserve) classification (MoHRI, 2021). This categorization was determined following the same categorization previously released by the World Health Organization (WHO) as a tool for evaluating antibiotic consumption to optimize antibiotic use and further slow down the progress of AMR. As part of the worldwide plan to prevent AMR, WHO has set a target of at least 60% availability and usage of antibiotics in the Access class from total antibiotic consumption.(WHO, 2020).

Reports on the evaluation of antibiotics use in Indonesia that have been published until 2022 indicate that the consumption of antibiotics from the Watch group continues to dominate in health facilities, up to more than 60% (Azyenela *et al*., 2022). Another study also reported that 30% of antibiotic use was irrational, and ceftriaxone was found to be the most used antibiotic (Diah, 2022). Similar findings have also been reported from an evaluation of antibiotic use conducted in Vietnam revealing a high proportion of antibiotic prescriptions for acute respiratory infections (ARI) in primary health care and high use of antibiotics from Watch class in children (Nguyen *et al*., 2023). These indicate that monitoring and evaluation of antibiotics use to achieve the prudent use of antibiotics should be continuously conducted.

To achieve the target of rational use of antibiotics, continuous studies to evaluate the profile and quality of antibiotics use are required both quantitatively and qualitatively (WHO, 2015). For quantitative evaluation, the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) method is recommended as one important key of the antibiotics stewardship program (WHO, 2022). The quantity of antibiotics used expressed in the DDD unit can provide a picture of the overall consumption of antibiotics and trends in their use for assessing the achievement of antibiotic control goals (Hollingworth & Kairuz, 2021). The purpose of this study was to capture the profile of antibiotic use for outpatients at a public tertiary teaching hospital in Bengkulu, Sumatera – Indonesia, specifically in accordance with the AWaRe classification by following the AWaRe categorization released by WHO and MoHRI.

MATERIALS AND METHODS

Study design

This study is a cross-sectional survey using aggregate data on antibiotics use for outpatients at a public tertiary teaching hospital in Bengkulu, Sumatera, Indonesia. Retrospective data of antibiotics use for five years during 2018-2022 were used for this study, including all systemic antibiotics coded as J01 in the ATC classification. The hospital has granted permission to conduct this study through the permission letter number 074/35/BID-DIK/II/2023.

Method of collecting data

Data were collected from the Hospital Pharmacy Department (HPD) using the Hospital Information System (SIMRS). Antibiotic use-related data were collected, including the name of antibiotic agents, dosage form and dosage strength, as well as the monthly quantity of antibiotics used during the study period (2018-2022). Data on the number of patient visits per year were collected from the medical record department.

Data analysis

The quantity of each antibiotic was calculated in DDD units by dividing the consumption of each antibiotic in grams by the DDD value as determined by WHO (WHO, 2022). The final unit used to express the quantity of antibiotic use in this study is DDD/1000 patient-days (DDD/1000PD), which is the unit widely used and globally accepted to quantify drug use for outpatients. The calculation of DDD/1000PD was

P-ISSN: 2406-9388
E-ISSN: 2580-8303

conducted by combining the data on antibiotics use and the data on the number of outpatient visits. This is accomplished by multiplying the quantity of antibiotic use per month expressed in DDD by 1000, and then the result is divided by the number of outpatient visits per month accordingly (Apriyanti & Saepudin, 2023). The antibiotics found in this study were then categorized as 'Access', 'Watch', and 'Reserve' by following the 2019 WHO AWaRe classification as well as the 2021 MoHRI AWaRe classification. Antibiotics not listed in those classifications were categorized as 'Unclassified'. The proportion of the consumption of antibiotics from each Access, Watch, and Reserve class was then determined by calculating the quantity of antibiotics in each class, expressed in DDD/1000PD, relative to the total antibiotic consumption. Finally, the proportion of antibiotic use from each class during the study period was calculated.

RESULTS AND DISCUSSION

Based on the generic names, this study identified 19 antibiotic agents that were used for the outpatient at the hospital during the study period. Table 1 displays all antibiotic agents used at the hospital categorized by following the AWaRe categorization released by WHO and MoHRI. Fourteen antibiotic agents were used consistently during the study period, and the highest number of antibiotic agents was found in 2018, in which 19 antibiotic agents were used. Meanwhile, the lowest number of antibiotic agents was found in 2022, with only 14 antibiotic agents used this year.

Ten and thirteen antibiotic agents used for outpatients at the hospital are from the Access class according to WHO and MoHRI AWaRe categorization, respectively. In the meantime, 9 and 5 antibiotic agents used for outpatients at the hospital are from Access class according to WHO and MoHRI AWaRe categorization, respectively. There are some differences in term of AWaRe categorization released by WHO and MoHRI, as the categorization released by MoHRI was determined by accommodating some circumstances related to antibiotics use nationally in Indonesia. For instance, erythromycin, spiramycin, and ciprofloxacin are categorized in the Access class by MoHRI, while WHO categorized those antibiotic agents in the Watch class. Meanwhile, pipemidic acid is listed in Watch class according to the WHO AWaRe categorization, and it is not listed in the MoHRI categorization. As the results of different categorizations, this study found that 50-60% and 65-73% of the 14-19 antibiotics used for outpatients at the hospital are from the Access class following WHO and MoHRI AWaRe classification, respectively.

In terms of the quantity, the consumption of antibiotics for outpatients at the hospital tends to fluctuate during the study period. On average, antibiotics consumption for outpatients at the hospital per year during the study period is 140.9 DDD/1000PD, with the highest and the lowest quantities of antibiotics were found in 2021 and 2022, with 155.1 DDD/1000PD and 106.1 DDD/1000PD, respectively. In contrast with the quantity of antibiotics consumption, the highest and the lowest number of outpatient visits were found in 2018 and 2021, with 105,142 and 58,226 visits, respectively. The quantity of antibiotics used was expressed in DDD/1000PD to eliminate the influence of the number of outpatient visits so that the quantity can be compared adequately. In comparison with the previously reported findings, the quantity of antibiotics used in this study is significantly lower compared to antibiotics consumption in Sao Paulo, Brazil, with 889.11 DDD/1000PD (Assis *et al*., 2022).

The selection of antibiotic agents used in hospitals could be influenced by the pattern of infectious diseases, as well as the policies on antibiotic use. Figure 1 shows that antibiotic agents from the quinolone subgroup, including ciprofloxacin, levofloxacin, ofloxacin, and other quinolones such as pipemidic acid, were the most commonly used antibiotics, especially from 2018 to 2020. Among the quinolone subgroup, ciprofloxacin was the most used antibiotic (19.35 DDD/1000PD). Other studies have reported that ciprofloxacin and other quinolone antibiotics are commonly prescribed in hospitals (Feroche & Alemu, 2021; Rehman *et al*., 2019). However, the use of fluoroquinolone antibiotics needs to be evaluated continuously, as their use is frequently inappropriate, and there is a significant increase in bacterial resistance to ciprofloxacin and other fluoroquinolone groups (Dobbyn *et al*., 2022). The ATC J01 M group and other quinolone groups, such as pipemidic acid, are also extensively used for outpatients at the hospital with an average quantity of 21.66 DDD/1000PD. Due to its effective antibacterial activity against gram-negative and some gram-positive (Alves *et al*., 2020), pipemidic acid is extensively used as a therapeutic agent to treat urinary tract infections.

In addition to the use of the quinolone subgroup, Figure 1 also shows that the other beta-lactam antibiotics were commonly used with relatively consistent in terms of quantity during the study period. First and third-generation of cephalosporins were used for outpatients at the hospital, and interestingly, the

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E-ISSN: 2580-8303

consumption of cefixime, which is categorized within Watch class, was higher (24.14 DDD/1000 PD) than cefadroxil (11.14 DDD/1000PD) which is categorized within Access class in both categorizations released by WHO and MoHRI.

Table 1. Antibiotic Consumption for outpatients at the hospital following ATC Classification and AWaRe Categorization from WHO and MoHRI during 2018-2022

ATC Code		AWaRe Categorization		Quantity of Antibiotic Use (DDD/1000PD)				
		WHO	**MoHRI**	**2018**	**2019**	**2020**	**2021**	**2022**
J01A	**TETRACYCLINES**			**1.08**	**0.87**	**0.81**	**0.51**	**0.85**
J01AA02	Doxycycline	ACCESS	ACCESS	1.08	0.87	0.81	0.51	0.85
JO1B	**AMPHENICOLS**			**0.95**	**1.44**	**0.73**	**0.24**	**0.88**
J01BA01	Chloramphenicol	ACCESS	ACCESS	0.06	0.08	0.18	0.15	0.06
J01BA02	Thiamphenicol	ACCESS	ACCESS	0.89	1.36	0.54	0.09	0.82
J01C	**BETA-LACTAM ANTIBACTERIALS, PENICILLINS**			**45.16**	**44.89**	**25.91**	**22.02**	**20.76**
J01CA01	Ampicillin	ACCESS	ACCESS	0.00				
J01CA04	Amoxicillin	ACCESS	ACCESS	41.35	43.49	25.07	21.40	20.76
J01CR02	Amoxicillin/clavulanic-acid	ACCESS	ACCESS	3.81	1.40	0.84	0.62	
J01D	**OTHER BETA-LACTAM ANTIBACTERIALS**			**31.38**	**34.04**	**38.16**	**40.30**	**32.51**
J01DB05	Cefadroxil	ACCESS	ACCESS	13.57	15.37	11.38	6.64	8.73
J01DD08	Cefixime	WATCH	WATCH	17.81	18.67	26.78	33.67	23.78
J01E	**SULFONAMIDES AND TRIMETHOPRIM**			**10.65**	**8.82**	**6.60**	**4.72**	**2.24**
J01EE01	Sulfamethoxazole/trimethoprim	ACCESS	ACCESS	10.65	8.82	6.60	4.72	2.24
J01F	**MACROLIDES, LINCOSAMIDES, AND STREPTOGRAMINS**			**6.09**	**7.04**	**20.75**	**49.06**	**8.17**
J01FA01	Erythromycin	WATCH	ACCESS	2.08	1.82	3.33	1.74	0.15
J01FA02	Spiramycin	WATCH	ACCESS	0.02	0.01			
J01FA09	Clarithromycin	WATCH	WATCH	0.57	2.69	1.88		
J01FA10	Azithromycin	WATCH	WATCH	2.52	1.73	15.13	46.90	5.03
J01FF01	Clindamycin	ACCESS	ACCESS	0.90	0.79	0.41	0.43	2.98
J01M	**QUINOLONE ANTIBACTERIALS**			**51.39**	**51.52**	**46.93**	**35.99**	**35.37**
J01MA01	Ofloxacin	WATCH	WATCH	1.55	0.27	0.13		
J01MA02	Ciprofloxacin	WATCH	ACCESS	29.40	24.60	17.75	12.78	12.22
J01MA12	Levofloxacin	WATCH	WATCH	2.56	2.60	3.78	1.47	3.80
J01MB04	Pipemidic-acid	WATCH	Uncategorized	17.88	24.05	25.28	21.74	19.36
J01X	**OTHER ANTIBACTERIALS**			**2.40**	**2.62**	**3.13**	**2.24**	**5.29**
J01XD00	Metronidazole	ACCESS	ACCESS	2.40	2.62	3,13	2,24	5.29
				149.10	**151.24**	**143.02**	**155.09**	**106.08**

P-ISSN: 2406-9388
E-ISSN: 2580-8303

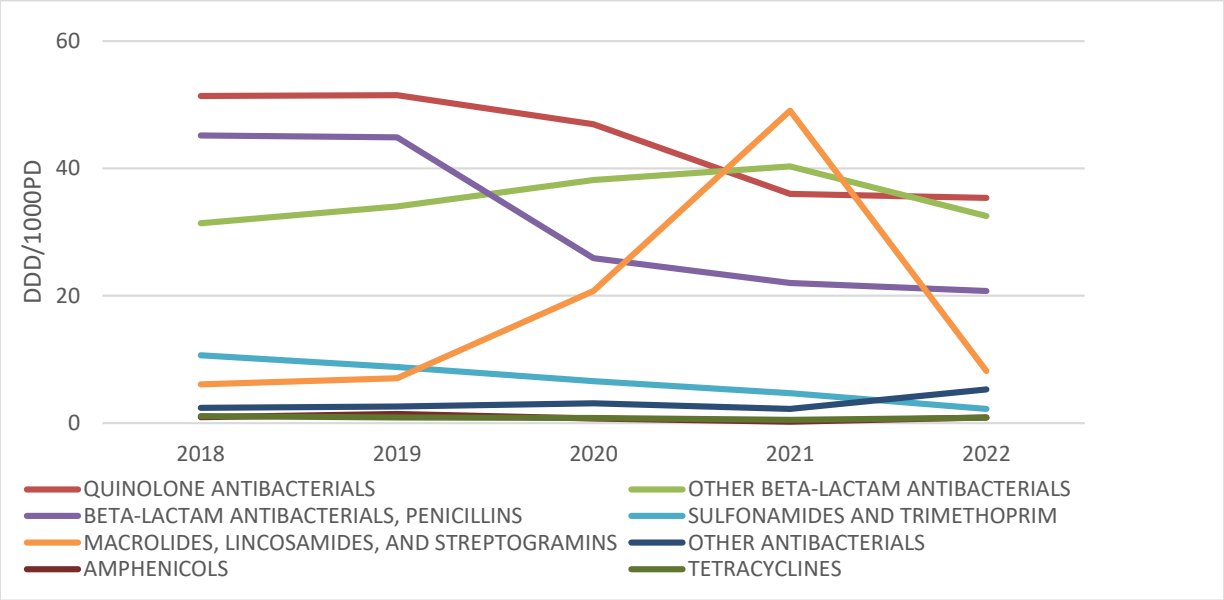

Figure 1. Quantity of antibiotic use at the hospital expressed in DDD/1000PD during the period 2018-2022 based on pharmacological group according to the ATC classification system

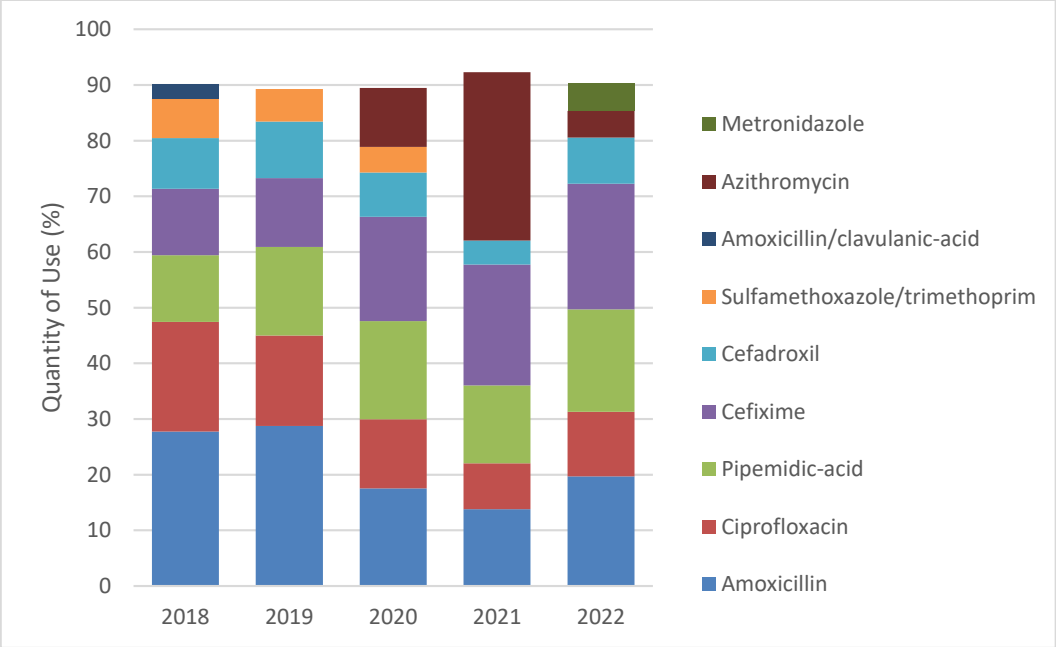

Figure 2. DU90% profiles of antibiotics used for outpatients at the hospital each year during the period of 2018-2022

Compared to other antibiotics in the beta-lactam class, beta-lactams were the second most commonly used in 2018 and 2019, but their usage declined in 2020 (Figure 1). Amoxicillin, which is Access class from both categories, was the most commonly used antibiotic in the beta-lactam class, with an average utilization of 30,41 DDD/1000 PD. The macrolide class of antibiotics, which includes azithromycin, clindamycin, erythromycin, spiramycin, and clarithromycin, was used more frequently in 2020 and 2021 as a result of the beta-lactam group's decline, with an average utilization of 18,22 DDD/1000 PD. In this investigation, antibiotics belonging to the trimethoprim and sulfonamide classes were found to have an average usage of 6.61 DDD/1000PD. Other antibacterial groups included metronidazole, with an average use of 3.13 DDD/1000PD. This study indicated that the average annual use of antibiotics from the amphenicol and tetracycline classes was less than 2 DDD/1000PD.

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E-ISSN: 2580-8303

Figure 2 depicts the DU profile of 90% annual use of antibiotics during the study period, which reveals that, despite the fact that 19 varieties of antibiotics were used in the hospital, only 6/7 of the 19 types had quantity use in the 90% usage area. These results indicate that approximately 60% of the antibiotic is utilized in the remaining 10%. In addition to being an exceptional clinical review, this profile can also be evaluated from an administration and management perspective to determine the efficiency and efficacy of drug management. Figure 2 also demonstrates that amoxicillin, ciprofloxacin, pipemidic acid, cefixime, and cefadroxil are the five most frequently prescribed antibiotics annually from 2018 to 2022.

Amoxicillin was the most used antibiotic for outpatients at the hospital during the study period, with an average consumption of 22%. Following amoxicillin, cefixime was the second most used antibiotic, with an average consumption of 17.5% during the study period. In contrast with the antibiotic consumption during 2018-2019, azithromycin is included in the segment of DU90% during 2020-2022 and became the most used antibiotic in 2021. Unsurprisingly, the use of azithromycin increased during 2021-2022 as this antibiotic was recommended for the treatment of COVID-19 patients (Oldenburg & Doan, 2020). Infection with the SARS-2 coronavirus has become a focal point of attention throughout 2020, which has influenced the selection of antibiotic therapy by medical professionals (Sinto, 2020). However, subsequent studies did not support the routine use of azithromycin for outpatient SARS, as a single dose of azithromycin compared to placebo did not increase the likelihood of being symptom-free by day 14 (Oldenburg et al., 2021). Overall, the segment of drug utilization 90% (DU90%) of antibiotics for outpatients at the hospital during the study period was dominated by antibiotics from Watch class according to WHO AWaRe classification. Azithromycin, cefixime, ciprofloxacin, and pipemidic acid, all of which are in the Watch category according to the WHO AWaRe classification, were included in DU90%.

The main aim of this study is to determine the proportion of antibiotic use from the Access class, so the quantity of antibiotic use was then grouped based on the classes defined by WHO and the MoHRI. The usage of each antibiotic is converted into percent and then grouped based on Access, Watch, Reserve and Unclassified classes, and the results are presented in Figures 3 and 4. The primary objective of implementing the AWaRe classification is to mitigate the utilization of antibiotics within the Watch and Reserve categories and, subsequently, enable an increase in the accessibility and utilization of antibiotics from the Access class to surpass 60% of the overall antibiotic consumption (WHO, 2020).

During the study period, consumption of antibiotics from the Access class comprises only 24-50% and 33-71% of total antibiotics consumption for outpatients following WHO and MoHRI AWaRe classification, respectively, as presented in Figure 3. Overall, the utilization of antibiotics from the Access class is lower than the target set by WHO. Consistent with prior research findings (Tomas *et al*., 2021; Zhussupova *et al*., 2021), it has been shown that a decline in the utilization of antibiotics from Access class according to WHO AWaRe Classification is subsequently accompanied by a corresponding rise in the consumption of antibiotics from Watch, and even Reserve, class.

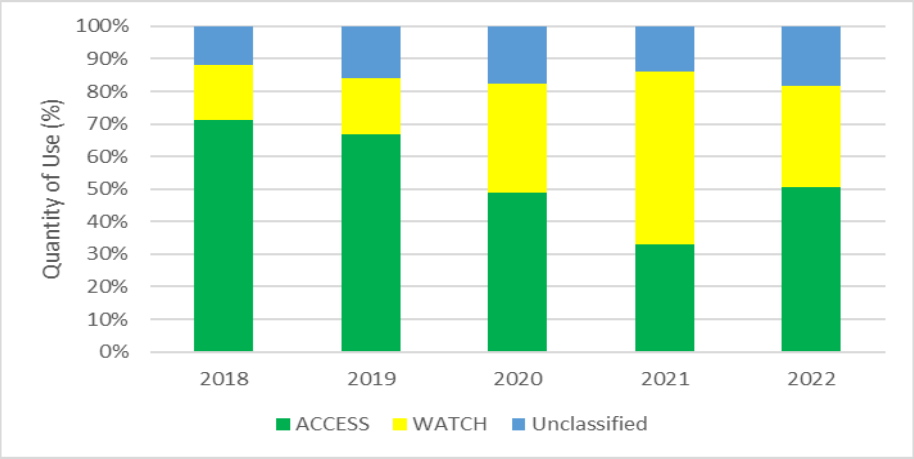

Figure 3. Proportion of the consumption of antibiotics from Access and Watch class for outpatients at the hospital during the period of 2018-2022 according to MoHRI AWaRe Classification

P-ISSN: 2406-9388
E-ISSN: 2580-8303

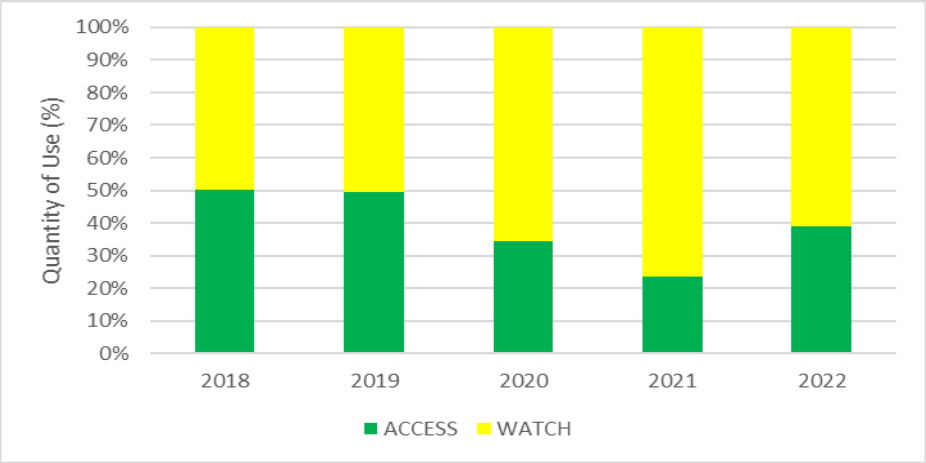

Figure 4. Proportion of the consumption of antibiotics from Access and Watch class for outpatients at the hospital during the period of 2018-2022 according to WHO AWaRe Classification

This study has some limitations, especially regarding the adjustment of antibiotics use with the epidemiological profile of infectious diseases at the hospital. Therefore, results from this study require further follow-up from both the clinical and management aspects. Further clinical research is needed to ensure that the consumption of antibiotics from Watch follows the national guidelines in order to achieve better outcomes without increasing the risk of adverse effects and, importantly, not significantly increasing the risk of developing bacterial resistance.

CONCLUSION

In term of antibiotics agents, antibiotics used for outpatients at the hospital were mostly from Access class. However, in term of quantity, the consumption of antibiotics from Access class still below the target of WHO. This indicates that the implementation of some effective strategies is still needed to achieve the target regarding antibiotics use.

ACKNOWLEDGMENT

Authors would like to thank the pharmacists and staffs at study site as well as the staffs at Master Program of Pharmacy, Universitas Islam Indonesia, for supporting the study.

AUTHOR CONTRIBUTIONS

Conceptualization, S., S. M. G., Y. F. A.; Methodology, S., S. M. G., Y. F. A.; Software S.; Validation, S.; Formal Analysis, S., Y. F. A.; Investigation, Y. F. A.; Resources, Y. F. A.; Data Curation, S., Y. F. A.; Writing - Original Draft, Y. F. A.; Writing - Review & Editing, S., Y. F. A.; Visualization, S., Y. F. A.; Supervision, S., S. M. G.; Project Administration, S., S. M. G., Y. F. A.; Funding Acquisition, Y. F. A.

FUNDING STATEMENT

This research did not receive any specific grant from funding agencies in the public, commercial, or not for profit sectors.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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