Antibiotic Susceptibility

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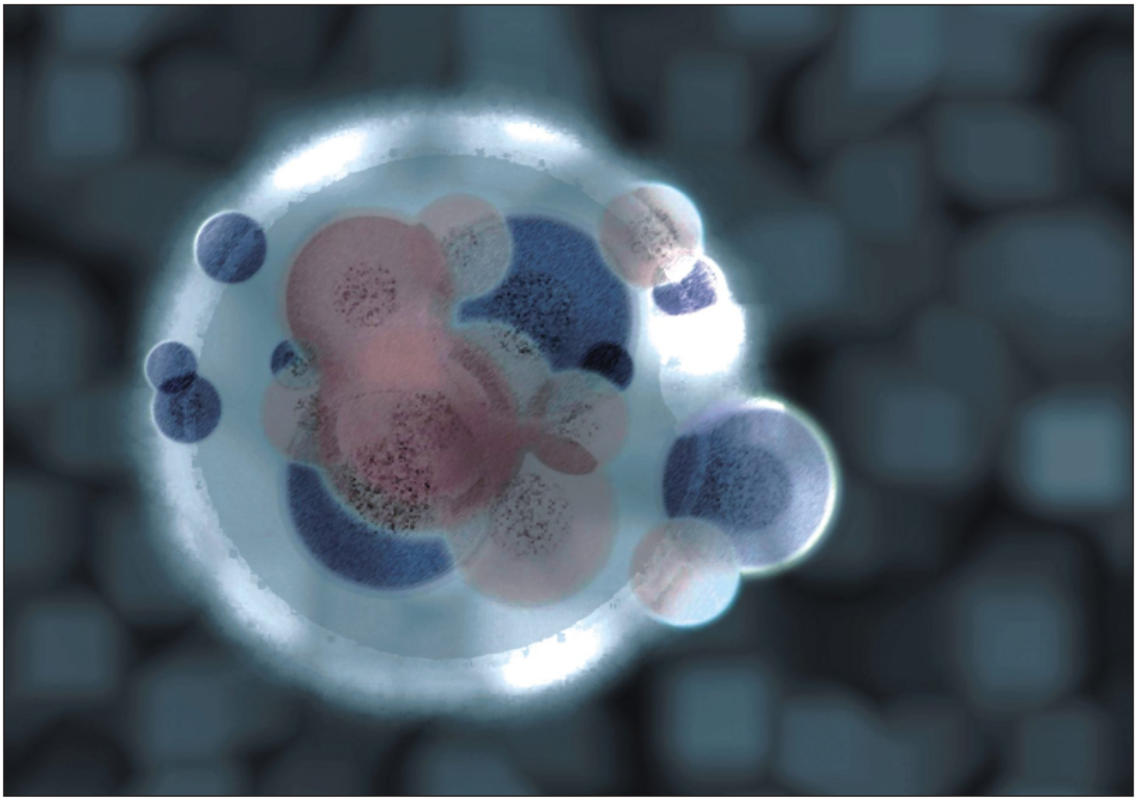

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Research Article

Antibiotic Susceptibility Patterns of *Salmonella* Typhi in Jakarta and its Trends Within the Past Decade

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Abstract

Background and Objective: A trend of changing susceptibility of *Salmonella* Typhi, the etiologic agent of typhoid fever to antibiotics, especially the first line occurred elsewhere to the worst, in which emerged the multiple drug resistance strains. This study aimed to investigate the susceptibility of *Salmonella* Typhi isolates from hospitalised patients in Jakarta and its satellite city to the 1st line antibiotics and others and evaluated whether there is a change of the pattern in the past decade. **Materials and Methods:** The study was a retrospective analysis. Records of antibiotic susceptibility of *Salmonella* Typhi from 2012-2017 in the hospitals in North, Central and West Jakarta and the satellite city, i.e., South Tangerang was retrieved from WHONET (5.4 and 5.6 version). Antibiotic susceptibility of 80% or greater was determined as good activity *in vitro*. The susceptibility of *Salmonella* Typhi in 2008-2010 from hospitals in Central and West Jakarta was also included to view its trend within a decade period. **Results:** Susceptibility of *Salmonella* Typhi isolates to the 1st line antibiotics i.e., Amoxicillin, Ampicillin, Chloramphenicol, Trimethoprim-sulfamethoxazole was good, also to Ceftriaxone, Nalidixic acid, Ciprofloxacin, Levofloxacin. The pattern relatively remained unchanged for the past 10 years towards most of the antibiotics tested. **Conclusion:** Susceptibility of *Salmonella* Typhi from Jakarta and the satellite city was good to the 1st line antibiotics and others within a decade period. Hence, these can be of choice for the treatment of typhoid fever, especially when microbiology laboratory diagnostic is not available.

Key words: *Salmonella typhi*, first line antibiotics, satellite city, hospitalised patients, antibiotic susceptibility

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Typhoid fever is still a problem in many developing countries, Indonesia is one of them. A study conducted in 2011 measured the cost for treatment of typhoid fever in 5 Asian countries, showed the average cost for hospitalised cases was far exceeded the average cost for out-patients. This becomes a burden for the country[1]. Punjabi *et al.*[2] observed that in North Jakarta, among 2,887.5 fever cases at clinics or hospitals a year, 1/1000 people a year suffered enteric fever. Thus it was estimated 4.4 confirmed Typhoid fever cases a day. Ochiai *et al.*[3] reported in slum area in Jakarta, the incidence rate of typhoid fever was at 148.7 per 100,000 person-years (age group 2-4 years old), 180.3 (age group 5-15 years old) and 51.2 of those over 16 years of age. The case fatality rate was high (10-30%) without effective treatment, but the number was reduced to 1-4% in those receiving appropriate treatment[4].

Despite of antibiotic resistance issues including multidrug resistance (MDR) and Nalidixic acid resistance *Salmonella* Typhi (*Salmonella* Typhi) has been reported from many places in the world[5-10]. Earlier study by Moehario and Sumanto[11] showed *Salmonella* Typhi isolated from sporadic typhoid fever cases in the East Jakarta area were all susceptible to Amoxicillin, Chloramphenicol, Trimethoprim-sulfamethoxazole, Ceftriaxone, Ciprofloxacin and Levofloxacin. A study by Singhal *et al.*[12] reported a re-emergence of susceptible *Salmonella* Typhi to the first line antibiotics i.e., susceptibility of >95% towards Chloramphenicol, Ampicillin and Trimethoprim-sulfamethoxazole. Also, they found the MDR isolates per year decreased over time with a present rate of around 1%. Nonetheless, resistance to Nalidixic acid was high and resistance to Ciprofloxacin was relatively stable over the time period studied with a drastic increase from 5.8% in 2008 to 10% in 2009 and up to 18.2% since 2011-2012[12].

Considering the trend of changing susceptibility elsewhere, this study was aimed to view the susceptibility of *Salmonella* Typhi isolated in Jakarta and the satellite city against the first line antibiotics and others as recommended by the Clinical and Laboratory Standards Institute (CLSI)[13] and evaluated the trend in the past 10 year period.

MATERIALS AND METHODS

The present study was part of *Salmonella* Typhi research in the Department of Microbiology, Faculty of Medicine and Health Science, Atma Jaya University (ethical approval number 08/03/KEP-FKUAJ/2018).

Study design: The study was a retrospective analysis of laboratory records regarding antibiotic susceptibility of *Salmonella* Typhi.

Sample collection: Records of antibiotic susceptibility of *Salmonella* Typhi in the year of 2012-2017 from 4 hospitals were collected. These hospitals were located in North, Central and West of Jakarta and the satellite city i.e., South Tangerang. Each hospital carried out the microbiology work up as follow: collected blood specimens from hospitalised patients suffered from typhoid fever, cultured and bacterial identification. In addition, 2 of the hospitals mentioned above i.e., from Central and West Jakarta also provided the susceptibility records from 2008-2010.

Antibiotic susceptibility test: Antimicrobial susceptibility tests (AST) were as recommended by Clinical and Laboratory Standards Institute CLSI[13] and carried out using disc diffusion method; automatic system was used instead in the laboratory of the hospital in South Tangerang.

WHONET: All records of the antibiotic susceptibility of *Salmonella* Typhi were retrieved from WHONET[14,15]. Antibiotics categorized as 1st line antibiotics for *Salmonella* Typhi are as follow: Ampicillin (AMP), Amoxicillin (AMX), Chloramphenicol (CHL) and Trimethoprim-sulfamethoxazole (SXT). In the present study the susceptibility towards AMP, AMX, CHL, SXT and also to Ceftriaxone (CRO), Nalidixic acid (NAL), Ciprofloxacin (CIP) and Levofloxacin (LVX) was analyzed. Antibiotic susceptibility of 80% or greater was determined as good activity *in vitro*.

RESULTS

Within a time span from 2012-2017 the total data retrieved from WHONET was 142. Antibiotic susceptibility of *Salmonella* Typhi (N: 60) obtained from the hospital in North Jakarta, showed good activity ranging from 87.5-98.3% against all antibiotics tested as followed: AMX, AMP, CRO, CHL, SXT, NAL, CIP and LVX (Table 1). The same situation was also shown from the hospital in Central Jakarta; the susceptibility against all antibiotics tested ranging from 97.1-100%. However, the number of isolates tested against antibiotic Chloramphenicol was low (N: 13) (Table 1). In West Jakarta the susceptibility was 100% against AMX, CRO, CIP, LVX (each N: 24), CHL (N: 20) and SXT (N: 12) (Table 1). Further, in South Tangerang, *Salmonella* Typhi was 100% susceptible to AMX, AMP, CRO, SXT, CIP and LVX (each N: 11) as shown in Table 1.

Table 1: Susceptibility of *Salmonella* Typhi isolates against antibiotics in Jakarta and South Tangerang from 2012-2017

	AMX		AMP		CRO		CHL		SXT		NAL		CIP		LVX	
Region	S (%)	N	S (%)	N	S (%)	N	S (%)	N	S (%)	N	S (%)	N	S (%)	N	S (%)	N
North Jakarta	96.5	57	96.6	58	98.3	60	98.2	55	96.7	60	87.5	56	93	57	96.6	58
Central Jakarta	97.1	34	97.9	47	97.9	47	100	13	100	47	NA	NA	100	47	100	31
West Jakarta	100	24	NA	NA	100	24	100	20	100	12	NA	NA	100	24	100	24
South Tangerang	100	11	100	11	100	11	NA	NA	100	11	NA	NA	100	11	100	11

S (%): Percentage susceptibility, N: Number of isolates, AMX: Amoxicillin, AMP: Ampicillin, CRO: Ceftriaxone, CHL: Chloramphenicol, SXT: Trimethoprim-sulfamethoxazole, NAL: Nalidixic acid, CIP: Ciprofloxacin, LVX: Levofloxacin, NA: Not Available

Table 2: Susceptibility of *Salmonella Typhi* isolates against antibiotics in Central and West Jakarta from 2008-2010

	AMX		CRO		CHL		SXT		CIP		LVX	
Region	S (%)	N	S (%)	N	S (%)	N	S (%)	N	S (%)	N	S (%)	N
Central Jakarta	98.5	139	99.2	139	100	139	100	139	100	139	NA	NA
West Jakarta	100	73	98.6	73	98.6	73	98.6	73	100	73	100	73

S (%): Percentage susceptibility, N: Number of isolates, AMX: Amoxicillin, CRO: Ceftriaxone, CHL: Chloramphenicol, SXT: Trimethoprim-sulfamethoxazole, CIP: Ciprofloxacin, LVX: Levofloxacin, NA: Not Available

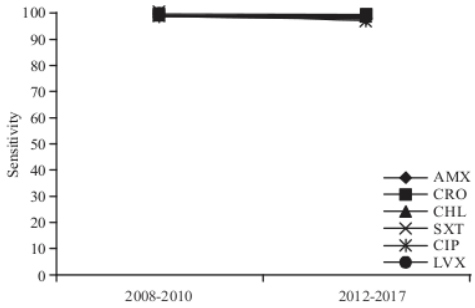

Fig. 1: Trend of *Salmonella* Typhi susceptibility to antibiotics in Jakarta from 2008 to 2017
AMX: Amoxicillin, CRO: Ceftriaxone, CHL: Chloramphenicol, SXT: Trimethoprim-sulfamethoxazole, CIP: Ciprofloxacin, LVX: Levofloxacin

Two hospitals located in West and Central Jakarta participated in this study also presented records of antibiotic susceptibility of *Salmonella* Typhi in earlier years i.e., 2008-2010. The susceptibility toward antibiotic AMX, CRO, CHL, SXT, CIP and LVX was good, ranged from 98.6-100% (N: 73) in West Jakarta; this situation was also observed in Central Jakarta, in which the range of susceptibility was 98.5-100% (N: 139); antibiotic LVX was not tested in this hospital (Table 2). The susceptibility patterns of *Salmonella* Typhi against antibiotics AMX, CRO, CHL, SXT, CIP and LVX in the period of 2008-2010 and 2012-2017 were further examined to see whether there was any change that needed attention. The results showed that the patterns were similar; on that account, the susceptibility of *Salmonella* Typhi to the 1st line antibiotics tested at present and earlier periods, i.e., Amoxicillin (AMX), Chloramphenicol (CHL), Trimethoprim-sulfamethoxazole (SXT) and towards other antibiotics i.e., Ceftriaxone (CRO), Ciprofloxacin (CIP) and Levofloxacin (LVX) remained good within a decade from 2008 to 2017 (Fig. 1).

DISCUSSION

Jakarta as the capital city is one most hectic and overpopulated city in Indonesia. Many people come and work in Jakarta since it is a promising place; none-theless, it also has problems as generally occur in other big cities in the developing countries, among other is poor sanitation and dense population in certain areas, clean water problems in some slum areas and endemic with some infectious diseases related to sanitation and personal hygiene such as typhoid fever. Laboratory data of *Salmonella* Typhi susceptibility to antibiotics collected from 4 hospitals (North, West and Central of Jakarta and South Tangerang) in 2012-2017 was 142. In comparison, in earlier period of time (2008-2010) as many as 212 was obtained from 2 hospitals (West and Central Jakarta). It seemed there was a decrease of hospitalised patients with typhoid fever, though there was cases that people did not seek for treatment in the medical facilities. Moreover, due to certain limitations in some health centres or hospitals, microbiology examinations were not generally performed as routine diagnostics.

The present study showed good susceptibility of *Salmonella* Typhi to all the antibiotics tested, including the 1st line antibiotics in the time span of a decade from 2008-2017. However, it should be noted that the numbers of *Salmonella* Typhi susceptibility data collected from West Jakarta and South Tangerang between the year 2012-2017 were less than 30. WHO recommended the ideal number of isolates in a cumulative antibiogram is 30 or more[16]. Thus, the

susceptibility shown might give a bias, therefore it should be interpreted cautiously. The results of the present study generally were in agreement with some reports by other investigators. Tjaniadi *et al.*[17] conducted a study on antibiotic resistance of bacterial pathogens causing diarrhea that included samples collected since 1995-2001 from many places in Indonesia spreading from West to East namely Medan, Batam, Padang, Jakarta, Denpasar, Pontianak and Makassar showed that 111 isolates of *Salmonella* Typhi were all susceptible to antibiotics commonly used for the treatment of typhoid fever, i.e., Ampicillin, Trimethoprim-sulfamethoxazole, Chloramphenicol, Tetracycline, Ceftriaxone and Ciprofloxacin[17]. Judio *et al.*[18] reported that all 22 *Salmonella* Typhi isolates, originated from 142 children in Jakarta diagnosed clinically by physicians suffering from typhoid fever were all susceptible to first line antibiotics, i.e., Chloramphenicol, Ampicillin and Trimethoprim-sulfamethoxazole. They also suggested that children with typhoid fever were treated with these antibiotics, especially when laboratory confirmation was limited. In developing countries, however, the selection of antibiotics was not only based on efficacy but also its availability and cost. In Indonesia, based on those factors, Chloramphenicol is still being used in many places for the treatment of typhoid fever in children[19]. The use of Chloramphenicol showed several advantages such as good efficacy i.e., fever drops to 4-5 days on average after treatment began. Moreover, the drug is easy to obtain and the cost is quite low. However, the disadvantage of the drug i.e., aplastic anaemia due to bone marrow suppression is important to be considered. High relapse rate in children had been reported among cases treated with Chloramphenicol[19]. Despite of being the 1st line antibiotics, Chloramphenicol treatment in adults with typhoid fever is less favourable than Fluoroquinolone and 3rd generation of Cephalosporin (i.e., Ceftriaxone)[20,21]. A retrospective study by Lugito *et al.*[22] reported that 93 *Salmonella* Typhi isolates from patients in the hospital in Tangerang within the year 2011-2015, showed low resistance against Ampicillin, Trimethoprim-sulfamethoxazole, Ceftriaxone, Ciprofloxacin and Levofloxacin.

Previous studies in Indonesia and other country such India and Africa, reported resistance of *Salmonella* Typhi to groups of antibiotics. A study by Hatta and Ratnawati[23] showed *Salmonella* Typhi resistance against Chloramphenicol and Ciprofloxacin was 1.04-7.84% and 0.11-6.83% respectively, in South Sulawesi. In the late 2000, since the 1st line antibiotics for *Salmonella* Typhi showed resistance, the Fluoroquinolone and 3rd generation of cephalosporin had been used in many endemic places and countries including Indonesia[6-8,24]. However, shortly after the frequent use of fluoroquinolone, *Salmonella* Typhi resistance to this group of antibiotic has widely reported[25-27]. Variation in the susceptibility patterns of *Salmonella* Typhi against antibiotics is worth noted. A study conducted by Chiou *et al.*[10] from Taiwan, in 2014, showed different clonality of *Salmonella* Typhi which exist and spread out in Southeast Asia and Bangladesh. The *Salmonella* Typhi isolates from Bangladesh and Vietnam were genetically closely related and were distant to those from Indonesia and Taiwan. The majority of *S. typhi* isolates from Bangladesh and Vietnam were MDR and belonged to the same haplotype. The resistance of *Salmonella* Typhi isolates from Bangladesh to Nalidixic Acid and Ciprofloxacin was as high as 82 and 40%, while it was only 1.8% and none respectively of those of isolates from Indonesia[10]. A study by Moehario[28] on genetic fingerprinting of *Salmonella* Typhi in Indonesia showed the heterogeneity of endemic strains in certain geographic areas and these *Salmonella* Typhi were all susceptible to Chloramphenicol, Ampicillin and Cotrimoxazole.

CONCLUSION

Antibiotic susceptibility of *Salmonella* Typhi to the 1st line antibiotic and others in Jakarta and South Tangerang had been investigated. The procedure was carried out as recommended by the Clinical and Laboratory Standards Institute; all laboratories used disc diffusion method except the one in the hospital in South Tangerang, it used automatic system. The data were then retrieved from WHONET. Antibiotic susceptibility of 80% or greater was determined as good activity *in-vitro*. Susceptibility of *Salmonella* Typhi to Amoxicillin, Ampicillin, Ceftriaxone, Chloramphenicol, Trimethoprim-sulfamethoxazole, Ciprofloxacin and Levofloxacin from 2012-2017 was good, ranged from as low as 93-100%. Susceptibility to Nalidixic acid was the lowest, i.e., 87.5%, however it was tested only in one hospital that was in North Jakarta. The susceptibility pattern was similar to the one obtained in 2008-2010, i.e., 92.6-100% against Amoxicillin, Ceftriaxone, Chloramphenicol, Trimethoprim-sulfamethoxazole, Ciprofloxacin and Levofloxacin. The susceptibility of *Salmonella* Typhi in Jakarta to all antibiotics tested was good within a decade since 2008.

SIGNIFICANCE STATEMENT

The present study showed that *Salmonella* Typhi isolates from Jakarta and its satellite city, South Tangerang, showed good activity *in-vitro* against antibiotics, namely Ampicillin, Amoxicillin, Chloramphenicol, Ceftriaxone, Trimethoprim-

sulfamethoxazole, Nalidixic acid, Ciprofloxacin and Levofloxacin. Overall, the susceptibility patterns of the isolates of *Salmonella* Typhi has been maintained unchanged within a time span of a decade since 2008. The information in this study is useful for empirical therapy for patients diagnosed with typhoid fever in Jakarta and its surroundings especially when microbiology laboratory examination is limited. Also, it can be used as a reference for other places in Java island and around.

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