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ANTIMICROBIAL SUSCEPTIBILITY AND PREVALENCE OF TWO SEROTYPES OF *SALMONELLA ENTERICA* IN NEPAL (REVIEW)

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ABSTRACT

This study aimed to find out the difference in the prevalence of enteric fever caused by *Salmonella* Typhi and *S.* Paratyphi A, antimicrobial resistance pattern and multi drug resistant (MDR) isolates in Nepal. Cochrane library, MEDLINE/PUBMED Central, HINARI and Open Access journals were searched for Nepal, enteric fever, antimicrobial resistance, prescription pattern, typhoid and paratyphoid fever for the published data in the period of 2000 to 2012. Data were extracted in the data extraction form and were entered into Microsoft Excel 2007 and MetaAnlyst (Beta 3.13). Studies included in the present study consisted of more than 106,678 blood/bone marrow samples with 11,252 confirmed cases for enteric fever. Prevalence of *S.* Typhi was found to be 49.2% to 91.4% [risk ratio (RR) 0.003 to 0.737] whereas it was 8.6% to 50.8% for *S.* Paratyphi A. Antimicrobial sensitivity pattern showed decreased susceptibility to flouroquinolones though the data were inconclusive. Prevalence of MDR isolates for *S.* Typhi was found to be 1.7% to 40.7% and 4.2% to 7% for *S.* Paratyphi A. Amoxicillin plus calvulanic acid, ofloxacin, ceftriaxone and cefotaxime may be more suitable for both serotypes of *S. enterica* in Nepal though comparative studies are not available.

KEYWORDS: Antibiotic resistance, Enteric fever, Nepal.

INTRODUCTION

Enteric fever is caused by different serotypes of the bacterium *Salmonella enterica.*[1] Typhoid fever caused by *S.* Typhi is generally more common and more severe. However, data in the literature suggest that the prevalence of paratyphoid fever caused by *S.* Paratyphi A has been increasing.[2-8] Signs and symptoms of enteric fever include fever, headache, and gastrointestinal upset-diarrhea, constipation, abdominal pain, nausea and vomiting, or loss of appetite.[9,10] If the disease is left untreated it lasts for 3 to 4 weeks with fever, septicemia and has 10-30% mortality rate. Enteric fever is treated with antimicrobial agents and most patients can be managed as outpatients.[1]

Enteric fever may have severe complications in 10 to15% of cases, and complications such as; intestinal perforation, intestinal bleeding, shock, pancreatitis, pneumonia, myocarditis, meningitis, or psychosis may occur, if the duration of illness persists for more than two weeks.[11] The bacteria may be excreted in the stool during the acute illness, during convalescence, and sometimes for prolonged periods when the patient is labeled a 'chronic carrier' - defined as excretion of the bacterium in the stool or urine for more than one year.[12] Infection occurs when contaminated food or water or raw vegetables are taken by healthy individuals. The bacteria then penetrate the intestinal lining, multiply in lymphoid tissues, and are released into the blood stream from where they go all over the body to various organs; most commonly the liver, spleen, bone marrow, and gall bladder.[13]

The enteric fever is a major public health problem in low- and middle-income countries like Nepal where water, sanitation and personal hygiene may be inadequate or inappropriate. It is endemic throughout Asia (with the highest incidence in South and Southeast Asia), the Middle East, Africa, and South and Central America.[14,15] In high-income countries, most cases occur in travelers returning from these endemic areas.[16] The highest incidence has been reported in children between five and 10 years of age,[17-19] and in those under five years of age.[20-22]

Difficulty may be faced while diagnosing enteric fever due to non specific nature of symptoms of the disease. However, a definitive diagnosis is possible when the bacteria are isolated from blood, bone marrow or other body fluids. Previous findings showed that blood

cultures were positive in 60 to 80% of cases, while bone marrow cultures are more sensitive with 80 to 95% positive, even after prior antibiotic therapy.[11] Serological tests, such as the Widal reaction, have been widely used but these are non-specific, giving false positive results, and can be difficult to interpret. Lately, there has been interest in the use of DNA probes and polymerase chain reaction (PCR) tests, but these are not widely available in enteric fever endemic areas.[11]

Recently, antimicrobial resistance of *S.* Typhi and *S.* Paratyphi to commonly used antibiotics has become problematic. Resistance to the highly effective chloramphenicol in the 1970's was associated with simultaneous resistance to sulfonamides, tetracycline and streptomycin. This led to the use of other agents such as co-trimoxazole and amoxicillin.[11] Subsequently, multi-drug resistant (MDR) strains -resistant to chloramphenicol, ampicillin, cotrimoxazole and streptomycin- emerged and are now prevalent in many parts of the world.[1] This study aimed to find out the difference in the prevalence of enteric fever caused by two serotypes- *S.* Typhi and *S.* Paratyphi- antimicrobial resistance pattern and MDR isolates in Nepal.

MATERIALS

Electronic searches

Cochrane library, MEDLINE/PUBMED Central through HINARI and Open Access journals were searched for Nepal, enteric fever, antimicrobial resistance, prescription pattern, typhoid and paratyphoid fever for the published data in the period of 2000 to 2012.

Selection criteria

Studies of enteric fever confirmed by blood/bone marrow culture and having antimicrobial sensitivity patterns conducted only in Nepal were included.

Validity assessment

Two reviewers examined the studies and data twice at two different time intervals.

Data extraction and management

For eligible studies, data were extracted in the pre-tested data extraction form for total number of patients and/ or blood samples, positive blood/bone marrow cultures for *S.* Typhi and *S.* Paratyphi A, number and percentage of *S.* Typhi and *S.* Paratyphi A, number and percentage of sensitivity pattern for different antimicrobials including MDR isolates. The extracted data were entered into Microsoft Excel 2007 and MetaAnlyst (Beta 3.13) and cross-checked by same author for the second time for accuracy.

Data Synthesis

Data were analyzed by using MetaAnalyst (Beta 3.13) for the comparison of prevalence of *S.* Typhi and *S.* Paratyphi A by Random- Der_ Simonian Laird Method. Comparison of sensitivity pattern for different antimicrobials could not be performed as there was no consistency among the studies for the antimicrobial use and only the percentages of sensitive, intermediate and resistant organisms have been reported in the study.

RESULTS

Twelve studies conducted in Nepal and published from 2000 to 2012 were included. Table 1 shows the characteristics of individual study. During this period, more than 106,678 blood/bone marrow samples were taken for culture (three studies have not mentioned the total number of blood samples) and 11,252 were confirmed for enteric fever. Three studies did not categorize between *S.* Typhi and *S.* Paratyphi A whereas data were not available in one study. So only eight studies have mentioned the prevalence of *S.* Typhi and *S.* Paratyphi A (Table 2). Age range of the patients was 1 - 71 years and male to female ratio was 1.1 to 2.1:1 (not shown in the tables or figures). Prevalence of *S.* Typhi was found to be 49.2% to 91.4% whereas 8.6% to 50.8% *S.* paratyphi A (Table 2). The meta-analysis for the prevalence rate of these two serotypes has been shown in figure 1 which showed that the RR for S. Typhi was from 0.003 to 0.737. Antimicrobial sensitivity pattern has been presented in table 3. Prevalence of MDR isolates for *S.* Typhi was found to be 1.7% to 40.7% and 4.2% to 7% for *S.* Paratyphi A. However, only six studies have reported MDR isolates.

Table 1: Descriptions of individual study conducted in Nepal at different times with positive cultures (blood and/or bone marrow) for *S. enterica* which are included in the present study.

Study with published date	Duration of study[#]	Samples	Positive cultures
Acharya D et al 2012 [54]	Jul 2009 to Dec 2010[a]	NM	114
Acharya D et al 2011 [55]	Jan to Dec 2008[b]	656	59
Prajapati B et al 2008 [56]	Apr 2007 to Mar 2008[c]	9 856	235
Maskey AP et al 2008 [8]	1993 to 2003[d]	82 467	9 124
Khanal B et al 2007 [57]	Jan 2000 to Dec 2004[e]	2 568	132
Malla T et al 2007 [58]	Jan 2000 to Dec 2005[f]	82	35
Tamang MD et al 2007 [59]	Feb 2004 to Jan 2006[d]	NM	121
Sharma NP et al 2006 [60]	Jul 2002 to Jun 2004[a]	1 774	63
Pokhrel BM et al 2006 [61]	Jan to Sept 2004[g]	4 105	541
Maskey AP et al 2006 [30]	Jan to Aug 2004[h]	2 535	609
Mathura KC et al 2005 [62]	Jul 2004 to Jun 2005[i]	NM	46
Guha S et al 2005 [63]	Jun 2000 to May 2003[f]	2 354	114

Numbers in parentheses indicate references; [#] Place of study; [a] Dhulikhel Hospital- Kathmandu University Teaching Hospital; [b] National Public Health Laboratory; [c] Kanti Children Hospital; [d] Nepal; [e] B P Koirala Institute of Health Sciences; [f] Manipal Teaching Hospital; [g] Tribhuvan Teaching Hospital; [h] Patan Hospital; [i] Kathmandu Medical College Teaching Hospital; NM- not mentioned.

Table 2: Prevalence rate of two serotypes of *S. enterica* reported in different studies.

Study **N= 103 829[a]; 10 780[b]**	***S.*Typhi *(%)*** **N=7 491**	***S.* Paratyphi A*(%)*** **N=3 289**
Acharya D et al 2011, N=656[a]; 59[b]	29 (49.2)	30 (50.8)
Prajapati B et al 2008, N=9 856[a]; 235[b]	195 (83)	40 (17)
Maskey AP et al 2008, N=82 467[a]; 9 124[b]	6 447 (70.7)	2 677 (29.3)
Malla T et al 2007, N=82[a]; 35[b]	32 (91.4)	3 (8.6)
Sharma NP et al 2006, N=1 774[a]; 63[b]	50 (79.4)	13 (20.6)
Pokhrel BM et al 2006, N=4 105[a]; 541[b]	253 (47)	288 (53)
Maskey AP et al 2006, N=2 535[a]; 609[b]	409 (67)	200 (33)
Guha S et al 2005, N= 2 354[a]; 114[b]	76 (66.7)	38 (33.3)

[a] total samples; [b] positive samples; N- number; Numbers in parentheses indicate percentage

Table 3: Antimicrobial susceptibility patterns of *S.* Typhi and *S.* Paratyphi A reported in different studies.

AMAs	***S.* Typhi**			***S.* Paratyphi A**		
	S (%)	**I (%)**	**R (%)**	**S (%)**	**I (%)**	**R (%)**
amox	37-66.7	14.8	1.5-18.5	15.0	67.5	2.1-17.5
chlor	37-98.2	0.5	1.8-27	92.5	2.5	1.5-5
cotri	15-97.4		2.2- 27	97.1		1.5-3
ampi	67.5	2.6	7- 30			10.0
am+cla	100					
nali	22.8		50.5-77.2			75.3-93
cipro	79.8-100	11.3-18.4	0.25-3	51.3	30.8	0.5-17.9
oflo	91.2-100	7	0.5-6.5	70.3	21.6	3.6-10
ceftri	96.5-100	3.5	1.1	97.4		0.5-2.6
cefo	87.8-100	9.6	2.6	100		
cefta	95.6	4.4				

AMAs- antimicrobial agents, S- sensitive, I- intermediate, R- resistant, amox- amoxicillin, chlor- chloramphenicol, cotri- cotrimoxazole, ampi- ampicillin, am+cla- amoxicillin and clavulanic acid, nali-nalidixic acid, cipro- ciprofloxacin, oflo- ofloxacin, ceftri- ceftriaxone, cefo- cefotaxime, cefta- ceftazidine.

Table 4: Multi-drug-resistant (MDR) isolates found in different studies.

Study	***S.* Typhi *(%)***	***S.* Paratyphi A *(%)***	**NC *(%)***
Acharya D et al 2012, N= NA[a]; 114[b]	1.7	NA	
Acharya D et al 2011,N=656[a]; 59[b]			5.08
Khanal B et al 2007 5, N=2 568[a]; 132[b]	26	NA	
Tamang MD et al 2007, N= NA[a]; 121[b]	5.8	NA	
Pokhrel BM et al 2006 , N= 4 105[a]; 541[b]	5	7	
Guha S et al 2005, N=2 354[a]; 114[b]	40.7	4.2	

N- number; NC- not categorized; [a] total samples; [b] positive samples; NA- not available

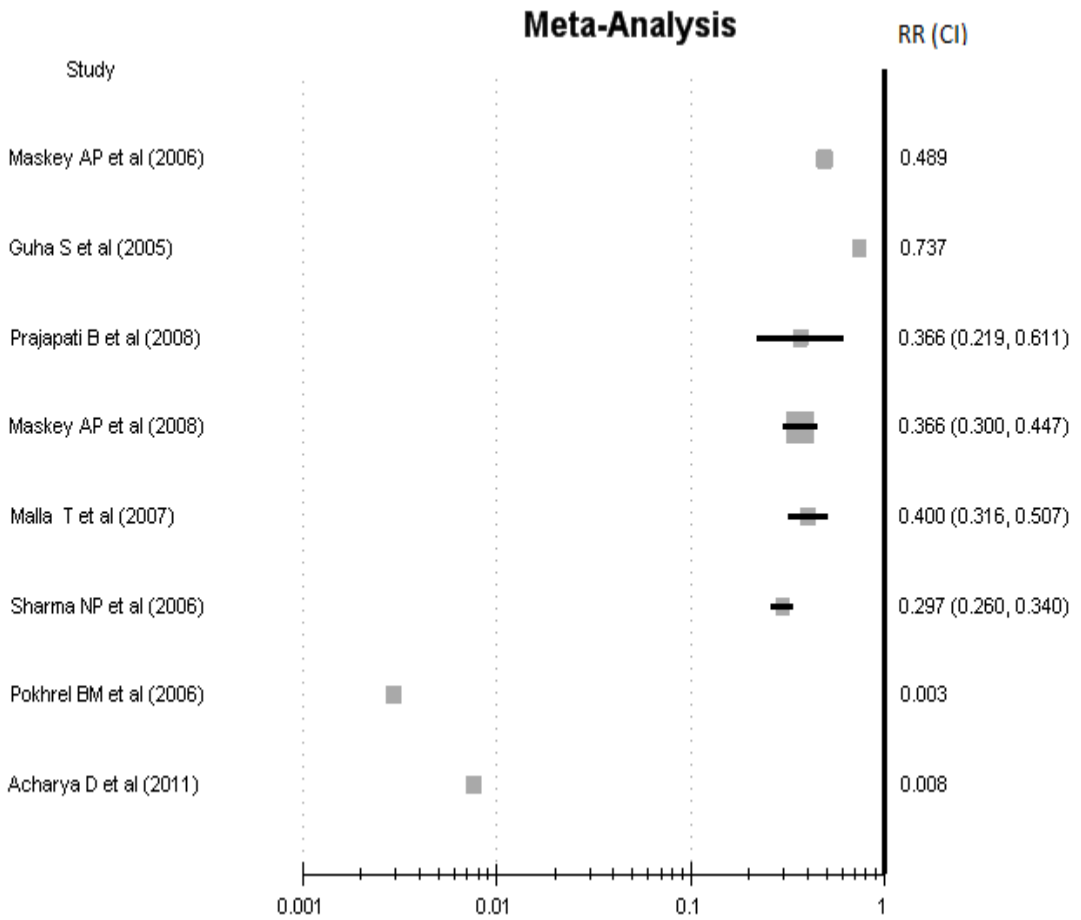

Fig 1: Comparison for the prevalence of *S.* Typhi with *S.* Paratyphi A infection showing Risk Ratio (RR) and Confidence Interval (CI).

DISCUSSION

Prevalence of S. Typhi *and S.* Paratyphi A

Based on different studies conducted in Nepal, prevalence of *S.* Typhi in enteric fever was found to be 49.2% to 91.4% (RR- 0.003 to 0.737). Paratyphoid fever, caused by *S.* Paratyphi A, was estimated to cause 5·4 million cases and previously considered as the silent febrile illness compared to typhoid fever with an estimated 21.6 million cases and 220,000 deaths worldwide.[12,23] Reports from China, Pakistan, India, Vietnam, Indonesia and Nepal show that *S.* Paratyphi A can contribute up to half of all the enteric fever cases in some settings and times and is emerging as a major cause of febrile illness.[24-28] Similarly, studies from developed countries also found an increasing incidence of *S.* Paratyphi A among travelers returned from endemic region.[29] *S.* Paratyphi A although previously believed to cause a milder disease than *S.* Typhi, several recent studies showed that it produces indistinguishable clinical features.[30,31] and possibly more complications.[32,33]

Antimicrobial susceptibility pattern

No uniform pattern of sensitivity results was observed among the studies. Based on few data, amoxicillin with clavulanic acid showed more sensitivity (100%) than amoxicillin (37% to 66.7%) alone for *S.* Typhi enteric fever. Chloramphenicol showed 37% to 98.2% sensitivity for *S.* Typhi and 92.5% for *S.* Paratyphi A. Similarly, cotrimoxazole showed 15% to 97.4% for *S.* Typhi and 97.1% for *S.* Paratyphi A. Ciprofloxacin showed 79.8% to 100% sensitivity for *S.* Typhi and 51.3% for *S.* Paratyphi A whereas ofloxacin showed 91.2% to 100% sensitivity for *S.* Typhi and 70.3% for *S.* Paratyphi A. Previously, enteric fevers responded very well to the fluoroquinolones, however, quinolone resistant strains of *S.* Typhi, especially in Asia, have become a major public health problem.[34-36] Ceftriaxone had 96.5% to 100% sensitivity for *S.* Typhi and 97.4% for *S.* Paratyphi A. Additionally, cefotaxime was sensitive in 87.5% to 100% *S.* Typhi infections whereas it was sensitive in 100% *S.* Paratyphi A infections in few studies. The occurrence of antibacterial resistance was first reported in 1950 after the introduction of chloramphenicol. In the 1980s and 1990s, *S.* Typhi developed simultaneous resistance to all first-line drugs-chloramphenicol, amoxicillin, and cotrimoxazole, encoded on a single plasmid.[35] These multidrug-resistant strains are now ubiquitous, and fluoroquinolones have largely displaced other antimicrobial agents as the drugs of choice. However, emergence of resistance to the fluoroquinolones, mainly to ciprofloxacin, has been a major problem in endemic

areas.[37] In Nepal, the extent of quinolone, fluoroquinolone and other antimicrobial resistance pattern is dubious as most laboratories do not have the facilities for susceptibility testing.[30]

MDR isolates

S. Typhi showed 1.7% to 40.7% MDR isolates whereas *S.* Paratyphi A showed 4.2% to 7% though the data are not sufficient enough for wide coverage in Nepal because only few studies had have reported MDR isolates. However, based on the data included in the study, whether the prevalence of MDR isolates has been increased or decreased is not clear, albeit present review consists of many studies from Kathmandu valley. Nevertheless, longitudinal studies based on the same geographical area may help answer this question. In the Indian subcontinent and China, the frequency of MDR strains ranges from 50% to 80% of all *S.* Typhi isolates and has reached 100% during outbreaks (9). In sub-Saharan Africa, MDR *S.* Typhi has been found in 61% and 82.4% of isolates in Nigeria and Kenya, respectively.[38,39] Surveillance studies can show considerable geographic differences in the proportion of MDR isolates within the same region; MDR *S.* Typhi is far more common in India, Pakistan and Vietnam than in areas of China and Indonesia.[40] Longitudinal studies have also shown that the proportion of MDR strains can decrease over time following changes in antibiotic use.[41,8] Indeed several areas have reported a re-emergence of strains susceptible to first-line antibiotics such as chloramphenicol.[42-45,4,46-48] Infection with resistant strains can lead to higher treatment failure rates, an increased risk of complications and an increased potential for transmission due to prolonged fecal carriage.[49-52,46,53]

There is some evidence that prevalence of *S.* Typhi is more than the *S.* Paratyphi A in enteric fever in Nepal. Amoxicillin plus calvulanic acid, ofloxacin, ceftriaxone and cefotaxime may be more suitable for both serotypes of *S. enterica*. However, this study is unable to draw the statistically significant conclusion that which antimicrobial agent is more sensitive, which serotype is more prevalent and more multi-drug resistant though *S.* Typhi showed more prevalence both in occurrence and MDR isolates in some reports.

Disclaimer: authors disclaim any validity or reliability error of the sensitivity patterns in the published data as this study involved the data from the published results only and authors disown any responsibility for the inherent quality error of the cultures, sensitivity tests and methods in different studies included in the present study.

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