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ANTIMICROBIAL SUSCEPTIBILITY PATTERNS OF *SALMONELLA SPECIES* IN CONTEMPORARY MEDICAL PRACTICE: CHALLENGES AND PROSPECTS IN TREATMENT OF ENTERIC FEVERS

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ABSTRACT

Treatment of enteric fever is increasingly becoming very challenging due to the increasing wave of antibiotic resistance. This study is a review of the contemporary antimicrobial susceptibility pattern of *Salmonella species*. The antimicrobial susceptibility pattern of *Salmonella species* to a wide range of antimicrobial agents was compiled for a period of 10 years (1997-2006). Data was obtained from published articles on both *in vitro* and *in vivo* susceptibility patterns of the organism to various drugs during the time interval. Data obtained were analysed using simple descriptive methods. Of the 23,504 isolates of *Salmonella* species reviewed, they were found to be 98% susceptible to cefepime and carbapenem, 91% to azithromycin, 82.1% to cefixime and 73% to quinolones. Also susceptibility to chloramphenicol, erythromycin, streptomycin, ampicillin, gentamicin, co-trimoxazole, augmentin and amikacin was found to be 11.9%, 10.9%, 13.0%, 16.8%, 46.3%, 38.0%, 54.3%, 6.9% and 63.0% respectively. This review has demonstrated increasing resistance of *Salmonella species* to antibiotics. Empirical treatment for enteric fevers should, therefore, be discouraged while quinolones, cefepime, carbapenem, azithromycin and third generation cephalosporins be given preference.

KEY WORDS: Susceptibility, Antimicrobial, *Salmonella species,* Enteric fever

INTRODUCTION

In the 21st century, enteric fever in the developed world is not much a disease of public health importance (Meltzer, *et al*., 2006; Agbakwuru, *et al*., 2003; and Mba, 2001). The disease however continues to occupy the central position among diseases of public health importance in parts of middle east, India and south-east Asia, parts of Latin America, the Caribbean, and sub-Saharan Africa where it is still endemic (Steinberg, *et al*., 2004; Nkuo-Akenji T, *et al*., 2001; and Fuller, *et al*., 2004).

One of the major challenges now in the management of typhoid fevers is the prevailing nature of the antimicrobial resistance patterns of *Salmonella species* (Parry, *et al*., 2007; Na'aya, *et al*., 2004; and Rathore, *et al*., 1996). In a study carried out in Tadjikistan (Makhnev, 2001) involving 14 antimicrobial agents representing almost all basic chemical classes against *Salmonella spp.,* there was no absolute (100%) efficacy of the investigated agents in vivo and invitro. In Saudi Arabia (Al-Tawfig, 2007), the susceptibility pattern of *Salmonella typhi/paratyhi* was reported as 81.3%/56%, 89%/77%, and 89%/84% susceptible to tetracycline, ampicillin, and trimethoprim-sulfamethoxazole respectively. Also 100% susceptibility was recorded for ceftriaxone and ciprofloxacin while multidrug resistance (MDR) was detected in 20% of the 266 *Salmonella spp.* Studied. In another study in Vietnam (Chinh, *et al*., 2000), 78%(68 out of 87) MDR and 53% nalidixic acid resistance was reported among adult males in a University Teaching Hospital typhoid ward in Ho Chi Minh

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city. Similar but varied patterns of resistance have as well been reported in Japan (Tamura, *et al*., 2002), Nigeria (Akinyemi, *et al*., 2005), and Brazil (Alecrim, *et al*., 2002).

In the tropical and sub-tropical regions of the world, more often than not, physicians result to empirical treatment for suspected typhoid fevers (loosely including paratyhoid fever) (Glauser, *et al*., 2002; and Oboegbulam, *et al*., 1995). Most a times as a result of either, delays in the release of laboratory reports, or due to outright lack of appropriate diagnostic laboratory facilities (Bates, and Maitland, 2006). A proper understanding of the current antimicrobial susceptibility patterns of *Salmonella spp.* becomes essential. Such information would be useful to clinicians who are often confronted with the limitations of unreliable or absent microbiological results in the course of managing typhoid patients Makhnev, 2003; and Moulin, *et al*., 2003). This therefore informed the need for the present study.

MATERIALS AND METHODS

A systematic literature search on antimicrobial susceptibility pattern of *Salmonella species* was undertaken on published articles for a 10 year interval (1997-2006). This consists of articles on both in vivo and in vitro antimicrobial susceptibility pattern of individual isolates of *Salmonella typhi* and *Salmonella paratyphi* on a wide range of antibiotics in various research centres across the globe. *In vivo* susceptibility reports based on the diagnosis of enteric fevers through serological methods were as well considered. The in vitro results were standardized by collating findings from studies whose methodologies were based on the diffusion and dilution methods of National Committee for Clinical Laboratory Standards (NCCLS) protocol. On the other hand the results obtained from the in vivo susceptibilities were standardized by collating data generated from monotherapies. Data obtained was analysed using simple descriptive methods.

RESULTS

Of the 23,504 isolates of *Salmonella species* reviewed, susceptibility to quinolones on average was found to be 73%(n=23,104), cefixime 82.1%(n=16,452), ceftriaxone 78.1%(n=11,701), azithromycin 91%(n=789), and chloramphenicol 11.9%(n=13,937). Also erythromycin, streptomycin, ampicillin, and gentamicin were found to be 10.9 %(n=17,776), 13.0%(n=873), 16.8%(n=18,329), and 46.3%(n=19,112) sensitive respectively. Co-trimoxazole, augmentin, tetracycline, cefepime, carbapenem and amikacin were found to be 38%(n=19,112), 54.3%(n=19,112), 6.9%(n=19,112), 98%(n=673), 98%(n=555) and 63%(11,332) sensitive respectively, (Figure 1).

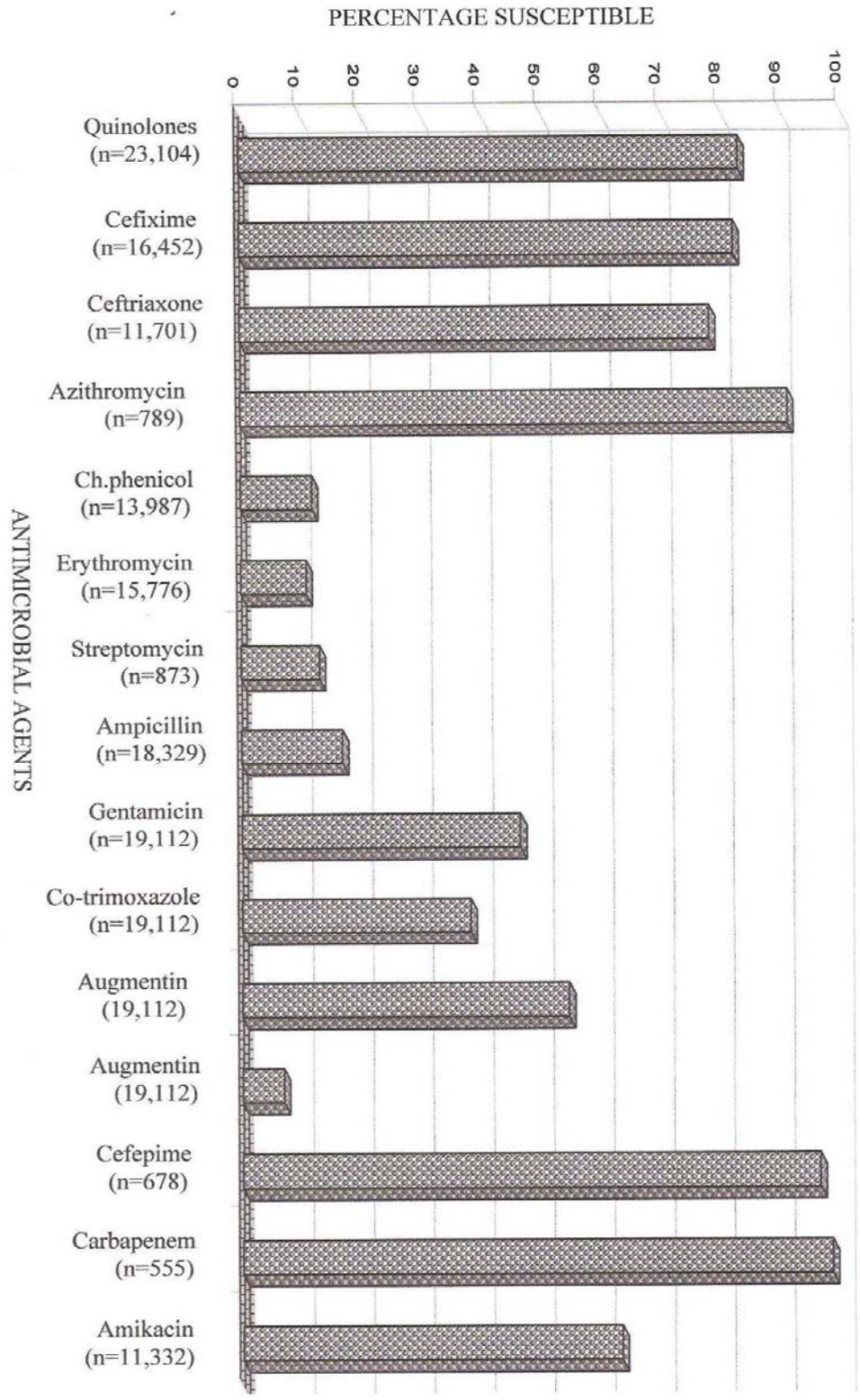

Figure 1 Antimicrobial susceptibility patterns of 23,504 isolates of *Salmonella species*, (n=number of isolates tested per antibiotic).

DISCUSSION

The findings from the present study showed the average percentage of *Salmonella* isolates susceptible to antimicrobial agents tested ranged from 6.9% (tetracycline) to 98% (carbapenem and cefepime). There were varying degrees of susceptibility of isolates among individual drugs as well as geographical strains.

Azithromycin though found to be 97% active against *Salmonella spp.* in the present study, findings from Egypt (Girgis, *et al*., 1999) showed a 100% activity against all the strains tested including the MDR strains. In Tadjikistan (Makhnev, 2003) on the other hand, azithromycin was found to be unable to produce a 100% activity, though a susceptibility of over 90% was severally recorded; and in Dong Thap province, Vietnam (Parry, *et al*., 2007), all the isolates of *Salmonella spp.* were found to be susceptible to azithromycin. Findings from Bangladesh (Isbandiro, *et al*., 1994) similarly showed a slightly higher susceptibility of 98% to azithromycin.

The quinolones had a wide but varying range of activity against the *Salmonella spp.* though an average susceptibility of 73% was recorded in the present study. In Switzerland (Glauser, *et al*., 2002), a higher figure of 84% susceptibility was recorded among patients placed on clinafloxacin monotherapy. In Lagos, Nigeria (Akinyemi, *et al*., 2005), a much higher susceptibility of 98% to ciprofloxacin and ofloxacin was recorded, while in Zaria, Nigeria (Ibrahim, *et al*., 2005) sensitivity to nalidixic acid was found to be as low as 40%. In Kuwait (Dimitrov, *et al*., 2007), a much higher resistance (over 50%) to nalidixic acid was recorded as well as treatment failures to ciprofloxacin monotherapy, while a resistance of over 78% by *Salmonella spp.* to nalidixic acid was recorded in India (Kadhiravan, *et al*., 2005).

Ceftriaxone and cefixime were found to have a susceptibility of 82% and 78% respectively with varying ranges along with the other cephalosporins. Susceptibility patterns of both drugs of over 95% have been recorded in some centres in both the United Kingdom (Threlfall, and Ward, 2001) and United States of America (Ackers, *et al*., 2000), with much lower susceptibility patterns (less than 60%) in several centres.

The percentage susceptibility of *Salmonella spp.* to ampicillin, tetracycline, co-trimoxazole, gentamicin, streptomycin, azithromycin and chloramphenicol was generally low (6.9% - 46%). This includes the findings of Ullah, *et al,* in Dera Ismail Khan, Pakistan (Ullah, *et al*., 2005), where 50%, 71.4%, and 75% resistance was recorded by the organism against chloramphenicol, amoxycilline and co-trimoxazole respectively; the over 70% resistance recorded by similar drugs in Bangkok, Thailand (Isenberger, *et al*., 2002); and the report from Ho Chi Minh city, Vietnam (Smith, *et al*., 1994) where about 63% of the *Salmonella* isolates were found to be multiply resistant to chloramphenicol, ampicillin, co-trimoxazole, and tetracycline. Findings from Kolkata, India (Kundu. 2005) on the contrary showed a renewed increase in susceptibility to chloramphenicol.

Considering the life threatening complications of untreated or improperly treated typhoid fever and, the high rate of resistance recorded by majority of the drugs for its treatment. Caution should be exercised in the selection of appropriate antibiotics for proper treatment. Selection of antibiotics for treatment of enteric fever should stem from a well conducted antimicrobial susceptibility report. Susceptibility tests should be carried out on all isolates of *Salmonella spp.* so as to adequately guide the personnel treating the patient and avoid relapse, a common phenomenon from drug failure.

Susceptibility to carbapenem, amikacin, clavulanate potentiated amoxycillin and cefepime was in the range of 98%, 63%, 54.3% and 98% respectively. The carbapenems and the 4th generation cephalosporins are relatively new drugs whose prescriptions has not been documented in several hospitals and clinics across the world (Chande, *et al*., 2002; and, Corrado, *et al*., 1992).and the extremely low resistance is expected. The susceptibility might be higher than this but for the interpersonal and procedural bias, which cannot be ruled out in a study of this magnitude.

The susceptibility profile of the local *Salmonella* isolates against the common antibiotics in use should be known by the concerned health personnel. Such data should be reviewed periodically so as to reflect the current antibiotic susceptibility pattern of the organism for quick reference. This would be very useful when patients present in very critical states leaving little or no time to wait for the susceptibility report. Such data would even be more useful in the developing world where laboratory facilities for diagnosis are either inadequate or lacking and, often times laboratory

results are not available on time. Furthermore, clinical diagnosis of enteric fever should be confirmed by laboratory investigations so as to reduce over diagnosis of enteric fevers. This carries with it the attendant unnecessary and unjustifiable antibiotics consumption from empirical treatments and the subsequent development and spread of resistance. This scenario is often encountered in clinical practice especially in the developing world (Akin, *et al*., 2003; and Kacprzak, *et al*., 2002).

In conclusion, this review has found that, no single drug at present holds the absolute promise for the treatment of *Salmonella* infections and globally, there is a high resistance of *Salmonella* to majority of the drugs hitherto commonly used for its treatment. Quinolones, azithromycin, ceftriaxone, cefixime, carbapenem and cefepime are presently the drugs with the highest activity against *Salmonella spp.* and hence on a general note should be considered on isolation of *Salmonella.* Efforts should be made to establish diagnosis of typhoid beyond doubt before treatment is started so as to avoid empirical prescriptions and unjustifiable antimicrobial intake.

REFERENCES

Ackers, M. L., Puhr, N. D., Tauxe, R. V. and Mintz, E. D., 2000. Laboratory based surveillance of *Salmonella serotype typhi* infections in the United States- Antimicrobial resistance on the rise. JAMA. 283: 2668-2673.

Agbakwuru, E. A., Adesunkanmi, A. R. K., Fadiora, S. O., Olayinka, O. S., Aderonmu, A. O. A and Ogundoyin O. O., 2003. A review of typhoid perforation in a rural African hospital. West Afr. J. Med.; 22(1): 22-25.

Akin, K., Yavuzddemir, S., Cesur, S., Levent, B., Esen, B. and Willke, A., 2003. A case with fever of unknown origin during treatment for malaria: multidrug-resistant *Salmonella typhi* infection. Microbiyol. Bul; 39(1): 83-87.

Akinyemi, K. O., Smith, S. I., Oyefolu, A. O. and Coker, A. O., 2005. Multidrug-resistance in *Salmonella enterica serovar typhi* isolated from patients with typhoid fever complications in Lagos, Nigeria. Public Health; 19(4): 321-327.

Alecrim, W. D., Loureiro, A. C., Moraes, R. S., Monte, R. L. and de Lacerda, M. V., 2002. Typhoid fever: relapse due to antimicrobial resistance. Rev. Soc. Bras. Med. Trop.; 35(6): 661-663.

Al-Tawfig, J. A., 2007. Antimicrobial susceptibility of *Salmonella typhi* and non-typhi in a hospital in eastern Saudi Arabia. J. Chemother.; 19(1): 62-65.

Bates, I., Maitland, K., 2006. Are laboratory services coming of age in sub-Saharan Africa? Clin. Infect. Dis.; 42: 383-384.

Chande, C., Shrikhande, S., Kapale, S., Agrawal, S. and Fule, R. P., 2002. Change in antimicrobial resistance pattern of *Salmonella typhi* in central India. Indian J. Med. Res.; 115: 248-250.

Chinh, N. T., Parry, C. M., Ly, N. T., Ha, H. D., Thong, M. X. and Diep, T. S., *et al,* .2000. A randomized controlled comparison of azithromycin and ofloxacin for treatment of multidrug-resistant or nalidixic acid-resistant enteric fever. Antimicrob. Agents Chemother.; 44(7): 1855-1859.

Corrado, M. L., Dupout, H. L., Cooperstock, M., Fekety, R. and Murray, D. M., 1992. Evaluation of new anti-infective drugs for the treatment of typhoid fever. Infectious diseases society of America and the Food and Drug Administration. Cllin. Infect. Dis; 15(suppl. 1): s236-240.

Dimitrov, T., Udo, E. E., Albaksami, O., Kilani, A. A. and Shehabel, D. M., 2007. Ciprofloxacin treatment failure in a case of typhoid fever caused by *Salmonella enterica* serotype paratyphoid A with reduced susceptibility to ciprofloxacin. J. Med. Microbiol.; 56(pt. 2): 277-279.

Fuller, D., Hasnat, M., Marks, M. K. and Curtis, N., 2004. Fever in a returned traveler. J. Paediatr. Child Health.; 40(5-6): 315-316.

Girgis, N. J., Butler, T., Frenck, R. W., Sultan, Y., Brown, F. M., Tribble, D. and Khakharia, R., 1999. Azithromycin versus ciprofloxacin for treatment of uncomplicated typhoid fever in a randomized trial in Egypt that included patients with multidrug

resistance. Antimicrob. Agents. Chemother.; 43: 1441-1444.

Glauser, M. P., Brennscheidt, U., Comely, O., Grigg, A., Figuera, A., Keyserling, C., Trostmann, U., Welling, L. and Tack, K., 2002. Cinofloxacin monotherapy (C1-960) versus ceftazidime plus amikacin for empirical treatment of febrile neutropenic cancer patients. Clin. Microbiol. Infect.; 8(1): 14-25.

Ibrahim, Y. K., Adedare, T. A. and Ehimmidu, J. O., 2005. Antibiotic susceptibility profiles of *Salmonella* organisms isolated from presumptive typhoid patients in Zaria, northern Nigeria. Afri. J. Med. Sci; 34(2): 109-114.

Isbandrio, B. B., Gasem, M. H., Dolmans, W. M. and Hoogkamp-Korstanje, J. A., 1994. Comparative activities of three quinolones and seven comparison standard drugs against *Salmonella typhi* from Indonesia. J. Antimicrob. Chemother.; 33(5): 1055-1056.

Isenberger, D. W., Hoge, C.W., Srijan, A., Pitarangsi, C., Vithavasai, N., Bodhigatta, L., Hickey, K. W. and Cam, P. D., 2002. Comparative antibiotic resistance of diarrhoeal pathogens from Vietnam and Thailand. Emerg. Infect. Dis. 8(2): 175-180.

Kacprzak, E., Stefaniak, J., Storyna-karcz, B., Wojtacha, A., Bolewska, B. and Juszczyk, J., 2002. Diagnostic difficulties in febrile travelers returning from the tropics. Two cases of typhoid imported from India. Pol. Merkur. Lekardski.; 13(78): 509-515.

Kadhiravan, T., Wig, N., Kapil, A., Kabra, S. K., Renuka, S. K. and Misra, A., 2005. Clinical outcomes in typhoid fever: adverse impact of infection with nalidixic acid-resistant *Salmonella typhi.* BMC Infect. Dis. 5: 37 eMay 18 doi: 10.1186/1471-2334-5-37.

Kundu, A. K., 2005. Drug resistant salmonellosis. J. Indian Med. Assoc; 103(6): 327-331.

Makhnev, M. V., 2001. Clinical aspects of typhoid fever epidemic in migrants. Ter. Arkh.; 73(11): 67-70.

Makhnev, M. V., 2003. Efficacy of various antimicrobial agents in the treatment of epidemic typhoid fever. Antibiot. Khimioter; 48(4): 27-34.

Mba, I. E. K., 2001. Clinical features of malaria and typhoid fever. Jnl. Med. Investigation and Practice. 3: 65-67.

Meltzer, E., Yossepowitch, O., Sadik, C., Dan, M. and Schwartz, E., 2006. Epidemiology and clinical aspects of enteric fever in Israel. Am. J Trop. Med. Hyg. 74(4): 540-543.

Moulin, F., Sauve-Martin, H., Marc, E., Lorrot, M. M., Ravilly, S., Raymond, J. and Gendrel, D., 2003. Ciprofloxacin after clinical failure of beta-Lactam antibiotics in children with salmonellosis. Arch. Paediatr.10(7): 608-614.

Na'aya, H. U., Eni, U. E., and Chama, C. M., 2004. Typhoid perforation in Maiduguri, Nigeria. Annals of Afr. Med; 3(2): 69-72.

Nkua-Akenji, T., Ndip, R., McThomas, A., and Chi Fru E., 2001. Anti-Salmonella activity of medicinal plants from Cameroon. Central Afr. J. Med. ; 47(6): 155-158.

Oboegbulam, B. I., Oguike, J. U. and Gugnani, H. C., 1995. Microbiological studies on cases diagnosed as typhoid/enteric fever in south-eastern Nigeria. J. Commun. Dis.; 27(2): 97-100.

Parry, C. M., Ho, V. A., Phuong, L. T., Bay, P. V. B., Lanh, M. N. and Tung, L. T,, et al., 2007. Randomized controlled comparison of ofloxacin, azithromycin, and an ofloxacin-azithromycin combination for treatment of multidrug-resistant and nalidixic acid-resistant typhoid fever. Antimicrob. Agents Chemother.; 51(3): 819-825.

Rathore, M. H., Bux, D. and Hasan, M., 1996. Multidrug-resistant *Salmonella typhi* in Pakistani children: Clinical features and treatment. South Med. J.; 89(2): 235-237.

Smith, M. D., Duong, M. M., Hoa, N. T., Wain, J., Ha, H. D., Diep, T. S., Day, N. P., Hien, T. T. and White, N., 1994. Comparison of ofloxacin and ceftriaxone for short-course treatment of enteric fever. Antimicrob. Agents and Chemother. ; 38(8): 1716-1720.

Steinberg, E. B., Bishop, R., Haber, P., Dempsey, A. F., Hoekstra, R. M., Nelson, J. M., Ackers, M., Calugar, A. and Mintz, E. D., 2004. Typhoid fever in travelers who should be targeted for prevention? Clin. Infect. Dis; 39: 186-191.

Tamura, K., Matsuoka, H., Tsukada, J., Masuda, M., Ikeda, S., Matsuishi, E. and Kawono, F., *et al.*, 2002. Cefepime or carbapenem treatment for febrile neutropenia as a single agent is as effective as a combination of 4th-generation cephalosporin + aminoglycosides: comparative study. Am. J. Haematol; 71(4): 248-255.

Threlfall, E. J. and Ward, L. R., 2001. Decreased susceptibility to ciprofloxacin in *Salmonella enterica serotype typhi,* United Kingdom. Emerg. Infect. Dis; 7: 448-450.

Ullah, Z., Ahmed, W., Khan, A. M., Khan, M. F., Qureshi, A. H. and Khan, A., 2005. Effects of pefloxacin in multidrug-resistant typhoid fever. Pak. J. Pharm. Sci. 2005; 18(4): 61-64.