In-vitro resistance of Salmonella Typhi and Paratyphi A raises concern on the use of older fluroquinolones in the empiric treatment of enteric fever in Nepal

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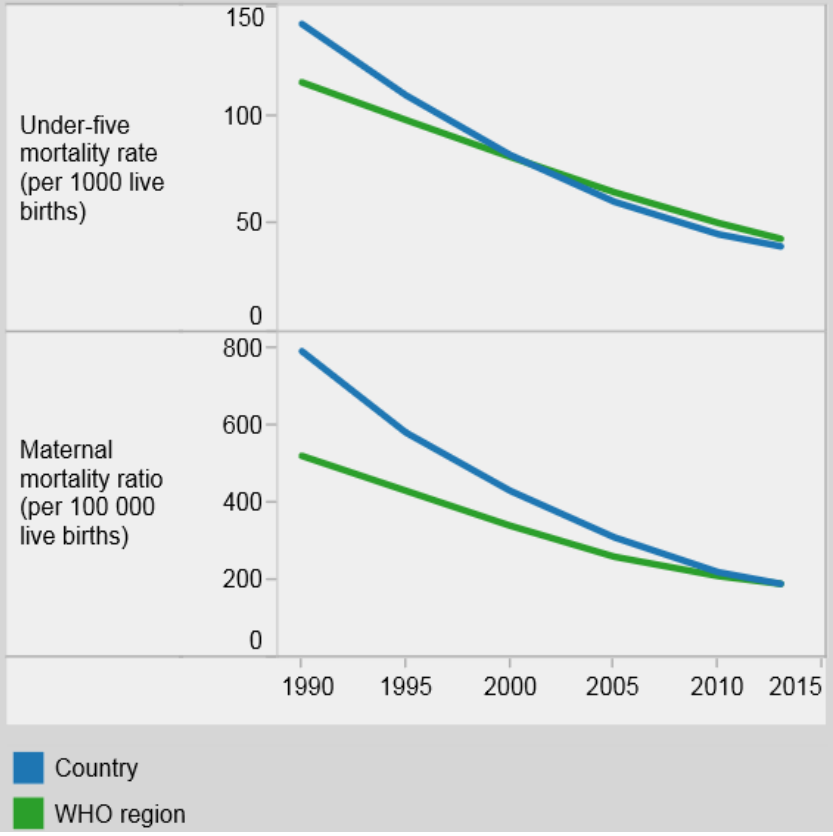
Country Profile: Nepal

- Total Area : 147,181 sq Km
- Total Population : 29million
- Gross National Per-capita income: $2260

Health Indicators

Indicators	Statistics Baseline*	Latest**
Under-five mortality rate (per 1000 live births)	142	40
Maternal mortality ratio (per 100 000 live births)	790	190
Deaths due to HIV/AIDS (per 100 000 population)	4.6	14.8
Deaths due to malaria (per 100 000 population)	0.1	0.1
Deaths due to tuberculosis among HIV-negative people (per 100 000 population)	20	17

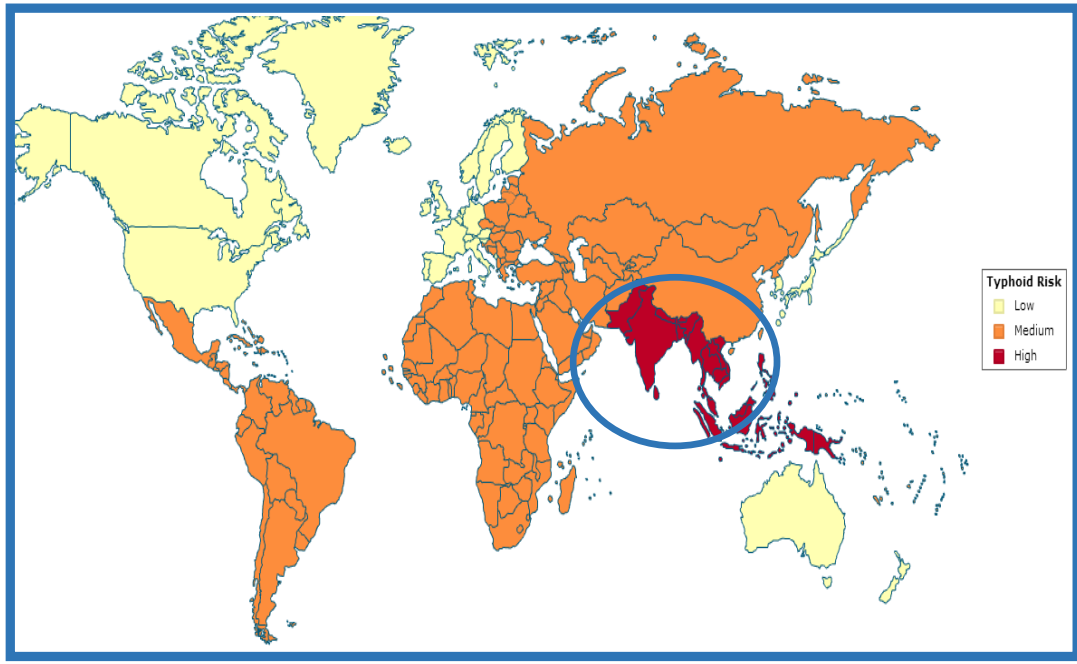
*1990 for under-five mortality and maternal mortality; 2000 for other indicators
**2012 for deaths due to HIV/AIDS and malaria ; 2013 for other indicators

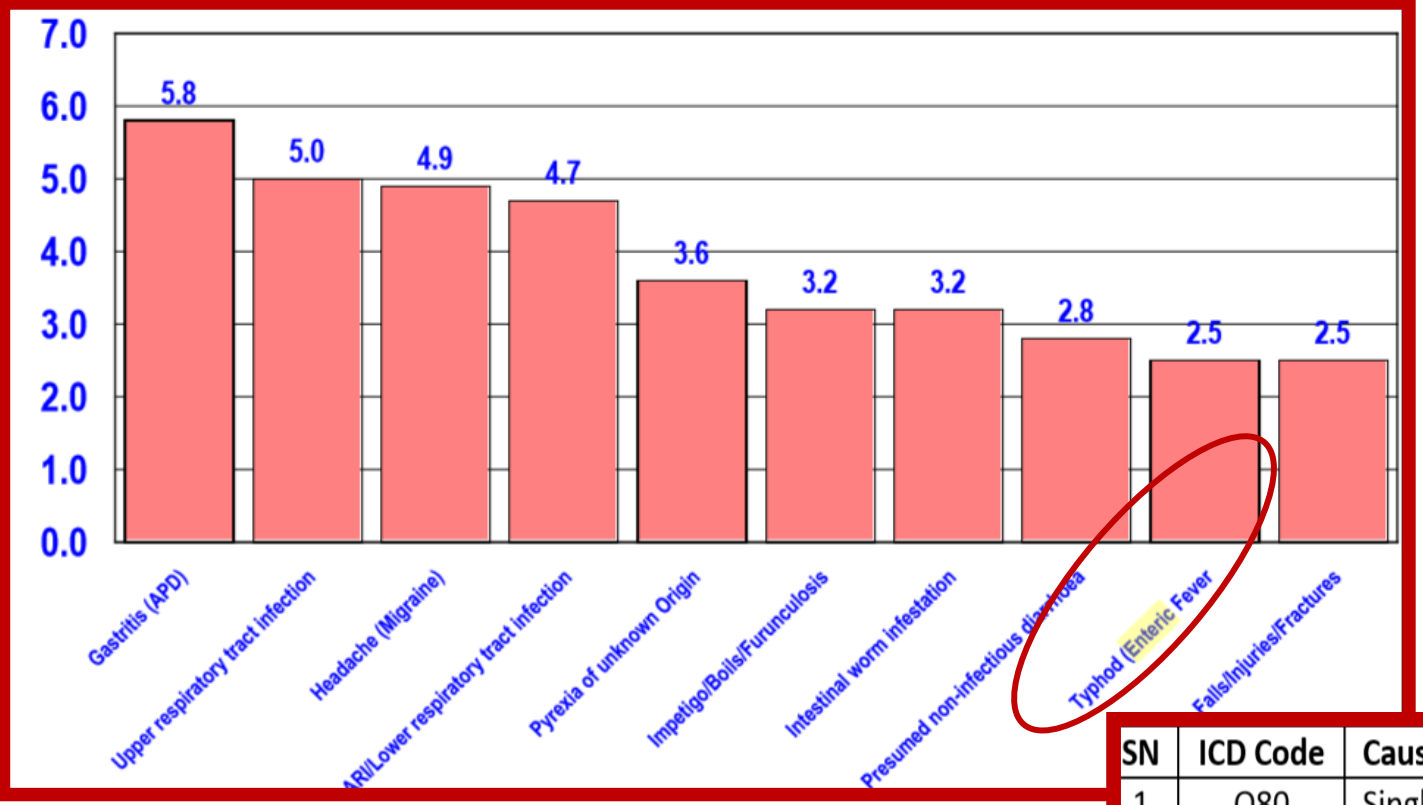


Data Source: WHO Nepal

Typhoid: Disease Burden

- Typhoid fever: a global public health problem
- Around 22 million cases of typhoid fever and 200,000 related deaths occur worldwide/year;
- Additional 6 million cases of paratyphoid fever annually
- Kathmandu, the capital city of Nepal, has previously been coined a typhoid fever capital of the world





Top ten causes for seeking hospital OPD visit in Nepal

Top ten causes for hospitalization in Nepal

SN	ICD Code	Cause of Hospitalization	Patients (N)	Percent
1	O80	Single spontaneous delivery	83,861	28.7
2	A09	Diarrhoea & gastroenteritis of presumed infectious origin	11,008	3.8
3	O82	Single delivery by caesarean section	10,836	3.7
4	J18	Pneumonia, organism unspecified	10,019	3.4
5	A01	Typhoid and paratyphoid fevers	9,422	3.2
6	J44	Other chronic obstructive pulmonary disease	9,382	3.2
7	J22	Unspecified acute lower respiratory infection	8,804	3.0
8	N39	Other disorders of urinary system	8,090	2.8
9	O99	Others maternal diseases classifiable elsewhere but complicating pregnancy, childbirth and the puerpeium	6,060	2.1
10	T14	Injury of Unspecified body region	4,735	1.6
		Others reasons	130,3014	44.5
	Total number of discharge patients		**292,518**	**100**

(Ref: Annual Report, Dept. of Health Services, 2012/2013)

Problem Statement

- Nepal->Access to healthcare is limited.
- Lack of correct diagnosis, inappropriate treatment and management of typhoid infections leads to more severe illness and death.
- Specific antimicrobial therapy shortens the clinical course of typhoid fever and reduces the risk for death.
- Empiric treatment in most parts of the world uses a fluoroquinolone, most often ciprofloxacin.
- Resistance to nalidixic acid/fluoroquinolones is high in the Indian subcontinent including in Nepal.
- National Antibiotic Treatment Guideline, Nepal (2014) recommends Ciprofloxacin (500mg) /Ofloxacin (400mg) (q 12 hrs for 14 days) for empirical treatment of typhoid

Questions the treatment of enteric fever with Ciprofloxacin / Ofloxacin in Nepal ?

Study Setting:

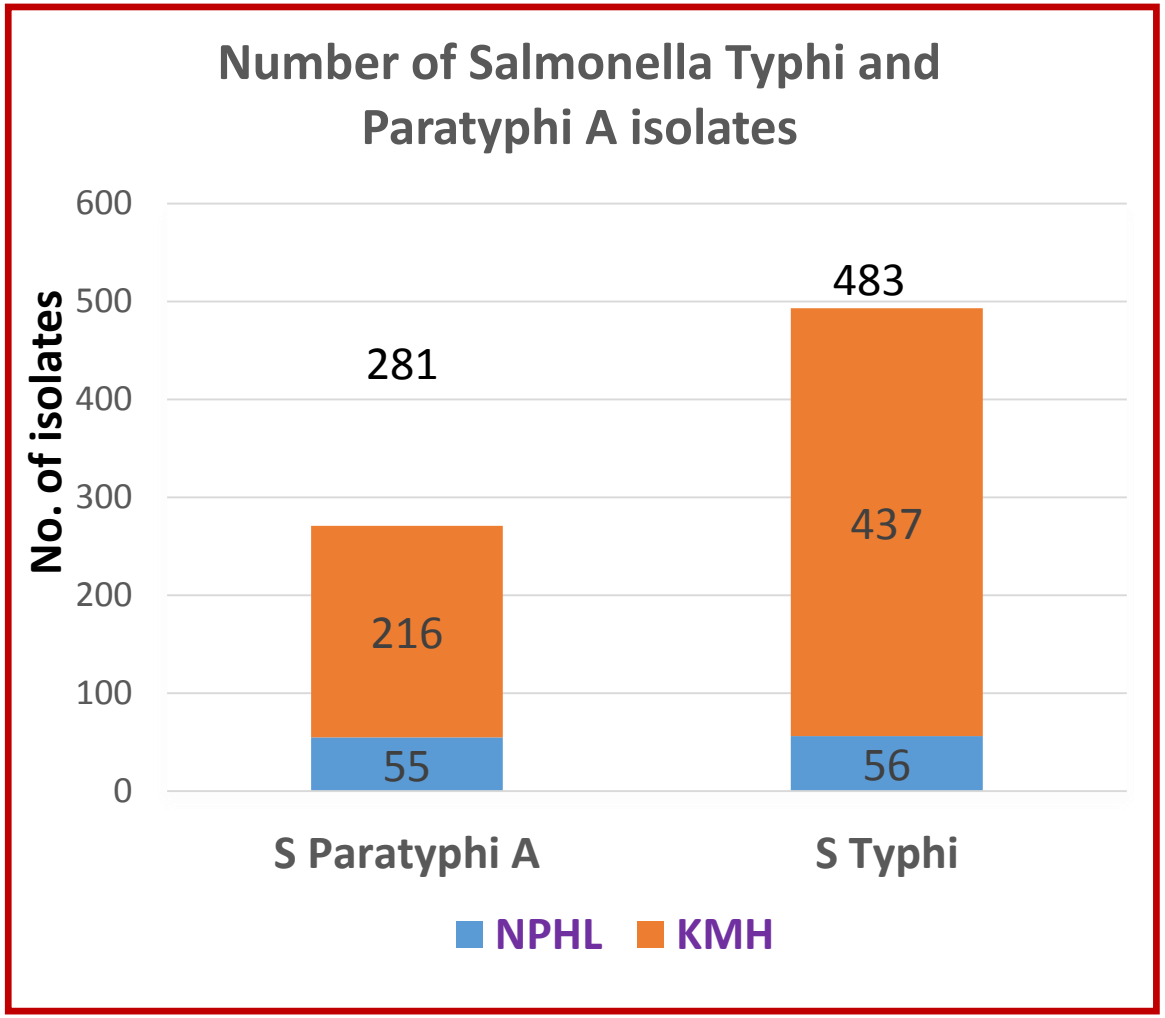
National Public health Laboratory (NPHL) Ministry of Health and Population (MoHP), Nepal.

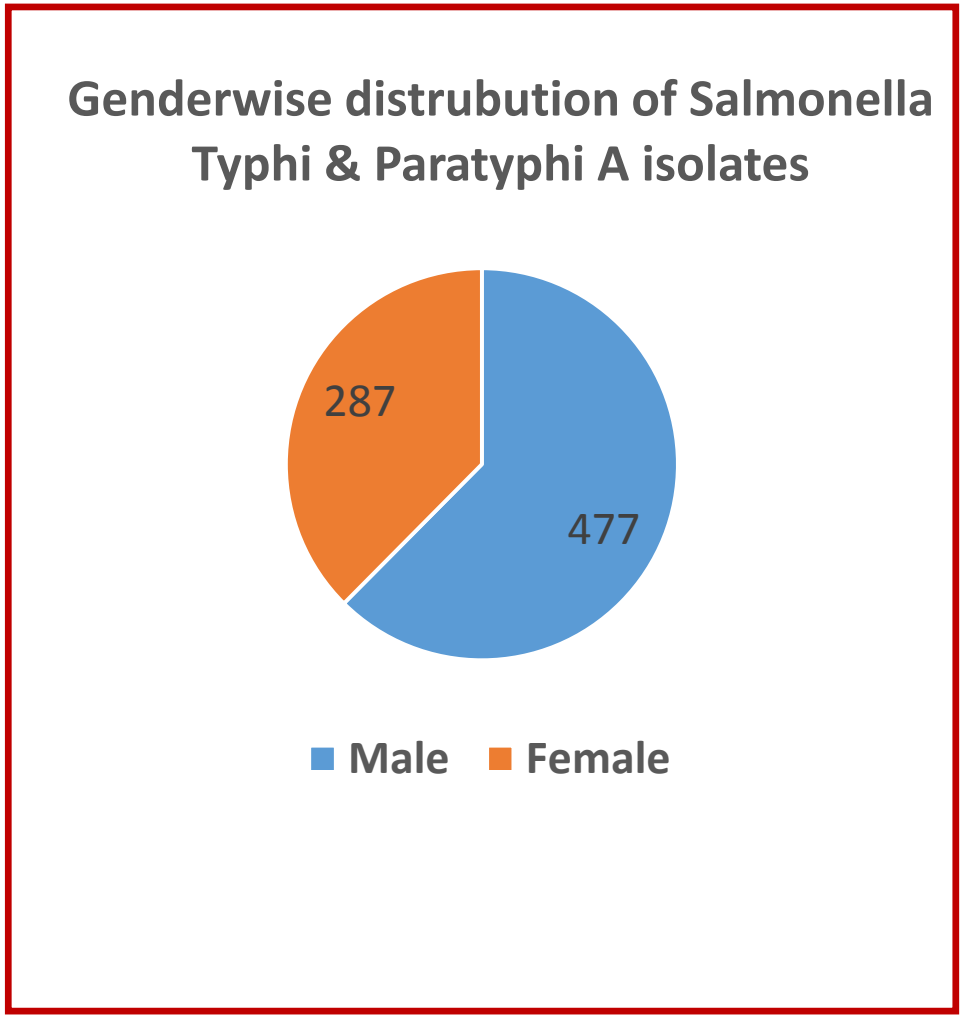
Methods:

- Salmonella Typhi and Salmonella Paratyphi A isolated during 2011 to 2013 at two major hospitals/laboratories in Kathmandu
  - National Public Health Laboratory (NPHL) and Kathmandu Model Hospital (KMH) included in study
- Isolates were tested for susceptibility to Ampicillin (10 mcg), Chloramphenicol (30 mcg), Cotrimoxazole (25 mcg), Ciprofloxacin (5 mcg) and Nalidixic Acid (30 mcg) (Disk diffusion technique at the time of initial isolation)
- Selected (N= 111) CIP intermediate/ resistant isolates further tested for susceptibilities towards Ofloxacin (5 mcg), Levofloxacin (5 mcg), Gatifloxacin (5 mcg), Ceftriaxone (30mcg) and Azithromycin (5 mcg) (MIC and Disk Diffusion)

(* Intermediate Isolates were categorized as Resistant during analysis)

Findings
Total Isolates Reported: 764



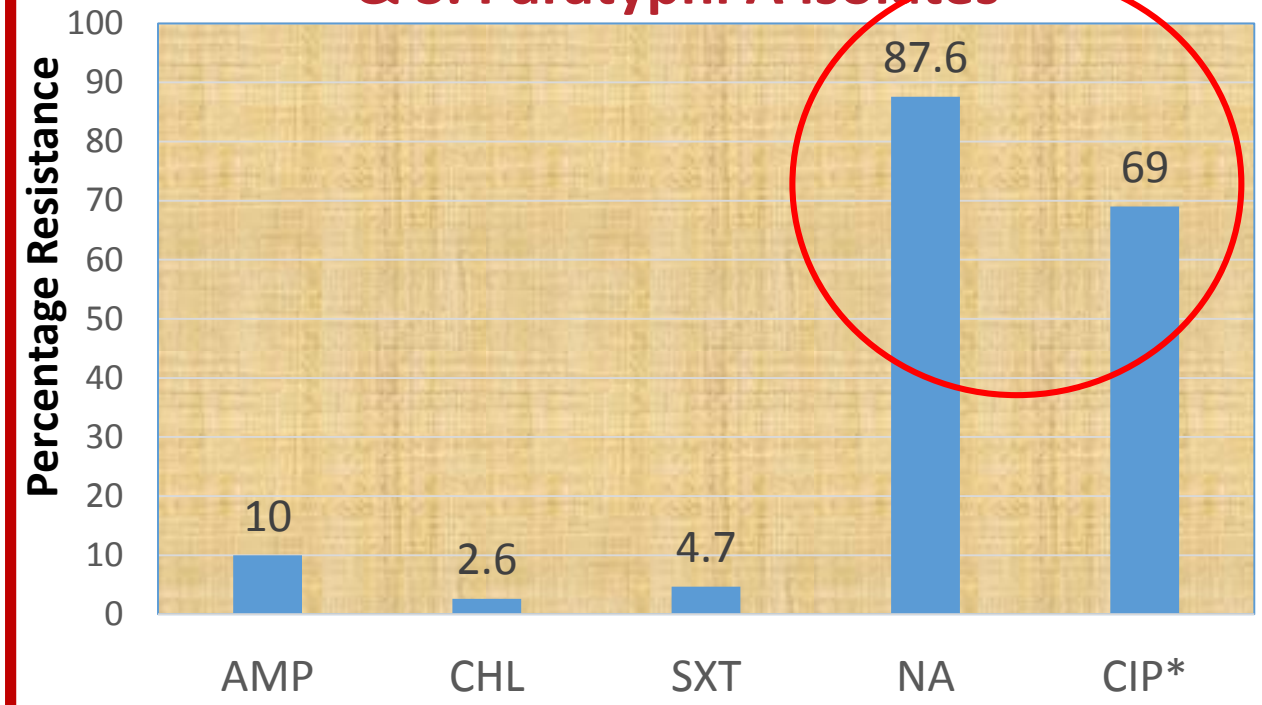


Yearly Distribution of Isolates

Year (total isolates)	Laboratory/ Hospital	Number of isolates
2011** (n= 36)	NPHL (n=36)	S. Typhi (8) S. ParatyphiA (28)
2012 (n=233)	NPHL (n= 36)	S. Typhi (19) S. Paratyphi A(17)
	KMH (n=197)	S. Typhi (n=90) S. Paratyphi A (107)
2013 (n=495)	NPHL (n=39)	S. Typhi (29) S. Paratyphi A (10)
	KMH (n=456)	S. Typhi (347) S. Paratyphi A (109)

* KMH joined the study in the year 2012 only

Antimicrobial Resistance of S Typhi & S. Paratyphi A isolates



AMP: Ampicillin, CHL: Chloramphenicol, SXT: Cotrimoxazole, NA: Nalidixic Acid, CIP: Ciprofloxacin

% of MDR (AMP-CHL-SXT Resistance) among S. Typhi & S. Paratyphi A = 21/764 (2.6 %)

MIC of Ciprofloxacin for NA screening test for 116 S. Typhi and S. Paratyphi A

CIP_MIC (mcg/ml)	S. Typhi (n=93)		S. Paratyphi A (n=23)		Sensitivity pattern for CIP	MIC breakpoint (mcg/ml)
	NAS	NAR	NAS	NAR		
0.008-0.06 (n=4)	4	0	0	0	Susceptible (n=4, 3%)	Sensitive (≤0.06 mcg/ml)
0.125-0.25 (n=15)	0	13	0	2	Intermediate (n=38, 32.7%)	Intermediate (0.12-0.5 mcg/ml)
0.38-0.5 (n=23)	0	9	1	13		
0.75 (n=7)	0	1	0	6	Resistant (n=74, 63.7%)	Resistant (≥1 mcg/ml)
16 (n=15)	0	15	0	0		
24 (n=1)	0	1	0	0		
≥32.0 (n=51)	0	50	0	1		

NAR- Nalidixic acid resistant, NAS- Nalidixic acid sensitive, CIP- Ciprofloxacin

Antimicrobial Susceptibility Pattern of 111 Nalidixic Acid Resistant Salmonella Typhi and Salmonella Paratyphi A

Year	Number (%) Susceptibility to Antimicrobials					
	CIP	OFX	LEV	GAT	AZM*	CRO
	MIC	DD	MIC	DD	DD	DD
2011 (n=10)	0 (100%)	10(100%)	10(100%)	10(100%)	10(100%)	10(100%)
2012 (n=10)	0(100%)	10 (100%)	10(100%)	10(100%)	10(100%)	10(100%)
2013 (n=91)	0 (100%)	57 (63%)	67/91(74%)	89 (98%)	91 (100%)	91 (100%)
Total (111)	0(100%)	77(69.3%)	87(78.3%)	109(98%)	111 (100%)	111(100%)

CIP-Ciprofloxacin, OFX-Ofloxacin, LEV-Levofloxacin, GAT-Gatifloxacin, AZM- Azithromycin, CRO-Ceftriaxone

DD- By Disc Diffusion, MIC- By Minimum Inhibitory Concentration Determination

*** For AZM No CLSI/EUCAST breakpoints defined for S typhi/Paratyphi A**

Yearly Distribution of MIC values of CIP and LEV for 116 Salmonella isolates

Year	CIP -MIC (mcg/ml)	Number of isolates	LEV -MIC (mcg/ml)	Number of isolates
2011 (n= 10)	0.008-0.19	1	0.008-0.25	2
	0.25-0.5	4	0.38-0.5	2
	0.75	5	0.75-1.0	6
	16	0	2-4	0
	24	0	6-8	0
	32	0	12	0
2012 (n=10)	0.008-0.19	1	0.008-0.25	3
	0.25-0.5	8	0.38-0.5	6
	0.75	1	0.75-1.0	1
	16	0	2-4	0
	24	0	6-8	0
	32	0	12	0
2013 (n=96)	0.008-0.19	6	0.008-0.25	15
	0.25-0.5	22	0.38-0.5	6
	0.75	1	0.75-1.0	8
	16	15	2-4	36
	24	1	6-8	30
	32	51	12	1

- ***Recent Trend (2014)***:

- Among the *Salmonella* isolates reported in 2014, 418 (65 %) and 219 (34%) were **S. Typhi** and **S. Paratyphi A** respectively

- Nalidixic acid resistance in S. Paratyphi A *was* 96% and in S. Typhi 91%.

- Resistance to Ciprofloxacin is alarming: *83%* S. Typhi and 88% S. Paratyphi A

- Susceptibility to Ceftriaxone(99%), Cotrimoxazole(98.5%) and Chloramphenicol (98.5%).

Summary

- The increasing fluoroquinolone resistance is alarming and warrants a review of the current therapy & National Treatment Guideline for enteric fever in Nepal

It may soon become necessary in our setting to treat all cases presumptively for fluoroquinolone resistant until laboratory sensitivity reports are obtained

Susceptibility trends suggest that problem of MDR(AMP-CHL-SXT Resistance) is lower compared to FQ resistance in our region: (older agents could still be considered for NA-CIP R strains??)

- New, effective, and affordable regimens are needed to treat these NAR/ CIP-R infections

Treatment Options??

Search for alternative drug for empiric therapy: New fluoroquinolones (Gatifloxacin), Azithromicin and Ceftriaxone showed good in vitro activity against CIP-R strains

Gatifloxacin: **In** vivo efficacy of this agent for treatment of NAR strains reported. However, resistance to this agent may become widespread (Any two of a number of *gyrA* mutations, when added to the *parC* mutation, confer full in vitro resistance to this agent).

Ceftriaxone/ Cefixime: ESBLs in typhoidal Salmonellae poses a new challenge. Susceptibility pattern and MICs for third-generation cephalosporins must be closely monitored in view of its emerging resistance

Azithromycin: Clinical trials have shown it to be effective in the management of uncomplicated typhoid fever though no clinical breakpoints have been defined by CLSI. Laboratory breakpoint needs to be established for monitoring in-vitro resistance.

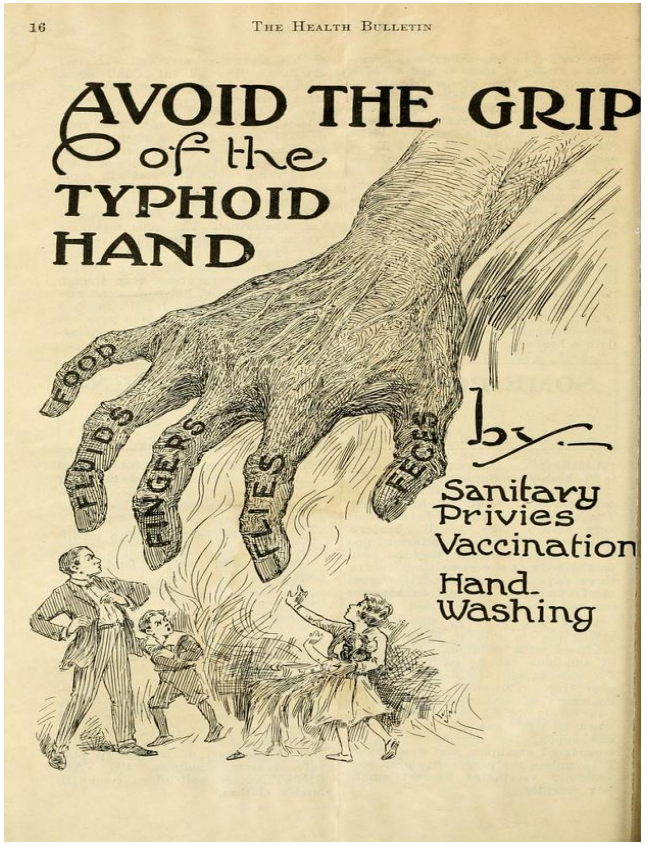
Recommendations

- Use antimicrobial treatment rationally based on local susceptibility data
  - Monitoring of resistance

- Reduce Disease Burden:
  -Infection Control
  -Vaccination

- Genotypic analysis might be useful in formulating strategies to control spread of the organism by appropriate interventions.

THANK YOU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Vaccination
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