‘Challenges for treating sepsis in African children'

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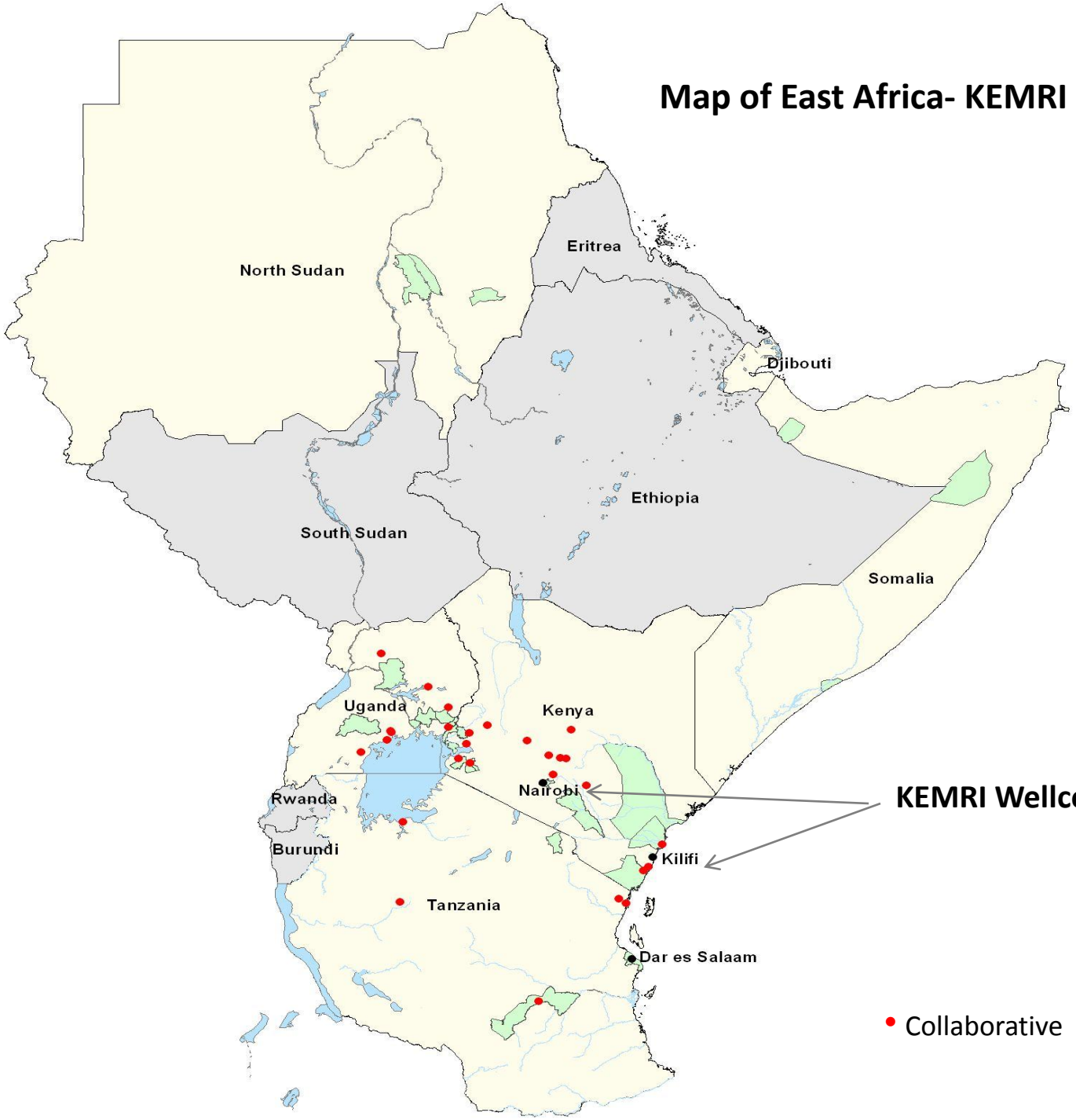
Based at
KEMRI Wellcome Trust Programme,
Kilifi, Kenya

Maitland – research portfolio

- Child survival : improving hospital care
- Evidence base guideline development
- Severe malaria/ Sepsis
  - pathophysiology
  - fluid resuscitation trials
- Severe malnutrition
  - severity indicators
  - Pathogenesis and intervention

Map of East Africa- KEMRI WT collaborations



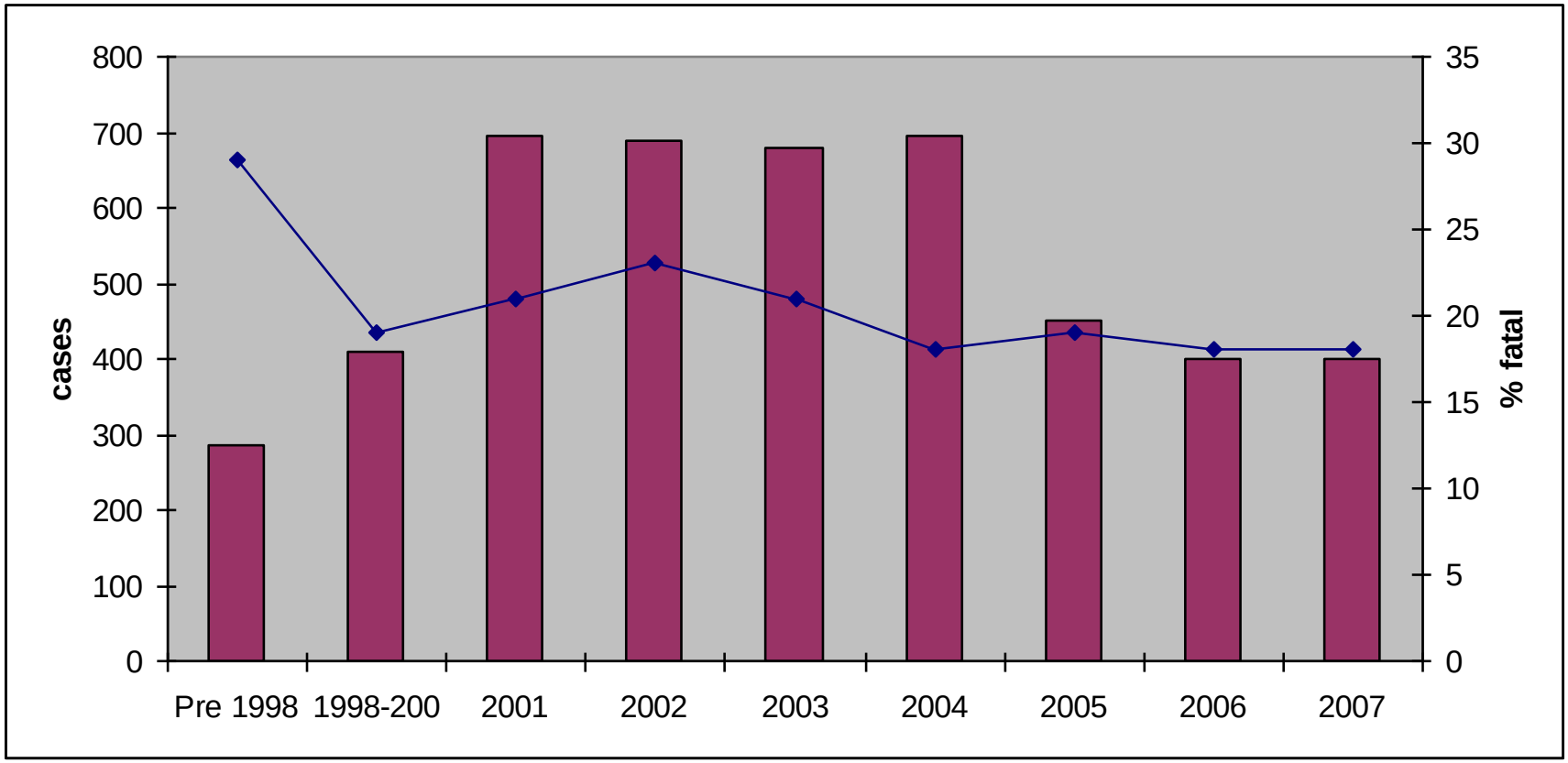
KEMRI Wellcome Trust Programme

• Collaborative sites/links

Kilifi District, Kenya

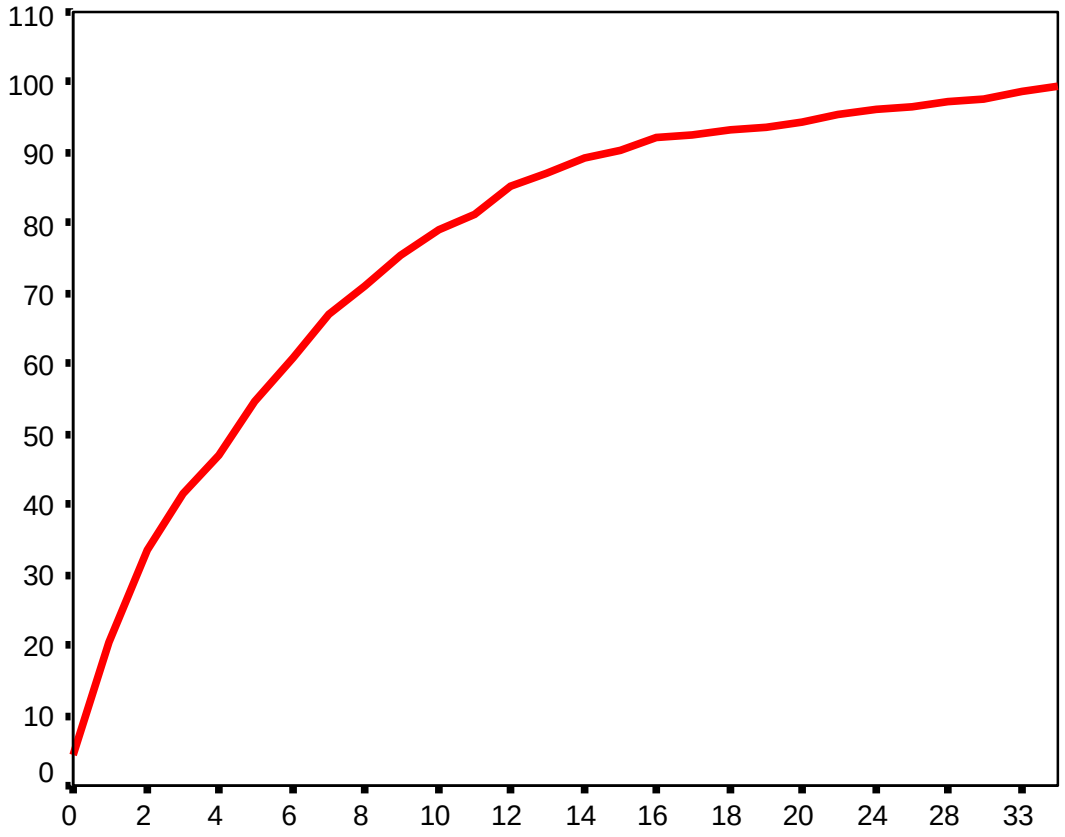
- ✓ Kilifi – 2nd poorest district in Kenya
- ✓ Community: > 40% anthropometric indices of under-nutrition
- ✓ > 400 cases of severe malnutrition admitted to Kilifi District Hospital annually, only ¼ have HIV-malnutrition.
- ✓ Case fatality ~ 20% (versus 2.2% for the well nourished)
- ✓ Stable over time despite improvement in care
- ➢ WHO treatment guideline with strict protocol adherence: mortality < 5%

Kilifi-trends



2001-2004 includes children >3m; 2005 + only includes children >6m

When are children dying?

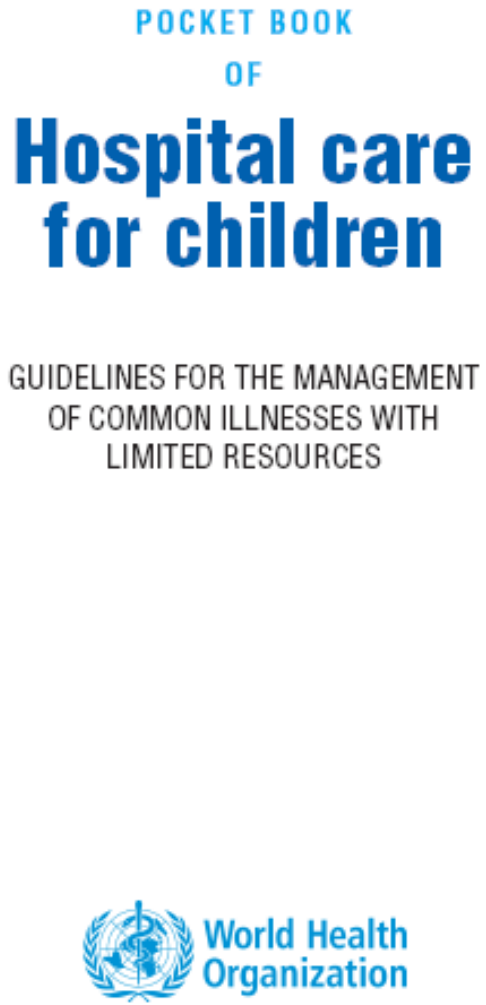


Timing:

33% <48 hrs

41% <72 hrs

‘IMCI for hospitals’



Management of severe malnutrition: Priorities: the ‘Ten steps’

Prevent and treat

1. Hypoglycaemia
2. Hypothermia
3. Dehydration
4. Electrolyte imbalance
5. Infection
6. Micronutrient deficiencies

Feed, keep warm, rehydrate orally: monitor glucose and temp

Start Ampicillin and Gentamicin: Infection and severe illness- major challenges to successful treatment!!

cial feeds for

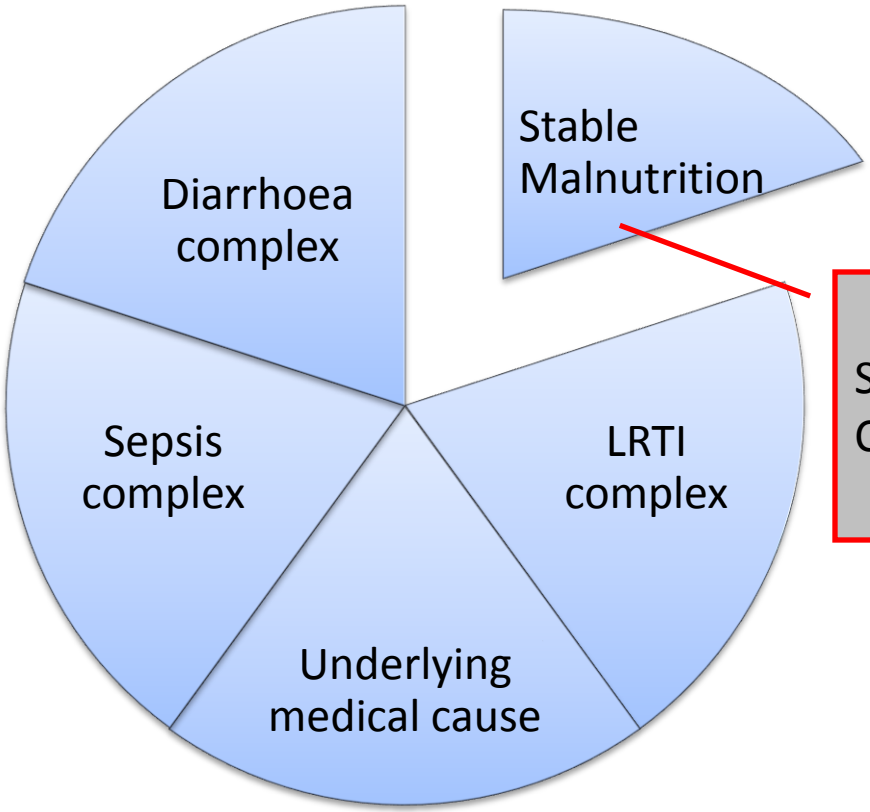
abilisation

and

stimulation

10. Prepare for follow-up after discharge

‘Stable’ severe malnutrition occurs in only 25% of admissions



Stable cases – 7% mortality
Complicated > 20 % mortality

Early mortality: Signs of Sepsis, shock and /or dehydration

High Risk

Immediate risk of early death & greatest requirement for close observation & monitoring

- **Depressed conscious state**
  - prostration (inability to sit up) or
  - coma (inability to localise a painful stimulus)
- **Bradycardia** (heart rate < 80 beats per minute),
- **Evidence of shock or dehydration**
  - Capillary refill time >= 2 secs
  - Weak pulse volume
- **Hypoglycemia <3mmols/L**

Intermediate risk

Need for close supervision

- Deep 'acidotic' breathing
- Signs of dehydration (*plus* diarrhea:>3 watery motions/24hours)
  - Sunken eyes or
  - decreased skin turgor
- Lethargy
- Hyponatremia (sodium<125mmols/L)
- Hypokalemia (potassium < 2.5mmols/L)

Low Risk

Limited requirement for close supervision

- None of the above

In hospital mortality in the three groups at Kilifi: High 34%; Moderate 23% and Low 7%.

Maitland PLoSMed 2006

WHO severe malnutrition: fluid resuscitation guideline

- Current recommendations- avoid intravenous fluid resuscitation-
- Concern regarding existing
  - Salt /water overload- evidenced by low sodium
  - cardiac failure common consequence
- Shock (including sepsis): - too little when ‘almost too late’
- Diarrhoea- oral rehydration all cases except severe shock (above)

Akech BMC Paedaitrics 2010

Epidemiological of Sepsis in African Children

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bacteremia among Children Admitted to a Rural Hospital in Kenya

James A. Berkley, M.D., Brett S. Lowe, M.Phil., Isaiah Mwangi, M.B., B.Ch., Thomas Williams, Ph.D., Evasius Bauni, M.Sc., Saleem Mwarumba, H.N.D., Caroline Ngetsa, H.N.D., Mary P.E. Slack, F.R.C.Path., Sally Njenga, H.N.D., C. Anthony Hart, F.R.C.Path., Kathryn Maitland, Ph.D., Mike English, M.D., Kevin Marsh, F.R.C.P., and J. Anthony G. Scott, M.R.C.P.

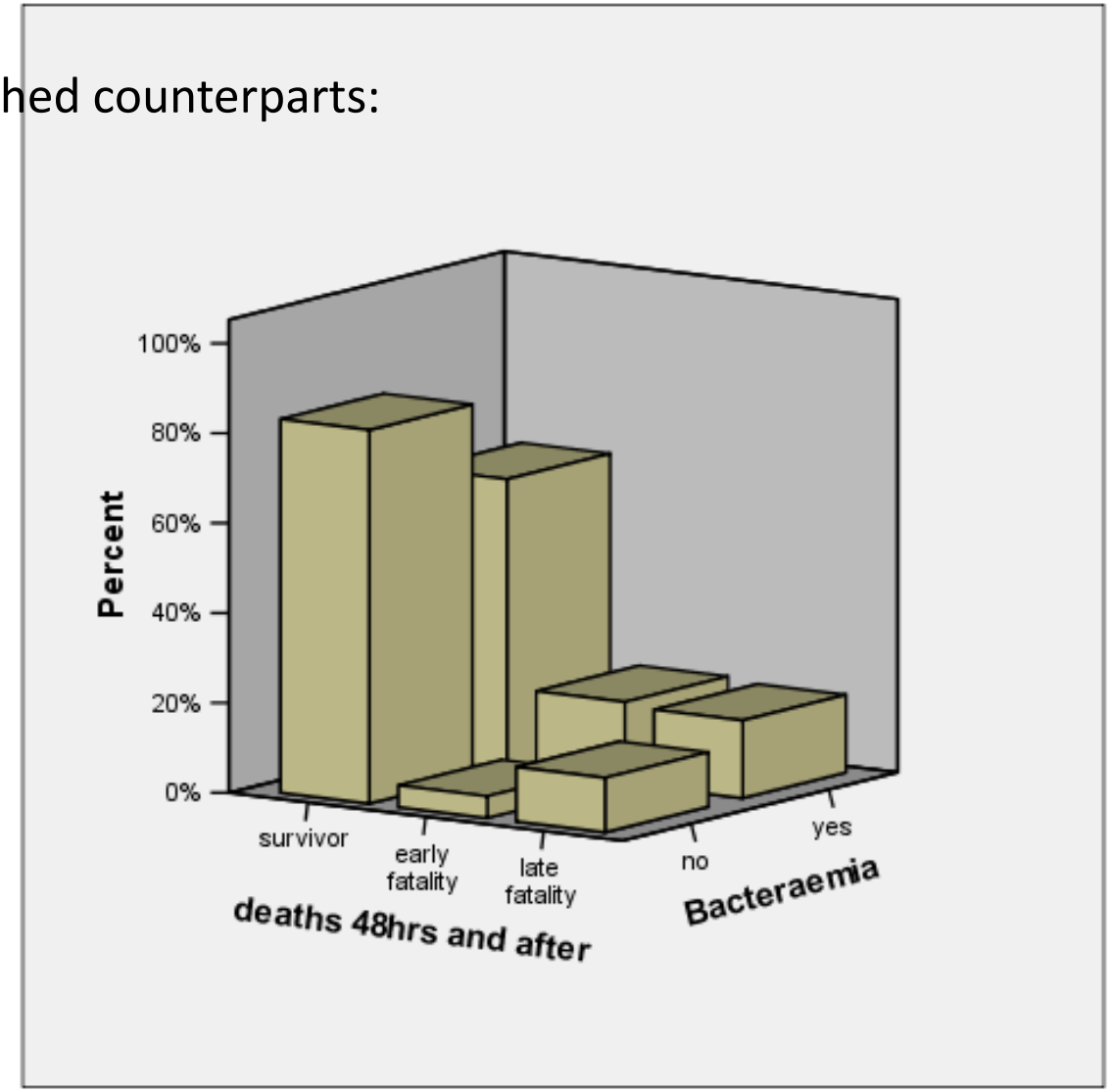
- ✓ 20,000 admissions –spectrum & incidence of community acquired bacteraemia (CAB)
- ✓ 25% of childhood deaths due to CAB

Invasive bacterial infection

Compared to non-malnourished counterparts:

✓Odds ratio 3.43 of IBD

✓Case fatality 39% vs 12%



IBD in severe malnutrition

- 3 organisms account for 60% of IBD invasive bacterial *Strep pneumoniae, E. coli* and non-typhoidal salmonellae
- Others: Staphylococcus, Streptococcus spp. Klebseilla Pseudomonas aeruginosa

✓ Host susceptibility
  - Immunosuppression (HIV in only 25% cohort)
  - Nutritional 'immunosuppression'
  - Epithelial or mucosal barrier dysfunction is important ?

✓ Considerations for choice of antimicrobials

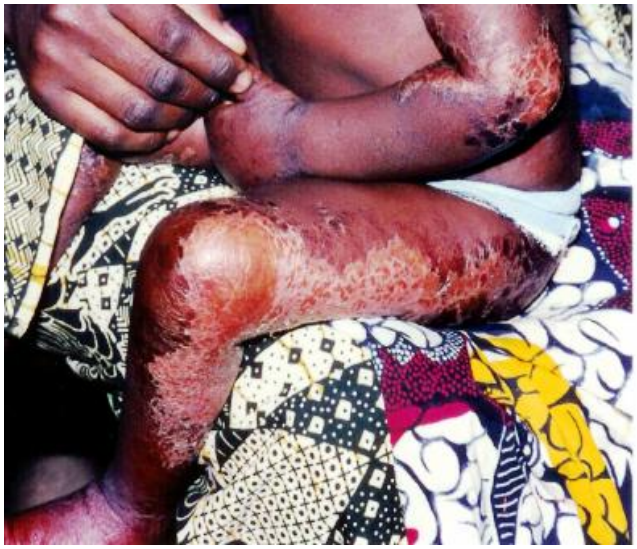
Severe malnutrition and Infection

- Suppressed immune function: negative cycle repeated infection and poor nutritional recovery
- T-cell dysfunction has been the most consistently implicated in severe malnutrition (thymic atrophy, impaired cutaneous tuberculin responses and abnormal dendritic cell function) pointing towards impaired in cell-mediated immunity.
- Neutrophil dysfunction proposed – no decent data
- Inability activate cytokine networks- data do not support this

➢ Most studies: No linking to clinical phenotype, stage of disease and outcome and fail to consider immune-modulating effects of acute infection.

Mucosal/ barrier dysfunction?

- Kwashiorkor :

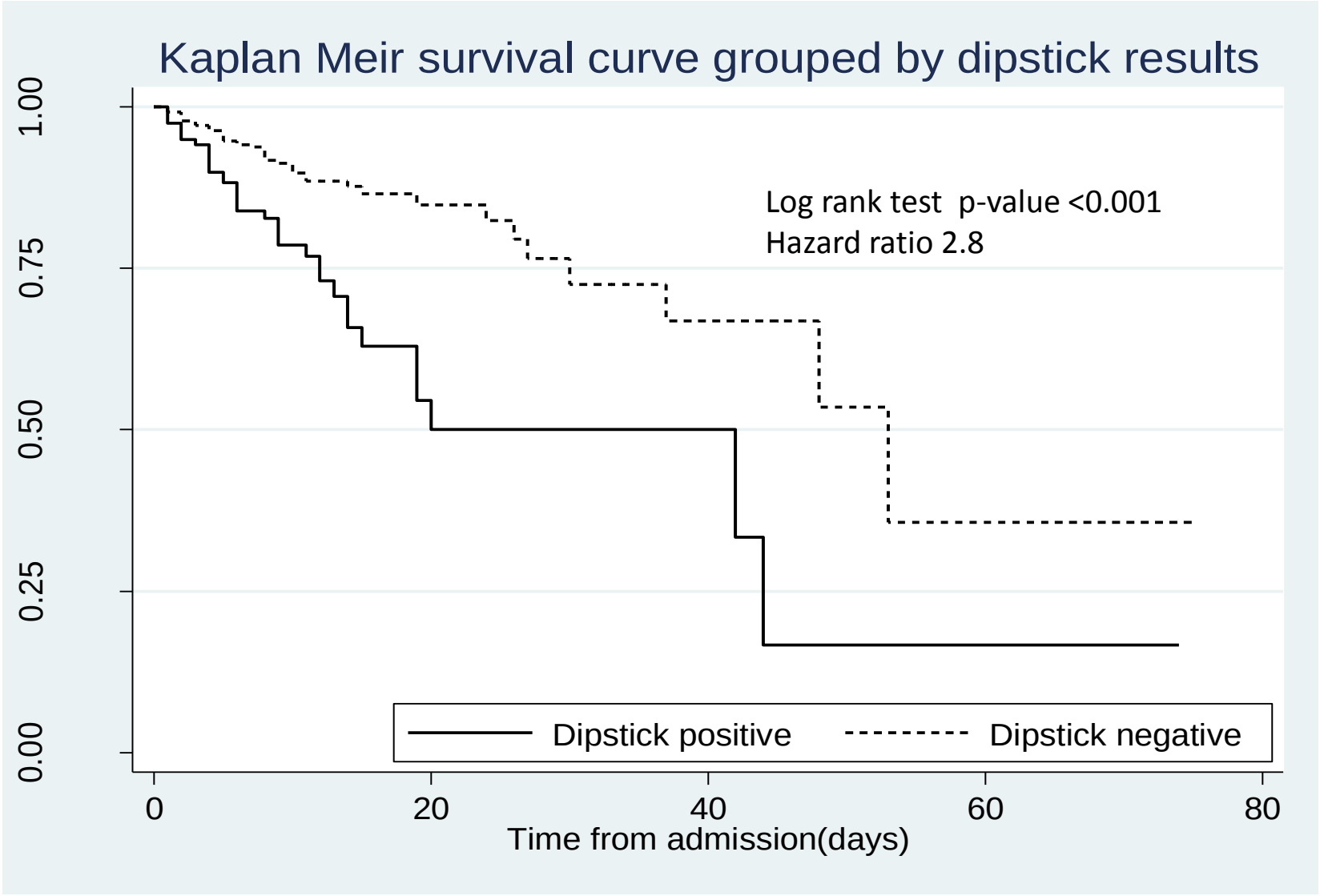


- Higher prevalence of urinary tract infection than non malnourished.
- Impaired gut permeability demonstrated: portal for bacterial or endotoxin?

Dipstick +ve vs. Dipstick -ve

Clinical variables	Dipstick+ve (LE+orNit+) n=120	Dipstick –ve(LE-Nit-) n=378	P value
Female	72(60)	155(41)	<0.001
Median age (IQR)	21(16-31)	23(17-37)	0.142
Oedema	51(43)	127(34)	0.076
HIV positive	25(22)	90(25)	0.542
Clinical signs			
Fever	45(38)	152(40)	0.597
Hypothermia	0	0	
Tachypnoea	25(21)	90(24)	0.500
Tachycardia	27(23)	110(29)	0.172
Hypoxia	19(16)	54(14)	0.651
Impaired consciousness	3(3)	8(2)	0.731
Severe dehydration	31(25)	70(19)	0.083
Severe anaemia	32(27)	128(34)	0.141
Shock	15(13)	61(16)	0.334
SIRS	50(42)	170(45)	0.525
Laboratory features			
Hyponatremia	63(60)	173(54)	0.237
Hypokalemia	50(49)	105(32)	0.003
Hyperkalemia	2(4)	2(1)	0.176
Bacteraemia	6(5)	25(7)	0.524
Leucocytosis	114(96)	347(94)	0.411
Died (%)	34(29)	47(12)	<0.001
Died within 48hrs	3(3)	3(1)	0.154

Time to death

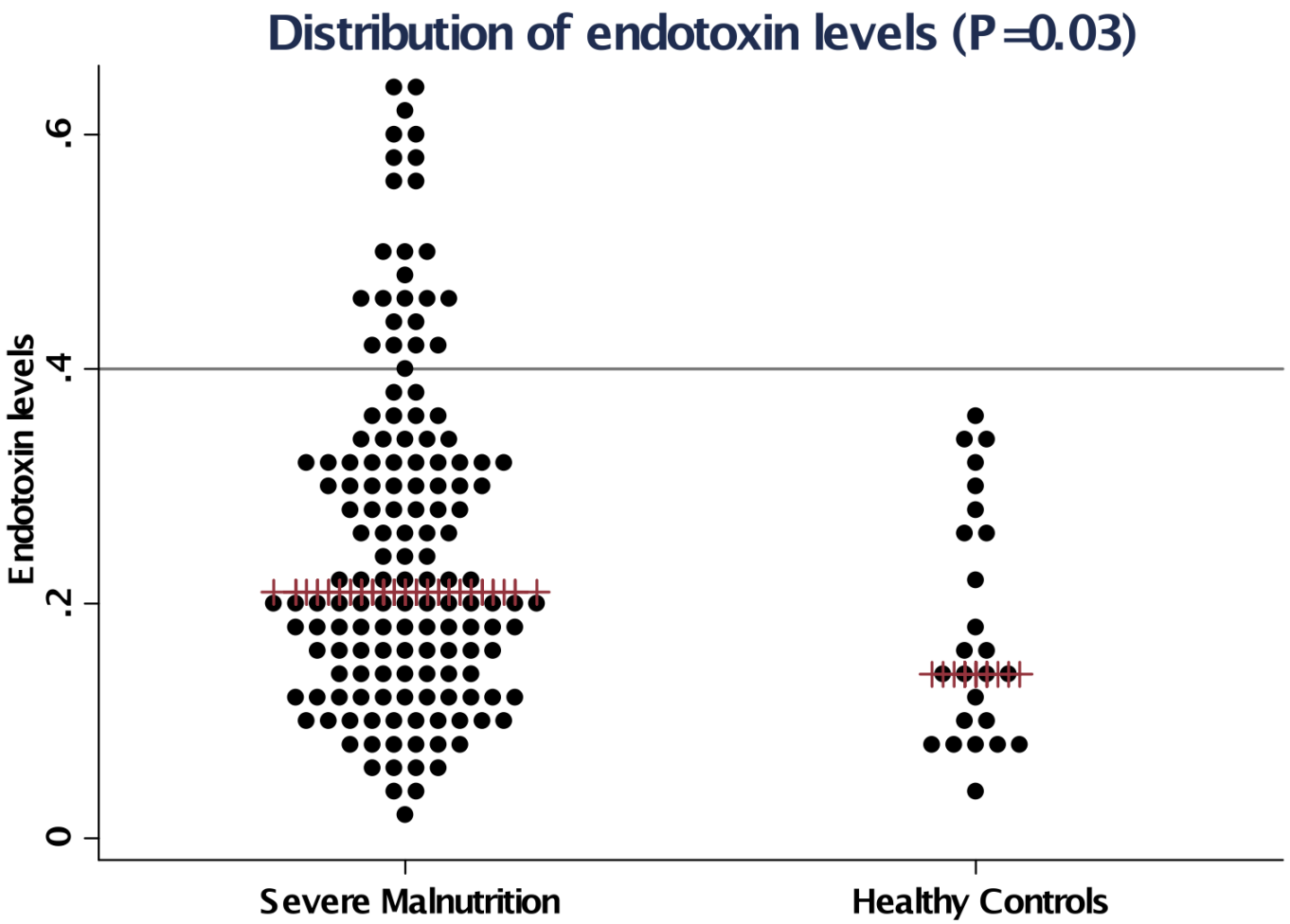


Major risk factors for poor outcome- diarrhoea

Variable	Odds Ratio	95% Conf. Interval		P value
Impaired consciousness	4.3	1.6	11.6	0.004
Bacteraemia	4.0	1.9	8.5	<0.001
MUAC < 10cm	2.2	1.3	3.6	0.002
Hyponatraemia	2.1	1.1	3.8	0.017
Hypokalaemia	2.0	1.3	3.3	0.004
Kwashiorkor (oedema)	1.9	1.1	3.2	0.013

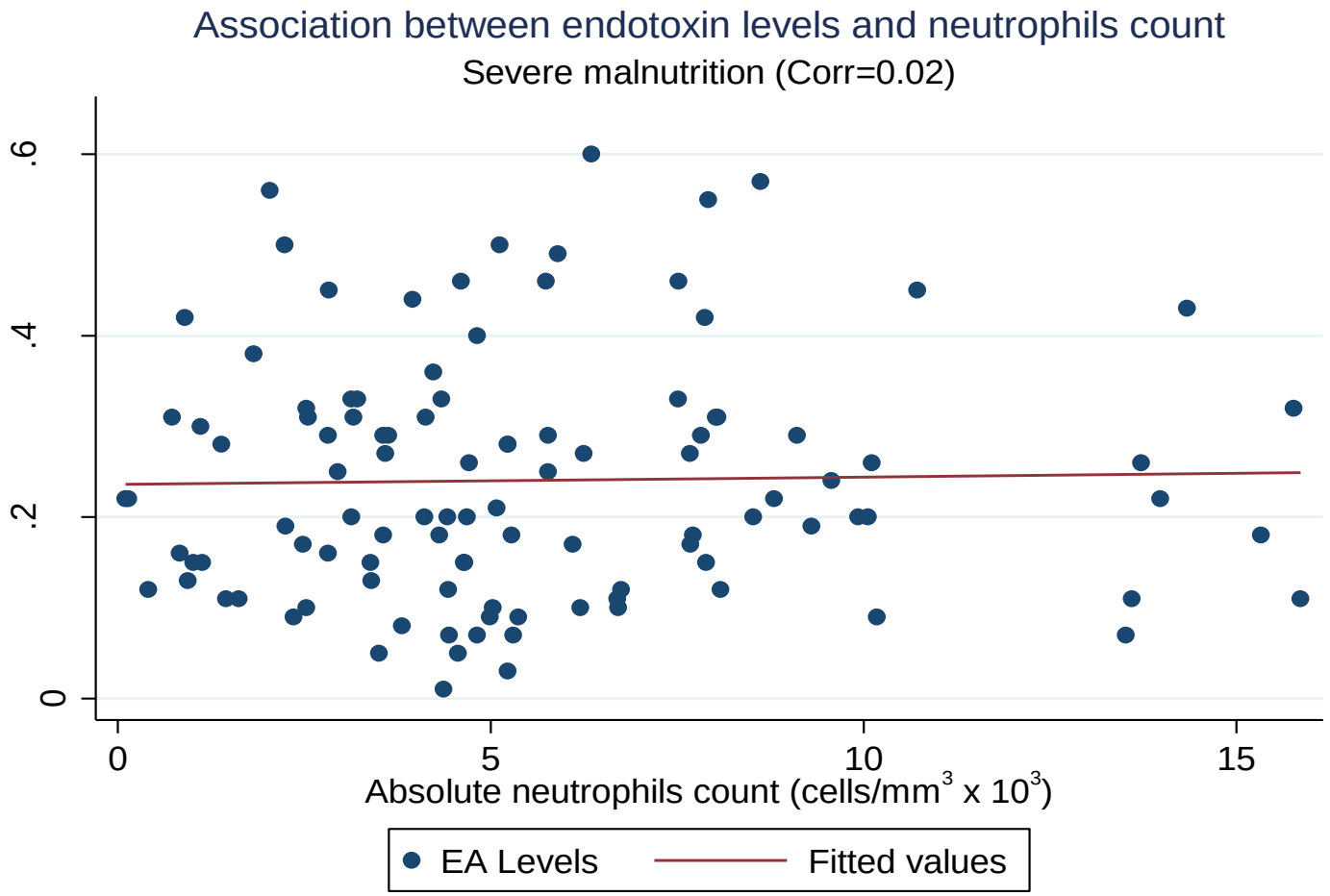
- ✓Higher prevalence of bacterial infection in cases complicated by diarrhoea
- ✓Major risk factor for poor outcome

Endotoxin



Endotoxin Activity Assay (EAA™ Spectral Diagnostics)

Neutrophil dysfunction?



Organisms/Antibiotic sensitivity

- *In vitro* sensitivity suggest (85%) isolates are fully sensitive to ampicillin/ gentamicin combination (not NTS).
- 50% Gram negative organisms (including NTS)

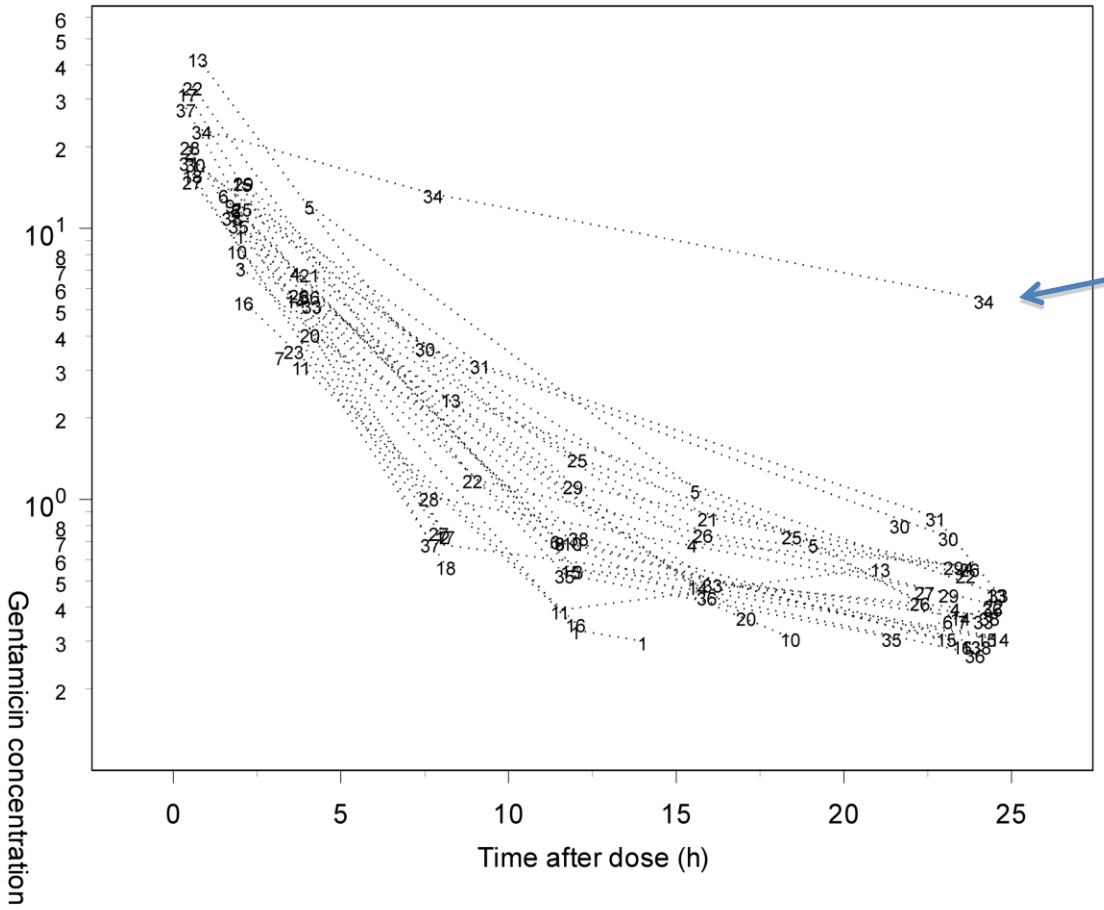
1. PK considerations for gentamicin in children with severe malnutrition?
2. Since NTS are not susceptible to gentamicin- consideration of other antimicrobials?

Gentamicin PK studies

Is poor outcome due to inadequate uptake?

- Population pharmacokinetics of a single daily intra-muscular dose (7.5 mg/kg) of Gentamicin
- Volume of distribution (Vd): most important parameter determining the peak concentration, & highly related to extracellular fluid volume
- Vd increased in oedematous states, burns (or extensive skin desquamation) and with capillary leak in severe infection.
- SM group are at risk of altered volume of distribution- problems of poor uptake (shock) and low Vd and/or toxicity?

PK Gentamicin

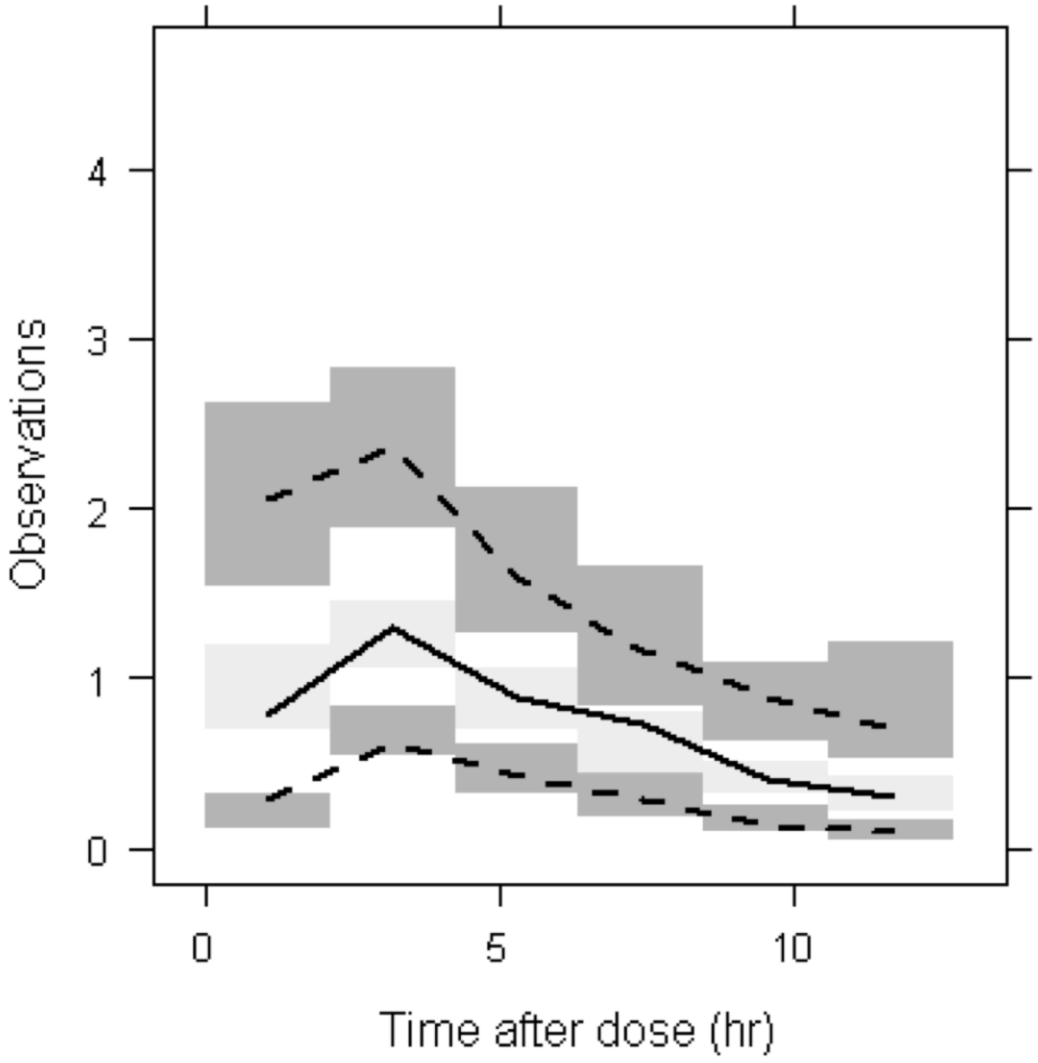


This child had shock

Ciprofloxacin?

- In-vitro resistance to first line antibiotics - associated with later deaths
- Second-line therapy (chloramphenicol) offered little advantage over the ampicillin and gentamicin combination.
- Quinolones mainstay in treatment of serious bacterial infections in adults and increasingly use in children
- No PK data in children with severe malnutrition
- Pragmatic dosing – milk feeds (4 hourly) may intefer with absorption- additional consideration

Ciprofloxacin PK



Children 52
Oral Ciprofloxaxin crushed tablets
10 mg / kg body weight every twelve ho
48 hours dosing only.

Poster: Wanchana Ungphakorn
Alison Thompson

Thank you

PK studies

- Nahashon Thuo
- Wanchana Ungphakorn
- Alex Muturi
- Japhet Karisa
- Simon Muchohi
- Gilbert Kokwaro
- Alison Thompson
- Kathryn Maitland

KISMAP Team, Kenya