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Multi-drug resistance and reduced susceptibility to ciprofloxacin among *Salmonella enterica* serovar Typhi isolates from the Middle East and Central Asia

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Abstract

Typhoid fever is common in developing countries, with an estimated 120 million infections and 700 000 annual deaths, worldwide. Fluoroquinolones have been the treatment of choice for infection with multidrug-resistant (MDR) *Salmonella enterica* serovar Typhi (*S.* Typhi). However, alarming reports of fluoroquinolone-resistance and failure of typhoid fever treatment have recently been published. To determine the proportion of *S.* Typhi isolates with reduced susceptibility to ciprofloxacin (RSC) from six countries in the Middle East and Central Asia, 968 *S.* Typhi isolates collected between 2002 and 2007 from Egypt, Uzbekistan, Pakistan, Qatar, Jordan and Iraq were tested for antibiotic susceptibility to five antibiotics using the disc-diffusion method. MDR was defined as resistance to amicillin, chloramphenicol and trimethoprim-sulfamethoxazole. The E-test was employed to determine the MIC of ciprofloxacin only. Nalidixic acid resistance was evaluated as a marker for RSC. Interpretations were made according to CLSI guidelines. MDR strains were considerably more prevalent in Iraq (83%) and Pakistan (52%) compared with the other countries studied (13–52%). Nearly all isolates were susceptible (99.7%) to ceftriaxone. RSC was detected in a total of 218 isolates (22%), mostly from Iraq (54/59, 92%), Uzbekistan (98/123, 80%), Qatar (23/43, 54%) and Pakistan (31/65, 47%). Many of these (21%) were also MDR. Use of nalidixic acid resistance as an indicator for RSC was 99% sensitive and 98% specific. This study reinforces the need for routine antimicrobial susceptibility surveillance of enteric fever isolates and close review of current therapeutic policies in the region.

Keywords: Decreased ciprofloxacin susceptibility, fluoroquinolone resistance, multidrug-resistant typhoid, nalidixic acid resistance, *Salmonella* Typhi

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Introduction

Typhoid fever presents a major public health problem where safe drinking water and sanitation are inadequate. Endemic regions include developing countries in south-central and South East Asia and many parts of Africa and Latin America [1]. The disease is caused by *Salmonella enterica* serovar Typhi (*S.* Typhi). In Egypt, population-based studies have shown an annual incidence of 13/100 000 persons in Belbis District in the Nile Delta [2] and 61/100 000 persons in Fayoum Governorate in the south [3]. Likewise, thousands of Iraqis are affected each year, with 10–20% mortality rates due to limited access to fresh water and dumping of sewage into the rivers [4]. Infection is also common in Jordan, but data and epidemiological studies from the Ministry of Health are limited and incidence is not well defined because of the lack of efficient reporting systems [5]. In Pakistan, the incidence of typhoid fever is comparatively high (451/100 000), supporting the previous findings of Kothari *et al.* [6] who had claimed higher

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typhoid fever burden in Asia than Africa. Meanwhile, increasing rates of typhoid fever have been detected in Uzbekistan due to the deterioration of water treatment and distribution systems in the republics of the former Soviet Union [7]. In Qatar, most infections are imported from the endemic Indian sub-continent and the Far East through expatriate workers and visitors [1].

In the past, *S.* Typhi infections were routinely treated with chloramphenicol, ampicillin, or trimethoprim-sulfamethoxazole, but multidrug-resistance (MDR) to these antibiotics started to emerge in 1990 [8]. In response, physicians in endemic areas shifted to fluoroquinolones or third-generation cephalosporins to ensure better treatment outcomes [9,10]. Although this has resulted in a gradual return of strain sensitivity to chloramphenicol [9,11,12], fluoroquinolones are often still preferentially used to achieve better recovery rates [13].

Despite the recently reported susceptibility of *S.* Typhi isolates to ciprofloxacin by the disc-diffusion method, patients in many endemic areas have begun to present with clinical treatment failures leading to serious consequences [14–16]. This treatment failure was observed for the first time in India in 1991 and subsequently recognized in other nearby countries. However, the minimum inhibitory concentrations (MICs) of these isolates indicated reduced susceptibility to ciprofloxacin (RSC) [14,17]. Since routine use of MIC methods is expensive, resistance to nalidixic acid, the predecessor of the quinolone family, has been used alternatively as an indirect evidence of fluoroquinolone resistance [14,16].

In this study, MDR resistance to ampicillin, chloramphenicol and trimethoprim-sulfamethoxazole was determined for 968 *S.* Typhi isolates that were collected from the Middle East and Central Asia between 2002 and 2007. Decreased susceptibility to fluoroquinolones was also evaluated for the first time in Egypt and neighbouring countries using standard ciprofloxacin and nalidixic acid disc-diffusion tests.

Materials and Methods

Salmonella Typhi blood culture isolates collected during acute febrile illness surveillance in Egypt and Uzbekistan were archived at −70°C at the U.S. Naval Medical Research Unit No. 3 (NAMRU-3) and used for the purposes of this study. Isolates from other countries were recovered from stool or blood cultures of patients during sporadic acute febrile illness outbreaks in Iraq, Jordan, Pakistan and Qatar. Ethical approval for all sample collection was obtained from the institutional review boards of NAMRU-3 and the respective authorities in the collaborating countries. All study subjects provided written informed consent for participation.

Definitive identification was attained using the API 20E kit (bioMérieux, Marcy l'Etoile, France) and commercial antisera (BD Biosciences, Frankland Lakes, NJ, USA). Susceptibility to antibiotic discs containing ampicillin (10 mg), chloramphenicol (30 mg), trimethoprim-sulfamethoxazole (25 mg), ciprofloxacin (5 mg), ceftriaxone (30 mg) and nalidixic acid (30 mg) (Becton-Dickinson, Sparks, MD, USA) was evaluated using the disc-diffusion method. The E-test (bioMérieux) was employed to determine the MICs of ciprofloxacin only. All interpretations were made according to CLSI, 2012. MDR was defined as the simultaneous resistance of bacteria to chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole. The sensitivity and specificity of the nalidixic acid assay as a surrogate of the ciprofloxacin E-test were calculated. Proportions were compared using the chi-squared test.

Results

A total of 968 *S.* Typhi isolates from Egypt (n = 654), Uzbekistan (n = 123), Pakistan (n = 65), Iraq (n = 59), Qatar (n = 43) and Jordan (n = 24) were used in this study. The prevalence of MDR *S.* Typhi isolates was significantly higher in Iraq (49/59, 83%) and Pakistan (34/65, 52%) than in other countries included in this study (13–17%, $p < 0.01$; Table 1). Within Egypt, the majority of isolates were from four different governorates: Fayoum (41%), Cairo (25%), Aswan (10%) and Alexandria (7%). Fayoum isolates showed a significantly higher MDR prevalence (29%; $p < 0.05$) when compared with the other governorates (0–7%; $p < 0.05$; Table 2).

Nearly all isolates were susceptible to ceftriaxone, except for two from Alexandria, Egypt, which showed intermediate resistance (total susceptibility 99.7%) and were negative for extended spectrum β-lactamase production. For ciprofloxacin, only 48% were susceptible by the disc-diffusion method, with zone diameters ≥31 mm (Table 1). The remaining isolates were either intermediate (47%, 21–30 mm) or fully resistant (5%, ≤20 mm), with relatively elevated MICs ranging from 0.125 to 0.75 μg/mL (mean 0.33 ± 0.12 μg/mL). Meanwhile, susceptibility to nalidixic acid by the disc-diffusion method was 74%, 4% were intermediate and 22% were resistant. Isolates that tested nalidixic acid resistant (n = 218, 22%) correspondingly showed elevated MICs for ciprofloxacin in 216 isolates, ranging from 0.125 to 0.94 μg/mL (average 0.29 ± 0.11 μg/mL) RSC. The remaining two isolates were susceptible to ciprofloxacin (<0.064 μg/mL). The distribution of RSC reflected a broad geographic variability: Iraq (92%); Uzbekistan (80%); Qatar (54%); Pakistan (47%); Jordan (8%) and; Egypt (2%) (Table 1). Use of nalidixic acid resistance as an indicator

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