

Ad Hoc Working Group

`Salmonella Azithromycin Break Point

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Typhoid (enteric) fever is the main problem

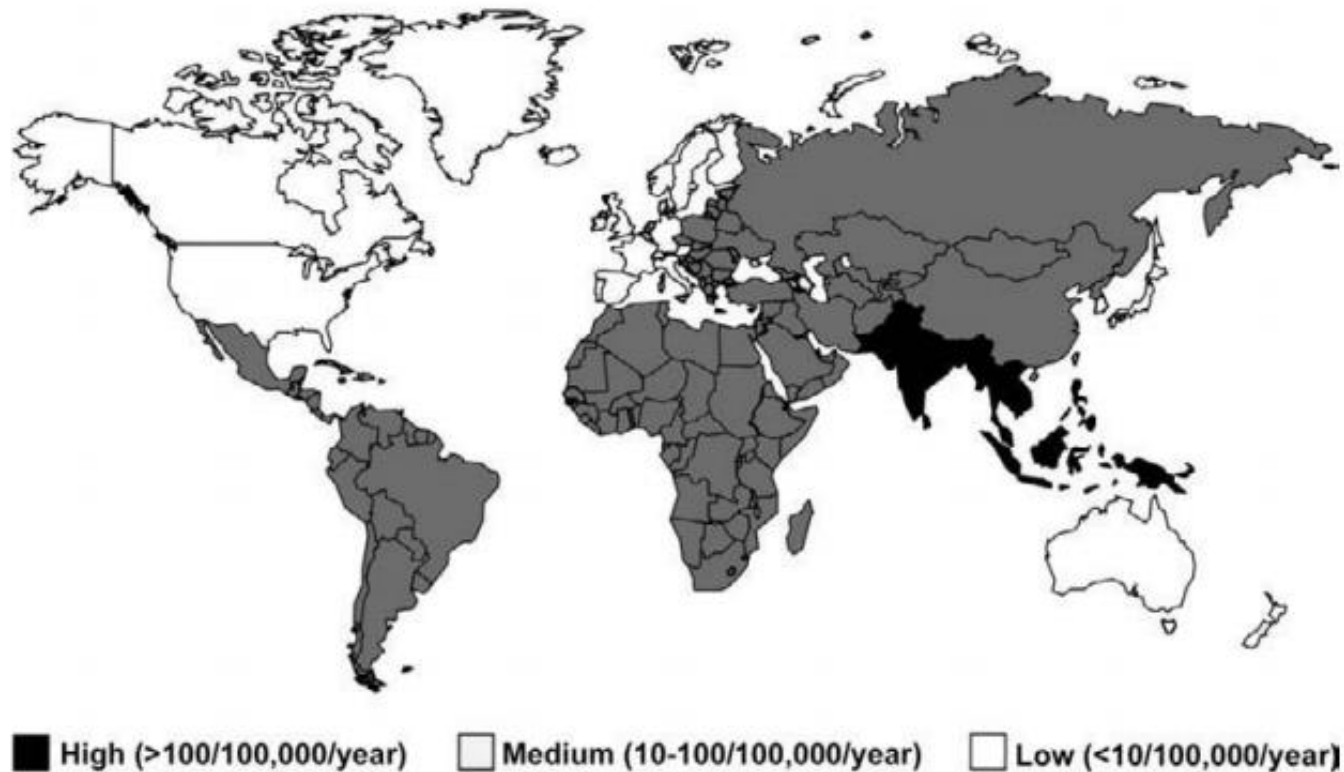


Figure 1. Geographic distribution of enteric fever. Values are no. of cases per 100,000 population per year. From [2]. (Permission was granted by the World Health Organization for reproduction in this journal.)

The Problem

- If untreated or untreatable
 - High morbidity and mortality
- Emerging resistance
 - Ampicillin
 - Chloramphenicol
 - Fluoroquinolones
 - 3rd generation cephalosporins
- More recommendations for azithromycin as 1st-line or 2nd-line therapy

Typhoid fever treatment (WHO)

Table 1. Treatment of uncomplicated typhoid fever

| | Optimal therapy | | | Alternative effective drugs | | |
|-----------------------------------|--|------------------|------------------|---|-------------------------|-------------------|
| Susceptibility | Antibiotic | Daily dose mg/kg | Days | Antibiotic | Daily dose mg/kg | Days |
| Fully sensitive | Fluoroquinolone e.g. ofloxacin or ciprofloxacin | 15 | 5–7 ^a | Chloramphenicol Amoxicillin TMP-SMX | 50–75 75–100 8–40 | 14–21 14 14 |
| Multidrug resistance | Fluoroquinolone or cefixime | 15 15–20 | 5–7 7–14 | Azithromycin Cefixime | 8–10 15–20 | 7 7–14 |
| Quinolone resistance ^b | Azithromycin or ceftriaxone | 8–10 75 | 7 10–14 | Cefixime | 20 | 7–14 |

^a Three-day courses are also effective and are particularly so in epidemic containment.

^b The optimum treatment for quinolone-resistant typhoid fever has not been determined. Azithromycin, the third-generation cephalosporins, or a 10–14 day course of high-dose fluoroquinolones, is effective. Combinations of these are now being evaluated.

WHO: 8-10 mg/kg/day (A dose of 1 g per day for five days was also effective in adults)

Registered FDA Azithromycin indications

Adults:

| Infection* | Recommended Dose/Duration of Therapy |
|--------------------------------|---|
| Community-acquired pneumonia | 500 mg once daily for 1 day, followed by 250 mg once daily through day 5. |
| Pharyngitis | |
| Skin/skin structure infections | |
| Acute bacterial sinusitis | 500 mg once daily for 1 day, followed by 250 mg once daily through day 5. |
| Acute bacterial otitis media | |
| Genital ulcers | |
| Non-gonococcal urethritis | |
| Gonococcal urethritis | |

IT IS NOT LIKELY THE
AZITHROMYCIN WILL BE
REGISTERED FOR
ENTERIC FEVER
ANYTIME SOON
- IF EVER -

2) 10 mg/kg/day Day 1 to 3

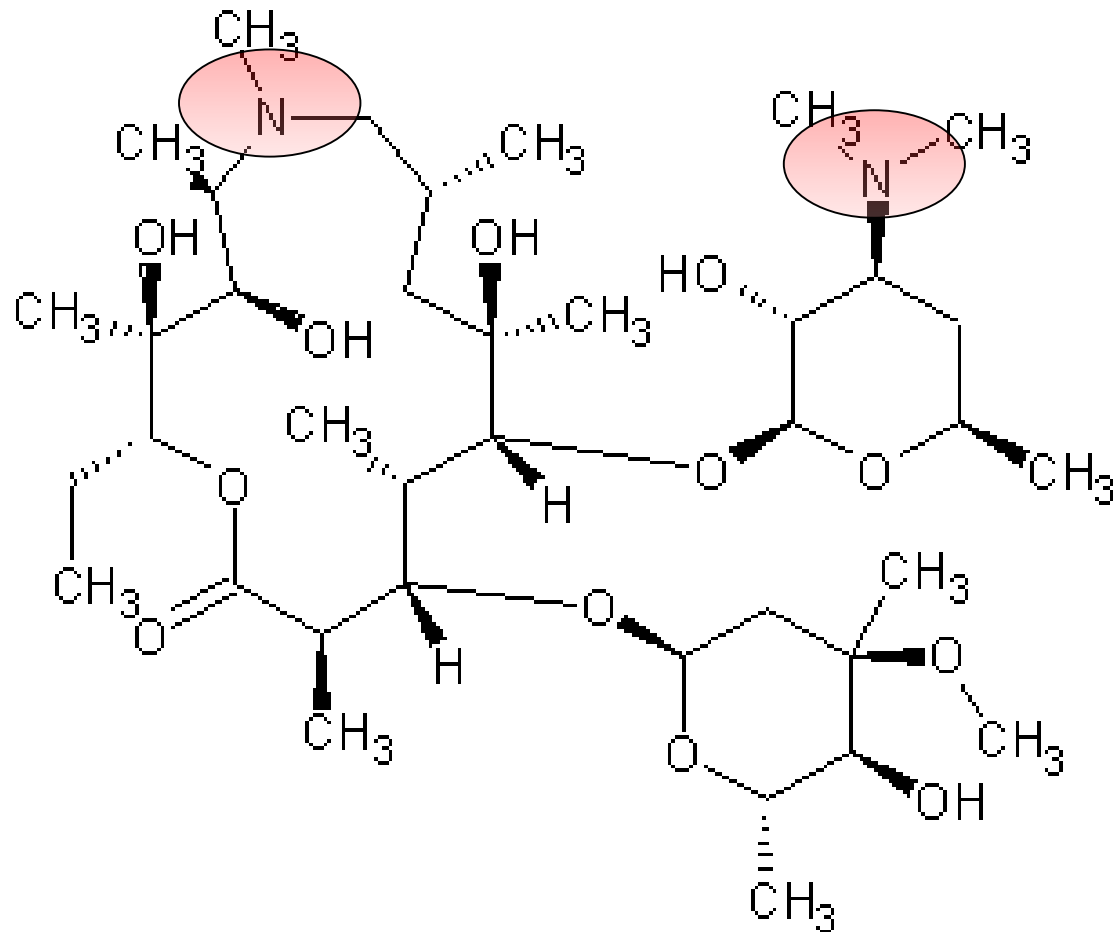
Currently used dosing regimens

No firmly established regimen

- 1) 500 mg one dose on Day 1 and 250 mg once daily for 5 to 7 days.
- 2) 500 mg once daily for 3 days
- 3) 1,000 mg on the first day and 500 mg a day for 6 more days
- 4) 10-20 mg/kg/day in children and 500 mg to 1g for adults for 5-7 days

AZITHROMYCIN

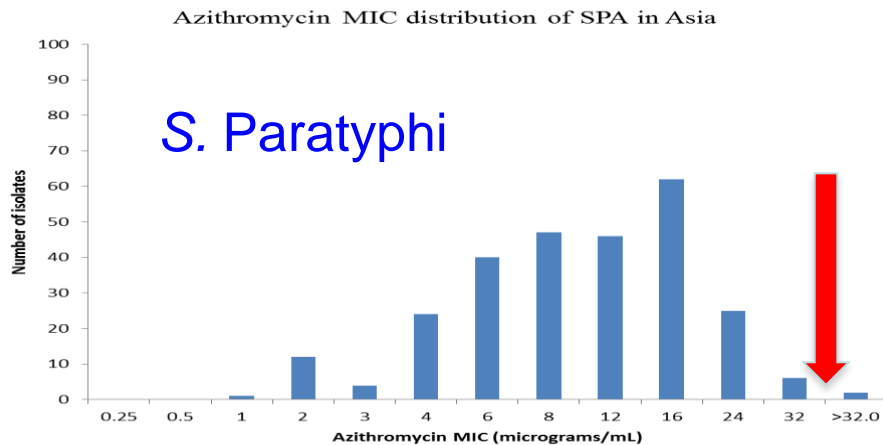
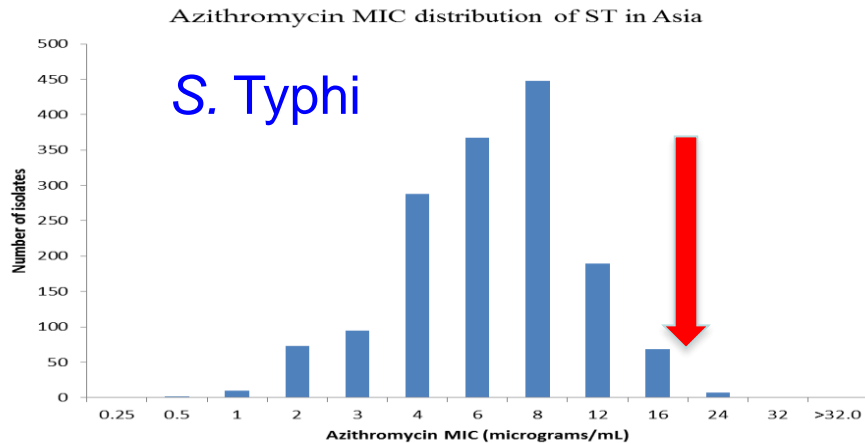
A 15-membered macrolide



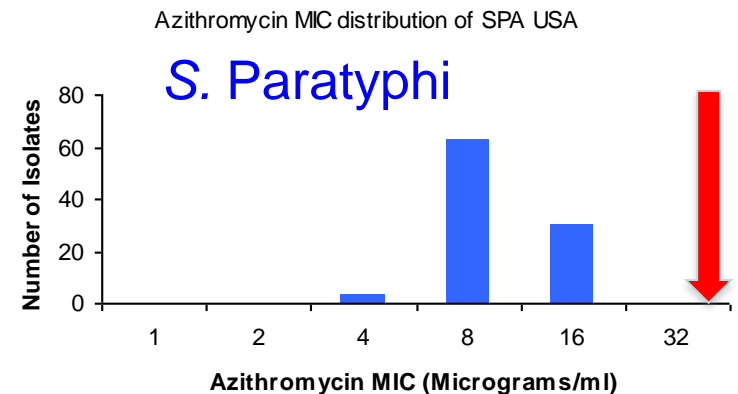
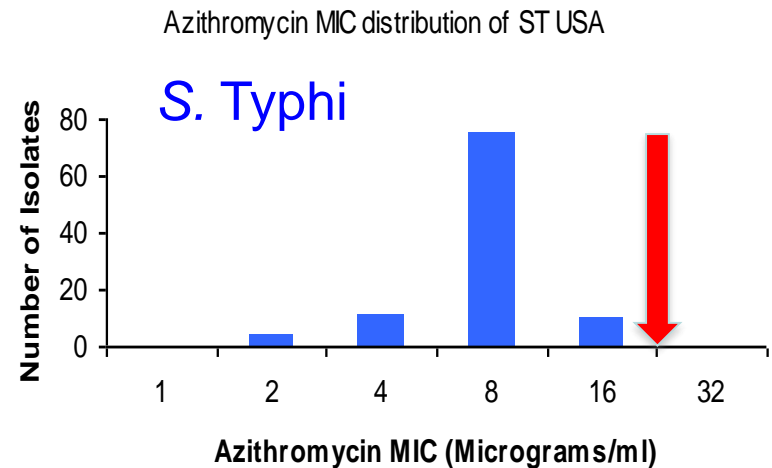
In vitro activity

MIC distributions and ECOFFs

SE Asia Etest®

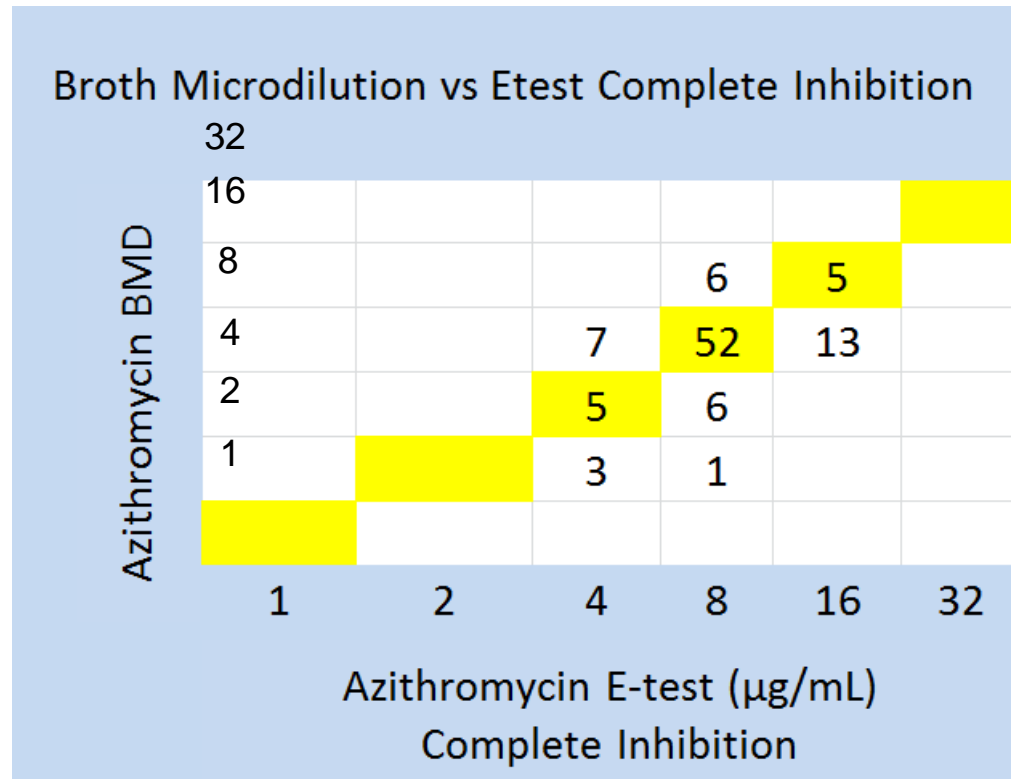


USA BMD



Is Etest equivalent to BMD?

CDC Study
Comparison of Etest versus BMD
for *S. Typhi* n=98
p>0.05 (t-test)



PK-PD -1-

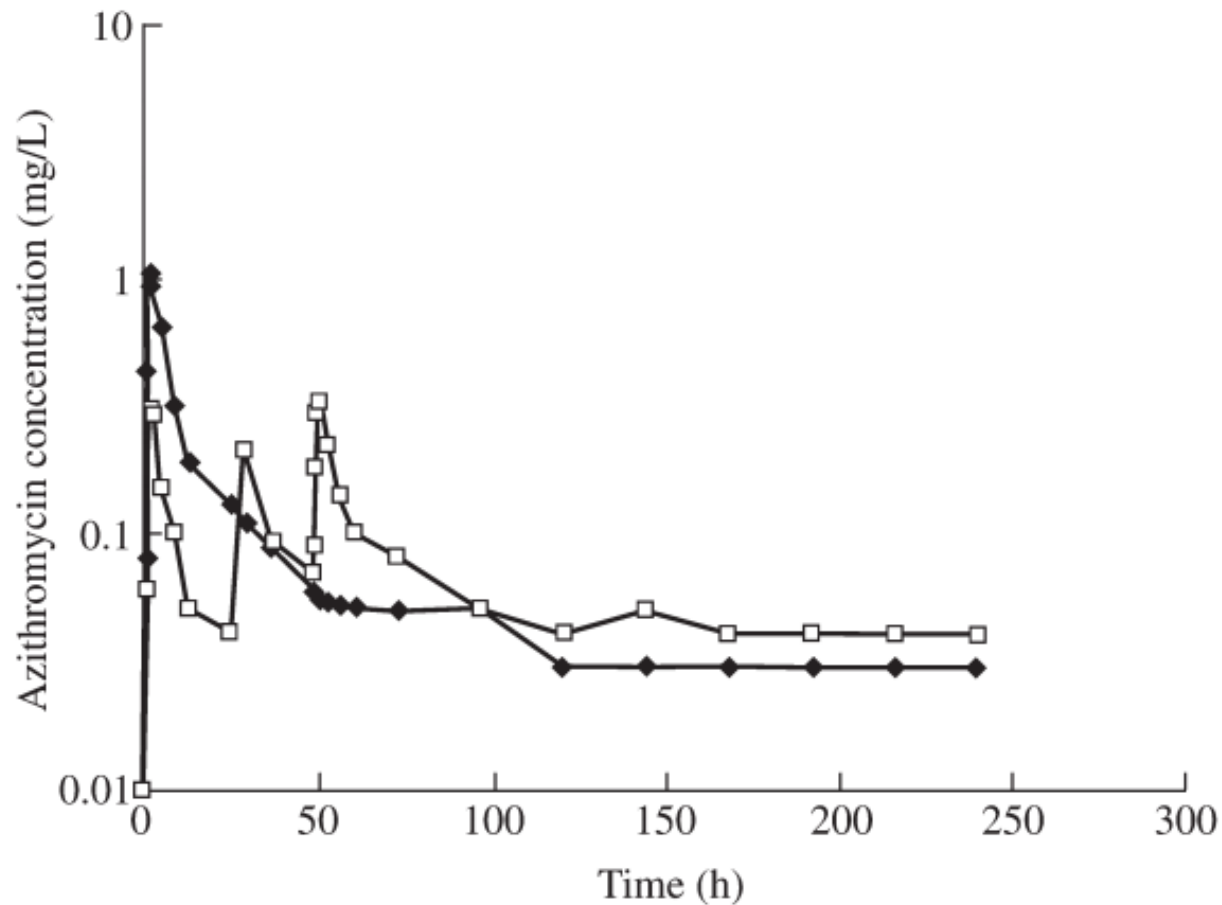
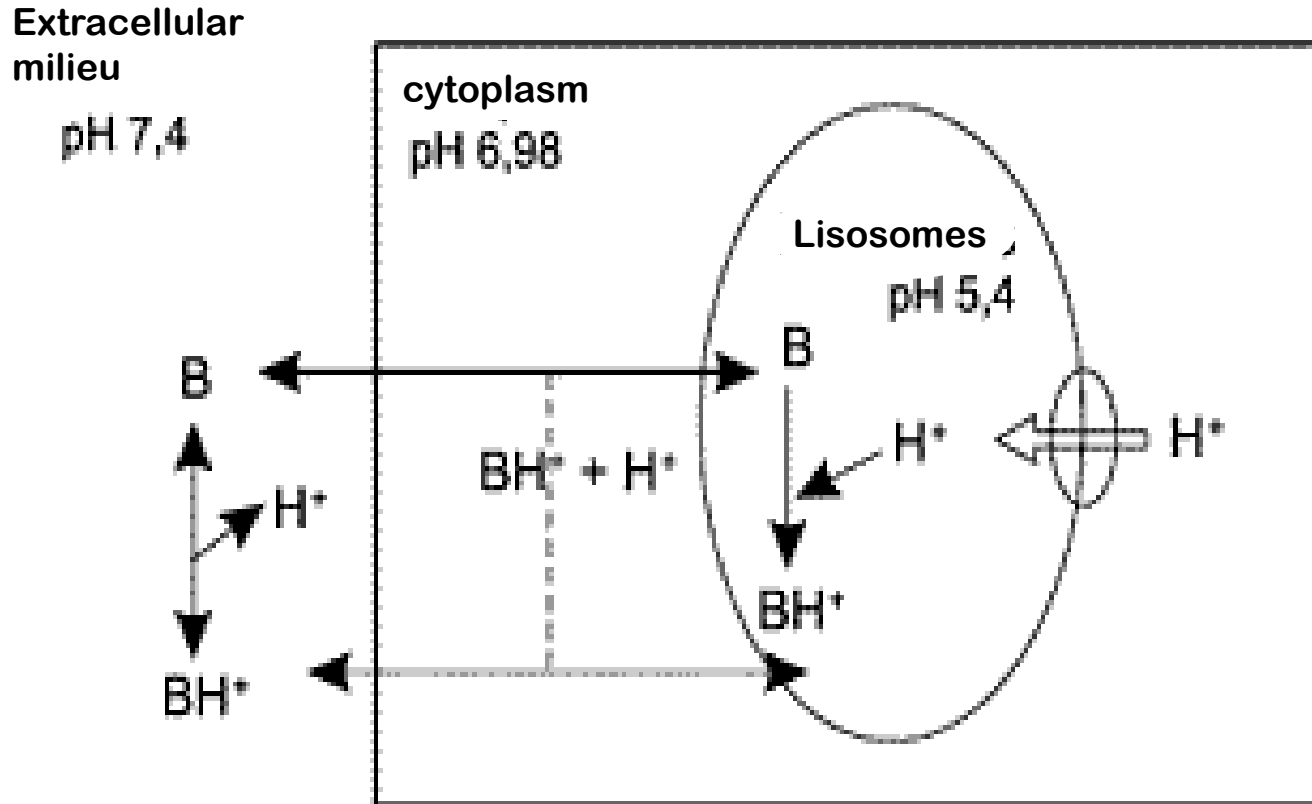


Figure. Mean azithromycin serum concentrations versus time, when azithromycin is administered as either a single dose (◆) or a three dose (□) regimen.

PK-PD -2-

Intracellular uptake of azithromycin



McDonald P J et al. Eur J Clin Microbiol Infect Dis, 1991, 10(10):828-833.
Otero et al. Rev Esp Quimioter 2002; 15(2):828

PK-PD -3-

Table I. Mean (range) serum azithromycin pharmacokinetic parameters when it is administered over a 1 or 3 day period

| Parameter (units) | Single dose | Three dose |
|---------------------------|--------------------|--------------------|
| C_{\max} (mg/L) | 1.46 (0.34–3.48)* | 0.54 (0.18–1.01) |
| $AUC_{0-\infty}$ (mg·h/L) | 13.1 (3.02–20.6) | 11.2 (2.98–24.5) |
| Cl/F (L/h) | 124.9 (64.2–345.6) | 152.9 (41.6–478.2) |
| V_d/F (L/kg) | 89.5 (45.5–194.4) | 109.2 (42.3–228.8) |

* $P = 0.001$.

Table II. Mean (range) PMN and M/L peak azithromycin concentrations and sampling time exposure when it is given as one dose or as three doses

| Cell type | Parameter (units) | Single dose | Three dose |
|------------------|----------------------|----------------------|----------------------|
| PMN ^a | C_{\max} (mg/L) | 41.1 (27.8–63.3) | 31.3 (14.8–53.3) |
| | AUC_{240} (mg·h/L) | 6447 (4077–10 830) | 5128 (2526–9317) |
| M/L ^a | C_{\max} (mg/L) | 312.7 (32.9–709.0) | 164.9 (38.9–563.0) |
| | AUC_{240} (mg·h/L) | 20 461 (4020–35 861) | 15 706 (4703–30 317) |

^aFor both parameters and both dosing regimens, M/L cell results were significantly ($P < 0.001$) greater than those for PMNs

PK-PD -4-

In vitro kill of
Salmonella Typhi with
MIC of 8 mg/L by
different concentrations
of azithromycin

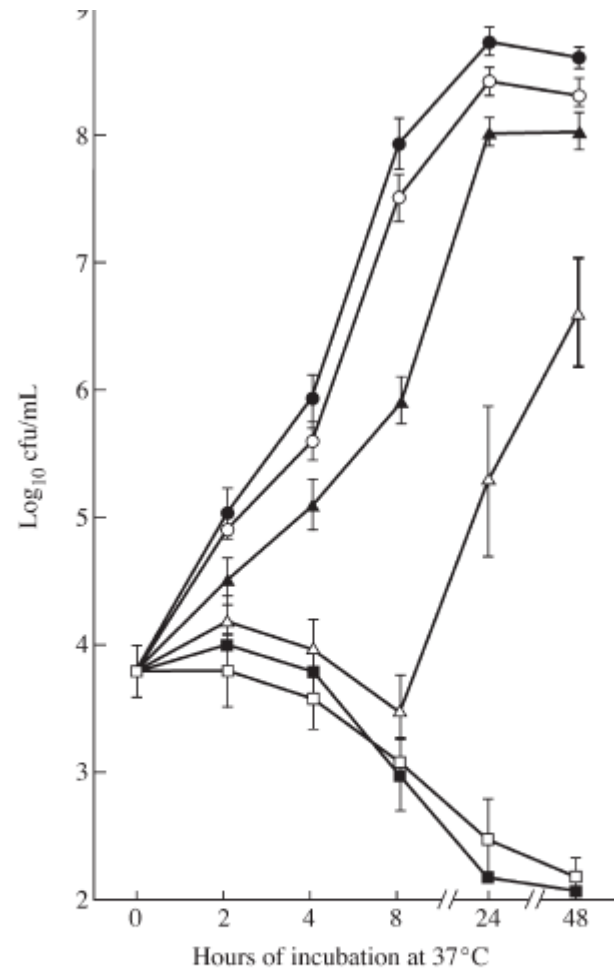


Figure. Growth curves of *S. typhi* in cation-adjusted Mueller-Hinton broth at 37°C for 48 h. Each point is the geometric mean of cfu per mL for eight strains. Bars are standard errors of means. Symbols for azithromycin concentration: (●) no azithromycin; (○) 1 mg/L; (▲) 2 mg/L; (△) 4 mg/L; (■) 8 mg/L; (□) 16 mg/L.

PK-PD -5-

Table. Inoculum effect of *S. typhi* on the MIC of azithromycin

| <i>S. typhi</i> inoculum size (cfu/mL) ^a | Median MIC (range) (mg/L) | |
|---|---|---|
| | cation-adjusted Mueller–Hinton broth, pH 7.2 ^b | Mueller–Hinton broth in phosphate-citrate buffer, pH 7.5 ^b |
| 10 ⁶ | 24 (16–32) | 0.50 (0.25–0.50) |
| 10 ⁵ | 16 (8–16) | 0.38 (0.25–0.50) |
| 10 ⁴ | 8 (4–8) | 0.25 (0.25–0.50) |
| 10 ³ | 4 (4–8) | 0.25 (0.25–0.50) |
| 10 ² | 4 (2–8) | 0.25 (all 0.25) |
| 10 ¹ | 4 (1–8) | 0.13 (0.13–0.25) |

^aActual inoculum sizes from plate counts for 10⁴ dilution were from 1.2×10^4 to 4.0×10^4 with a geometric mean of 2.1×10^4 per mL for cation-adjusted Mueller–Hinton broth, and from 5.4×10^3 to 1.8×10^4 with a geometric mean of 9.5×10^3 per mL for Mueller–Hinton broth in phosphate-citrate buffer.

^bMedian (range) of MICs of azithromycin for six strains tested in three experiments.

Breakpoints from other organizations



BSAC Methods for Antimicrobial Susceptibility Testing Version 12 May 2013

Table 6. MIC and zone diameter breakpoints for Enterobacteriaceae (including *Salmonella*, *Shigella* spp. and *Yersinia enterocolitica*)

| | MIC breakpoint (mg/L) | | | | Interpretation of zone diameters (mm) | | | |
|--|-----------------------|---|-----|-------------------|---------------------------------------|-------|-----|--|
| Antibiotic | R> | I | S ≤ | Disc content (µg) | R ≤ | I | S ≥ | |
| Quinolones | | | | | | | | |
| Ciprofloxacin | 1 | 1 | 0.5 | 1 | 16 | 17-19 | 20 | For ciprofloxacin, there is clinical evidence to indicate a poor response in systemic infections caused by <i>Salmonella</i> spp. with reduced susceptibility to fluoroquinolones. Isolates with MICs greater than 0.06 mg/L should be reported as resistant. It is recommended that the ciprofloxacin MIC should be determined for all invasive salmonellae infections. |
| Levofloxacin | 2 | 2 | 1 | 1 | 13 | 14-16 | 17 | |
| Moxifloxacin | 1 | 1 | 0.5 | 1 | 16 | 17-19 | 20 | |
| Nalidixic acid UTI ¹⁻⁵ | 16 | - | 16 | 30 | 17 | - | 18 | |
| Norfloxacin (Systemic) | 1 | 1 | 0.5 | 2 | 18 | 19-25 | 26 | |
| Norfloxacin UTI ¹⁻⁵ | 4 | - | 4 | 2 | 15 | - | 16 | No EUCAST breakpoint. BSAC data used. |
| Ofloxacin | 1 | 1 | 0.5 | 5 | 25 | 26-28 | 29 | |
| Macrolides, lincosamides and streptogramins | | | | | | | | |
| Azithromycin <i>S. typhi</i> only | - | - | - | 15 | 18 | - | 19 | Azithromycin has been used in the treatment of infections with <i>S. typhi</i> (MIC ≤16 mg/L for wild type isolates) and some enteric infections. |

Breakpoints from other organizations



COMITE DE L'ANTIBIOGRAMME DE LA SOCIETE FRANCAISE DE MICROBIOLOGIE Recommandations 2010

Tableau VII (suite) – Concentrations, diamètres critiques et règles de lecture interprétative pour *Enterobacteriaceae*.

| Antibiotique | Charge du disque | Concentrations critiques (mg/L) | | Diamètres critiques (mm) | | Remarques |
|-------------------------------|----------------------|---------------------------------|--------|--------------------------|------|--|
| | | S | R | S | R | |
| Chloramphénicol | 30 µg | ≤ 8 | > 8 | ≥ 23 | < 23 | Interprétation valable pour thiamphénicol. |
| Tétracycline | 30 UI | ≤ 4 | > 8 | ≥ 19 | < 17 | Interprétation valable pour les autres tétracyclines, sauf la minocycline. <i>En cas d'utilisation thérapeutique, il y a lieu de déterminer la CMI pour les diamètres de 19 et 20 mm.</i> |
| Minocycline | 30 UI | ≤ 4 | > 8 | ≥ 19 | < 17 | |
| Tigécycline | 15 µg | ≤ 1 | > 2 | ≥ 21 | < 19 | |
| Colistine | 50 µg | ≤ 2 | > 2 | ≥ 15 | < 15 | Les diamètres ont pour but de vérifier la résistance naturelle de certaines espèces, mais ne permettent pas de détecter toutes les résistances acquises ce qui impose de déterminer la CMI en cas d'utilisation thérapeutique. Interprétation valable pour polymyxine B |
| Sulfamides | 200 µg | ≤ 64 | > 256 | ≥ 17 | < 12 | Interprétation valable uniquement pour les souches isolées des urines. |
| Triméthoprim | 5 µg | ≤ 2 | > 4 | ≥ 20 | < 16 | Interprétation valable uniquement pour les souches isolées des urines. |
| Triméthoprim/sulfaméthoxazole | 1,25/23,75 µg | ≤ 2/38 | > 4/76 | ≥ 16 | < 13 | Interprétation valable pour les autres associations triméthoprim-sulfamide. |
| Nitrofuranes | 300 µg | ≤ 64 | > 64 | ≥ 15 | < 15 | Interprétation valable uniquement pour les souches isolées des urines. |
| Acide oxolinique | 10 µg | ≤ 2 | > 4 | ≥ 20 | < 17 | Il est justifié de fournir une réponse globale pour l'ensemble du groupe des quinolones classiques (parfois appelées de première génération) en n'étudiant qu'un seul représentant de ce groupe. Interprétation valable uniquement pour les souches isolées des urines. |
| Fluméquine | 30 µg | ≤ 4 | > 8 | ≥ 25 | < 21 | |
| Acide nalidixique | 30 µg | ≤ 8 | > 16 | ≥ 20 | < 15 | |
| Acide pipémidique | 20 µg | ≤ 8 | > 16 | ≥ 19 | < 14 | |
| Acide piromidique | 25 µg | ≤ 16 | > 32 | ≥ 20 | < 16 | |
| Ciprofloxacine | 5 µg | ≤ 0,5 | > 1 | ≥ 25 | < 22 | La résistance aux fluoroquinolones est croisée entre les différentes molécules mais son niveau d'expression peut varier pour chaque molécule. Les souches d'entérobactéries sensibles à la norfloxacine (NOR) sont sensibles aux autres fluoroquinolones. Pour les souches I (ou R) à NOR, des différences d'activité intrinsèque impliquent un test et une réponse indépendante pour les autres molécules. Les souches de <i>Salmonella</i> spp. résistantes à l'acide nalidixique doivent être catégorisées résistantes aux fluoroquinolones. |
| Enoxacine | 5 µg | ≤ 1 | > 2 | ≥ 22 | < 19 | |
| Lévofloxacine | 5 µg | ≤ 1 | > 2 | ≥ 20 | < 17 | |
| Loméfloxacine | 5 µg | ≤ 1 | > 2 | ≥ 22 | < 19 | |
| Moxifloxacine | 5 µg | ≤ 0,5 | > 1 | ≥ 24 | < 21 | |
| Norfloxacine | 5 µg | ≤ 0,5 | > 1 | ≥ 25 | < 22 | |
| Ofloxacine | 5 µg | ≤ 0,5 | > 1 | ≥ 25 | < 22 | |
| Péfloxacine | 5 µg | ≤ 1 | > 4 | ≥ 22 | < 16 | |
| Fosfomycine | 50 µg + 50 µg G6P | ≤ 32 | > 32 | ≥ 14 | < 14 | La résistance acquise à la fosfomycine est homogène. La présence de colonies dans la zone d'inhibition ne doit pas être prise en compte. Interprétation valable pour la fosfomycine trométamol. |
| Azithromycine | | ≤ 16 | | | | Valable pour <i>Salmonella</i> sérotype Typhimurium et <i>Shigella</i> spp. |

3) MIC distribution and ECOFF



EUCAST EUROPEAN COMMITTEE
ON ANTIMICROBIAL
SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

Enterobacteriaceae

EUCAST Clinical Breakpoint Table v. 4.0, valid from 2014-01-01

| Glycopeptides | MIC breakpoint (mg/L) | | Disk content (µg) | Zone diameter breakpoint (mm) | | Notes Numbers for comments on MIC breakpoints Letters for comments on disk diffusion |
|---------------|-----------------------|-----|-------------------|-------------------------------|-----|--|
| | S ≤ | R > | | S ≥ | R < | |
| Telooplanin | - | - | | - | - | |
| Telavancin | - | - | | - | - | |
| Vancomycin | - | - | | - | - | |

| Macrolides, lincosamides and streptogramins | MIC breakpoint (mg/L) | | Disk content (µg) | Zone diameter breakpoint (mm) | | Notes Numbers for comments on MIC breakpoints Letters for comments on disk diffusion |
|---|-----------------------|-----|-------------------|-------------------------------|-----|--|
| | S ≤ | R > | | S ≥ | R < | |
| Azithromycin ¹ | - | - | | - | - | 1. Azithromycin has been used in the treatment of infections with <i>Salmonella typhi</i> (MIC ≤16 mg/L for wild type isolates) and <i>Shigella</i> spp. |
| Clarithromycin | - | - | | - | - | |
| Erythromycin ¹ | - | - | | - | - | |
| Roxithromycin | - | - | | - | - | |
| Telithromycin | - | - | | - | - | |
| Clindamycin | - | - | | - | - | |
| Quinupristin-dalfopristin | - | - | | - | - | |

Clinical findings

JOURNAL OF CLINICAL MICROBIOLOGY, Dec. 2010, p. 4655–4657
0095-1137/10/\$12.00 doi:10.1128/JCM.00648-10
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Vol. 48, No. 12

CASE REPORTS

First Report of *Salmonella enterica* Serotype Paratyphi A Azithromycin Resistance Leading to Treatment Failure[▽]

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Paul J. Lehner,¹ and M. Estee Torok¹

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Received 28 March 2010/Returned for modification 20 May 2010/Accepted 29 August 2010

MIC of 64 ug/ml

Clinical findings

Individual patient analysis of clinical response to azithromycin in three RCTs in uncomplicated enteric fever

Chinh NT, Parry CM, Ly NT, et al. A randomised controlled comparison of azithromycin and ofloxacin for multidrug-resistant and nalidixic acid resistant enteric fever. *Antimicrob Agents Chemother* 2000; 44: 1855-1859

Parry CM, Ho VA, Phuong LT, et al. A randomised controlled comparison of ofloxacin, azithromycin and an ofloxacin-azithromycin combination for treatment of multidrug resistant and nalidixic acid resistant typhoid fever. *Antimicrob Agents Chemother*. 2007; 51:819-825

Dolecek C, La TTP, Rang NN et al. A Multi-Center Randomised Controlled Trial of Gatifloxacin versus Azithromycin for the Treatment of Uncomplicated Typhoid Fever in Children and Adults in Vietnam. *PLoS ONE* 3(5): e2188

Individual patient analysis of clinical response to azithromycin in three RCTs in uncomplicated enteric fever

Study 1: Azithromycin (Zithromax®, Pfizer, USA; 500 mg/tablet) 1gm orally once daily for 5 days (Mean of 20 mg/kg/day).

Adults

Study 2: Azithromycin suspension (Zithromax® suspension, Pfizer, USA; 200 mg/5 mL or Zithromax® tablets, Pfizer, USA; 500 mg/tablet) 10mg/kg/day orally once a day (maximum 500 mg daily) for 7 days.

Adults and children

Study 3: Azithromycin (Zithromax® suspension, Pfizer, USA; 200 mg/5 mL or Zithromax® tablets, Pfizer, USA; 500 mg/tablet) 20 mg/kg orally once a day (maximum 1 gm daily) for 7 days

Adults and children

Individual patient analysis of clinical response to azithromycin in three RCTs in uncomplicated enteric fever

214 patients eligible for analysis

42 from study 1; 45 from study 2; 127 from study 3

Median (IQR, range) age of 13 years (8-20, 1-68)

Median (IQR, range) duration of illness of 8 days (6-10, 2-30)

Infecting isolate was

S.enterica Typhi (209 patients)

S.enterica Paratyphi (5 patients)

137 (64%) were multidrug resistant (resistant to C, A, Sxt)

184 (86%) were intermediate to ciprofloxacin

All isolates were susceptible to ceftriaxone

Median (IQR, range) azithromycin MIC was 8 mcg/mL (8-12, 4-16).

| Variable/Azithromycin MIC | 4 mg/L | 6-8 mg/L | 12-16 mg/L | p |
|---------------------------------|------------------|------------------|------------------|--------|
| Number | 13 | 116 | 85 | |
| Age | 14 (9-17) | 14 (9-21) | 11 (8-19) | 0.256 |
| Sex (Male) | 8 (61.5) | 59 (50.9) | 35 (41.2) | 0.233 |
| Duration of illness (days) | 9 (6-14) | 8 (6-10) | 7 (5-10) | 0.078 |
| Dong Thap/An Giang | 8 (61) | 78 (73) | 79 (93) | <0.001 |
| HCMC | 5 (39) | 31 (27) | 6 (7) | - |
| Headache | 9 (69) | 31 (75) | 58 (68) | 0.582 |
| Cough | 3 (23) | 28 (24) | 27 (32) | 0.428 |
| Vomiting | 5 (39) | 41 (35) | 31 (37) | 0.969 |
| Abdominal pain | 4 (31) | 55 (47) | 43(51) | 0.410 |
| Constipation | 1 (8) | 12 (10) | 24 (29) | 0.002 |
| Diarrhoea | 8 (62) | 86 (74) | 54 (64) | 0.227 |
| Previous antibiotics | 1 (8) | 20 (17) | 10 (12) | 0.252 |
| Admission temperature (°C) | 39.5 (39.0-39.9) | 39.0 (38.9-40.0) | 39.0 (38.5-39.5) | 0.677 |
| Hepatomegaly | 7 (54) | 47 (41) | 41 (48) | 0.431 |
| Splenomegaly | 1 (8) | 9 (8) | 7 (8) | 0.994 |
| Haematocrit (%) | 38 (34-40) | 37 (32-40) | 34 (31-38) | 0.041 |
| WCC (x10 ⁹ /L) | 7.7 (5.5-9.2) | 6.8 (5.0-8.3) | 7.2 (5.5-8.8) | 0.326 |
| Neutrophil (%) | 72 (63-79) | 66 (55-73) | 67 (58-76) | 0.316 |
| Lymphocytes (%) | 19 (15-35) | 29 (20-37) | 26 (19-35) | 0.378 |
| Platelets (x10 ⁹ /L) | 213 (187-270) | 166 (120-213) | 175 (140-259) | 0.004 |
| AST (IU/L) | 154 (68-202) | 77 (44-131) | 96 (60-145) | 0.065 |
| ALT (IU/L) | 100 (38-221) | 63 (40-103) | 69 (43-127) | 0.207 |
| <i>S.enterica</i> Typhi | 13 (6) | 115 (55) | 81 (39) | 0.173 |
| <i>S.enterica</i> Paratyphi A | 0 (0) | 1 (20) | 4 (80) | - |
| MDR (%) | 7 (54) | 78 (67) | 52 (61) | 0.495 |
| Ciprofloxacin intermediate (%) | 8 (62) | 102 (88) | 74 (87) | 0.032 |

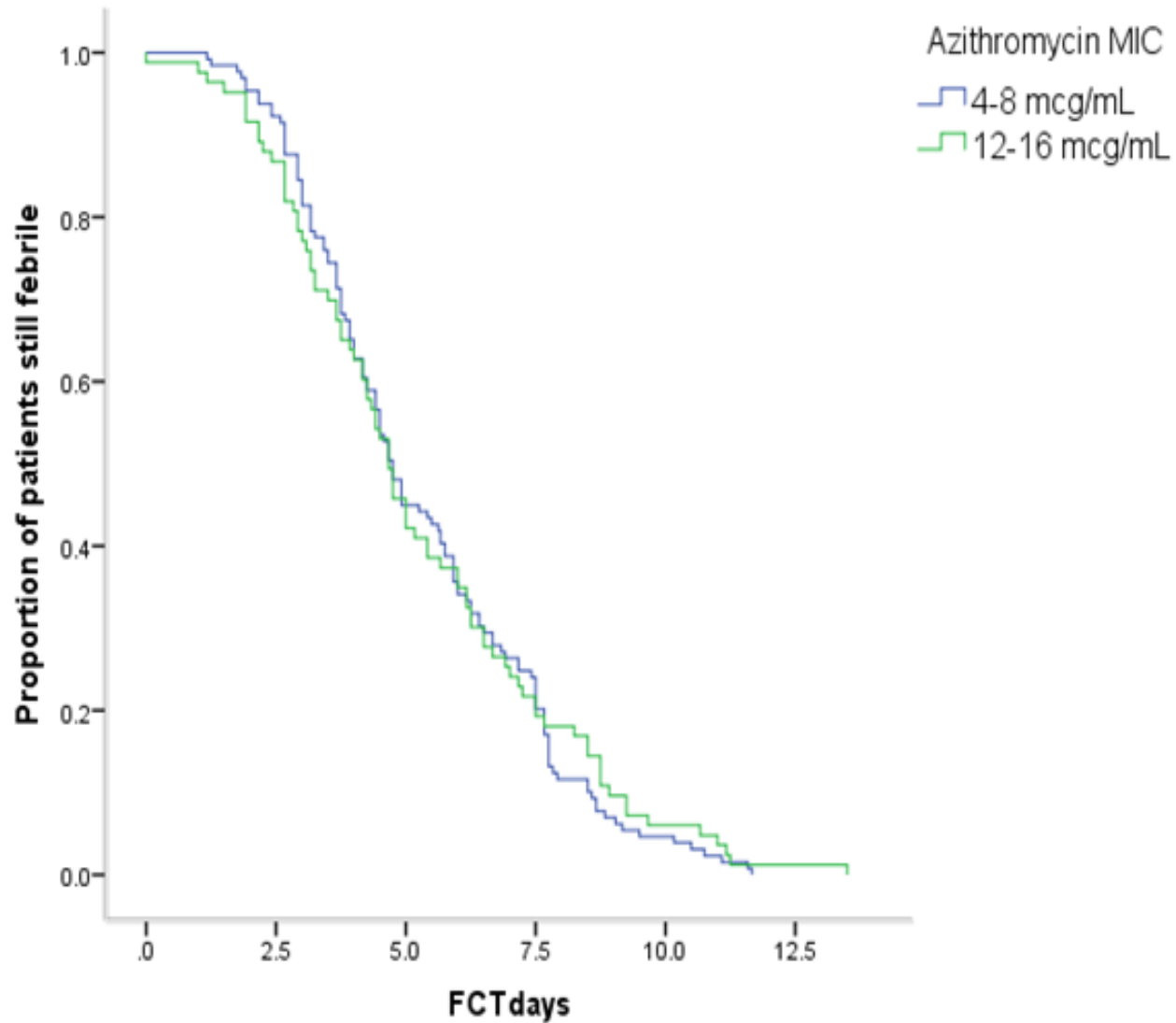
Outcome: By azithromycin MIC

| Variable/Azithromycin MIC | 4 mg/L | 6-8 mg/L | 12-16 mg/L | p |
|------------------------------|---------------|---------------|---------------|-------|
| Number | 13 | 116 | 85 | |
| Fever clearance time (days) | 4.4 (3.7-4.5) | 4.9 (3.4-7.5) | 4.7 (3.2-7.0) | 0.249 |
| Failure (any reason) | 1 (8) | 9 (8) | 9 (11) | 0.775 |
| Clinical failure | 1 (8) | 9 (8) | 8 (9) | 0.912 |
| Microbiological failure | 1 (8) | 1 (1) | 3 (4) | 0.195 |
| Complicated disease | 0 (0) | 4 (3) | 6 (7) | 0.347 |
| Duration of admission (days) | 12 (11-14) | 13 (12-15) | 13 (12-15) | 0.714 |
| Convalescent faecal carriage | 0/10 (0) | 0/98 (0) | 3/72 (4) | |
| Relapse | 0/10 (0) | 0/98 (0) | 0/72 (0) | |

Outcome: Comparison of failures and successes

| Variable | Failure | Success | p | OR (95% CI) |
|-----------------------------------|-----------|------------|-------|------------------|
| Number | 19 | 195 | | |
| Age (years) | 12 (8-22) | 13 (8-20) | 0.966 | |
| Duration of illness (days) | 7 (4-14) | 8 (6-10) | 0.601 | |
| Sex (Male) | 10 (52.6) | 92 (47.2) | 0.831 | 1.24 (0.44-3.51) |
| Site (Mekong Delta) | 17 (89.5) | 155 (79.5) | 0.379 | 2.19 (0.49-20.3) |
| <i>S.enterica</i> Typhi | 19 (100) | 190 (97) | 1.000 | - |
| <i>S.enterica</i> Paratyphi A | 0 (0) | 5 (3) | | |
| MDR | 15 (78.9) | 122 (62.6) | 0.242 | 2.24 (0.68-9.61) |
| Ciprofloxacin intermediate | 17 (89.5) | 167 (85.6) | 1.00 | 1.43 (0.31-13.4) |
| Azithromycin MIC >8 mcg/mL | 9 (47.4) | 76 (39.0) | 0.640 | 1.41 (0.50-3.97) |
| Duration of azithromycin < 7 days | 2 (10.5) | 40 (20.5) | 0.379 | 0.46 (0.05-2.06) |
| Dose of azithromycin 10mg/kg | 5 (26.3) | 40 (20.5) | 0.559 | 1.38 (0.37-4.37) |

Outcome: Kaplan Meier curve



Azithromycin in Enteric Fever

In 214 Vietnamese patients with uncomplicated enteric fever infected with an isolate with an azithromycin MIC between 4 and 16 mcg/mL treated with 5-7 azithromycin at 10-20 mg/kg:

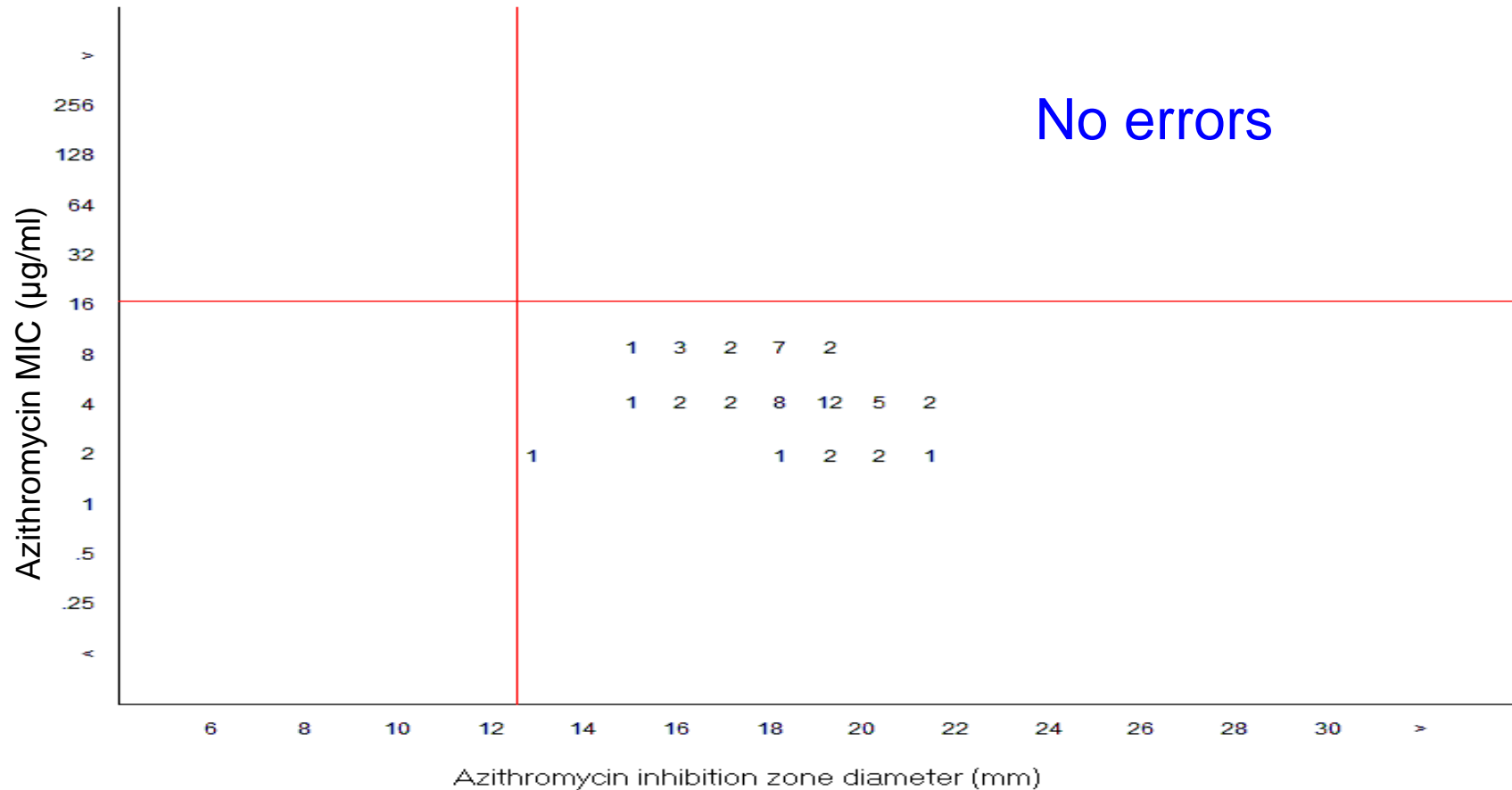
> 90% of patients were cured with a median fever clearance of 4-5 days and no relapses

There was no difference in the response between patients with an infection with isolates with different MICs

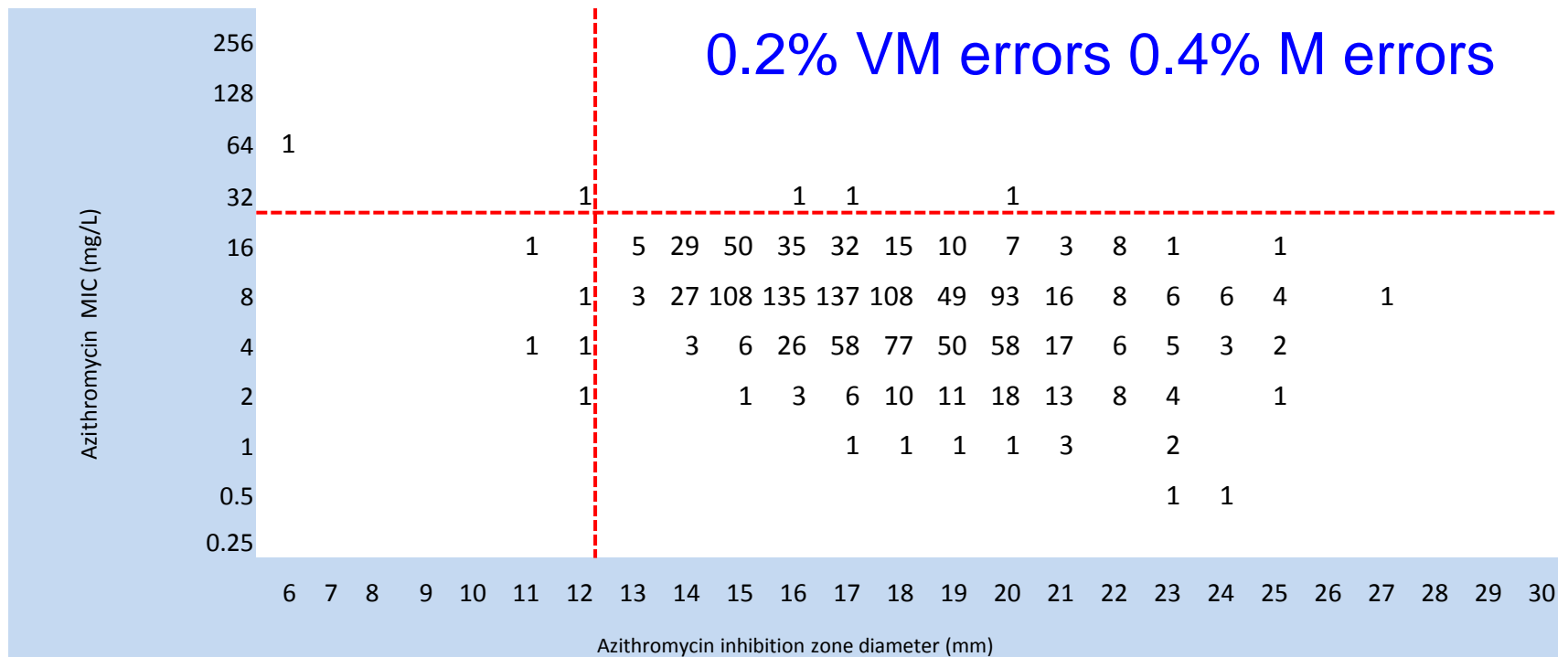
Disk Diffusion Correlates

Correlation between MIC and ZD

S. Typhi n=55 [Latin America and Canada]

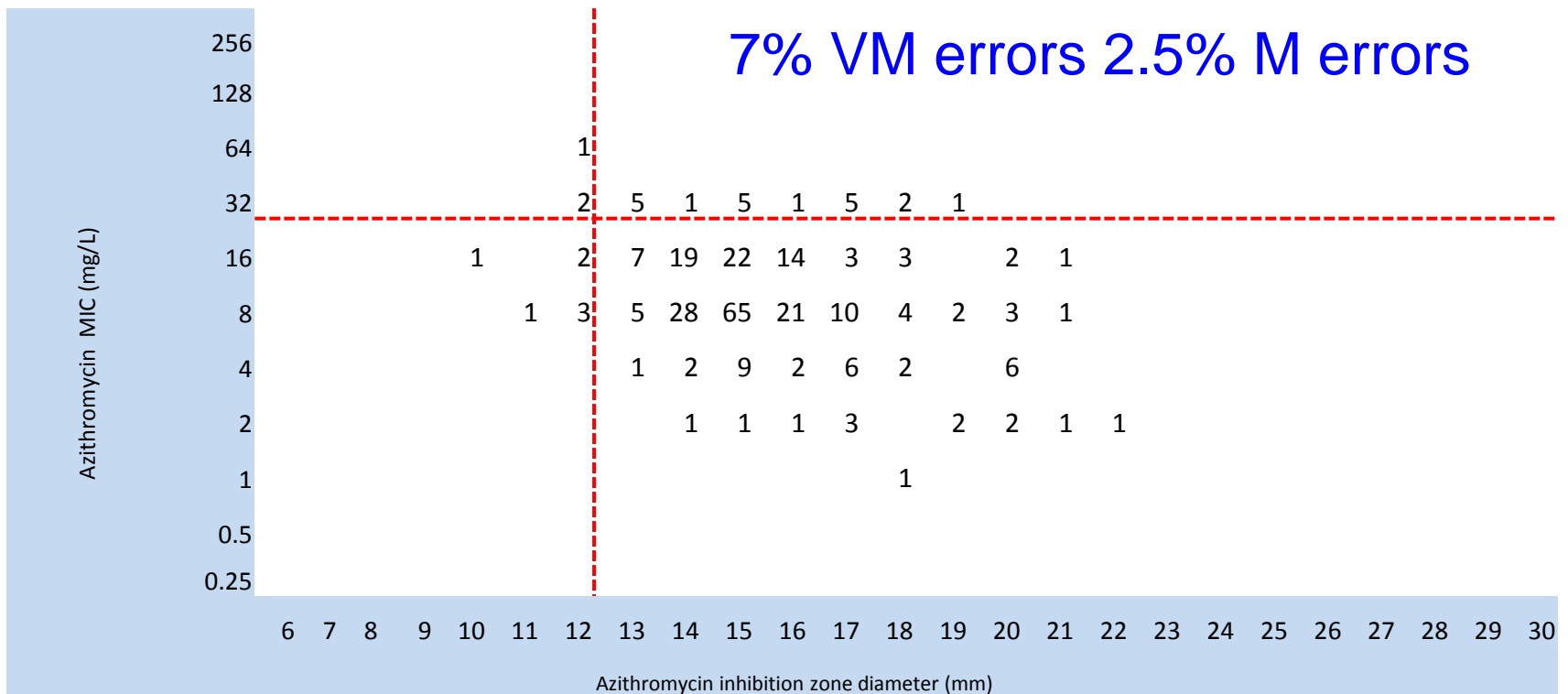


S. Typhi merged

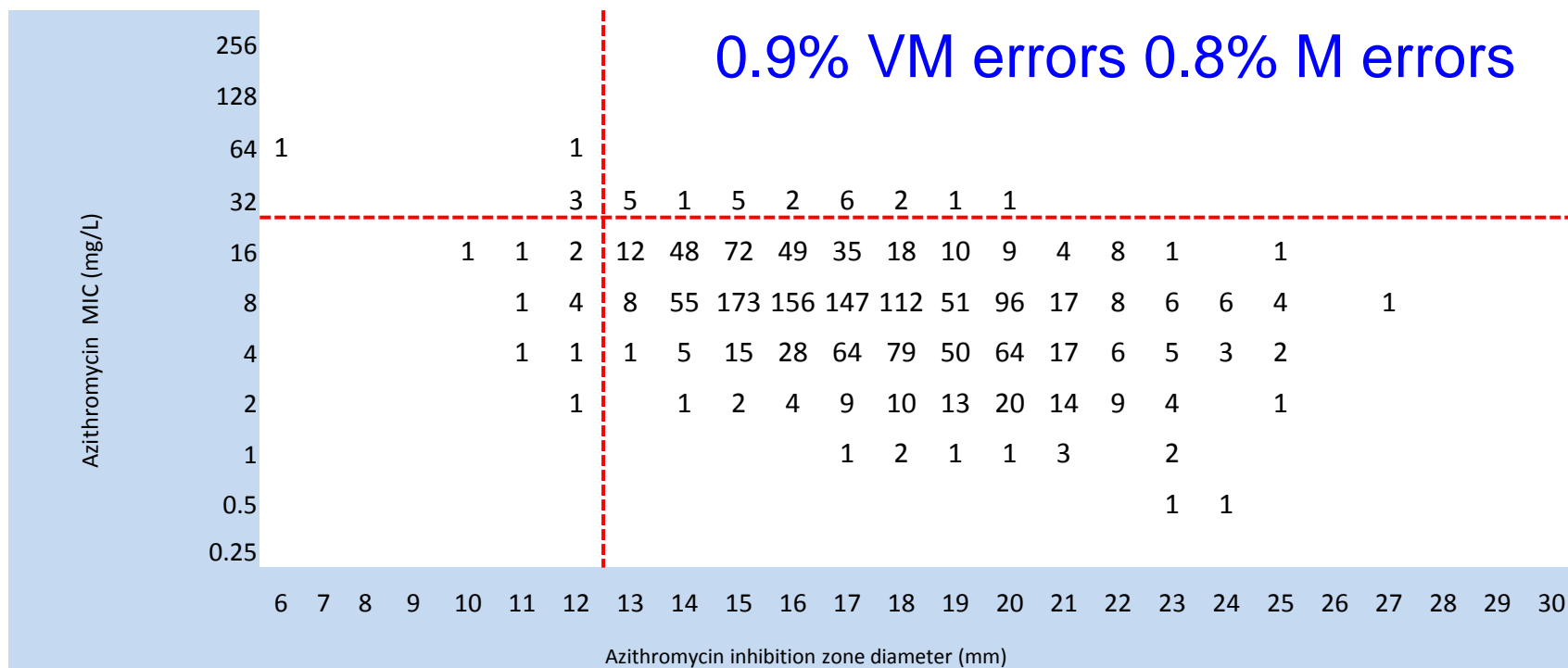


S. Paratyphi A merged

7% VM errors 2.5% M errors



Both merged



Breakpoint Proposal -1-

Ad Hoc Working Group proposes an MIC Breakpoint of:

Susceptible ≤ 16 mg/L, Non-susceptible, ≥ 32 mg/L

1)The rational for not introducing an intermediate category at this time is the rarity of strains with MICs above 16 mg/L (except for a small proportion of wild-type *S. Paratyphi A*), and the corresponding lack of clinical outcome data (only 1 reported failure at 64 mg/L).

2)These breakpoints should apply to *S. enterica* serovar Typhi and *S. enterica* serovar Paratyphi A only. There are few reliable data for other *Salmonella enterica* strains, and none for other species

Breakpoint Proposal -2-

Disk diffusion zone diameter correlates

- For an MIC breakpoint of susceptible ≤ 16 mg/L, the corresponding disk zone correlate for 15 μ g disk of azithromycin is:

susceptible ≥ 13 mm non-susceptible ≤ 12 mm

Issues

- The MIC distribution for *S. Paratyphi A* is statistically significantly higher than that of *S. Typhi*, by ~1.3 fold. This is unexpected, given that these are both purported to be members of the same species, *Salmonella enterica*. This phenomenon has been noted in several studies.
- The consequence is the estimated ECOFF for *S. Paratyphi A* is ≥ 32 mg/L, while that of *S. Typhi* is ≥ 16 mg/L. As the proportion of enteric fever cause by *S. Paratyphi A* is lower than *S. Typhi*, and the proportion of *S. Paratyphi A* with MICs above 16 mg/L is low, the fact that the proposed breakpoint cuts into the *S. Paratyphi A* is of minor consequence.

Issues

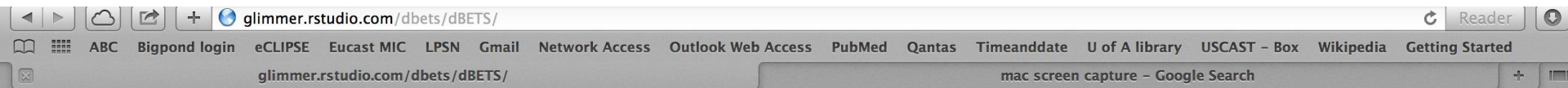
- Disk diffusion error rates with *S. Paratyphi A*
 - Are they sufficiently troubling to set different breakpoints?
- Breakpoints can't be linked to a specific dosing regimen

Breakpoint Working Group

- Proposal for vote
 - *S. Typhi* only
 - MIC BP: $S \leq 16$ mg/L, $NS \geq 32$ mg/L
 - Zone diameter BP: $S \geq 13$ mm, $NS \leq 12$ mm

Zone Diameter Estimation Software

Now freely available on-line



dBETS - diffusion Breakpoint Estimation Testing Software

Navigate

Data Entry

Refresh

☐ Use a file stored on my local machine.

File URL:

Are MIC values on log2 scale?

Yes

MIC Breakpoints (log2 scale)

Lower (\leq)

-1

Upper (\geq)

1

☐ One MIC Breakpoint

**Load Data / Set Breakpoints /
Produce Descriptives**

Welcome to dBETS software! (V. 0.6)

App created by Glen DePalma and Bruce A. Craig (Department of Statistics, Purdue University).

For software details and how to format data for use with dBETS [see the documentation](http://glimmer.rstudio.com/dbets/dBETS/).

<http://glimmer.rstudio.com/dbets/dBETS/>