Original Article

A three-year review of antimicrobial resistance of *Salmonella enterica* serovars Typhi and Paratyphi A in Pakistan

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Abstract

Introduction: Enteric fever is among the most common bacteraemic illnesses in South Asia. Multidrug resistance as well as fluoroquinolone resistance has severely limited therapeutic options in high disease burden countries such as Pakistan. This review was conducted to determine the frequency of drug-resistant *Salmonella enterica* serovar Typhi (*S*.Typhi) and *Salmonella enterica* serovar Paratyphi A (*S.* Paratyphi A) between2009 and 2011.

Methodology: This study was a review of laboratory data. The antibiotic susceptibility of typhoidal *Salmonellae* isolated from blood cultures submitted to the Aga Khan University Hospital's laboratory from all over Pakistan between January 2009 and December 2011 were reviewed.

Results: The sensitivity data of 4,323 positive isolates of *S.* Typhi and *S.* Paratyphi A isolated during the three-year period were reviewed. The majority of isolates were *S.* Typhi (59.6%).Over three years, the incidence of multidrug-resistant (MDR) *S.*Typhi remained high, ranging from 64.8%–66.0%, while MDR *S.* Paratyphi A decreased from 4.2% to 0.6%.Fluoroquinolone resistance increased for *S*. Typhi from 84.7% to 91.7%.Cefixime- and ceftriaxone-resistant *S.* Typhi were isolated in two children.

Conclusions: Our results show high rates of multidrug and fluoroquinolone resistance among *S.* Typhi and *S.* Paratyphi. The occurrence of two cases of ceftriaxone resistance is alarming.

Key words: typhoid fever; *Salmonella* typhi; paratyphi; resistance.

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Introduction

Enteric fever, caused by *Salmonella enterica* serovars Typhi and Paratyphi A, continues to be a major health problem in developing countries, particularly in South Asia and Pakistan [1,2]. In the year 2000, there were an estimated 21.6 million cases of typhoid fever globally, with 210,000 deaths and 5.4 million cases of paratyphoid fever [3,4]. Untreated, the disease carries a mortality rate of up to a 30% [5,6], and up to 90% of deaths due to enteric fever occur in Asia alone [4]. Definitive diagnosis is made by isolation of causative organisms from blood, bone marrow, or other body fluids; however, the yield of blood culture is 60% to 80% [7].

Multidrug resistance, defined as resistance to the three first-line classes of antimicrobial agents (chloramphenicol, ampicillin, and trimethoprim / sulphamethoxazole) has become prevalent in most of South Asia, with a frequency ranging from 50% to 80% of all *S*. Typhi isolates [7-10]. MDR *S*. Paratyphi has been reported globally at rates of up to 25% [11] and is a significant problem in South Asia, ranging from 13% in India [12] to 44% in Pakistan [13].

Fluoroquinolones became the first-line drug for treatment after the emergence of MDR strains. However, from 2000 onwards, there has been a dramatic rise in fluoroquinolone-resistant *S.* Typhi isolates [14-18]. There are reports from parts of South Asia of isolates that are MDR and have reduced sensitivity to fluoroquinolones [19]. Recently, cephalosporins (ceftriaxone and cefixime) and azithromycin have been suggested as alternatives for treating MDR infections [6,7,20,21]. High levels of multidrug and fluoroquinolone resistance have made cephalosporins the drug of choice for empiric therapy in SouthAsia [20,22].

An increasing trend of fluoroquinolone resistance in *S.* Typhi and *S.* Paratyphi has been reported earlier from Pakistan [23]. Shortfalls in diagnosis due to lack of laboratory facilities, easy availability of antimicrobial agents, and cheap substandard formulations of fluoroquinolones are the underlying risk factors for high antimicrobial resistance in

developing countries [24]. Also of concern is the sporadic occurrence of resistance to third-generation cephalosporins observed among typhoidal *Salmonellae* [25-27].

Keeping surveillance of resistance trends among strains, monitoring rational use of antimicrobial agents, and developing clinical management guidelines to standardize therapy can be useful strategies in curtailing the development of resistance against the remaining mainstay of therapy –third-generation cephalosporins. We reviewed antibiotic susceptibility data of *S.* Typhi and *S.* Paratyphi A isolated from blood cultures at the Aga Khan University's Clinical Microbiology Laboratory between 2009 and 2011.

Methodology

Antimicrobial susceptibility data of *Salmonella enterica* serovars Typhi and Paratyphi A isolated from blood cultures submitted to the Aga Khan University Hospital's (AKUH) Clinical Microbiology Laboratory were reviewed.Thelaboratory receives samples from more than 190 collection units located in all major cities and towns across the country. The AKUH laboratory operates according to laboratory guidelines of international standards (certified by ISO and Joint Commission International Accreditation).

Laboratory methods

A venous blood sample was collected from all patients referred to the lab for blood culture. Blood was inoculated into enriched soybean-casein digest broth with resins in BACTEC (Becton-Dickinson, New Jersey, USA) bottles. For patients less than five years of age, BACTEC PEDS Plus bottles were used. Upon growth as indicated by the BACTEC machine, blood culture bottles were sub-cultured onto a MacConkey agar plate. Colonies giving biochemical reactions suggestive of *Salmonellae* were confirmed serologically with specific O and H antisera (BD Laboratories). Salmonella isolates were tested for antimicrobial susceptibility by the Kirby-Bauerdisk diffusion method [28] on Muller-Hinton agar with standard antimicrobial disks (Clinical Laboratory Standards Institute 2009) [29].Antimicrobial susceptibility for seven antimicrobial agents – ampicillin, chloramphenicol, trimethoprim / sulphamethoxazole, cefixime, ceftriaxone, ciprofloxacin, and/or ofloxacin– was performed.

From January 2009 to December 2011, a total of 116,690 blood culture specimens from patients belonging to all age groups were submitted to the clinical laboratory. Laboratory data pertaining to isolate species, age of patient, year of collection, and area of collection were collected.

Multidrug resistance was considered if isolates were resistant to three antimicrobial classes (ampicillin, chloramphenicol, and trimethoprim / sulphamethoxazole), while isolates were considered fluoroquinolone resistant if they were resistant to ofloxacin. Sequencing for the quinolone resistance-determining regions was not performed. Due to the very low number of *S.* Paratyphi B and C (n = 21), they were omitted from the analysis.

Results were tabulated and analyzed using Microsoft Excel 2007.

Results

A total of 4,323 isolates of *Salmonella enterica* serovars Typhi and Paratyphi A, B, and C strains were isolated from 116,690 blood cultures submitted between 2009 and 2011. The majority of blood cultures (93.3%; n = 4,035) were from subjects seen in Karachi at the inpatient and outpatient departments of AKUH. Most of the isolates were from adults 15–30years of age (27.5%, with a 6%culture positivity rate), followed by children 5–10 years of age and children under 5 years of age (Table 1).

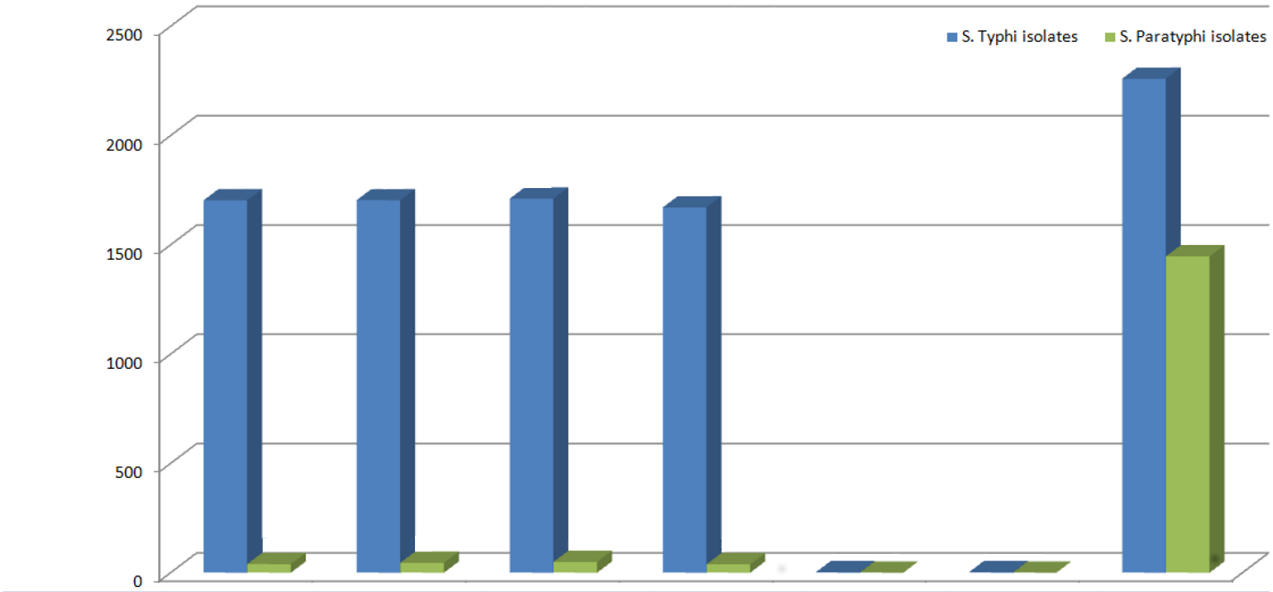
Isolates were predominantly *S.* Typhi (59.6%; n = 2,576) and *S.* Paratyphi A (39.9%; n = 1,726).

Table 1. Breakdown of total blood cultures, percentage culture positivity and distribution of *S.* Typhi and *S.* Paratyphi A isolates by age groups

Age	*S.* Typhi n (%)	*S.* Paratyphi A n (%)	Positive for typhoidal *Salmonellae* n*/N** (%)	% of total positive samples
Ages < 5	718 (79.2%)	174 (19.2%)	906/35,297 (2.6%)	21.0%
Ages 5 – 10 years	688 (68.3%)	319 (31.6%)	1,008/9,263 (10.9%)	23.3%
Ages 10 – 15 years	400 (58.2%)	285 (41.5%)	687/6,645 (10.3%)	15.9%
Ages 15 – 30 years	553 (46.5%)	634 (53.4%)	1,188/19,805 (6.0%)	27.5%
Ages 30 – 50 years	164 (39.6%)	248 (59.9%)	414/18,683 (2.2%)	9.6%
Ages > 50 years	53 (44.2%)	66 (55.0%)	120/26,997 (0.4%)	2.8%
All ages	2,576 (59.6%)	1,726 (39.9%)	4323/116690 (3.7%)	100.0%

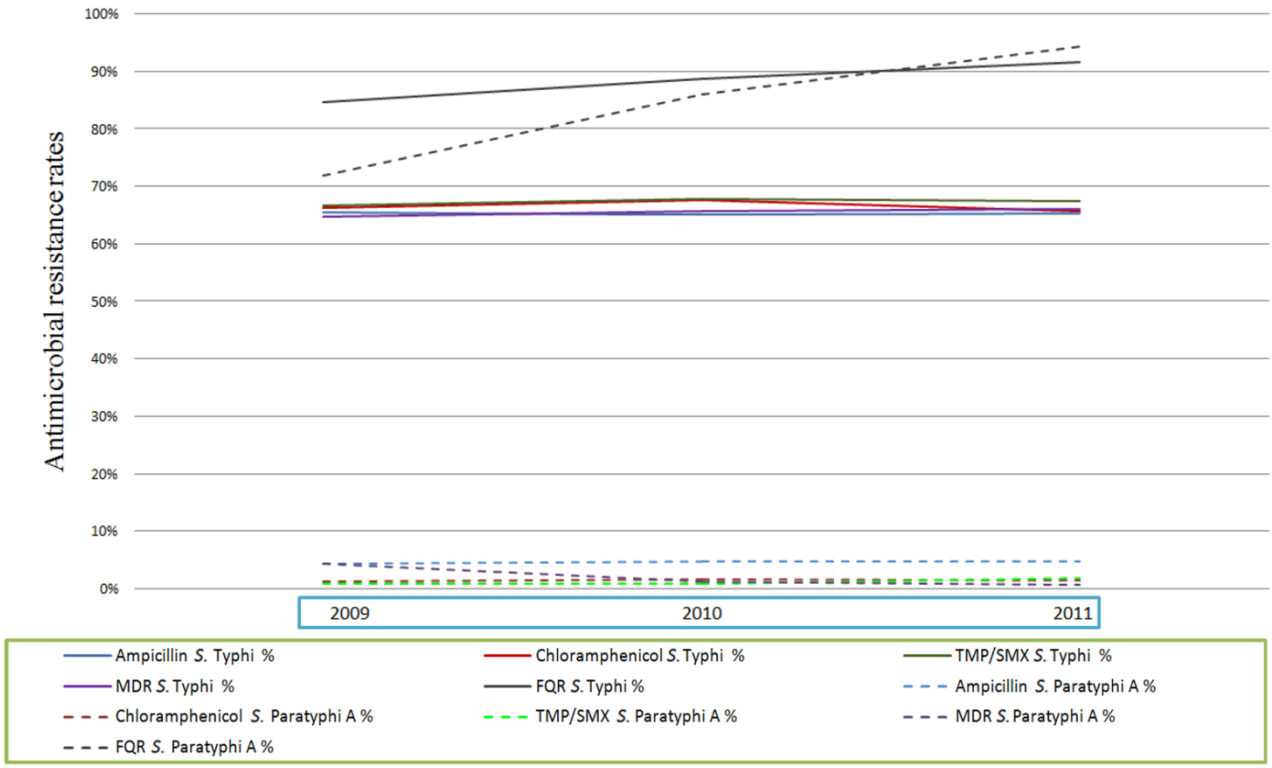
* total number of positive blood cultures; ** total blood cultures in that age group; *S.* Paratyphi B and C are omitted from table as only 21 isolates were identified.

Figure 1. Antimicrobial resistance of *S.* Typhi and *S.* Paratyphi identified in blood cultures between 2009 and 2011.



	Ampicillin	Chloramphenicol	TMP/SMX	MDR	Cefixime	Ceftriaxone	Fluoroquinolone
S . Typhi n/N(%)	1,703/2,576 (66.1%)	1,704/2,522 (66.8%)	1,711/2,574 (66.5%)	1,671/2,552 (65.5%)	2/2,574 (0.08%)	2/2,575 (0.08%)	2,260/2,562 (88.2%)
S . Paratyphi A n/N(%)	39/1,724 (2.3%)	45/1,720 (2.6%)	49/1,726 (2.8%)	38/1,720 (2.2%)	0/1,724 (0%)	0/1,725 (0%)	1,447/1,725 (83.9%)

Figure 2. Trends of antimicrobial resistance of *S.*Typhi and *S.* Paratyphi A over three years (2009-2011).



The remaining 0.48% (n = 21) were *S.* Paratyphi B and C (Table 1).

The resistance to antimicrobial agents of all isolates over the three years is shown in Figure 1.Almost identical resistance was seen to ampicillin (66.1%), chloramphenicol (66.8%), and trimethoprim / sulphamethoxazole (66.5%) for *S.* Typhi, from a total of 2,576 positive isolates. Fluoroquinolone resistance in *S*. Typhi was seen in 88.2%of the isolates. Lower resistance rates for *S.* Paratyphi A species were reported: 2.3% (ampicillin), 2.6% (chloramphenicol), and 2.8% (trimethoprim / sulphamethoxazole). The rate of fluoroquinolone resistance in *S*. Paratyphi was 83.9%.

From 2009 to 2011, MDR *S.* Typhi remained high, ranging from 64.8% in 2009 to 66.0% in 2011 (Figure 2). However, fluoroquinolone resistance increased for *S.* Typhi, from 84.7% in 2009to 91.7% in 2011.MDR *S.* Paratyphi A decreased from 4.2% to 0.6% from 2009 to 2011; however, fluoroquinolone resistance for *S.* Paratyphi increased, from 72.1% to 95% (Figure 2).

The pattern of antimicrobial resistance was uniform across all ages except for two isolates (0.08%) recovered from children three and four years of age, respectively, with resistance to third-generation cephalosporins (ceftriaxone and cefixime). Both were residents of Karachi. Ceftriaxone minimum inhibitory concentration was performed for both of these isolates and was found to be >32 μg/mL. No further genotyping was performed.

Discussion

Since the 1980s, outbreaks caused by strains of *S.* Typhi resistant to chloramphenicol, ampicillin, and trimethoprim/sulphamethoxazole have been reported to such an extent as to be considered endemic in many developing countries and areas, especially Pakistan and South Asia [3]. Such multidrug-resistant strains most likely arise from unchecked use of antimicrobials for every febrile illness in both adults and children, which is especially true in South Asia [20,30]. More recently, third-generation cephalosporins have emerged as necessary agents against enteric fever. The emergence of MDR *Salmonella* strains with resistance to fluoroquinolones and now reports of resistance to third-generation cephalosporins is alarming, resulting in a shortage of therapeutic options against enteric fever.

We report a very high rate of MDR *S*. Typhi over the three-year period. This trend of multidrug resistance over the last three years reflects the endemicity of such resistant strains in this region and is much higher than that seen in eight countries of Asia [31] and in a study by Hasan *et al*., which showed multidrug resistance rates of 34.2% to 48.5% for *S.* Typhi from 2001 to 2006 [23]. Our results, however, are similar to those reported from Pakistan by Hazir *et al.* in 2002, who reported a cumulative prevalence of MDR *S.* Typhi of 67.2%, although this was from one center only [10].We report low rates of MDR *S.* Paratyphi A over the last three years, similar to results reported by Hasan *et al*. (a decrease from 44.5% to 8.6%). This is in contradiction to an increasing rate of MDR *S*. Paratyphi A, from 14% in 1996 to 44% in 2003, from other parts of Pakistan [13]. The decreasing trend of multidrug resistance over time [32,33] in other regions maybe due a change in choice of therapy and a decrease in usage of these three agents [27]. It may also represent isolated outbreaks of susceptible strains [34]. However, no such decrease in resistance of *S.* Typhi was seen in this study, suggesting stable genomic changes in *S.* Typhi and more unstable genomic mutations in *S.* Paratyphi in this region. Although advocated by some [35], use of these antimicrobial agents should not be advised for empiric treatment of enteric fever in Pakistan.

The *S.*Typhi resistance to fluoroquinolones of 91.7%was observed in this review during 2011, much higher than the 5%–30% resistance to fluoroquinolones seen in India [17,18,36], and higher than the previously reported 54% resistance seen in children in southern Pakistan in 2007–2008 [37]. Indiscriminate use of fluoroquinolones is seen in Pakistan for many febrile illnesses [38], with resistance to a number of organisms increasing as well [39,40]. Weak health systems together with ready availability of low-cost substandard formulations of fluoroquinolones on the market aggravate the development and spread of resistant strains [24]. Not enough efforts on regional and international levels are being made to curb the uncontrolled use of antimicrobial agents, to promote culture confirmed sensitivity-based therapy, and to spread awareness among prescribing physicians and the public.

The two cases of resistance to third-generation cephalosporins is the most worrisome finding in this review, and the potential spread of such extensively resistant *S.* Typhi isolates is an alarming situation. Cephalosporin-resistant *S.* Typhi have been reported from other regions in Asia [25-27]. The threat of a regional spread of such resistance patterns, and even

sporadic occurrences of these cases, are major concerns since both limit therapeutic options.

This review of lab data of blood cultures collected from more than 190 laboratories throughout Pakistan included strains from communities as well as hospital inpatients. Our results are therefore reflective of the resistance patterns of *S* .Typhi and *S.* Paratyphi throughout the country. There was a similar trend of antimicrobial susceptibility among strains from all over the country.

The present study shows that the antimicrobial resistance patterns among *S.* Typhi isolates can also change significantly over relatively short periods, with the prevalence of multidrug and fluoroquinolone resistance *S.* Typhi isolates increasing substantially within a six-year period. Therefore, routine surveillance of antimicrobial resistance patterns is critical.

Vaccination is a valuable tool for preventing enteric fever in travelers from developed countries to endemic countries, for preventing and controlling epidemics, and for preventing illness in children in endemic settings. Further development in this area is warranted, and this is especially true in children attending school, where the burden of *S.* Typhi infection is highest, based on the distribution of positive isolates identified in this study. Proposals for the incorporation of typhoid vaccines into extended programs of immunization are required, as is the development of paratyphoid vaccines.

Our review has limitations. Being an extract of a laboratory database, percent positivity does not reflect prevalence figures. Furthermore, no clinical information of the severity of illness in the subjects with MDR strains is reported. Of note, further characterization of cephalosporin-resistant isolates was not possible since the isolates have not been archived.

Conclusion

We report a high rate of multidrug and fluoroquinolone resistance; this can have implications for empiric antimicrobial therapy in a country endemic for typhoid. Vaccination against typhoid and measures to reduce antimicrobial overuse and misuse of antimicrobials should be developed and implemented to limit the disease and spread of resistance.

Authors contribution

All authors listed have made substantial contributions to the work reported in the manuscript. Individual role in the manuscript is as detailed: Clinical lab data was reviewed by E. Khan and F. Qamar as part of larger study design currently in process. F. Qamar helped in the conception and design of the manuscript as well as analysis and interpretation of the data and writing and review of the manuscript; A. Azmatullah analyzed the data, contributed to data interpretation, tabulation of results, and manuscript writing. AM Kazi helped in retrieving the data and analysis of data. E. Khan and A. Zaidi reviewed and revised the final manuscript.

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