Antimicrobial Resistance in Typhoid: implications for policy & immunization strategies

Zulfiqar A Bhutta, Imran Ahmed, Daina Als, Amruta Radhakrishnan, Farah Qamar, Jeffrey Stanaway, Christopher Parry

SickKids® | Centre for Global Child Health

THE AGA KHAN UNIVERSITY

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LSTM

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

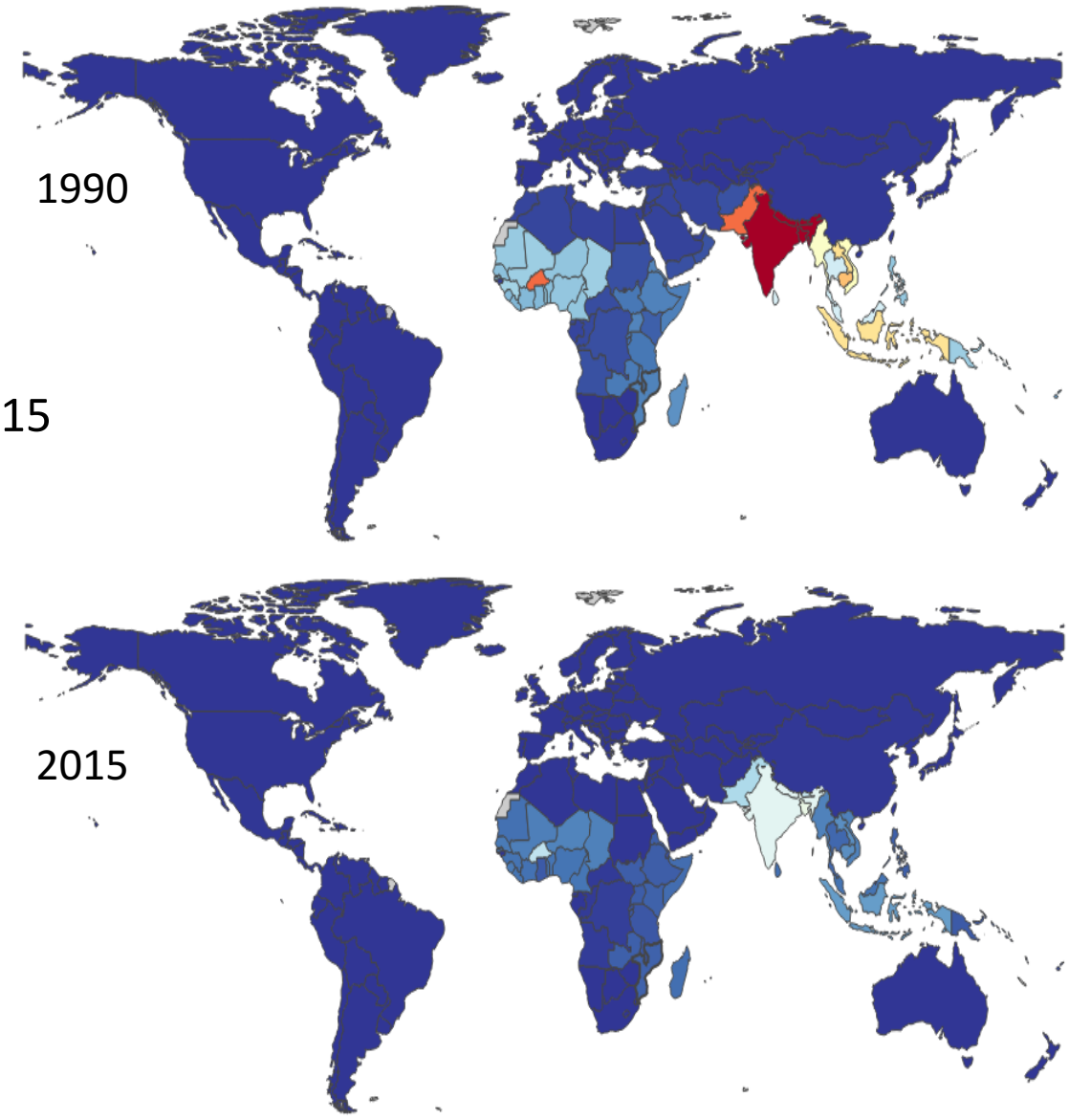
- Potential impact of vaccination strategies on disease burden and AMR burden/spread

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	■		

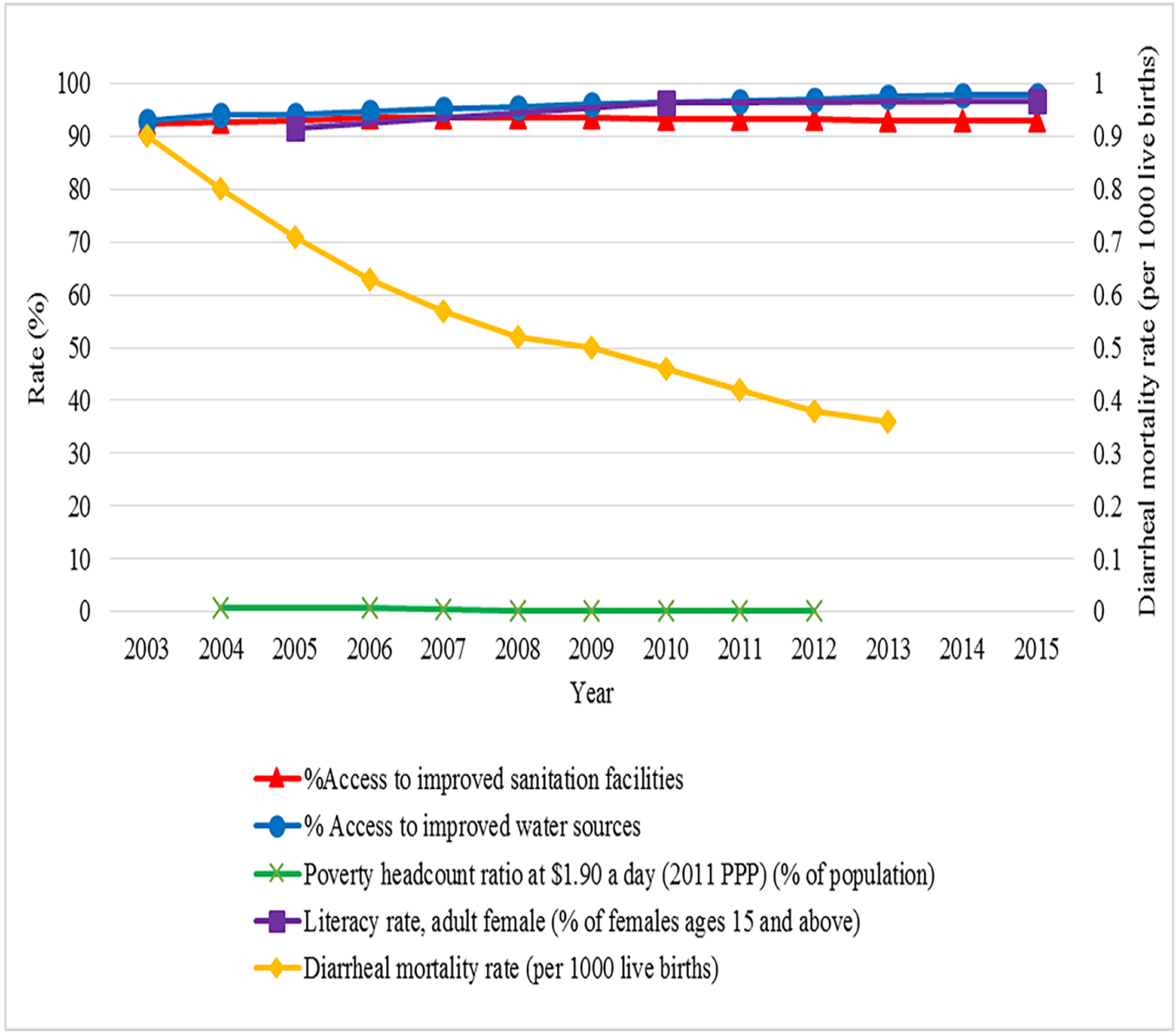
Contextual risk factors for typhoid

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	■			■	
Khan 2012	Pakistan	■				
Ram 2007	Bangladesh	■		■	■	
Srikantiah 2007	Uzbekistan	■				
Gasem 2001	Indonesia	■	■			■
Sharma 2009	India	■		■	■	
Tran 2005	Vietnam	■				
Vollard 2004	Indonesia		■			■
Kabwama 2017	Uganda	■				

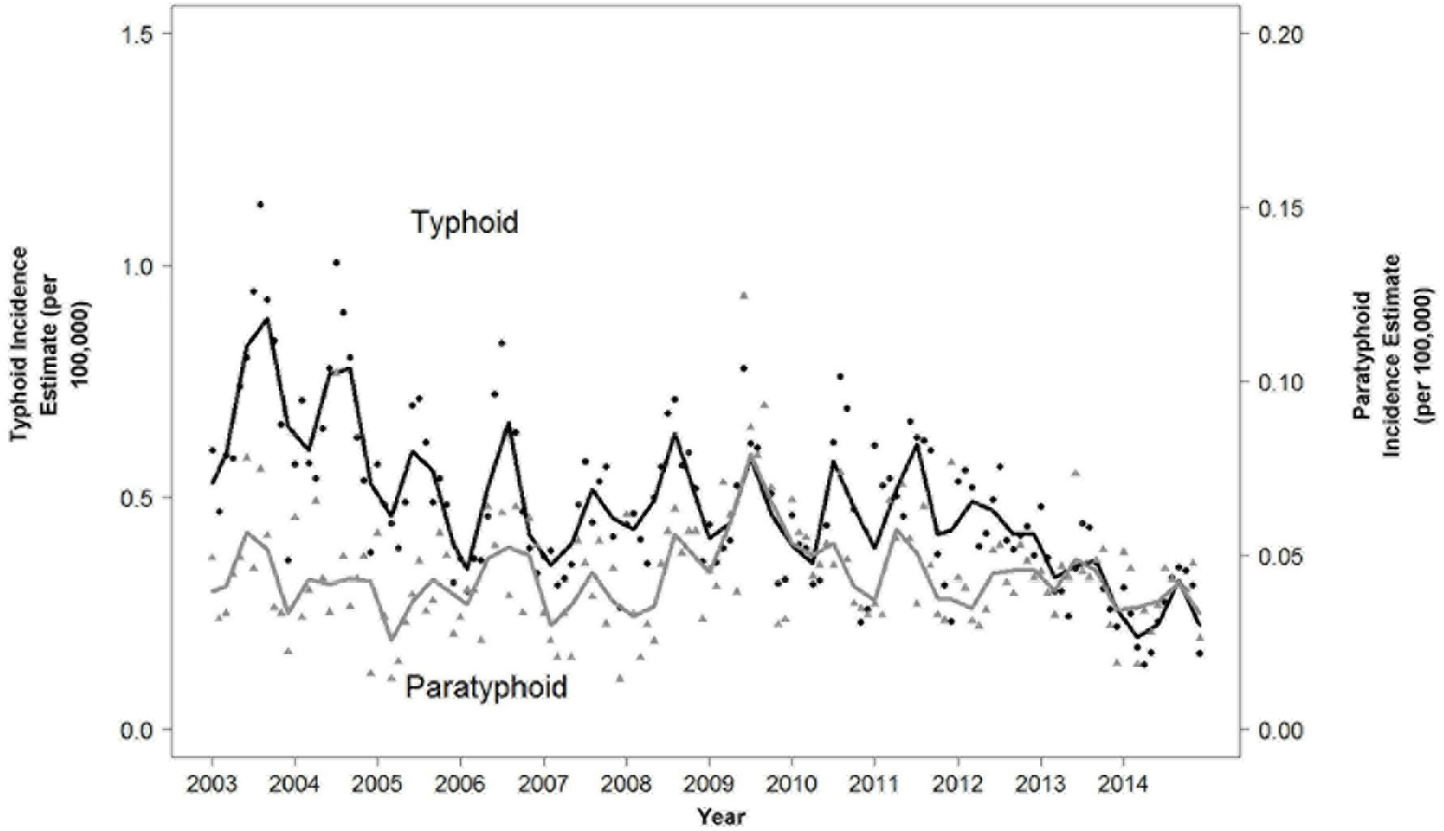
Contextual risk factors for typhoid

Study	Country	Drinking water	Hand washing	Open defecation	Consumption of raw vegetables/fruits	Street Foods	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



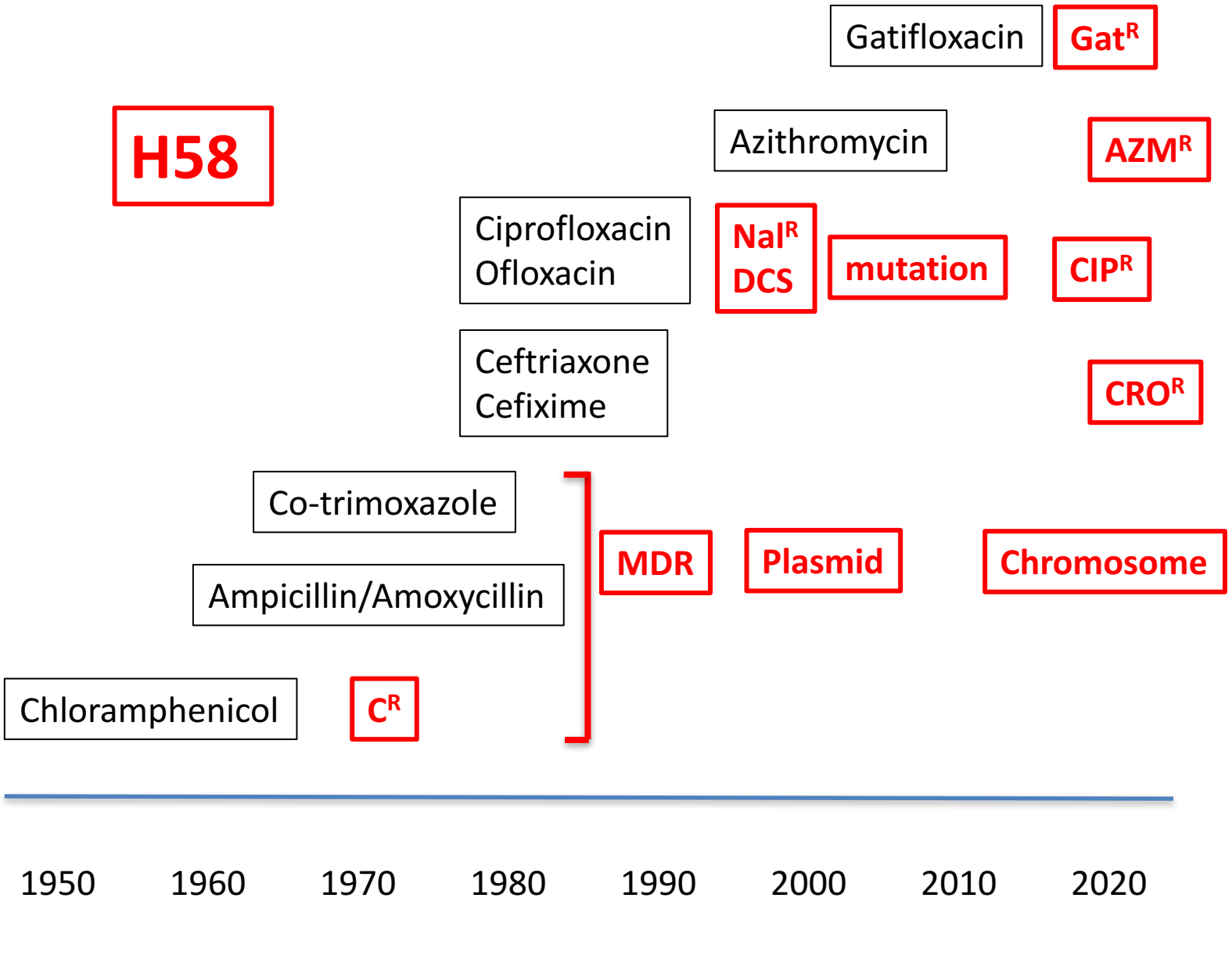
Thailand incidence trend



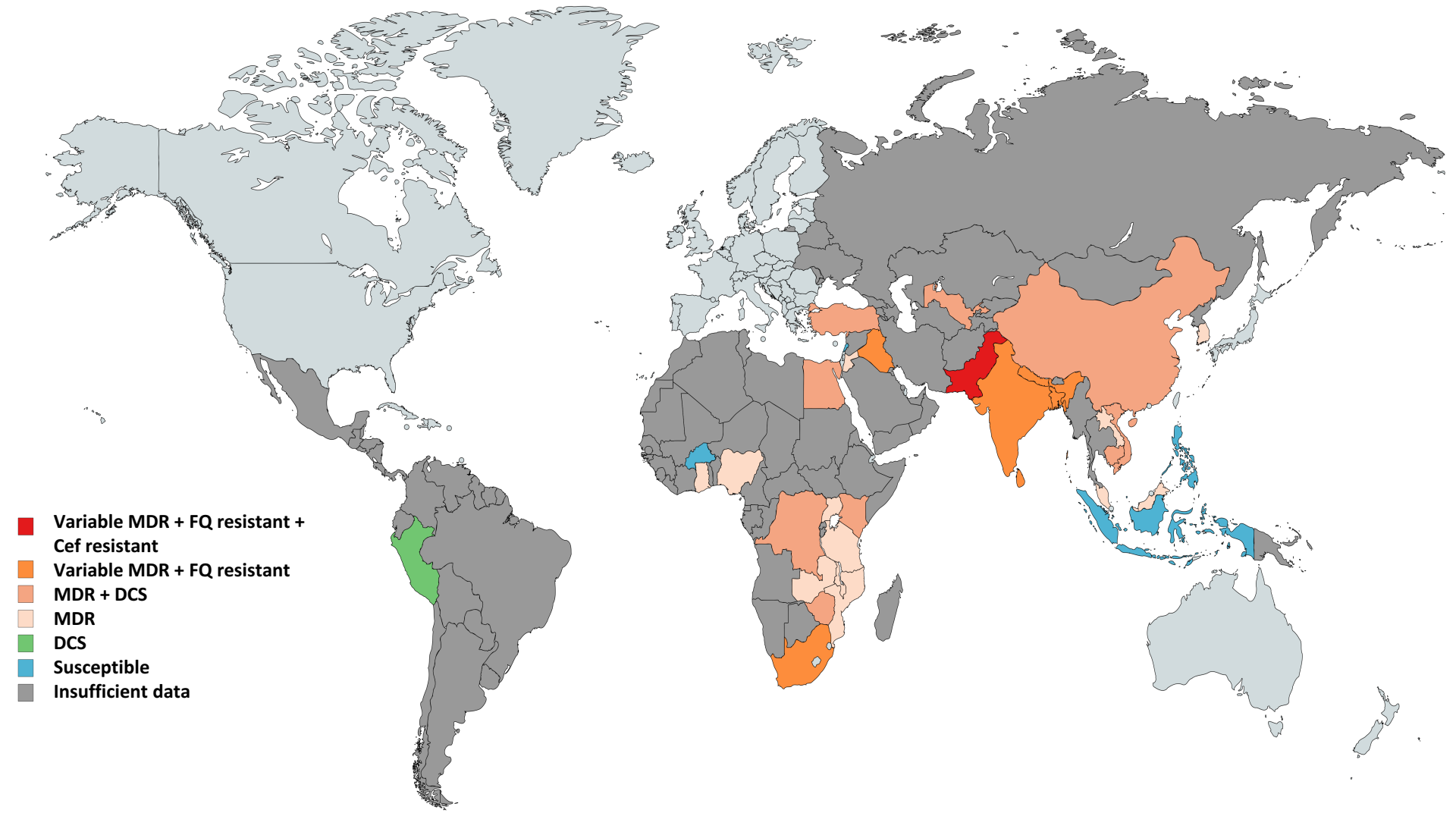
Year	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Reported Typhoid Cases	5443	5051	3878	3692	3168	3906	3671	3412	3887	3543	2603	1972
Reported Paratyphoid Cases	348	357	276	354	263	338	490	379	385	327	332	297
Total Population (in millions)	62.9	62.5	62.2	62.6	62.9	63.2	63.4	63.7	63.9	64.3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

Source: Ministry of Public Health, Thailand

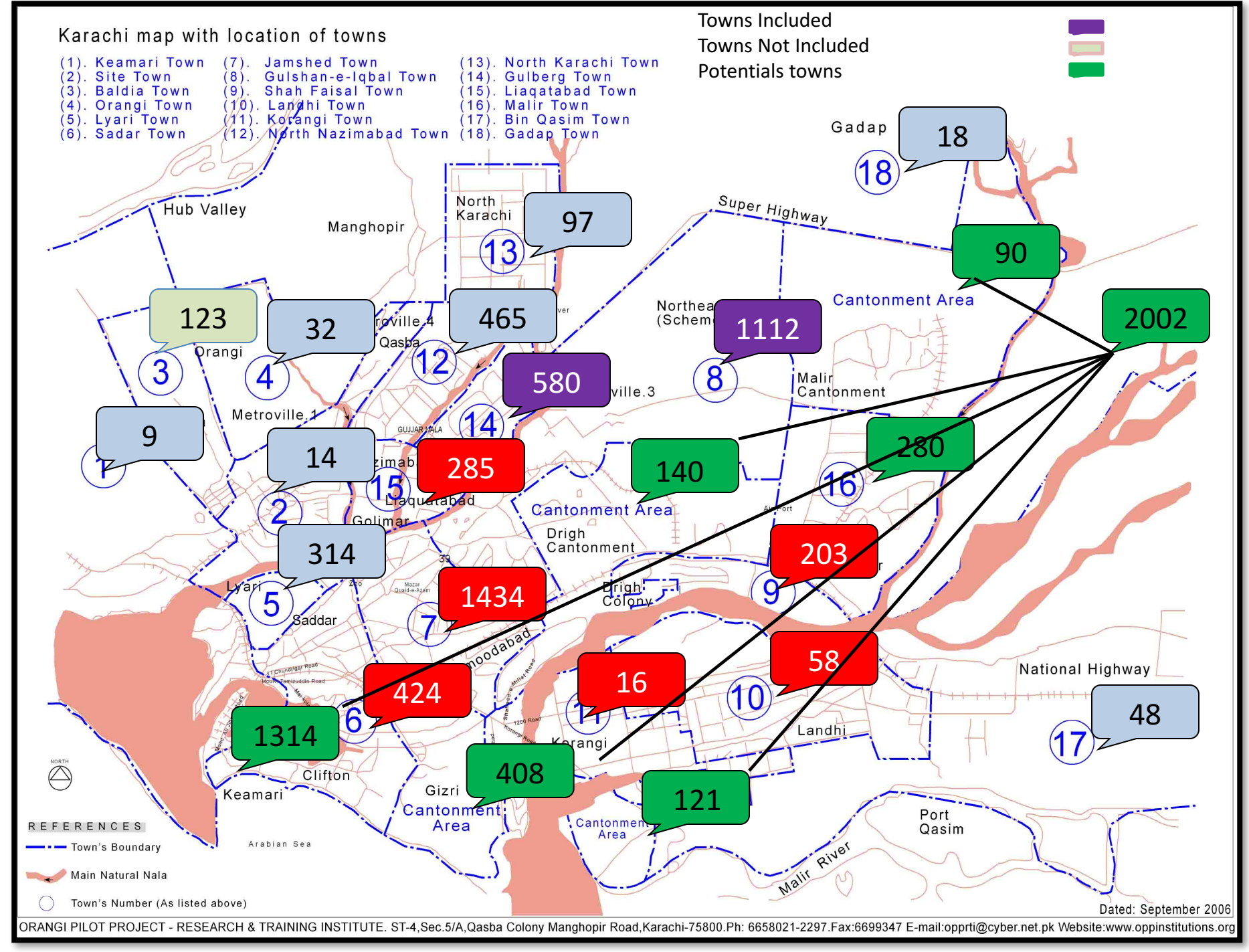
Typhoid & Antimicrobial Resistance


Gatifloxacin
Gat^R
H58
Azithromycin
AZM^R
Ciprofloxacin
Ofloxacin
Nal^R
DCS
mutation
CIP^R
Ceftriaxone
Cefixime
CRO^R
Co-trimoxazole
MDR
Plasmid
Chromosome
Ampicillin/Amoxycillin
Chloramphenicol
C^R
1950
1960
1970
1980
1990
2000
2010
2020

Anti-microbial resistance in Typhoid (2017)



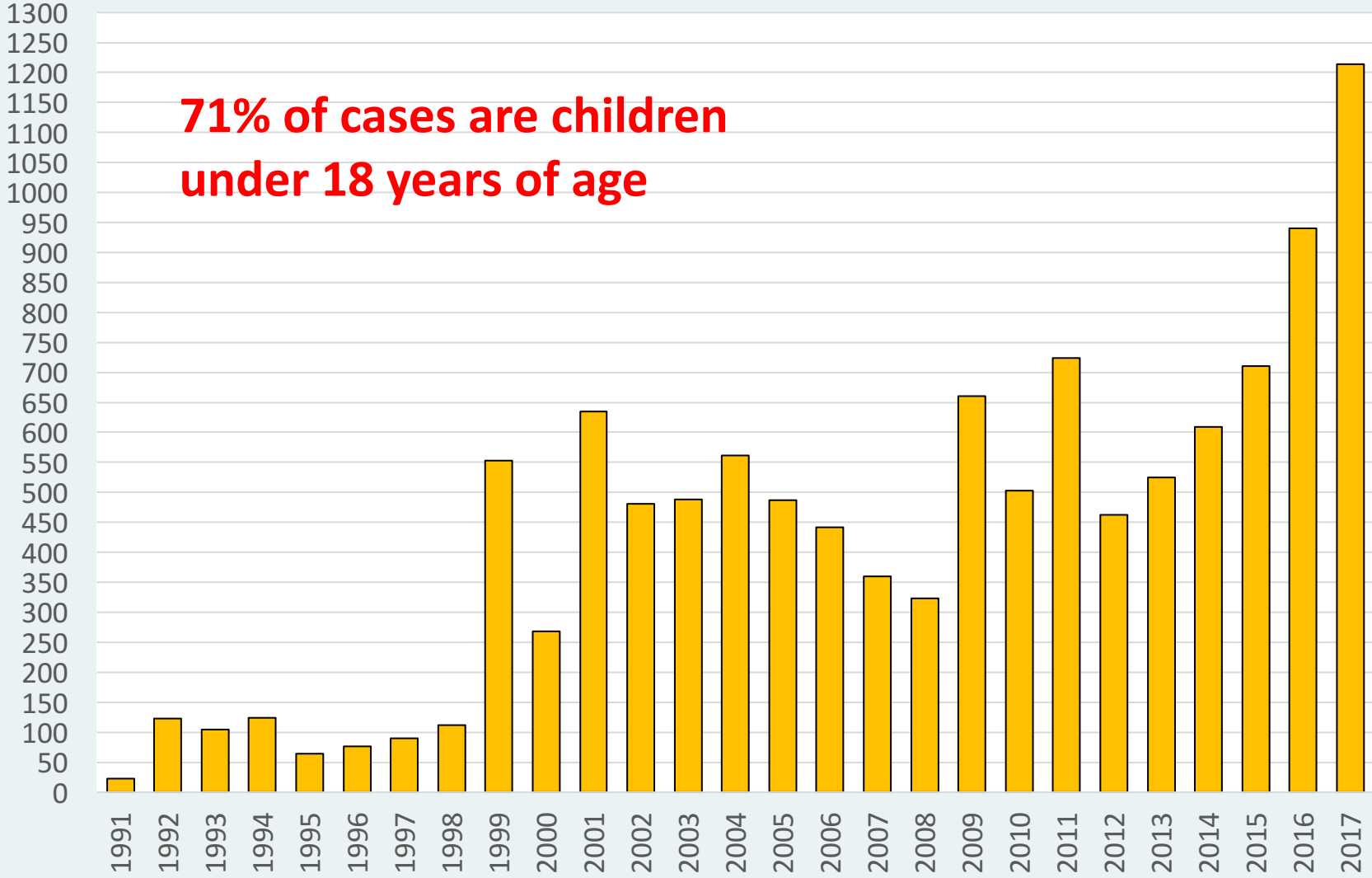
The Case Study from Karachi (Trends in AMR for typhoid)



ORANGI PILOT PROJECT - RESEARCH & TRAINING INSTITUTE. ST-4,Sec.5/A,Qasba Colony Manghopir Road,Karachi-75800.Ph: 6658021-2297.Fax:6699347 E-mail:opprti@cyber.net.pk Website:www.oppinstitutions.org

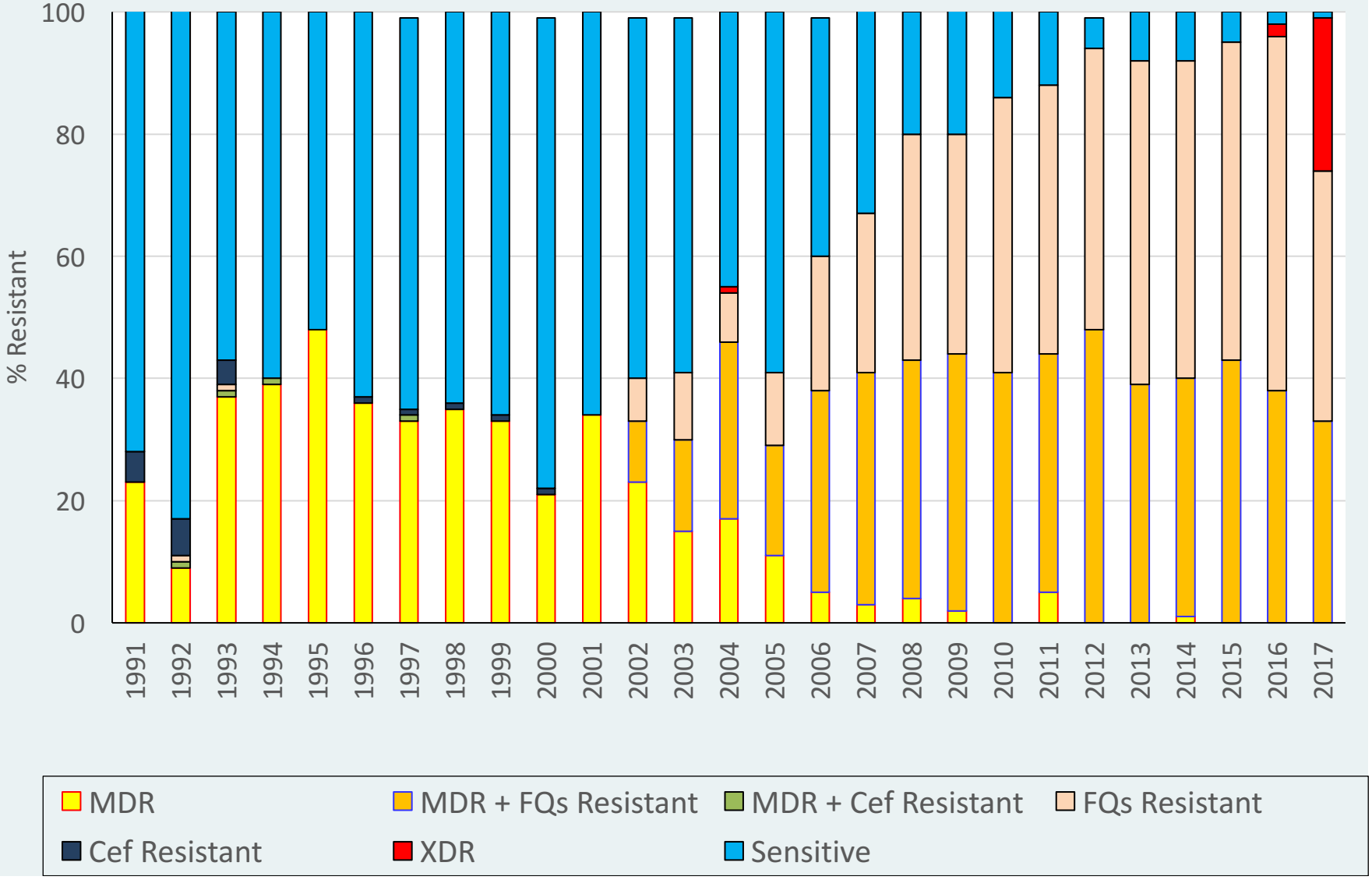
Number of Culture Positive Typhoid Specimens

Non Admission data 1991-2017



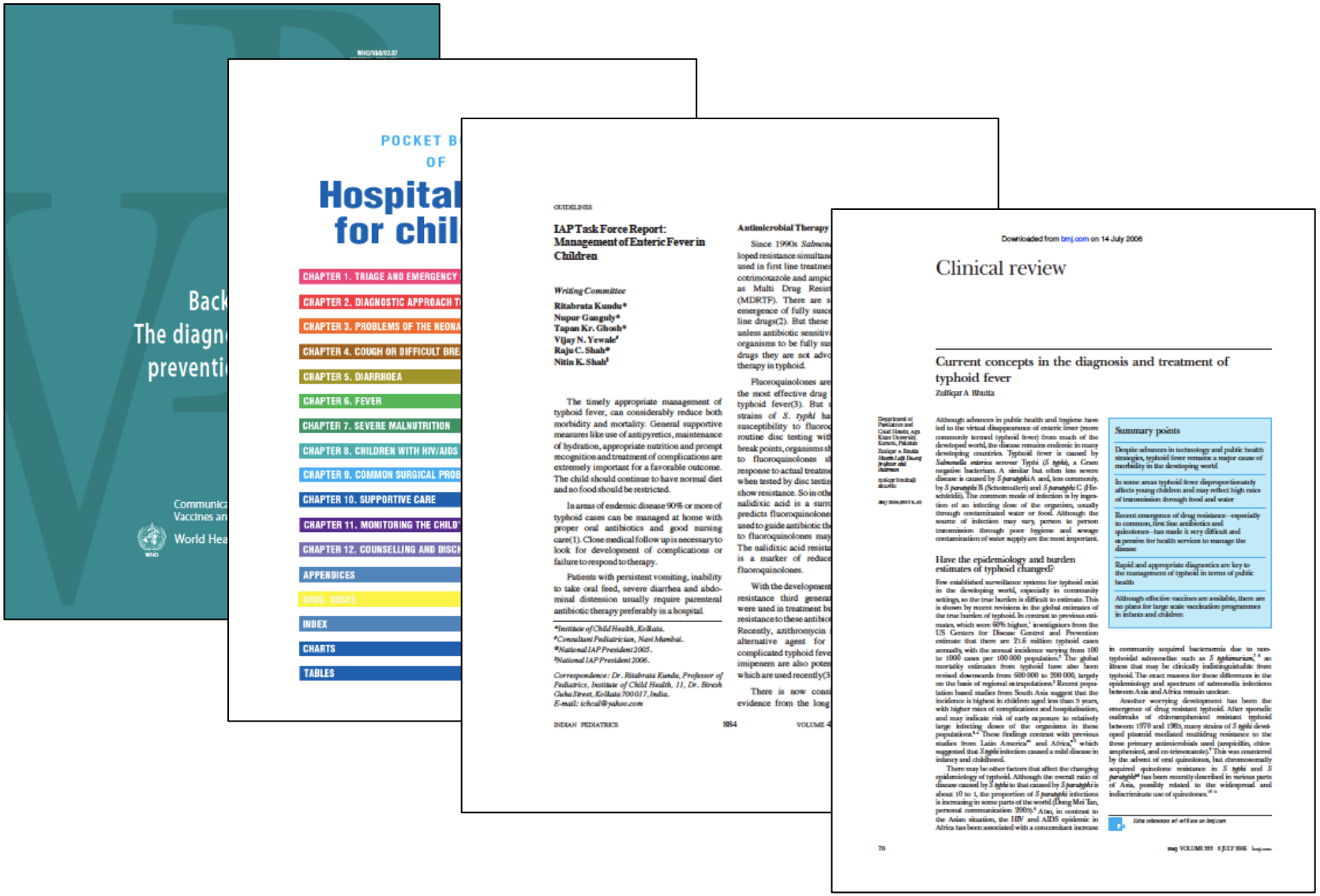
Antimicrobial Resistance for S. Typhi & Para Typhi

Non Admission data 1991-2017

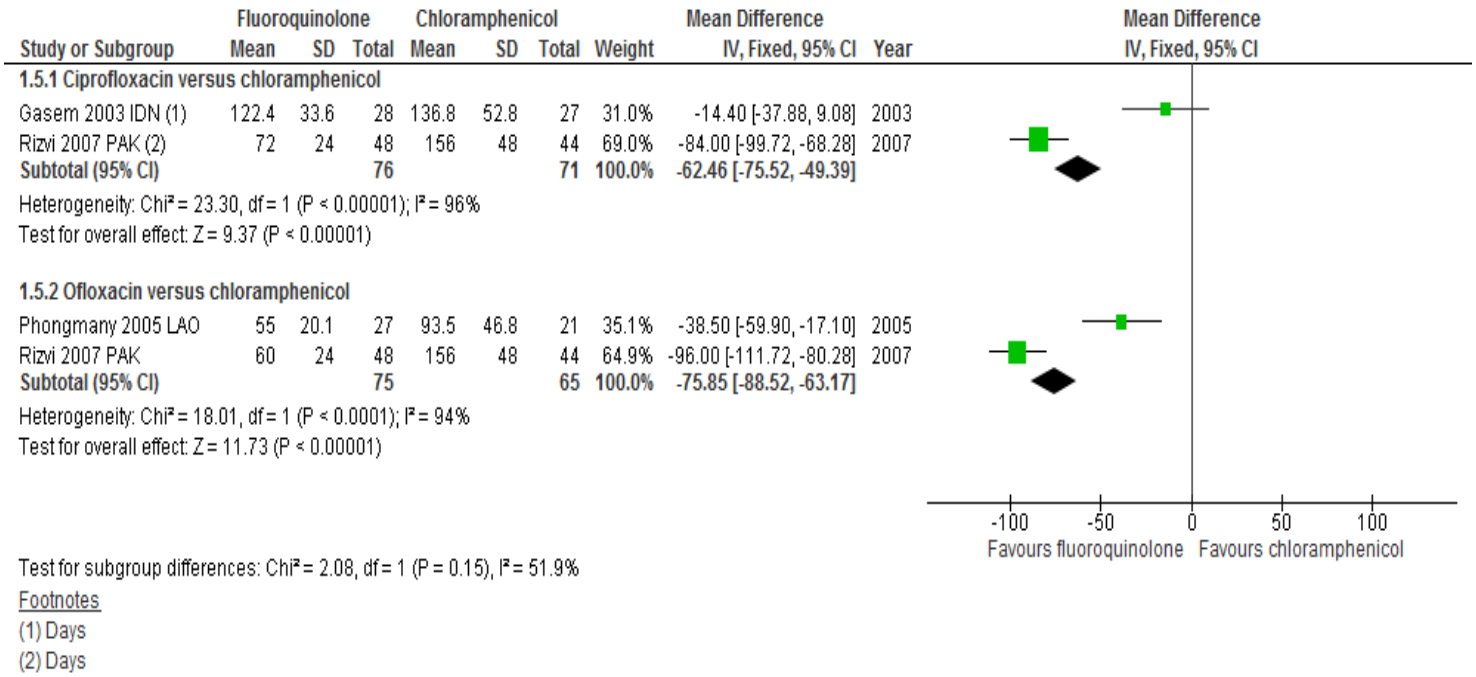


What about Antimicrobial Therapy?

Treatment guidelines & trends



Impact on fever clearance time



Study or Subgroup	Fluoroquinolone Mean	SD	Total	Chloramphenicol Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Year
1.5.1 Ciprofloxacin versus chloramphenicol									
Gasem 2003 IDN (1)	122.4	33.6	28	136.8	52.8	27	31.0%	-14.40 [-37.88, 9.08]	2003
Rizvi 2007 PAK (2)	72	24	48	156	48	44	69.0%	-84.00 [-99.72, -68.28]	2007
Subtotal (95% CI)			**76**			**71**	**100.0%**	**-62.46 [-75.52, -49.39]**	
Heterogeneity: Chi² = 23.30, df = 1 (P < 0.00001); I² = 96%									
Test for overall effect: Z = 9.37 (P < 0.00001)									
1.5.2 Ofloxacin versus chloramphenicol									
Phongmany 2005 LAO	55	20.1	27	93.5	46.8	21	35.1%	-38.50 [-59.90, -17.10]	2005
Rizvi 2007 PAK	60	24	48	156	48	44	64.9%	-96.00 [-111.72, -80.28]	2007
Subtotal (95% CI)			**75**			**65**	**100.0%**	**-75.85 [-88.52, -63.17]**	
Heterogeneity: Chi² = 18.01, df = 1 (P < 0.0001); I² = 94%									
Test for overall effect: Z = 11.73 (P < 0.00001)									

Test for subgroup differences: Chi² = 2.08, df = 1 (P = 0.15), I² = 51.9%

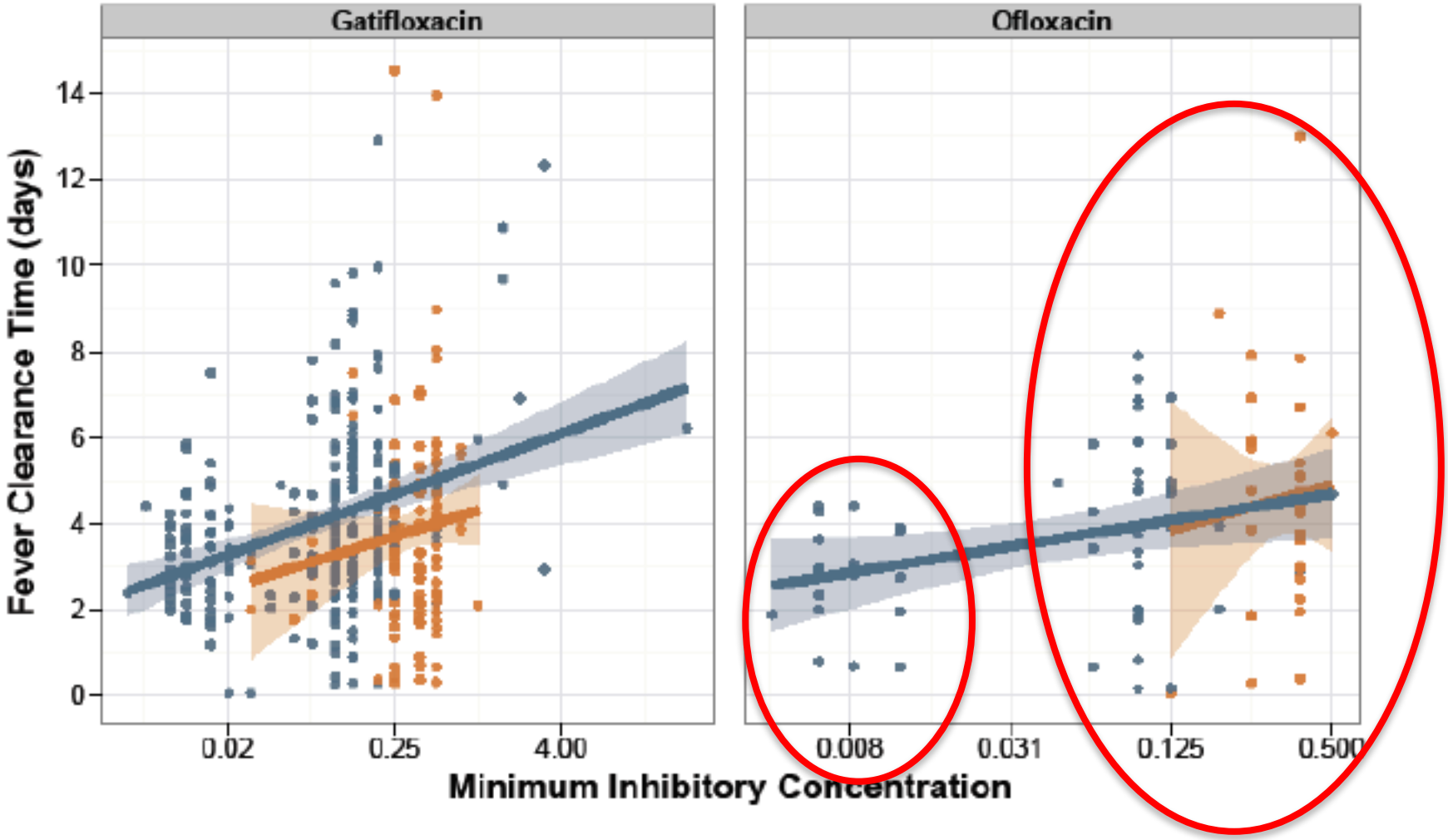
Footnotes

(1) Days

(2) Days

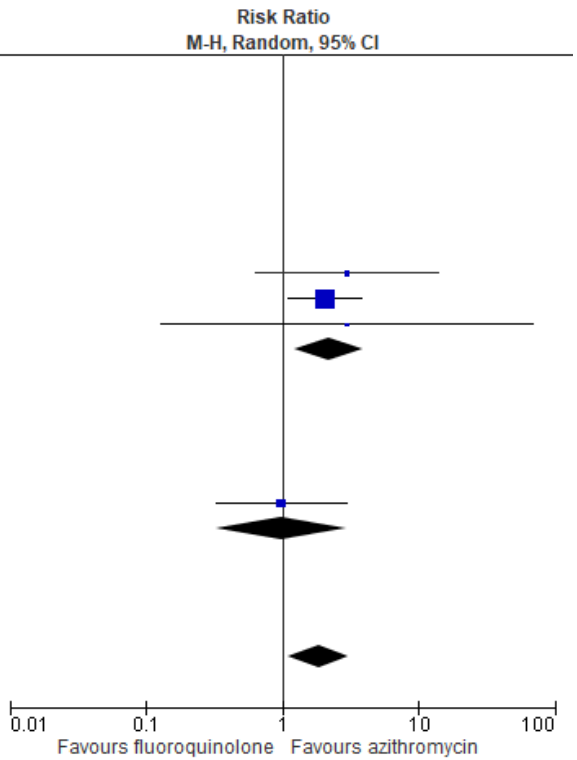
Effa et al (Cochrane Library) update 2018 (unpublished)

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

Study or Subgroup	Fluoroquinolone Events	Total	Azithromycin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
6.1.1 Ciprofloxacin versus azithromycin							
Girgis 1999 EGY (1)	0	28	0	36		Not estimable	1999
Subtotal (95% CI)		**28**		**36**		**Not estimable**	
Total events	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
6.1.2 Ofloxacin versus azithromycin							
Chinh 2000 VNM (2)	6	44	2	44	10.8%	3.00 [0.64, 14.06]	2000
Parry 2007 VNM (3)	23	63	11	62	65.6%	2.06 [1.10, 3.85]	2007
Chandey 2012 IND	1	20	0	20	2.6%	3.00 [0.13, 69.52]	2012
Subtotal (95% CI)		**127**		**126**	**79.0%**	**2.19 [1.24, 3.88]**	
Total events	30		13				
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 2 (P = 0.89); I² = 0%							
Test for overall effect: Z = 2.69 (P = 0.007)							
6.1.3 Gatifloxacin versus azithromycin							
Dolecek 2008 VNM (4)	6	145	6	142	21.0%	0.98 [0.32, 2.96]	2008
Subtotal (95% CI)		**145**		**142**	**21.0%**	**0.98 [0.32, 2.96]**	
Total events	6		6				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.04 (P = 0.97)							
Total (95% CI)		**300**		**304**	**100.0%**	**1.85 [1.11, 3.08]**	
Total events	36		19				
Heterogeneity: Tau² = 0.00; Chi² = 1.84, df = 3 (P = 0.61); I² = 0%							
Test for overall effect: Z = 2.38 (P = 0.02)							
Test for subgroup differences: Chi² = 1.61, df = 1 (P = 0.20), I² = 37.8%							



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

Effa et al (Cochrane Library) update 2018 (unpublished)

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 multiresistant 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.

journal of global health

PAPERS

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

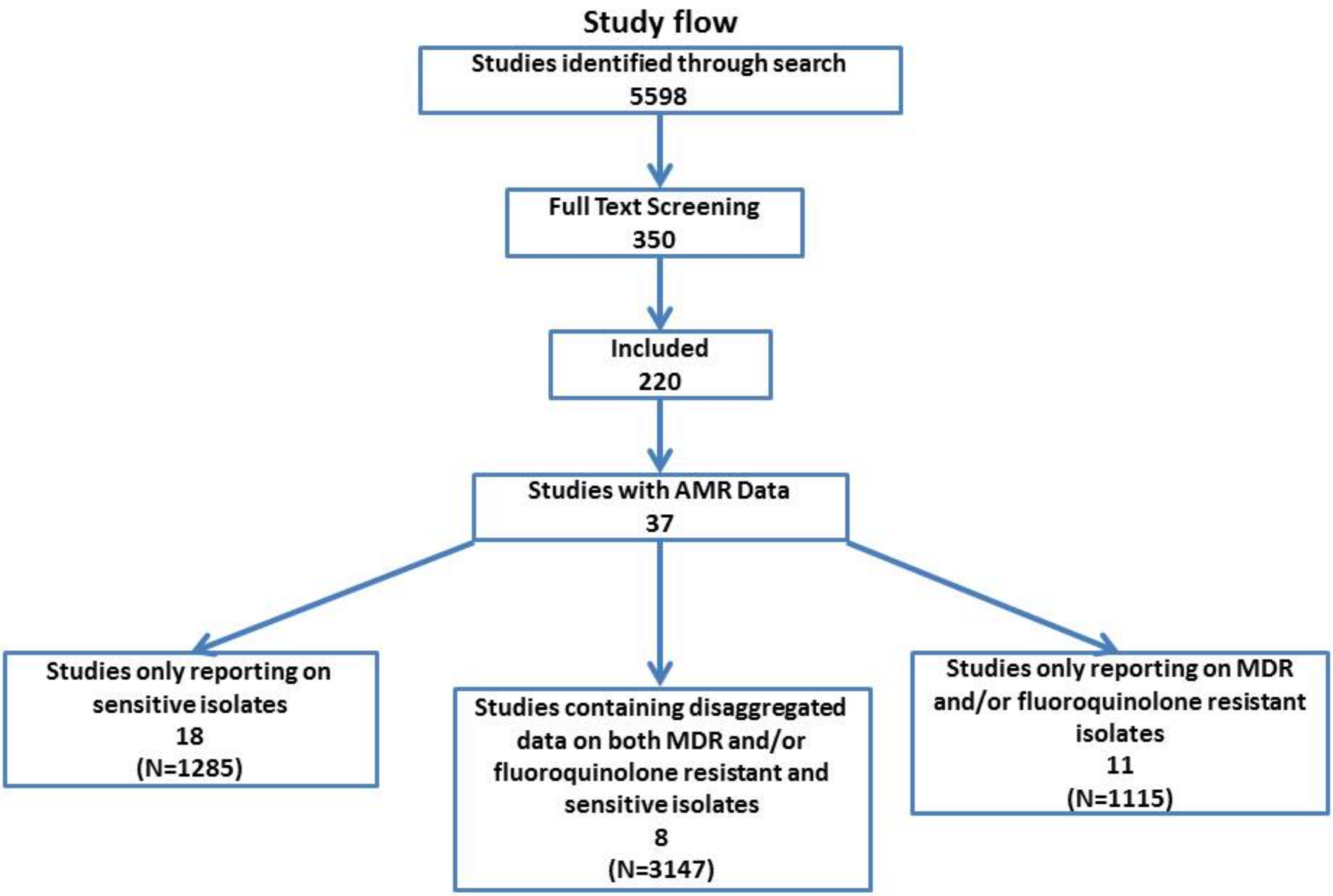
Asma Azmatullah[1], Farah Naz Qamar[1], Durrane Thaver[1], Anita KM Zaidi[1], Zulfiqar A Bhutta[2,3]

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



N refers to the number of isolates tested from patients

Complications & Clinical Outcomes

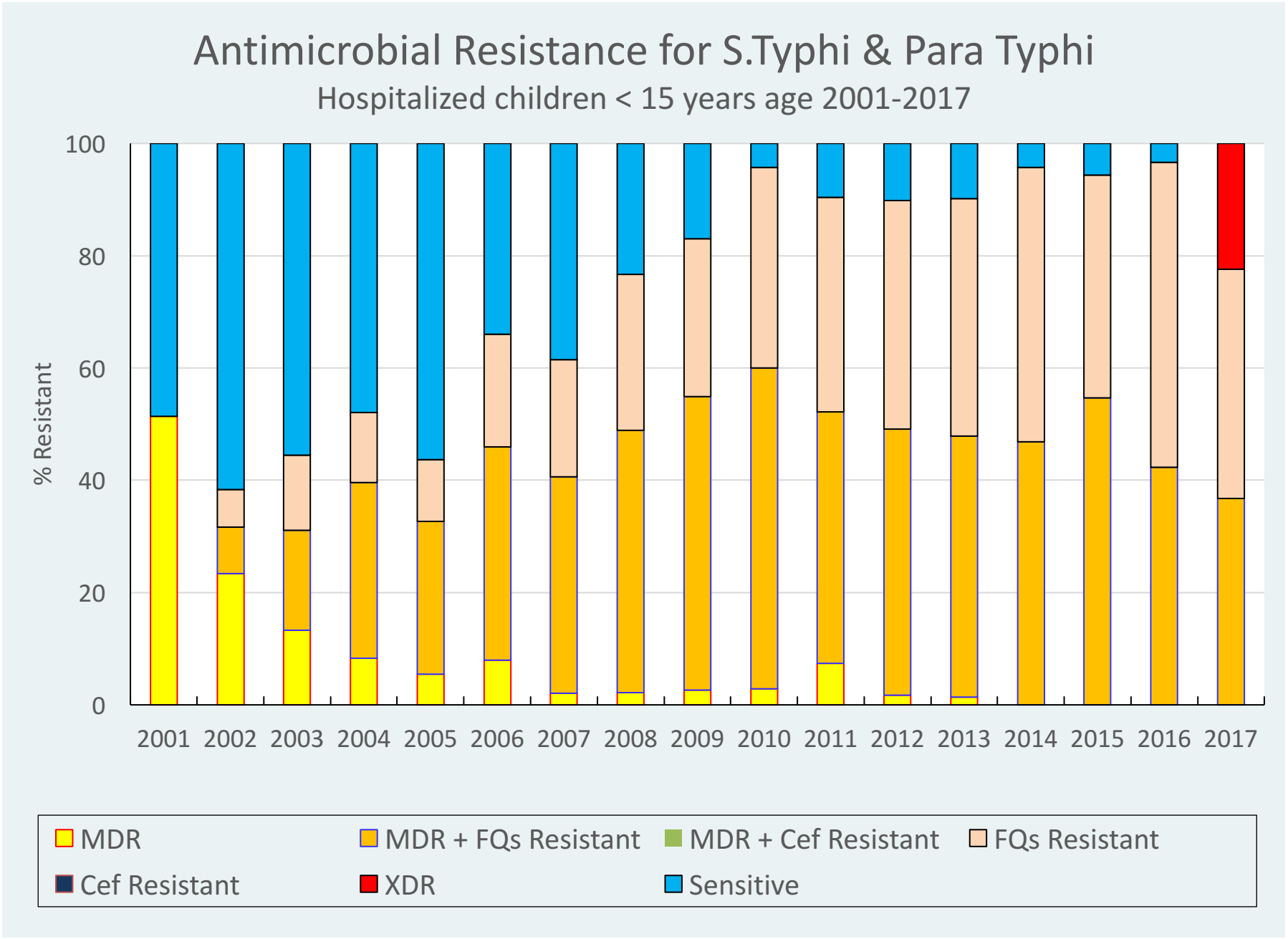
	Multi-drug and/or fluoroquinolone resistant 2311 cases from 19 Studies				Sensitive 3236 cases from 26 Studies			
	n	**N**	**%**	**Studies**	**n**	**N**	**%**	**Studies**
Shock or hypotension	22	133	**16.5**	4	7	105	**6.7**	3
Toxicity	208	427	**48.7**	5	310	968	**32.0**	5
GI Bleeding	29	316	**9.2**	8	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

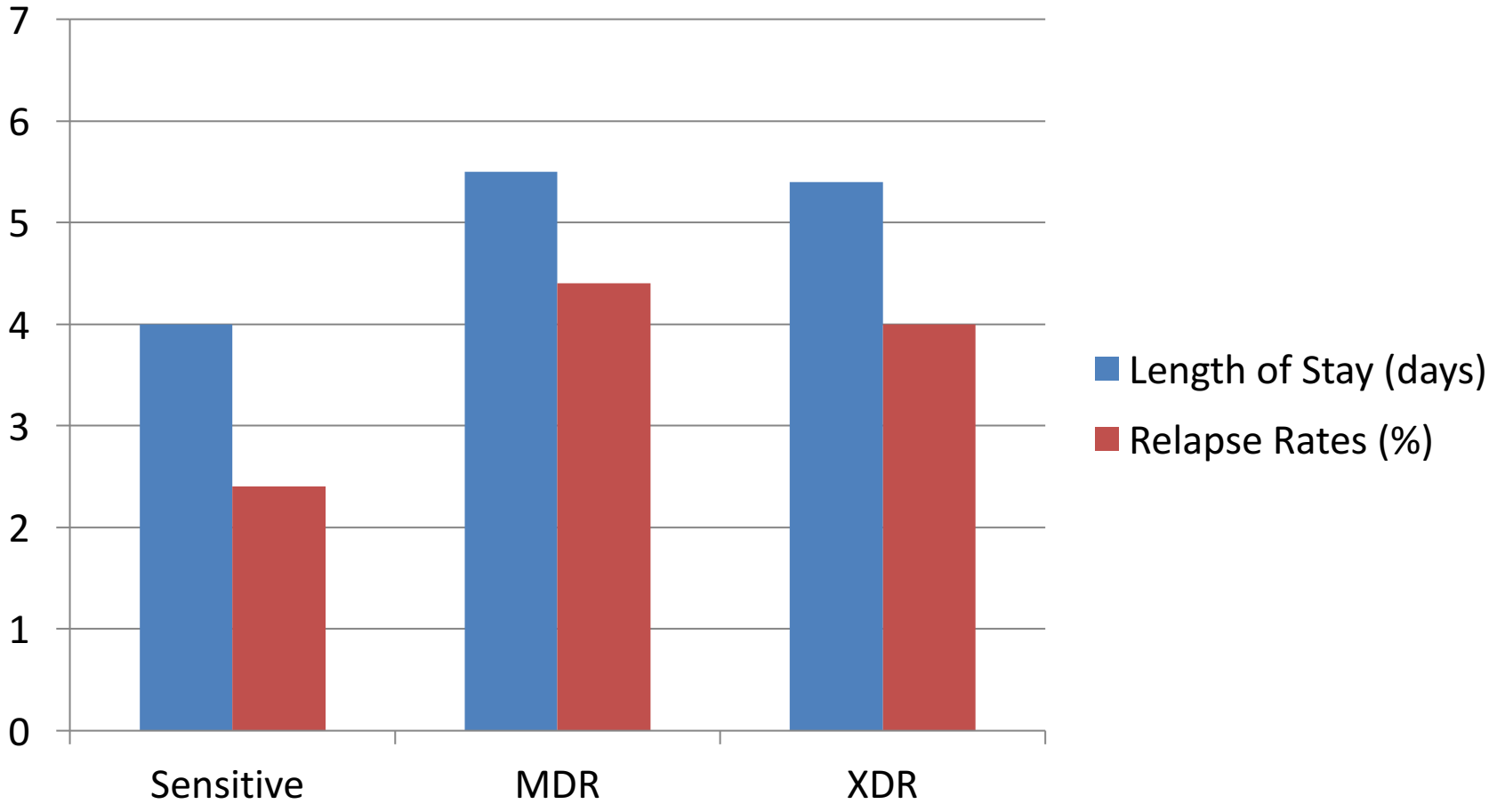
	Multi-drug and/or fluoroquinolone resistant 2311 cases from 19 Studies				Sensitive 3236 cases from 26 Studies				Comparison	
	n	N	%	Studies	n	N	%	Studies	Odds Ratio	95% CI
Shock or hypotension	22	133	**16.5**	4	7	105	**6.7**	3	**2.77**	(1.14, 6.78)
Toxicity	208	427	**48.7**	5	310	968	**32.0**	5	**2.02**	(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?


01:10

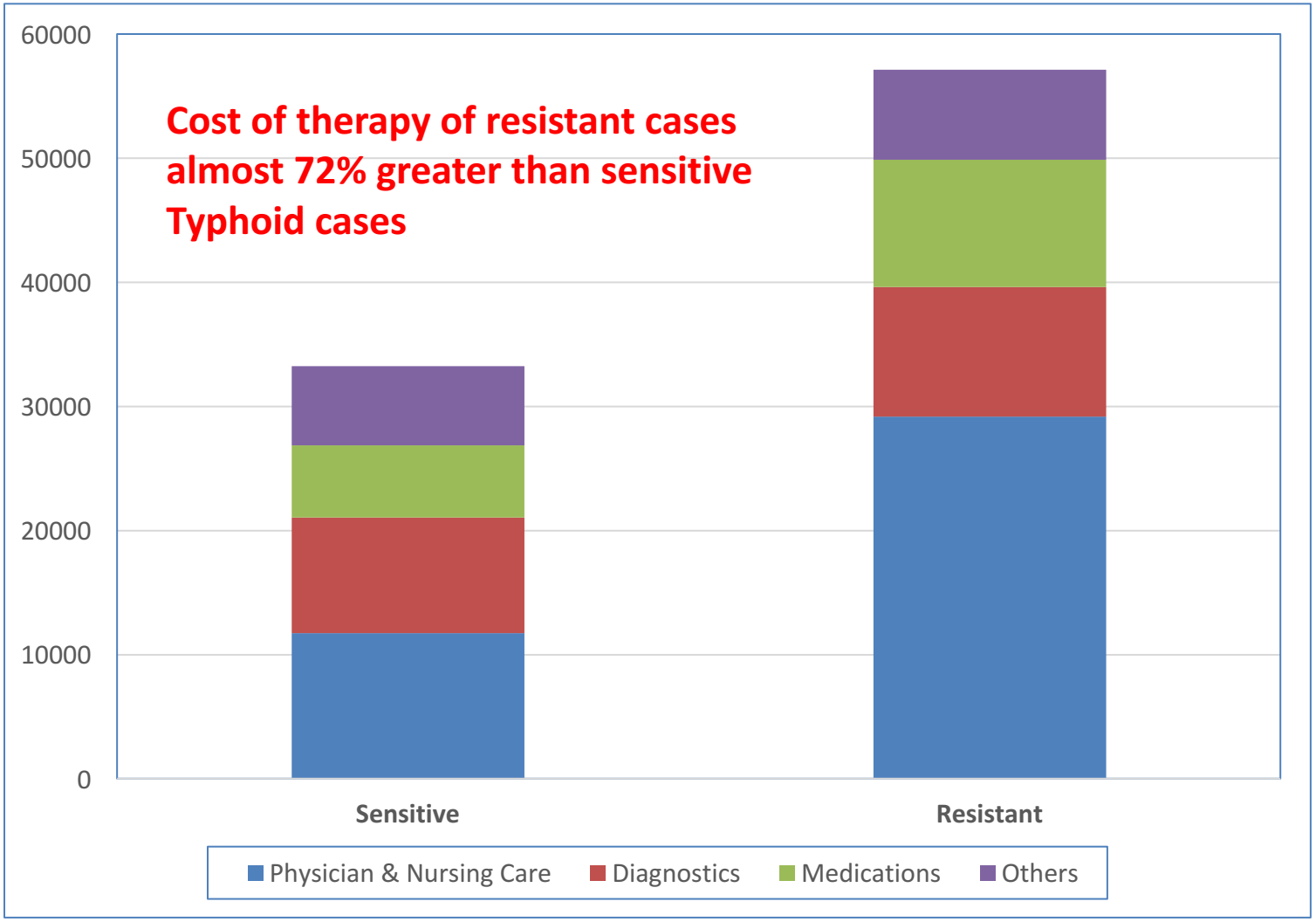

Antimicrobial Resistance for S.Typhi & Para Typhi
Hospitalized children < 15 years age 2001-2017
% Resistant
100
80
60
40
20
0
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
MDR
MDR + FQs Resistant
MDR + Cef Resistant
FQs Resistant
Cef Resistant
XDR
Sensitive

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

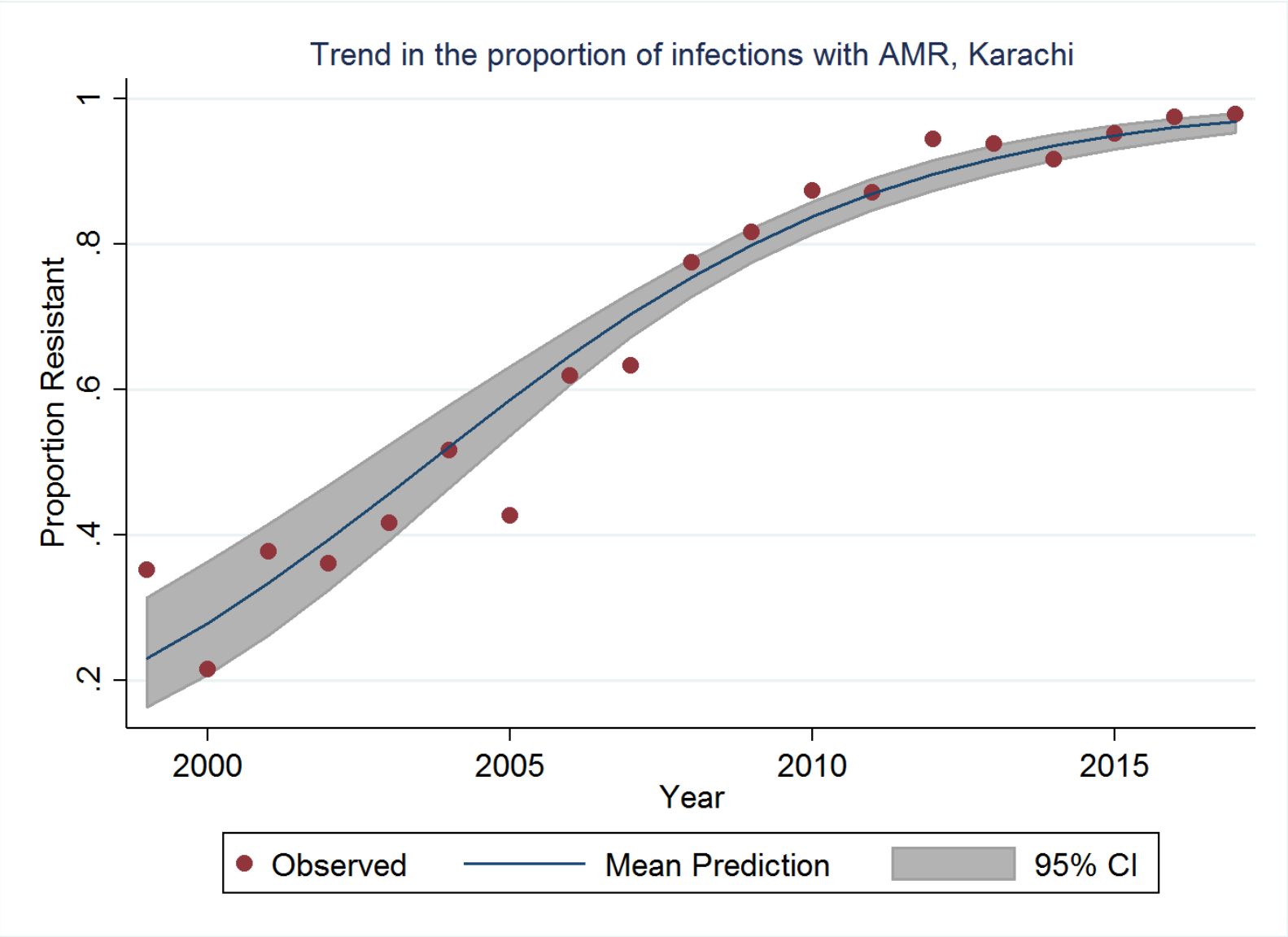
- Calculated YLD per case multipliers for sensitive and resistant infections as

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

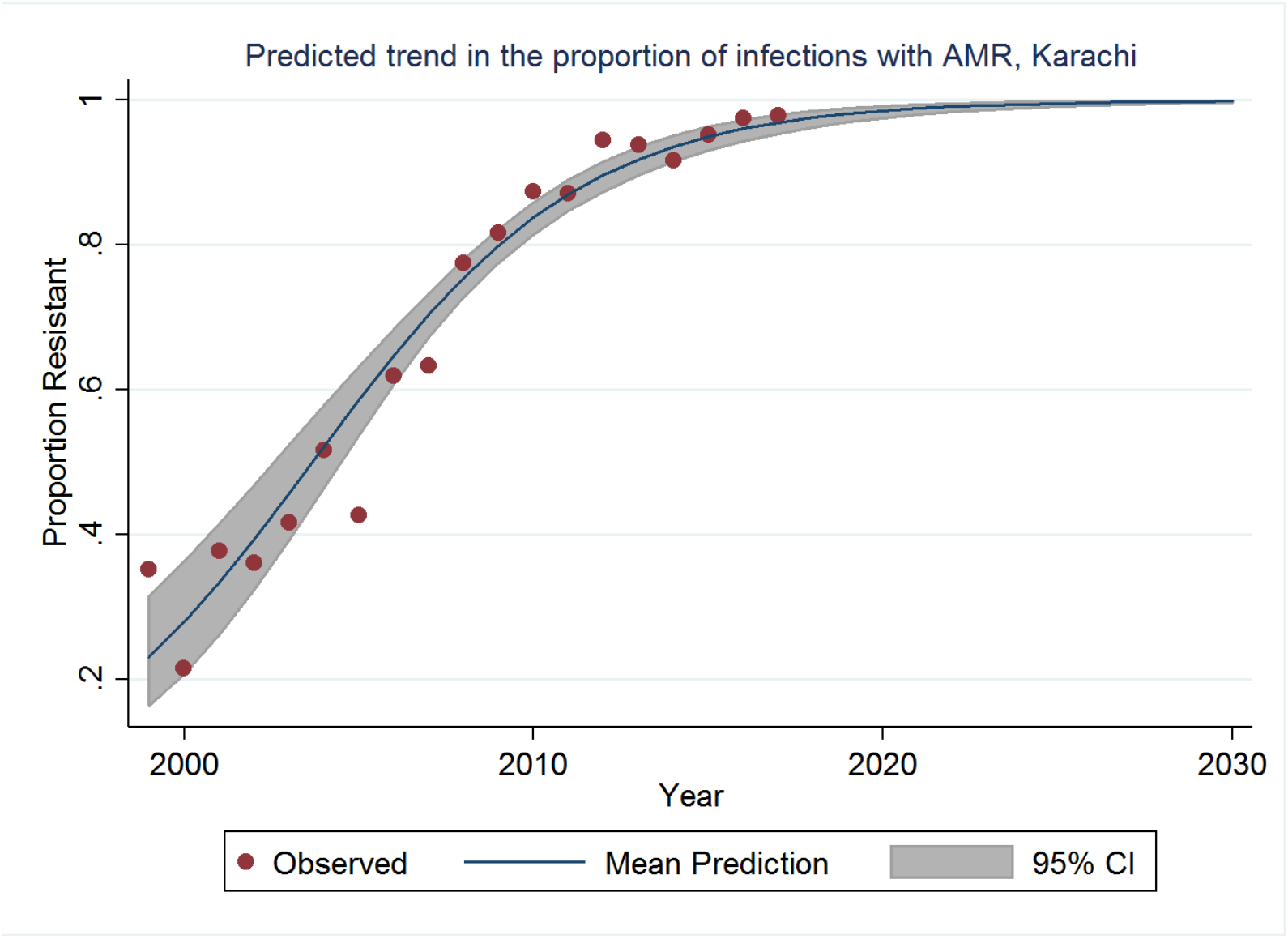
$$M_{resist} = \frac{YLD_{resist}}{YLD_{gbd}}$$

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%)



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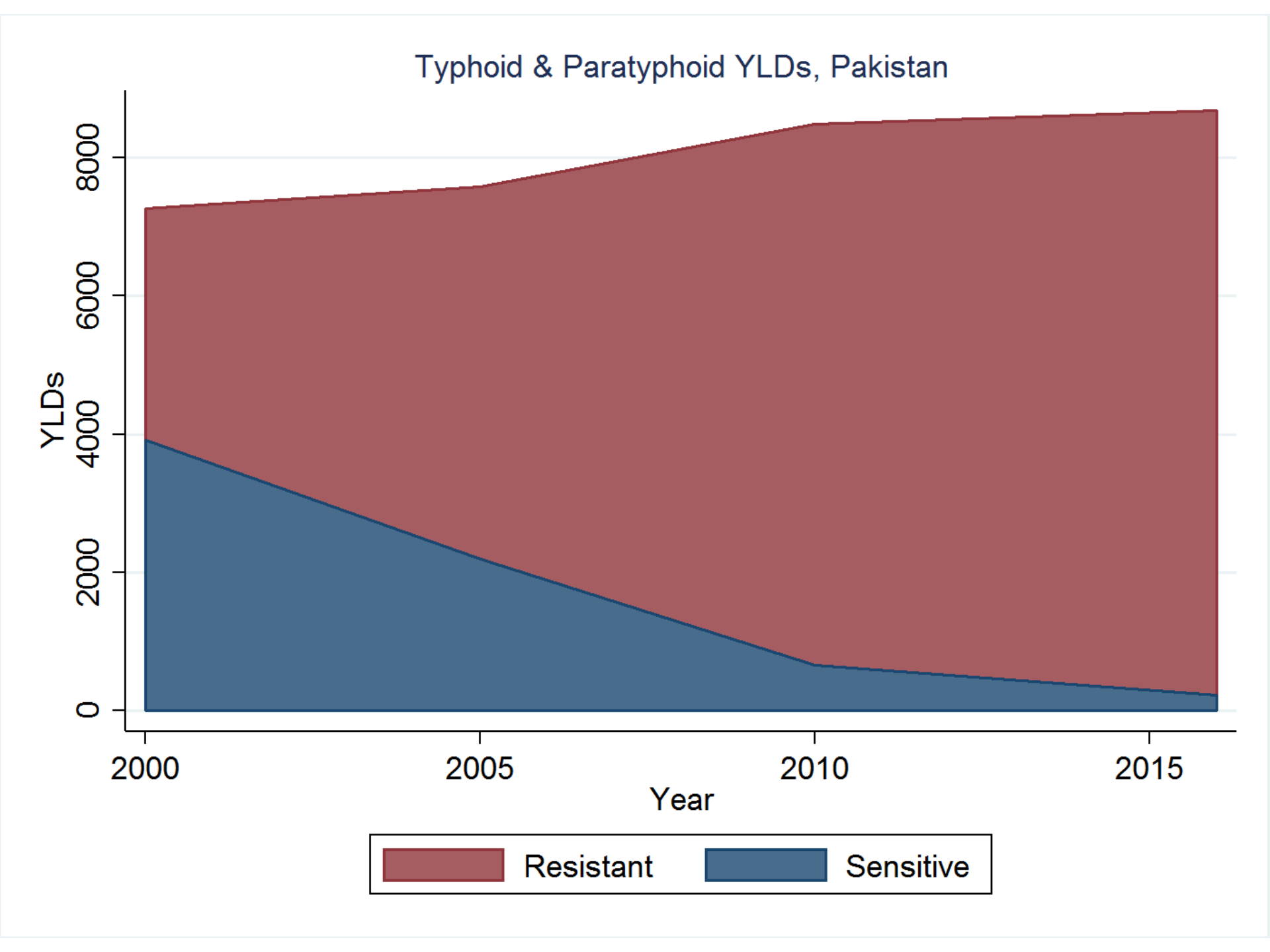
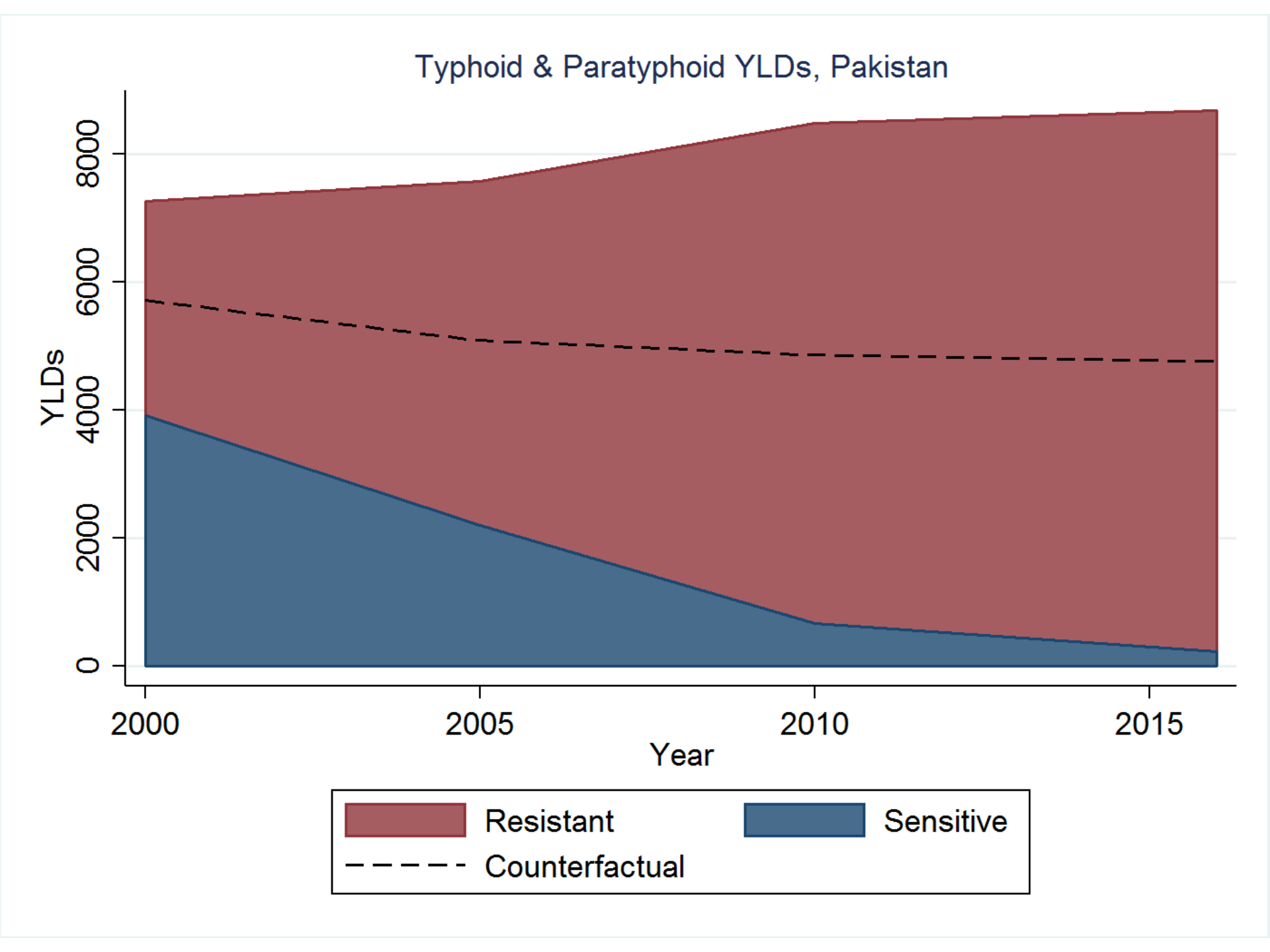
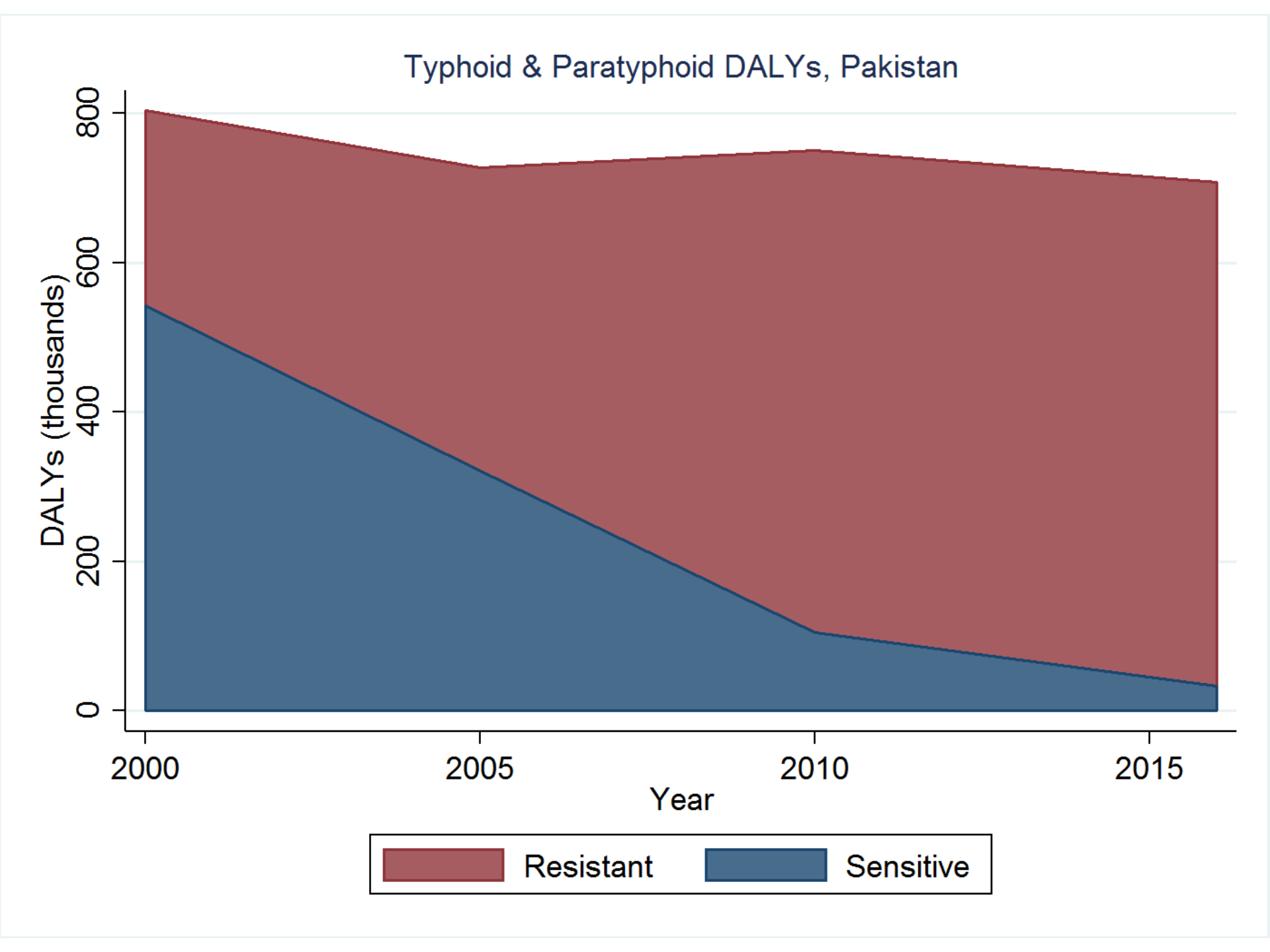

Typhoid & Paratyphoid YLDs, Pakistan
YLDs
0
2000
4000
6000
8000
2000
2005
2010
2015
Year
Resistant
Sensitive


Typhoid & Paratyphoid YLDs, Pakistan
YLDs
0
2000
4000
6000
8000
2000
2005
2010
2015
Year
Resistant
Sensitive
Counterfactual


Typhoid & Paratyphoid DALYs, Pakistan
DALYs (thousands)
0
200
400
600
800
2000
2005
2010
2015
Year
Resistant
Sensitive

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