



Oxford University Clinical Research Unit

The burden of *S. Paratyphi A* in Kathmandu: epidemiological observations from a decade of clinical trials

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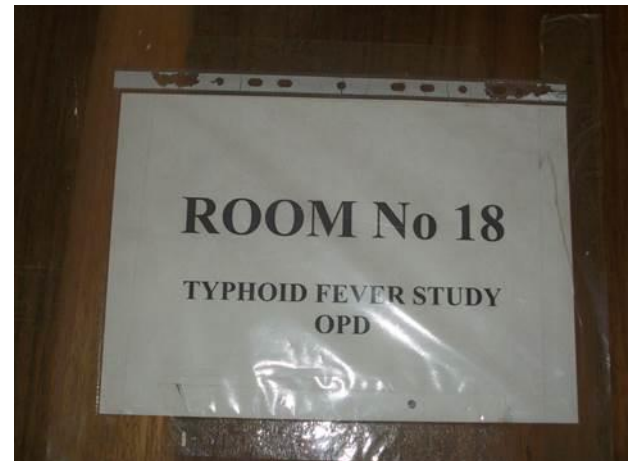
Kathmandu, Nepal

- Nepal: 28 million people
- GNI per capita: \$730
- Under 5 mortality rate: 40/1000
- Kathmandu: 2.5 million people



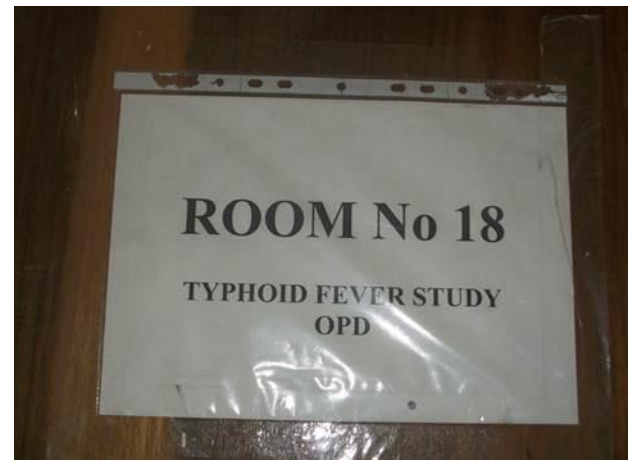
Enteric fever treatment trials

- 4 clinical trials conducted at Patan Hospital, 2005-2014



Enteric fever treatment trials

- 4 clinical trials conducted at Patan Hospital, 2005-2014
- Same protocol throughout



Inclusion

- Visiting OPD
- Clinically diagnosed enteric fever
- >2 years of age
- Live in Lalitpur

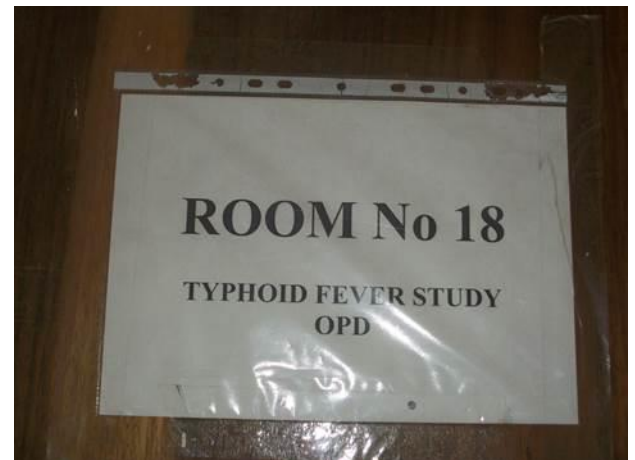
Exclusion

- Pregnant or lactating
- Complicated typhoid
- FLQ, macrolide or 3rd generation cephalosporin in week prior



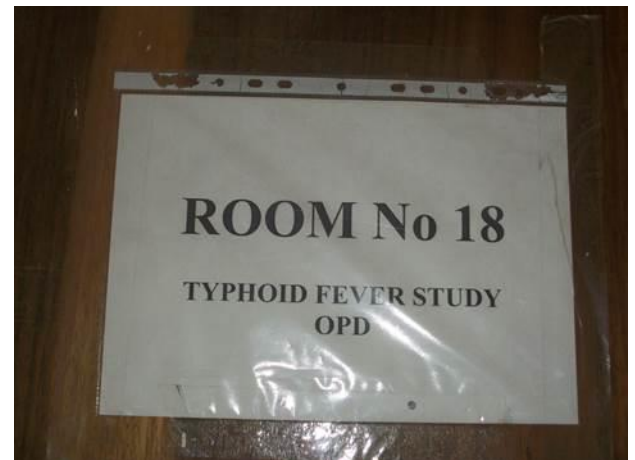
Enteric fever treatment trials

- 4 clinical trials conducted at Patan Hospital, 2005-2014
- Same protocol throughout
- 2,118 patients total



Enteric fever treatment trials

- 4 clinical trials conducted at Patan Hospital, 2005-2014
- Same protocol throughout
- 2,118 patients total
- Gatifloxacin in every trial



An Open Randomized Comparison of Gatifloxacin versus Cefixime for the Treatment of Uncomplicated Enteric Fever

Anil Pandit^{1*}, Amit Arjyal^{1*}, Jeremy N. Day^{2,3,4}, Buddhi Paudyal¹, Sabina Dangol¹, Mark D. Zimmerman¹, Bharat Yadav¹, Kasia Stepniewska², James I. Campbell^{2,3}, Christiane Dolecek^{2,3}, Jeremy J. Farrar^{2,3}, Buddha Basnyat^{1,5*}

1 Patan Hospital, Lagankhel, Lalitpur, Nepal, 2 Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam,

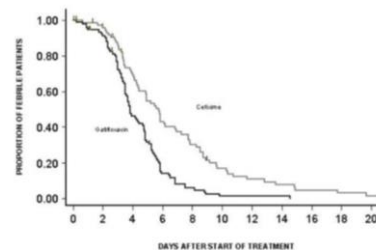
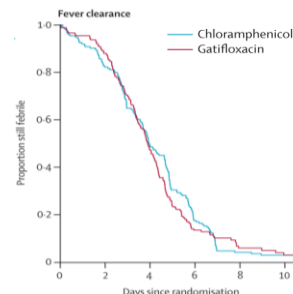


Figure 3. Proportion of culture positive patients still febrile. Kaplan-

2005
n=390

Gatifloxacin versus chloramphenicol for uncomplicated enteric fever: an open-label, randomised, controlled trial

Amit Arjyal, Buddha Basnyat, Samir Koirala, Abhilasha Karkey, Sabina Dongol, Krishna Kumar Agrawaal, Nikki Shakya, Kabina Shrestha, Manish Sharma, Sanju Lama, Kasturi Shrestha, Nely Shrestha Khatri, Umesh Shrestha, James I Campbell, Stephen Baker, Jeremy Farrar, Marcel Wolbers, Christiane Dolecek

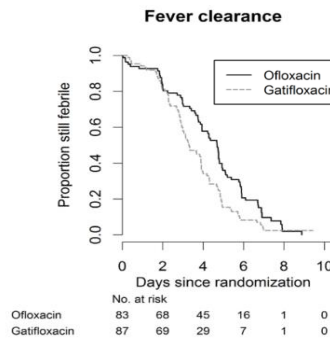


2006-08
n=853

Gatifloxacin Versus Ofloxacin for the Treatment of Uncomplicated Enteric Fever in Nepal: An Open-Label, Randomized, Controlled Trial

Samir Koirala¹, Buddha Basnyat^{1*}, Amit Arjyal¹, Olita Shilpakar¹, Kabina Shrestha¹, Rishav Shrestha¹, Upendra Man Shrestha¹, Krishna Agrawal¹, Kanika Deshpande Koirala¹, Sudeep Dhoj Thapa¹, Abhilasha Karkey¹, Sabina Dongol¹, Abhishek Giri¹, Mila Shakya¹, Kamal Raj Pathak¹, James Campbell¹, Stephen Baker^{2,3,4}, Jeremy Farrar^{2,3}, Marcel Wolbers^{2,3}, Christiane Dolecek^{2,3,4}

1 Oxford University Clinical Research Unit–Nepal, Patan Academy of Health Sciences, Patan Hospital, Patan, Nepal, 2 The Hospital for Tropical Disease, Wellcome T



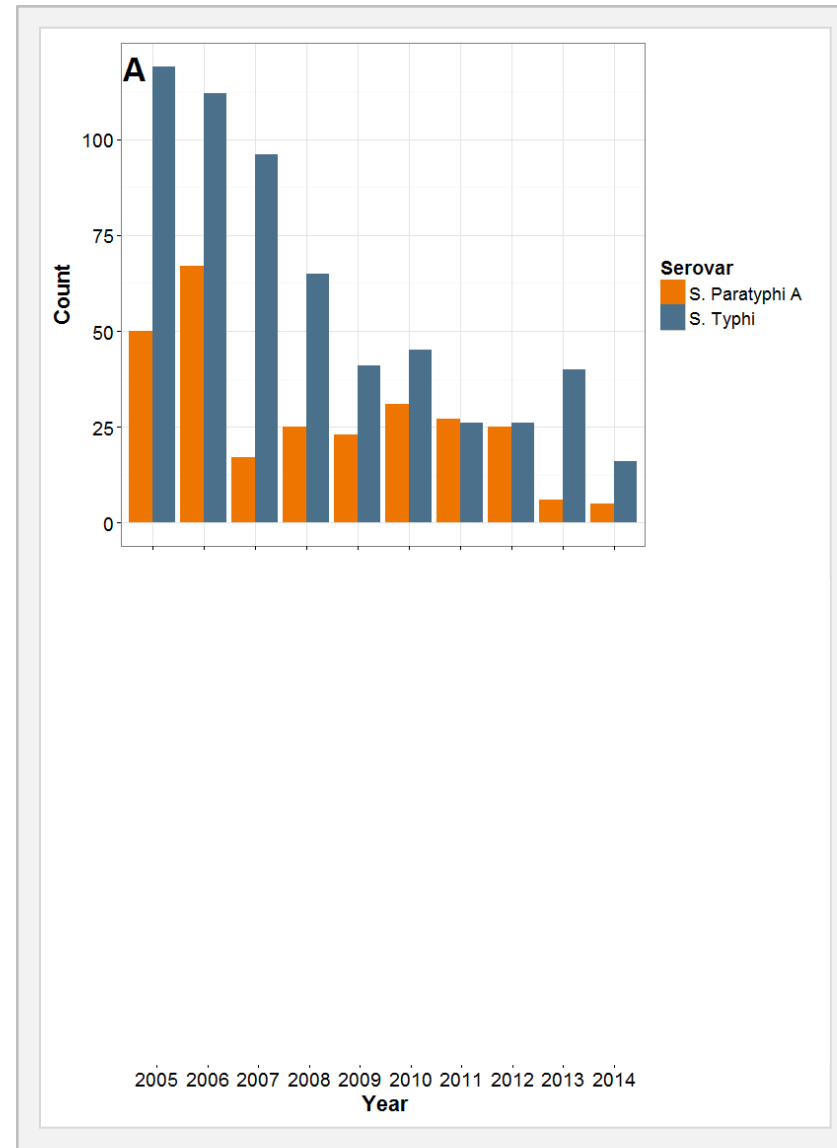
2008-11
n=629

Gatifloxacin versus ceftriaxone for the treatment of uncomplicated enteric fever

2011-14
n=246

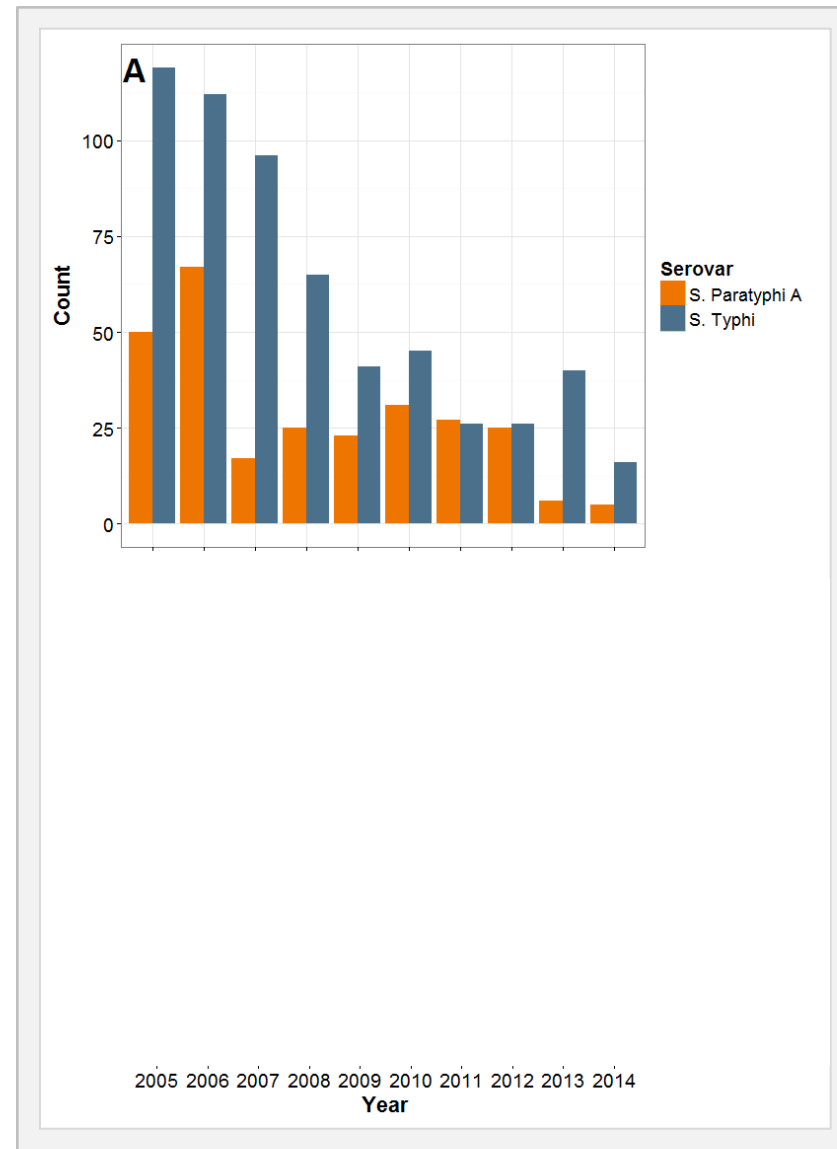
Baseline

- 41% culture positive (862/2,118)
 - > 28% *S. Typhi*
 - > 13% *S. Paratyphi A*



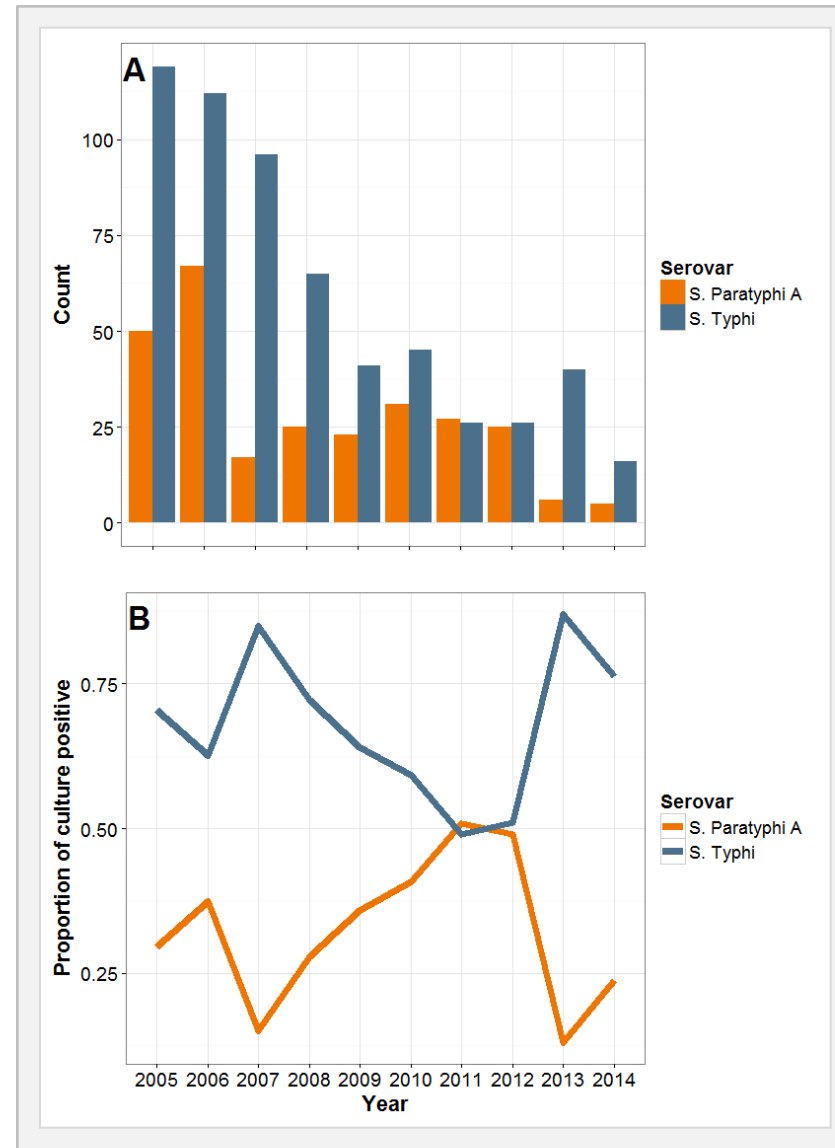
Baseline

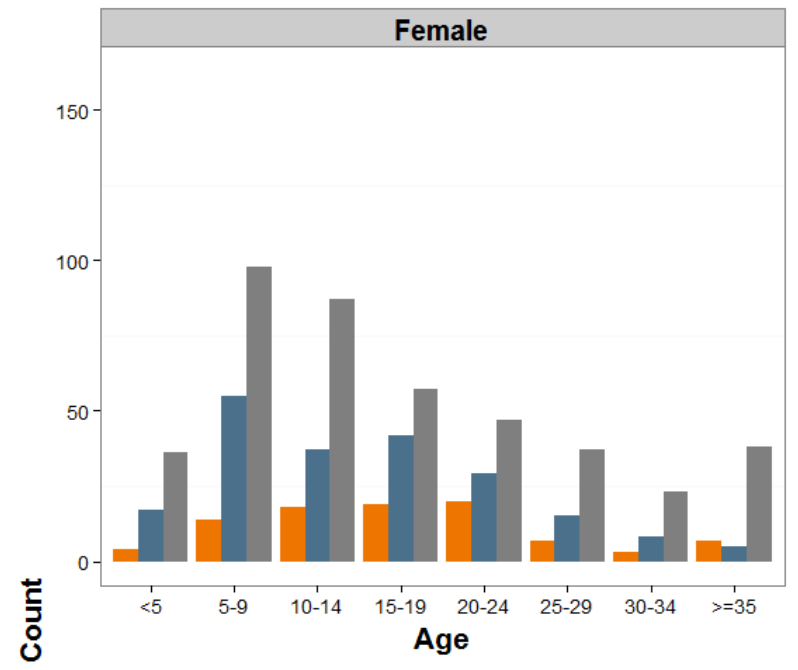
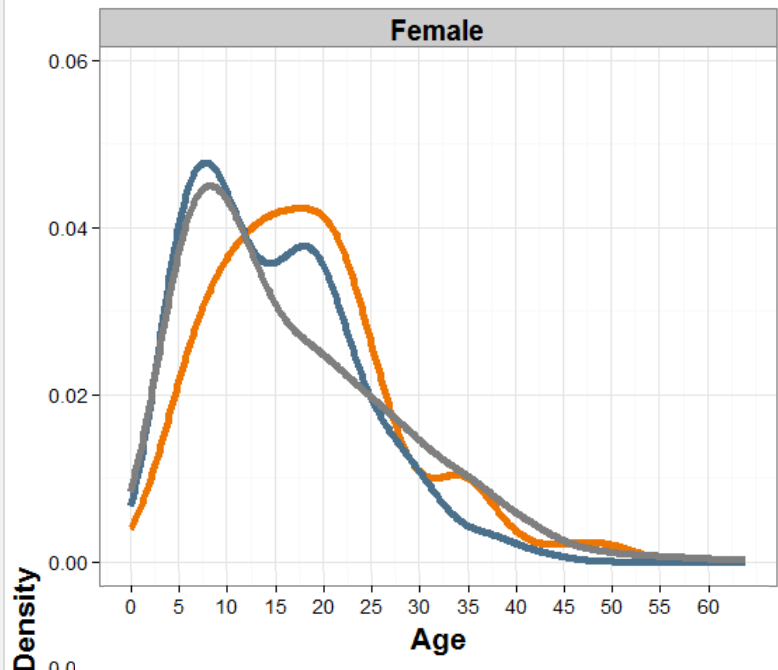
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- Decline in enteric fever cases overall



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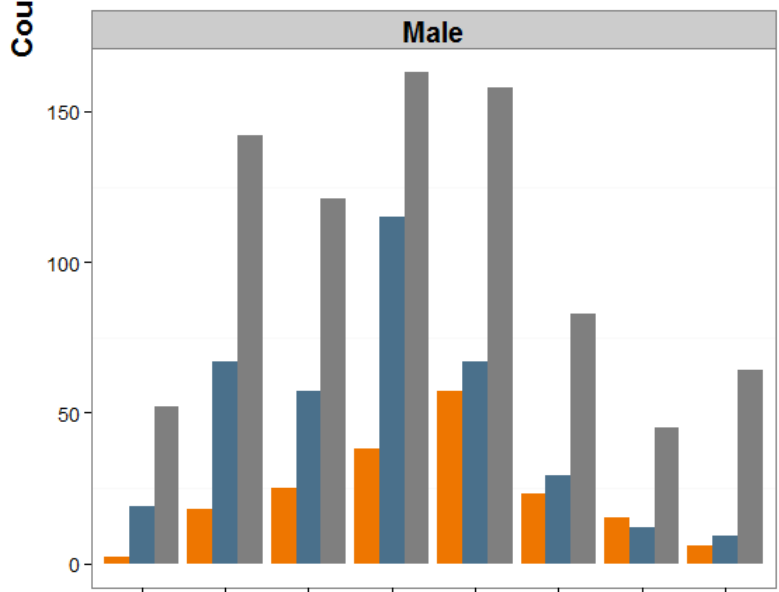
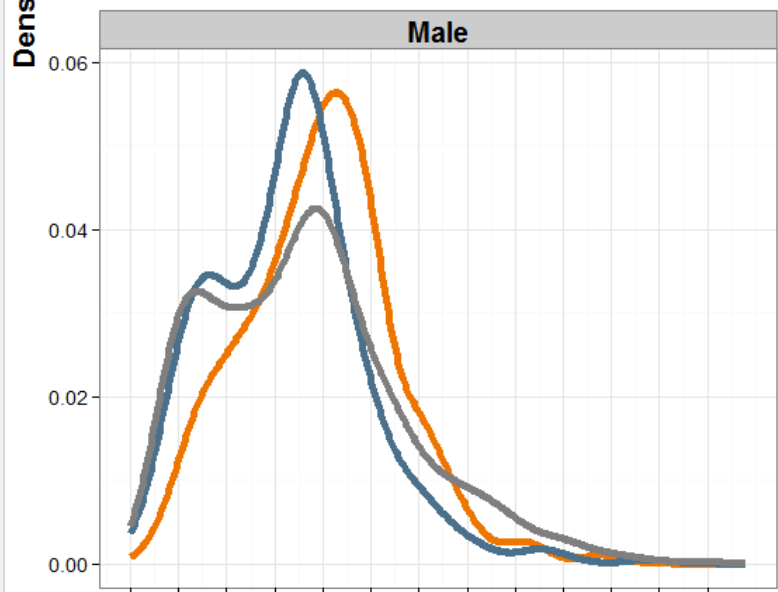
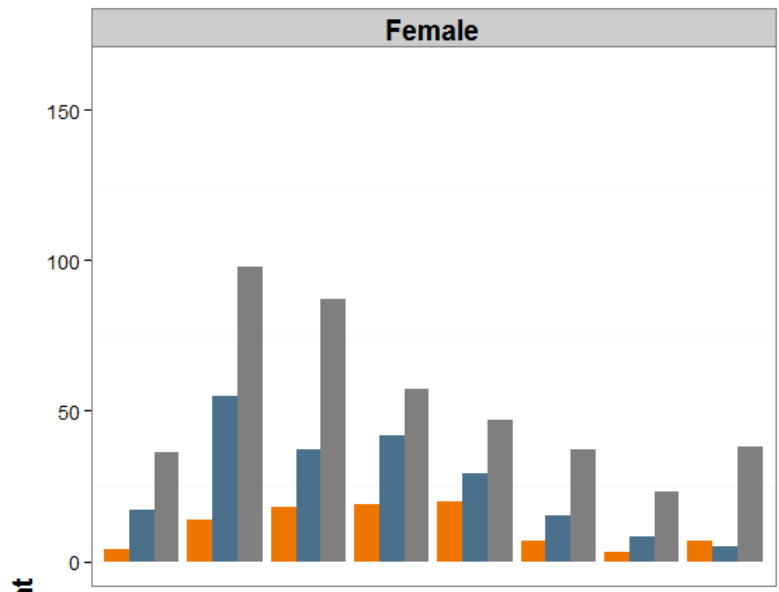
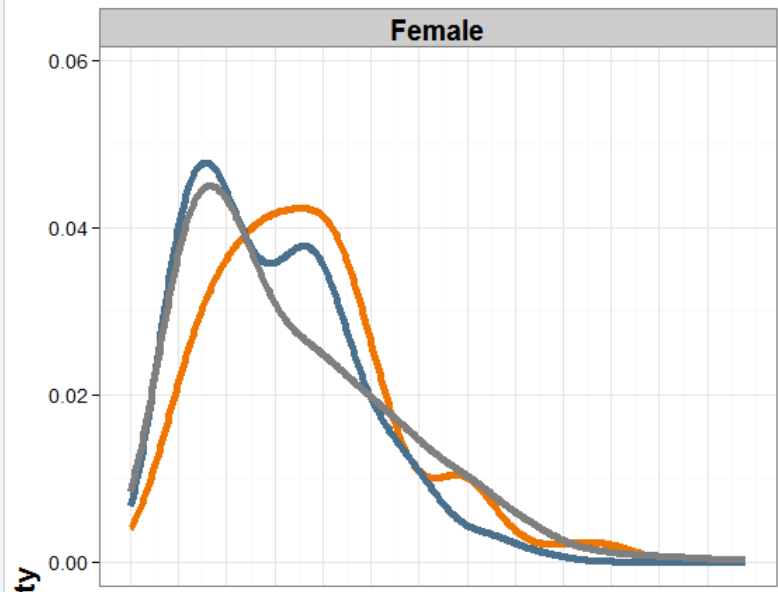
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 — S. Typhi
 — Negative

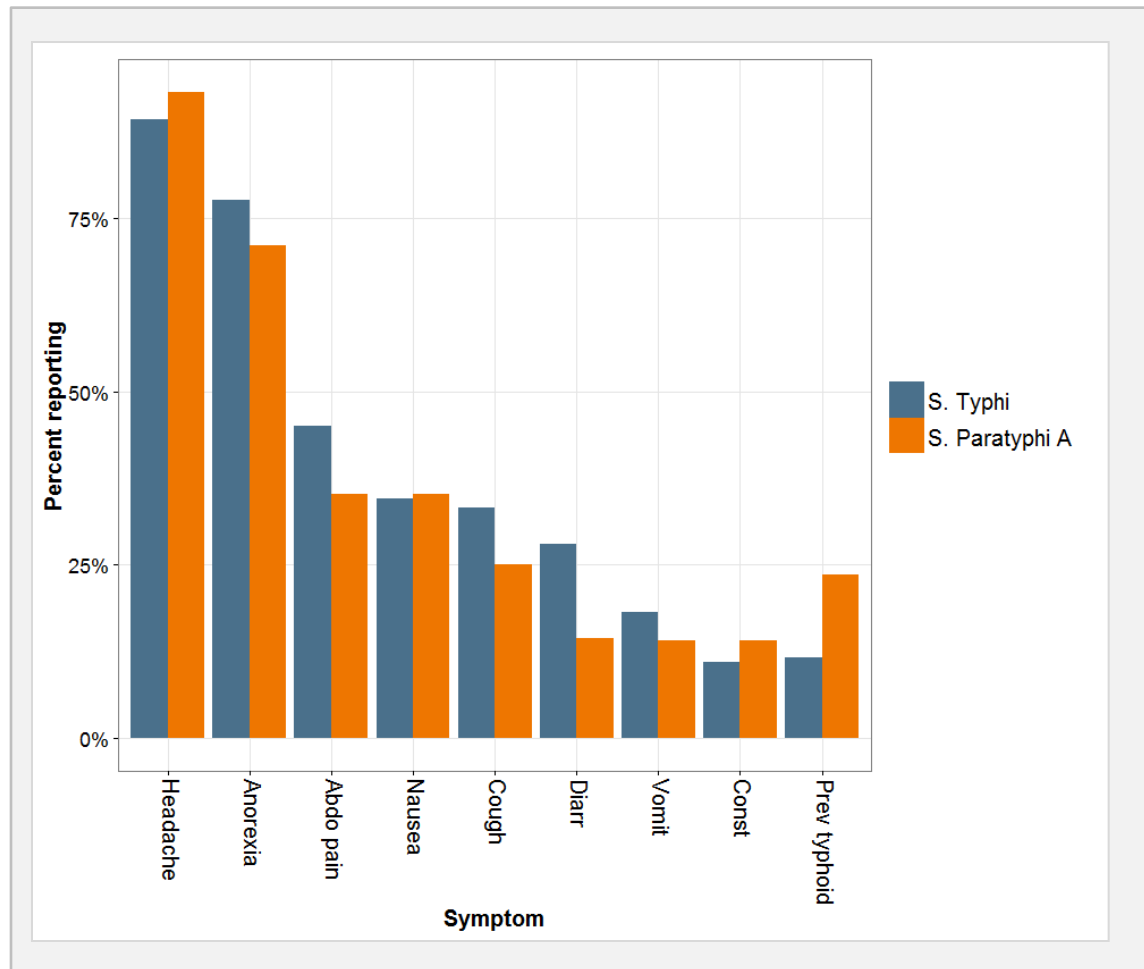
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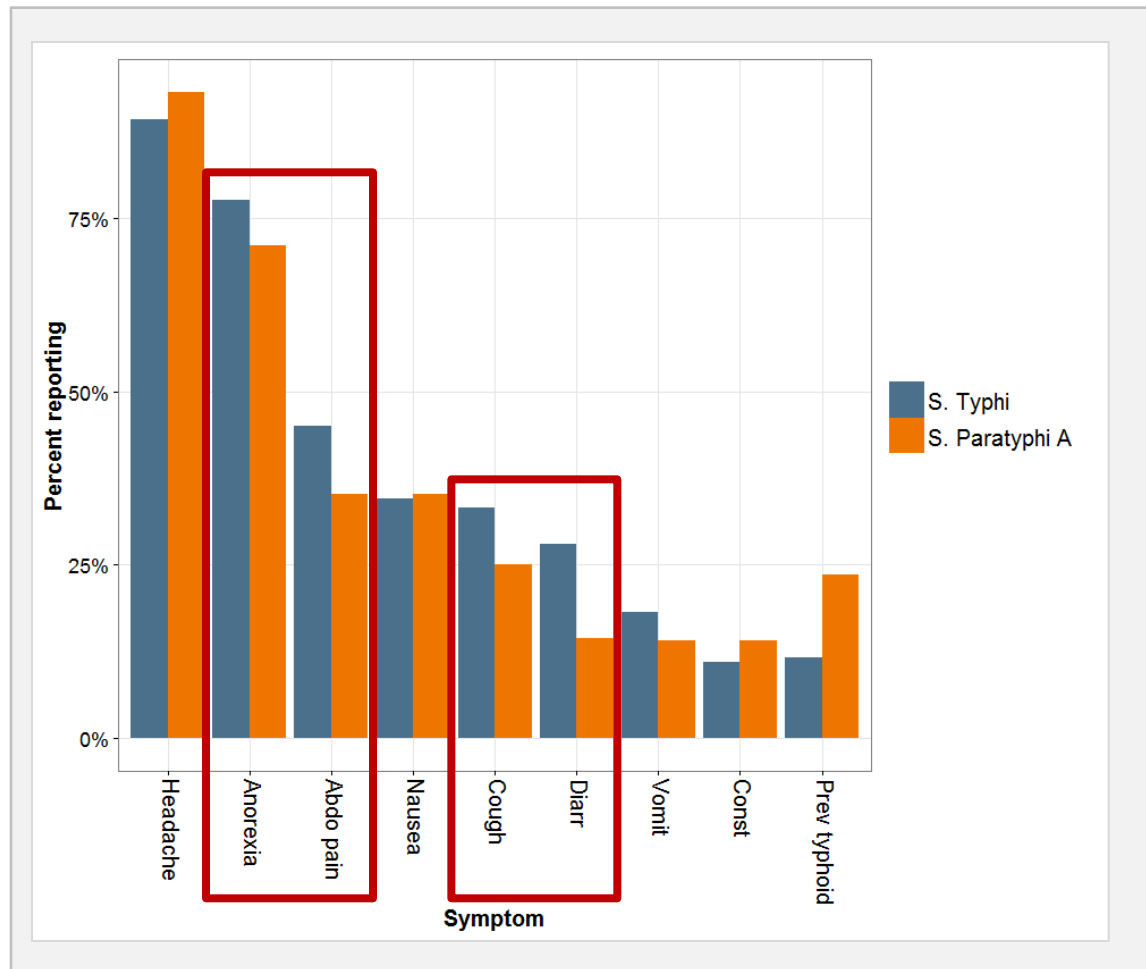
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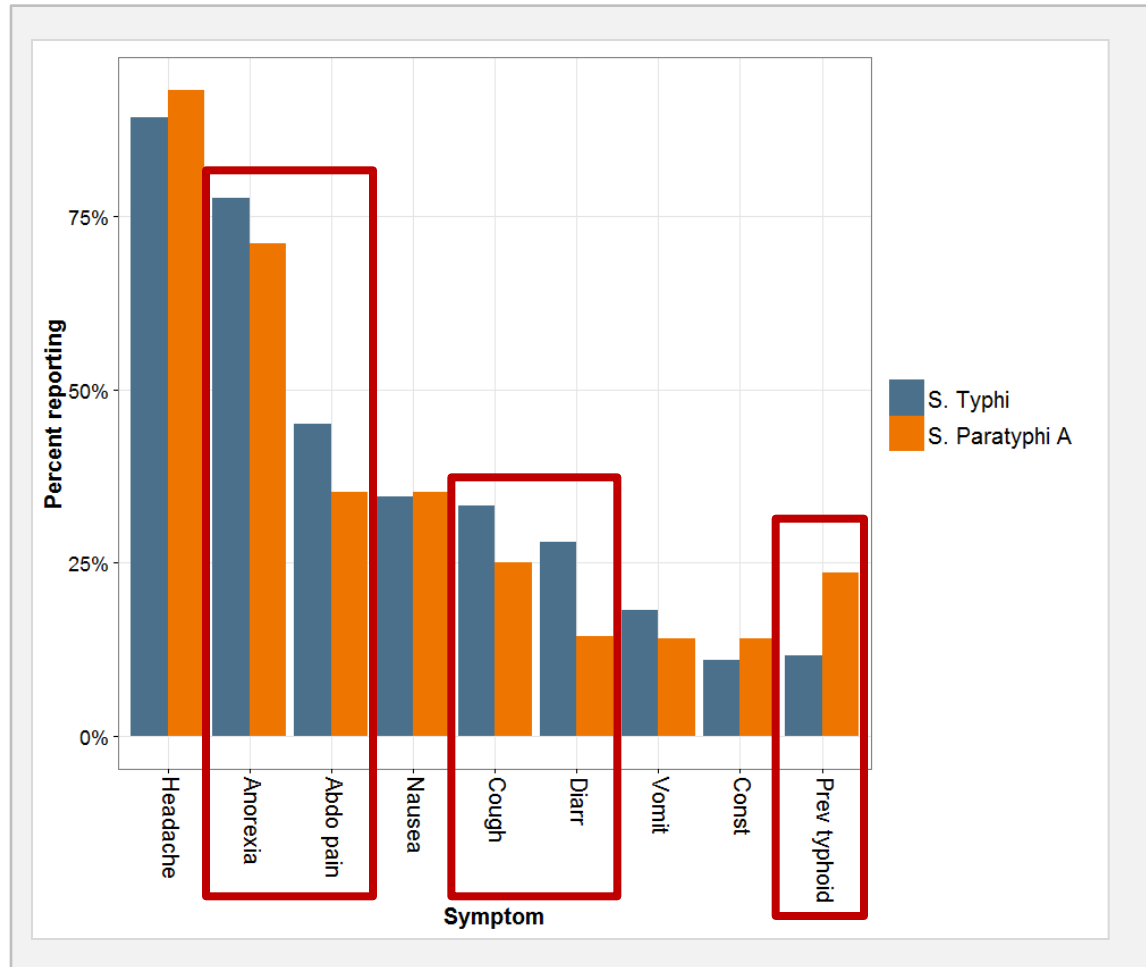
Clinical history



Clinical history



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Water use

Water characteristic	S. Typhi n=468	S. Paratyphi A n=226	Negatives n=1034	Total n=1728	p
<i>Drinking water</i>					
Tap water	233 (49.8)	129 (57.1)	561 (54.3)	923 (53.4)	0.071
Well	79 (16.9)	37 (16.4)	181 (17.5)	297 (17.2)	0.866
Tube well	26 (5.6)	15 (6.6)	53 (5.1)	94 (5.4)	0.571
Stone spout	132 (28.2)	46 (20.4)	216 (20.9)	394 (22.8)	0.026
Tanker	16 (3.4)	7 (3.1)	38 (3.7)	61 (3.5)	0.825
Jar	19 (4.1)	14 (6.2)	46 (4.4)	79 (4.6)	0.216
<i>Treat water</i>					
Untreated	193 (41.2)	66 (29.2)	387 (37.4)	646 (37.4)	0.002
Filter	190 (40.6)	111 (49.1)	477 (46.1)	778 (45)	0.034
Chlorine	30 (6.4)	10 (4.4)	47 (4.5)	87 (5)	0.293
Boil	84 (17.9)	50 (22.1)	185 (17.9)	319 (18.5)	0.192
Other	26 (5.6)	14 (6.2)	39 (3.8)	79 (4.6)	0.735

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Antimicrobial susceptibility

- Minimum inhibitory concentration

Augmentin

Ampicilin

Amoxicilin

Azithromycin

Cefixime

Chloramphenicol

Ciprofloxacin

Ceftriaxone

Gatifloxacin

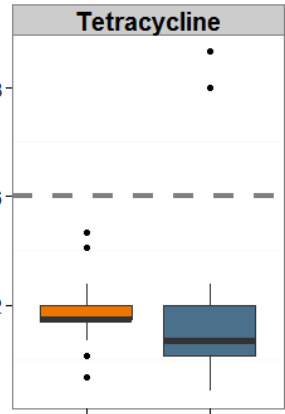
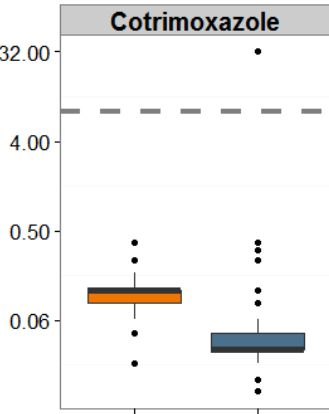
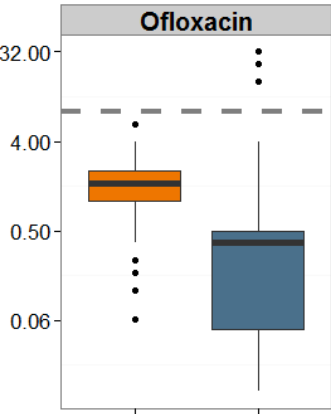
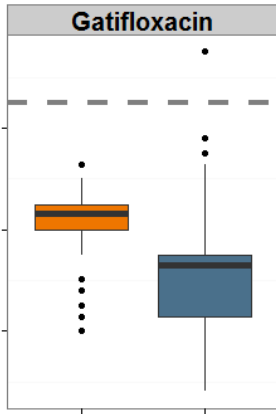
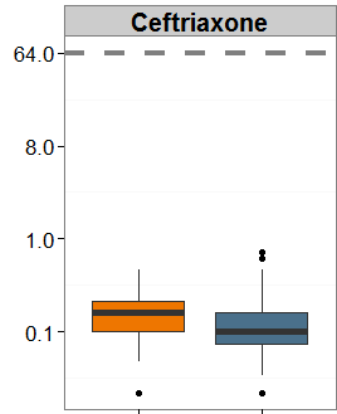
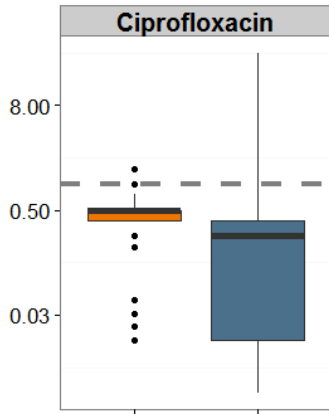
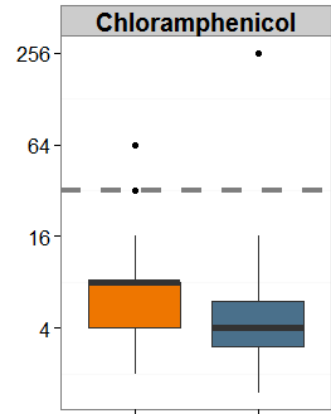
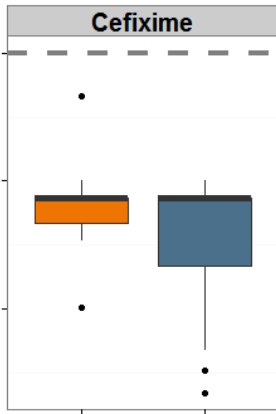
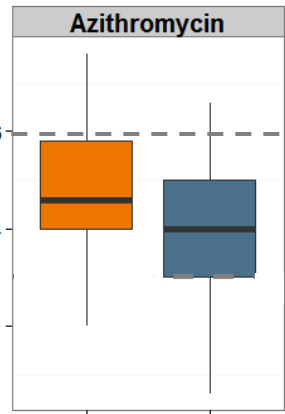
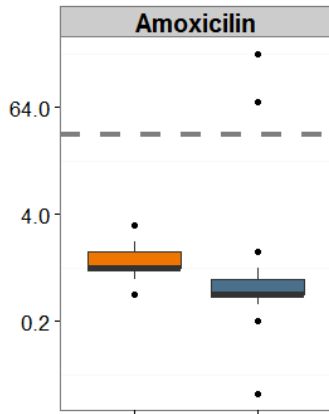
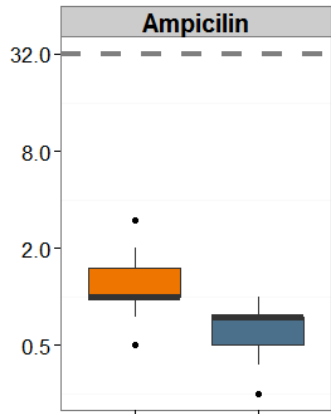
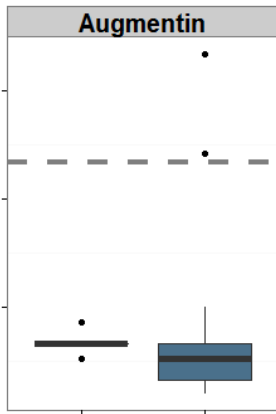
Nalidixic Acid

Ofloxacin

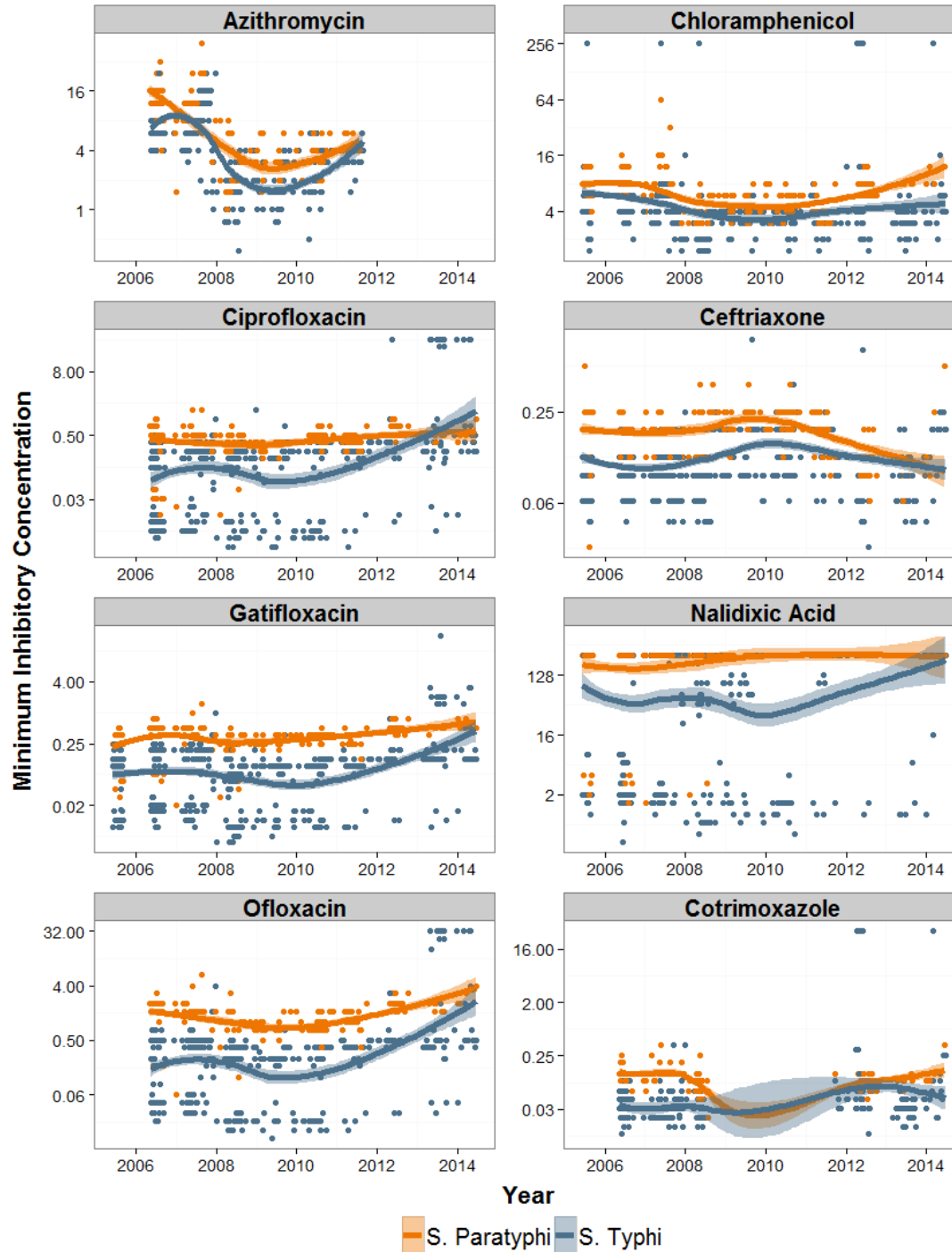
Cotrimoxazole

Tetracycline

Minimum Inhibitory Concentration

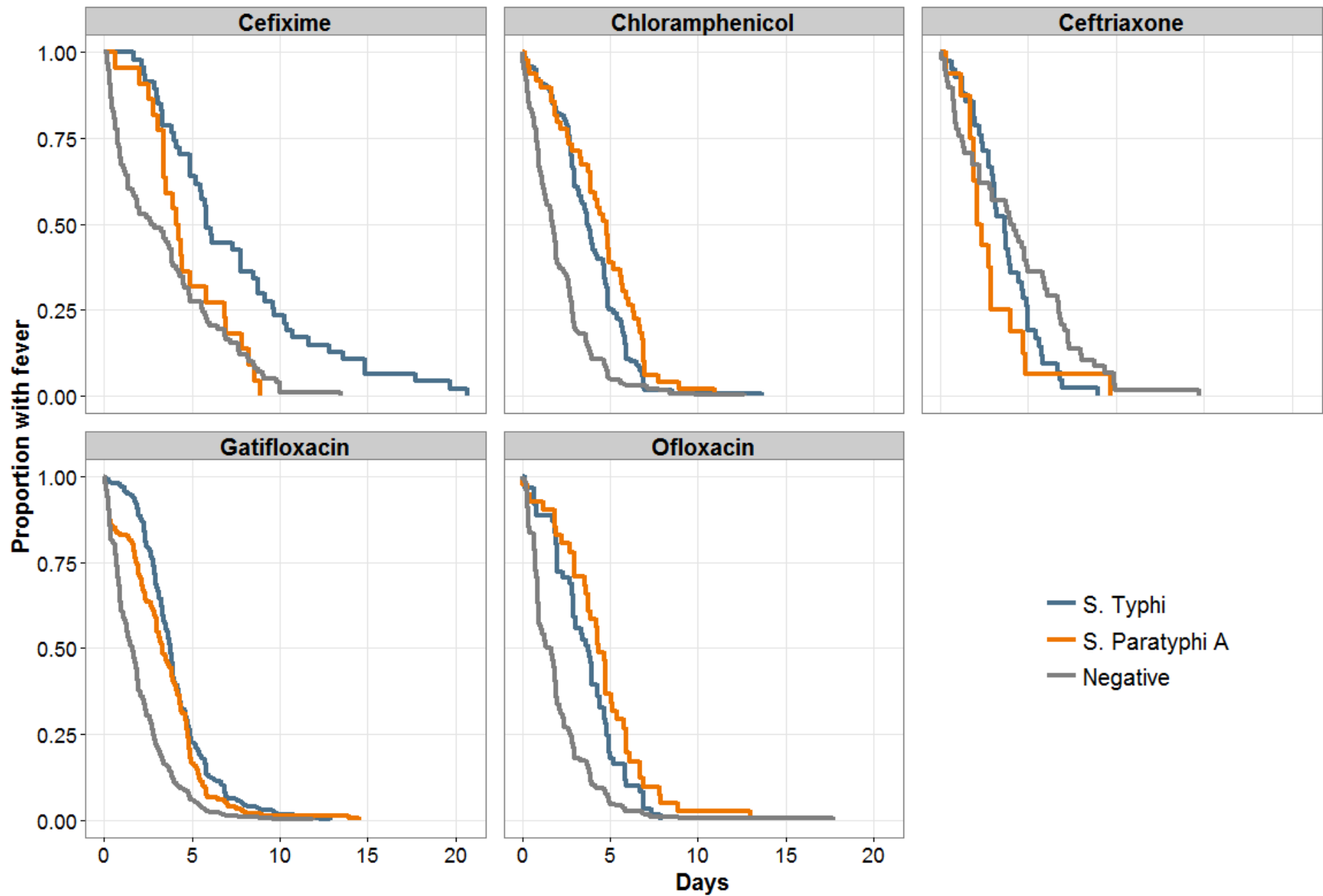


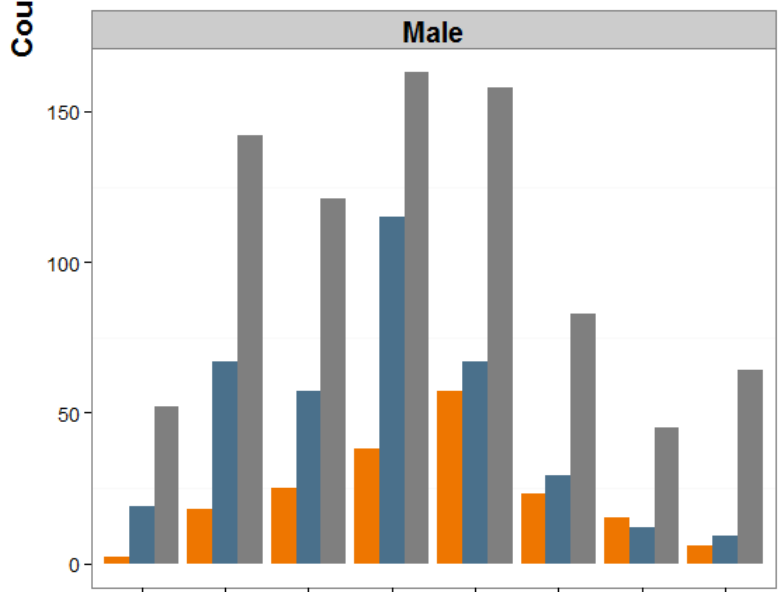
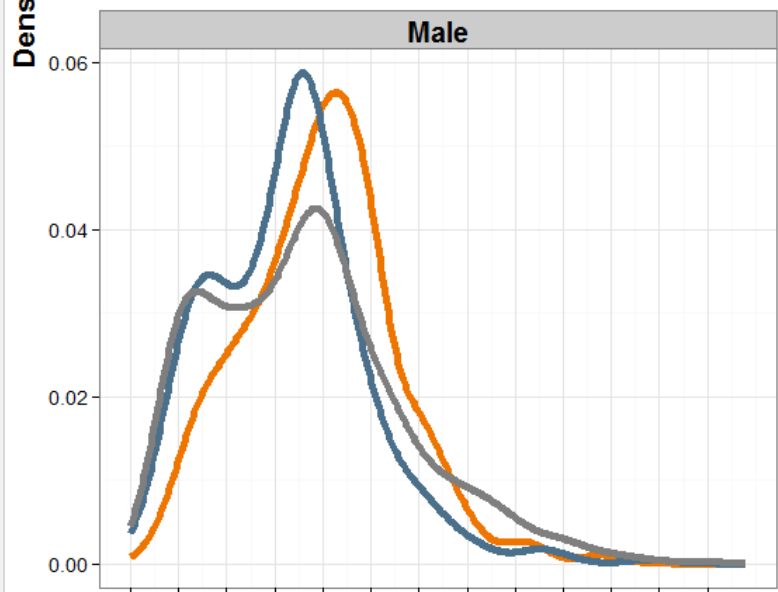
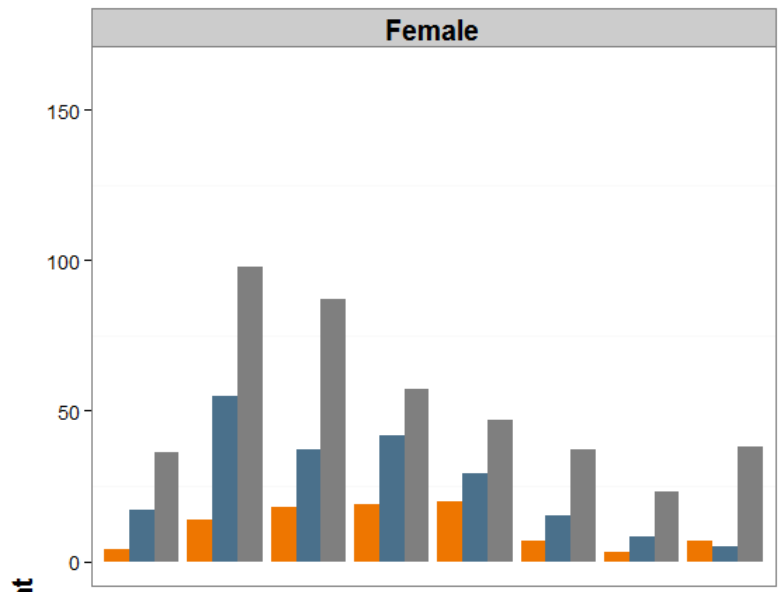
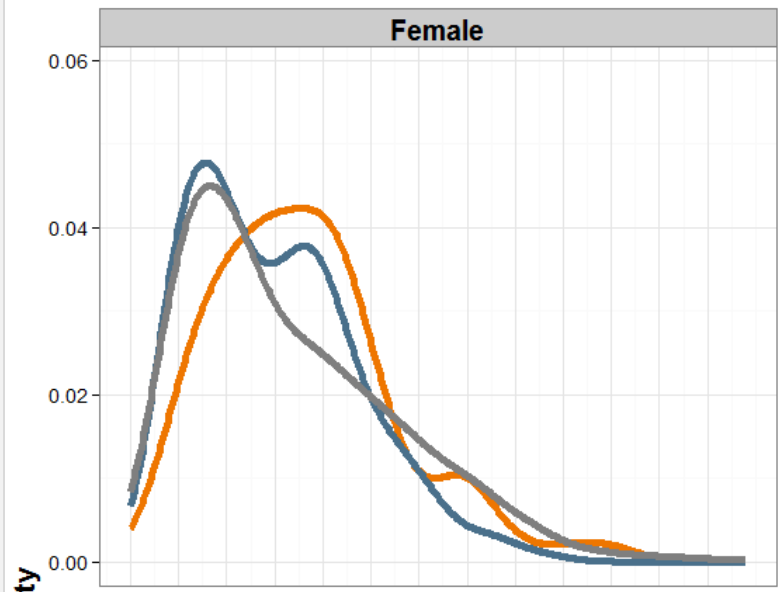
■ S. Paratyphi ■ S. Typhi



Fever clearance time

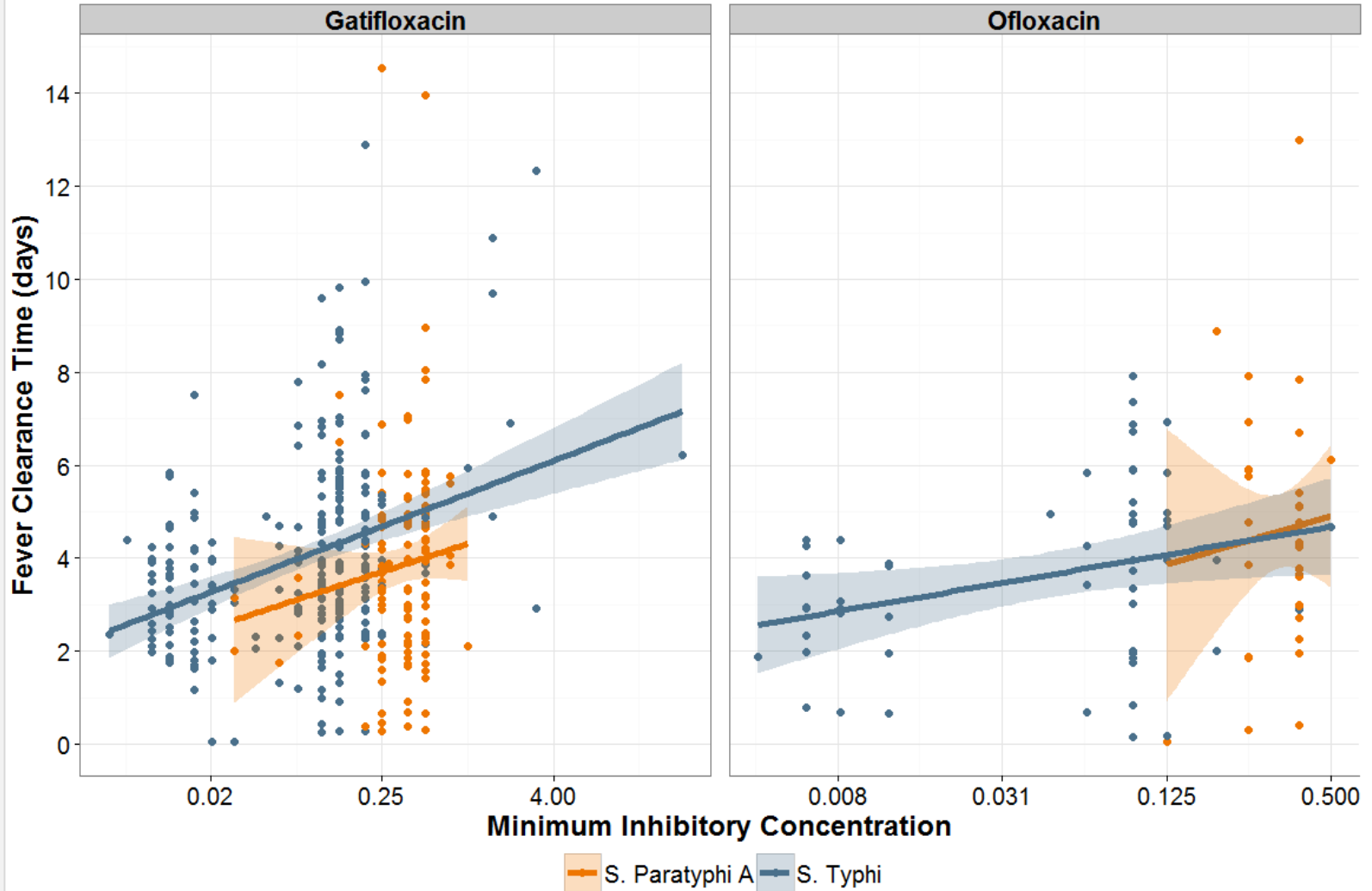
- Time from the first dose of treatment given until the temperature drops to $\leq 37.5^{\circ}\text{C}$ and remains afebrile for at least 48 hours
- Calculated based on twice-daily recorded temperatures





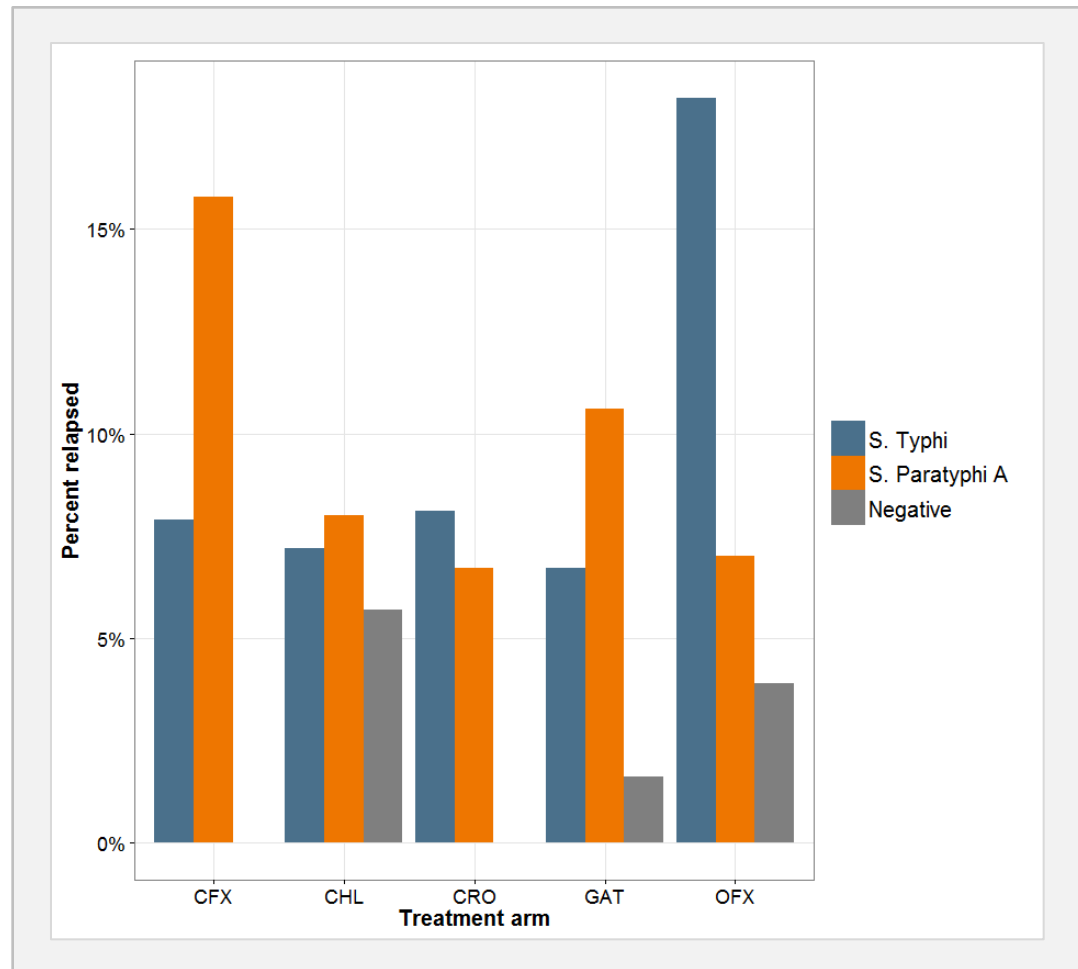
— S. Paratyphi A
 — S. Typhi
 — Negative

█ S. Paratyphi A
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 █ Negative



Relapse

- Syndromic and culture confirmed
- Majority within the first month



Summary

- Overall decline in enteric fever cases
- *S. Typhi* seems to be clinically slightly more severe
- *S. Paratyphi A* consistently higher MICs to all tested drugs
- Higher MICs correlate with prolonged fever clearance time
- Gatifloxacin unlikely to remain effective in coming years

Next steps

- Teasing apart relapse and reinfection
- Identifying a molecular basis for the differences in behavior to different antimicrobials between serovars
- Collection of detailed home location information to extend work on genomic epidemiology
- Investigate aetiology of culture negative patients
- Plans for next trial: azithromycin v ceftriaxone

With thanks

- **OUCRU Vietnam**

Stephen Baker
Marcel Wolbers
Christiane Dolecek
Pham Thanh Duy

- **OUCRU Nepal**

Buddha Basnyat
Abhilasha Karkey
Sabina Dongol
Amit Arjyal
Samir Koirala



