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# Antibiotic Use Evaluation Based on AWaRe Classification in Hospitalized Patients (Intensive and Non-Intensive Care) at Universitas Indonesia Hospital

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**ABSTRACT:** Antibiotic stewardship program has been largely implemented to optimize the use of antibiotics and reduce the rate of antibiotic resistance rates. The present study aimed to evaluate antibiotic use based on the AWaRe (Access, Watch, Reserve) classification in intensive and non-intensive care unit inpatients using the ATC/DDD method and Drug Utilization 90% (DU 90%). This descriptive study used a cross-sectional study design and retrospective data collection using a total sampling technique involving data from non-intensive and intensive care unit inpatients aged ≥ 18 years at Universitas Indonesia Hospital who had been prescribed antibiotics from 1 January - 31 December 2022. Data from patients who only received topical antibiotic or antibiotics without a DDD standard value from WHO, or patients who had incomplete medical record data were excluded from the study. Data was processed by Microsoft Excel®. The results of this study identified that the total use of antibiotics in non-intensive and intensive care unit inpatients were 258.43 and 169.48 DDD/100 patient-days, respectively. Based on the AWaRe classification, the Watch class became the most frequently used antibiotic group, followed by the Access and Reserve classes. The 90% DU segment was mostly composed of third-generation cephalosporin group and fluoroquinolones which were included in the Watch class. These findings underscore the need for continuous implementation of antibiotic stewardship programs to optimize the use of antibiotics and reduce the rate of antibiotic resistance.

**Keywords**: **antibiotic use evaluation; antimicrobial resistance; ATC/DDD; AWaRe classification; DU 90%.**

## Introduction

Bacterial infection remains one of the global health issues today. Based on a study conducted by Ikuta et al. [1], bacterial infections caused 7.7 million (13.6%) global deaths in 2019. According to the Health Office of Depok City, there was an increase in the number of inpatient visits for patients with bacterial infections (1,519 to 6,747) and pneumonia (1,394 to 3,573) from 2019 to 2022 [2,3]. According to the Regulation of the Minister of Health of the Republic of Indonesia (Permenkes RI) Number 28 of 2021, the efforts to cure bacterial infections include the administration of antibiotics as antimicrobials [4]. However, inappropriate use of antibiotics can result in antibiotic resistance [5].

Regulation of Health Minister of The Republic of Indonesia Number 8 of 2015 defines antimicrobial resistance as a condition in which microbes can survive even though they are exposed to antimicrobials, making treatment ineffective [6]. Data from the study of the Antimicrobial Resistance in Indonesia (AMRIN) suggested that antimicrobial resistance resulted in 700,000 deaths in 2018 [7]. To control antibiotic resistance, multidisciplinary collaboration from health workers, including doctors, microbiologists, nurses, and pharmacists is necessary. Specifically, pharmacists should be able to monitor antibiotic use and contribute to suppressing antibiotic resistance rates [8].

To reduce the number of antibiotic resistance, the Ministry of Health of the Republic of Indonesia and the World Health Organization (WHO) have initiated the Antimicrobial Resistance Control Program (PPRA) or antimicrobial stewardship. Antibiotic stewardship aims to promote the proper use of antibiotics [4]. The

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program includes guidelines for antibiotic use based on the Access, Watch, Reserve (AWaRe) classification as well as evaluation of antibiotic use [6,9].

The development of the AWaRe antibiotic classification was carried out to reduce the incidence of antimicrobial resistance on a local, national, and global scale, as well as maintain the long-term usefulness of antibiotics, and improve the outcomes of treatment of infectious diseases [4,9]. Meanwhile, according to Regulation of the Minister of Health of The Republic of Indonesia Number 72 of 2016 evaluation of drug use, including antibiotics, becomes one of the standard pharmaceutical services in hospitals [10]. The use of antibiotics in hospitals can be evaluated quantitatively and qualitatively. Qualitative evaluation is performed through the Gyssens or Drug Utilization 90% (DU90%) category, while quantitative evaluation is performed through the Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) method [6,11]. DDD is an assumed measurement of the average daily maintenance dose of antibiotics used by adult patients for certain indications and DDD calculations for inpatients are carried out in units of DDD/100 patient-days [6,12]. The ATC/DDD method is often combined with DU 90% which also uses DDD data to identify drug groups with the highest percentage of use [13].

Based on the above background, the pattern of antibiotic use in Indonesia and in the world still brings the risk of antimicrobial resistance. Therefore, regular evaluation of antibiotic use in each health facility is necessary as the patterns of antibiotic use may differ from year to year. Furthermore, research evaluating antibiotic use based on the AWaRe classification had never been carried out at Universitas Indonesia Hospital (UIH) and is limited in Indonesia. For this reason, this study was conducted to evaluate the use of antibiotics in both non-intensive and intensive care unit inpatients data at UIH. The results of this study are expected to provide information for the Antibiotic Resistance Control Committee supporting the antibiotic stewardship program promoted by the Ministry of Health and WHO thus they can optimize the use of antibiotics and reduce resistance.

# Methods

## Research Design

This study is a descriptive-analytic observational study with a cross-sectional study design. The data collection for inpatient antibiotic use was performed retrospectively. The data involved the medical record and drug administration data of the patients from the Pharmacy Unit and Central Sterile Supply Department (CSSD) at UIH for the period 1 January–31 December 2022. Data collection was conducted during April–June 2023.

## Data Collection

Data on antibiotic use were collected on the study population, which involved data on non-intensive and intensive care unit inpatients at UIH from 1 January to 31 December 2022 based on inclusion criteria and exclusion criteria. As for the sampling technique, this study used total sampling. Inclusion criteria included complete data on patients aged ≥ 18 years who received antibiotics, while exclusion criteria included patient data with zero medical record data, patients who used topical antibiotics, and antibiotics that do not have a DDD standard value from WHO.

## Data Analysis

The data that have been collected were processed using Microsoft Excel. The DDD value for inpatients was calculated using DDD units/100 patient-days which has the following formula [6]:

**Total DDD = Total amount of drug dispensed/ Standard DDD**

**DDD/100 patients–days= (Total DDD)/(Total LoS) x 100**

Note:
1. Total LoS (Length of Stay) is the total duration of treatment for all patients in the inpatient installation from the start of admission to discharge from the hospital.
2. The standard DDD standard is a dose unit that has been determined by WHO for the ATC/DDD system in grams (g), milligrams (mg), or International Units (IU).

Meanwhile, the 90% DU value, which is the number of drugs with the highest 90% use based on DDD calculations in a certain period, can be calculated using the following formula [14–16]:

**DU 90% = (DDD Value/100 patients–day of each drug)/(Total DDD value/100 patient–day) x 100%**

Data was analyzed using univariate and descriptive analysis using Microsoft Excel® which divided into non-intensive and intensive care unit groups, and presented separately. Univariate analysis was employed to delineate

the characteristics of the research variables presenting data as frequency distributions, percentages, and means ± SD and medians [Interquartile range]. Data processing was carried out to obtain quantity values for antibiotic use employing ATC/DDD method presenting DDD units, DDD/100 patient days, and DU90% segments. The descriptive analysis aimed to describe patient characteristics and explore patterns (type, class and quantity) of antibiotic use based on the AWaRe classification.

# Result and Discussion

## Patient Characteristics

The total sample obtained in this study was 3,658 data from non-intensive care unit inpatients and 591 data from intensive care unit inpatients. In non-intensive care unit, 1,279 patient data were excluded because they were <18 years old, and 1,643 patient data were excluded because information on drug use was incomplete, and they did not receive antibiotics. Meanwhile, in the intensive care unit, 48 patient data were excluded because they were <18 years old, and 153 patient data were excluded because information on drug use was incomplete, and they did not use antibiotics.

From 1 January to 31 December 2022 in non-intensive care unit inpatients, the number of female patients (61.36%) who used antibiotics was higher than male patients (38.64%). The 18-44 years-old patients dominated the total research sample, with 1,889 patients (52.94%). In addition, the majority of non-intensive care unit inpatients had a short treatment period (< 10 days), with 3,243 (90.89%). Meanwhile, in the intensive care unit inpatients, there were 304 male patients (51.44%). The results of the analysis also showed that the majority of patients aged ≥ 60 years or the elderly (46.87%). As for the duration of hospitalization, most patients stayed less than ten days (53.64%) in the hospital. The age groups in the presentation of patient characteristic data are divided based on the Regulation of the Minister of Health of the Republic of Indonesia Number 25 of 2016 [17]. The length of stay categories are divided based on the median data (Table 1).

The most common diagnoses occurring in non-intensive care unit inpatients were tooth impaction (560 cases), followed by COVID-19 (375 cases) and labor (196 cases). This condition is consistent with the data from the

**Table 1.** Patient Characteristics.

| Patient Characteristic | Frequency Data (%) | | Data Distribution | |
|---|---|---|---|---|
| | Non-ICU (n = 3,568) | ICU (n = 591) | Non-ICU | ICU |
| **Gender** | | | | |
| Male | 1,378 (38.62) | 304 (51.44) | | |
| Female | 2,190 (61.38) | 287 (48.56) | | |
| **Age group** | | | | |
| **Mean ± SD** | | | **44.69 ± 18.68** | **56.58 ± 15.68** |
| 18–44 years old | 1,889 (52.94) | 121 (20.30) | | |
| 45–49 years old | 776 (21.75) | 193 (32.83) | | |
| ≥ 60 years-old | 903 (25.31) | 277 (46.87) | | |
| **Length of stay** | | | | |
| **Median (IQR)** | | | **3 (2–6)** | **9 (5-16)** |
| < 4 days | 1,954 (54.76) | | | |
| ≥ 4 days | 1,614 (45.24) | | | |
| < 10 days | | 317 (53.64) | | |
| ≥ 10 days | | 274 (46.36) | | |
| **Number of Diagnosis** | | | | |
| 1 | 1,059 (29.68) | 67 (11.34) | | |
| > 1 | 2,509 (70.32) | 524 (88.66) | | |

Note: ICU = Intensive Care Unit; SD: Standard deviation; IQR: Interquartile range

2022 [18], report of Health Profile of Depok City, where COVID-19 was ranked 6th out of the top 20 inpatient diseases in hospitals. The same report also revealed the increase in the number of births from 43,110 in 2021 to 44,884 in 2022. Apart from that, tooth impaction cases were among the top 20 outpatient diseases in hospitals. However, there are considerations as to whether or not there are local and/or systemic complications that determine whether patients with impacted teeth need to undergo a period of hospitalization [19]. The most common diagnoses found in ICU inpatients were COVID-19 (21.17%), pneumonia (7.92%), and benign neoplasm (4.99%). These results are in line with the 2022 [18] Depok City Health Profile data because coronavirus infections, pneumonia, and benign neoplasms are included in the top 20 inpatient diseases in hospitals. COVID-19 became the diagnosis with the highest number because of the omicron coronavirus variant which appeared at the end of 2021. This variant is more contagious and spreads more quickly compared to the previous variant resulting in a significant increase in the number of COVID-19 patients at UIH in 2022 [20].

## Types and Classes of Antibiotics

Cephalosporins, especially the third generation, became the most widely used antibiotics in non-intensive care unit and intensive care unit inpatients. During the study period, non-intensive care unit inpatients used cephalosporin antibiotics with a total of 43,167 (45.31%) preparations, while ICU inpatients used cephalosporin with a total of 8,423 (30.00%) preparations. Third-generation cephalosporins have broader activity compared to the previous two generations of cephalosporins [21]. In addition, third-generation cephalosporins are more stable against gram-negative bacteria that produce beta-lactamase enzymes due to the replacement of the side chain of the furan ring from the Oxyamino cephalosporin structure, to an aminothiazole ring which increases the penetration of antibiotics into the walls of gram-negative bacteria and increases affinity for the transpeptidase enzyme [23,24].

In non-intensive care unit inpatients, the most frequently used type of antibiotic was cefixime with a total of 21,249 preparations (22.09%) followed by ceftriaxone with 16,588 preparations (17.41%). Both are third-generation cephalosporins. According to PPAB RS [22], third-generation cephalosporins are antibiotics that are active against gram-negative and positive bacteria so that they can be used as empirical therapy for community-originated infections in non-intensive care unit inpatients. Based on the Integrated Patient Progress Record (CPPT) data, cefixime is the most commonly given antibiotic as a switch therapy from intravenous to peroral as well as a follow-up therapy (discharge medication). These results are consistent with the National Formulary in 2013, where cefixime is only intended for hospitalized patients who previously received parenteral antibiotic therapy and its use can be continued at home [25].

Similar results were also observed in the ICU inpatients. The type of antibiotic with the highest number of preparations was ceftriaxone, with a total of 5,382 preparations (19.17%). In addition, meropenem (15.57%) and levofloxacin (11.81%) also had a considerably large percentage of use. Meropenem and levofloxacin are

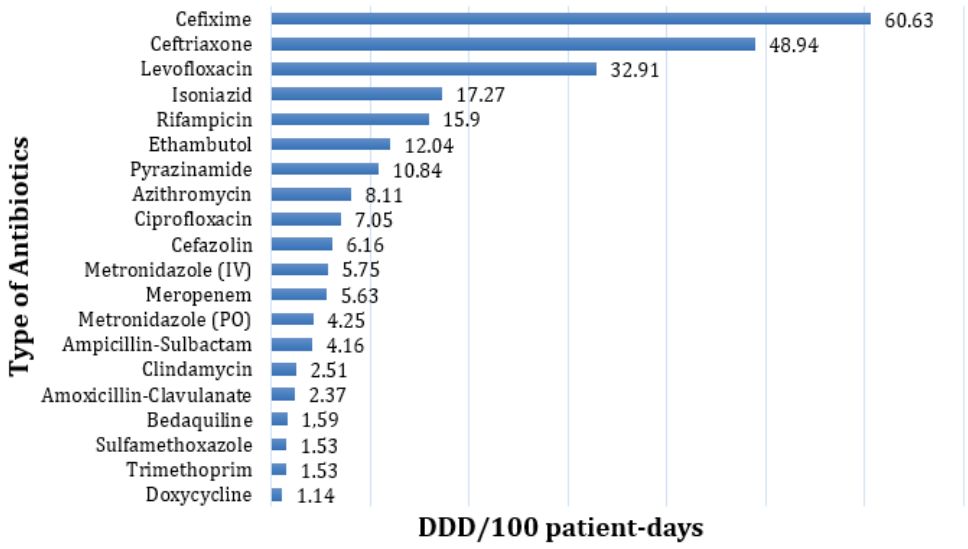


**Figure 1.** Top 20 antibiotics used as DDD/100 patient-days in non-intensive care unit inpatients.

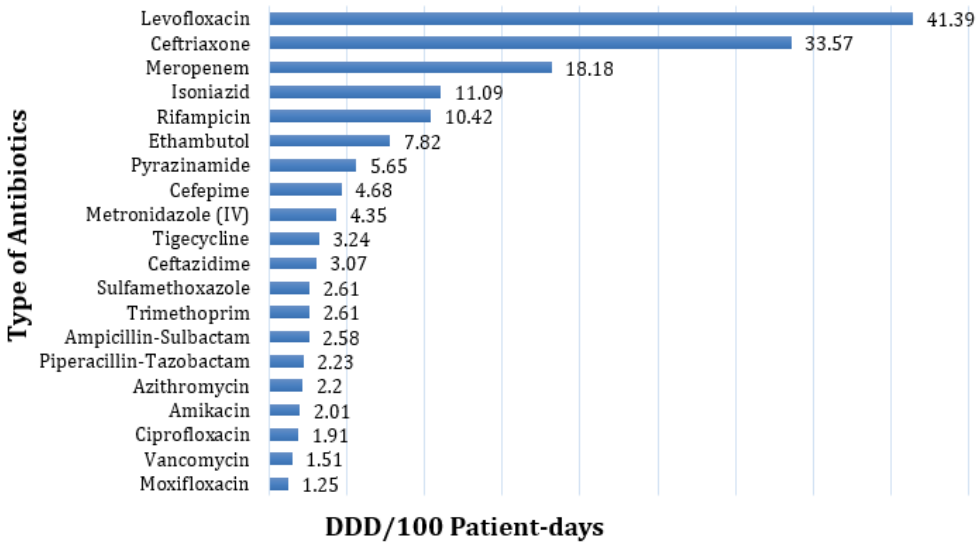


**Figure 2.** Top 20 antibiotics used as DDD/100 patient-days in intensive care unit inpatients.

frequently prescribed because both have a broad spectrum of antibiotics that are effective against both Gram-positive and Gram-negative bacteria [4]. According to the Guidelines of Antibiotic Use formulated by UIH [22], some antibiotics that can be used as empirical therapy in ICU inpatients are levofloxacin and meropenem. As such, the use of antibiotics in this study is in line with the hospital guidelines and the previous study.

## Quantity of Antibiotic Usage Based on ATC/DDD Method

Quantitative analysis of antibiotic use in non-intensive and intensive care unit inpatient data was performed based on the ATC/DDD method and presented in units of DDD/100 patient days. The quantity of antibiotic use in non-intensive care unit inpatients from January 1 to 31 December 2022 amounted to 258.37 DDD/100 patient-days, while in ICU inpatients a value of 169.48 DDD/100 patient-days was obtained. The DDD/100 patient-days value means that out of 100 non-intensive care unit inpatients, the amount of antibiotic consumption per day is 258.37 DDD. This interpretation also applies to ICU inpatients. The DDD/100 patient-days value obtained may differ from the previous studies due to differences in the population and period of study.

In non-intensive care unit inpatients, the antibiotic with the highest usage was cefixime (60.63 DDD/100 patient-days) followed by ceftriaxone (48.94 DDD/100 patient-days) and levofloxacin (32.87 DDD/100 patient-days). In contrast, in ICU inpatients, the antibiotic with the highest DDD/100 patient-days value was levofloxacin (41.39 DDD/100 patient-days) and the second highest use was ceftriaxone, which was 33.57 DDD/100 patient-days and the third was meropenem with 18.18 DDD/100 patient-days (Figure 1 and Figure 2). The DDD value describes the estimated amount of use of an antibiotic by a patient every day [6]. The smaller the DDD value obtained, the fewer antibiotics used, resulting in a smaller risk of antimicrobial resistance. As such, one of the efforts in reducing the rate of resistance is by restricting the use of antibiotics. It is important to detect evidence of infection before administering antibiotics. In addition, hospitals can also develop guidelines for antibiotic use to control resistance and use antibiotics wisely [16,21]. UIH has developed an antibiotic use guidelines in the Decree of the President Director [22] which became the first step in antibiotic stewardship.

In this present study, some antibiotics werre administered to inpatients in fixed-dose combinations, such as anti-tuberculosis drugs and 480 mg cotrimoxazole consisting of sulfamethoxazole and trimethoprim. The preparation was calculated as 1 sulfamethoxazole with a dosage strength of 400 mg and 1 trimethoprim with a dosage strength of 80 mg. According to Hollingworth & Kairuz [28], the use of fixed-dose combination products is calculated as a single dose, regardless of the number of active ingredients in the combination. Therefore, in this study, the fixed-dose combination preparation was calculated using the single-dose WHO DDD unit.

**Table 2.** Percentage of antibiotics used based on the WHO AWaRe classification.

| AWaRe and Antibiotic Classification | DDD/100 patient-days | | Percentage of Usage (%) | |
|---|---|---|---|---|
| | Non-ICU inpatients | ICU inpatients | Non-ICU inpatients | ICU inpatients |
| ***Access*** | **31.79** | **15.74** | **14.80** | **10.97** |
| Amikacin | 0.33 | 2.01 | 0.15 | 1.40 |
| Amoxicillin | 0.88 | - | 0.41 | - |
| Amoxicillin-Clavulanate | 2.37 | - | 1.10 | - |
| Ampicillin | 0.02 | - | 0.01 | - |
| Ampicillin-Sulbactam | 4.16 | 2.58 | 1.94 | 1.80 |
| Benzathine Benzylpenicillin | 0.01 | 0.01 | 0.00 | 0.00 |
| Doxycycline | 1.14 | - | 0.53 | - |
| Gentamicin | 0.21 | 0.05 | 0.10 | 0.03 |
| Clindamycin | 2.51 | 0.17 | 1.17 | 0.12 |
| Metronidazole (IV) | 5.75 | 4.35 | 2.68 | 3.03 |
| Metronidazole (PO) | 4.25 | 0.96 | 1.98 | 0.67 |
| Cefadroxil | 0.65 | - | 0.30 | - |
| Cefazolin | 6.16 | 0.38 | 2.87 | 0.27 |
| Sulfamethoxazole | 1.53 | 2.61 | 0.71 | 1.82 |
| Sultamicillin | 0.30 | - | 0.14 | - |
| Trimethoprim | 1.53 | 2.61 | 0.71 | 1.82 |
| ***Watch*** | **182.60** | **124.43** | **85.01** | **86.68** |
| Pipemidic Acid | 0.06 | - | 0.03 | - |
| Azithromycin | 8.11 | 2.20 | 3.78 | 1.53 |
| Doripenem | - | 0.12 | - | 0.09 |
| Erythromycin | 0.05 | 0.38 | 0.02 | 0.27 |
| Fosfomycin (PO) | 0.01 | - | 0.01 | - |
| Imipenem-Cilastatin | 0.09 | 1.20 | 0.04 | 0.84 |
| Clarithromycin | 0.31 | 0.05 | 0.14 | 0.03 |
| Levofloxacin | 32.91 | 41.39 | 15.32 | 28.83 |
| Meropenem | 5.63 | 18.18 | 2.62 | 12.66 |
| Minocycline (PO) | 0.12 | - | 0.05 | - |
| Moxifloxacin | 0.48 | 1.25 | 0.22 | 0.87 |
| Piperacillin-Tazobactam | 0.07 | 2.23 | 0.03 | 1.56 |
| Rifampicin | 15.90 | 10.42 | 7.40 | 7.26 |
| Cefepim | 0.44 | 4.68 | 0.21 | 3.26 |
| Cefixime | 60.63 | 1.19 | 28.23 | 0.83 |
| Cefoperazone | 0.30 | 0.35 | 0.14 | 0.24 |
| Cefotaxime | 0.74 | 0.49 | 0.35 | 0.34 |
| Ceftazidime | 0.07 | 3.07 | 0.03 | 2.14 |
| Ceftriaxone | 48.94 | 33.57 | 22.78 | 23.39 |
| Ciprofloxacin | 7.05 | 1.91 | 3.28 | 1.33 |
| Streptomycin | 0.41 | 0.25 | 0.19 | 0.17 |
| Vancomycin | 0.27 | 1.51 | 0.13 | 1.05 |
| ***Reserve*** | **0.40** | **3.38** | **0.19** | **2.35** |
| Linezolid | 0.27 | 0.03 | 0.12 | 0.02 |
| Ceftazidime-Avibactam | - | 0.11 | - | 0.08 |
| Tigecycline | 0.14 | 3.24 | 0.06 | 226 |
| **Total** | **214.79** | **143.55** | **100** | **100.00** |

Note: ICU : Intensive Care Unit; PO : Peroral; IV : Intravenous.

### Quality of Antibiotic Use Based on AWaRe Classification

Qualitative use of antibiotics in this study was also analyzed based on the AWaRe classification. The results showed the Watch classification antibiotics to be the highest percentage of use of classification, both in non-intensive care unit inpatients (85.01%) and ICU (86.68%) (Table 2). In ICU inpatients, the results were consistent with several previous studies in the ICU that also showed the Watch classification as the most widely used classification [1,2]. However, in non-intensive care unit inpatients, a high rate of Watch classification may occur due to the prevalence of antimicrobial resistance conditions. Resistance conditions lead to a tendency to treat infections with antibiotics from the Watch classification, even Reserve. The use of Watch classification antibiotics, such as third-generation cephalosporins and carbapenems, should be reserved for intensive care unit patients or patients who experience clinical deterioration after being treated with first-line antibiotics included in the Access classification [3]. Nonetheless, the percentage of Access classification antibiotic use remained higher in non-intensive care unit inpatients (14.80%) compared to ICU inpatients (10.97%). Meanwhile, Reserve classification antibiotics had a higher percentage of use in ICU inpatients (2.35%) than non-intensive care unit inpatients (0.19%).

The WHO's 2019-2023 work program also sets a target that at least 60% of total antibiotic prescriptions at the country level should be Access classification antibiotics by 2023 [4]. UIH also has its own list of AWaRe classification antibiotics. However, the types of antibiotics listed in the AWaRe classification from UIH have not yet covered all antibiotics compiled by the Ministry of Health and WHO. The Ministry of Health and this study hospital implement a Special Access Scheme (SAS) in the administration of Reserve class antibiotics, such as linezolid and polymyxin, as a form of controlling the use of antibiotics that have a high risk of causing antimicrobial resistance.

### Quality of Antibiotics Use Based on DU 90%

The results of the analysis of antibiotic use based on DU 90% in non-intensive care unit and intensive care unit inpatients are slightly different. Of the 48 types of antibiotics used in non-intensive care unit inpatients, there were 13 antibiotics included in the 90% segment, namely cefixime, ceftriaxone, levofloxacin, isoniazid, rifampicin, ethambutol, pyrazinamide, azithromycin, ciprofloxacin, cefazolin, metronidazole (IV), meropenem, metronidazole (PO). Meanwhile, the data of ICU inpatients showed that the 90% segment consisted of 15 types from a total of 39 types, namely levofloxacin, ceftriaxone, meropenem, isoniazid, rifampicin, ethambutol, pyrazinamide, cefepime, metronidazole (IV), tigesicline, cefazidim, sulfamethoxazole, trimethoprim, ampicillin-sulbactam, and piperacillin-tazobactam. The order of the percentage of antibiotic use obtained in the 90% DU calculation is the same as the order of antibiotic use in the DDD/100 patient-days calculation because the 90% DU value is calculated based on the DDD/100 patient-days value.

Based on the AWaRe classification from WHO, 7 antibiotics included in the 90% segment of each inpatient room are from the Watch classification which poses a higher risk of resistance. The results of the 90% DU calculation indicated that antibiotics included in the 90% segment need to be monitored because they are used in large quantities [15,16]. The higher the number of antibiotics used, the higher the risk of resistance, especially in the use of broad-spectrum antibiotics [33].

## Conclusion

The most frequently used antibiotics in UIH in 2022, both in non-intensive care unit inpatients (cefixime and ceftriaxone) and intensive care unit inpatients (levofloxacin and ceftriaxone), were broad-spectrum antibiotics that are included in the Watch class in the AWaRe classification. The higher the number of antibiotics used, the higher the risk of resistance, especially in the use of broad-spectrum antibiotics. From this result, antibiotic stewardship programs need to be continuously implemented to optimize the use of antibiotics and reduce the rate of antibiotic resistance.

## Conflict of Interest

The authors have no conflicts of interest regarding this investigation.

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