

INTRODUCTION

- Undernutrition causes 3.1 million deaths
- SAM causes 1 million deaths
- In Africa, between 15% and 18% of paediatric patients have SAM
- Children with complicated SAM have a case fatality of between 12 to >20%



CURRENT WHO GUIDELINES FOR SAM

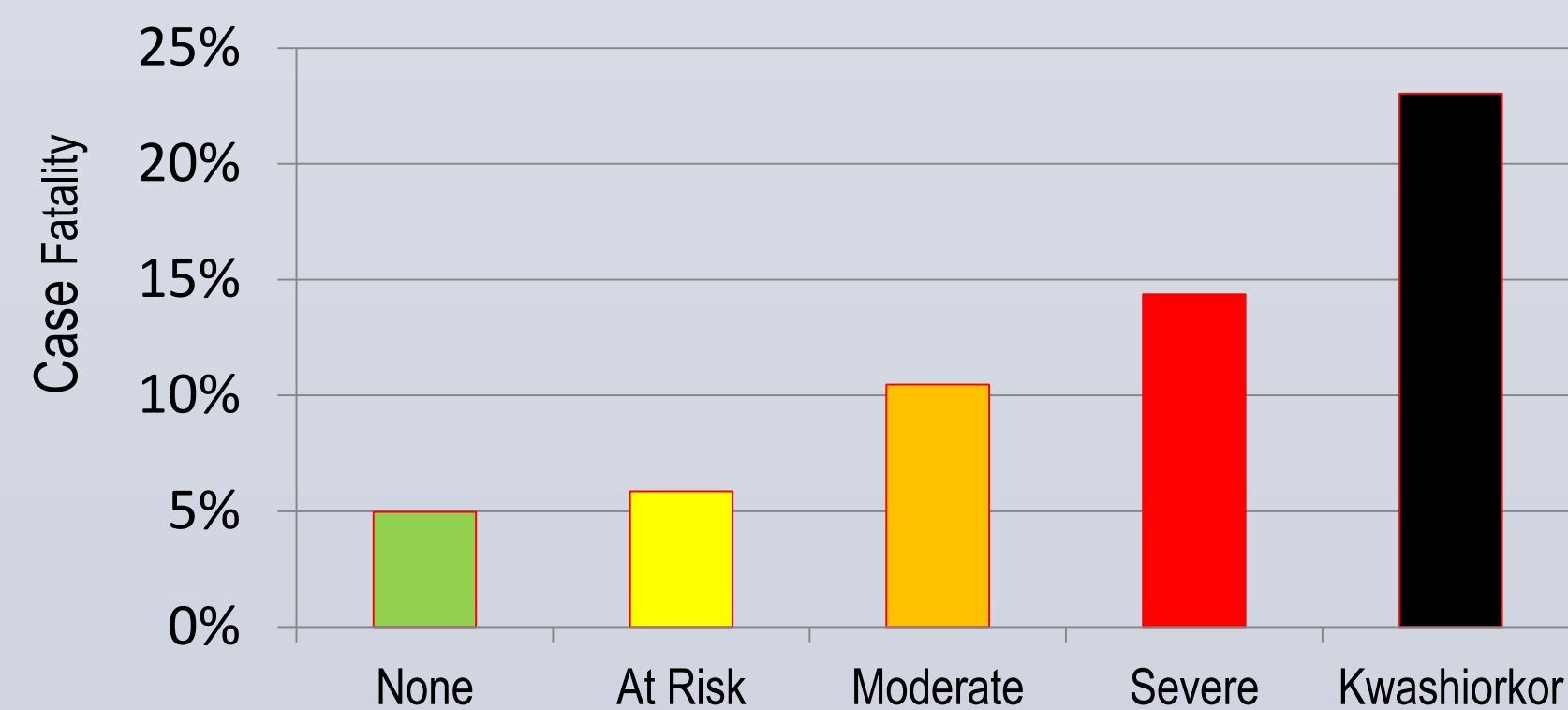
- ▶ If there are complications (hypoglycaemia, hypothermia or the child looks lethargic or sickly) or any other medical complication, give parenteral antibiotics:
 - benzylpenicillin (50 000 U/kg IM or IV every 6 h) or ampicillin (50 mg/kg IM or IV every 6 h) for 2 days, then oral amoxicillin (25–40 mg/kg every 8 h for 5 days)
 - plus
 - gentamicin (7.5 mg/kg IM or IV) once a day for 7 days.
- These regimens should be adapted to local resistance patterns.
- Note:** Metronidazole 7.5 mg/kg every 8 h for 7 days may be given in addition to broad-spectrum antibiotics; however, the efficacy of this treatment has not been established in clinical trials.



WHAT IS THE PROBLEM?

- WHO guidelines for routine antibiotics are based on “low quality evidence”.
- High inpatient and post-discharge mortality for SAM despite guidelines
- Bacterial resistance to the currently recommended first-line antibiotics is an uncertain problem where lab facilities are lacking
- Some hospitals in Africa are already increasing use of ceftriaxone as a first-line treatment. This is not based on any data that ceftriaxone actually improves outcomes.
- Ceftriaxone use may also lead to increased antimicrobial resistance, including extended spectrum beta-lactamases (ESBL) and other classes of resistance.
- No data on efficacy of metronidazole on nutritional recovery.
- Concerns over pharmacokinetics for both drugs in malnourished children. A pharmacokinetic study in 80 malnourished children who received ceftriaxone and metronidazole has recently been concluded.

Inpatient Case Fatality by Nutritional Status
COAST GENERAL HOSPITAL



RANDOMISED CLINICAL TRIAL

Phase 1 (2016)

- Pharmacokinetics of ceftriaxone & metronidazole
- Faecal carriage of ESBL at admission & discharge
 - SAM & non-SAM at 3 hospitals

Phase 2 (2017-)

- 2x2 factorial trial → mortality & growth
- Trial participants - 2000 children
- 4 study hospitals: in Kilifi, Mombasa, Nairobi and Mbale (in Uganda)
- 2 treatment interventions:
 - Pen/Gent vs Ceftriaxone
 - Metronidazole vs Placebo
- Sub-studies:
 - Economics – costs, cost effectiveness and costs relating to antimicrobial resistance (AMR)
 - Faecal carriage of ESBL, including non-SAM
 - Further PK work

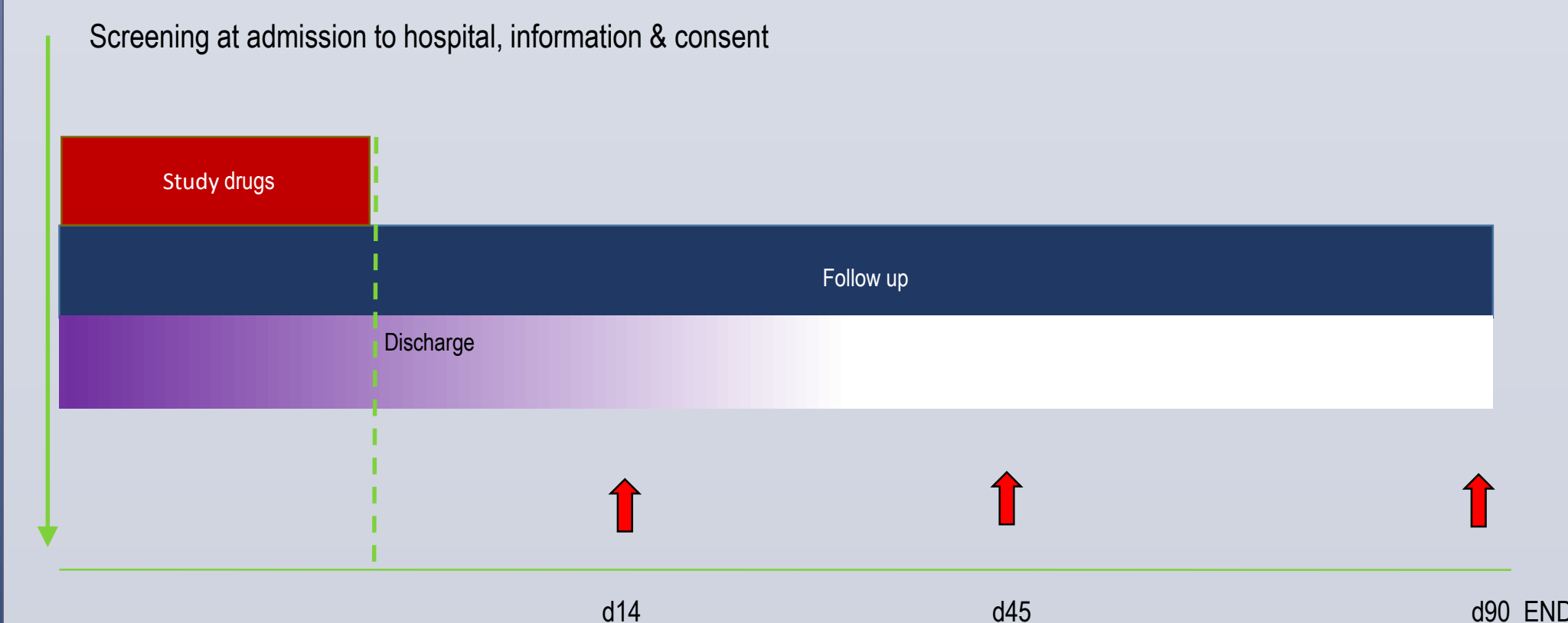
Inclusion criteria – clinical trial participants (SAM)

- Age 2 months to 13 years inclusive
- Severe malnutrition defined as:
 - kwashiorkor at any age; or
 - for children between 6 to 59 months: MUAC <11.5cm or weight-for length Z score <-3
 - for children aged 2 to 5 months: MUAC <11cm or weight-for length Z score <-3
 - for children aged 5 to 13 years: BMI-for-age Z score <-3 or MUAC <11.5cm
- Admitted to hospital and eligible for intravenous antibiotics according to WHO guidelines
- Planning to remain within the hospital catchment area and willing to come for specified visits during the 90 day follow up period
- Informed consent provided by the parents/guardian

Exclusion criteria – clinical trial participants (SAM)

- Known allergy or contraindication to penicillin, gentamicin, ceftriaxone or metronidazole
- A specific and documented clinical indication for another class of antibiotic
- Previously enrolled in this study

FLACSAM Trial Schedule



PHARMACOKINETICS

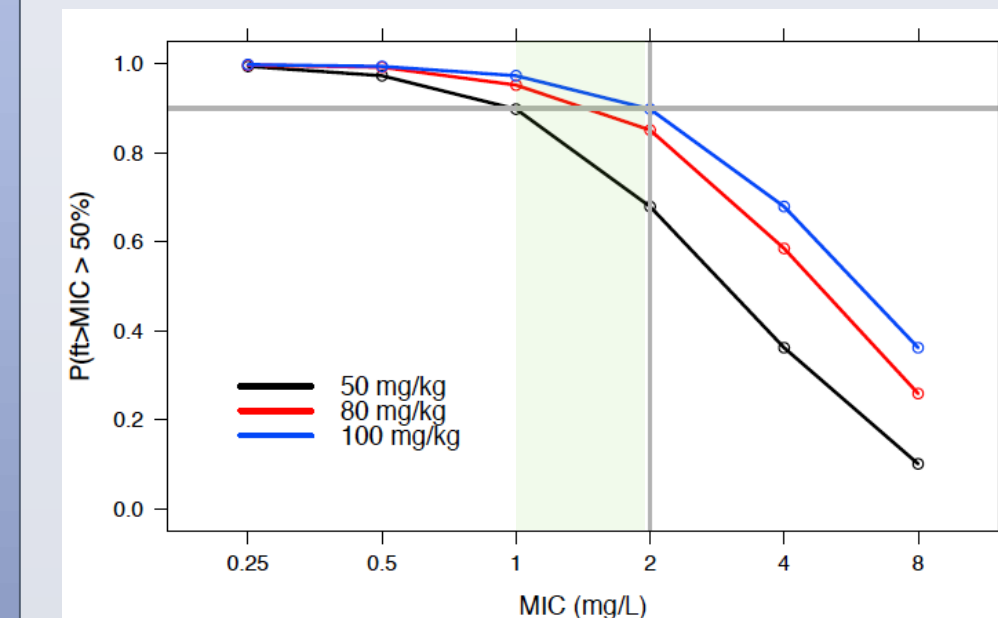
- Decreased absorption
- Reduced protein binding
- Altered volume of distribution
- Altered hepatic metabolism
- Altered renal elimination

SITE	Enrolled
Kilifi County Hospital	28
Coast General Hospital	25
Mbagathi Hospital	28
Total	81

Time points	Children
5 min	26
30 min	26
60 min	29
2h	28
4h	24
8h	27
24h	26
48h	29
72h	28

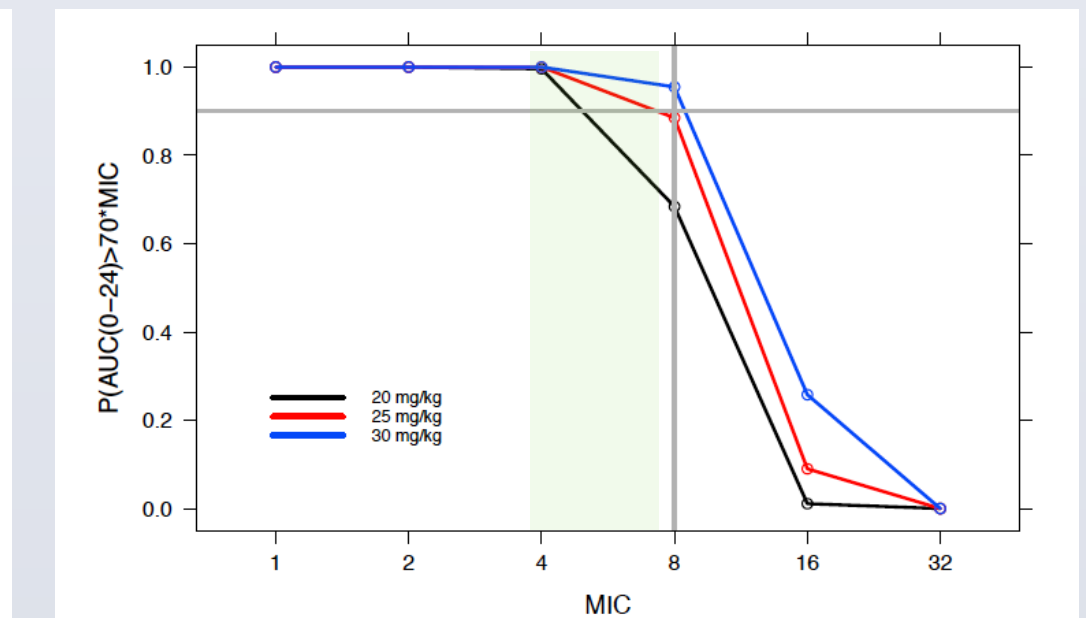
CEFTRIAXONE

Target: ~90% of patients to spend >50% time with levels above 1 to 2 mg/L



METRONIDAZOLE

Target: ~90% of patients to have an AUC above 70x an MIC of ~4 to 8 mg/L



CEFTRIAXONE: 50 mg/kg/od is too low for malnourished children; 80 mg/kg od is better

METRONIDAZOLE: 7.5 mg/kg/tds is slow to reach therapeutic levels; bd dosing (10-15 mg/kg) is better

CONTACTS

FLACSAM Trial Group :

KEMRI/Wellcome Trust Research Programme, Kilifi, Kenya: Isaiah Njagi, Nancy Kagwanja, Caroline Ogwang, Sheila Murunga, Joseph Waichungo, Moses M Ngari, Johnstone Thitiri, Molline Timbwa, Laura Mwalekwa, Shalton Mwaringa, Alexander Makazi, Rehema Ali, Fauzat Mohammed, Jimmy Shangala, Mwanamvua Boga, John P Odhiambo, Joshua Kyallo, Grace Dena, Boniface Luganje, Julie Jemutai, Kathryn Maitland, Neema Mturi, James A Berkley, and the fieldwork, data entry and laboratory staff.

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