

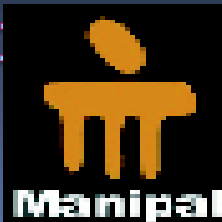
CHANGING TRENDS IN ANTIBIOGRAMS
OF SALMONELLA ENTERICA IN
PEDIATRIC POPULATION-A HOSPITAL
BASED STUDY

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BACKGROUND

Fig. 2. Geographical distribution of typhoid fever

BURDEN OF ENTERIC FEVER



Global burden as estimated in year 2000

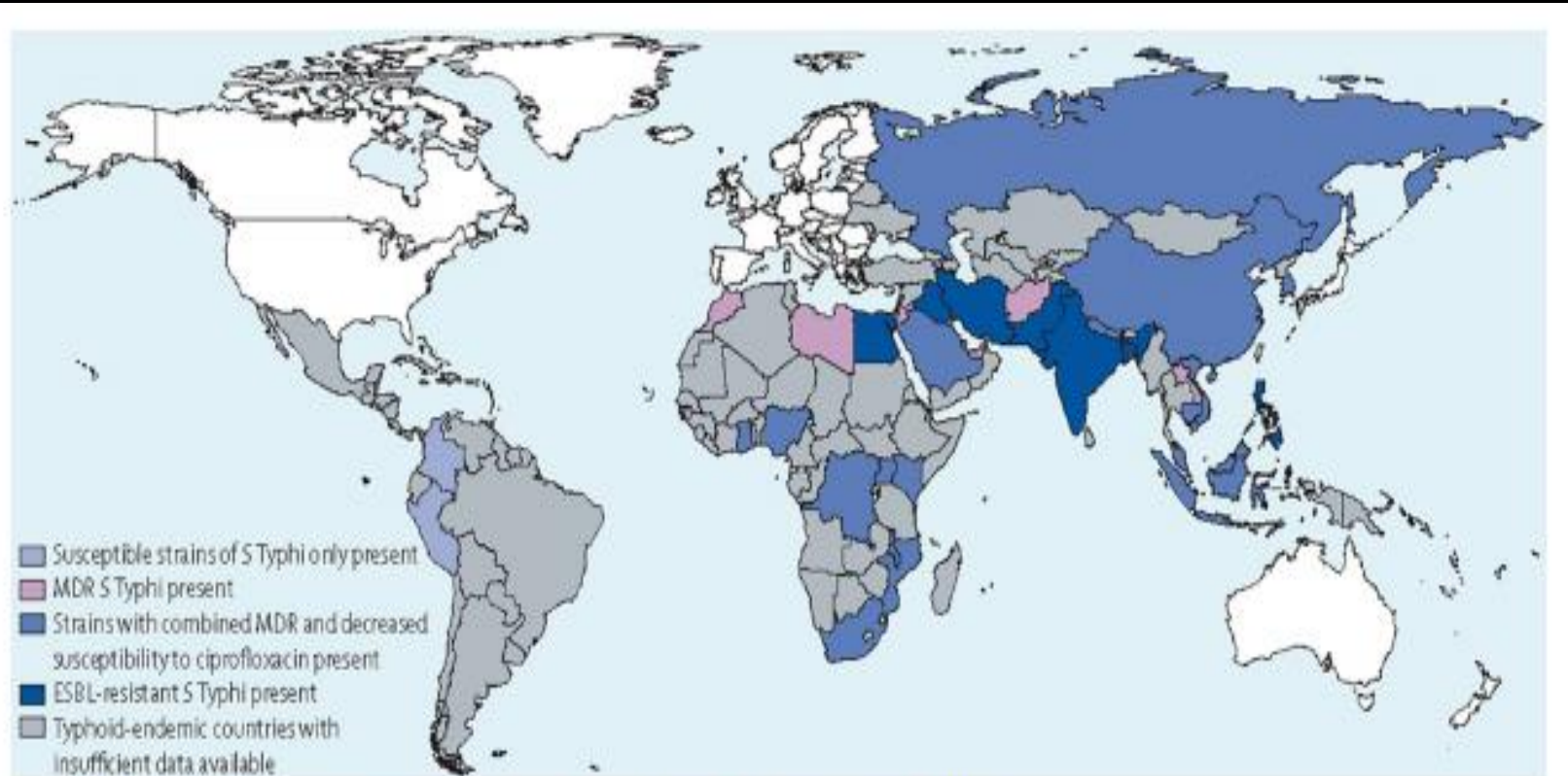
Typhoid fever – 21.65 million cases/yr

Paratyphoid fever – 5.4 million cases/yr

Asia-10.1 million/yr

Deaths-2,16,510/yr

WORLDWIDE DISTRIBUTION OF ANTIMICROBIAL DRUG RESISTANCE IN *SALMONELLA enterica* serovar Typhi



Worldwide distribution of antimicrobial drug resistance in *Salmonella enterica* serovar Typhi.

Crump JA, Sjölund-Karlsson M, Gordon MA, Parry CM. 15 July 2015. Epidemiology, clinical presentation, laboratory diagnosis, antimicrobial resistance, and antimicrobial management of invasive *Salmonella* infections. *Clin Microbiol Rev* doi:10.1128/CMR.00002-15.

- Since its introduction in 1948, chloramphenicol has been the treatment of choice for typhoid fever
- Plasmid mediated chloramphenicol resistance emerged in *S.typhi* in the early 1970s
- Ampicillin and co-trimoxazole were found to be effective alternative drugs until late 1980s when they became resistant due to the rampant use.

V Lakshmi. CHANGING TRENDS IN THE ANTIBIOGRAMS OF SALMONELLA ISOLATES AT A TERTIARY CARE HOSPITAL IN HYDERABAD



- ❖ **Multidrug resistance**, defined as resistance to the three first-line classes of antimicrobial agents (chloramphenicol, ampicillin, and trimethoprim / sulphamethoxazole)
- ❖ Global burden of MDR enteric fever (Majority – South Asia)
 - 50% to 80% of all *S. Typhi* isolates
 - 25% of MDR *S. Paratyphi*

Farah Naz Qamar. A three-year review of antimicrobial resistance of Salmonella enterica serovars Typhi and Paratyphi A in Pakistan. J Infect Dev Ctries 2014; 8(8):981-986



- ❖ Fluoroquinolones became the first-line drug since 1980 after emergence of MDR strains.

However, from 2000 onwards, there has been a dramatic rise in fluoroquinolone-resistant *S. Typhi* isolates

- ❖ Mortality and complications are higher in MDR strains of *S.typhi* and paratyphi and fluoroquinolone resistant cases.
- ❖ Emergence of MDR enteric fever has necessitated use of newer antibiotics

F.N. Qamar. et al. A three-year review of antimicrobial resistance of Salmonella enterica serovars Typhi and Paratyphi A in Pakistan. J Infect Dev Ctries 2014; 8(8):981-986

F.N. Qamar et al. .Challenges in measuring complications and deaths due to invasive salmonella infections. Vaccine 33 (2015) C16–C20



- High levels of multidrug and fluoroquinolone resistance have made cephalosporins the drug of choice for empiric therapy in South Asia
- Since the 1990s, azithromycin has been showing good results and is a promising alternative to fluoroquinolones and cephalosporins
- Azithromycin resistant *S. Typhi* and *S. Paratyphi A* have been reported from Delhi (MIC 24 mg/ml), Pakistan (MIC 64 mg/ml) and Cambodia (MIC 96 mg/ml), which is a threat.
- Recent studies have shown a shifting of susceptibility to conventional drugs like chloramphenicol, ampicillin and cotrimoxazole

Farah Naz Qamar. A three-year review of antimicrobial resistance of *Salmonella enterica* serovars *Typhi* and *Paratyphi A* in Pakistan. *J Infect Dev Ctries* 2014; 8(8):981-986

Dutta S, et al. (2014) Antimicrobial Resistance, Virulence Profiles and Molecular Subtypes of *Salmonella enterica* Serovars *Typhi* and *Paratyphi A* Blood Isolates from Kolkata, India during 2009-2013. *PLoS ONE* 9(8): e10134



Aims & Objectives

- To analyze the antibiotic sensitivity pattern of culture positive enteric fever.
- To evaluate the prevalence, changing trends in antibiotic resistance and demographic profile

Materials and Methods

- Type of study- Retrospective study of case records of 826 children
- Age group - 0-18 years
- Place of study- Manipal hospital, Bangalore, India
- Study period- November 2008 to June 2016.
- Statistical method- Descriptive univariate analysis

Inclusion criteria

- ❖ Presence of clinical signs & symptoms compatible with enteric fever
- ❖ Isolation of *S. typhi* or *S. paratyphi* A, B, or C from blood.

Exclusion criteria

- ❖ Diagnosis based only on clinical and serologic grounds

- **Blood c/s** → Brain heart infusion broth → BacT/Alert 3D system
→ +ve → 1) gram stain
2) subculture in blood agar and MacConkey agar (NLF colonies)

- **Identification-**

Biochemical tests (negative for Indole, Urease, Oxidase, Citrate and positive for Motility and gives an alkaline slant/acid but no gas on triple sugar iron agar) or

Vitek method

KIRBY BAUER METHOD

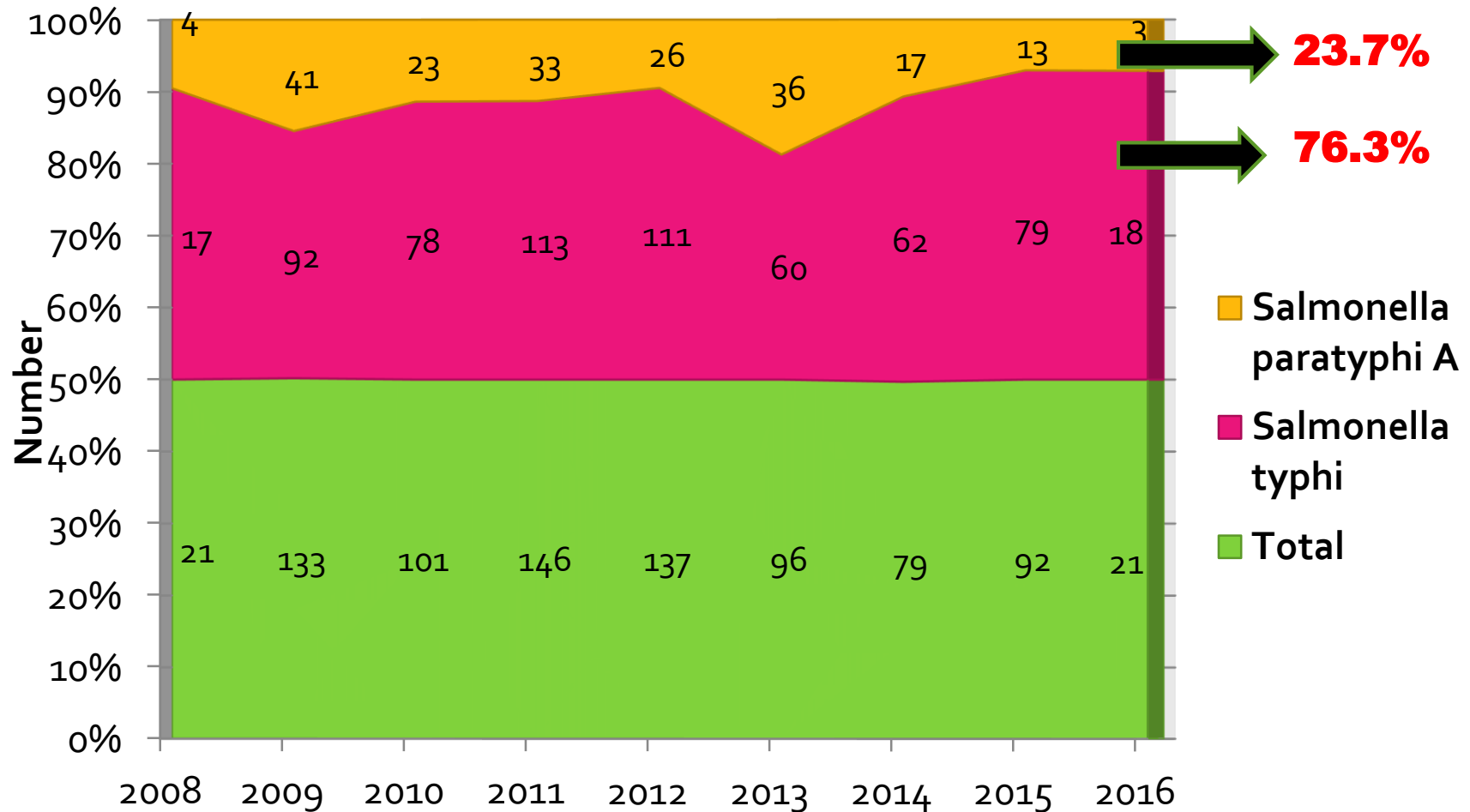
- ❖ Clinical laboratory standards institute reference-M100S 26th edition Tables

Indicators	Ampi	Cotrimoxazole	Chloramphenicol	Ciprofloxacin	Nalidixic acid	Ceftriaxone
Inhibition zone dia (mm)	≤ 13	≤ 10	≤ 12	≤ 20	≤ 13	≤ 19

- ❖ BSAC guidelines
 - MIC of Azithromycin $\geq 16\text{mm}$ was considered resistant (now zone dia $\geq 12\text{mm}$ - CLSI)

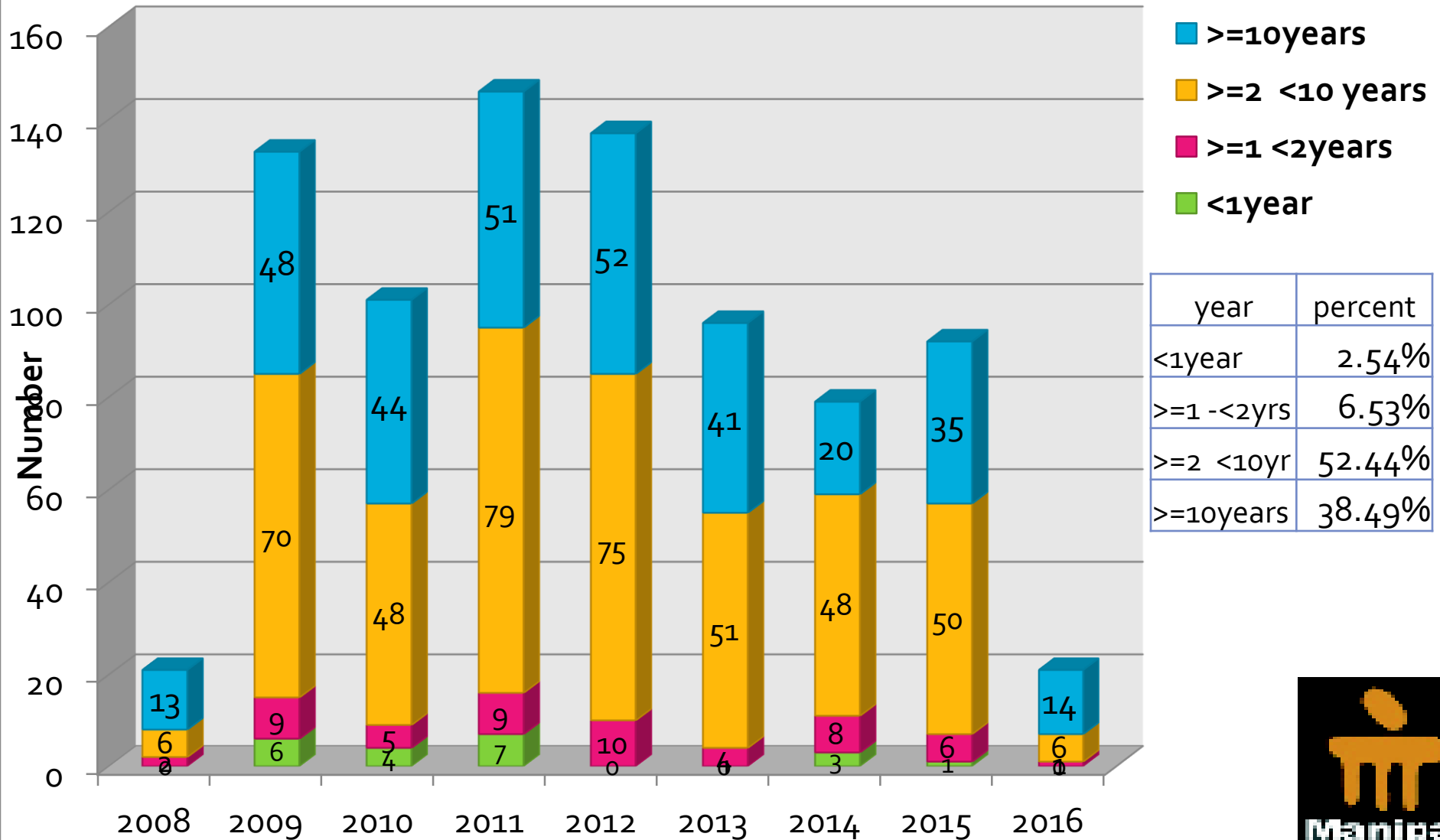
RESULTS

BLOOD CULTURE



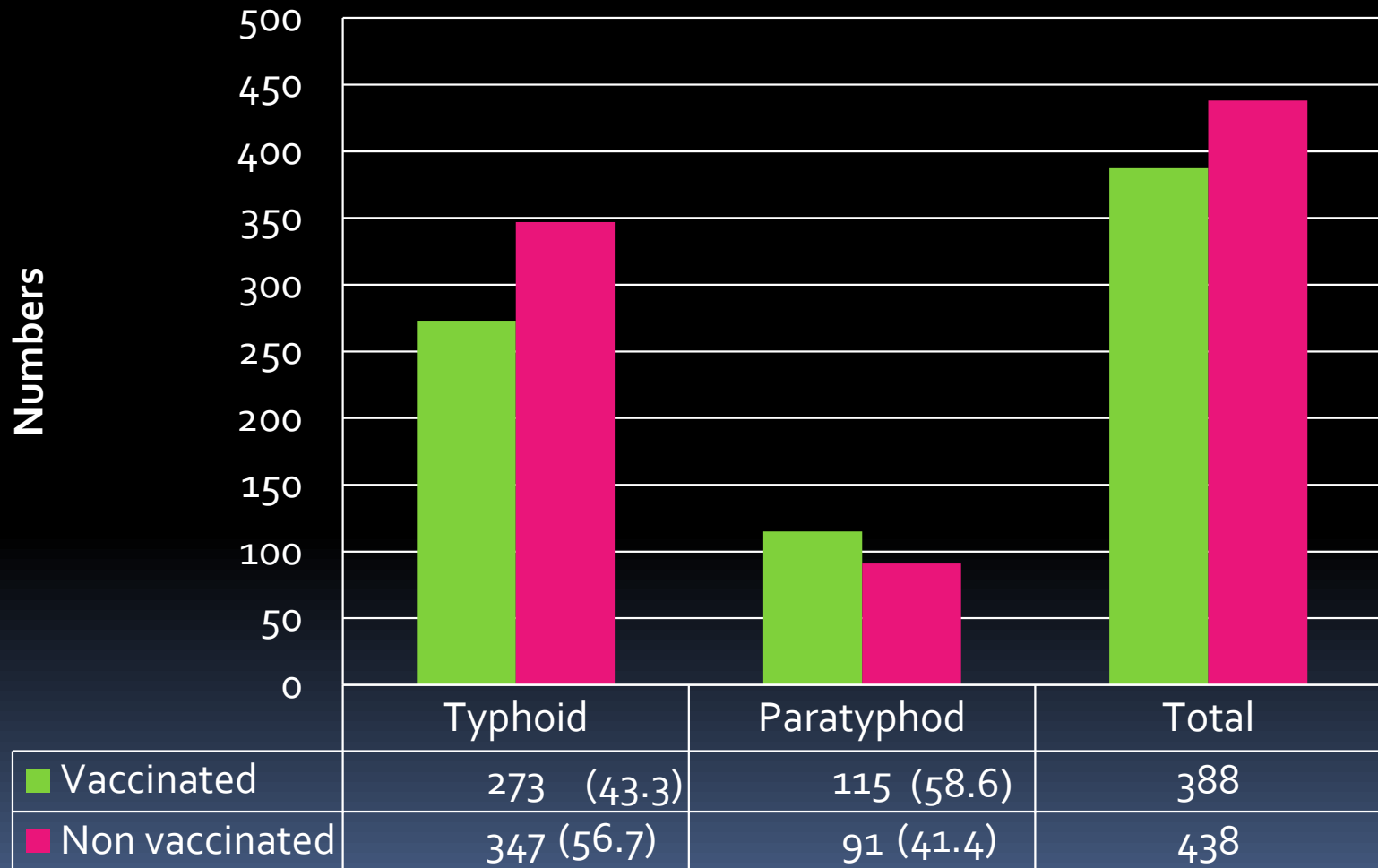
DEMOGRAPHIC PROFILE

Age wise distribution



Vaccination Status(N=826)

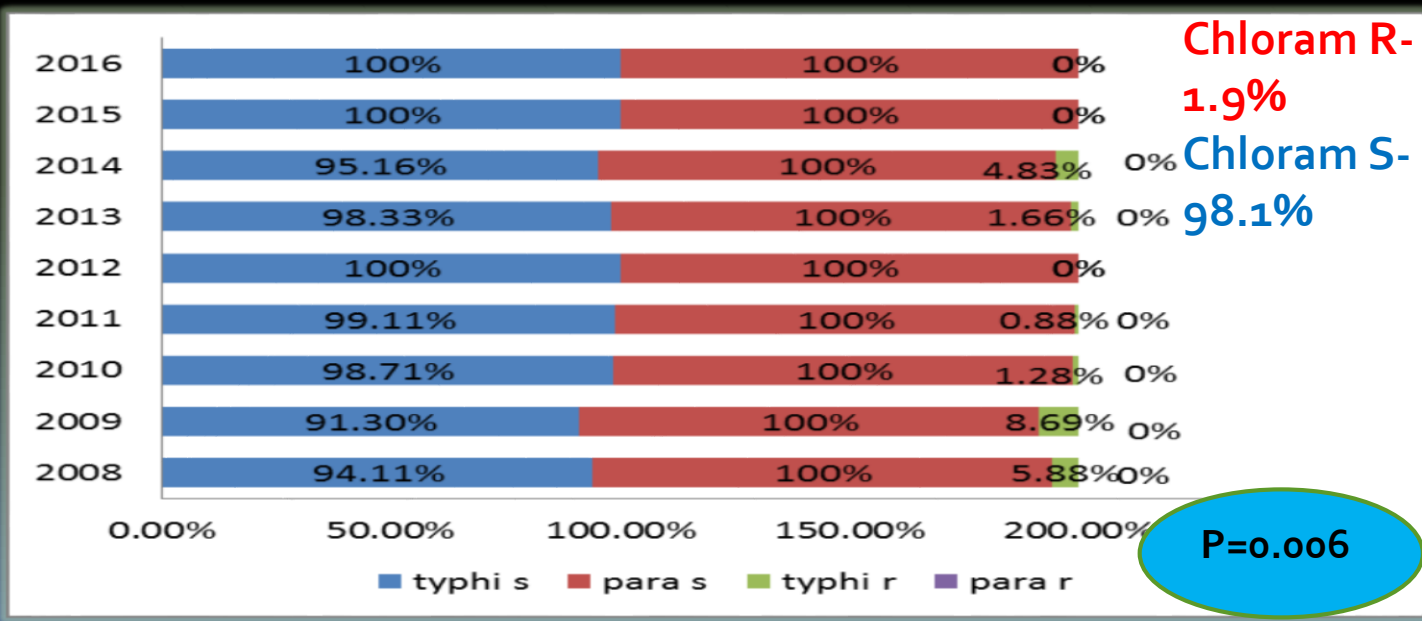
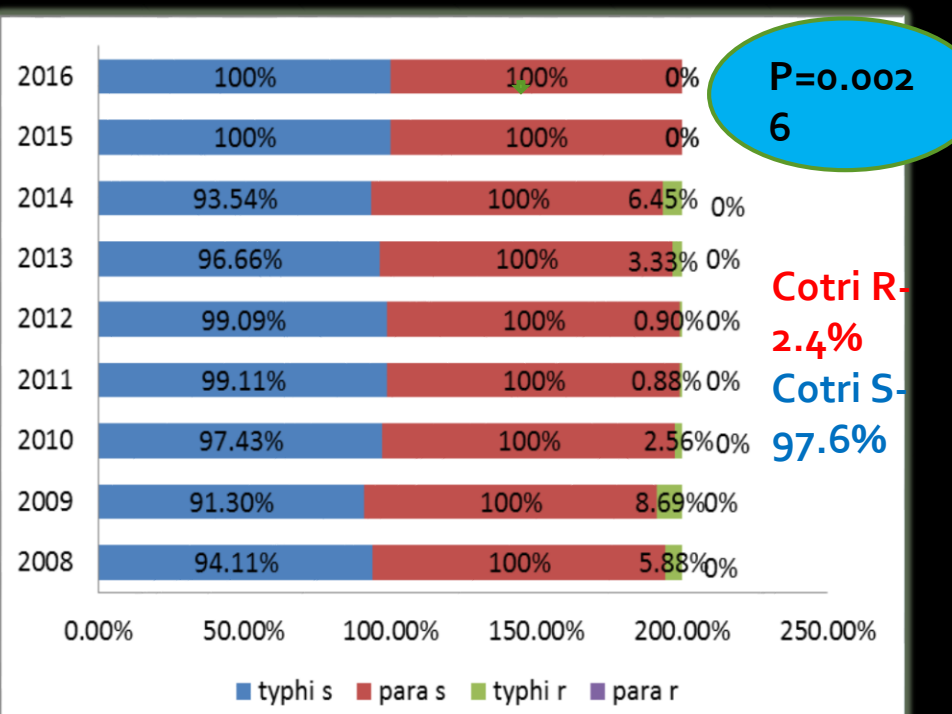
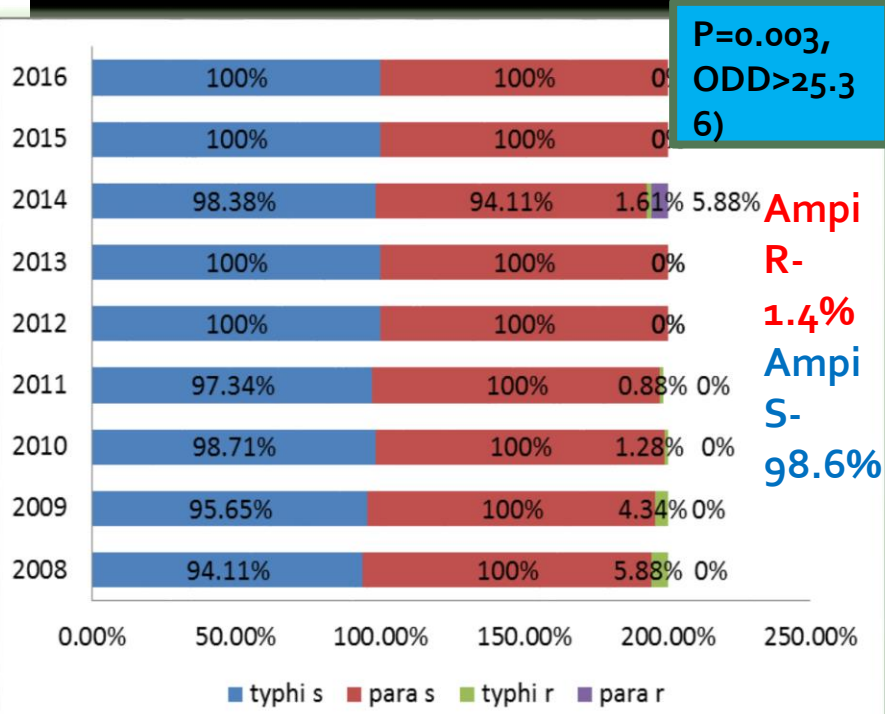
Vaccination status



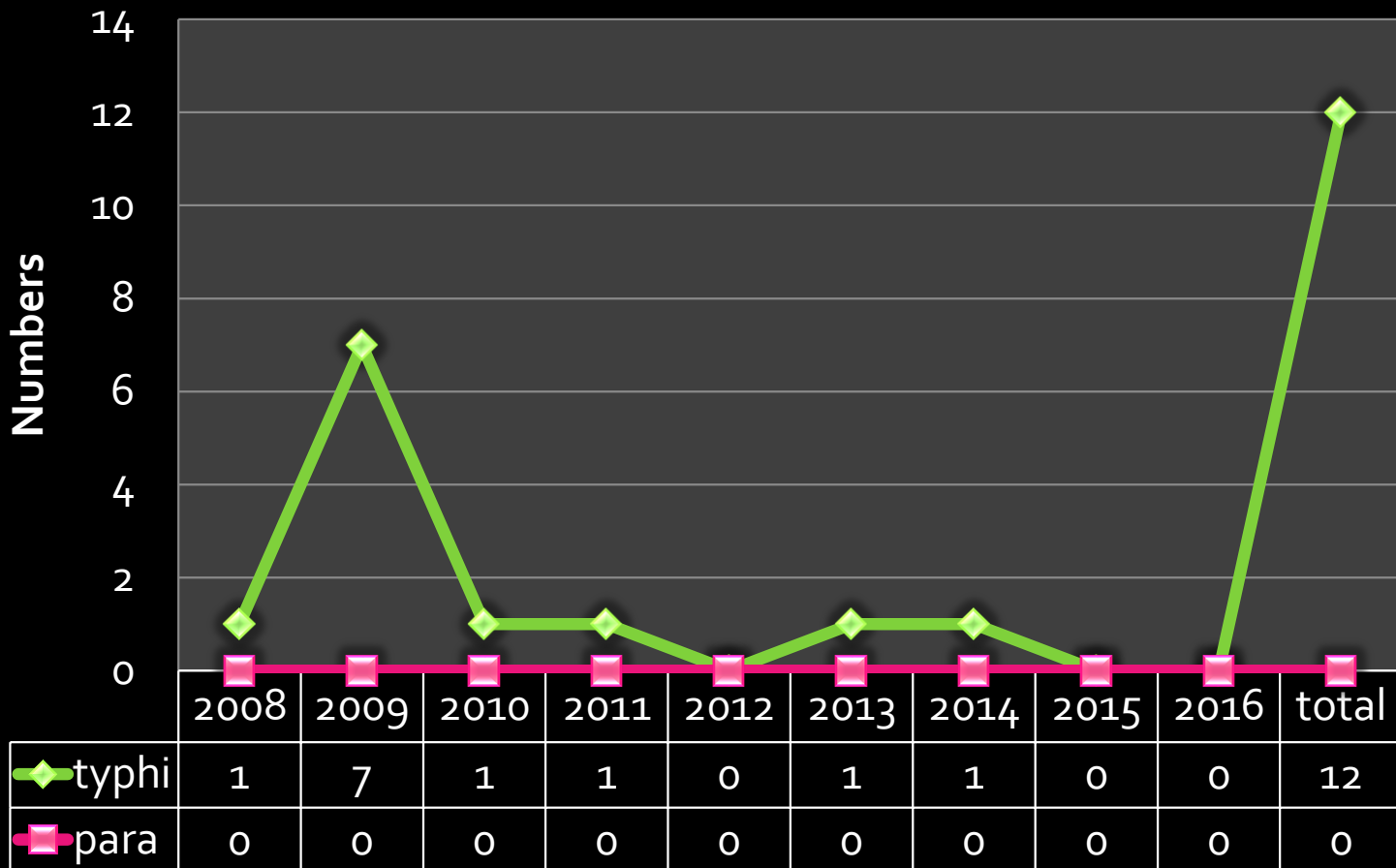
Sensitivity pattern

Year	Isolate	Amp	Chlor	Cotri	Ciplox	Nalid	Ceftri	Azithr
2008	Typhi	16 (94%)	16 (94%)	16 (94%)	17 (100%)	5 (29%)	17 (100%)	17 (100%)
	Para	4 (100%)	4 (100%)	4 (100%)	4 (100%)	0 (0%)	4 (100%)	4 (100%)
2009	Typhi	88 (95.65%)	84 (91.3%)	84 (91.3%)	91 (98.9%)	9 (9.78%)	92 (100%)	91 (98.9%)
	Para	41 (100%)	41 (100%)	41 (100%)	41 (100%)	3 (7.31%)	41 (100%)	41 (100%)
2010	Typhi	77 (98.71%)	77 (98.71%)	76 (97.43%)	74 (94.8%)	8 (10.25%)	78 (100%)	77 (98.7%)
	Para	23 (100%)	23 (100%)	23 (100%)	23 (100%)	1 (4.34%)	23 (100%)	23 (100%)
2011	Typhi	110 (97.34%)	112 (99.11%)	112 (99.11%)	108 (95.5%)	7 (6.19%)	113 (100%)	112 (99.11%)
	Para	33 (100%)	33 (100%)	33 (100%)	33 (100%)	1 (3.03%)	33 (100%)	33 (100%)

Year	Isolate	Amp	Chlor	Cotri	Ciplox	Nalidi	Ceftri	Azithr
2012	Typhi	111 (100%)	111 (100%)	110 (99%)	110 (99%)	4 (3.6%)	111 (100%)	111 (100%)
	Para	26 (100%)	26 (100%)	26 (100%)	26 (100%)	1 (3.84%)	26 (100%)	26 (100%)
2013	Typhi	60 (100%)	59 (98.33%)	58 (96.66%)	52 (86.6%)	1 (1.66%)	60 (100%)	60 (100%)
	Para	36 (100%)	36 (100%)	36 (100%)	0 (0%)	1 (2.77%)	36 (100%)	36 (100%)
2014	Typhi	61 (93.3%)	59 (95.1%)	58 (93.5%)	55 (88.7%)	12 (19.3%)	62 (100%)	62 (100%)
	Para	16 (94.1%)	17 (100%)	17 (100%)	15 (88.2%)	0 (0%)	17 (100%)	17 (100%)
2015	Typhi	79 (100%)	79 (100%)	79 (100%)	74 (93.6%)	7 (8.8%)	79 (100%)	79 (100%)
	Para	13 (100%)	13 (100%)	13 (100%)	13 (100%)	0 (0%)	13 (100%)	13 (100%)
2016	Typhi	18 (100%)	18 (100%)	18 (100%)	15 (83.3%)	6 (33.3%)	18 (100%)	18 (100%)
	Para	3 (100%)	3 (100%)	3 (100%)	3 (100%)	0 (0%)	3 (100%)	3 (100%)

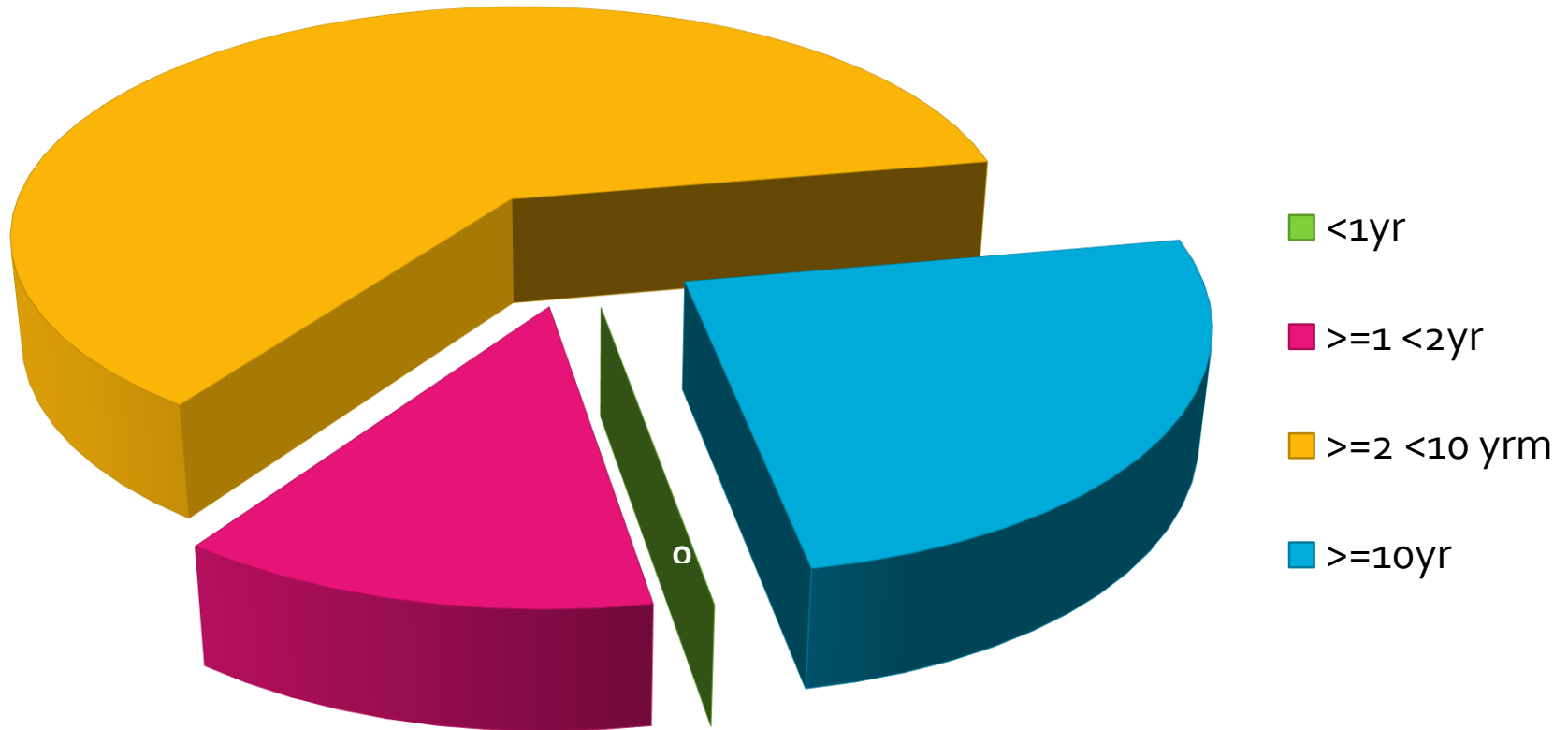


MDR TYPHI



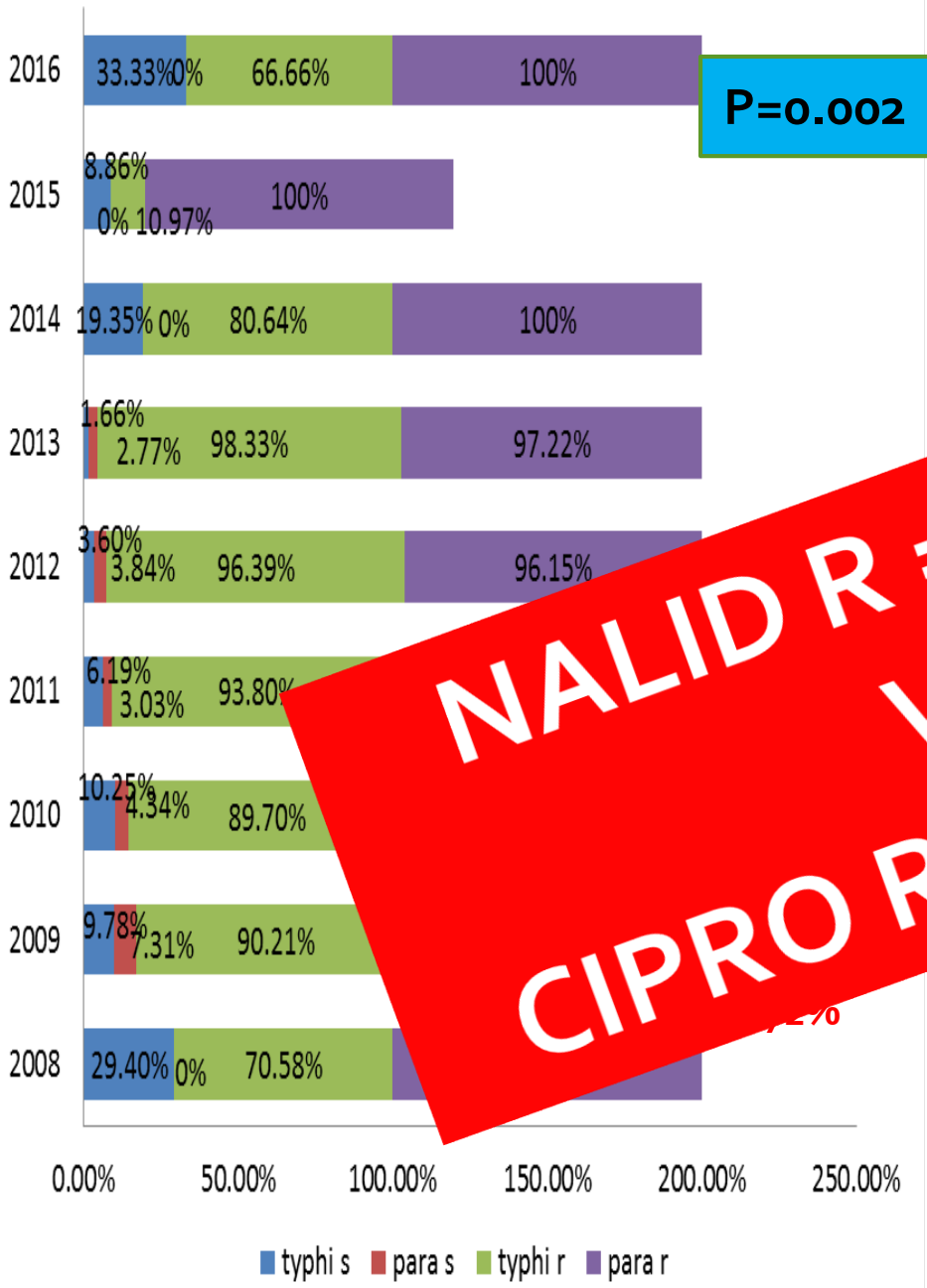
MDR	MDR Typhi	MDR para
12 (1.45%)	12 (1.9%)	0

Age distribution of MDR

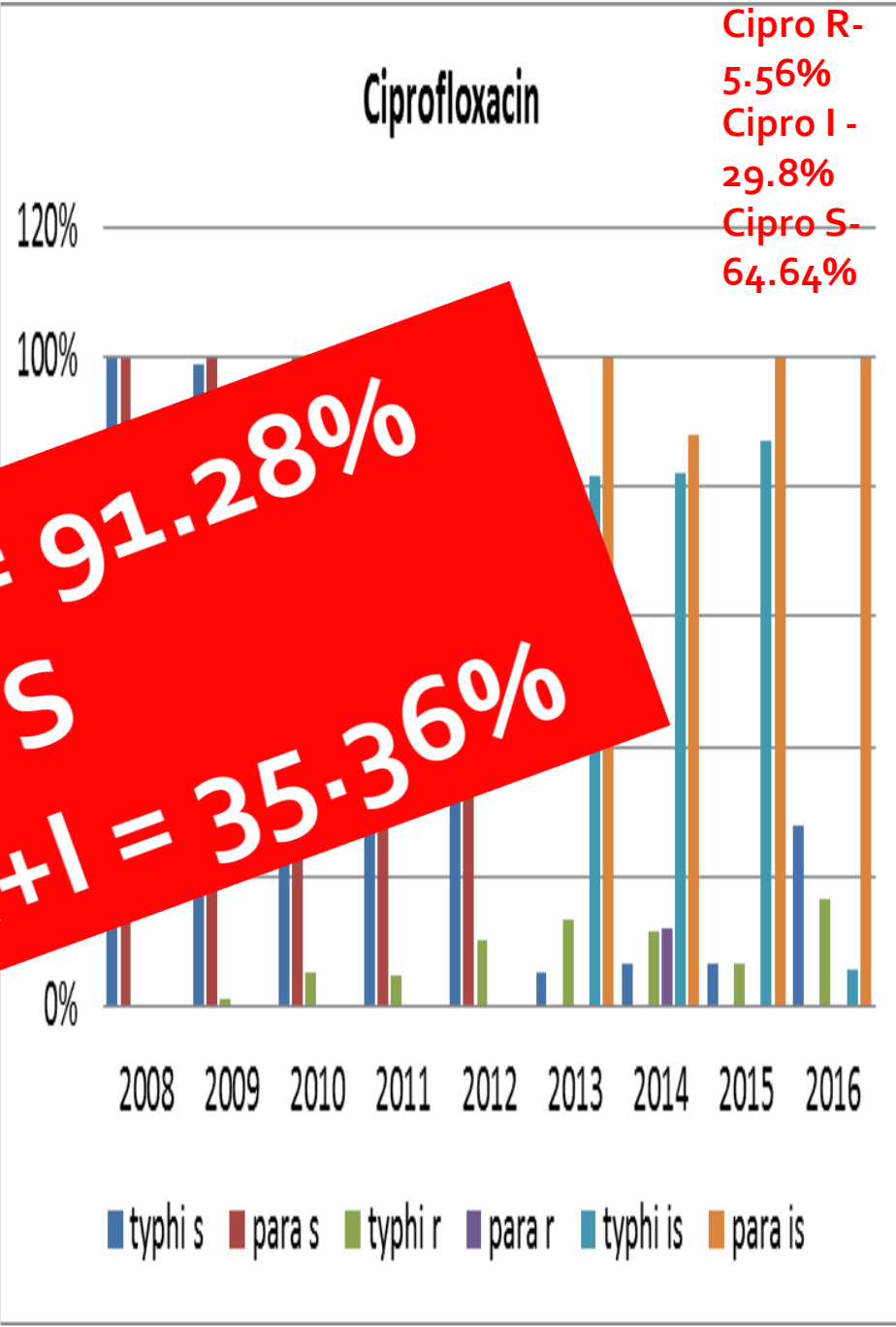


Age	%
<1yr	0
>=1 <2yr	12.5
>=2 <10 yr	62.5
>=10yr	25

SECOND LINE DRUGS



NALID R = 91.28%
VS
CIPRO R+I = 35.36%



Antibiotic of choice

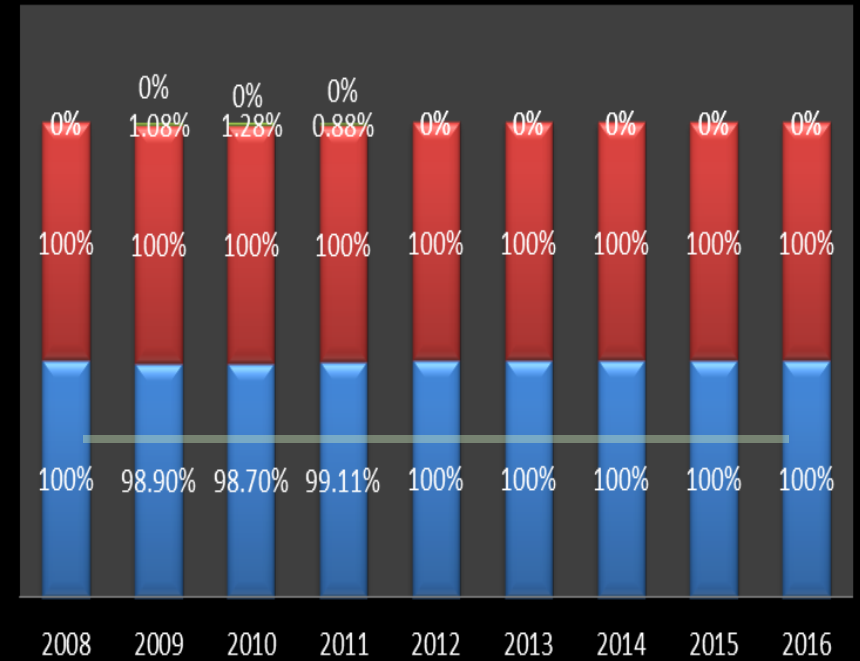
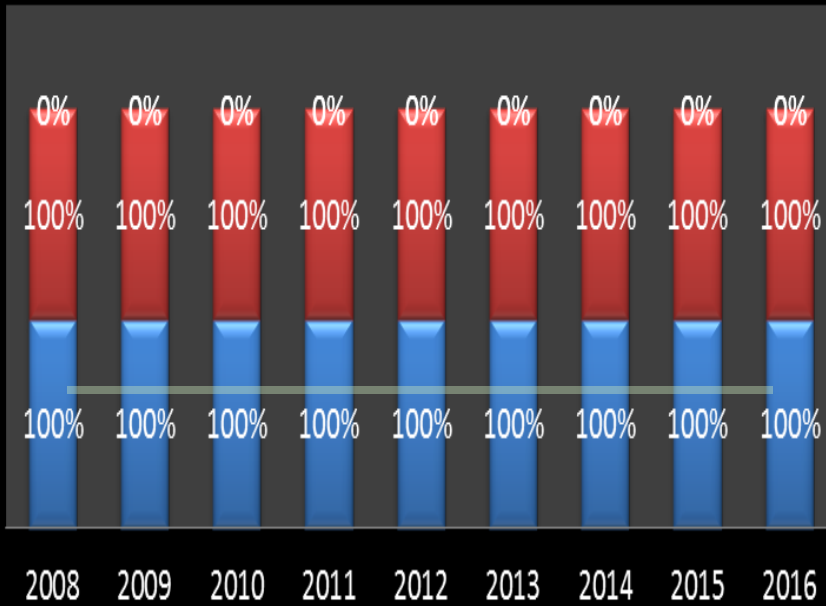
Ceftriaxone



Azithromycin

■ typhi s ■ para s ■ typhi r ■ para r

■ typhi s ■ para s ■ typhi r ■ para r



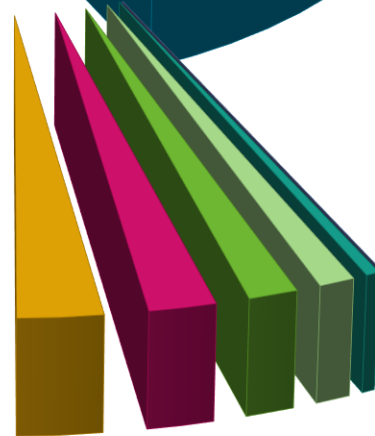
year	2008	2009	2010	2011	2012	2013	2014	2015	2016	total	%
azithro resist	0	1	1	1	0	0	0	0	0	3	0.36%

DISTRIBUTION OF ANTIBIOTIC RESISTANCE

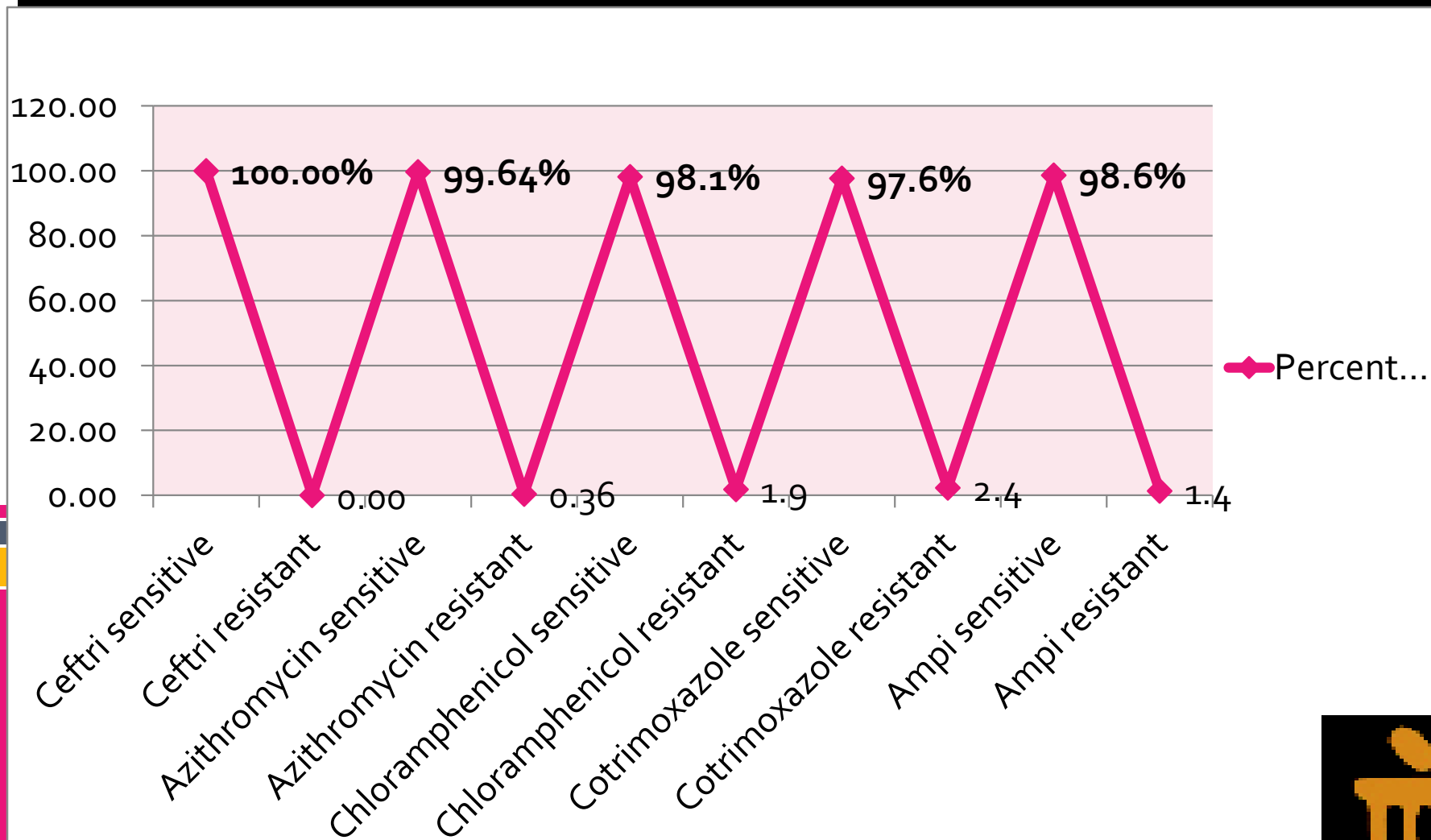


- Ampi
- Chloram
- Cotrimox
- Nalidix
- Ceftri
- Azithro
- MDR

Ampi	1.4%
Chloram	1.9%
Cotri	2.4%
Nalidix	91.2%
Ceftri	0%
Azithro	0.36%
MDR	1.45%



Pooled Percent sensitivity



DISCUSSION

PREVALENCE

- Prevalence of MDR typhoid is 1.45% when compared to previous study done in same geographical area, which showed resistance of 95% in the year 1991-92.
- MDR strains seen only among S.typhi
- Rise in enteric fever caused by Paratyphi A (23.7%)

ANTIBIOTIC SUSCEPTIBILITY

Nalidixic acid resistance

Correlation with ciprofloxacin resistance and intermediate sensitivity (high MIC) was poor.



Ceftriaxone remains 100% sensitive.

Azithromycin still remains a viable alternative to ceftriaxone in the treatment of most fluoroquinolone-resistant strains of *S. typhi*

Comparison of results

Country	year	Serovar	No of isolates	Am p	Chlo	Sxt	Cip	Nal	Cef	Azi	MDR
Kolkata	2009-2013	typhi/para	102 (77/25)	18.2/0	22.1/0	23.4/0	19.5/20	98.7/96	0/0	0/28	18.2/0
India	2010-2012	Typhi/para	266/77	13/3	10/0	5/0	35/49	-	-	-	3/0
Pakistan	2009-2011	Typhi/para	2576/1726	66/2	67/3	67/3	0/0	-	-	-	66/2
Iraq	2002-2007	typhi	59	88	86	-	17	92	0	-	83
Egypt	2002-2007	typhi	654	15	15	-	<1	2	0	-	14
Uganda	2011	typhi	18	83	83	83	0	-	-	-	83
Present study	2008-2016	typhi/para	826 (630/196)	1.6/0.5	2.4/0	3.01/0	6.9/1.0	90.6/96.4	0/0	0.47/0	1.9/0

CONCLUSION

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- The incidence of MDR typhoid has drastically reduced over years
 - The sensitivity to 1st line drugs has come back
 - S.typhi and S.paratyphi still remain fully sensitive to ceftriaxone and azithromycin

- Ceftriaxone should be reserved for
 - MDR typhoid cases
 - non responsiveness to first line drugs
- Azithromycin has to be used as the last resort-as resistant strains have started to emerge
- Indiscriminate use of drugs leading to drug resistance has to be curbed.

It is necessary to perform regular surveys of local antibiogram patterns

Reemergence of sensitivity to first line drugs is a boon to the developing countries-


- cost effective
- Can be given orally
- Increases compliance

.



Better surrogate markers like pefloxacin can be used for assessing fluoroquinolones resistance*

Development of bivalent and conjugate vaccines is a high priority




Vaccination for children including <2 yrs has to be strengthened

**Balaji Veeraraghavan et al. Pefloxacin as a Surrogate Marker for Fluoroquinolone Susceptibility for Salmonella typhi: Problems and Prospects. Journal of Clinical and Diagnostic Research. 2016 Aug, Vol-10(8): DL01-DL02*



LIMITATIONS OF THE STUDY

- Hospital based study, single centre study
 - Correlation with clinical course and severity
 - Genetic studies not done
- 



THANK YOU