

Antimicrobial Resistance in Typhoid: implications for policy & immunization strategies

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Amruta Radhakrishnan, Farah Qamar, Jeffrey
Stanaway, Christopher Parry**



Outline

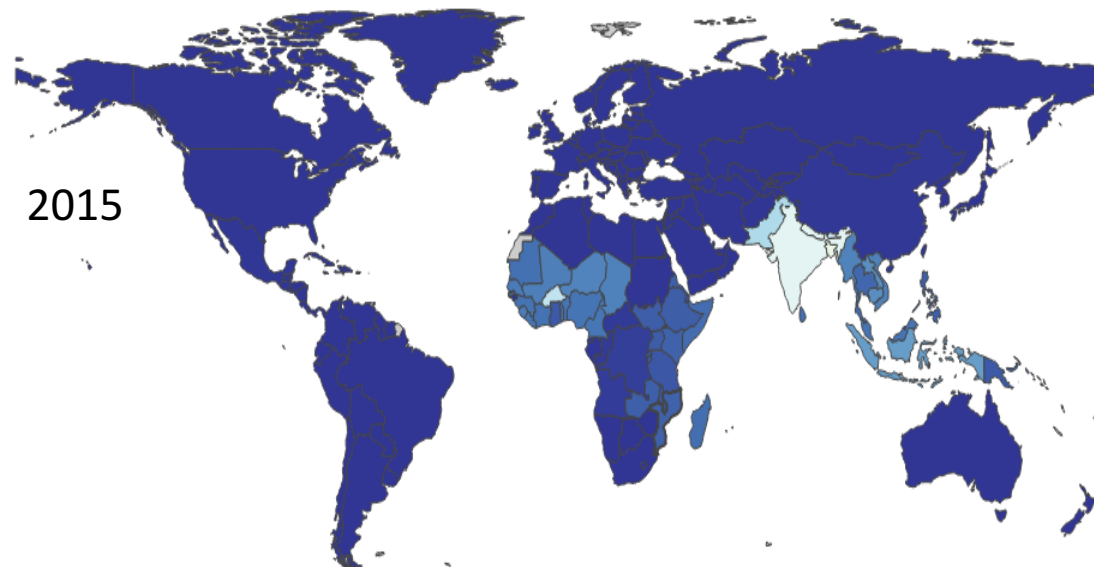
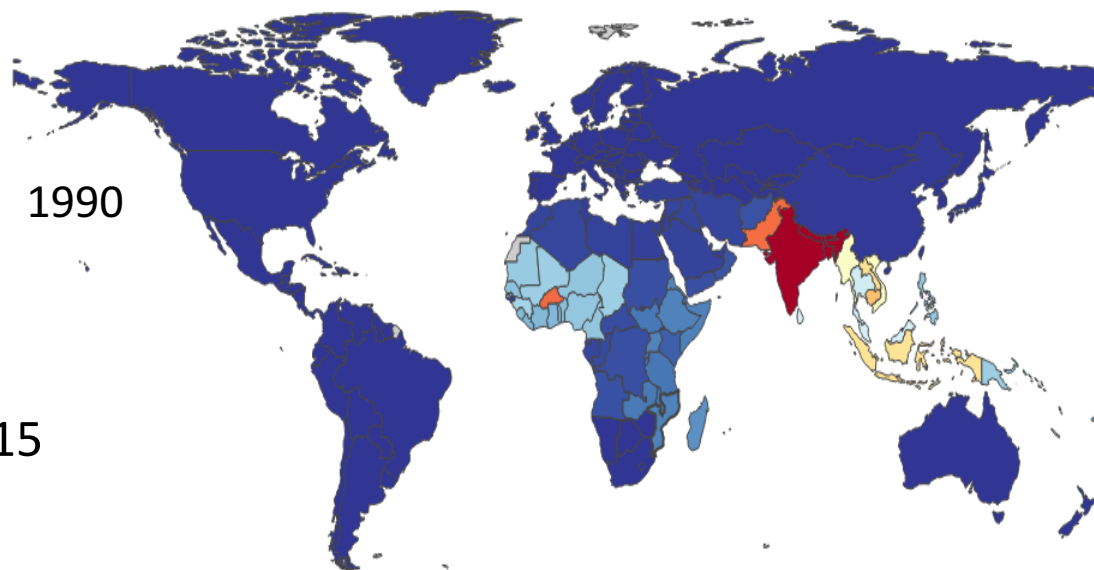
- Typhoid trends & brief overview of current control strategies (Typhoid Trends Project T2)
- Issues with anti-microbial resistance (AMR) in typhoid
 - recent trends and challenges
 - Implications for disease severity & response
 - Cost of therapy and potential infectivity/spread
- Potential impact of vaccination strategies on disease burden and AMR burden/spread

Methodology & data sources

- Systematic review and country case studies T2 project (2015-2017) [PLoS NTD Supplement planned for 2018]
- Update Cochrane Review of Antimicrobial therapy of Typhoid (Fluoroquinolones) 2018
- Systematic review of typhoid features in cohorts [Update of JoGH review 2016].
- Review of cohort data from AKUH information systems (ambulatory and inpatient data 1990-2017) with outcomes and costs of care.
- Review of GBD data on Typhoid for South Asia based on drug resistance patterns and outcomes (in partnership with IHME)

Typhoid trends & preventive strategies (sans vaccination)

The changing typhoid map:
incidence rate in 1990 & 2015



Contextual risk factors for typhoid

Study	Country	Drinking water	Hand washing	Open defecation
Sur 2007	India			
Alba et al 2016	Indonesia			
Hosoglu 2006	Turkey			
Puran et al 2009.	India			
Khan 2012	Pakistan			
Ram 2007	Bangladesh			
Srikantiah 2007	Uzbekistan			
Gasem 2001	Indonesia			
Sharma 2009	India			
Tran 2005	Vietnam			
Vollard 2004	Indonesia			
Kabwama 2017	Uganda			

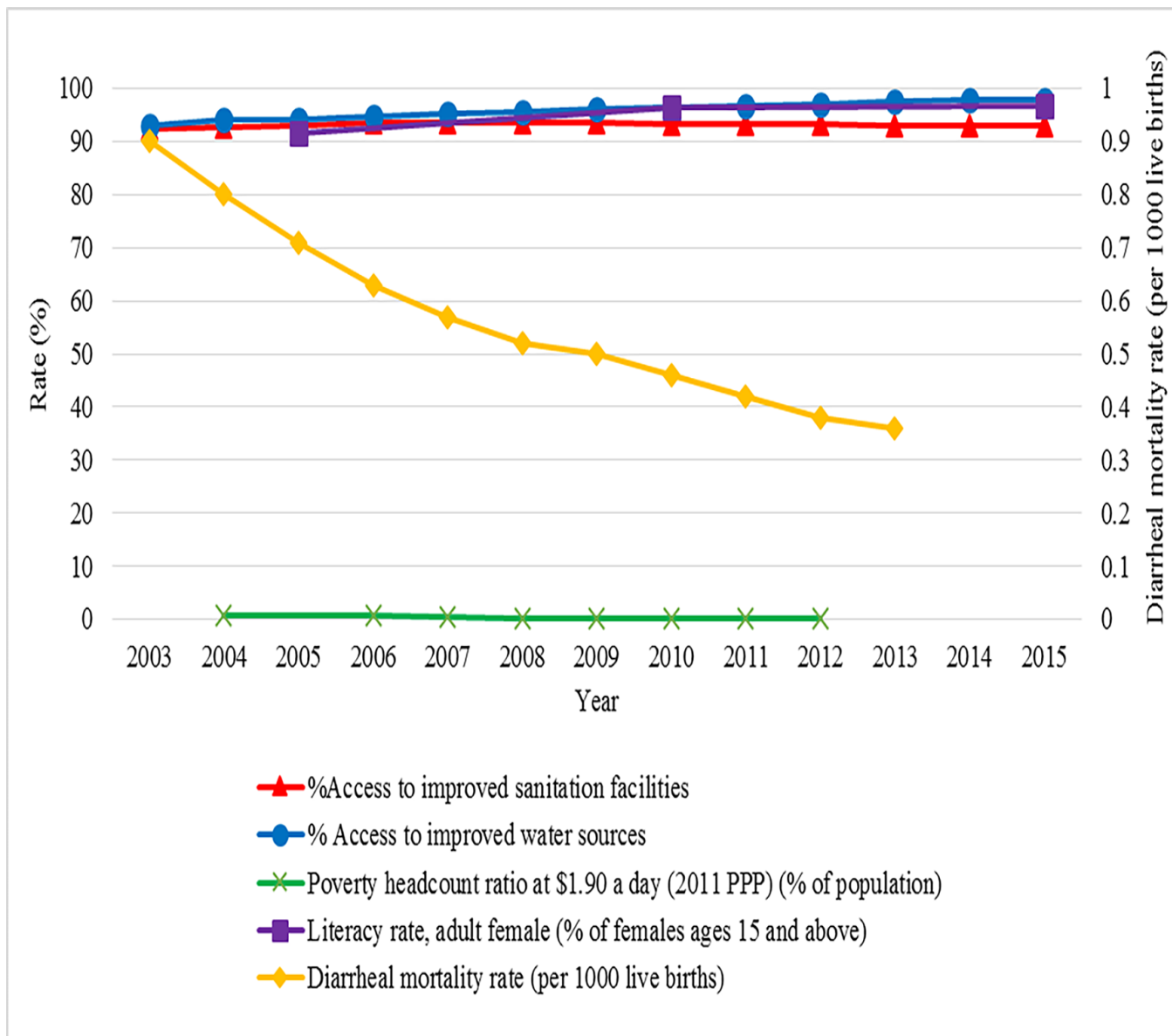
Contextual risk factors for typhoid

Study	Country	Drinking water	Hand washing	Open defecation	Consumption of raw vegetables/fruits	Street Foods
Sur 2007	India					
Alba et al 2016	Indonesia					
Hosoglu 2006	Turkey					
Puran et al 2009.	India					
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Tran 2005	Vietnam					
Vollard 2004	Indonesia					
Kabwama 2017	Uganda					

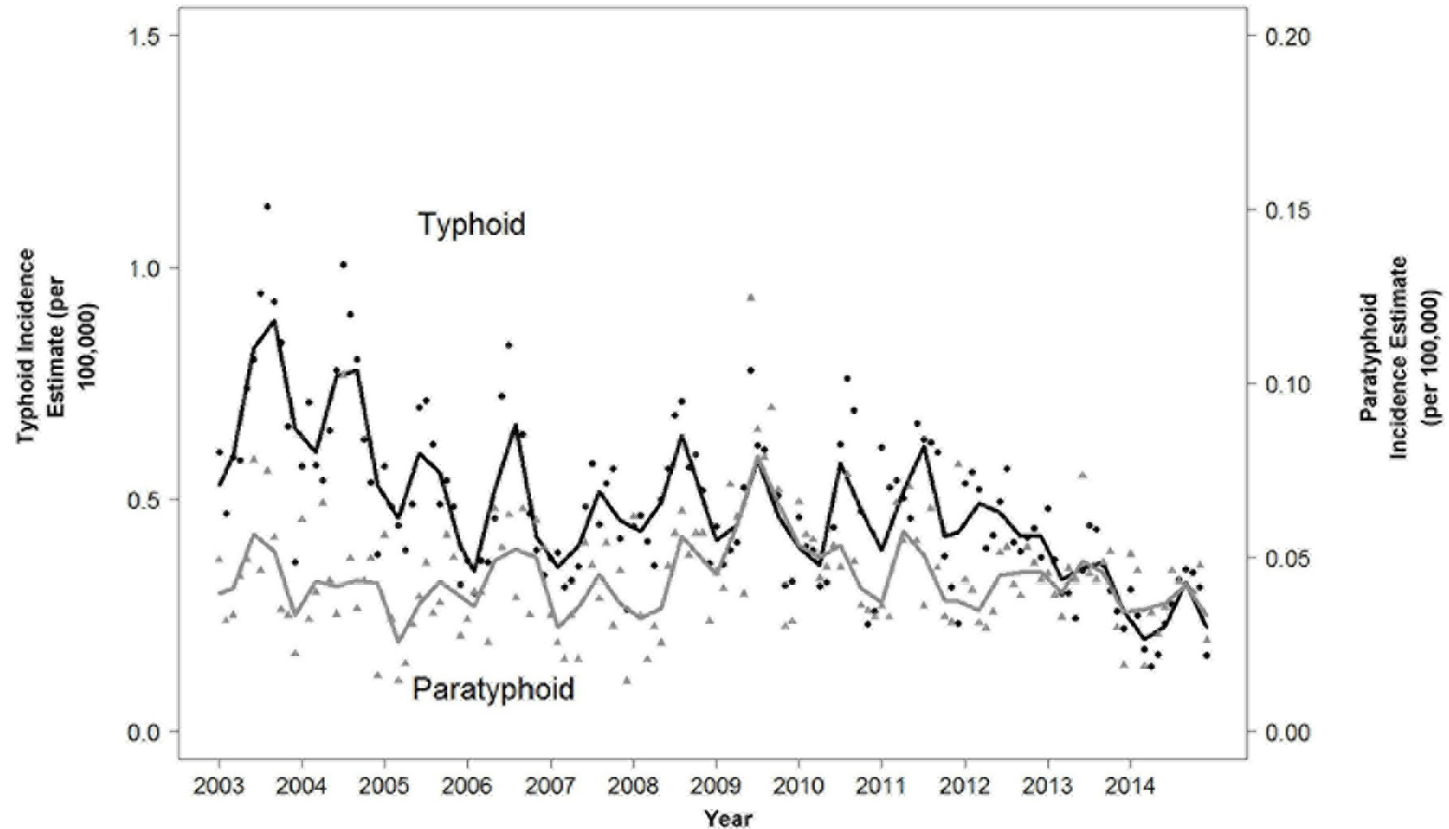
Contextual risk factors for typhoid

Study	Country	Drinking water	Hand washing	Open defecation	Consumption of raw vegetables/fruits	Street Foods	Household size	Literacy rates	Use of Antibiotics two weeks prior
Sur 2007	India								
Alba et al 2016	Indonesia								
Hosoglu 2006	Turkey								
Puran et al 2009.	India								
Khan 2012	Pakistan								
Ram 2007	Bangladesh								
Srikantiah 2007	Uzbekistan								
Gasem 2001	Indonesia								
Sharma 2009	India								
Tran 2005	Vietnam								
Vollard 2004	Indonesia								
Kabwama 2017	Uganda								

Thailand contextual factor trends



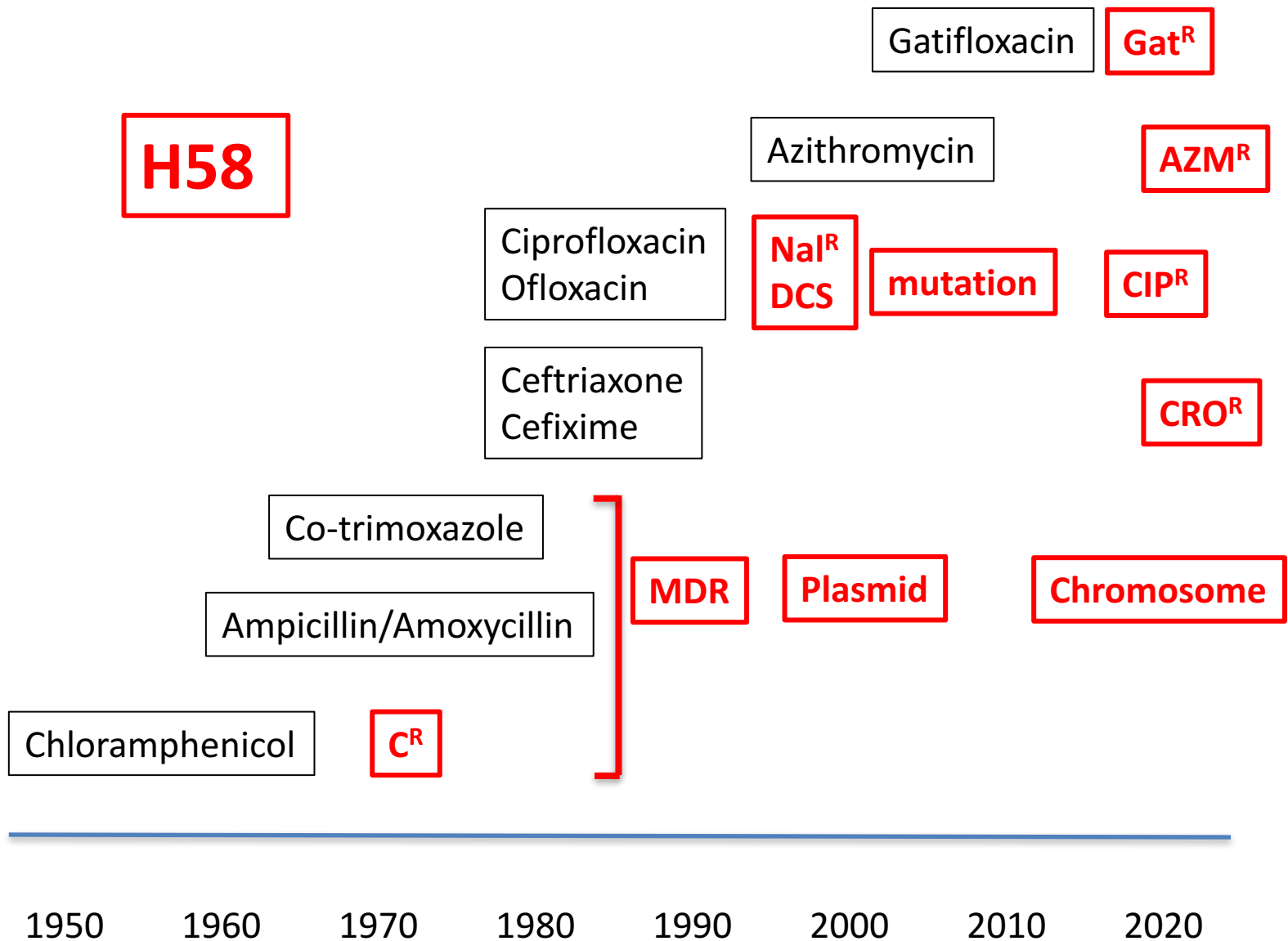
Thailand incidence trend



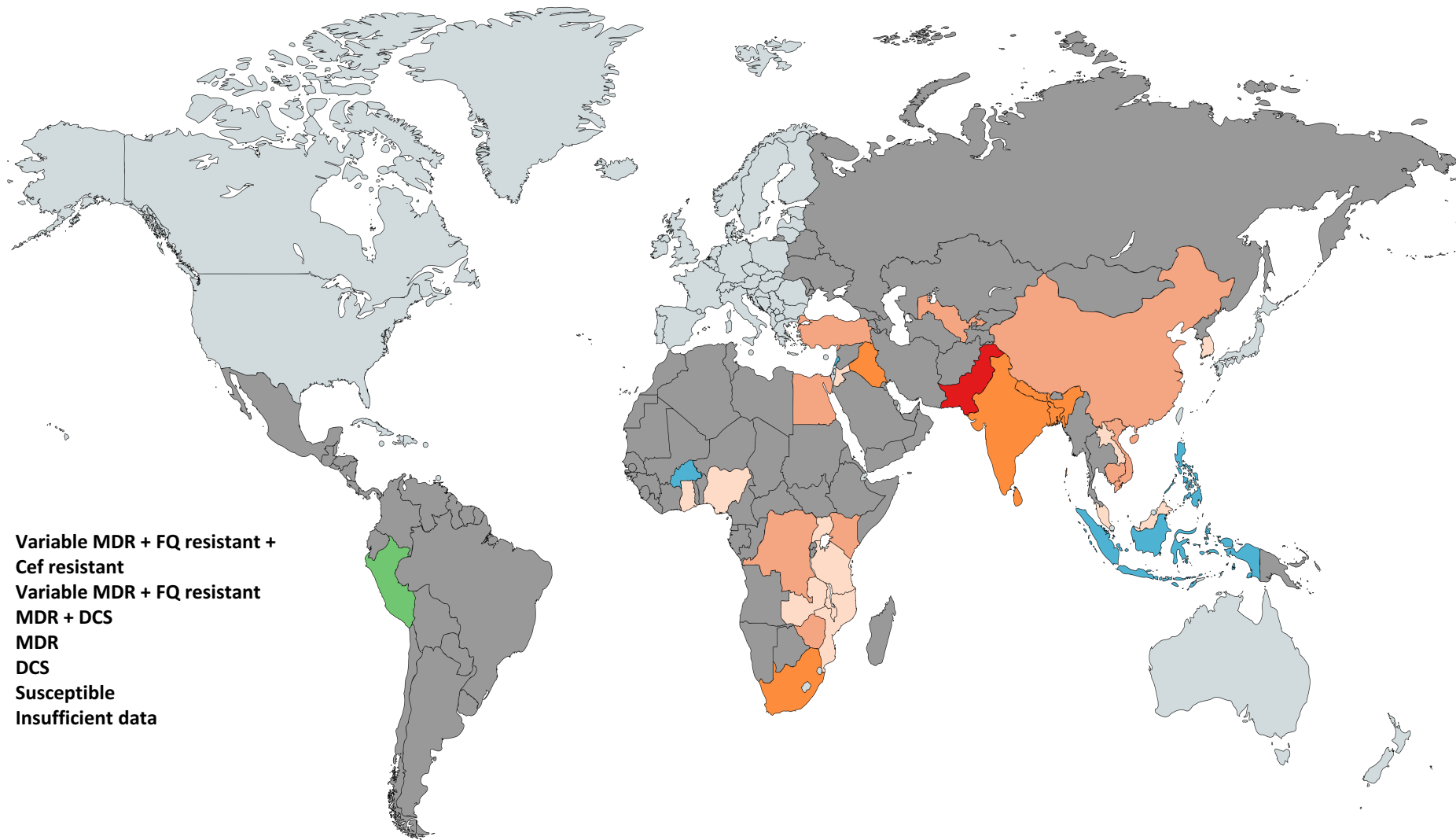
Year	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Reported Typhoid Cases	5443	5051	3878	3692	3168	3906	3671	3412	3887	3543	2603	1972
Reported Paratyphoid Cases	348	357	276	354	263	338	490	379	385	327	332	297
Total Population (in millions)	62.9	62.5	62.2	62.6	62.9	63.2	63.4	63.7	63.9	64.3	64.1	64.9

Source: Ministry of Public Health, Thailand

Typhoid & Antimicrobial Resistance



Anti-microbial resistance in Typhoid (2017)

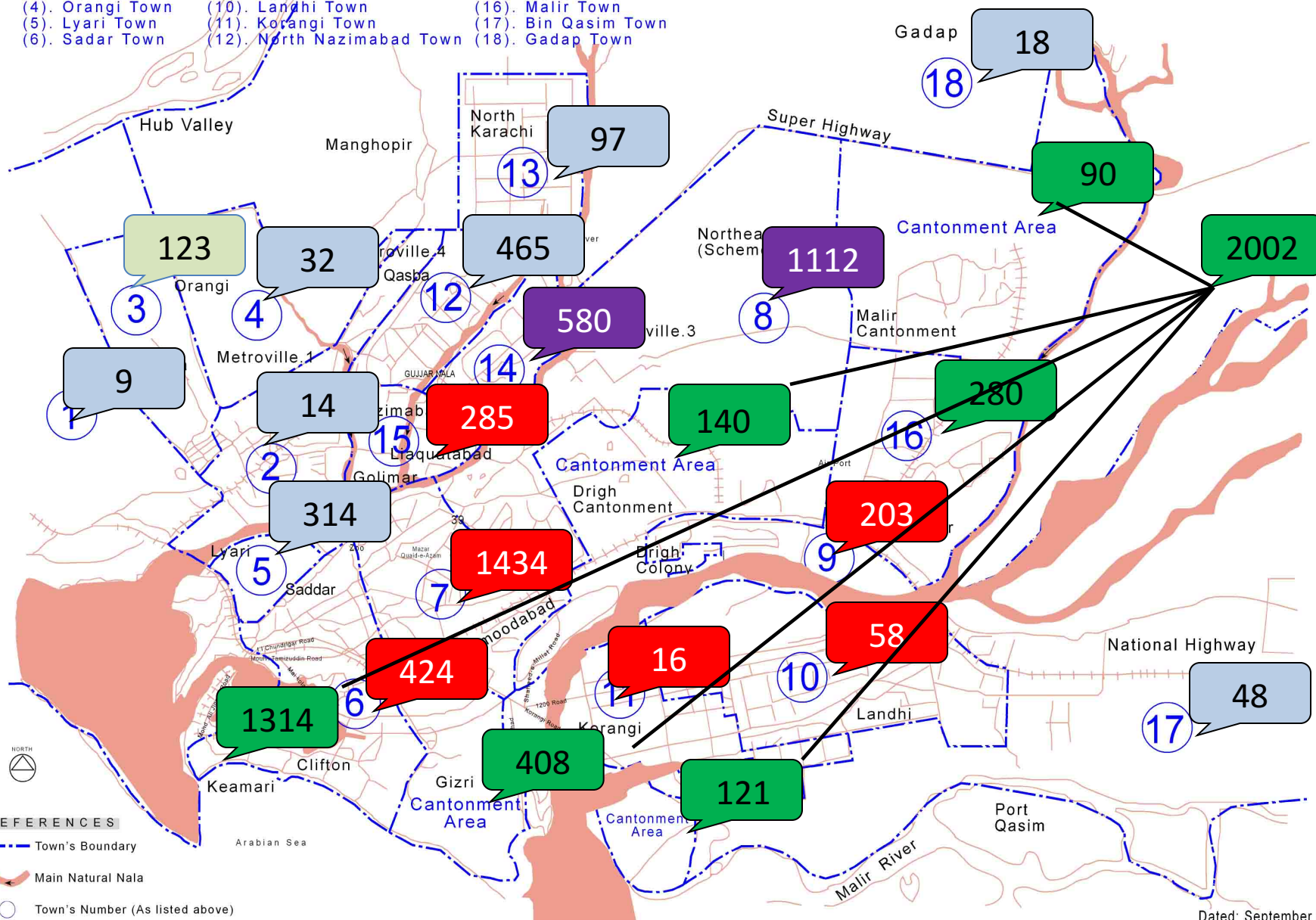


The Case Study from Karachi (Trends in AMR for typhoid)

Karachi map with location of towns

- | | | |
|-------------------|----------------------------|--------------------------|
| (1). Keamari Town | (7). Jamshed Town | (13). North Karachi Town |
| (2). Site Town | (8). Gulshan-e-Iqbal Town | (14). Gulberg Town |
| (3). Baldia Town | (9). Shah Faisal Town | (15). Liaqatabad Town |
| (4). Orangi Town | (10). Landhi Town | (16). Malir Town |
| (5). Lyari Town | (11). Korangi Town | (17). Bin Qasim Town |
| (6). Sadar Town | (12). North Nazimabad Town | (18). Gadap Town |

Towns Included
Towns Not Included
Potentials towns



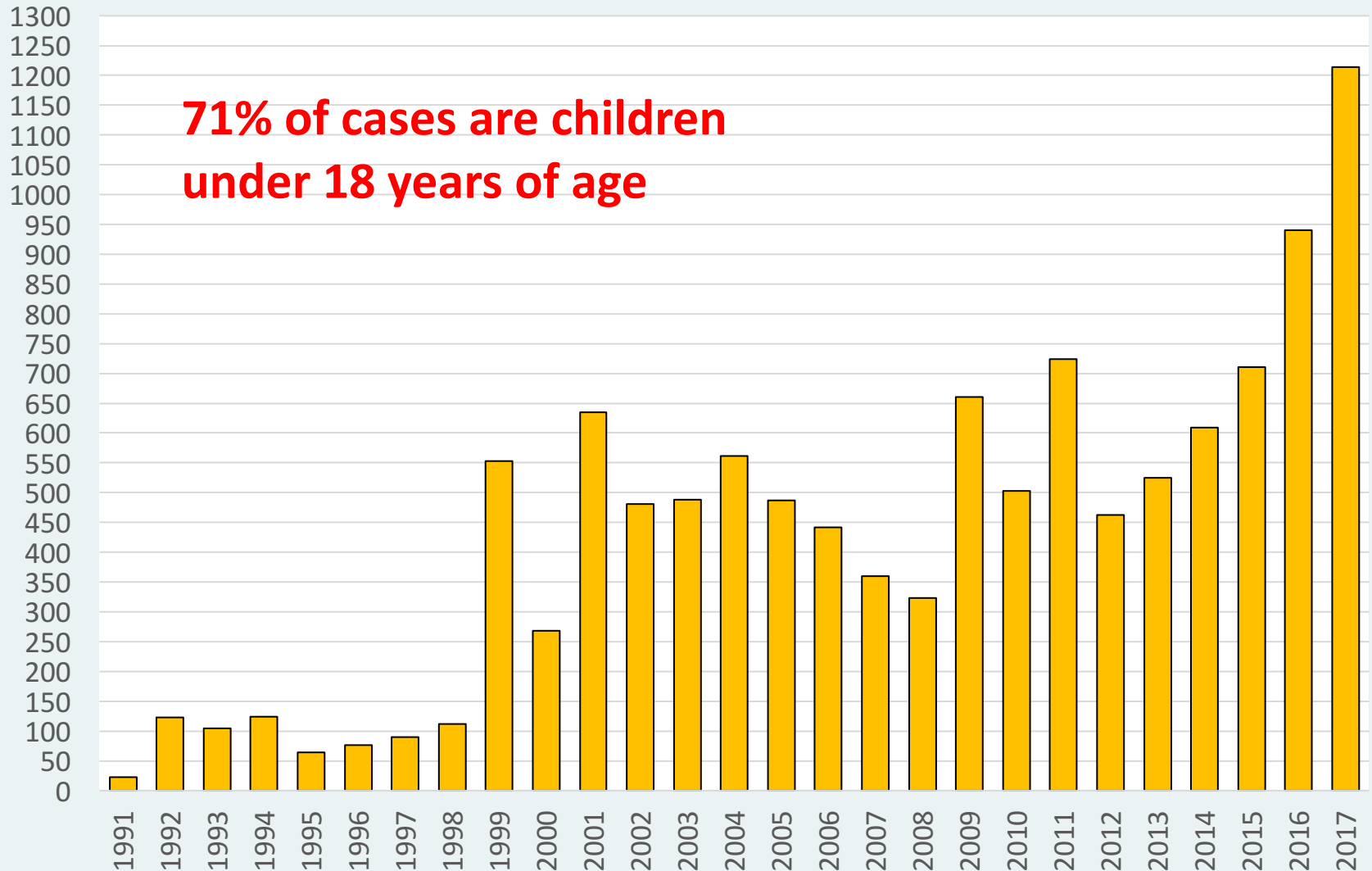
REFERENCES

- Town's Boundary
- Main Natural Nala
- Town's Number (As listed above)

Dated: September 2006

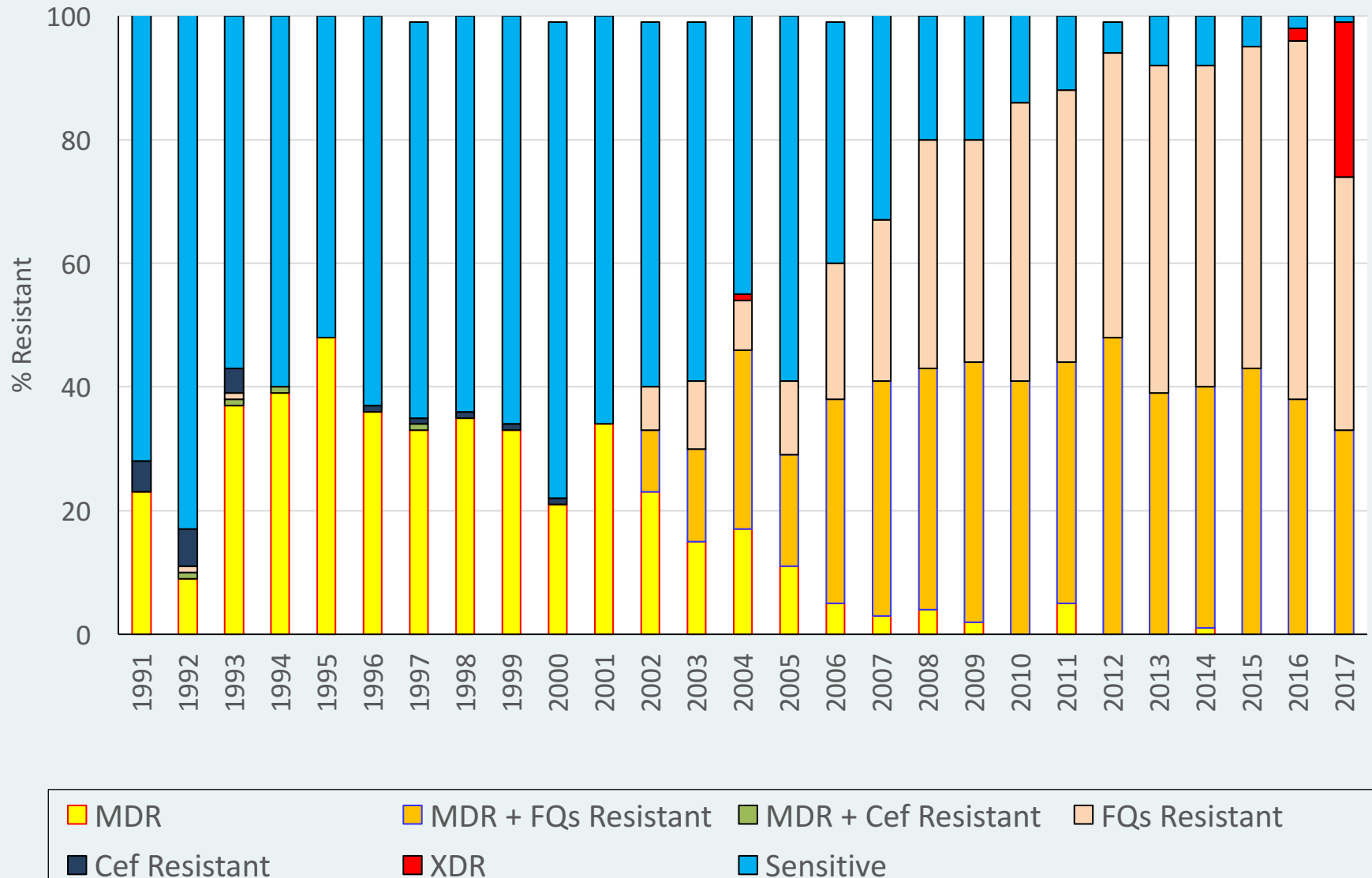
Number of Culture Positive Typhoid Specimens

Non Admission data 1991-2017



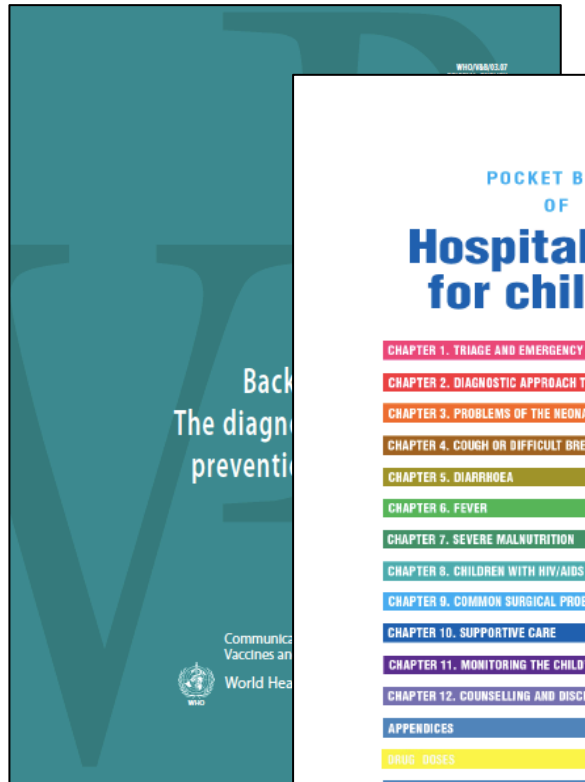
Antimicrobial Resistance for S. Typhi & Para Typhi

Non Admission data 1991-2017



What about Antimicrobial Therapy?

Treatment guidelines & trends



OUTLINE

IAP Task Force Report: Management of Enteric Fever in Children

Writing Committee

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The timely appropriate management of typhoid fever, can considerably reduce both morbidity and mortality. General supportive measures like use of antipyretics, maintenance of hydration, appropriate nutrition and prompt recognition and treatment of complications are extremely important for a favorable outcome. The child should continue to have normal diet and no food should be restricted.

In areas of endemic disease 90% or more of typhoid cases can be managed at home with proper oral antibiotics and good nursing care(1). Close medical follow up is necessary to look for development of complications or failure to respond to therapy.

Patients with persistent vomiting, inability to take oral feed, severe diarrhea and abdominal distension usually require parenteral antibiotic therapy preferably in a hospital.

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INDIAN PEDIATRICS

Antimicrobial Therapy

Since 1990s *Salmonella* developed resistance simultaneously used in first line treatment cotrimoxazole and ampicillin as Multi Drug Resistant (MDR). There is an emergence of fully susceptible strains(2). But these are not antibiotic sensitive organisms to be fully sensitive drugs they are not adequate therapy in typhoid.

Fluoroquinolones are the most effective drug for typhoid fever(3). But strains of *S. typhi* have susceptibility to fluoroquinolones at routine disc testing with break points, organisms still respond to actual treatment when tested by disc testing show resistance. So in the nalidixic acid is a surrogate predicts fluoroquinolone use to guide antibiotic therapy. The nalidixic acid resistance is a marker of reduced fluoroquinolones.

With the development of resistance third generation cephalosporins were used in treatment but resistance to these antibiotics. Recently, azithromycin alternative agent for complicated typhoid fever is also potent which are used recently(3).

There is now convincing evidence from the long

Clinical review

Current concepts in the diagnosis and treatment of typhoid fever

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Syed Ali
Syed Ali
Syed Ali

Although advances in public health and hygiene have led to the virtual disappearance of enteric fever (more commonly termed typhoid fever) from much of the developed world, the disease remains endemic in many developing countries. Typhoid fever is caused by *Salmonella enterica* serovar *Typhi* (S. *typhi*), a Gram negative bacillus. A similar but often less severe disease is caused by *S. paratyphi* A, and less commonly by *S. paratyphi* B (Schickell) and *S. paratyphi* C (Schickell). The common mode of infection is by ingestion of an infecting dose of the organism, usually through contaminated water or food. Although the source of infection may vary person to person transmission through poor hygiene and sewage contamination of water supply are the most important.

Have the epidemiology and burden estimates of typhoid changed?

Few established surveillance systems for typhoid exist in the developing world, especially in community settings, so the true burden is difficult to estimate. This is shown by recent estimates in the global estimates of the true burden of typhoid. In contrast to previous estimates, which were 60% higher, investigators from the US Centers for Disease Control and Prevention estimate that there are 21.6 million typhoid cases annually, with the annual incidence varying from 100 to 1000 cases per 100,000 population(4). The global mortality estimates from typhoid have also been revised downwards from 600,000 to 200,000, largely on the basis of regional extrapolations(5). Recent population based studies from South Asia suggest that the incidence is highest in children aged less than 5 years, with higher rates of complications and hospitalization, and may indicate risk of early exposure to relatively large infecting doses of the organism in these populations(6). These findings contrast with previous studies from Latin America(7) and Africa(8) which suggested that *S. typhi* infection caused a mild disease in infancy and childhood.

There may be other factors that affect the changing epidemiology of typhoid. Although the overall rate of disease caused by *S. typhi* has declined by 50% globally in about 10 to 15 years, the proportion of *S. paratyphi* infections is increasing in some parts of the world (Kang-Mei Tan, personal communication 2005)(9). Also, in contrast to the Asian situation, the HIV and AIDS epidemic in Africa has been associated with a concomitant increase

Summary points

Despite advances in technology and public health strategies, typhoid fever remains a major cause of morbidity in the developing world.

In some areas typhoid fever disproportionately affects young children and may reflect high rates of transmission through food and water.

Recent emergence of drug resistance—especially to common, first line antibiotics and quinolones—has made it very difficult and expensive for health services to manage the disease.

Rapid and appropriate diagnostics are key to the management of typhoid in terms of public health.

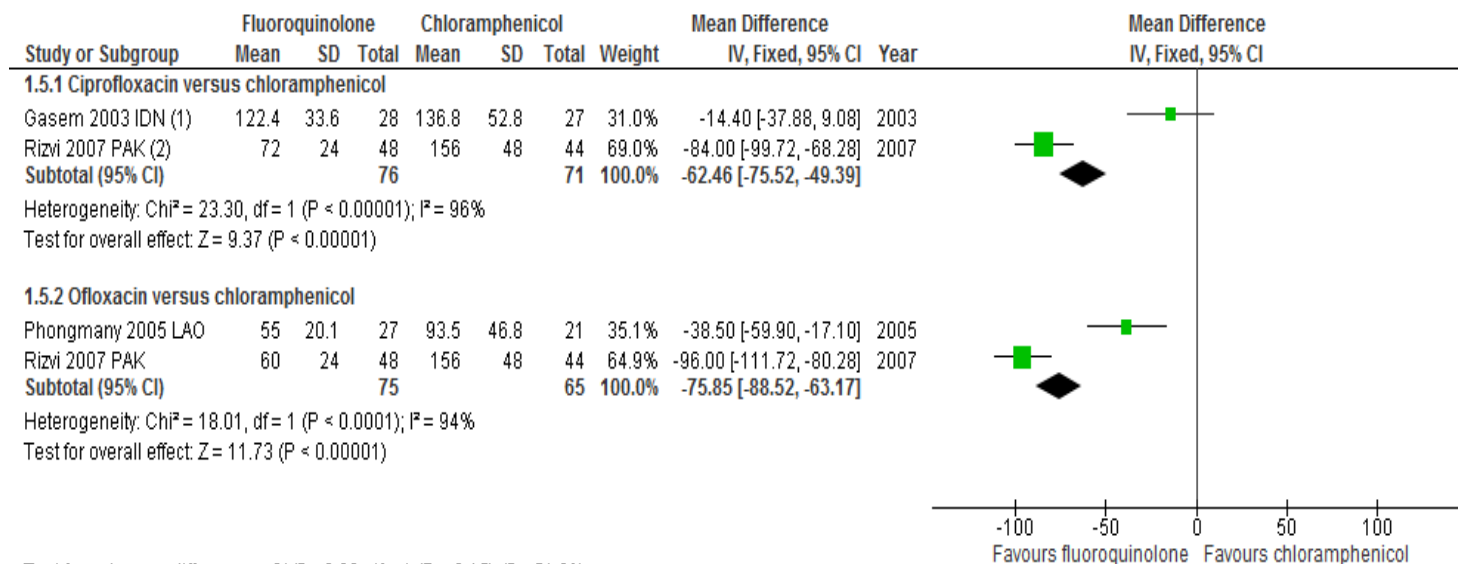
Although effective vaccines are available, there are no plans for large scale vaccination programmes in infants and children.

In community acquired bacteremia due to non-typhoidal *Salmonella* such as *S. agona*(10), it is shown that may be clinically indistinguishable from typhoid. The exact reasons for these differences in the epidemiology and spectrum of *Salmonella* infections between Asia and Africa remain unclear.

Another worrying development has been the emergence of drug resistant typhoid. After sporadic outbreaks of chloramphenicol resistant typhoid between 1970 and 1980, many strains of *S. typhi* developed plasmid mediated resistance to the three primary antimicrobials used (ampicillin, chloramphenicol, and co-trimoxazole)(11). This was countered by the advent of oral quinolones, but chronologically acquired quinolone resistance in *S. typhi* and *S. paratyphi* has been recently described in various parts of Asia, possibly related to the widespread and indiscriminate use of quinolones(12).

Downloaded from bmj.com on 14 July 2008

Impact on fever clearance time

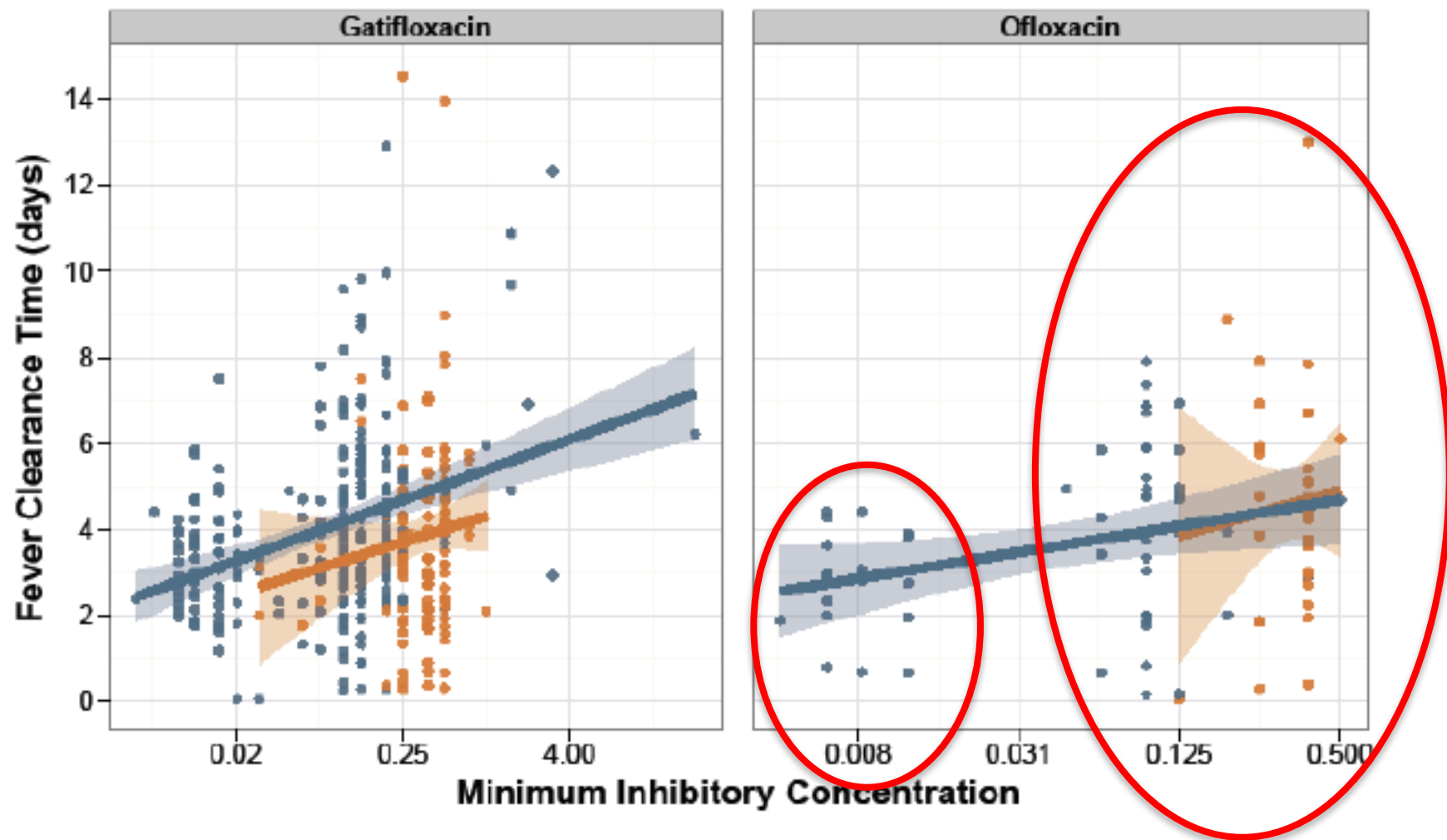


Footnotes

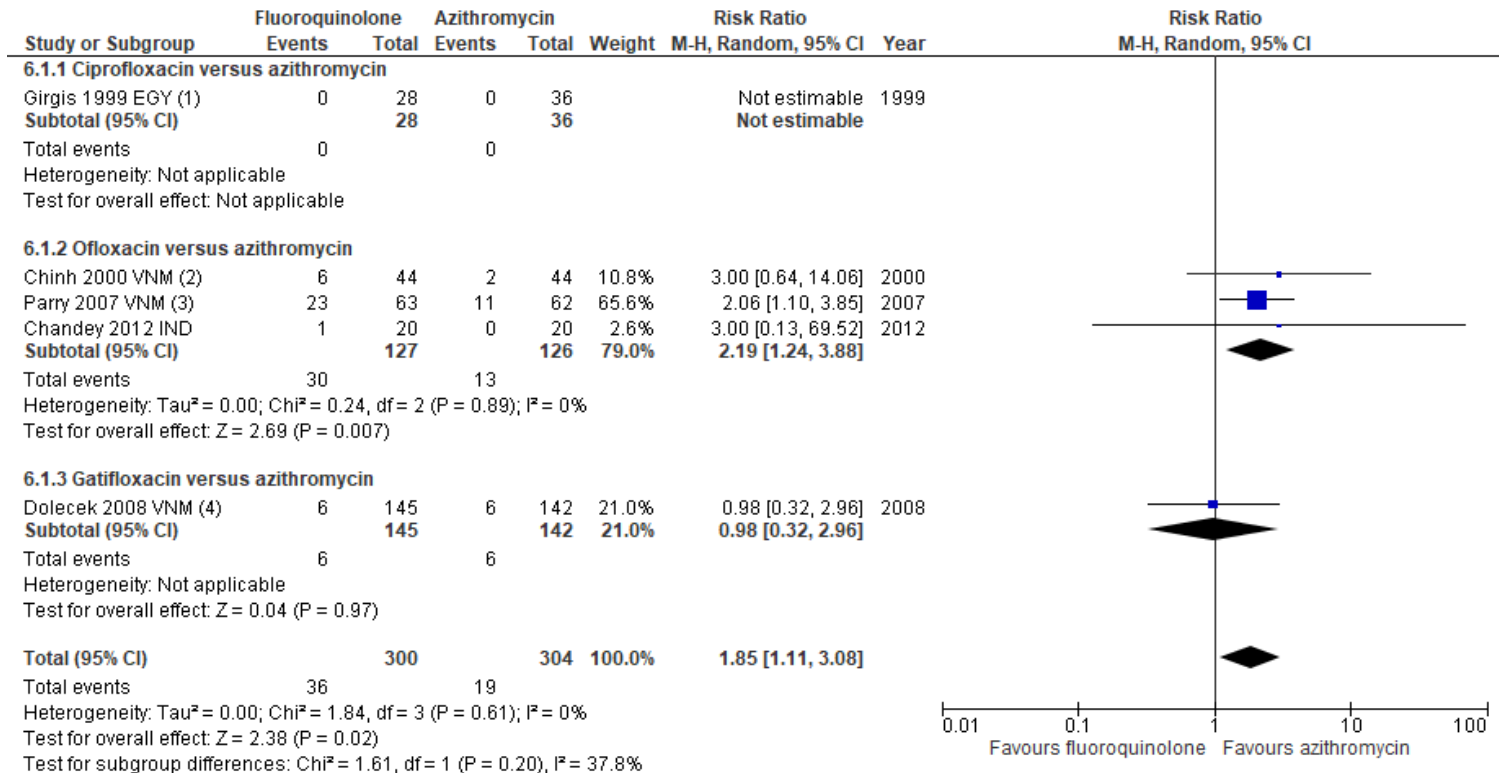
(1) Days

(2) Days

Treatment response in enteric fever in an era of increasing antimicrobial resistance: an individual patient data analysis of 2,092 participants enrolled into four randomised controlled trials in Nepal



Impact on clinical failure



Footnotes

- (1) Ciprofloxacin 500 mg BD for 7 days vs Azithromycin 1 g OD followed by 500 mg OD for 6 days
- (2) Ofloxacin 200 mg BD for 5 days vs Azithromycin 1 gm OD for 5 days
- (3) Ofloxacin 10 mg/kg BD for 7 days vs Azithromycin 10 mg/kg OD for 7 days
- (4) Gatifloxacin 10 mg/kg OD for 7 days vs Azithromycin 20 mg/kg OD for 7 days

Does Antimicrobial Resistance Matter in Typhoid?

Impact of age and drug resistance on mortality in typhoid fever

Zulfiqar Ahmed Bhutta

Archives of Disease in Childhood 1996;75:214-217

Table 1 Comparison of infection with multidrug resistant and sensitive strains of typhoid; values are number (%)

	Multidrug resistant strains (n=261, 23%)	Drug sensitive strains (n=897, 77%)	Relative risk (95% CI)	p Value
M : F ratio	168:93	514:383		
Duration of illness (weeks)				
< 1	106 (41)	525 (59)	0.5 (0.4 to 0.6)	< 0.0001
1-2	77 (30)	208 (23)	1.4 (1.0 to 1.9)	0.03
2-4	60 (23)	110 (12)	2.1 (1.5 to 3.0)	< 0.0001
> 4	18 (7)	54 (6)	1.2 (0.7 to 2.1)	0.61
Fever at presentation				
High grade	232 (89)	812 (91)	0.8 (0.5 to 1.3)	0.43
Low grade	17 (6)	52 (6)	1.1 (0.6 to 2.0)	0.67
Afebrile/hypothermic	12 (5)	33 (3)	1.3 (0.6 to 2.5)	0.50
Toxicity at admission	115 (44)	262 (29)	1.9 (1.4 to 2.5)	< 0.0001
Pallor	25 (10)	93 (10)	0.9 (0.6 to 1.5)	0.71
Diarrhoea	106 (41)	300 (33)	1.4 (1.0 to 1.8)	0.03
Constipation	32 (12)	95 (11)	1.2 (0.8 to 1.8)	0.45
Abdominal tenderness	91 (35)	229 (26)	1.6 (1.2 to 2.1)	< 0.01
Hepatomegaly	134 (51)	337 (38)	1.8 (1.3 to 2.3)	< 0.0001
Splenomegaly	54 (21)	172 (19)	1.1 (0.8 to 1.6)	0.59
Admission haemoglobin (g/l)				
< 80	35 (14)	89 (10)	1.4 (0.9 to 2.1)	0.11
80-120	142 (54)	494 (55)	1.0 (0.7 to 1.3)	0.85
> 120	82 (31)	296 (33)	0.9 (0.7 to 1.3)	0.63
Admission white cell count ($\times 10^9/l$)				
< 4	13 (5)	43 (5)	1.0 (0.6 to 2.0)	0.90
4-15	172 (66)	619 (69)	0.9 (0.7 to 1.2)	0.34
> 15	74 (28)	231 (26)	1.1 (0.8 to 1.6)	0.40
Mortality	6 (2)	13 (1)	0.6 (0.2 to 1.7)	0.34

Electronic supplementary material:

The online version of this article contains supplementary material.

Systematic review of the global epidemiology, clinical and laboratory profile of enteric fever



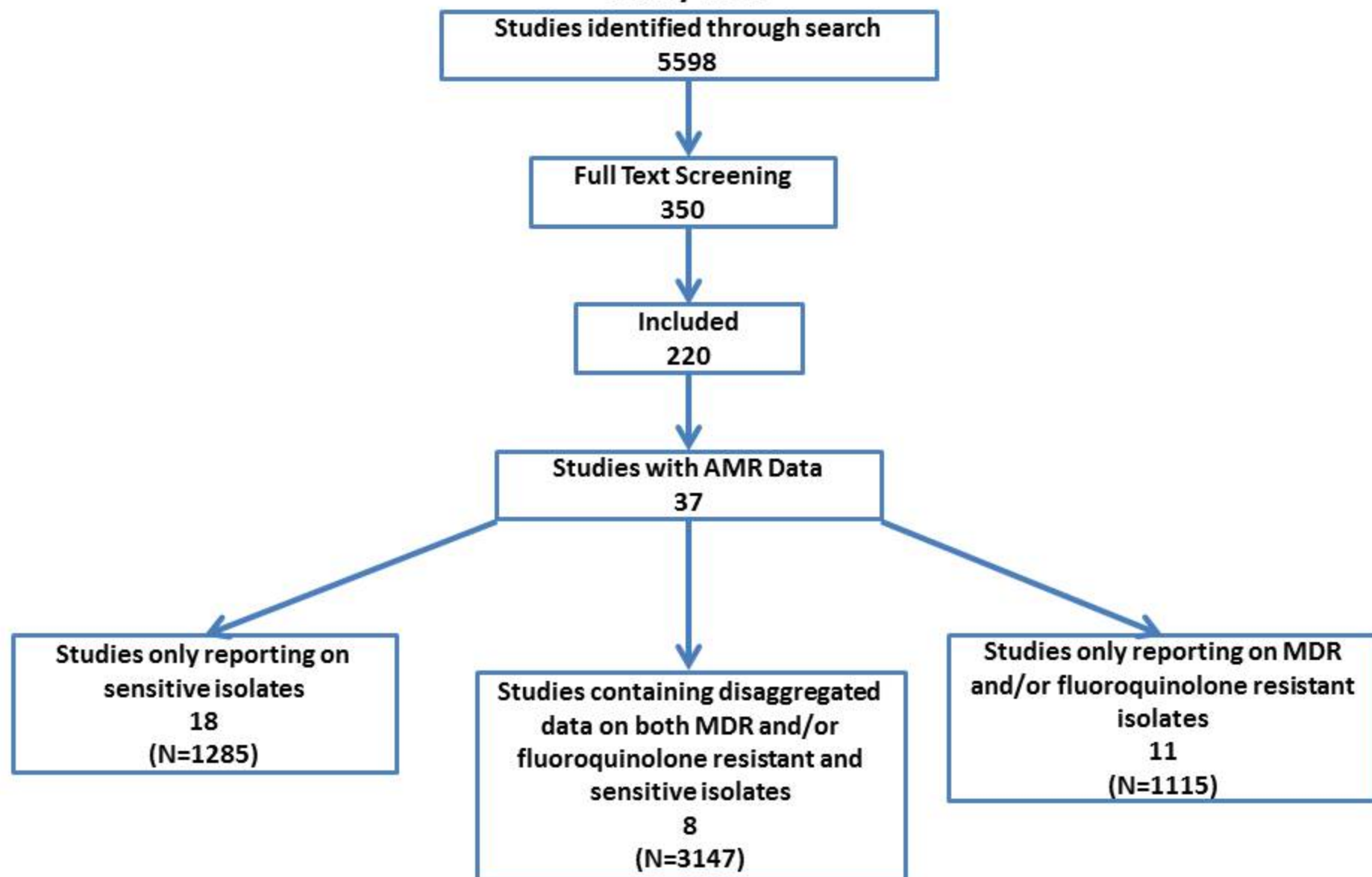
Asma Azmatullah¹, Farah Naz Qamar¹,
Durrane Thaver¹, Anita KM Zaidi¹, Zulfiqar
A Bhutta^{2,3}

Background Children suffer the highest burden of enteric fever among populations in South Asian countries. The clinical features are

Methods

- An extensive literature search covering January 1964 to Sep 2017 was conducted to assess unselected cohorts of cases with case descriptions
- Inclusion criteria necessitated
 - A sample size greater than 5 & documented clinical features
 - Blood culture confirmed cases
 - All levels of disease severity
 - Patients not representing special populations (ie; all HIV positive, only malnourished children etc.)
 - Outcome information where available

Study flow



N refers to the number of isolates tested from patients

Complications & Clinical Outcomes

	Multi-drug and/or fluoroquinolone resistant 2311 cases from 19 Studies				Sensitive 3236 cases from 26 Studies			
	n	N	%	Studies	n	N	%	Studies
Shock or hypotension	22	133	16.5	4	7	105	6.7	3
Toxicity	208	427	48.7	5	310	968	32.0	5
GI Bleeding	29	316	9.2	8	13	365	3.6	10
GI Perforation	4	142	2.8	2	2	493	0.4	4
Relapse rates (%)	36	942	3.8	10	13	524	2.5	8
Case Fatality (%)	24	1582	1.5	14	31	2399	1.3	15

Complications & Clinical Outcomes

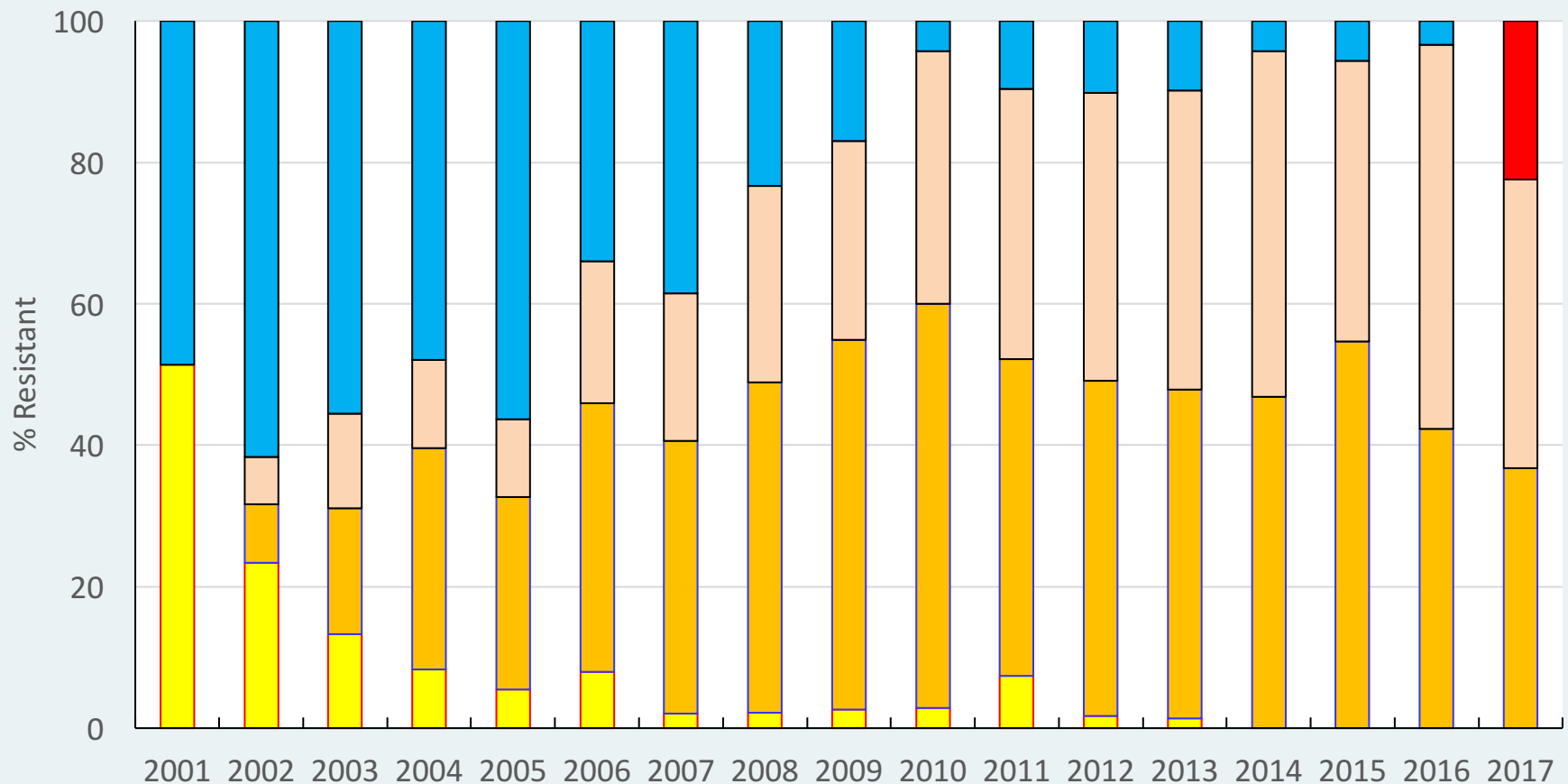
	Multi-drug and/or fluoroquinolone resistant 2311 cases from 19 Studies				Sensitive 3236 cases from 26 Studies				Comparison	
	n	N	%	Studies	n	N	%	Studies	Odds Ratio	95% CI
Shock or hypotension	22	133	16.5	4	7	105	6.7	3	2.77	(1.14, 6.78)
Toxicity	208	427	48.7	5	310	968	32.0	5	2.02	(1.60, 2.54)
GI Bleeding	29	316	9.2	8	13	365	3.6	10	2.74	(1.40, 5.36)
GI Perforation	4	142	2.8	2	2	493	0.4	4	7.12	(1.29, 39.26)
Relapse rates (%)	36	942	3.8	10	13	524	2.5	8	1.56	(0.82, 2.97)
Case Fatality (%)	24	1582	1.5	14	31	2399	1.3	15	1.18	(0.69, 2.01)

**Does Antimicrobial Resistance Matter
in Hospitalized cases of Typhoid?**



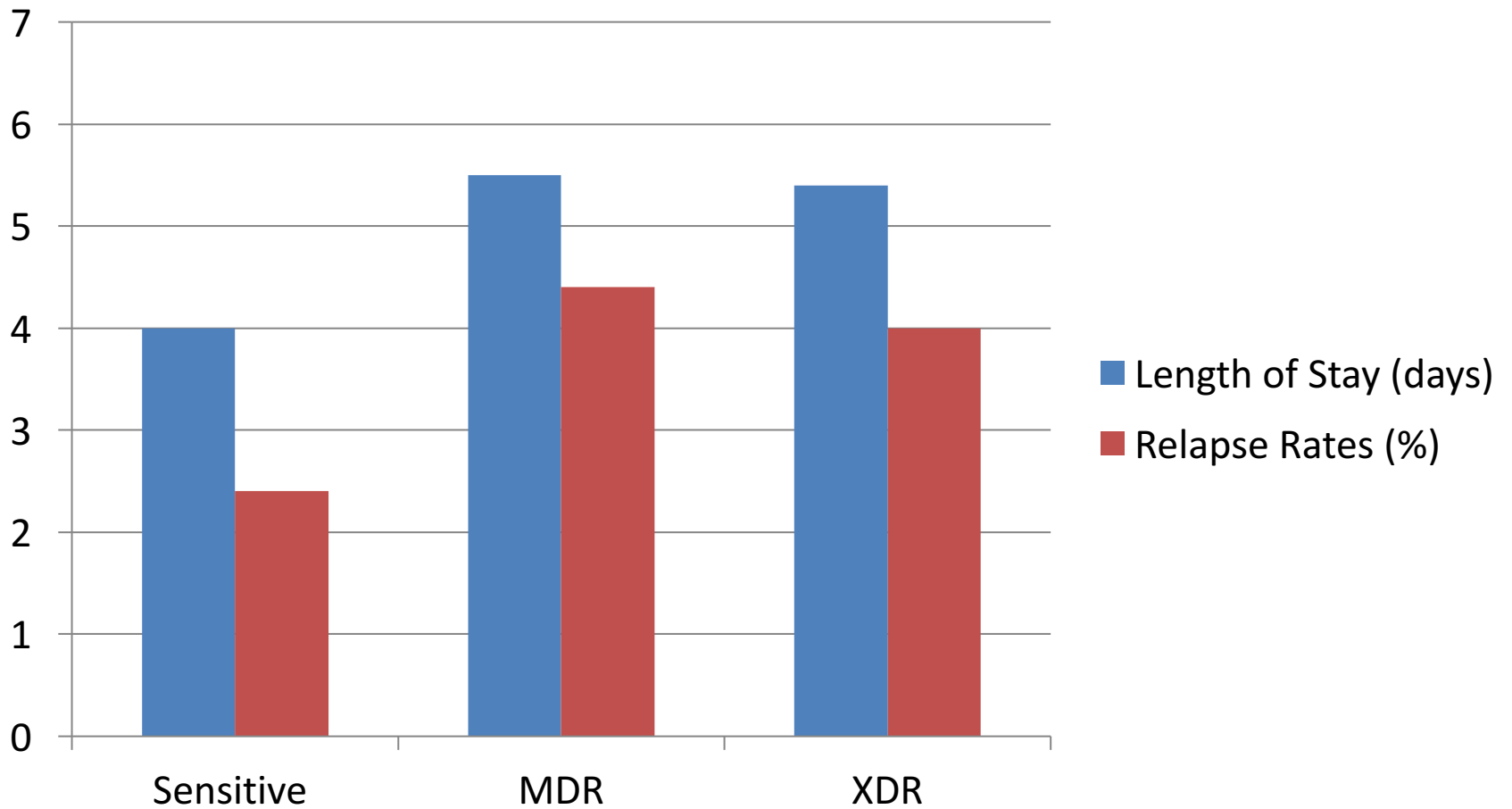
Antimicrobial Resistance for S.Typhi & Para Typhi

Hospitalized children < 15 years age 2001-2017



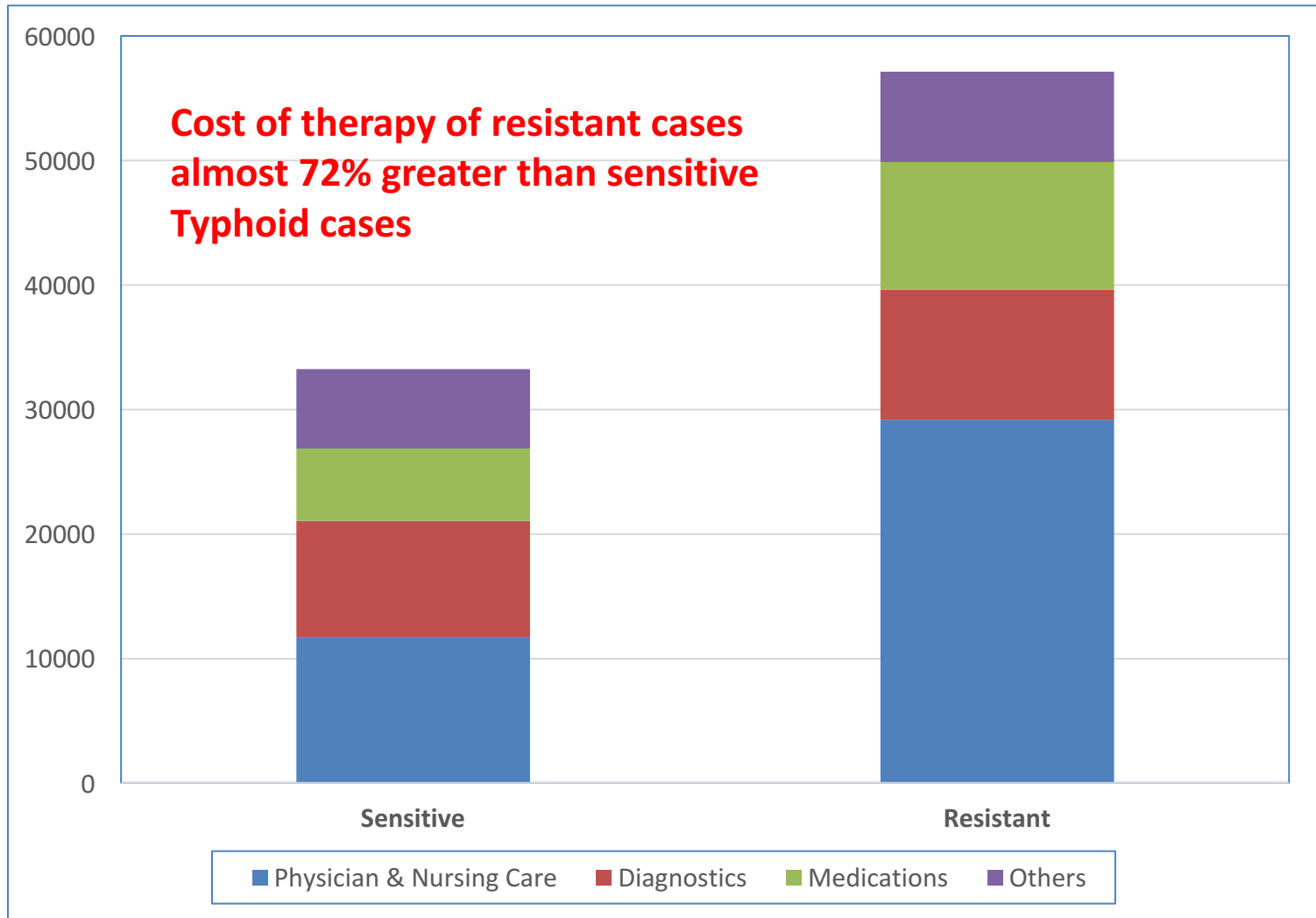
MDR MDR + FQs Resistant MDR + Cef Resistant FQs Resistant Cef Resistant XDR Sensitive

Outcome data



Cost of care

PKR



Methods: YLD adjustments

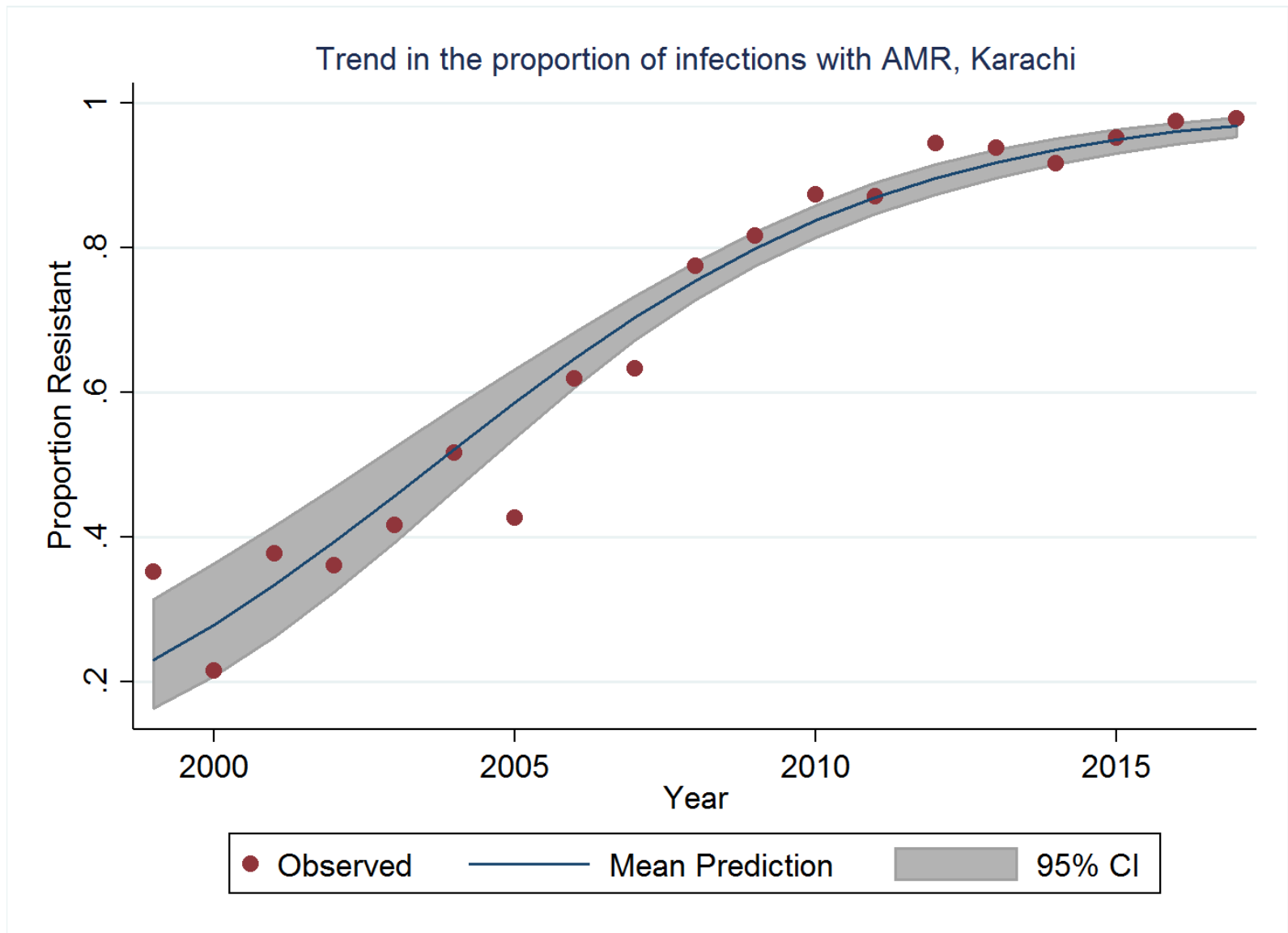
- Estimated YLDs per case for resistant and sensitive infections based on frequency of clinical outcomes in each group
- Calculated YLD per case multipliers for sensitive and resistant infections as

$$M_{sens} = \frac{YLD_{sens}}{YLD_{gbd}}$$

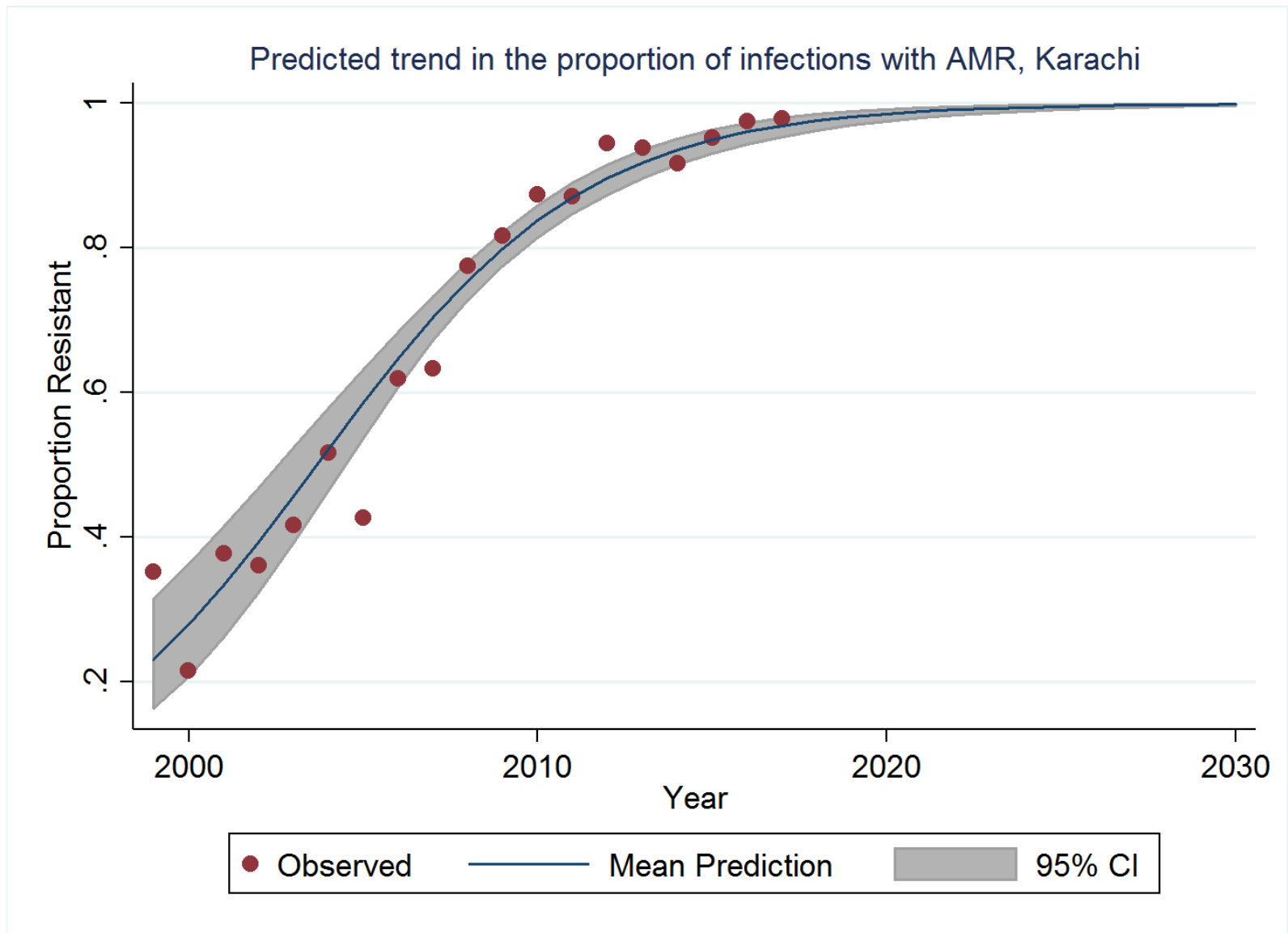
$$M_{resist} = \frac{YLD_{resist}}{YLD_{gbd}}$$

Methods: AMR split

- Estimated the proportion resistant by year based on Karachi data
 - Incorporated uncertainty using beta distribution and posterior simulation with 1,000 draws
- Split deaths, cases, YLLs, and YLDs between sensitive and resistant
- Adjusted YLDs for sensitive and resistant infections using YLD multipliers
- Re-calculated DALYs as sum of YLLs and updated YLDs

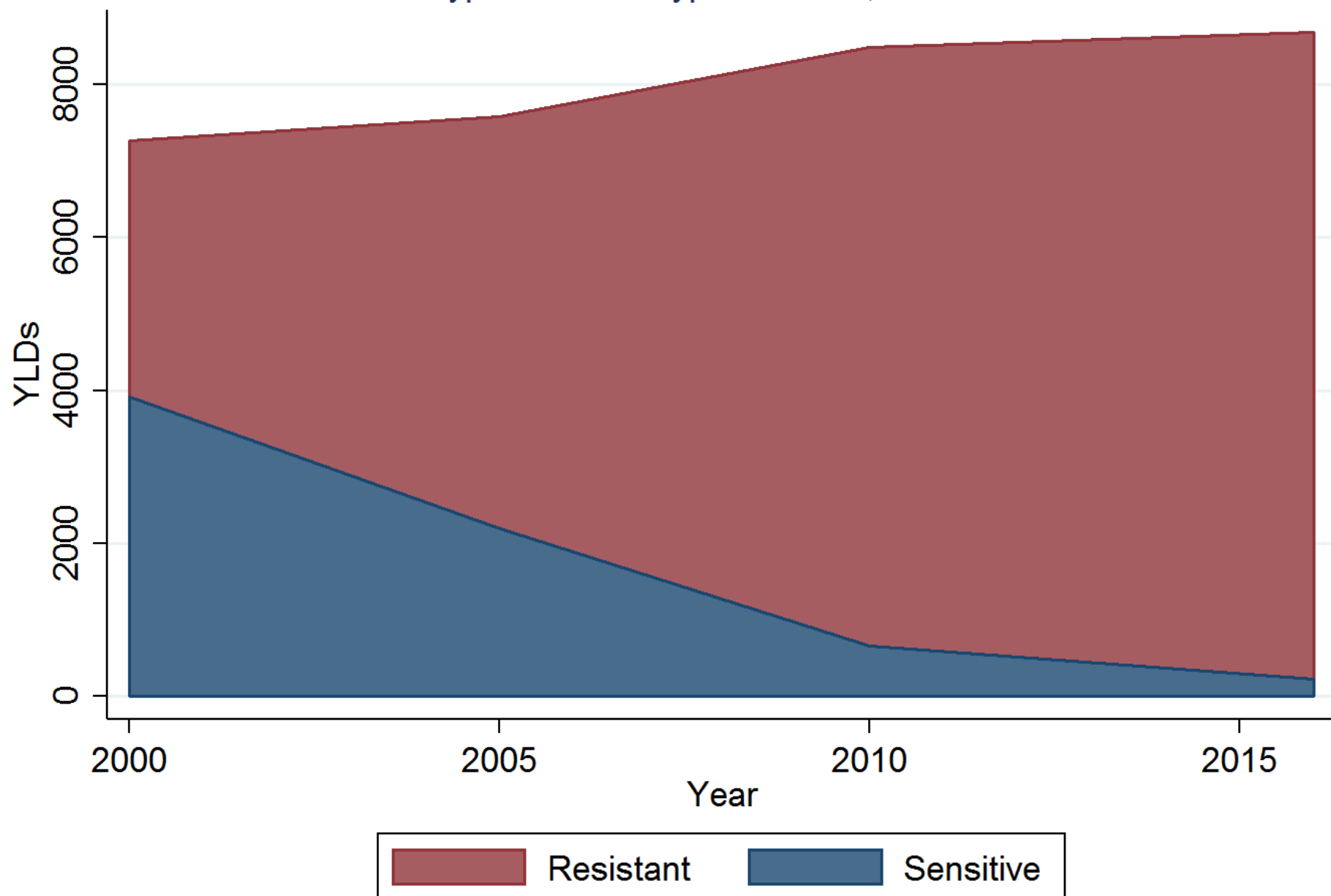


Each year the odds of a infection being resistant increase 30% (24 - 35%)

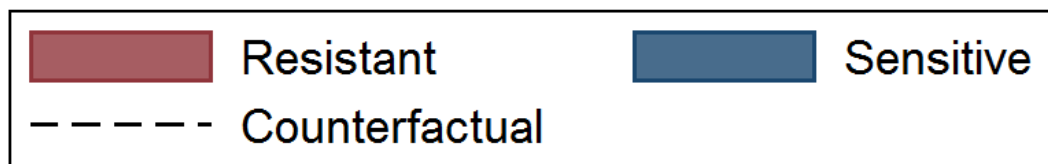
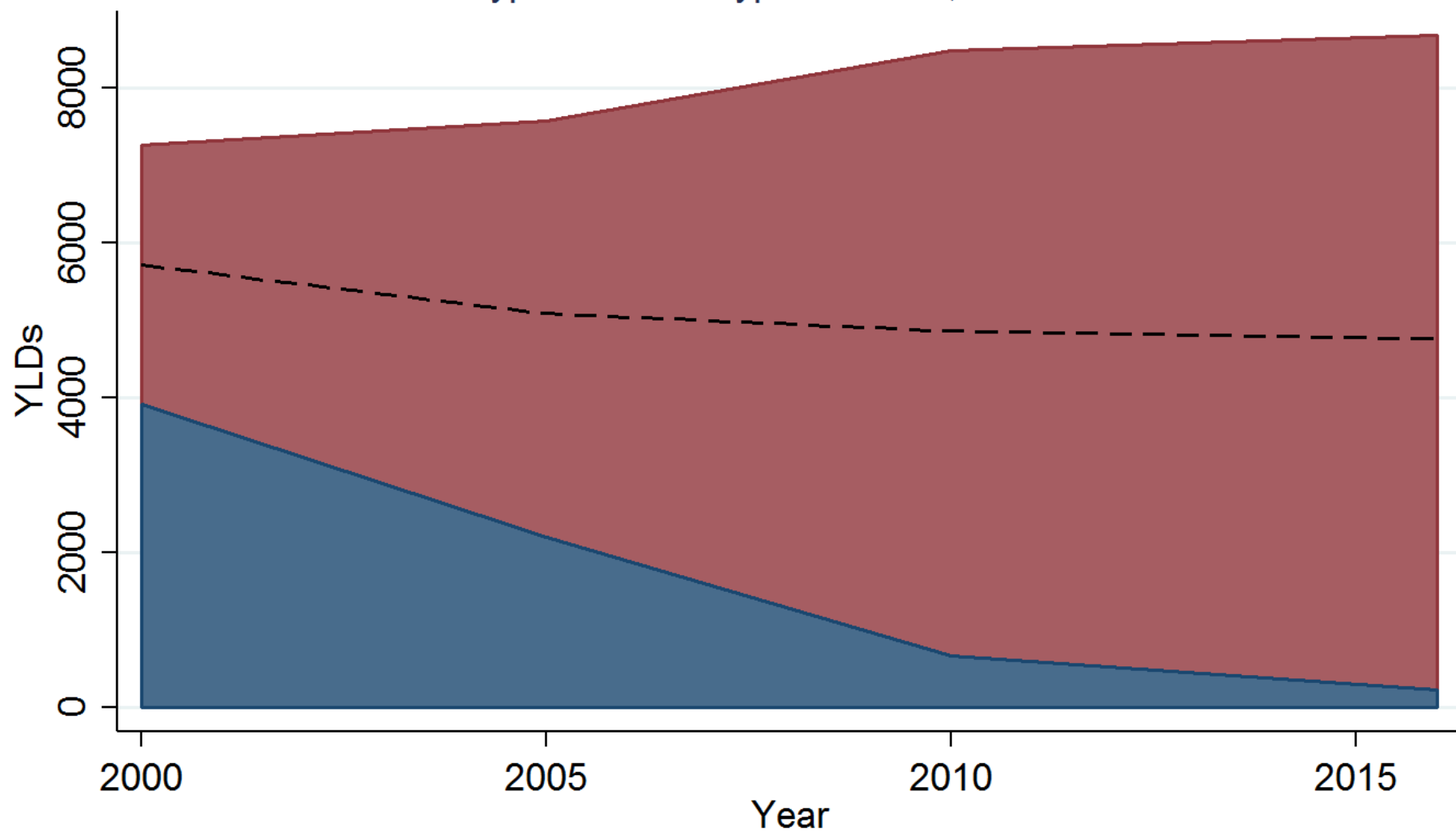


Each year the odds of a infection being resistant increase 30% (24 - 35%)

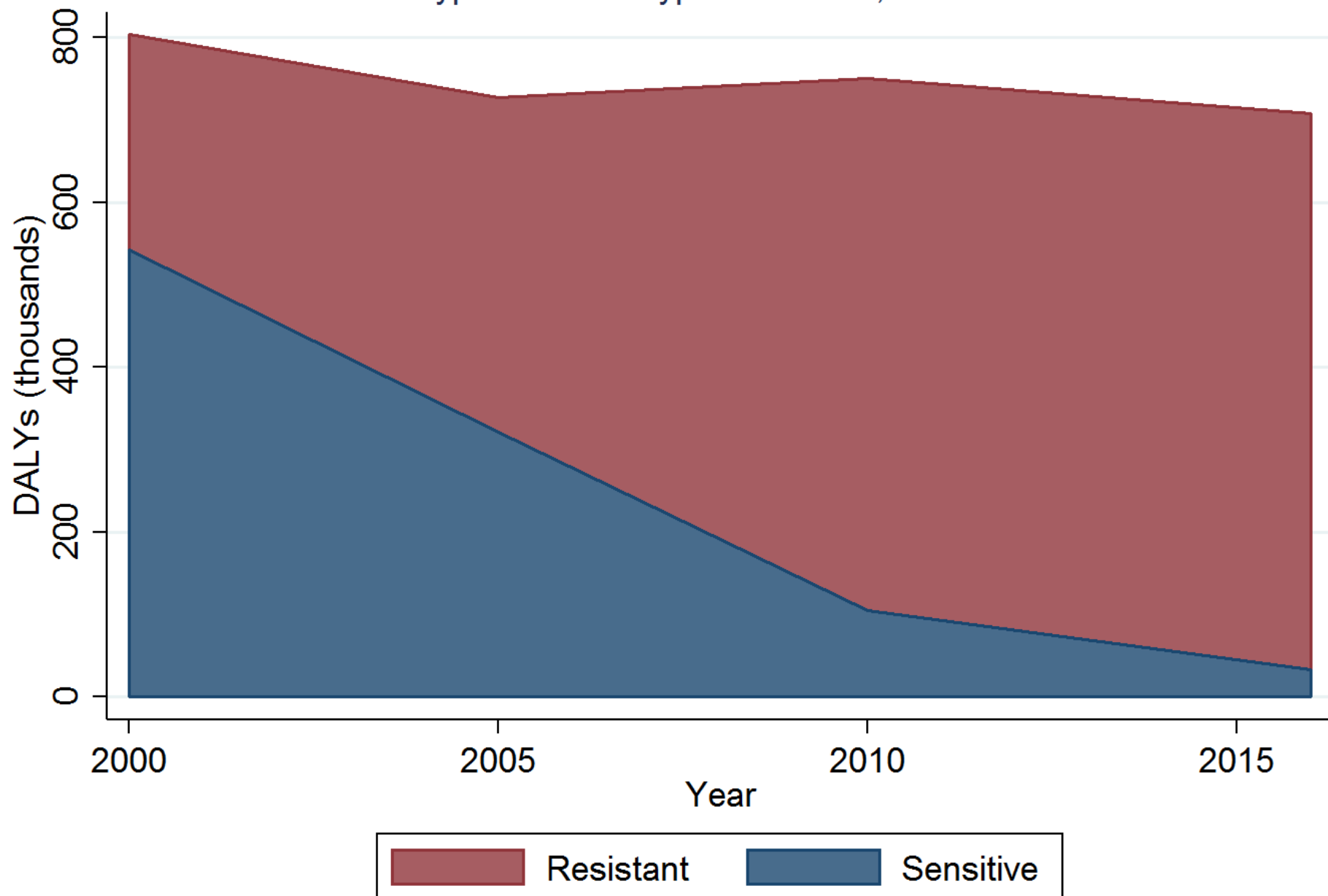
Typhoid & Paratyphoid YLDs, Pakistan



Typhoid & Paratyphoid YLDs, Pakistan



Typhoid & Paratyphoid DALYs, Pakistan



Conclusions

- The increase in AMR in typhoid is real and of special concern is the rise of XDR typhoid (MDR plus FQ and Ceftriaxone resistant strains), severely limiting treatment options. These strains pose a major threat of trans-continental and regional spread.
- In general MDR typhoid appears to be a more severe disease with excess morbidity, at least 1.5 days longer hospitalization & 72% higher direct costs of illness.
- Of the DALYs and YLDs associated with typhoid, the bulk now appears to be due to antimicrobial-resistant typhoid, projected to almost replace all sensitive typhoid infections in South Asia
- Of potential interventions in the near future, large scale vaccination strategies for typhoid are the most promising to reduce the burden of illness, especially the incidence of MDR and XDR typhoid