Building Evidence for Enteric Fever Treatment across South Asia: From Early Trials to the Azithromycin and Cefixime Typhoid Trial

Presented by :

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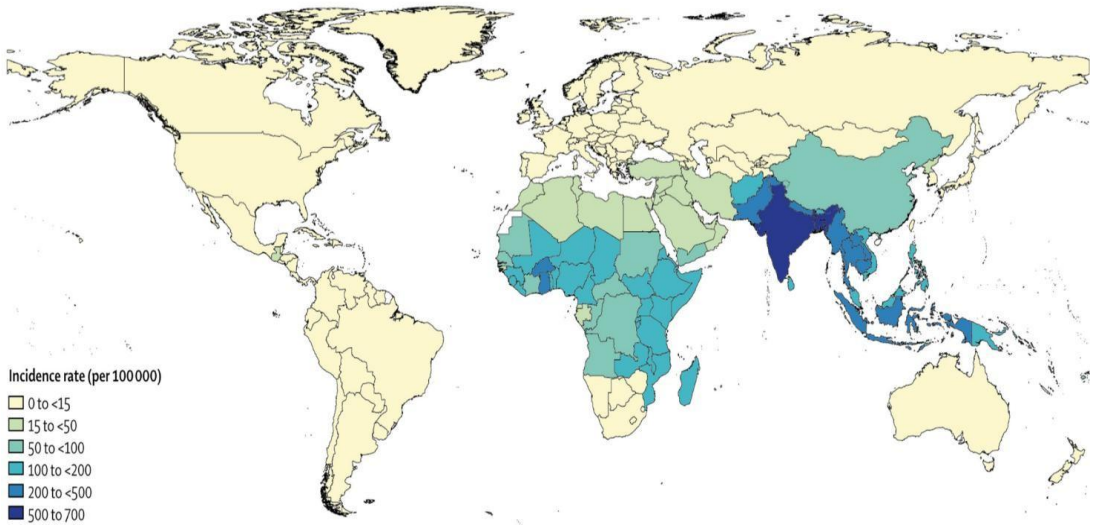
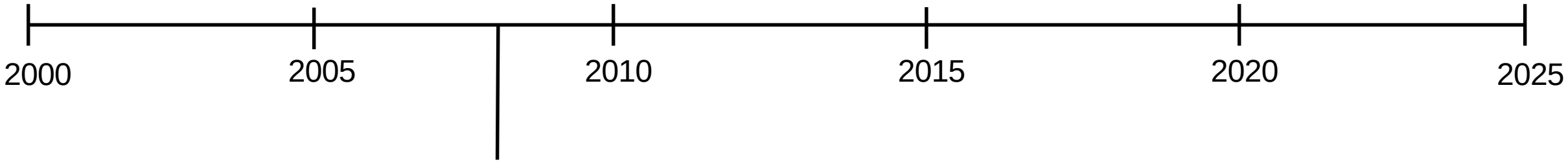
Background : Global Burden of Enteric Fever



Source: *Piovani, Daniele et al. eClinicalMedicine 2024;77: 102883*

- An estimated 9.3 million cases of enteric fever occur globally each year.
- These lead to approximately 107,000 deaths annually.
- The disease predominantly affects children and young adults.
- Affects estimated 6.7 million living in South Asia. With 72,000 (67%of total deaths world wide) deaths per year.

- *Salmonella enterica* Serovar Paratyphi A and *S. enterica* Serovar Typhi Cause Indistinguishable Clinical Syndromes in Kathmandu, Nepal



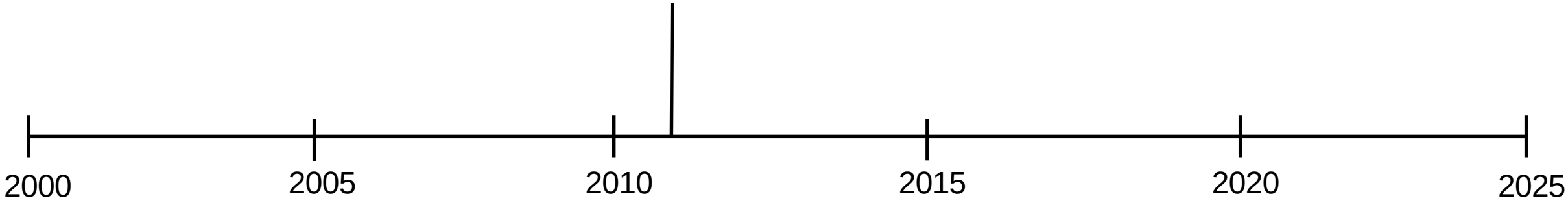
- An Open Randomized Comparison of Gatifloxacin versus Cefixime for the treatment of Uncomplicated Enteric Fever

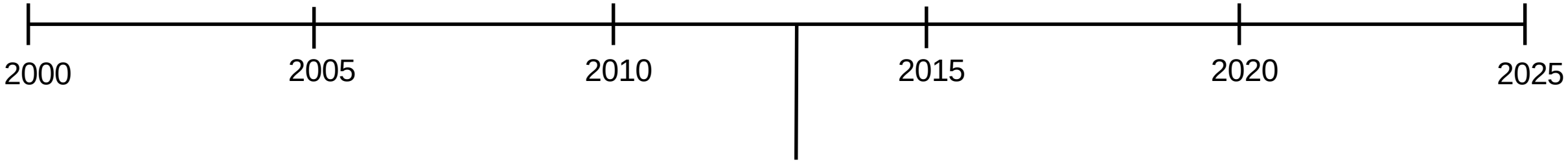
PLoS One. 2007; 2(6): e542.
Published online 2007 Jun 27. doi: 10.1371/journal.pone.0000542
PMCID: PMC1891439
PMID: 17593957

N=390

- Gatifloxacin versus Chloramphenicol for uncomplicated enteric fever:an open-label,randomized, controlled Trial

Lancet Infect Dis. 2011 Jun; 11(6): 445–454.
doi: 10.1016/S1473-3099(11)70089-5
PMCID: PMC3108101
PMID: 21531174



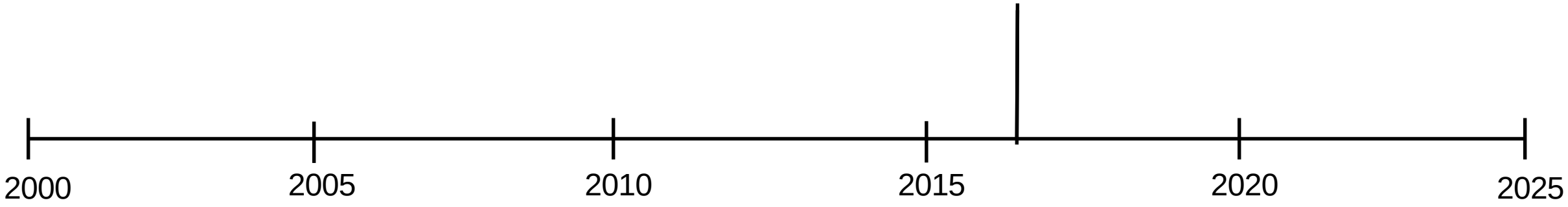


- Gatifloxacin versus Ofloxacin for the treatment of uncomplicated enteric fever in Nepal:an open-label,randomized, controlled Trial

PLoS Negl Trop Dis. 2013 Oct; 7(10): e2523.
Published online 2013 Oct 31. doi: 10.1371/journal.pntd.0002523
PMCID: PMC3837022
PMID: 24282626

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

Randomized Controlled Trial › Lancet Infect Dis. 2016 May;16(5):535-545.
doi: 10.1016/S1473-3099(15)00530-7. Epub 2016 Jan 20.



The NEW ENGLAND JOURNAL of MEDICINE

Phase 3 Efficacy Analysis of a Typhoid Conjugate Vaccine Trial in Nepal

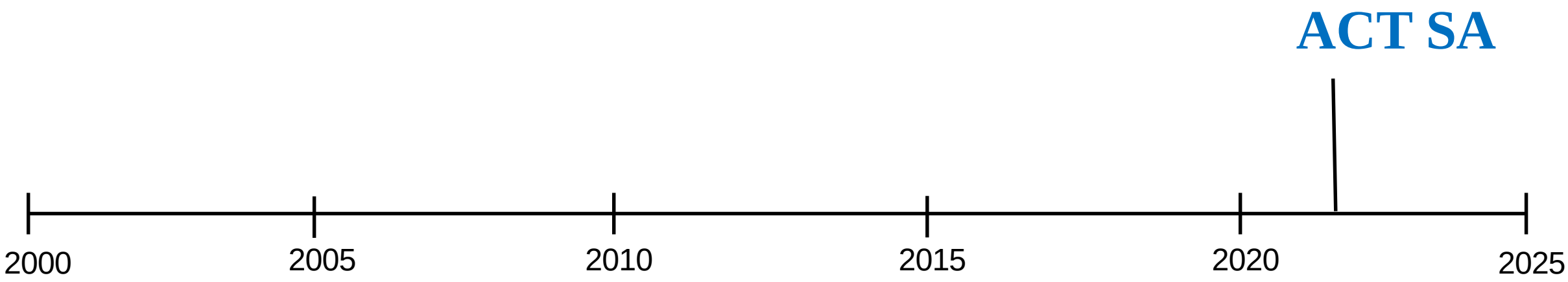
Published December 4, 2019 | N Engl J Med 2019;381:2209-2218
DOI: 10.1056/NEJMoa1905047 | VOL. 381 NO. 23 | Copyright © 2019

JOURNAL ARTICLE

Trimethoprim-sulfamethoxazole Versus Azithromycin for the Treatment of Undifferentiated Febrile Illness in Nepal: A Double-blind, Randomized, Placebo-controlled Trial

Clinical Infectious Diseases, Volume 73, Issue 7, 1 October 2021, Pages e1478–e1486, https://doi.org/10.1093/cid/ciaa1489

Published: 29 September 2020 **Article history** ▾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Azithromycin-Cephalosporin combinations

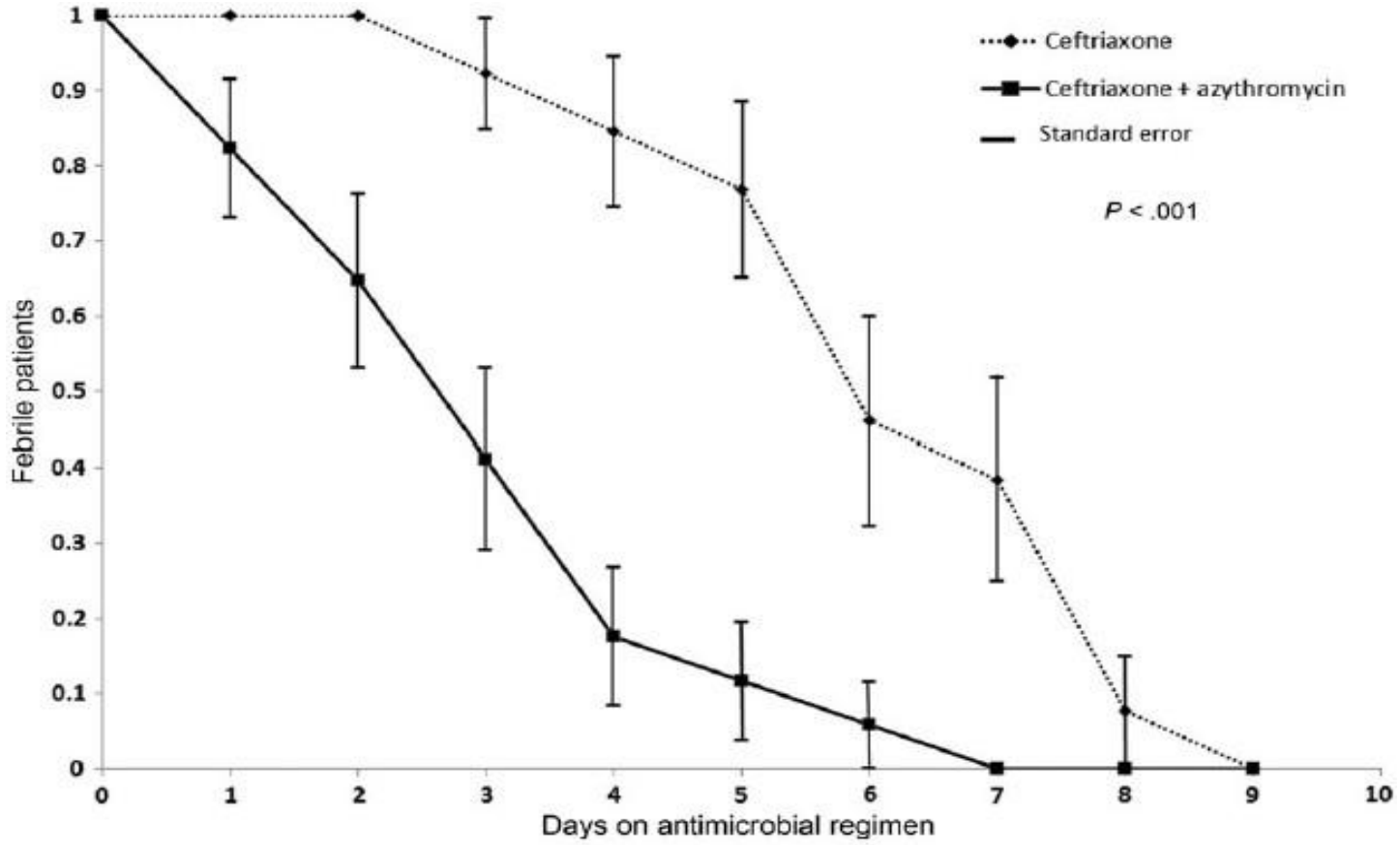


Figure 2. Time to defervescence according to antibiotic regimen used.

A large outbreak of ***Salmonella paratyphi A*** infection among Israeli travelers to Nepal

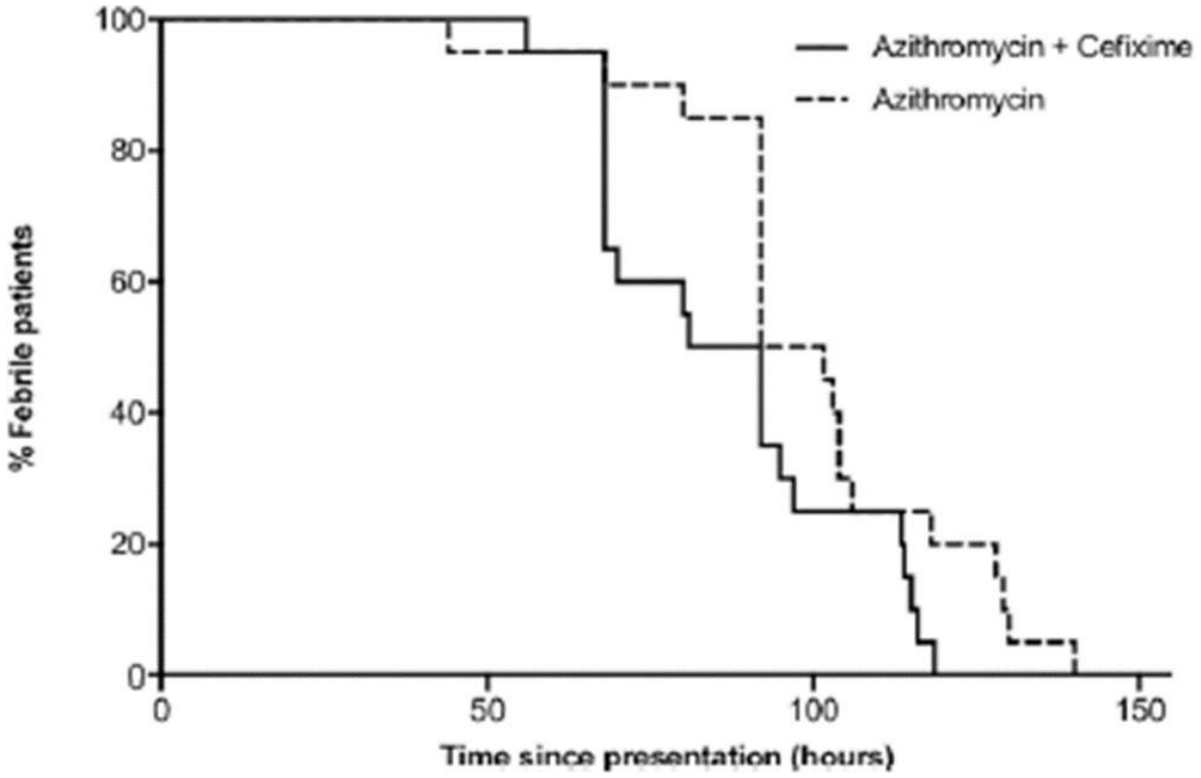
Melzer et al. Clin Infect Dis 2014;58:359

Azithromycin-Cephalosporin combinations

Open label comparative trial of mono versus dual antibiotic therapy for Typhoid Fever in adults

Niv Zmora[1,2☯], Sudeep Shrestha[3☯], Ami Neuberger[4,5☯], Yael Paran[1,2], Rajendra Tamrakar[3], Ashish Shrestha[3], Surendra K. Madhup[3], T. R. S. Bedi[3], Rajendra Koju[3], Eli Schwartz[2,6]*

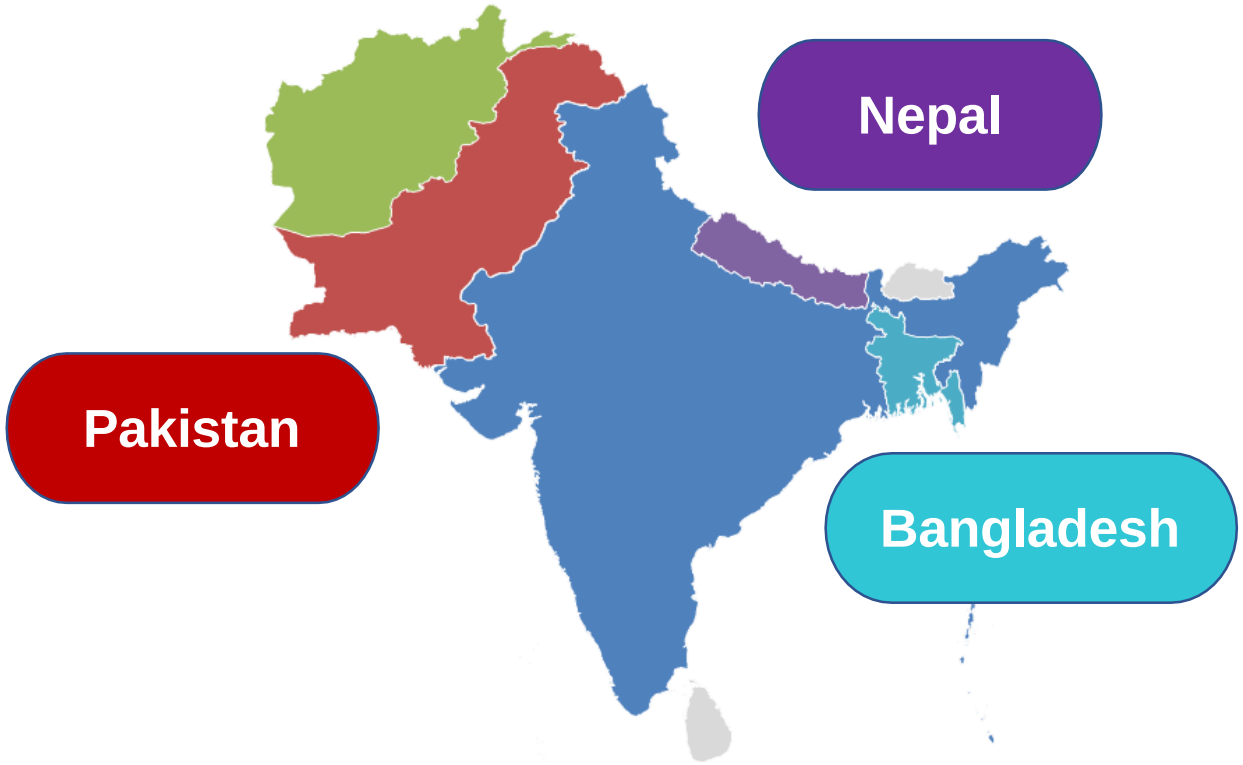
Zmora et al. PLoS NTD 2018



Azithromycin and cefixime combination versus azithromycin alone for the out-patient treatment of clinically suspected or confirmed uncomplicated typhoid fever in South Asia; a randomised controlled trial

ACT-South Asia

- A randomized (1:1), participant- and observer-blind , multi-centre phase IV trial.
- Multi country Collaboration
- Sample size: 2150



PRIMARY OBJECTIVE

To determine whether treatment with seven days of an azithromycin and cefixime combination is **Superior** to seven days of azithromycin and placebo in preventing treatment failure in patients with clinically suspected or confirmed uncomplicated typhoid fever.

Secondary Objectives

To compare

- Fever Clearance Time in each arm
- Time from onset of treatment to treatment failure
- Time from onset of symptoms to treatment failure
- Occurrence of adverse events in each treatment arm
- Clearance of faecal carriage of S.Typhi or S.Paratyphi
- The cost-effectiveness of the treatment in each treatment arms

Exploratory Objectives

- To determine the diagnosis in participants who do not have blood culture confirmed typhoid fever
- To compare the faecal microbiome of patients with confirmed and suspected typhoid fever
- To describe the pharmacokinetics and pharmacodynamics of oral azithromycin in blood culture positive enteric fever

Methodology: TRIAL SCHEMA

Child (≥ 2 years or ≥ 10 kg) or adult with suspected typhoid fever

- Documented fever >48 hours
- CRP ≥ 10 mg/L
- Malaria, Dengue, and Scrub typhus RDT negative
- Covid
- No features of complicated or severe typhoid fever

Randomize consented patients (1:1)

Day 0 investigation

Group 1: Azithromycin plus placebo for 7 days

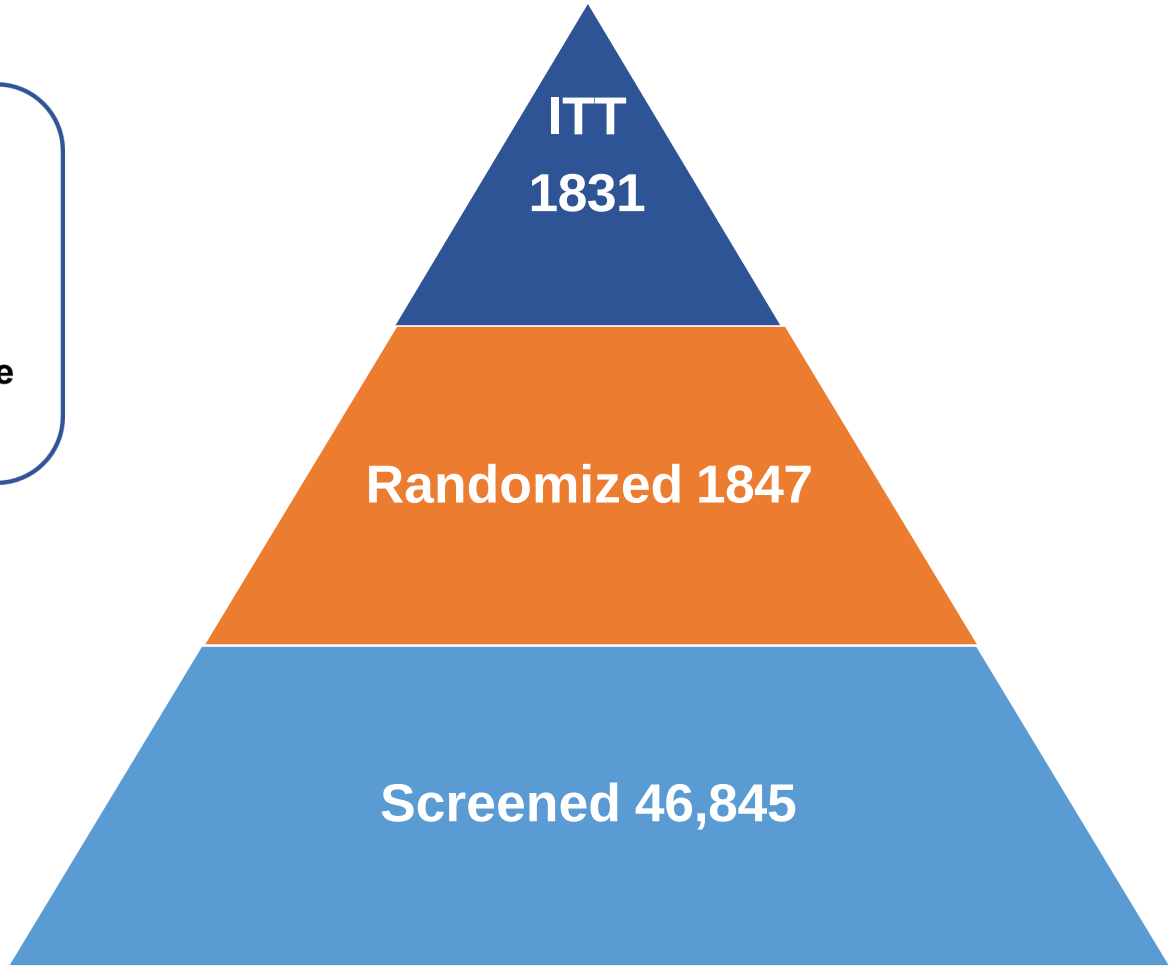
Group 2: Azithromycin plus cefixime for 7 days

Follow-up:
Daily telephone calls; CMA visits to home on day 2 and 4; day 7, 14, and 28 clinic attendance; 3-month clinic attendance for subjects with blood and stool culture confirmed typhoid.

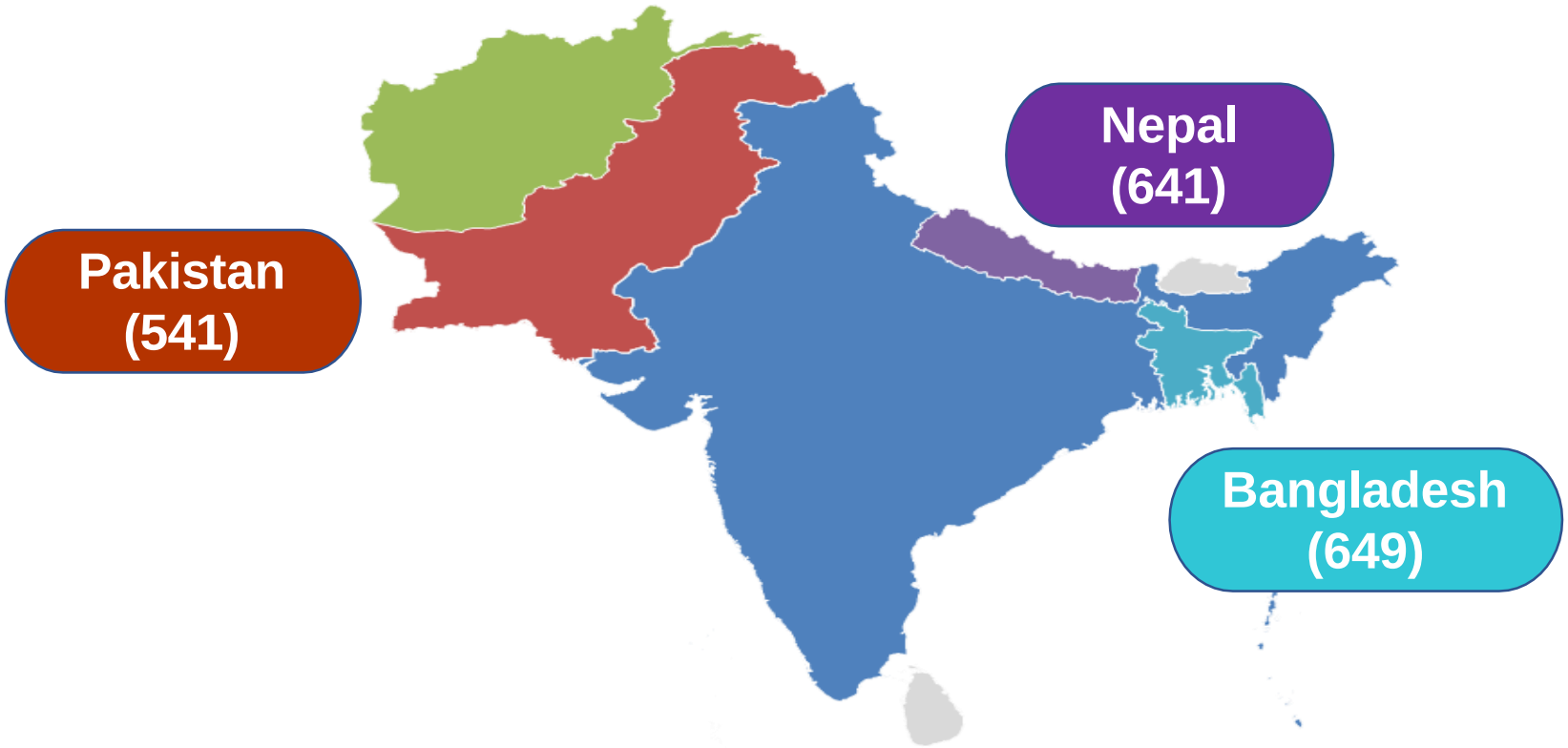
Results: Summary of trial participant flowchart

16 patients excluded after randomization

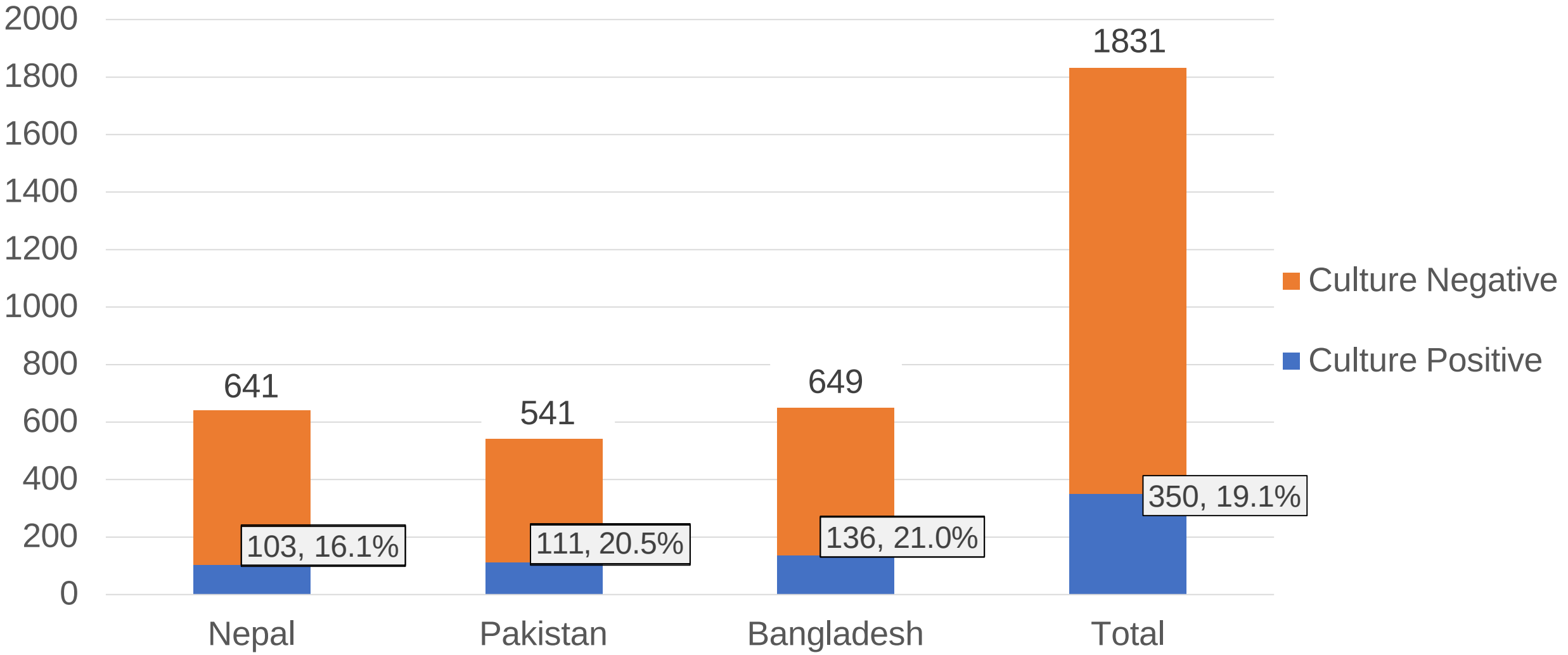
- 12 patients refused to take any study medication after randomization
- 4 patients were PCR positive for COVID-19



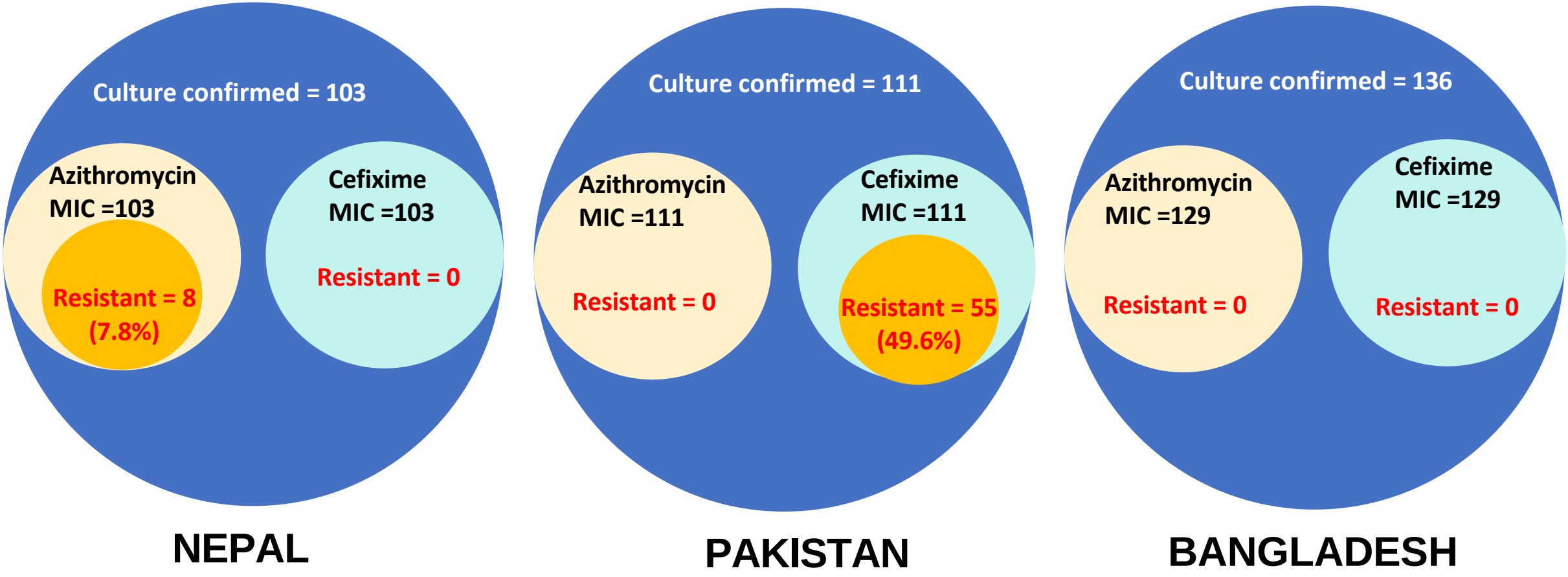
ACT-South Asia Trial
Intention-to-treat (ITT) population by country



Intention-to-treat population (ITT) by blood culture positivity

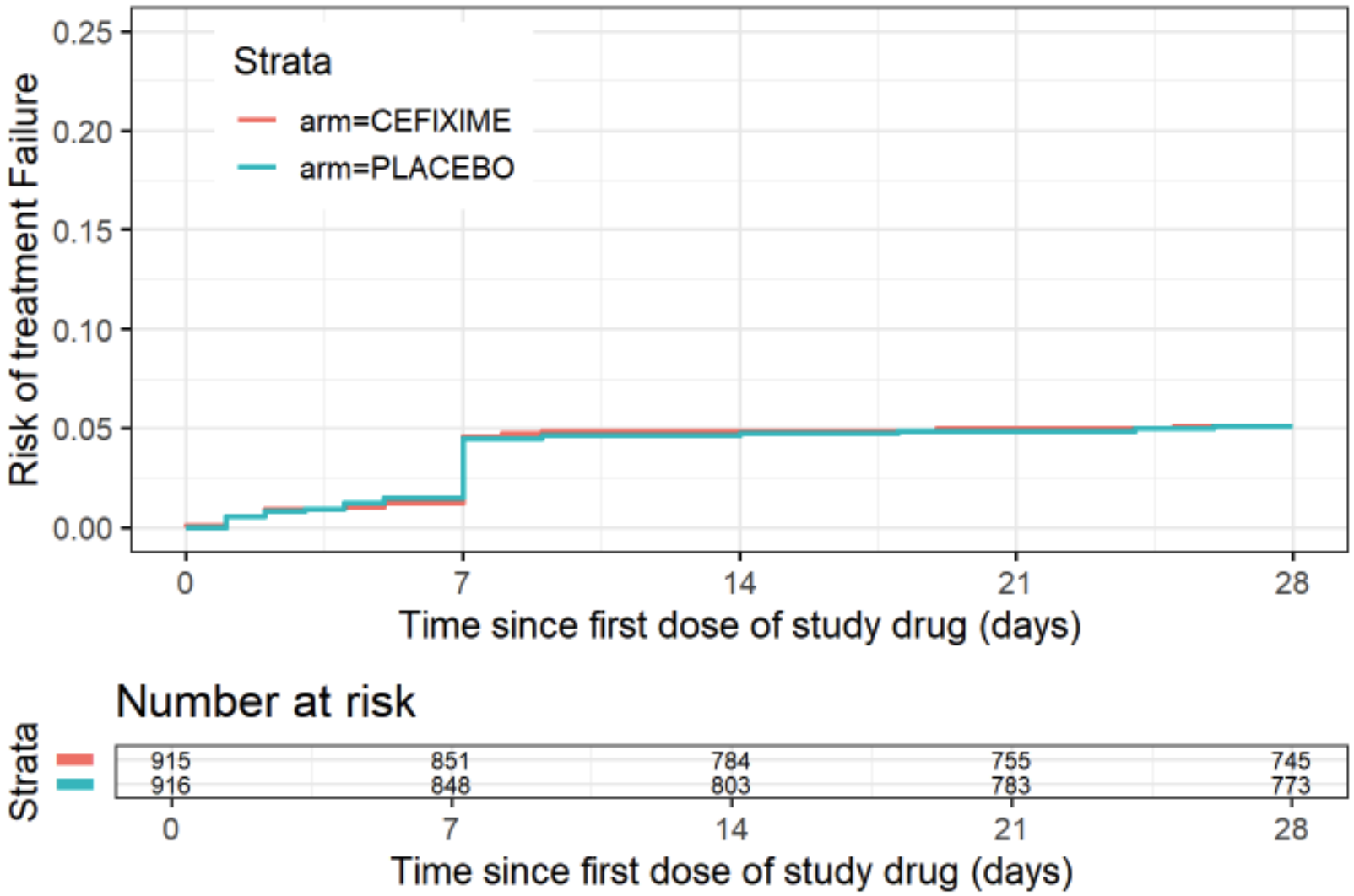


Antimicrobial susceptibility testing by MIC (Minimum Inhibitory Concentration)



Primary Outcome- ITT Population

Treatment failure Subgroup	Azithromycin Cefixime Events/n (risk [%])	Azithromycin Events/n (risk [%])	Absolute risk difference [%] (95% CI)	Test for superiority P-value
All participants	44/915 [5.1]	44/916 [5.1]	-0.0 [-2.1 to 2.1]	1.00



Kaplan-Meier Plot of Time to Treatment Failure (ITT Population)

Primary Outcome- Blood Culture Result

Treatment failure Subgroup	Azithromycin Cefixime Events/n (risk [%])	Azithromycin Events/n (risk [%])	Absolute risk difference [%] (95% CI)	Test for superiority P-value	Test for heterogeneity P-value
Blood culture subgroup					0.14
Culture confirmed enteric fever	19/179 [11.2]	26/171 [16.0]	4.84 [-2.52 to 12.2]	0.20	
Clinically suspected enteric fever (culture negative)	22/728 [3.2]	16/736 [2.3]	-0.89 [-2.6 to 0.85]	0.31	

Discussion

- No difference in treatment failure between azithromycin-cefixime and azithromycin alone for 7 days in treatment of culture-confirmed or clinically suspected enteric fever
- Among culture-confirmed subgroup, the risk decreased by 4.84%, but not statistically significant

Conclusion and take-home message

- Azithromycin remains an effective treatment for enteric fever in South Asia, both for culture-confirmed and clinically suspected.
- The study supports WHO recommendation for enteric fever treatment.
- Importantly in most of South Asia, where culture facilities are generally unavailable, azithromycin alone can be effectively used in the treatment of UFIs.(Undifferentiated febrile illness)

Acknowledgement

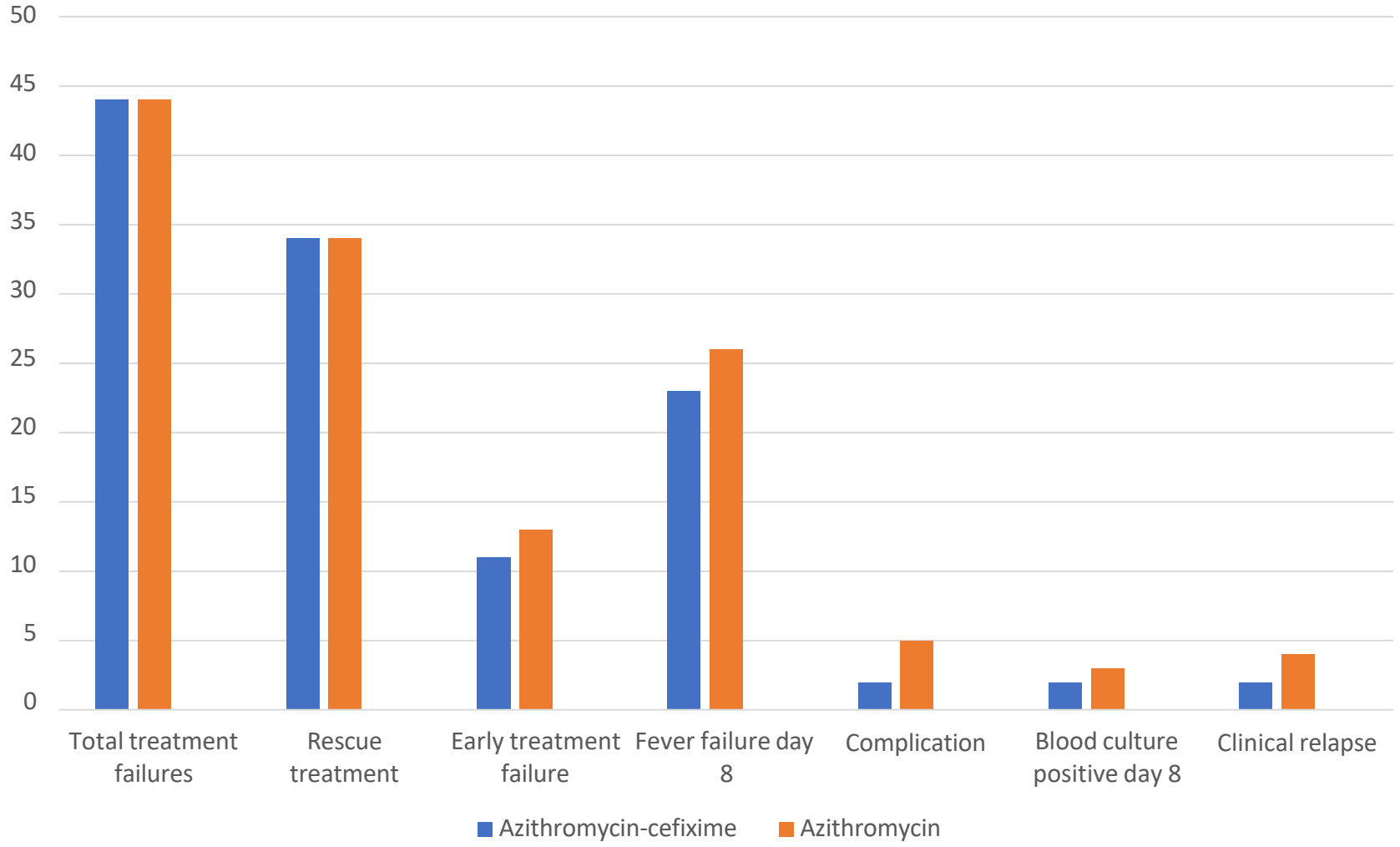
- Study participants and families
- Site teams in Nepal, Bangladesh, and Pakistan
- ACT–South Asia team
- Collaborating institutions
- Funders (MRC’s Dr Caroline Harris was outstanding)

OUR FUNDERS

- Saraswati Budhathoki is a Coordination Lead in a Clinical Trials Unit, specializing in overseeing a diverse range of clinical studies.
- Her expertise lies in managing trial protocols efficiently to ensure high-quality data and successful study outcome.

धन्यवाद!

Treatment failure events in each arm



Intention-to-treat population (ITT) by age and gender