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Antibiotic consumption and antibiotics occurrence into the environment: a case study of hospital in Metro, Lampung

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ABSTRACT

Increased antibiotic consumption has exposed bacterial communities and environmental ecosystems to large amounts of antibiotic residues derived from the excretion of irrationally consumed antibiotics. This study provides an overview of antibiotic consumption patterns in hospital inpatients and the distribution of residues released into the environment. Medical record data was used to calculate the amount of consumption from hospital inpatients, and based on the type of antibiotics that have a DU90% value, ecotoxicological risk calculations were carried out to estimate the level of danger that occurs in the environment. A total of 27 types of antibiotics were prescribed, with a total consumption of 20504.42 Kg/year. Antibiotics such as ceftriaxone, cefixime, cefadroxil, and levofloxacin are the most widely used antibiotics based on medical record data. The results of estimating the release of antibiotic residues in wastewater obtained ecotoxicological risk values for algae, invertebrates, and fish greater than one (RQs>1). This condition indicates an ecotoxicological risk at the health facility site due to the release of antibiotic residues into the river water body from the WWTP outlet. The release of antibiotic residues into the water can result in ecosystem damage and pollution of the aquatic environment.

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1. Introduction

Over the past few decades since the discovery of antibiotics, it has been observed that the use of antibiotics in human, animal, fisheries, and agricultural medicine correlates with contamination from various aspects of the environment (e.g., surface water, groundwater, drinking water, municipal waste, soil, vegetables, mud). This condition results in increased antibiotic resistance and adverse ecological effects (Polianciuc et al., 2020). In addition, the use of antibiotics enriches antibiotic-resistant bacteria or resistance genes, which can be transferred from the environment to humans. It is assumed that increased antibiotic consumption can lead to treatment failure in humans (infections caused by antibiotic-resistant bacteria), increasing disease duration, morbidity, and mortality (WHO, 2021). Addressing the challenge of antibiotic resistance requires a "one-health perspective" making it essential for all stakeholders to engage in effective management across all aspects from antibiotic production, use, and disposal.

Indonesia is a developing country that has severe problems in managing the use of antibiotics. Through the Minister of Health Regulation Number 28 of 2021 concerning Guidelines for the Use of Antibiotics, the government plays a role in the management of antibiotics in healthcare facilities. Various studies have found that around 40–62% of antibiotics are misused for diseases that do not require antibiotics. Research on the quality of antibiotic use in various parts of the hospital found that 30–80% are not based on indications (Hadi et al., 2008). The results of research conducted by Siahaan et al. (2022) showed that antibiotic misuse does not only occur in health facilities but also the community. Medical officers, as well as officers in the livestock and fisheries sectors, still need to familiarize themselves with policies related to bacterial resistance. Limited coordination also triggered a broader increase in resistance. In another study, the easy access and over-the-counter sale of antibiotics was one of the determinants of antibiotic misuse. People commonly buy antibiotics without a doctor's prescription at pharmacies to treat fever, colds, and headaches (Widayati et al., 2011). The understanding and education level of the community is a big challenge in tackling the misuse and overuse of antibiotics. The irrational use of antibiotics leads to increased bacterial resistance and broader ecosystem damage.

Consumers play an essential role in the overconsumption of antibiotics. A study in China showed that 58% of antibiotics were used due to consumer pressure and irrational demands (Wang et al., 2018). The result of this problem is expected to cause 10 million deaths/year by 2050 if there are no effective interventions. The cumulative economic loss will also increase to 100.2 billion US dollars worldwide (Sriram et al., 2021). In Indonesia, the irrationality of its use has resulted in many problems, especially the deficit of social security funds (BPJS) due to the inefficient use of drugs (Lekok et al., 2021). The role of doctors and health workers is also essential, as consumers ultimately leave their health conditions to the advice of doctors based on prescribed drugs. Therefore, the rationality of antibiotic use includes not only pollution but also the social, economic, and environmental health conditions of the community.

Each region in Indonesia has different socio-cultural characteristics, so the level of resistance and patterns of antibiotic use will also be different. An in-depth analysis of the pattern of antibiotic use in a location can correlate with describing the condition of pollution that occurs due to antibiotic residues in a region. In addition, the identification of usage patterns can also illustrate alternative methods needed in tackling antibiotic misuse in the community. In this study, the identification of antibiotic use patterns in inpatients in one of the hospitals in Metro City, Lampung, was carried out to obtain predictions of antibiotic residue contamination in surface water. In this study, the prediction of antibiotic residues released to the environment was calculated to obtain ecotoxicological risks that occur due to the pattern of use carried out in healthcare facilities. Thus, there has been no publication that describes this condition in Indonesia, so it is hoped that this will be a basic overview for policymakers in evaluating policies.

2. Methods

This study used a retrospective observational study at one of the hospitals in Metro City, Lampung. This study has received ethical clearance from the ethics commission number 000/055/KEPK-LE/LL-3/2021 (*Appendix* 1). This study used a cross-sectional method on medical record data during 2020. The characteristics of inpatients at the study site were identified by age and gender to see the distribution of antibiotic use patterns. Medical record data during 2020 were analysed for the most common antibiotic use patterns that fell into the 90% segment determined based on the DU90% method by sorting the percentage of antibiotic use from largest to smallest and accumulated until it reached 90%. After that, several types of antibiotics that were included in high usage (DU>90%) were calculated based on the following formula (Iatrou et al., 2014):

$$Total\ Consuption = \sum Dose\ x\ N \qquad \text{Eq. (1)}$$

The component descriptions of Eq. (1) include *total consumption* as units of kg/year, dose is the weight of the antibiotic in one tablet/vial (kg), and *N* is the number of tablets/vials sold during the year (1/year).

$$Total\ excretion\ (A) = total\ consumption\ x\ excretion\ rate \qquad \text{Eq. (2)}$$

The component descriptions in Eq. (2), such as the consumption amount of the target compound is the type of antibiotic considered for one year (kg/year), and the excretion rate is the percentage of excretion of each type of antibiotic in the relevant human body metabolism. According to Frade et al. (2014), the human body only breaks down and absorbs 30% to 90% of antibiotics in full, with the remaining portion eliminated through urine and faeces 8 to 24 hours after ingestion. Thus, the authors used the results of this study at the lowest excretion rate of 10%.

The data was collected by directly observing the wastewater treatment plant and the effluent treatment process to obtain calculation data needed to assess ecotoxicological risks. Field information data in the form of WWTP working system, daily amount of wastewater, parameters and monitoring data, and other treatments carried out during the treatment process. The data were obtained from interviews and discussions with the hospital sanitation department.

Ecotoxicological risks were estimated by calculating the ratio of predicted environmental concentration (PEC) to predicted no-effect concentration (PNEC) for three categories of aquatic biota (algae, invertebrates, and fish). The predicted environmental concentration (PEC, as μg/l) in wastewater (Iatrou et al., 2014) was calculated from the following equation:

$$PEC = \frac{A\ x\left[1-\frac{R}{100}\right]}{365\ x\ P\ x\ V} \qquad \text{Eq. (3)}$$

Where, in Eq. (3) there are variables *A* which is the amount of antibiotics excreted per year that enters the WWTP wastewater (kg/year) obtained from Eq. (2), *R* is the removal rate (%) of antibiotics during the wastewater treatment process at the location study (biological: aerobic + anaerobic method by 51% based on the research of de Ilurdoz et al. (2022), *P* is the total population of Metro City in 2020 from BPS (168676 people) plus the number of hospital employees (664 people) obtained from interviews with hospital management, *V* is the volume of wastewater generated per day (m^3/day) at the location which is 20 m^3/day. The PNEC value was calculated based on experimental ecotoxicity data conducted by AMR industry Alliance 2023.

The environmental dispersion of selected antibiotics (DU90%) from hospital wastewater to municipal surface water and finally to receiving water bodies was investigated by predicting antibiotic residues released. The release of antibiotic residues into the environment was measured by calculating the ecotoxicological risk estimated from the predicted environmental concentration (PEC) to the predicted no-effect concentration (PNEC) for three categories of aquatic biota (algae, invertebrates, and fish). Risk quotients (RQs) values can be estimated with the following Eq. (4) (Iatrou et al., 2014):

$$RQs = \frac{PEC}{PNEC} \qquad \text{Eq. (4)}$$

In general, ecotoxicological risk assessment is based on ratio values (RQs). When the RQs value is <1, the presence of antibiotic residues indicates no expected ecotoxicological risk. As for the case of RQs>1, ecotoxicological risks to aquatic biota are considered possible.

3. Results and discussion

3.1. Antibiotic use pattern of inpatients

The object of this study was inpatients who received antibiotic therapy and were over 18 years old in 2020. There were 9690 patients with a distribution of 5137 (53,01%) male patients and 4553 (46,99%) female patients with an average bed occupation rate of 55% (Table 1). The data shows that males of the gender and over 55 years are the most frequent users of antibiotics in one of the hospitals in Metro City, Lampung. According to Smith et al. (2018), the gender gap in antibiotic prescribing can largely be explained by consultation behavior. However, in most cases, adult men and women are equally likely to be prescribed antibiotics. Pham-Duc and Sriparamananthan (2021) stated that gender differences in antibiotic use are highly contextual and intersect with other sociodemographic factors, especially education and socioeconomic status. Therefore, gender factors have an insignificant influence in terms of antibiotic use patterns in the community, especially inpatients.

Other factors, such as education, take an essential role in the pattern of antibiotic use through the level of public understanding of the uses, benefits, and side effects of antibiotics. The average level of education is still low, which causes low understanding, so people are accustomed to taking antibiotics without a doctor's prescription when sick (Widayati et al., 2011). Indonesian people tend to repeat treatment with the same indication of pain quickly. Even though the same disease does not necessarily cause the same indication, there could be different causes of illness even with the same indication. Prior to seeking biomedical assistance, the majority of Indonesians would self-medicate, sometimes using antibiotics. According to a study conducted in an Indonesian hospital, the majority of bacteria were resistant to quinolone and the third generation of cephalosporins (Widayati et al., 2020). The high dependence on antibiotics leads to more significant misuse of antibiotics at the community level. Therefore, the government needs to make a considerable effort to improve public understanding so that antibiotic abuse is not widespread.

Table 1. Demographic conditions of inpatients at the research site

Characteristics	N	%
Gender:		
Male	5137	53.01
Female	4553	46.99
Age:		
18–25	814	8.40
26–35	1024	10.57
36–45	1380	14.24
46–55	2093	21.60
>55	4379	45.19

The DU90% method was used to quantitatively identify the pattern of antibiotic use used in inpatients at one of the hospitals in Metro City, Lampung. Based on the results of the analysis, 27 types of antibiotics were prescribed during 2020. The total use of antibiotics as a whole was 20504.42 Kg/year for all types of antibiotics. According to Mahmudah et al. (2016), the smaller the quantity of antibiotics used, the more selective and rational doctors are in prescribing antibiotics. This calculation cannot indicate the details of the rational use of antibiotics. However, it can map the amount of antibiotic residue contamination released into the environment from health facilities.

The results found as many as four types of antibiotics from a total of 27 types that were included in the 90% usage segment. The four types of antibiotics are ceftriaxone, cefixime, cefadroxil, and levofloxacin (Table 2). Antibiotics of the cephalosporin group, such as ceftriaxone, cefadroxil, and cefixime, occupied the most prominent position in drug consumption, exceeding other antibiotic groups. As for fluoroquinolone class, antibiotics such as levofloxacin are another type of antibiotic class that is included in the 90% usage segment. This type of antibiotic has a broad therapeutic spectrum with various mechanisms and side effects, so it is often used in Indonesia. Based on previous research, cephalosporins and fluoroquinolones are alternative antibiotics for treating bacterial infections in patients who are resistant to penicillin antibiotics (Raini, 2016).

Cephalosporins are antibiotics that have a β-lactam ring and are obtained from the fungus acremonium, also known as *cephalosporium* (Shahbaz, 2017). The broad spectrum is one of the reasons for the high use of this type of antibiotic. Cephalosporins are used for the therapy of diseases such as septicaemia, pneumonia, meningitis, biliary tract infections, peritonitis, and urinary tract infections. The pharmacological activity of cephalosporins is similar to penicillin, mainly excreted through the kidneys. The ability of cephalosporins to cross the brain is deficient except in inflammatory conditions; cefotaxime is a good cephalosporin for central nervous system infections (e.g., meningitis). The main side effect of cephalosporins is hypersensitivity, as about 10% of patients sensitive to penicillin will also be allergic to cephalosporins.

Cephalosporins generally have activity based on their generation level. Gram-positive activity is prevalent in low-generation cephalosporins. The high-generation level has better gram-negative activity due to more excellent stability against beta-lactamases of gram-negative bacteria (Riaz and Khatoon, 2013). Cephalosporins have a very simple pharmacology and have a short half-life. Therefore, this type of antibiotic is taken chiefly parenterally, although there is also oral administration (Shahbaz, 2017).

Fluoroquinolones are antibiotics that healthcare facilities in Indonesia widely used to treat urinary tract infections (Hasyul et al., 2020). The side effects are gastrointestinal disorders, renal disorders, visual disturbances, skin disorders, liver disorders, atrophy and tendinitis, cardiovascular disorders, haematological disorders, immunological reactions, metabolic disorders, and teratogenic. Therefore, fluoroquinolone-class antibiotics are only used for severe infections that can cause death. In addition, fluoroquinolones are also used in patients who fail therapy with other antibiotics or bacterial infections that respond well to fluoroquinolones (Raini, 2016).

The high use of several types of antibiotics indicates that the level of antibiotic consumption in the study location is only focused on some types of antibiotics. This condition can indicate an irrational level of antibiotic use, so it is necessary to control the use of antibiotics, which can result in microbial susceptibility to antibiotics (bacterial resistance). According to Dahesihdewi et al. (2019), there is bacterial resistance in hospitals based on surveys conducted nationally, although antibiotic susceptibility patterns vary slightly between hospitals and various clinical specimens. For example, *Pseudomonas aeruginosa* has good resistance to cephalosporin (ceftazidime), fluoroquinolone (ciprofloxacin) and aminoglycoside (amikacin) antibiotics in some hospital types. The results illustrated from the DU90% segment is expected to be a step towards preventing bacterial resistance in health facilities.

Table 2. Results of DU90% of antibiotic use at the study site

No	Antibiotic	Total consumption (g)	Percentage (%)	Percentage cumulative (%)	DU segment
1	Ceftriaxone	11031915.00	53.80	53.80	90%
2	Cefixime	4248194.50	20.72	74.52	
3	Cefadroxil	1924503.00	9.39	83.91	
4	Levofloxacin	838672.50	4.09	88.00	
5	Cefuroxime	682267.50	3.33	91.32	10%
6	Metronidazole	438010.00	2.14	93.46	
7	Cefotaxime	283131.00	1.38	94.84	
8	Azithromycin	252726.50	1.23	96.07	
9	Cefazolin	222588.00	1.09	97.16	
10	Ciprofloxacin	200519.00	0.98	98.14	
11	Meropenem	112726.00	0.55	98.69	

12	Amoxicillin	67840.00	0.33	99.02
13	Sefoperazone	64485.00	0.31	99.33
14	Sulbactam	46816.00	0.23	99.56
15	Clindamycin	44970.90	0.22	99.78
16	Cotrimoxazole/sulfamethoxazole	23688.00	0.12	99.90
17	Ceftazidime	10290.00	0.05	99.95
18	Moxifloxacin	4692.00	0.02	99.97
19	Rifampicin	2830.50	0.01	99.98
20	Sagestam/Gentamicin	1820.07	0.01	99.99
21	Cefpirome	555.00	0.00	99.99
22	Streptomycin	495.00	0.00	100.00
23	Amikacin	325.00	0.00	100.00
24	Ampicillin	174.00	0.00	100.00
25	Fosfomycin	81.00	0.00	100.00
26	Erythromycin	67.00	0.00	100.00
27	Lincomycin	40.50	0.00	100.00

3.2. Total antibiotic consumption for a year

Ceftriaxone was the most widely used antibiotic across all ages (Fig. 1). Ceftriaxone ranks highest in use in the under-18 age group and is in the top three most widely used antibiotics in all age ranges (Fig. 1). According to Khan et al. (2017), ceftriaxone is a type of broad-spectrum cephalosporin antibiotic that can be used for various types of bacterial infections, can be used for various ages, and as an effort to prevent infection (prophylaxis).

The calculation of the amount of ceftriaxone entering the WWTP is the result of urinary excretion of all inpatients, so if there is expired ceftriaxone, it is managed based on solid waste rules and does not enter the WWTP. The human body only processes and absorbs a portion of antibiotics; within 8 to 24 hours after ingestion, 30–90% are eliminated through urine and feces (Frade et al., 2014); in the case of data with excretion rates of target compounds that have a range, the lowest excretion rate is recommended to be used in the calculation. Regardless of differences in the patient's body metabolism and other diseases suffered by the patient. In the calculations, only the parent compound was considered, and no calculations were made for the resulting metabolites, as information on the fraction of excreted metabolites varies widely.

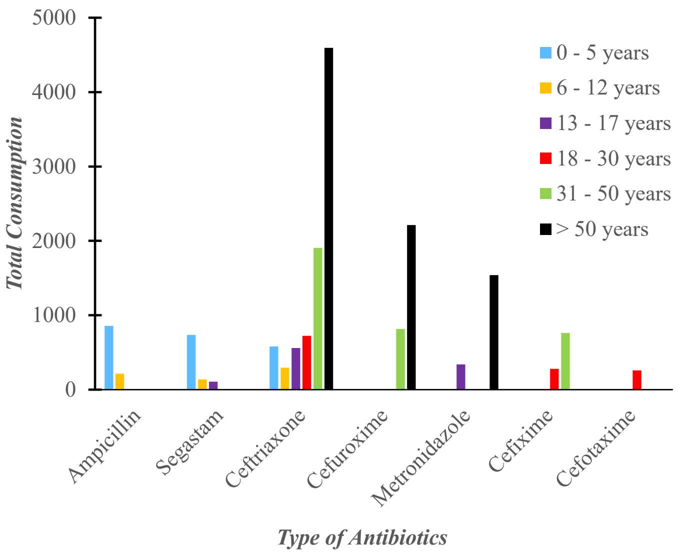

Fig. 1. Graph of antibiotic use of inpatients of various ages in one of the hospitals in Metro City, Lampung

The total consumption was obtained from the initial calculation using Eq. (1), and the excretion rate from the literature had the lowest value of 10%. Based on the data, the total consumption of ceftriaxone in one of the hospitals in Metro City, Lampung, was 11031.92 kg/year. As for the amount of ceftriaxone excreted, it was used as data for the estimated release of ceftriaxone in wastewater entering the WWTP of 7391.38 kg/year. According to Zhou et al. (2021), the release of antibiotic residues through urine can last less than a day, depending on the type of antibiotic. The low-efficiency level of the WWTP with a biological system, which is 51% based on the research of de Ilurdoz et al. (2022), will cause antibiotic residues to be released into the aquatic environment. The inability of WWTP to treat antibiotic residues contained in hospital domestic wastewater causes antibiotic residues to enter river bodies and cause various ecosystem damage.

Ecosystem damage that is currently in the spotlight is bacterial resistance. A study conducted by Kristanto and Koven (2019) showed that the number of *E. coli* colonies resistant to several types of antibiotics, such as meropenem, ciprofloxacin, and cefixime, increased at the wastewater outlet. This research shows that the potential for bacterial resistance has begun to be felt in some areas, so severe handling of this problem is needed. Another study conducted by Birošová et al. (2014) also found bacterial resistance in some hospitals. The percentage of bacteria resistant to ciprofloxacin can reach 74%, with an average above 50%. The existence of bacterial resistance will increase the dose of antibiotic use, which is getting higher. Higher doses will correlate with higher treatment costs. This condition results in sustainable impacts on various sectors, including the social and economic sectors. In addition, antibiotic residues released into the waters will also increase, resulting in broader ecosystem damage.

3.3. Ecotoxicological risk assessment

Ecotoxicological risks were estimated by calculating the ratio of the predicted environmental concentration (PEC) to the predicted no-effect concentration (PNEC) for three categories of aquatic organisms (algae, invertebrates and fish). $PNEC_{Env}$ values were calculated based on experimental toxicity data. The PEC value in wastewater was calculated based on the estimated amount of antibiotics present in the environment, resulting in the RQ values in Table 3. Based on the calculation results, the risk quotients (RQs) values higher than one for ceftriaxone, cefixime, and cefadroxil in wastewater indicate that the ecotoxicological risk of antibiotic exposure is high in all three aquatic biotas (algae, invertebrates, and fish). However, further studies on the toxicity of antibiotic mixtures should be conducted because, in this study, the risk quotients (RQs) ratio values were calculated for only one type of antibiotic, even though almost all antibiotics showed toxicity effects.

Table 3. The risk quotients (RQ) of higher DU90% of antibiotic use at the study site

No	Type of Antibiotic	PEC	$PNEC_{ENV}$*	RQ
1	Ceftriaxone	0.44	0.33	1.33
2	Cefixime	0.17	0.60	0.28
3	Cefadroxil	0.08	0.14	0.54
4	Levofloxacin	0.03	1.50	0.02

*AMR industry Alliance 2023

Based on the ecotoxicological risk assessment for algae, invertebrates and fish against antibiotics conducted by Cui et al. (2018) showed that algae are the most sensitive species. The RQ for algae to several types of antibiotics such as sulfamethazine, sulfamethoxazole, enrofloxacin, ofloxacin, norfloxacin, ciprofloxacin, tetracycline, oxytetracycline, and roxithromycin were all higher. This condition indicates that antibiotic pollution in wastewater carries significant ecotoxicological risks to aquatic biota.

Aquatic biota, such as algae, have an important role in aquatic ecosystems. Based on previous research, algae act as a nutrient supplier for another aquatic biota. Its ability to absorb CO_2 and photosynthesize to produce oxygen will increase dissolved oxygen in the water. Once mass algal die-off occurs, the aquatic ecosystem can be disrupted and will also worsen water quality.

In addition, other aquatic biota, such as invertebrates and fish, also have a role that is no less important than algae. Humans often use the existence of invertebrates and fish as food. If these aquatic biotas absorb and contain relatively large amounts of antibiotic residues, it will cause other diseases that arise in humans. On the other hand, antibiotic residues can also cause selective stress and antibiotic resistance problems in microbes (Zhang et al. 2014). Therefore, the high ecotoxicological risk of antibiotic residues should receive further attention.

In several recent studies, the potential risk of antibiotics on aquatic organisms and the selection of microbial resistance have been evaluated using the risk quotients (RQ) method according to the European Medicine Agency (EMA) guidelines, based on the ratio between the measured effect concentration (PEC) and the predicted no-effect concentration (PNEC), derived from ecotoxicological data from the European Medicine Agency/EMA (Niegowska et al., 2021). Despite low RQ values in major rivers, the risk from some antibiotics is estimated to be significant due to accumulation due to high utilization and inefficient removal (Qiu et al., 2019). This approach was adopted to evaluate the risk to aquatic biota, including algae, invertebrates, and fish in rivers.

3.4. Antibiotics dissemination in environment

Treatment for acute, infectious, and non-communicable diseases requires the use of medicines. To help in the review and evaluation of the prescription, dispensing, and use of medications, the World Health Organization created a toolkit for drug (medicine) use studies. Particularly in the context of universal health care, there is an increasing demand for thorough investigations of medication usage in low- and middle-income countries (LMIC) utilizing conventional methods. The Defined Daily Dose (DDD) is the unit of measurement used by Drug Utilization Research (DUR), which classifies drugs using the Anatomical Therapeutic Chemical (ATC). The ATC categorization scheme arranges medicinal active ingredients based on their chemical, pharmacologic, and therapeutic qualities as well as the organ or system on which they target.

The technique is a generally applicable instrument that supports essential information regarding the use of medications. In order to promote improved outcomes and high-quality medicine use, pharmacoepidemiologic research employing the ATC/DDD approach offer reliable and consistent comparisons of medication use within and between nations (Hollingworth and Kairuz, 2021). A technique like this can help to encourage improved results and high-quality medication use by providing an accurate presentation and comparison of drug usage both within and between nations. The World Health Organization has approved the technique and suggested it as the global norm for drug use research and tracking. Increasing user acceptance of ATC/DDD makes cross-border data comparability even easier. In this method, the most important thing is to use the data to answer the research question. Regardless of the data source, the main steps are to link drug data to ATC codes, apply the DDD formula to calculate drug utilisation, and interpret patterns in the context of patients, regulations and policies, and health systems. Other researchers have recommended the use of the RECORD-PE initiative (Hollingworth and Kairuz, 2021), which focuses on methods for conducting pharmacoepidemiologic studies that further detail drug use.

The Ministry of Health of the Republic of Indonesia has issued Minister of Health Regulation Number 2406 of 2016 concerning General Guidelines for using Antibiotics to control bacterial resistance. One of the other steps taken by the Indonesian government to reduce the rate of bacterial resistance is implementing the Antibiotic Resistance Control Programme (PPRA), which is accommodated by the PPRA team of each hospital. This program aims to reduce bacterial resistance, prevent toxicity due to antibiotic use, reduce costs due to irrational use of antibiotics and reduce nosocomial infections. In 2018, the program was included in the hospital accreditation assessment criteria. In addition, active collaboration between various stakeholders is required for the success of the bacterial resistance control program.

However, the government's policies have yet to reduce the rationality of antibiotic use in some areas, such as Lampung Province. Previous studies have shown that there is irrationality in the use of antibiotics in hospitals both in big cities and in the regions. This is triggered by the easy access to antibiotic drugs and also the low level of understanding of the community regarding the impact and effects of irrational use of antibiotics. In addition, this condition will damage the ecosystem, which significantly impacts the health of the environment and society.

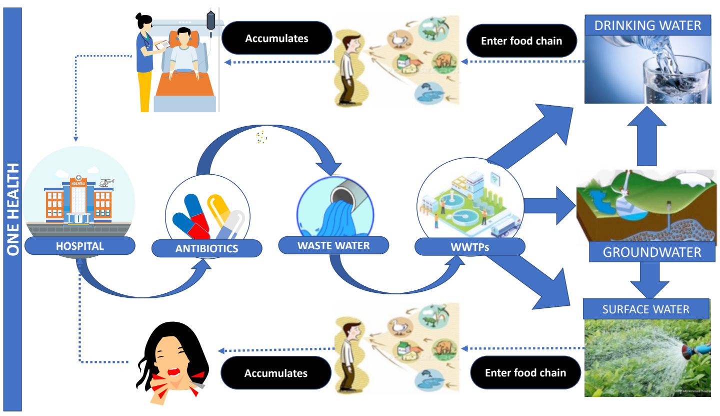

Fig. 2. The pathways and contamination of antibiotic residues that are toxic to aquatic biota and humans are based on ecotoxicological risk assessment.

In terms of the environmental dimension, antibiotics pose a significant risk to aquatic biota. This condition can be seen from the value of ecotoxicological risk to algae, invertebrates, and fish. Based on the calculation of the local PEC/PNEC ratio for the three types of antibiotics, it has a value of RQ>1. This value indicates the ecotoxicological level of the three types of antibiotics calculated locally and the amount of exposure that can cause damage to aquatic biota. The death of algae can disrupt the balance of the ecosystem in the water and can worsen water quality. In addition, some invertebrates are also considered indicators of the ecosystem quality of a water body. In general, the ecotoxicity of invertebrates and fish is much higher than that of algae. Although the impact of ecosystem damage due to antibiotic residues is not felt directly by humans, it needs to be a severe concern in overcoming these damage conditions.

On the other hand, antibiotic residues can cause diseases that arise in humans via waterborne or foodborne (Fig. 2). Based on previous studies, the highest risk due to antibiotic residues will be experienced by infants, the age group most susceptible to bacterial infections. Siahaan et al. (2022) demonstrate that the misuse of antibiotics occurs not just in hospitals but also in local populations. Neither medical personnel nor officers in the livestock and fishery sectors are conversant with AMR-related policy. In addition, the dairy product such as milk and meat showed that the most common residue found was chlortetracycline (8.37%), tetracycline (7.88%) and oxytetracycline (5.91%) in the concentration range of 14.8–498.4, 11.7–49.4, and 11.6–85.6 ng/g, respectively (Widiastuti et al., 2023). Regarding Indonesia's AMR status, there is little sectoral collaboration. The government must act more forcefully to ensure that AMR policies are implemented more effectively. Therefore, a thorough understanding and socialization of various stakeholders are needed to reduce the impact of antibiotic residues.

This study displayed results from an estimated calculation of antibiotic use data in hospitals based on the number of patients (9690 patients) who consume antibiotics as antibiotic residue producers with an excretion rate of 10%. This data cannot confirm the level of pollution that occurs; it is necessary to conduct laboratory tests on the outlet wastewater to confirm the presence of antibiotic residues in the waters. In addition, a detailed calculation of the population affected by antibiotic residues in the waters was not carried out. However, it only used the population of the metro city based on BPS data in the year the sampling took place. However, this research has provided an overview of the damage that could occur if antibiotic consumption is not monitored and evaluated in its use.

4. Conclusion

Levofloxacin, ceftriaxone, cefixime, cefadroxil, and cefixime were the most commonly used antibiotics. The ecotoxicological risk values for fish, algae, and invertebrates that are more significant than 1 (RQs>1) are used to compute the estimated release of antibiotic residues in wastewater. Due to the WWTP outlet's release of antibiotic residues into the river water body, this condition suggests an ecotoxicological concern near the location of the health institution. The aquatic environment can become contaminated and ecosystems harmed when antibiotic residues are released into the water. The government needs to take more decisive action for policies to be executed more successfully. Therefore, a full awareness and socialization of diverse stakeholders are required to lessen the impact of antibiotic residues.

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Conflict of interest

Authors should declare any or no conflict of interest

References

AMR Industry Alliance. 2023. AMR Alliance Science-Based PNEC Targets for Risk Assessments. As of 22 February 2023: AMR-Table-1-Update-20230222_corrected.pdf (amrindustryalliance.org)

Birošová L, Mackuľak T, Bodík I, Ryba J, Škubák J, Grabic R. 2014. Pilot study of seasonal occurrence and distribution of antibiotics and drug resistant bacteria in wastewater treatment plants in Slovakia. *Sci Total Environ* 490: 440–4. doi: 10.1016/j.scitotenv.2014.05.030

Cui C, Han Q, Jiang L, Ma L, Jin L, Zhang D, Lin K, Zhang T. 2018. Occurrence, distribution, and seasonal variation of antibiotics in an artificial water source reservoir in the Yangtze River delta, East China. *Environ Sci Pollut Res* 25(20): 19393–402. doi: 10.1007/s11356-018-2124-x

Dahesihdewi A, Sugianli AK, Parwati I. 2019. The surveillance of antibiotics resistance in Indonesia: a current reports. *Bali Med J* 8(2): 565. doi: 10.15562/bmj.v8i2.1386

Frade VMF, Dias M, Teixeira ACSC, Palma MSA. 2014. Environmental contamination by fluoroquinolones. *Brazilian J Pharm Sci* 50(1): 41-54. doi: 10.1590/s1984-82502011000100004

Hadi U, Duerink DO, Lestari ES, Nagelkerke NJ, Keuter M, Huis In't Veld D, Suwandojo E, Rahardjo E, Van Den Broek P, Gyssens IC. 2008. Audit of antibiotic prescribing in two governmental teaching hospitals in Indonesia. *Clin Microbiol Infect* 14(7): 698–707. doi: 10.1111/j.1469-0691.2008.02014.x

Hasyul SFP, Nuari DA, Anggraini S, Aditya A, Lisni I. 2020. Analysis of drug-related problems in the use of fluoroquinolone antibiotics in one of the Garut regency health centers (in Indonesian). *J Ilm Farm Bahari* 11(2): 137. doi: 10.52434/jfb.v11i2.888.

Hollingworth S, Kairuz T. 2021. Measuring medicine use: applying ATC/DDD methodology to real-world data. *Pharmacy* 9: 60. doi: 10.3390/pharmacy9010060

Iatrou EI, Stasinakis AS, Thomaidis NS. 2014. Consumption-based approach for predicting environmental risk in Greece due to the presence of antimicrobials in domestic wastewater. *Environ Sci Pollut Res* 21(22): 12941–50. doi: 10.1007/s11356-014-3243-7.

de Ilurdoz MS, Sadhwani JJ, Reboso JV. 2022. Antibiotic removal processes from water & wastewater for the protection of the aquatic environment - a review. *J Water Proc Engineering* 45: 102474. doi: 10.1016/j.jwpe.2021.102474

Khan MY, Roy M, Rawal RK, Bansal UK. 2017. Ceftriaxone for Life. *Asian J Pharm Res* 7(1): 35–48. doi: 10.5958/2231-5691.2017.00007

Kristanto GA, Koven W. 2019. Preliminary study of antibiotic resistant Escherichia coli in hospital wastewater treatment plants in Indonesia. *Int J Technol.* 10(4):765–775. doi:10.14716/ijtech.v10i4.776.

Lekok W, Irwanto Natadidjaja R, Dharmayanti A. 2021. Prospective system antimicrobial regulation (raspro): antibiotic use system for quality control and cost control in hospitals as an effort to reduce the burden on health BPJS (in Indonesian). *Media Bisnis* 12(1): 83–8. doi: 10.34208/mb.v12i1.906.

Mahmudah F, Sumiwi SA, Hartini S. 2016. Study of the Use of Antibiotics with ATC/DDD System and DU 90% in Digestive Surgery in Hospital in Bandung. *Indones J Clin Pharm* 5(4): 293–8. doi: 10.15416/ijcp.2016.5.4.293.

Niegowska M, Sanseverino I, Navarro A, Lettieri T. 2021. Knowledge gaps in the assessment of antimicrobial resistance in surface waters. *FEMS Microbiol Ecol* 97(11): 1–17. doi: 10.1093/femsec/fiab140

Pham-Duc P, Sriparamananthan K. 2021. Exploring gender differences in knowledge and practices related to antibiotic use in Southeast Asia: A scoping review. *PLoS ONE* 16(10): e0259069. doi: 10.1371/journal.pone.0259069

Polianciuc SI, Gurzău AE, Kiss B, Ştefan MG, Loghin F. 2020. Antibiotics in the environment: causes and consequences. *Med Pharm Rep* 93(3): 231–40. doi: 10.15386/mpr-1742

Qiu W, Sun J, Fang M, Luo S, Tian Y, Dong P, Xu B, Zheng C. 2019. Occurrence of antibiotics in the main rivers of Shenzhen, China: Association with antibiotic resistance genes and microbial community. *Sci Total Environ* 653: 334–41. doi: 10.1016/j.scitotenv.2018.10.398

Raini M. 2016. Fluoroquinolones antibiotics: benefit and side effects. *Media Litbangkes* 26(3): 163–74

Riaz B, Khatoon H. 2013. Evaluation of the use of cephalosporin antibiotics in pediatrics. *J Appl Pharm Sci* 3(4): 063–6. doi: 10.7324/JAPS.2013.3411

Shahbaz K. 2017. Cephalosporins: pharmacology and chemistry. *Pharm Biol Eval* 4(6): 234. doi: 10.26510/2394-0859.pbe.2017.36

Siahaan S, Herman MJ, Fitri N. 2022. Antimicrobial resistance situation in Indonesia: a challenge of multisector and global coordination. *J Trop Med* 2783300: 1-10.doi: 10.1155/2022/2783300

Smith DRM, Christiaan KD, Smieszek T, Robotham JV, Pouwels KB. 2018.

Understanding the gender gap in antibiotic prescribing: a cross-sectional analysis of English primary care. *BMJ Open* 2018(8): e020203. doi: 10.1136/bmjopen-2017-020203

Sriram A, Kalanxhi E, Kapoor G, Craig J, Ruchita Balasubramanian SB, Criscuolo N, Hamilton A, Klein E, Tseng K, Boeckel T Van, et al. 2021. The state of the world's antibiotics in 2021: A Global Analysis of Antimicrobial Resistance and Its Drivers. Cent Dis Dyn Econ Policy.

Wang W, Arshad MI, Khurshid M, Rasool MH, Nisar MA, Aslam MA, Qamar MU. 2018. Antibiotic resistance : a rundown of a global crisis. *Infect Drug Resist* 11:1645–58. doi: 10.2147/IDR.S173867

WHO. 2021. Monitoring global progress on antimicrobial resistance: tripartite amr country self-assessment survey (tracss) 2019-2020 global analysis report. Genewa: WHO

Widiastuti R, Martindah E, Anastasia Y. 2023. Tetracycline residues in fresh dairy milk from three districts in Indonesia: occurrence and dietary exposure assessment. *Vet World* 16(11): 2230–5. doi: 10.14202/vetworld.2023.2230-2235

Widayati AW, Green JA, Heydon S, Norris P. 2020. Health-seeking behavior of people in Indonesia: a narrative review. *J Epidemiol Glob Health* 10(1): 6–15. doi: 10.2991/jegh.k.200102.001

Widayati A, Suryawati S, De Crespigny C, Hiller JE. 2011. Self medication with antibiotics in Yogyakarta city Indonesia: a cross sectional population-based survey. *BMC Res Notes* 4(1): 491. doi: 10.1186/1756-0500-4-491

Zhang Q, Jia A, Wan Y, Liu H, Wang K, Peng H, Dong Z, Hu J. 2014. Occurrences of three classes of antibiotics in a natural river basin: association with antibiotik-resistant Escherichia coli. *Environ Sci Technol* 48(24): 14317–25. doi: 10.1021/es503700j

Zhou X, Cuasquer GJP, Li Z, Mang HP, Lv Y. 2021. Occurrence of typical antibiotics, representative antibiotic-resistant bacteria, and genes in fresh and stored source-separated human urine. *Environ Int* 146: 106280. doi: 10.1016/j.envint.2020.106280