JULY - Vol. - 9, No. - 2, 2024 int. med. col. J.

Original Article

Clinical Features and Antibiotic Sensitivity Patterns among Typhoid / Enteric Fever in outpatient: A Hospital Based Prospective Study from a Tertiary Care Center, Keraniganj, Dhaka

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Abstract:

Background: *Enteric fever is caused by Salmonella enterica var Typhi and Salmonella enterica Var Paratyphi A being the major causative microorganisms transmitted by the fecal-oral route. The disease is mainly associated with low socioeconomic status and poor hygienic practices of human beings the only natural host and reservoir of infection. Typhoid fever is an earnest public health problem in many developing countries including Bangladesh. There is a wide spectrum of clinical presentations and with the emergence of multidrug-resistant typhoid, the treatment nowadays has become more challenging.*

Objective: *The main objectives of the study were to evaluate the various clinical features & effects of Antibiotic Sensitivity Patterns among Typhoid / Enteric Fever patients.*

Methods and Materials: This hospital-based prospective observational study was done on 96 outpatients of five Upazila level tertiary care private clinics in Dhaka division over a period of one year from June 2020 to May 2021. Written informed consent was obtained from the outpatients of the hospital. All outpatients diagnosed with typhoid fever if presented with fever (temperature >38ºC) for at least 3 days with positive blood culture for Typhi or paratyphi were included in the study. The demographic profile and clinical data were recorded and tests including antibiotic sensitivity and resistance were done.

Results: *A total of 96 patients were included in the study. The majority of the patients were between 31 to 45-year age group (33.33%). Out of 96 patients, 56 were males and 40 were females. The majority of the cases were from rural areas accounting for 69%. The drinking water source was tap water in 63% of cases and bore well water in 37% of cases. The majority (65%) belonged to the lower socioeconomic class and 68% were during rainy seasons. The clinical findings observed were fever (100%), vomiting (98, 72%), diarrhea (55.8%), headache (45.5%), and splenomegaly (42.6%). Other clinical features found were coated tongue, abdominal pain, hepatomegaly, constipation, and dehydration. Six patients had complications, 3 had enteric hepatitis, 2 had a shock, and 1 had encephalopathy. Cefixime, Azithromycin, Ampicillin and Cefuroxime resistance were observed in 26.53%, 88.16%, 53.95 and 19.74% of patients with typhoid fever respectively in the present study. Maximum sensitivity was observed with Imipenem (100%), Meropenem (100%), Levofloxacin (93.42%), Amikacin (93.42%), followed by Ceftazidime (86.84%), Ceftriaxone 85.41, and Cefepime (77.63)*

Conclusions: *Clinical presentation in the study subjects were mainly fever, vomiting, diarrhea, headache and splenomegaly. Increasing resistance of salmonella to Ampicillin and amoxicillin was observed.*

Keywords: *Antibiotic sensitivity, Ceftriaxone, Salmonella, Typhoid fever.*

Int. Med. Col. J. 2024; 9(2): 57-63

Introduction:

Typhoid and Paratyphoid fever is caused by *Salmonella enterica* serovar Typhi (*S. typhi*) and *Salmonella enterica* serovar Paratyphi (*S. paratyphi*). *S. paratyphi* A and B (and, uncommonly, *S. paratyphi* C) cause a disease

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that is clinically indistinguishable from typhoid fever, particularly in parts of Asia. Invasive non-typhoidal salmonellosis (iNTS) is an invasive infection caused by non-typhoidal serovars of S. enterica, most commonly S. enterica serovars Enteritidis and Typhimurium. Collectively, invasive Salmonella infections are responsible for a significant burden of morbidity and mortality worldwide. There are an estimated 11–21 million cases of typhoid fever and approximately 128 000–161 000 deaths annually, compared to an estimated 6 million cases of paratyphoid fever and 54 000 deaths annually.[1,2,3,4] The majority of cases occur in South and South-East Asia and sub-Saharan Africa. An estimated 2.1– 6.5 million cases of iNTS disease occur annually, with the highest incidence in Africa.[5] The case fatality rate is high in those with HIV infection. Typhoid fever is an acute, life-threatening, febrile illness. Without treatment, the case fatality rate of typhoid fever is 10–30%, dropping to 1–4% with appropriate therapy.[6]

Common symptoms include sustained fever, chills and abdominal pain. The non-specific symptom profile complicates clinical diagnosis, with symptoms that are common to other diseases occurring in typhoid-endemic areas. The mainstay for laboratory confirmation is blood culture but this has limited sensitivity of approximately 40–60%,[7] due in part to the widespread use of antimicrobials before patients present to a health service. This disease is the most prevalent in South Central Asia and Southeast Asia with more than 100 cases per 100 000 persons per year. Regions of medium incidence (10-100 cases per 100 000 persons per year) include the rest of Asia, Latin America, Africa and the Caribbean, and Oceania, except for Australia and New Zealand. It is estimated that there are 22 million new cases of enteric fever annually, with 200 000 deaths [8]. In the early 1970s, the emergence of plasmid-mediated chloramphenicol resistance was reported and the effectiveness of chloramphenicol as a first-line drug decreased gradually by outbreaks caused by resistant strains in countries as far apart as Mexico and India. Outbreaks occurred in Vietnam, Indonesia, Korea, Chile, and Bangladesh in the next five years.[9]

It was reported that, in Bangladesh, third-generation cephalosporins (ceftriaxone and cefixime) are still the effective drugs for treating typhoid fever if used in proper dose and duration. Though azithromycin is prescribed as an alternative to ciprofloxacin in resistant cases, recently it has lost credibility due to the emergence of resistance [10, 11]. Eventually, it causes the extra cost of health care, extended stay in the hospital, sudden or prolonged health complications including significant excess morbidity and mortality [12,13].The disease is mainly associated with low socioeconomic status and poor hygienic practices, with human beings the only natural host and reservoir of infection.[14]

Varied presentations of typhoid fever are known in the paediatric age group, such as septicemia in neonates, as diarrhoea in infants, and as lower respiratory tract infections in older children[15]. Due to these varied and atypical presentations, it is common for typhoid fever in children to be diagnosed late or even remain unrecognized. Also, no vaccine against typhoid fever is available commercially for children under two years of age [16]. Fluoroquinolones were widely regarded as the most effective drug for the treatment of typhoid fever [17].But unfortunately, some strains of Typhi have shown reduced susceptibility to fluoroquinolones.[18] Also, there is high rate of clinical failure seen with fluoroquinolones. At present third-generation cephalosporins are used in treatment but there are sporadic reports of resistance to these antibiotics[19]. Recently, Azithromycin is being used as an alternative agent in uncomplicated enteric fever. It has been found that it reduces the clinical failure rate and duration of hospital stay in comparison to fluoroquinolones and relapse rate in comparison to ceftriaxone, when used in the treatment of multidrug resistant typhoid fever.[20]

Methods and Materials:

This prospective observational study was carried out on 96 outpatients of five Upazila level tertiary care private clinics in Dhaka Division over a period of one year from June 2020 to May 2021. Written informed consent

was obtained from the outpatients of the hospital. All outpatientsdiagnosed with typhoid fever if presented with fever (temperature >38oC) for at least 3 days with positive blood culture for S. Typhi or paratyphi were included in the study. Patients who were clinically diagnosed with typhoid fever with negative blood culture were excluded from the study. After obtaining the informed written consent, the patients' details, clinical data, laboratory parameters, and treatment were noted in a predesigned and pre-validated proforma and analyzed. Statistical analysis was done using SPSS version 14. The two-sample test was used to compare continuous variables and the chi-square test was used to compare categorical variables. A p-value of less than 0.05 was considered significant.

The patients were selected according to clinical features which include fever, chills, rigor, altered bowel habit, rose spot on the trunk, bradycardia, headache, myalgia etc. and having fever for more than 7 days were considered as typhoid suspects. Blood samples were taken for culture sensitivity, Widal test and ICT from 100 clinically suspected cases of typhoid fever. Trypticase soya broth which establishes the growth of all common pathogens causing bacteraemia/ septicaemia was used as a culture medium. Collection of blood, incubation, and subculture onto MacConkey agar were done as per the standard methods14.

Results:

A total of 96 clinically suspected cases of typhoid fever were studied. The study population was from all age groups. Among the suspected cases 56 were male and 40 were female; the male to female ratio is 1.40: 1 (Table –I).

Table-I

Sex distribution of the patients (n=100)

Sex	No. of patients	Ratio
Male	56	1.40
Female	40	1

Out of 100 suspected cases of typhoid fever, blood culture positive for *S.* Typhi were 16 (16%) and the remaining 84 (84%) were negative (Figure: I).

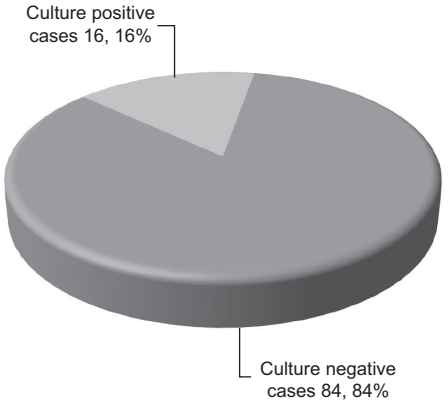

Figure 1: *Rate of isolation of S. Typhi in blood culture*

Table-II

Distribution of patients according to age with typhoid fever. (n=96)

Age group	Frequency (n=96)	Frequency (%)
≤15	18	18.75
16 – 30	20	20.83
31 – 45	32	33.33
46 – 60	12	12.50
>60	14	14.58
Median (in years)	53	
Age range (in years)	4 – 77	

Table-2 shows that out of 96patients maximum 32 (33.33%) patients belonged to 31-45 years age group which was subsequently followed by 20 (20.83%) in 16-30 years age group. 18(18.75%), 12 (12.50%) and 14 (14.58) patients belonged to d"15 years, 46 – 60 years and >60 years age group respectively.

A total of 71(73.95%) patients were from rural areas, whereas 25 (26.04%) were from urban areas. Drinking water source was tap water in 64 (61.44%) cases and bore well water in 32 (30.72%) cases. According to Modified Kuppuswamy Scale 89 (65.44%) were from lower class, 33 (24.26%) from middle class, and 14 (10.02%) from upper socioeconomic class.

Table-III

Seasonal variation observed among confirmed cases of typhoid Fever.

Season	Number (n=96)	Percentage (%)
Summer	31	29.76
Rainy	54	51.84
Winter	11	10.56

Seasonal variation among enteric fever cases showed that the maximum number of patients were observed during rainy seasons (54, 51.84%), followed by summer (31, 29.76%) and winter (11, 10.56%) (Table III).

Table-IV

Distribution of the patients as per theclinical feature of Typhoid Fever.

Clinical feature	Number (n=96)	Percentage (%)
Fever	96	100
Vomiting	69	71.9
Diarrhea	53	55.2
Headache	44	45.8
Splenomegaly	41	42.7
Coated tongue	35	36.5
Abdominal pain	32	33.3
Hepatomegaly	30	31.3
Constipation	16	16.7
Dehydration	13	13.5

The common clinical features of typhoid fever observed were fever (100%), vomiting (69, 71.9%), diarrhea (53, 55.2%), headache (44, 45.8%), and splenomegaly (41, 42.7%). Other clinical features found were coated tongue, abdominal pain, hepatomegaly, constipation, and dehydration (Fig 2). In this study, 6 patients had complications, 3 had enteric hepatitis, 2 had a shock, and 1 had encephalopathy.

Cefixime, Azithromycin, Ampicillin and Cefuroxime resistance were observed in 6.25%, 88.16%,53.95 and 19.74% of patients with typhoid fever respectively in the present study. Maximum sensitivity was observed with Imipenem (100%), Meropenem (100%), Levofloxacin (93.42%), Amikacin (93.42%), followed by Ceftazidime (86.84%), Ceftriaxone 85.41, and Cefepime (77.63) (Table V).

Most of the patients diagnosed with typhoid fever were treated with Cefixime. In outpatient 06 patients are resistant to cefixime were treated with ceftriaxone. Four patients were treated with Meropenemand were hospitalized. The mean duration of hospital stay was 7 days for uncomplicated cases and there was no mortality in this series.

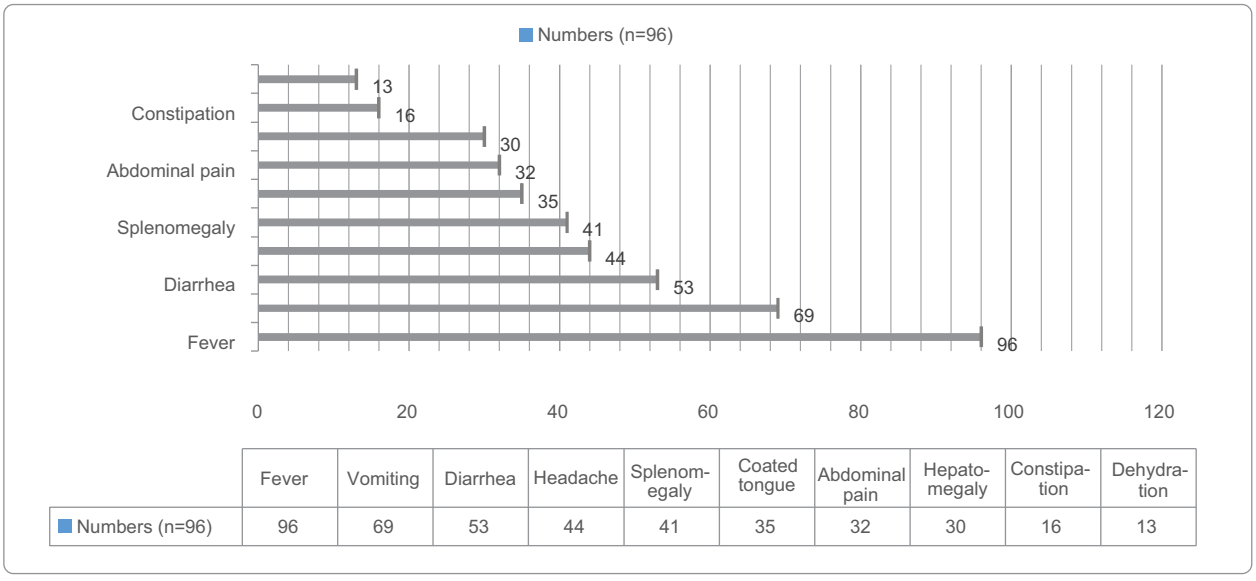

Figure 2: *Patients as per the clinical feature of Typhoid Fever*

Table-V

Antibiotic sensitivity pattern of culture-positive salmonella. (n=96)

Name of the antibiotic	Sensitive n (%)	Resistant n (%)	Intermediate n (%)
Cefixime	82 (85.41)	6 (6.25)	8 (8.33)
Ceftriaxone	61 (77.1)	21 (26.53)	17 (44.7)
Ceftazidime	83 (86.84)	5 (5.26)	8 (7.89)
Amikacin	90 (93.42)	1 (1.32)	5 (5.26)
Azithromycin	5 (5.26)	85 (88.16)	6 (6.58)
Cefepime	75 (77.63)	11 (11.84)	10 (10.53)
Ampicillin	29 (30.26)	52 (53.95)	15 (15.79)
Cefuroxime	13 (13.16)	19 (19.74)	51 (67.11)
Gentamycin,	23 (23.68)	5 (5.26)	68 (71.05)
Ciprofloxacin	19 (19.74)	11 (11.84)	66 (68.42)
Levofloxacin	90 (93.42)	0 (0)	6 (6.58)
Imipenem	96 (100)	0 (0)	0 (0)
Meropenem	96 (100)	0 (0)	0 (0)
Tetracycline	28 (28.95)	32 (32.89)	37 (38.16)
Amoxiclav	20 (21.05)	53 (55.26)	23 (23.68)
Cotrimoxazole	57 (59.21)	23 (23.68)	16 (17.11)
Chloramphenicol	30 (31.58)	54 (56.58)	11 (11.84)

Discussion

The threat to human health posed by the growth of antibiotic-resistant bacterial pathogens is of growing concern in medical practice. Drug resistance in typhoid fever is considered to be an important factor in the morbidity and mortality of this disease. In Jakarta, Indonesia, susceptibility of Salmonella Typhi isolates to the 1st line antibiotics i.e., amoxicillin, ampicillin, chloramphenicol, trimethoprim-sulfamethoxazole, ceftriaxone, nalidixic acid, ciprofloxacin and Levofloxacin was good (more than 80% sensitivity) and the trend remain unchanged from 2008 to 2017. But, we are observing increasing antibiotic resistance in Bangladesh[30]. The emergence of multidrug-resistant enteric fever led to the use of fluoroquinolones as the first-line of therapy. Unfortunately, broad-spectrum antibacterial activity, affordability, and easy availability led to their indiscriminate use in human medicine. Enteric fever is still a significant public health problem in many developing countries. It is a dreaded disease because of its long course and associated complications if not detected and treated early. There are reports of changing clinical features in typhoid fever caused by drug-resistant*S.* Typhi leads to difficulty in clinical diagnosis [22,22].. Since the introduction of chloramphenicol in 1948, it has been the drug of choice in the treatment of typhoid fever in most parts of the world. But indiscriminate use of the drug and acquisition of plasmid-mediated R factor has led to the development of resistance to *S.* Typhi against this drug[23].Typhoid fever is endemic in Bangladesh, where there is a high incidence in children[24]. The emergence of MDR *S.* Typhiisolates in the early 1990s, particularly from the Indian subcontinent, prompted the suggestion that ceftriaxone, ceftazidim, and ciprofloxacin should be the drug of choice for empirical treatment of typhoid fever[25,26,27]. Initially, reduced use of amoxicillin, cotrimoxazole, or chloramphenicol was associated with a decreased prevalence of MDR strains, but more recently, continued dependence on ciprofloxacin for the empirical treatment of typhoid fever in Bangladesh and elsewhere has led to the emergence of resistance of *S.* Typhito this drug[28,29].

Conclusion:

The public health burden of typhoid fever can be substantially reduced by rapid diagnosis and appropriate antibiotic therapy. The main clinical findings observed in this study were

fever (100%), vomiting (72%), diarrhea (55.8%), headache (45.5%), and splenomegaly (42.6%). Other clinical features found were coated tongue, abdominal pain, hepatomegaly, constipation, and dehydration. It also revealed that Cefixime and Ceftriaxone are the most sensitive drug against Typhi. Although the role of Ciprofloxacin in the treatment of typhoid fever has recently been made controversial among clinicians but the efficacy of Ciprofloxacin in the present study has been found to be more than 80%. So, more work needs to be carried out to evaluate the status of Ciprofloxacin. This study also helps the physician to calculate the proper therapeutic dose of Ciprofloxacin by E-test and thus minimize drug resistance. E-test can be done to determine the appropriate therapeutic dose of commonly used antibiotics in typhoid fever in case of drug resistance or pediatric population.

Reference:

1. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;386(9995):743–800. doi: https://doi.org/10.1016/S0140-6736(15)60692-4.
2. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(9963):117–71. doi: https://doi.org/10.1016/S0140-6736(14)61682-2.
3. Kirk MD, Pires SM, Black RE, Caipo M, Crump JA, Devleesschauwer B, et al. World Health Organization estimates of the global and regional disease burden of 22 foodborne bacterial, protozoal and viral diseases, 2010: a data synthesis. PLoS Med. 2015;12:e1001921. doi: https://doi.org/10.1371/journal.pmed.1001921.
4. Global Burden of Disease 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017;390:1151–1210. doi: https://doi.org/10.1016/S0140-6736(17)32152-9.
5. Ao TT, Feasey NA, Gordon MA, Keddy KH, Angulo FJ, Crump JA. (2015) Global burden of invasive nontyphoidal
6. Salmonella disease, 2010. Emerg Infect Dis. 2015;21(6):941–9 (https://wwwnc.cdc.gov/eid/article/21/6/14-0999_article).
7. World Health Organization. Typhoid vaccines: WHO position paper – March 2018. Wkly Epidemiol Rec. Wkly Epidemol Rec. 2018;93(13):153-72. (http://apps.who.int/iris/bitstream/handle/10665/272272/WER9313.pdf?ua=1)
8. Nagshetty K, Channappa ST, Gaddad SM. Antimicrobial susceptibility of Salmonella typhi in India. J Infect Dev Ctries 2010; 4: 70-73.
9. Harish B, Menezes G. Antimicrobial resistance in typhoidal Salmonellae. Indian J Med Microbiol 2011; 29: 223.
10. Islam M, Das K, Sharmin N, Hasan M, Azad A. Antimicrobial susceptibility of Salmonella serovars isolated from blood. J Innov Dev Strategy 2008; 2: 22-27.
11. Rahman A, Ahmed M, Begum R, Ghosh A, Hossain M. Multidrug resistant typhoid fever in children: a review. J Dhaka Med Coll 2008; 17: 121-126.
12. Radji M, Fauziah S, Aribinuko N. Antibiotic sensitivity pattern of bacterial pathogens in the intensive care unit of Fatmawati Hospital, Indonesia. Asian Pac J Trop Biomed 2011; 1: 39-42.
13. Sun L, Klein EY, Laxminarayan R. Seasonality and temporal correlation between community antibiotic use and resistance in the United States. Clin Infect Dis 2012; 55: 687-694.
14. Evanson Mweu and Mike English. Typhoid fever in children in Africa. Trop Med Int Health. 2008;13(4): 532–40.
15. Mohanty S, Gaind R, Sehgal R, Chellani H, Deb M. Neonatal sepsis due to Salmonella Typhi and Paratyphi A. J Infect Dev Ctries. 2009; 3: 633-38.
16. Cleary T. Salmonella. In: Feigin RD, Cherry JD, Demmler GJ, Kaplan SL (eds). Feigin and Cherry's Textbook of Pediatric Infectious Diseases, 5th ed.2005; Philadelphia,Saunders:1473-87.
17. Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid fever. N Engl J Med. 2002; 347:1770-82.
18. Gupta A, Swarnkar NK, Choudhary SP. Changing antibiotic sensitivity in enteric fever. J Trop Ped.2001; 47: 369-71.
19. Saha SK, Talukder SY, Islam M. Saha S. A highly Ceftriaxone resistant Salmonella typhi in Bangladesh.Pediatr Infect Dis J. 1999; 18: 297-303.

20. Dheeraj Shah. Role of Azithromycin in enteric fever.Cochranecollection.Indian Pediatrics.2009; 46: 51-2.

21. Bhutta ZA, Nagvi SH, Razzaq RA, Farooqui BJ. Multidrug resistant typhoid in children : Presentation and Clinical features. Rev Infec Dis 1991 ; 13 : 832 - 836.

22. Butta ZA. Impact of age and drug resistance on mortality in typhoid fever. Arch Dis Chi 1996; 75: 214-217.

23. Agarwal KC, PanHotra BR, Mahanta J. Typhoid fever due to chloramphenicol resistant S. typhi associated with 'r' plasmid. Indian J Med Res 1981;73 :484-8.

24. Saha S K, Baqui A H, Hanif M, et al. Typhoid fever in Bangladesh: implications for vaccination policy. Pediatr Infect Dis J. 2001;20:521–524.

25. Jesudassan M V, Jacob J T. Multiresistant Salmonella typhi in India. Lancet. 1990;336:252.

26. Saha S K, Saha S. Antibiotic resistance of Salmonella typhi in Bangladesh. J Antimicrob Chemother. 1994; 33:190–191.

27. Hasan Bulbul. Study on the Laboratory Diagnosis and Drug Resistance in Typhoid Fever [M. Phil (Microbiology) Thesis], RMC. 2007; 83.

28. Murdoch D A, Banatvaia N, Bone A, Shoismatulloev B I, Ward L R, Threlfall E J. Epidemic ciprofloxacin-resistant Salmonella typhi in Tajakistan. Lancet. 1998;351:339.

29. Saha S K, Talukder S Y, Islam M, Saha S. A highly cefriaxone-resistant Salmonella typhi in Bangladesh. Pediatr Infect Dis J. 1999;18:387.

30. Lucky H. Moehario, T. Robertus, Enty Tjoa, Wani D. Gunardi, Angela Ch. M. Nusatia and Daniel Edbert, 2019. Antibiotic Susceptibility Patterns of Salmonella Typhi in Jakarta and its Trends Within the Past Decade. Journal of Biological Sciences. 2019; 19(1): 40-45.