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## **A Snapshot of Antibiotic Resistances in Air Particulate of a Provincial Capital City, Indonesia**

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Received: January 2022; Revision: February 2022; Accepted: March 2022; Available online: May 2022

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### **Abstract**

Bacteria may become resistant to antibiotics due to gene mutation or adopting resistance genes from other bacteria via horizontal gene transfer. The existence of toxic substances to bacteria, such as antibiotics, biocides, and heavy metals, may influence the pathway into the genome. This study aimed to detect the presence of antibiotic-resistance bacteria in air particulates in Makassar - a provincial capital located in Indonesia with a low to moderate air quality index (AQI). We determined the correlations between antibiotic resistance (resistance rate, RR) and the heavy-metal concentrations in the air particulates. Air particulate samples were taken from seven locations in the summer (Dry Season: July - August 2019). We analyzed the concentration of As, Cu, and Zn of the air particulates and determined RR from presumptive *Escherichia coli* (*E. coli*) isolated from the air particulates. We estimated the RR towards five antibiotics with different mechanisms of action: amoxicillin-clavulanate, chloramphenicol, amikacin, norfloxacin, and trimethoprim. The concentrations of the heavy metals were relatively low, ranging from ( $\mu\text{g}/\text{Nm}^3$ ) 0.001 – 0.009 for As, 0.001 – 0.003 for Cu, and 0.007 to 0.783 for Zn. We observed different antibiotic resistance at various locations, ranging from 25% to 100% RR. While there were indications of possible antibiotic resistance patterns in the different areas sampled, the power of this perspective snapshot was insufficient to make statistically valid generalizations.

**Keywords:** Air particulate, antibiotic-resistant bacteria, heavy metal, percent resistance.

**DOI:** [10.15408/jkv.v8i1.24559](https://doi.org/10.15408/jkv.v8i1.24559)

### **1. INTRODUCTION**

Antibiotic resistance in bacteria has become a problem in the health sector because it causes an increase in treatment costs and mortality rates. Moreover, it is increasingly widespread in various parts of the world (WHO Fact Sheet, 2021). The lack of government regulations regarding the use of antibiotics, the misuse of antibiotics in agriculture and fisheries, and the over-the-counter sale of antibiotics are known to be the leading causes of the emergence of super-bacteria, such as MRSA (Methicillin-resistant

*Staphylococcus Aureus*), KPC (*Klebsiella pneumonia carbapenemase*), and NDM (New-Delhi Metallo beta-lactamase) (Klein *et al.*, 2021; Ventola, 2015).

Because of the severity of the consequences caused by antibiotic-resistant bacteria, The World Health Organization (WHO) has designated antimicrobial resistance as one of the top 10 global public health priorities. WHO also classifies antibiotics into three categories to control the misuse of antibiotics: Access, Watch, and Reserve, where Access are antibiotics for first-line therapies

(e.g., amikacin, amoxicillin-clavulanate, oxacillin), and Watch (e.g., norfloxacin, rifampicin, vancomycin) and Reserve (e.g., aztreonam, colistin, polymyxin B) are antibiotics for specialized and last resort uses, respectively (WHO, 2019).

Bacteria can become resistant by gene mutation, heredity, or adopting resistant genes from other bacteria (gene exchange/transfer) (Davison, 1999; Davies & Davies, 2010). Hotspots where gene exchange may occur, are in the intestines of humans/animals, in landfills or wastewater treatment plants, and in sewers. The closer a site to a wastewater treatment plant, a hospital's discharge point, or an urban area, the more antibiotic-resistant bacteria are found (Lien et al., 2016). Environmental physicochemical conditions such as oxygen concentration, pH, nutrient availability, and various toxic compounds such as antibiotics, biocides, and heavy metals, affect the resistance mechanism activated by bacteria (Moore et al., 2014; Ye et al., 2017a). In addition, the specific growth and development needs of bacterial species and the energy burden required to adopt the resistance genes may also be responsible (Guo et al., 2014; Knopp & Andersson, 2015; Roux et al., 2015).

Another resistance mechanism is adaptive resistance (Fernández & Hancock, 2012). For example, the exponential growth phase of bacteria is skipped and goes directly to the stationary phase at the time of antibiotic exposure (Nyström, 1998). This mechanism allows bacteria to withstand antibiotic toxicity during antibiotic exposure temporarily. However, when antibiotics are removed, the defense mechanism is then terminated.

Recent findings show that it is not only antibiotics that cause bacteria to become resistant but also heavy metals, detergents, biocides, and oxygen radicals that can trigger the emergence of antibiotic resistance in bacteria (Sulfikar et al., 2018; Ye et al., 2017a). For example, Hobman and Crossman (2015) and Pal et al. (2017) described the correlation between resistance to heavy metals and resistance to antibiotics. The current findings indicate that the correlation is caused, among other things, by the location of genes that regulate resistance to heavy metals and antibiotics located at the same site or controlled by the promoter of the same gene, namely the stress-response gene (Imlay, 2008; Poole, 2012). These systems, among others,

regulate the activation of genes that produce efflux-pump proteins that remove pollutants such as heavy metals and antibiotics from the cell or take genes that help prevent bacteria from pollutant toxicity or by activating a temporary adaptation system.

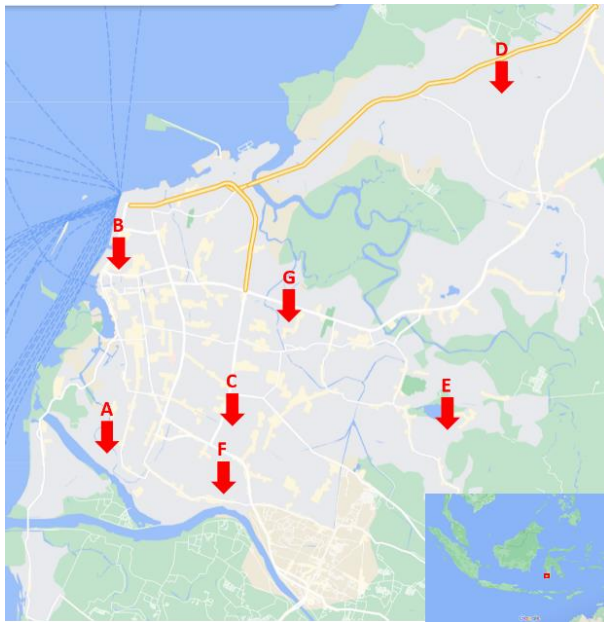
There are still many gaps in our knowledge about how the process of emergence, spread, and persistence of antibiotic-resistant bacteria in the environment and the possible transfer of antibiotic-resistant genes to pathogenic bacteria (Bengtsson-Palme et al., 2018). Genetic transfer mechanisms have been investigated in water samples and sediments and observed under laboratory conditions (Proia et al., 2016; Xu et al., 2017; Yang et al., 2012). Meanwhile, antibiotic-resistant bacteria in airborne particulates and whether other pollutants such as heavy metals correlate with bacterial resistance have not been widely studied. For example, few studies on antibiotic resistance in the air particulate in tropical countries such as Indonesia, where the temperature and humidity are favorable for bacteria to grow (Dinter & Müller, 1984; Tang, 2009). Meanwhile, high levels of heavy metal pollution can trigger the activation of the bacterial stress-response system.

There have been no studies regarding antibiotic-resistant bacteria in the air particulate of Makassar City, and only a few studies on air quality in Makassar City can be found in electronic journals. One study conducted in 2012 already showed enrichment factors of >1 for Cd, Cr, Cu, Pb, and Zn that may indicate anthropogenic or marine origins (Yunus et al., 2019). Therefore, we investigate whether antibiotic-resistant bacteria have polluted Makassar City and a correlation between resistant bacteria and heavy metal concentrations. This knowledge is essential as input for policymakers about other possible risks of heavy metal contamination as a trigger for antibiotic resistance in bacteria.

## 2. MATERIALS AND METHODS

### Sampling Sites

Air particulate samples were taken during July and August 2019 at several sites in Makassar City (Figure 1), suspected of showing differences in concentrations and types of air pollutants. The sampling locations include:



**Figure 1.** Sampling sites

- a. Jl. Mount Malabar, Tanjung Bunga (**Tanjung Bunga**, point A). This location was chosen because it is an elite residential location, and there is no industry around it.
- b. Fort Rotterdam, Jl. Ujung Pandang (**Fort Rotterdam**, Point B). The sampling point was in front of the fort, and ~50 m from the seafront and ~1 km from Makassar Port. This location is dominated by public transportation.
- c. Phinisi Building UNM, Jl. Petta Rani (**Phinisi Building**, Point C). This point represents the city centre with quite heavy motorised vehicle traffic. A flyover was under construction when sampling was carried out, and the wind was blowing from the west.
- d. Makassar City Industrial Estate (**KIMA**, Point D). This point represents an industrial area. Sampling was carried out right in front of the aluminium bar cutting factory. There were many parts of the road surface were not covered with asphalt.
- e. Antang Final Disposal Area (**TPA Antang**, Point E). This point represents a waste disposal area where waste-generating fires often occur. The sampling site is approximately 1 km from the waste area, in a shaded residential area.
- f. FMIPA UNM Parang Tambung campus (**FMIPA**, Point F). This point represents

the lower-middle-class residential area. About 2 km to the south is the Jeneberang River. Motor vehicle traffic is quite heavy during the hours of going (7:00-9:00) and returning from work (16:00-18:00). The sampling point is in the FMIPA campus garden, where the ground surface is covered with grass and shady trees and a fountain pond. Campus buildings border the garden.

- g. Balai Besar Industri dan Hasil Pertanian, Jl. Sultan Basalamah (**BBIHP**, Point G). This point represents the middle to lower residential area. Two major roads, flank this area: Jl. Perintis Kemerdekaan and Jl. Abdullah Daeng Sirua. Sampling was carried out at the BBIHP office yard.

### Data Collections

Air particulates were actively collected using a small-volume air particulate sampling device (Mini Vol Air Sampler, Model 2 HOL ZN. SN:026, Global Engineers Solution). This sampling device has two intakes to take samples simultaneously for metals and bacteria. Both intakes were fitted with a gridded sterile polycarbonate membrane with a pore size of 0.45  $\mu$ m and a diameter of 47 mm (Pall Gellman, UK). Before installing the membrane, all parts of the intake device and the forceps were rinsed with 75% alcohol. In addition, to avoid bacterial contamination from the skin surface or the sampler's breath, both hands of the sampler and wearing medical quality rubber gloves were also rinsed with alcohol, and they wore surgical masks.

The height of the sampling device is set at 1.5 m from the ground, except for the Phinisi Building. The height is 3 m from the road surface, so the total air intake height is 4.5 m. This precaution was done to avoid the dust from the open grounds. The suction airflow rate was set at 3 L/min for 2 hours, except for samples taken at the FMIPA UNM Parangtambung Campus, the flow rate was 6 L/min for 1 hour. After the air suction was complete, the membrane was put into a sterile HDPE tube. Sterile membranes were attached to the apparatus without air suction for blank samples. Data regarding sampling conditions can be seen in Table 1.

**Tabel 1.** Sampling site conditions

Sites	Coordinates	Sampling Time	T <sub>air</sub> (°C)	Humidity (%RH <sup>1</sup> )
Tanjung Bunga	S: 5°10'40,79" T: 119°23'51,59"	14:00 – 16:00	31.7	47
Fort Rotterdam	S: 5°08'01,27" T: 119°24'17,64"	10:00 – 12:00	31.1	54
Phinisi Building	S: 5°10'06,92" T: 119°26'04,18"	13:30 – 15:30	31	47
KIMA	S: 5°05'36,74" T: 119°30'00,96"	11:00 – 12:00	33	51
TPA Antang	S: 5°10'13,40" T: 119°29'31,79"	13:30 – 15:30	32.7	47
FMIPA	S: 5°11'10,32" T: 119°25'46,09"	17:00 – 18:00	31.6	51
BBIHP	S: 5°08'46,11" T: 119°26'58,00"	14:00 – 16:00	n/a	n/a

<sup>1</sup>RH = relative humidity

Heavy metal concentration data were obtained by analyzing Cd, Zn, and Cu in airborne particulates collected on the membrane. The analysis and preparation of metal samples were carried out using an atomic absorption spectrometer (Thermo Scientific iCE3500 Spectrometer) in a KAN accredited laboratory of BBIHP, Makassar. Bacterial resistance data were obtained by testing the resistance of *Escherichia coli* (*E. coli*) bacteria to five antibiotics with different types of the mechanism of action, namely amoxicillin-clavulamate, chloramphenicol, amikacin, norfloxacin, and trimethoprim. *E. coli* was chosen because these bacteria are the preferred pathogenic bacteria by WHO to be studied in connection with the high antibiotic resistance. *E. coli* was obtained by incubating one of the membranes on chromocult agar (Merck, Germany) at 37 °C for 2x24 hours. Agar chromocult can be used for the presumption of *E. coli* (blue colonies) and other coliforms (pink colonies). The blue colonies on the membrane were then transferred aseptically and used for the antibiotic resistance test.

Antibiotic resistance testing was carried out following the CLSI protocol (CLSI, 2012). Briefly, *E. coli* isolates were suspended in the saline solution until they matched the MacFarland 0.5 standard. This suspension was then spread evenly on the Mueller-Hinton, and antibiotic discs were fixed on the agar surface. The diameter of the inhibition of bacterial

growth around the antibiotic disc was measured after incubation at 37 °C for 18 h. Determination of resistant or susceptible bacterial isolates refers to the MIC Breakpoint Table (European Committee on Antimicrobial Testing ver. 6.0, 2016). Resistance rate (RR) is determined based on the ratio of presumed resistant *E. coli* isolates to the total *E. coli* isolates (Equation 1). To control the quality of the measurement of this resistance test, we repeated the test for the same isolate and measured the resistance of *E. coli* ATCC 25922.

$$RR = \frac{\text{The number of resistant } E.coli}{\text{The total number of } E.coli} \quad (1)$$

### 3. RESULTS AND DISCUSSIONS

The number of presumed *E. coli* isolates on the membrane filter used for air particulate sampling was very small (<10 CFU, Table 2) compared to the number of *E. coli* isolated from wastewater (10<sup>1</sup> - 10<sup>7</sup> CFU/mL), river water (10<sup>12</sup>-10<sup>13</sup> CFU/mL), and sediment (10<sup>11</sup>– 10<sup>12</sup> CFU/mL) and compared to samples in other studies (Asadi-Ghalhari *et al.*, 2020; Fluke *et al.*, 2019; Kumar *et al.*, 2020). The lack of isolates suggests that air particulate is probably more a vehicle for *E. coli* to survive than to thrive. Or else, it may be due to the sampling time during the day, when UV exposure is relatively high (Kodoth & Jones, 2015).



Our results showed that antibiotic-resistant *E. coli* was present in airborne particulates in Makassar City. This finding supports other studies in urban, rural, and industrial areas, showing that airborne particulates are a significant source of resistant bacteria (Gandolfi et al., 2013; Li et al., 2018; Sianturi et al., 2012). In addition, the *E. coli* observed in our study can survive in the air even though the sampling was done in the dry season when the UV radiation is high enough to harm bacteria (Kodoth & Jones, 2015; Pereira et al., 2014).

In general, bacteria may survive in the aerosol because they could switch to a dormant state in unfavorable conditions, such as a lack of nutrients and humidity (van Vliet, 2015). When inactive, bacteria may become more resistant to antibiotics (Bengtsson-Palme et al., 2018; Rittershaus et al., 2013). Furthermore, a recent study shows that *B. subtilis* can multiply in low nutrient concentrations, although much slower than average (Gray et al., 2019). Switching to the dormant cycle stage was observed after 18 hours of incubation. Then, there was only one or two *E. coli* colonies grew. However, after further incubation for up to 2 x 24 hours, we observed more *E. coli* colonies.

Resistant *E. coli* were found at almost every sampling point, except in the Phinisi Building sampling sample samples. The percentage resistance between locations varied in magnitude, from 0% at the Phinisi Building site to 100% at the KIMA site. It should be noted that we only found one *E. coli* isolate in these two locations. The resistant *E. coli*, which came from the BBIHP, Tanjung Bunga, and KIMA sites, were resistant to only one antibiotic. In other locations, resistance was

found to two or three types of antibiotics. For example, resistance to three types of antibiotics was found in the TPA Antang and Fort Rotterdam; one isolate for each location.

The antibiotic test results showed that *E. coli* isolated in different locations were resistant to different types of antibiotics (Table 3). For example, isolates from BBIHP were resistant to norfloxacin or trimethoprim; and those from Tanjung Bunga were resistant to norfloxacin. Meanwhile, isolates from Fort Rotterdam were resistant to amoxicillin-clavulanate, chloramphenicol, and norfloxacin; those from the FMIPA were resistant to amoxicillin-clavulanate and trimethoprim, and those from the TPA Antang were resistant to almost all the antibiotics tested except amikacin. At all locations, none of the isolates was resistant to amikacin. Sensitivity to amikacin has also been observed for *Staphylococcus sp.*, *Pseudomonas sp.*, and *Enterobacter sp.*, which were isolated from a hospital in Medan (Sianturi et al., 2012). The resistance of *E. coli* to the tested antibiotics was dominated by trimethoprim and amoxicillin-clavulanate; 9 and 8 of 14 *E. coli* isolates were resistant to these antibiotics.

Other studies have investigated resistant bacteria in aerosols by using real-time qPCR or metagenomics methods (Danko et al., 2021; Hu et al., 2018; Ouyang et al., 2020). These studies provide extensive information on bacterial species and antibiotic-resistant genes (ARG). However, they do not provide phenotypic information: whether bacteria possess ARGs to express the resistance gene (except in Solomon et al. (2014) studies). Our study complements these studies by showing that the *E. coli* isolated from airborne particulates exhibit resistance to antibiotics.

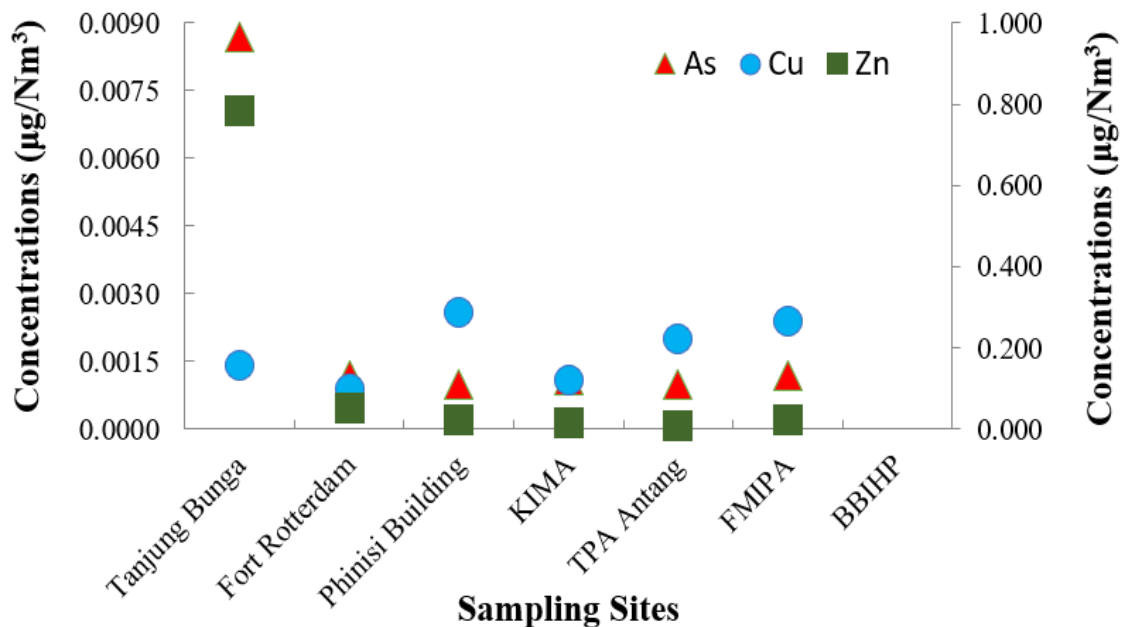
**Table 2.** *E. coli*, Other *Coli*, and percentage of resistant colonies

Sites	<i>E. coli</i>	Other <i>coli</i>	Resistance (%)
Tanjung Bunga	3	7	33
Fort Rotterdam	5	54	25
Phinisi Building	1	4	0
KIMA	1	3	100
TPA Antang	7	20	71
FMIPA	9	87	44
BBIHP	4	9	75

**Table 3.** Distribution of antibiotic resistance of *E. coli* isolates

Isolates	AK	AMX-C	C	NOR	W
Tanjung Bunga				■	
Fort Rotterdam		■	■	■	
FMIPA1		■	■		■
FMIPA2		■	■		■
FMIPA3		■	■		■
FMIPA4		■	■		■
TPA Antang1			■	■	
TPA Antang2		■	■		■
TPA Antang4		■	■		■
TPA Antang6			■	■	
TPA Antang7		■	■	■	■
KIMA				■	
BBIHP1					■
BBIHP2				■	■
BBIHP3					■

AK = akamycin, AMX-C = amoxicillin-clavulanate, C = chloramphenicol, NOR = norfloxacin, W = trimethoprim.



**Figure 2.** The metal concentration in air particulate samples from each site.

Our study also indicates there may be variations in the expression of antibiotic resistance according to demographic and geographic locations within a city. For example, in the elite residential area of Tanjung Bunga, the suspected *E. coli* isolate is resistant to one type of antibiotic, namely norfloxacin. Resistance to the same antibiotics was also found for isolates from KIMA, an industrial center area in Indonesia Makassar. For samples collected in BBIHP, a middle-

lower residential area, the isolated *E. coli* were resistant to norfloxacin or trimethoprim. The isolates from FMIPA were all resistant to two antibiotics, amoxicillin-clavulanate, and trimethoprim. The location near landfills showed resistance to four out of five antibiotics tested. This multiple resistance may be because this location is a waste disposal center for Makassar City. The source of bacteria may come from many areas where the waste originates. If this resistance pattern

holds, a more thorough study is warranted, considering whether or not the pattern was governed by differences in antibiotic consumption pattern, the quality of water infrastructure, land use, air pollutants, and by taking into account local meteorological parameters.

We could not be more definitive in explaining the distribution pattern of the antibiotic resistance in our data since the number of *E. coli* colonies we found per site was small, and the number of sites was also limited. Thus, the observed distribution pattern cannot be guaranteed solely due to chance. The small number of isolates we obtained might be due to the small volume of air we collected (3 L min<sup>-1</sup> for 2 hours and 6 L min<sup>-1</sup> for 1 hour). However, Solomon and Oliver (2014) also found a relatively small number of *E. coli* isolates compared to other species, e.g., six and eight vs. 72 and 64 CFU for *S. aureus* and *P. aeruginosa*, respectively. They collected air particulates passively using tryptic soy agar in a petri dish in a hospital delivery room and ICU for one hour. In addition, particulate deposition between 9:00 – 21:00 was found to fluctuate (Zhang et al., 2019), so the number of *E. coli* did. We found more isolates from FMIPA samples collected between peak traffic hours (17:00 – 18:00), when more particulates would probably be released into the air during this particular time.

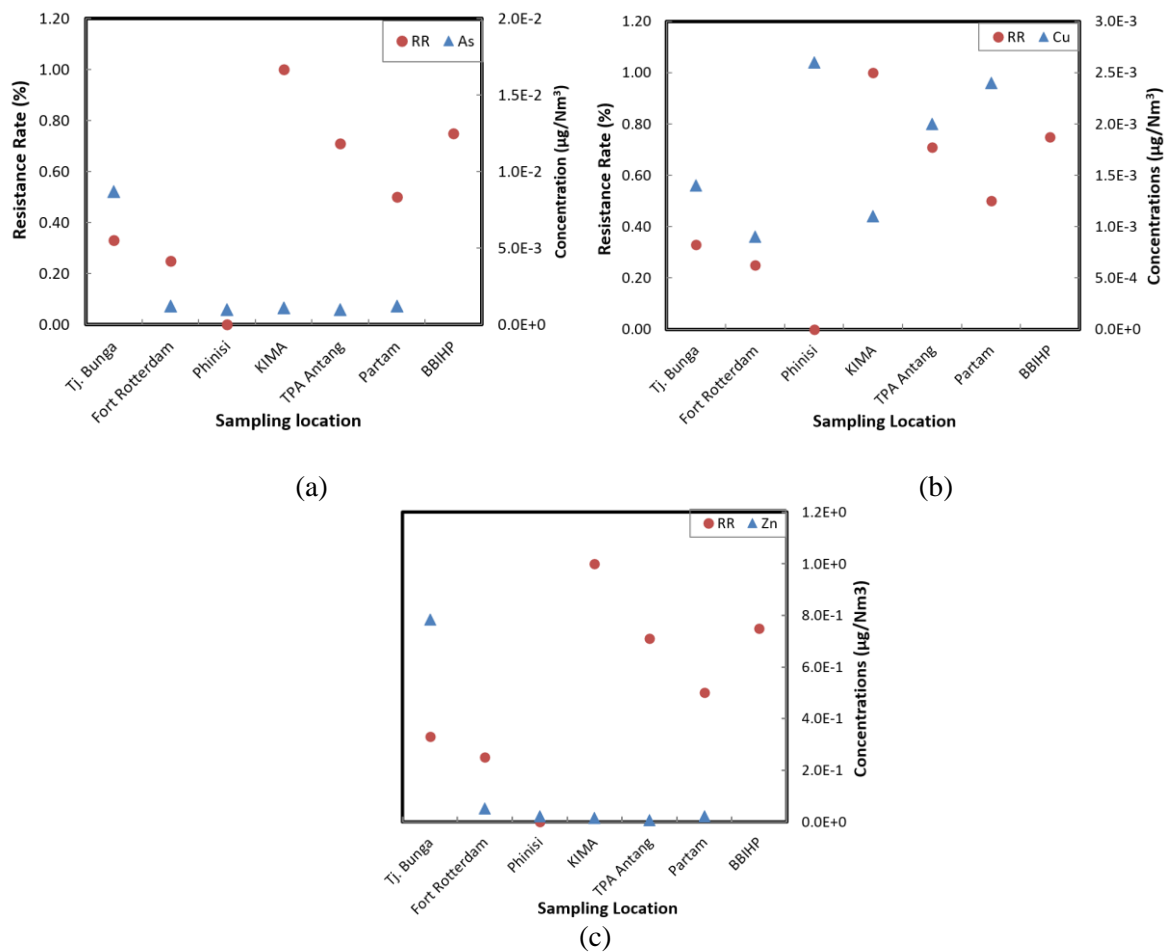
Furthermore, the less intense UV light could increase bacterial survival during this period. In contrast, we found only one isolate from KIMA, sampled in an open area at mid-day. For future studies, we recommend doing sampling simultaneously and for a longer time to get a better picture of the resistance profile of a site but without exhausting the sampling resources.

The analysis of metal concentrations showed that Cu was below the method detection limit in all sampling locations. The measured concentration was near the detection limit at the Phinisi Building, KIMA, and TPA Antang area samples for Zn. In Tanjung Bunga, As and Zn concentrations were far above the concentrations in other locations, seven and 36 times higher for As and Zn, respectively (Figure 2). We have hypothesized that the heavy metals may affect bacterial resistance to antibiotics via co-resistance (different resistance determinants co-exist in the same genetic element) and cross-resistance

(the same genetic factor is responsible for both antibiotics and metals) (Nguyen et al., 2019; Ye et al., 2017b). However, our data also showed no simple correlation between the Resistance Rate and the concentrations of the three metals (Figure 3).

The lack of correlation between heavy metal concentrations and resistance levels could be because of the small number of isolates that have been found per location. As explained previously, the daily fluctuations of airborne particulate deposition may affect the number of obtained isolates. Or, the concentrations of the metals that we observed were too low to have a role in the induction of antibiotic resistance. SOS responses can be triggered by sub-inhibitory concentrations of heavy metals, inducing the production of reactive oxygen substances (ROS). This ROS subsequently started SOS responses that prompt increased permeability of the outer cells to allow conjugated transfer of ARGs between *E. coli* strains (Zhang et al., 2018). These sequence reactions occurred at concentrations as low as 0.005 mg/L of Cu and 0.5 mg/L of Zn. For As, a concentration of 150 mg/L was found to induce tetracycline resistance (Zhang et al., 2018). These concentrations are far above the concentration of As, Cu, and Zn that we have observed.

ARB has been found to vary geographically: cities, countries (MacFadden et al., 2018; McGough et al., 2020) and temporally: hourly, seasonally (Xie et al., 2018; Zhang et al., 2019). Some studies have looked at the variation in ARG distribution according to altitude, and land-use gradients on a larger scale, i.e., within or between countries (Gandolfi et al., 2013; Xie et al., 2018). Or, the studies focus on local features such as river water, wastewater treatment plants, and hospitals (Jiang et al., 2018; Solomon et al., 2017; Wengenroth et al., 2021) that also influence ARG distribution. The antibiotic resistance snapshot profile that we observed within Makassar city air particulates might be due to demographic differences in antibiotic usage, local variations in air particulate, chemical pollutants, or differences in land use (e.g., open/close drainage, industrial sites, waste dumps sites). Which factors remain faithful to these differences still need further study. Our study might be the first to capture a more satisfactory resolution profile of antibiotic resistance within a city.



**Figure 3.** There were no correlations between heavy metals concentrations ( $\mu\text{g}/\text{Nm}^3$ ) and the resistance rate (RR, %). (a) RR vs As, (b) RR vs. Cu, (c) RR vs Zn.

#### 4. CONCLUSIONS

Our finding of antibiotic-resistant bacteria in airborne particulates reinforces the critical contribution of airborne particulates to the spread of antibiotic-resistant bacteria. For the time being, we cannot conclude whether or not there is a correlation between the percent resistance to antibiotics and the heavy metals that we analyzed in *E. coli* isolates from airborne particulates in Makassar City. Perhaps the heavy metal concentrations that we measured were too low to induce antibiotic resistance in *E. coli*. However, our study indicates that there may be a distribution pattern of antibiotic-resistant bacteria to certain types of antibiotics following a demographic pattern. If this resistance pattern holds, a more thorough study is warranted to investigate whether or not the pattern was governed by differences in antibiotic consumption patterns, the quality of water infrastructure, land use, and air pollutants. We also need to investigate

the origin of the air particulate by considering the meteorological parameters.

#### ACKNOWLEDGEMENT

This research was funded by DIPA Makassar State University Number: SP DIPA -042.01:2.400964/2019.

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