Gaps in knowledge in therapeutics and treatment

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Outline

Trends in antibiotic resistance

Impact of resistance

Case finding and treatment as control

Antimicrobial combinations

Clinical trials

PRELIMINARY REPORT ON THE BENEFICIAL EFFECT OF CHLOROMYCETIN IN THE TREATMENT OF TYPHOID FEVER*

By Theodore E. Woodward, M.D., Joseph E. Smadel, M.D., Herbert L. Ley, Jr., M.D., *Baltimore, Maryland,* and *Washington, D. C.*, Richard Green, M.D., and D. S. Mankikar, M.D., *Kuala Lumpur, Federation of Malaya*

A new antibiotic Chloromycetin has been clinically tested in the treatment of typhoid fever and has been found to exhibit significant chemotherapeutic effects. A description of the results in 10 cases is submitted as a preliminary report.

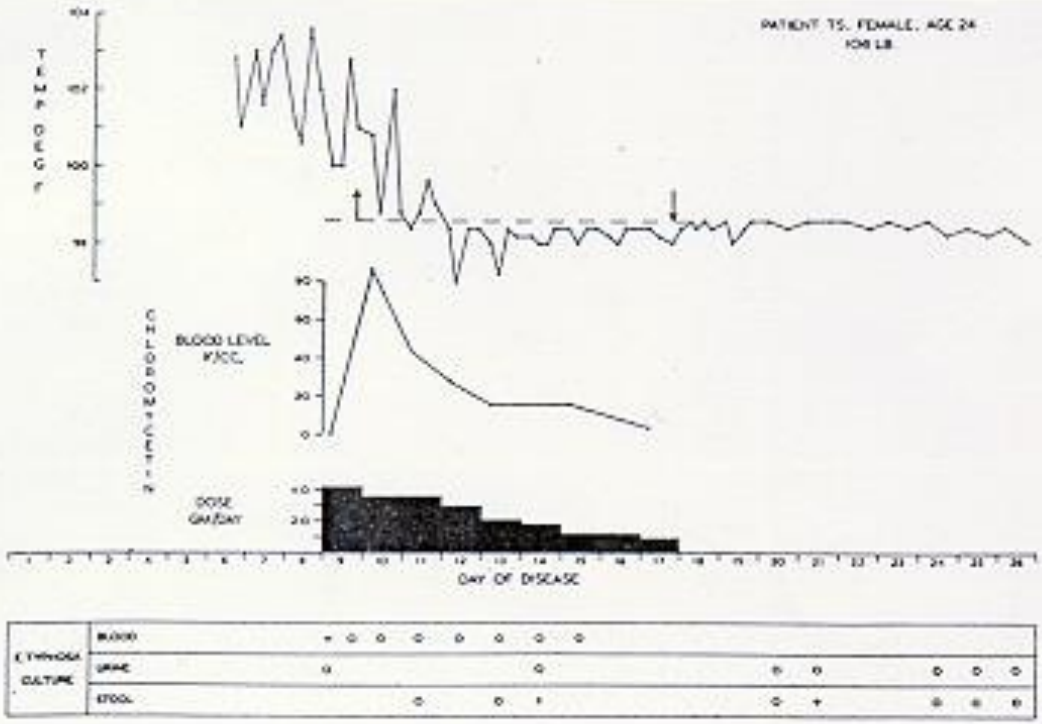
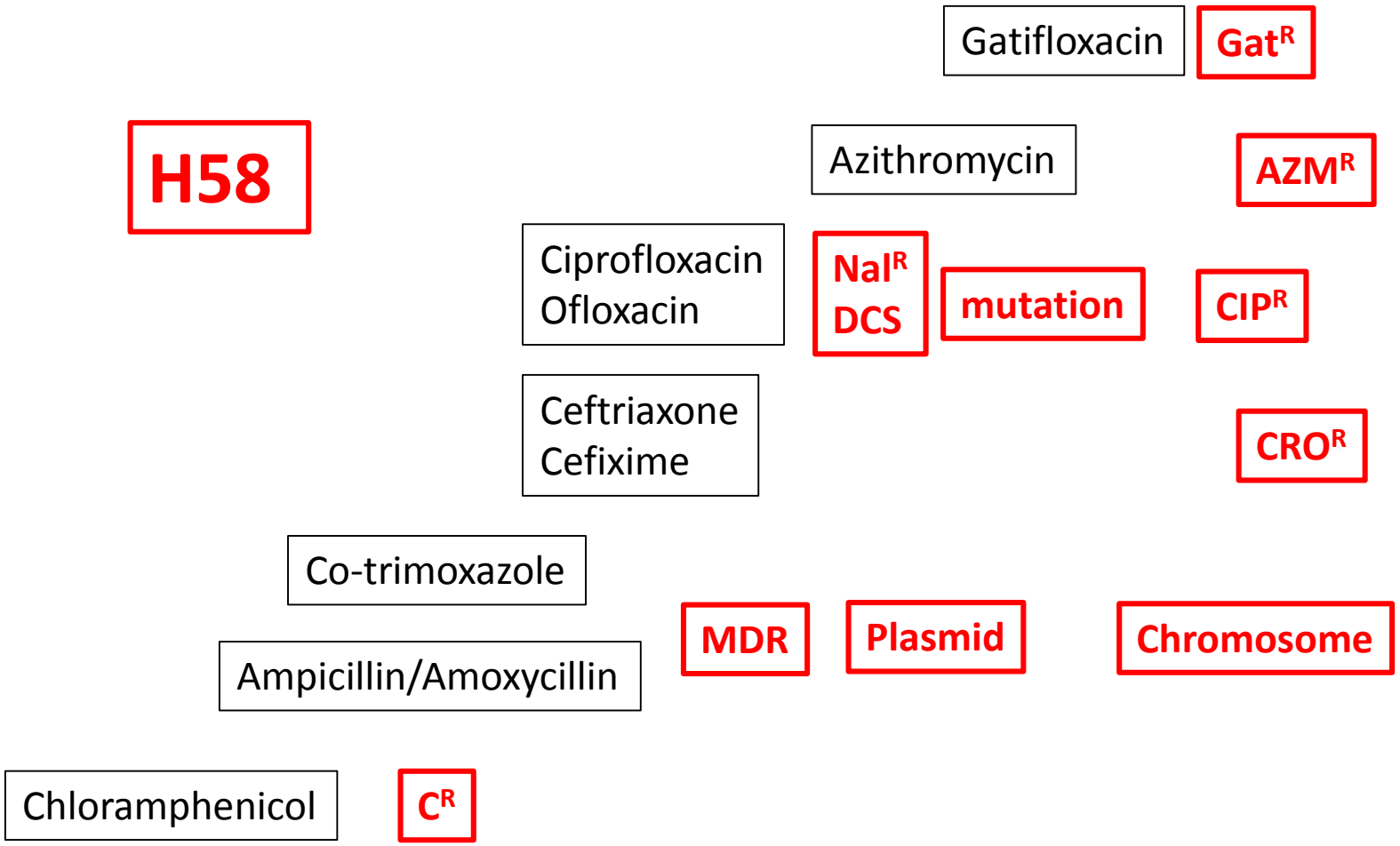


Fig. 1.

Chloramphenicol in typhoid fever

'…the clinical improvement and complete transformation in a few days can only be appreciated by clinicians who have had previous experience of typhoid fever and have known their own helplessness in the past to affect its protracted course…its great value in saving life and curtailing morbidity in this disease is incontestable'

Edge W. 1950. Typhoid fever treated with chloramphenicol: review of 16 cases. Lancet **255:**710-712.


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

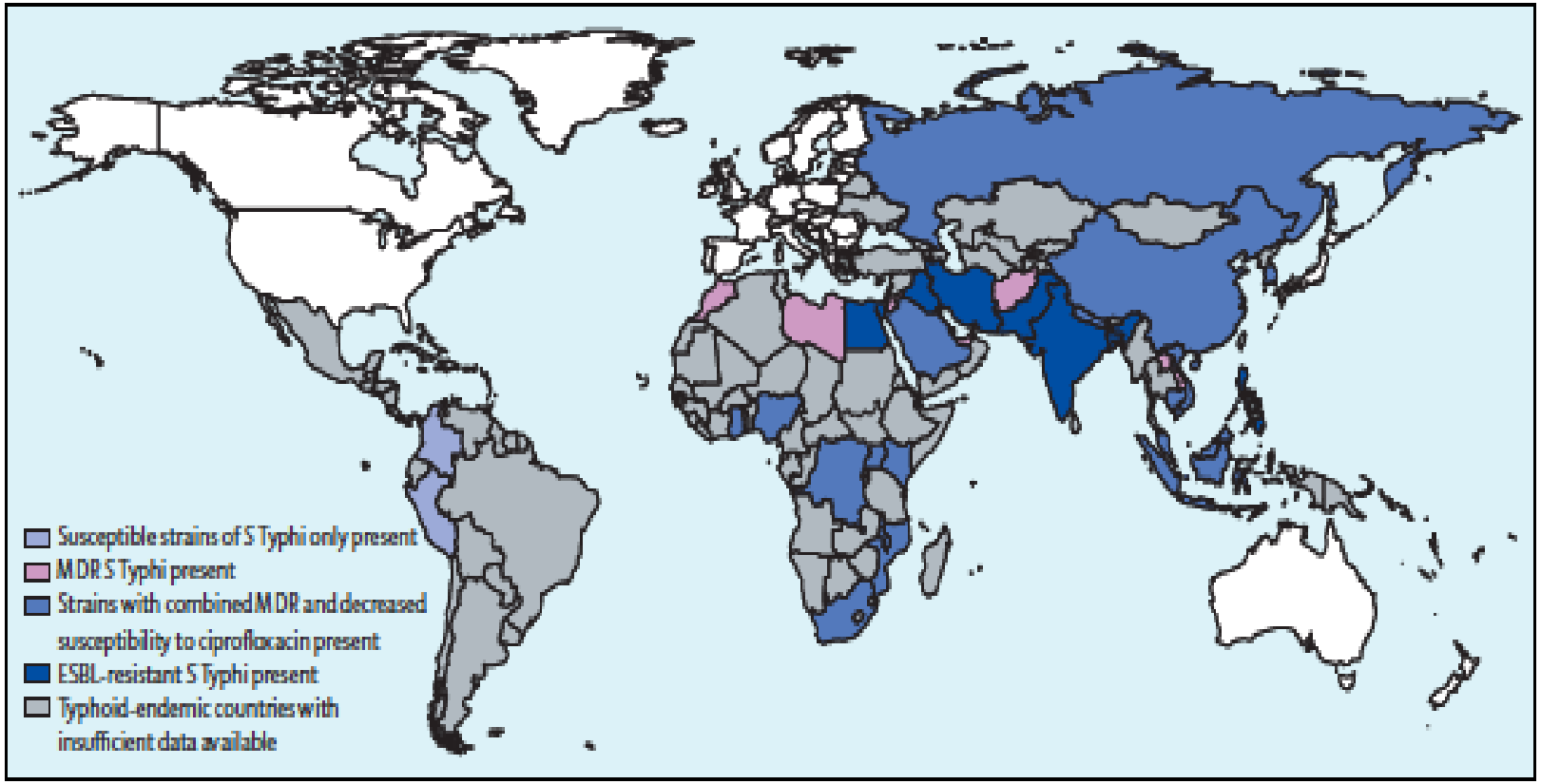


Figure 2: Worldwide distribution of antimicrobial drug resistance in *Salmonella enterica* serovar Typhi

MDR is defined as resistance to the first-line antimicrobial drugs ampicillin, co-trimoxazole, and chloramphenicol. MDR=multi-drug resistant. ESBL=extended-spectrum beta-lactamase-producer. Adapted from Bhan and colleagues,[18] with data up to April, 2013.

Wain et al, Lancet 2016

Gatifloxacin versus ceftriaxone for uncomplicated enteric fever in Nepal: an open-label, two-centre, randomised controlled trial

Amit Arjyal, Buddha Basnyat, Ho Thi Nhan, Samir Koirala, Abhishek Giri, Niva Joshi, Mila Shakya, Kamal Raj Pathak, Saruna Pathak Mahat, Shanti Pradhan Prajapati, Nabin Adhikari, Rajkumar Thapa, Laura Merson, Damodar Gajurel, Kamal Lamsal, Dinesh Lamsal, Bharat Kumar Yadav, Ganesh Shah, Poojan Shrestha, Sabina Dongol, Abhilasha Karkey, Corinne N Thompson, Nga Tran Vu Thieu, Duy Pham Thanh, Stephen Baker, Guy E Thwaites, Marcel Wolbers, Christiane Dolecek

Lancet Infect Dis 2016

In the culture-confirmed population, 16 (26%) of 62 patient who received gatifloxacin failed treatment compared with four (7%) of 54 who received ceftriaxone (HR 0.24 (95% CI 0.08-0.73) p=0.01]. Treatment failure was associated with the of *S.*Typhi exhibiting resistance against fluoroquinolones requiring the trial to be stopped.

Gatifloxacin versus ceftriaxone for uncomplicated enteric fever in Nepal: an open-label, two-centre, randomised controlled trial

Amit Arjyal, Buddha Basnyat, Ho Thi Nhan, Samir Koirala, Abhishek Giri, Niva Joshi, Mila Shakya, Kamal Raj Pathak, Saruna Pathak Mahat, Shanti Pradhan Prajapati, Nabin Adhikari, Rajkumar Thapa, Laura Merson, Damodar Gajurel, Kamal Lamsal, Dinesh Lamsal, Bharat Kumar Yadav, Ganesh Shah, Poojan Shrestha, Sabina Dongol, Abhilasha Karkey, Corinne N Thompson, Nga Tran Vu Thieu, Duy Pham Thanh, Stephen Baker, Guy E Thwaites, Marcel Wolbers, Christiane Dolecek

Lancet Infect Dis 2016

By contrast, in patients with a negative blood culture, only two (3%) of 58 who received gatifloxacin failed treatment versus 15 (23%) of 65 who received ceftriaxone [HR7.5 (95% CI 1.71-32.80), p =0.01).

Alternatives

Carbapenems

- iv Meropenem/Imipenem
- iv Ertapenem
- oral Faropenem

iv 4th generation cephalosporins

iv Tigecycline

Oral Mecillinam

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

Current perspectives of enteric fever: a hospital-based study from India

MANDEEP WALIA, RAJNI GAIND*, RAJESH MEHTA, PREMILA PAUL, PUSHPA AGGARWAL* & MANI KALAIVANI†

Annals of Tropical Paediatrics (2005) 25, 161–174

TABLE 3. *Logistic regression analysis of risk factors for complications in enteric fever.*

Risk factors	Complications n=41	No complications n=47	OR (95% CI)	AOR (95% CI)	p-value
Age (y)					
<5	14	4	8.17 (1.88–35.38)	22.11 (3.04–161.06)	0.002
5–12	21	29	1.69 (0.56–5.12)	2.36 (0.64–8.73)	NS
>12	6	14	1	1	
Duration of illness (d)					
<7	7	13	1		
7–14	20	22	1.69 (0.56–5.07)	–	–
>14	14	12	2.17 (0.65–7.19)	–	–
Hepatomegaly	26	20	2.34 (0.99–5.53)	0.975 (0.33–2.91)	NS
Splenomegaly	22	19	1.706 (0.73–3.98)		
Serotype					
S. typhi	41	44	–	–	–
S. paratyphi A	0	3	–	–	–
Resistance phenotype					
MDRS	16	10	2.37 (0.93–6.06)	1.78 (0.59–5.40)	NS
Non-MDRS	25	37			
NARS	35	28	3.96(1.39–11.24)	7.95 (1.96–32.25)	0.004
NASS	6	19			

Risk factors for the development of severe typhoid fever in Vietnam

Christopher M Parry[1,2*], Corinne Thompson[1,3], Ha Vinh[4], Nguyen Tran Chinh[4], Le Thi Phuong[5], Vo Anh Ho[5], Tran Tinh Hien[1,4], John Wain[1,6], Jeremy J Farrar[1,3] and Stephen Baker[1,3,7]

Parry *et al. BMC Infectious Diseases* 2014, **14**:73

Table 4 Factors associated with severe or fatal typhoid fever

Covariate	Severe or fatal n = 90	Non severe n = 491	OR	95% CI	p value	AOR	95% CI	p value
Age (years)[1]	14 (10–23)	12 (7–21)	1.01	0.99-1.03	0.243	1.02	0.99-1.04	0.122
Male	54 (60.6)	242 (49.3)	1.54	0.98-2.44	0.062	1.61	1.00-2.57	0.048
Days ill prior to admission[1]	10 (7–14)	8 (6–10)	1.03	0.99-1.07	0.081	1.04	.99-1.08	0.065
Fully susceptible organism	9 (10.0)	66 (13.4)	0.72	0.34-1.49	0.371	NI		
MDR	78 (86.7)	391 (79.6)	1.66	0.87-3.17	0.123	1.41	0.72-2.75	0.316
Intermediate ciprofloxacin resistance	45 (50.0)	170 (34.6)	1.89	1.20-2.97	0.005	1.90	1.18-3.07	0.009
Site								
Ho Chi Minh City	52/350 (14.9)	298/350 (85.1)	1.00	-	-	1.00	-	-
Dong Thap	38/231 (16.5)	193/231 (83.5)	1.13	0.72-1.78	0.603	1.19	0.72-1.98	0.501

[1]Median (IQR).
AOR: adjusted odds ratio; *NI*: Not included.

What are we trying to achieve when we treat a patient with typhoid fever?

- Individual patient
  - Cure the patient, prevent complications and death
  - Prevent relapse
  - Safe in children and adults
  - Affordable, available, easy adherence

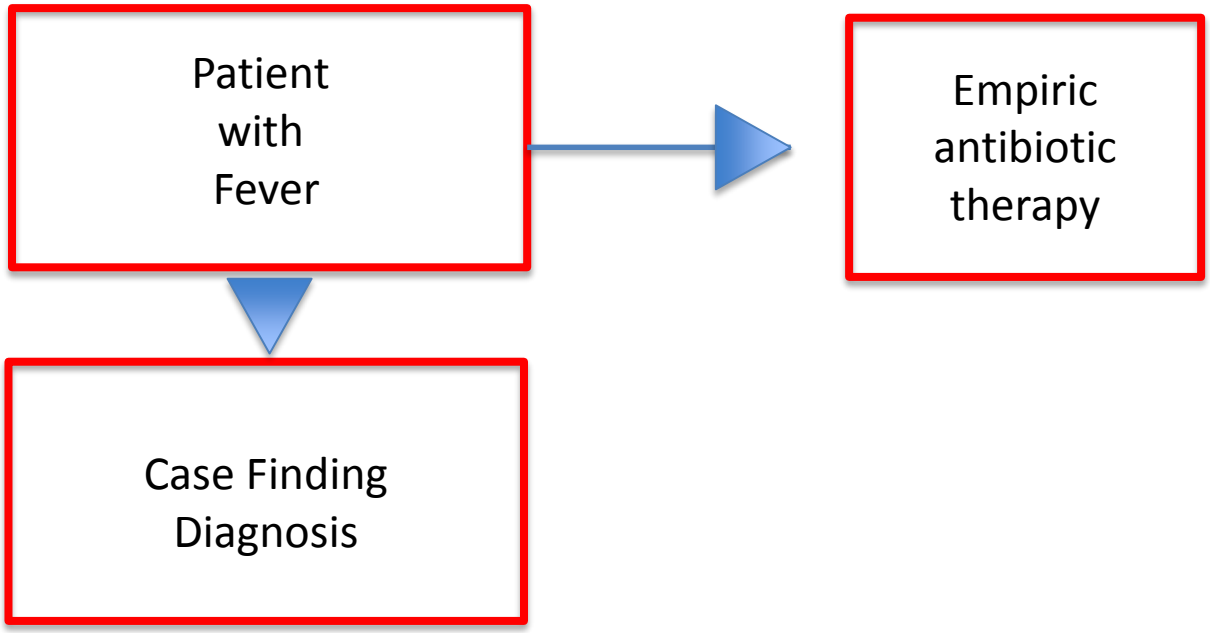
Parry. Trans Roy Soc Trop Med Hyg 2004;98:413

What are we trying to achieve when we treat a patient with typhoid fever?

- Individual patient
  - Cure the patient, prevent complications and death
  - Prevent relapse
  - Safe in children and adults
  - Affordable, available, easy adherence

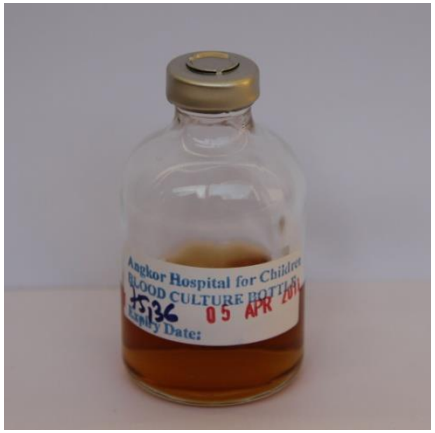
- Public health ("treat the patient, treat their community")
  - Prevent acute faecal shedding, convalescent and chronic carriage - reduce transmission

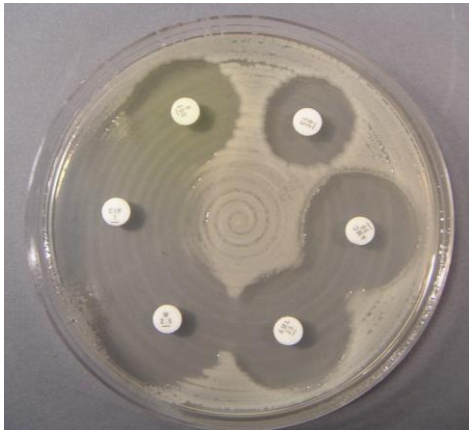
Parry. Trans Roy Soc Trop Med Hyg 2004;98:413


Patient
with
Fever
Empiric
antibiotic
therapy
Case Finding
Diagnosis

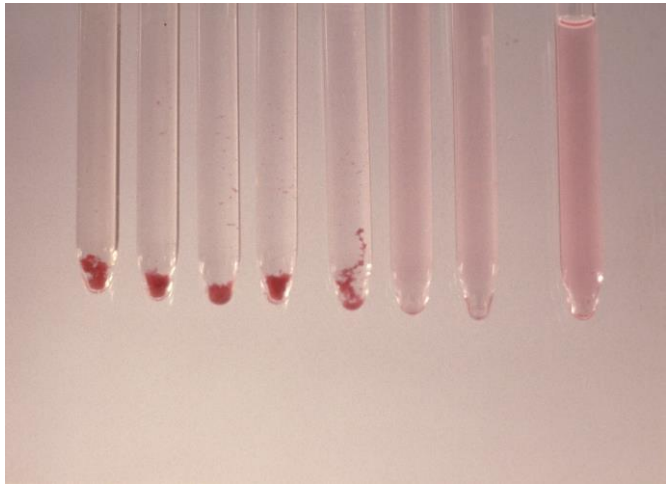
Case finding for enteric fever

Blood culture





Widal



Point of care RDT

Expert Rev. Anti Infect. Ther. 9(6), 711–725 (2011)

Rapid Diagnostic Tests for Typhoid and Paratyphoid (Enteric) Fever

Review information

Review type: Diagnostic test accuracy

Authors

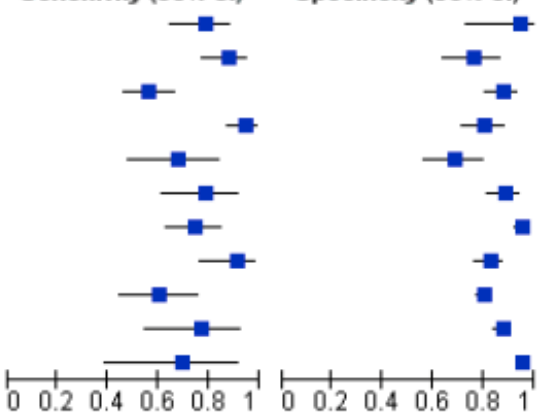
Lalith Wijedoru[1], Susan Mallett[2], Sarah Donegan[3], Christopher M Parry[4]

[1]Liverpool School of Tropical Medicine, Liverpool, UK

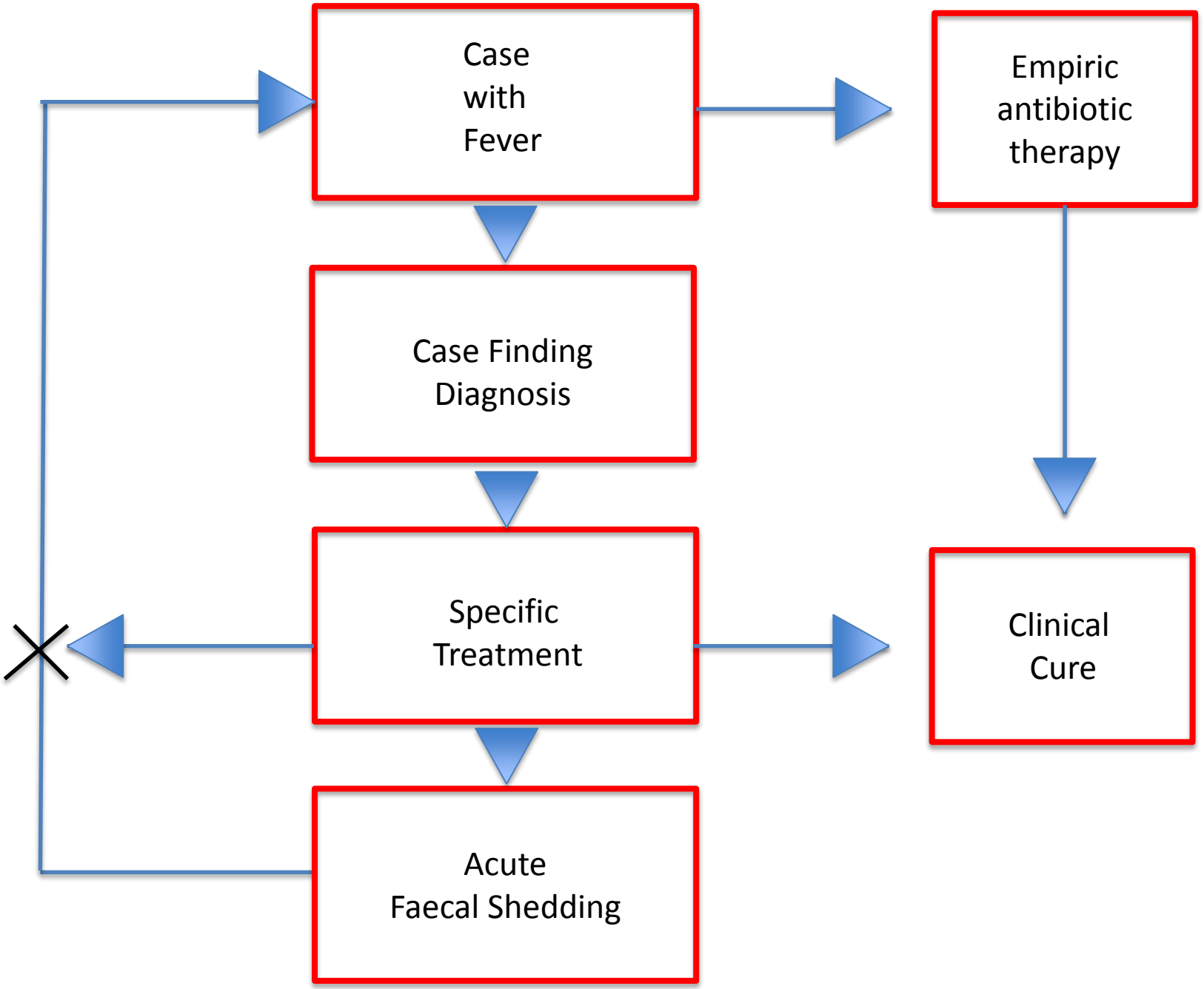
[2]Public Health, Epidemiology and Biostatistics, University of Birmingham, Birmingham, UK

Figure 7 (Analysis 3)

Study	TP	FP	FN	TN	Prevalence	case control	Sensitivity (95% CI)	Specificity (95% CI)
Olsen 2004	43	1	12	17	75.0	Case control	0.78 [0.65, 0.88]	0.94 [0.73, 1.00]
House 2001	56	15	8	48	50.0	Case control	0.88 [0.77, 0.94]	0.76 [0.64, 0.86]
Dutta 2006	58	14	45	99	48.0	Not case control	0.56 [0.46, 0.66]	0.88 [0.80, 0.93]
Kawano 2007	71	20	4	82	42.0	Not case control	0.95 [0.87, 0.99]	0.80 [0.71, 0.88]
Keddy 2011	19	20	9	44	30.0	Not case control	0.68 [0.48, 0.84]	0.69 [0.56, 0.80]
Ley 2011	26	12	7	94	24.0	Case control	0.79 [0.61, 0.91]	0.89 [0.81, 0.94]
Fadeel 2011	50	15	17	299	18.0	Case control	0.75 [0.63, 0.84]	0.95 [0.92, 0.97]
Rahman 2007	31	37	3	172	14.0	Not case control	0.91 [0.76, 0.98]	0.82 [0.76, 0.87]
Naheed 2008	26	166	17	658	5.0	Not case control	0.60 [0.44, 0.75]	0.80 [0.77, 0.83]
Siba 2012	17	60	5	418	4.0	Not case control	0.77 [0.55, 0.92]	0.87 [0.84, 0.90]
Dong 2007	9	89	4	1630	1.0	Not case control	0.69 [0.39, 0.91]	0.95 [0.94, 0.96]



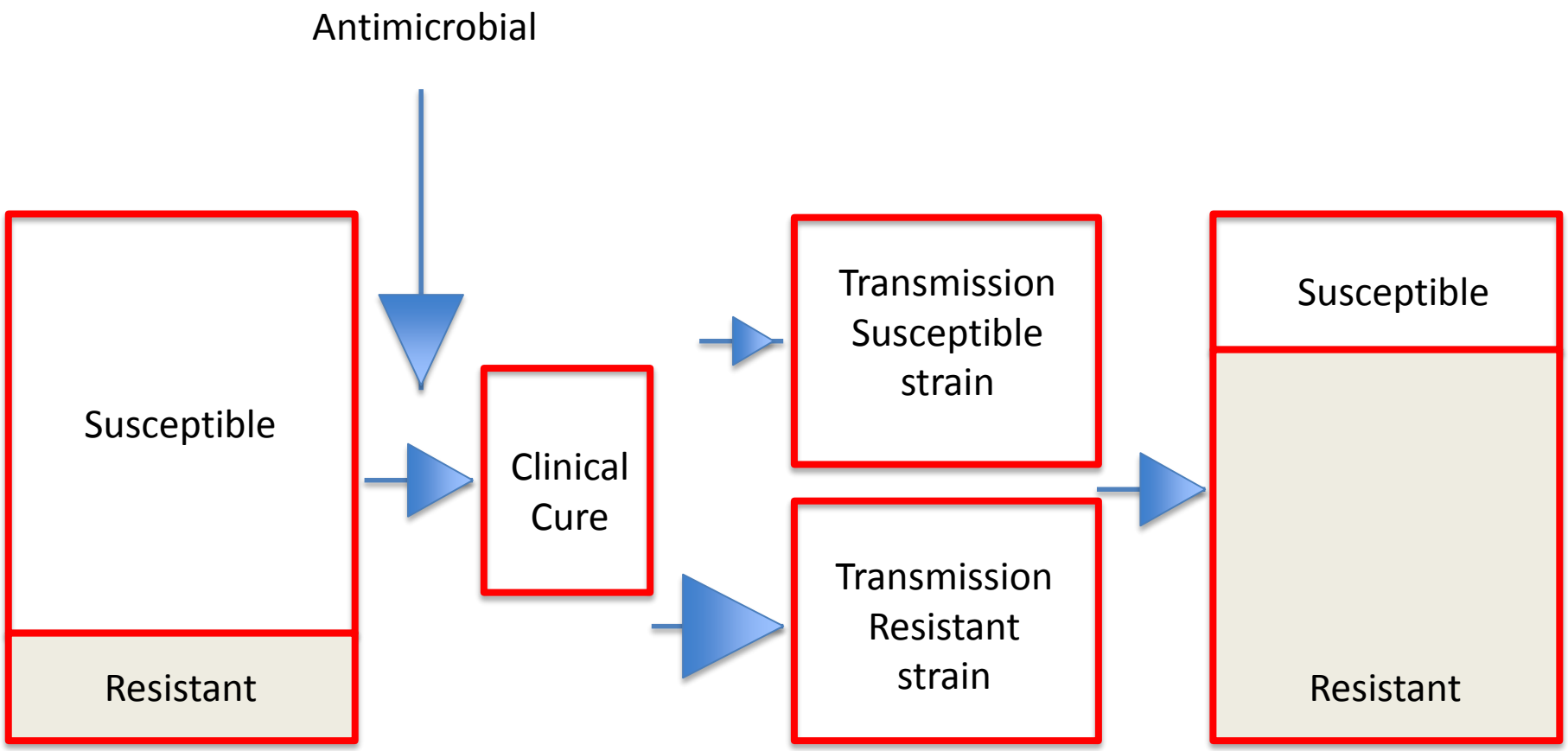
Wijedoru et al Cochrane Systematic Review. 2017 (unpublished)


Case
with
Fever
Empiric
antibiotic
therapy
Case Finding
Diagnosis
Specific
Treatment
Clinical
Cure
Acute
Faecal Shedding

Acute faecal shedding
RCT Uncomplicated typhoid fever
Rx Ofloxacin for 2/3/5/7 days

		Pre treatment		Post treatment	
	No	All	> 2 samples	All	> 2 samples
Na^S	572	14%	22%	2%	4%
Na^R	177	32%	38%	17%	20%

Parry. Trans Roy Soc Trop Med Hyg 2004;98:413


Antimicrobial
Susceptible
Resistant
Clinical Cure
Transmission Susceptible strain
Transmission Resistant strain
Susceptible
Resistant

Antimicrobial combinations

Initial empirical therapy

- Broaden coverage against resistant organisms
- Widen spectrum of organisms covered

Synergy

Prevent resistance

Increased adverse reactions

Increase cost

Formulation of combinations

Fixed dose combinations

Antimicrobial combinations with - liposomes/nanoparticles/antimicrobial peptides

In vitro efficacy of the combination of ciprofloxacin and cefotaxime against nalidixic acid-resistant *Salmonella enterica* serotype Typhi

Dong-Min Kim[a,1], Ganesh Prasad Neupane[a,1], Sook Jin Jang[b,*], Sung Hun Kim[c], Bok Kwon Lee[c]

International Journal of Antimicrobial Agents 36 (2010) 155–158

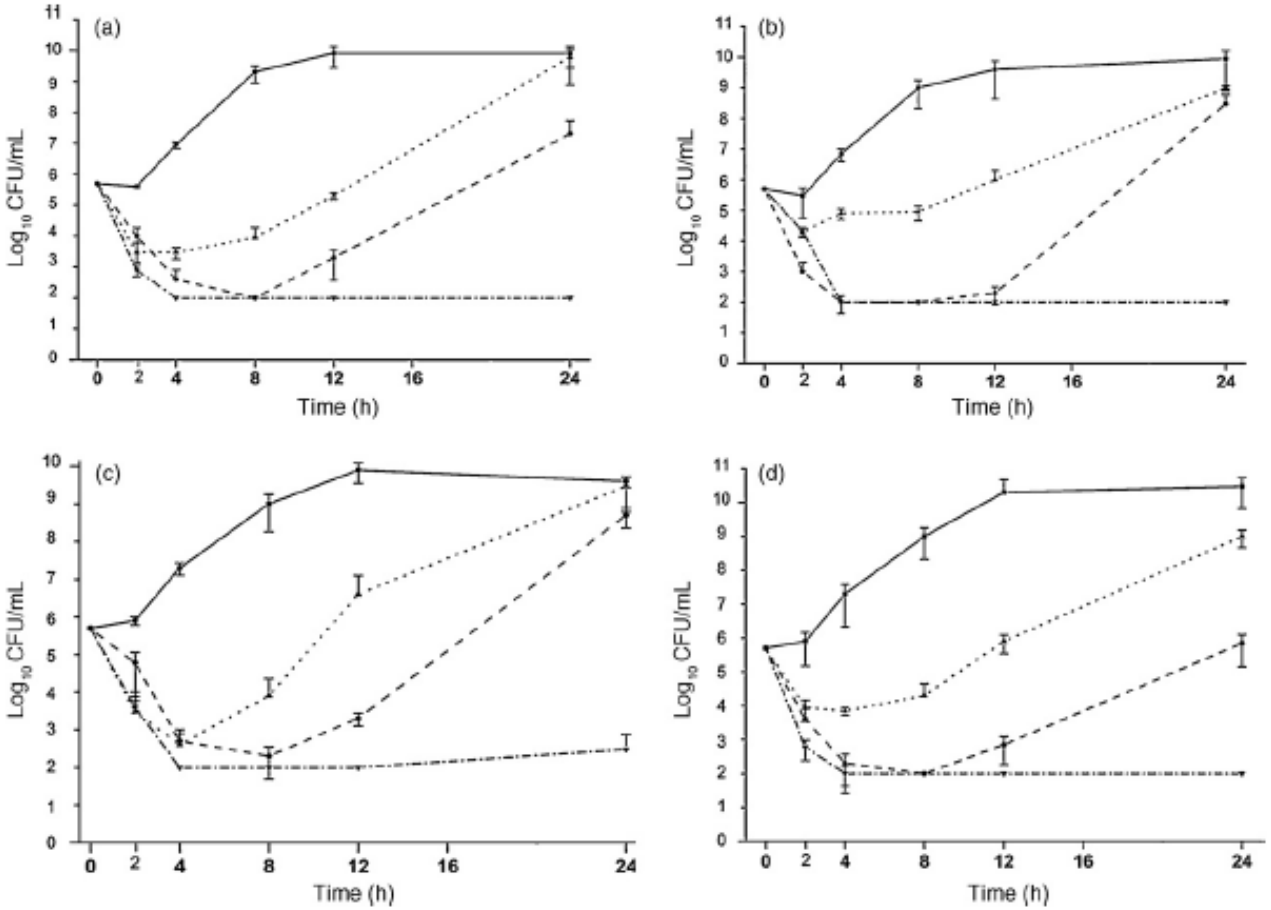


Fig. 1. Time–kill curves for *Salmonella enterica* serovar Typhi: (a) nalidixic acid-susceptible *S.* Typhi (NASST) ATCC 9992; (b) nalidixic acid-resistant *S.* Typhi (NARST) CUH-61275; (c) NARST KCDC 738; and (d) NARST KCDC 3697. CFU, colony-forming units; MIC, minimal inhibitory concentration. –■–, control; —●—, 0.75× MIC of ciprofloxacin; --▲--, 1× MIC of cefotaxime; -—▼—-, 0.75× MIC of ciprofloxacin plus 1× MIC of cefotaxime.

Randomized Controlled Comparison of Ofloxacin, Azithromycin, and an Ofloxacin-Azithromycin Combination for Treatment of Multidrug-Resistant and Nalidixic Acid-Resistant Typhoid Fever[▽]

Christopher M. Parry,[1,4]* Vo Anh Ho,[2] Le Thi Phuong,[2] Phan Van Be Bay,[2] Mai Ngoc Lanh,[2] Le Thanh Tung,[2] Nguyen Thi Hong Tham,[2] John Wain,[1,4]† Tran Tinh Hien,[3] and Jeremy J. Farrar[1,4]

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2007, p. 819–825

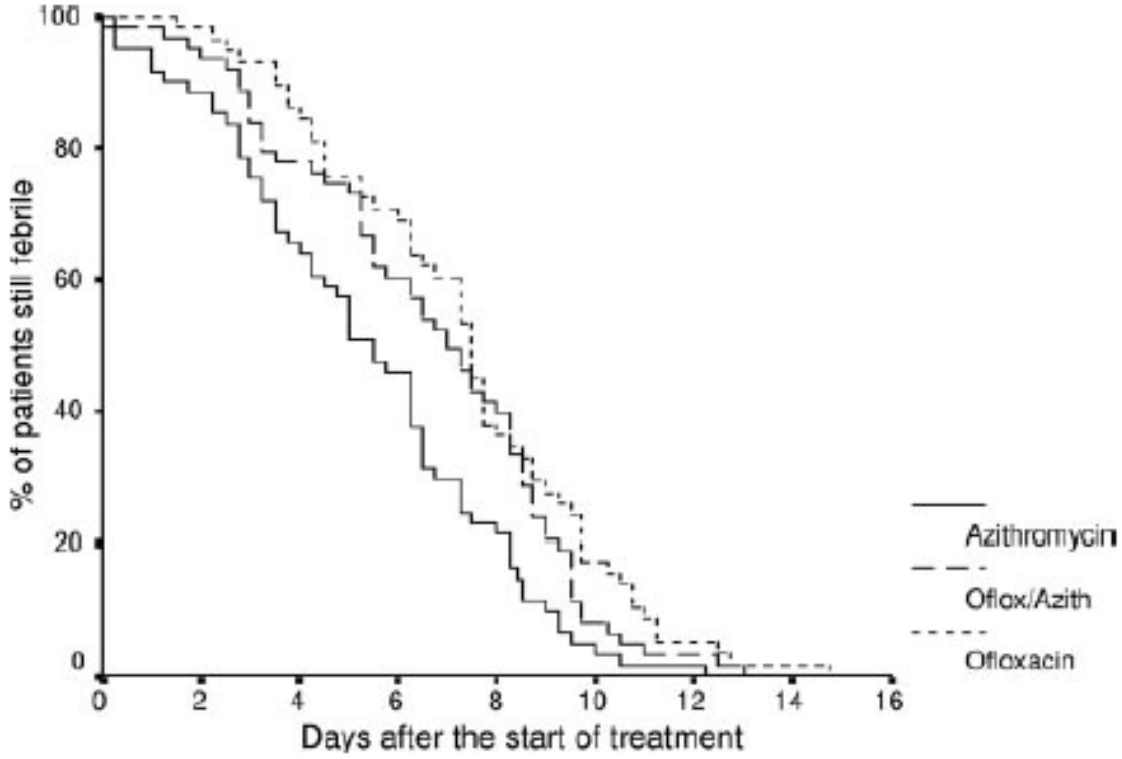


FIG. 2. Kaplan-Meier survival curve showing the percentage of patients still febrile following the start of treatment. The patients who failed treatment and required retreatment with a further course of antimicrobial are excluded. Oflox, ofloxacin; Azith, azithromycin.

A Large Outbreak of *Salmonella* Paratyphi A Infection Among Israeli Travelers to Nepal

Eyal Meltzer, Shmuel Stienlauf, Eyal Leshem, Yechezkel Sidi, and Eli Schwartz

Clinical Infectious Diseases 2014;58(3):359–64

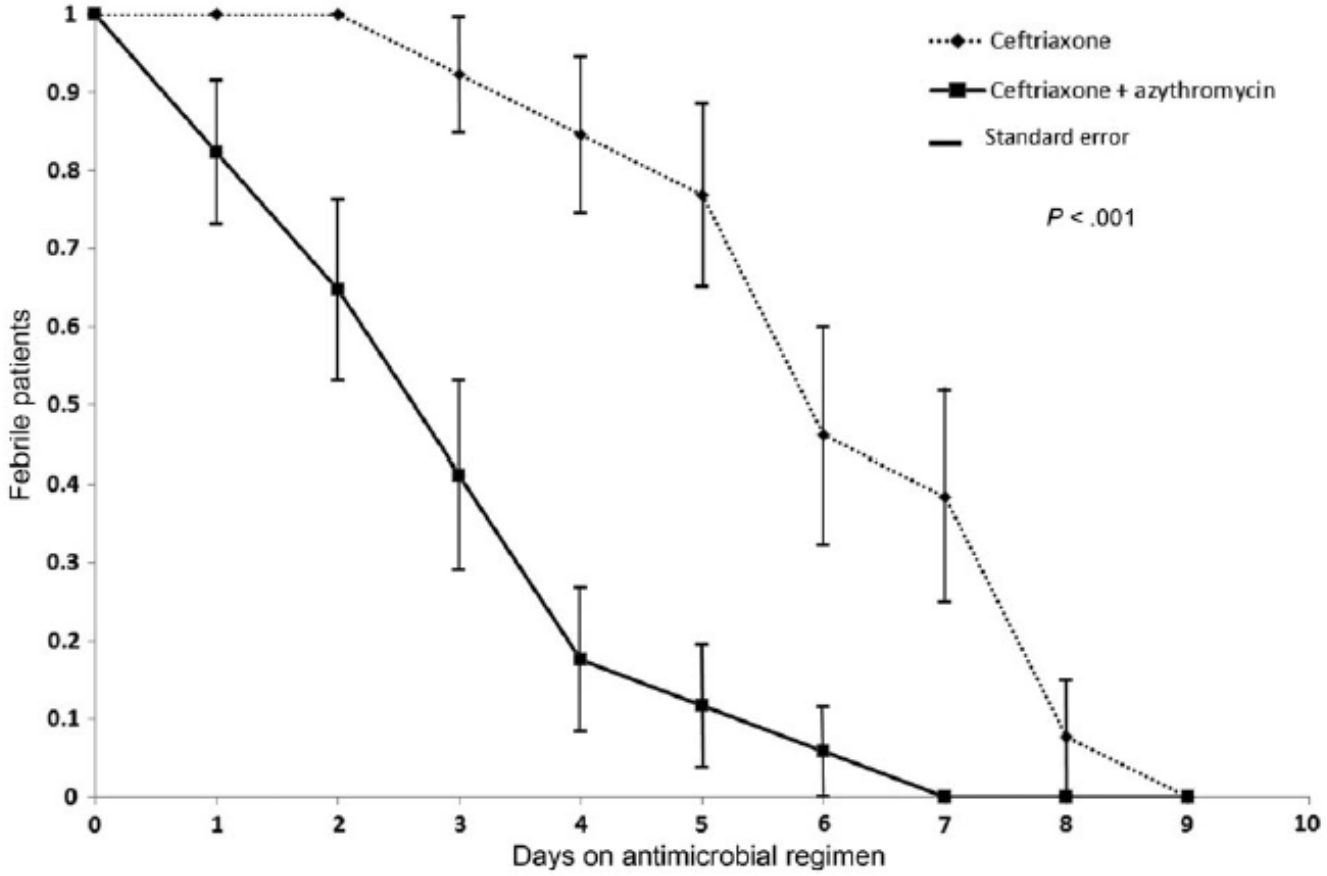


Figure 2. Time to defervescence according to antibiotic regimen used.

Discussion

Relentless increase in resistance
Resistance has an impact on morbidity and mortality

Case finding and treatment is a neglected method of control

Antimicrobial combinations/New formulations
Multi-centre RCTs

WHO list of AMR organisms of concern

WHO - Drugs for Neglected Tropical Diseases Initiative (DNDi)
Incubating:
Global antibiotic resistance development (GARD) partnership

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LSTM

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Hellen Gelband

DNDi

Isabel Ribiero

Liverpool Clinical Laboratories

LSTM

長崎大学大学院

Multicentre RCT

Single drugs versus combinations

Large numbers for adequate power

Simple protocol

Post treatment faecal carriage

Incorporate PK/PD

Complete in sensible time period

Translation results into policy