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Trends in *Salmonella enteric serovar Typhi* in Nairobi, Kenya from 2004 to 2006

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Abstract

Background: Typhoid fever is a global health problem. The World Health Organization (WHO) estimates that the current annual global burden of typhoid is approximately 22 million new cases, 5% of which are fatal.

Methodology: To assess the trends in antibiotic resistance in 100 *Salmonella enterica serovar Typhi* strains were isolated from the blood of patients in Nairobi, Kenya, from 2004 to 2006. All isolates were tested against ampicillin, chloramphenicol, nalidixic acid, ciprofloxacin, cotrimoxazole, cefuroxime, ceftriaxone, amoxicillin/clavulanic acid, tetracycline and gentamycin. Susceptibility and resistance were determined using MIC and disk diffusion tests.

Results: From 2004 to 2006 a total of 100 strains were studied; 70% of the isolates were multidrug resistant (MDR) while 15% of the isolates were sensitive to all drugs tested. Of 13 isolates that were resistant to ciprofloxacin and nalidixic acid by disk diffusion, 11 had an MIC of 0.25 µg/ml while two isolates had an MIC of 1.00 µg/ml. Resistance in ampicillin decreased from 88% in 2004 to 64% in 2005; this increased to 76% in 2006. Similar trends were observed for four other antibiotics tested.

Conclusion: The prescription of first-line antibiotics used in the treatment of *S. Typhi* should be stopped temporarily. Drugs such as ciprofloxacin would be useful in the treatment of typhoid caused by MDR *S. Typhi*. There is need to monitor the resistance in fluoroquinolones as resistance to these drugs has been observed and they are the current drugs used to treat typhoid.

Key words: quinolone; multidrug resistance; disk diffusion; minimum inhibitory concentration (MIC)

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Introduction

Typhoid fever is a global health problem [1]. The World Health Organization (WHO) estimates that the current annual global burden of typhoid is approximately 22 million new cases, 5% of which are fatal [2,3]. Typhoid fever is endemic in most parts of Central America, and large epidemics occur in many parts of Southeast Asia, including India, Pakistan, Bangladesh, Vietnam, Malaysia, Indonesia, China and Tajikistan [4]. Clinically apparent bacteraemic *S. Typhi* infection in children aged less than three years has been described in Bangladesh, India, Jordan, and Nigeria [5].

Since 1997 increasing numbers of multidrug-resistant (MDR) *S. Typhi* have been isolated from patients in outbreaks in Nairobi and Embu, Kenya, which were related to damaged water supply systems [6]. From these outbreaks MDR *S. Typhi* were sensitive to nalidixic acid and ciprofloxacin but the

minimum inhibition concentrations (MICs) were ten times higher than for the non-MDR strains.

The antibiotics that form the mainstay of therapy for typhoid patients in developing countries are ampicillin, co-trimoxazole and chloramphenicol. Due to the increasing resistance to antibacterials used traditionally for therapy, the use of fluoroquinolones, such as ciprofloxacin and ofloxacin, for the treatment of typhoid has become more common in the Asian countries. This in turn has led to an increase in fluoroquinolone resistance in *S. Typhi* [9].

Sporadic cases of ciprofloxacin treatment failure in typhoid fever have been reported in Europe and more recently, in Asia [10,11]. Njinkeng *et al.* (2005) report that MDR *S. Typhi* and nalidixic acid resistant *S. Typhi* (NARST) strains were found in Cameroon, Central Africa. NARST have also been reported in East Africa [8]. The aim of this study was to characterize *S. Typhi* using antibiotic susceptibility

patterns. The *S. Typhi* studied was isolated from patients presenting to the Aga Khan University and the Kenyatta National Hospitals in Nairobi Kenya, suspected to have typhoid fever.

Materials and methods

Study Design

A descriptive, cross-sectional study design was used.

Setting

Isolates of *S. Typhi* were obtained from stock cultures at the Center for Microbiology Research at KEMRI, Nairobi. The isolates had originated from blood cultures of patients with suspected cases of typhoid fever who had presented themselves to the Aga Khan University Hospital and the Kenyatta National Hospital in Nairobi, Kenya.

Bacterial strains

One hundred *S. Typhi* isolates were obtained from blood cultures of patients with suspected cases of typhoid fever who had presented themselves to the Aga Khan University Hospital and the Kenyatta National Hospital in Nairobi, Kenya. Bacterial strains had been isolated between 2004 and 2006.

Antibiotic susceptibility testing

Antimicrobial susceptibility testing was performed using a disc diffusion method according to CLSI guidelines (CLSI, 2005). *Escherichia coli* ATCC 25922[®] (with known disc zones and MICs) was used as a control for growth and potency of antibiotics. The antibiotic discs, (all from Himedia, Maharashtra, India) contained ampicillin (30 µg), tetracycline (30 µg), cotrimoxazole (1:25 µg), chloramphenicol (30 µg), gentamicin (10 µg), amoxicillin/clavulanic acid (30µg), ciprofloxacin (5 µg), cefuroxime (30 µg), ceftriaxone (30 µg), and nalidixic acid (30 µg) from Becton Dickinson, San Jose, California, USA. The zones of inhibition were measured in millimeters (mm) and recorded.

Minimum inhibitory concentration

S. Typhi isolates that were resistant to nalidixic acid and ciprofloxacin by disc diffusion test had MIC performed for using an automated Vitek 2 compact system (bioMérieux, Inc., Durham NC, USA).

Results

A total of 70 isolates were MDR (resistant to ampicillin, cotrimoxazole and chloramphenicol) while 15 isolates were sensitive to all drugs tested.

Only one isolate was resistant to tetracycline alone while four isolates were multiply resistant to two drugs each, which included ampicillin, chloramphenicol, amoxicillin/clavulanic acid and tetracycline. Five isolates were resistant to five drugs, which included tetracycline, ampicillin, cotrimoxazole, chloramphenicol, and nalidixic acid. The most effective drugs were gentamicin, with 99 isolates being susceptible to the drug; this was followed by ceftriaxone in which 94 isolates were susceptible to the drug. Of the 100 isolates, 82 were sensitive to ciprofloxacin, 78 isolates were sensitive to cefuroxime, and 65 isolates were sensitive to nalidixic acid. The least effective drugs included tetracycline and ampicillin (only 24 isolates were sensitive to both drugs).

Resistance to individual antibiotics varied slightly during the study period. For instance, the prevalence of chloramphenicol-resistant isolates, which was 81% in 2004, reduced gradually to 67% by 2005 and slightly increased to 76% in 2006. Similar trends were observed in ciprofloxacin, ampicillin, tetracycline, cotrimoxazole, nalidixic acid and ciprofloxacin. There was a gradual decrease in resistance in Augmentin observed over the study period.

The highest number of MDR *S. Typhi* was recorded in 2004, when 73% of the organisms isolated were MDR. There was no significant increase in MDR from 2005 (68%) to 2006 (69%) (Table 1).

Thirteen *S. Typhi* isolates that were resistant to ciprofloxacin and nalidixic acid by disk diffusion technique had MIC tests performed on them. The MICs of the 13 isolates ranged from 0.25 to 1.00 µg/ml. Eleven *S. Typhi* had an MIC of 0.25 µg/ml while two isolates had an MIC of 1.00 µg/ml.

Discussion

Typhoid fever continues to pose a public health challenge in developing countries and the World Health Organization (WHO) estimates that the current annual global burden of typhoid is approximately 22 million new cases, 5% of which are fatal [2,3]. There has been an increasing concern about the prevalence of MDR *S. Typhi* strains in developing countries; several reports showing that MDR *S. Typhi* with plasmid-mediated resistance to conventional antibiotics including chloramphenicol, ampicillin, and cotrimoxazole, abound in different parts of the developing world including Kenya [7]. This study examined a total of 70 MDR isolates of *S.*

Table 1. Antimicrobial resistant *Salmonella Typhi* isolated from patients from 2004 – 2006 in Nairobi

Year	Number of isolates	Number of isolates resistant to each antimicrobial (%)										No. of MDR
		Amp	Chlo	Tet	Cot	Nal	Cip	Ceft	Aug	gent	Cefu	
2004	32	88%	81%	75%	75%	31%	19%	13%	81%	0%	16%	68%
2005	39	64%	67%	69%	67%	38%	18%	0%	62%	3%	3%	68%
2006	29	76%	76%	38%	72%	34%	14%	0%	62%	0%	0%	69%
Total	100	75%	74%	62%	73%	35%	18%	40%	68%	1%	6%	70%

Amp = ampicillin, Chlo = Chloramphenicol, Tet = Tetracycline, Cot = Cotrimoxazole, Nal = Nalidixic Acid, Cip = Ciprofloxacin, Ceft = ceftriaxone, Aug = augmentin, Gent = gentamycin, Cefu = cefuroxime

Typhi isolated from the Aga Khan University Hospital and the Kenyatta National Hospital. Previous studies have shown that the prevalence of MDR *S. Typhi* has been rising steadily from 50 to 65% in 1997 to 1999 [7] to the present level of 70% in this study. The rise in MDR could be attributed to an increase in misuse of drugs that are commonly available to the public for treatment of infections. Threlfall *et al.* (2001) established that in Britain, the increase in MDR to chloramphenicol, ampicillin, and trimethoprim increased from 21% in 1991 to 36% in 1994. The increasing levels of resistance were also reported by Kariuki *et al.* (2000) who established that from 1988 to 1993, all the *S. Typhi* isolated from Kenya were fully sensitive to all drugs used, which was in contrast to 82% of *S. Typhi* isolated in 1997 to 1999 which were resistant to ampicillin, tetracycline and chloramphenicol.

The emergence of MDR *S. Typhi* in Kenya is of concern because it limits the number of first-line antibiotics that are commonly used for treating typhoid as well other bacterial infections in hospitals. This poses a major challenge to health care. Currently, due to the increase of MDR strains in many parts of the world, the drugs of choice for treatment of *S. Typhi* are fluoroquinolones. However, sporadic cases of ciprofloxacin treatment failure in typhoid fever have been reported in Europe and more recently, in Asia [10,11]. Resistance to nalidixic acid has also been reported in Cameroon where there has been a treatment failure to fluoroquinolones [12].

In this study, *S. Typhi* that were resistant to nalidixic acid were reported. Resistance in nalidixic acid was 31% in 2004 and increased to 38% in 2005. Although ciprofloxacin is recommended as the drug of choice for treatment of MDR *S. Typhi* infections [13], a study by the National Institute of Health of Korea (NIHK) suggested that the clinical failure of empirical fluoroquinolone treatment might occur as the nalidixic acid resistance rate had rapidly increased from 3.5% in 2001 to 23.3% in 2002 in

Korea [14]. In the present study, 18% of the organisms were resistant to ciprofloxacin and 15% were recorded as intermediate by disk diffusion technique.

In conclusion, the high levels of resistance to commonly available antibiotics including fluoroquinolones is of major public health concern in the treatment of typhoid fever and other bacterial infections in Kenya. To minimize the emergence and spread of resistance we recommend a prudent approach to the availability and usage of antibiotics in Kenya so that only qualified trained and medical personnel should administer antibiotics to patients. Also, the drug resistance in *S. Typhi* should be continuously monitored in Kenya to determine the extent of resistance to currently used drugs in the treatment of typhoid. There is also need to improve laboratory capacity detection and surveillance of typhoid. Despite improvements in health care facilities in Kenya, many areas still lack proper sanitation and good quality drinking water, which contributes to increased risk of transmission of all enteric pathogens. To minimize the emergence and spread of resistance we recommend a prudent approach to the availability and usage of antibiotics. Tools that are more specific and sensitive such as PCR should be adopted to improve surveillance for resistant strains of *S. Typhi*.

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